Mathematical modelling of prostate cancer growth and its application to hormone therapy

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Hormone therapy in the form of androgen deprivation is a major treatment for advanced prostate cancer. However, if such therapy is overly prolonged, tumour cells may become resistant to this treatment and result in recurrent fatal disease. Long-term hormone deprivation also is associated with side effects poorly tolerated by patients. In contrast, intermittent hormone therapy with alternating on- and off-treatment periods is a possible clinical strategy to delay progression to hormone-refractory disease with the advantage of reduced side effects during the off-treatment periods. In this paper, we first overview previous studies on mathematical modelling of prostate tumour growth under intermittent hormone therapy. The model is categorized into a hybrid dynamical system because switching between on-treatment and off-treatment intervals is treated in addition to continuous dynamics of tumour growth. Next, we present an extended model of stochastic differential equations and examine how well the model is able to capture the characteristics of authentic serum prostate-specific antigen (PSA) data. We also highlight recent advances in time-series analysis and prediction of changes in serum PSA concentrations. Finally, we discuss practical issues to be considered towards establishment of mathematical model-based tailor-made medicine, which defines how to realize personalized hormone therapy for individual patients based on monitored serum PSA levels.

Keywords: prostate cancer; prostate-specific antigen; intermittent hormone therapy; hybrid dynamical systems; stochastic differential equations; time-series analysis

1. Introduction

Hormone therapy has been a major treatment for advanced or metastasized prostate cancer (Brawer 2006). The principle of hormone therapy is androgen suppression, which reduces the level of androgens and thereby inhibits the stimulation for growth of prostate cancer cells. Androgen deprivation, or castration, can be achieved by surgical removal of testes which are the primary source of androgens (Huggins & Hodges 1941) or administration of

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Figure 1. Schematic of the cycles of prostate tumour growth and regression under IAS. The introduction of off-treatment periods aims at preventing the tumour from entering the androgen-refractory state in which androgen deprivation can no longer evoke the apoptotic ability of the malignant cells nor induce the regression of the tumour.

pharmacological agents such as luteinizing hormone-releasing hormone analogues. Androgen-receptor antagonists, or antiandrogens, are capable of inhibiting the binding of androgens to their receptors and obstructing the normal activation pathway. Combined usage of medical castration and antiandrogens, called maximal androgen blockade or combined androgen blockade, is often adopted for advanced prostate cancer (Chodak 2005).

A good biomarker for prostate cancer is serum prostate-specific antigen (PSA), which is a protein produced by cells in the prostate gland (Rao et al. 2008). When a rising serum PSA level exceeds a certain critical value, androgen suppression is initiated. In most cases, androgen deprivation is temporarily effective in reducing the serum PSA level, which implies tumour regression. Cancer cells sensitive to androgen suppression are called androgen-dependent (AD) cells. During several years of continuous androgen suppression (CAS), however, many patients will suffer a relapse, or recurrent tumour growth. The cause of a relapse is considered to be progression to androgen-independent (AI) prostate cancer, which is no longer responsive to androgen suppression and likely to grow even in androgen-poor conditions (Rennie et al. 1990; Bladou et al. 1996).

To delay progression to androgen independence, intermittent androgen suppression (IAS) was proposed first in animal models (Bruchovsky et al. 1990; Akakura et al. 1993; Sato et al. 1996) and since then has been explored in clinical studies to establish efficacy of the therapy (Akakura et al. 1993; Goldenberg 1995; Bruchovsky et al. 2000, 2001, 2006, 2007; Hurtado-Coll et al. 2002). The status of further phase-II and ongoing phase-III trials of IAS is the subject of several review articles (Gleave 1998; Rashid & Chaudhary 2004; Bhandari et al. 2005; Abrahamsson 2010). Figure 1 is a schematic illustration showing a continuation of cycles of on- and off-treatment periods under IAS with the serum PSA levels oscillating in a clinically feasible range.
Intermittent hormone therapy

To understand the mechanism of progression to androgen independence and examine the effects of CAS and IAS therapies, mathematical approaches to hormone therapy for prostate cancer have been developed recently. The present paper deals with mathematical modelling of prostate cancer growth and its application to clinical data analysis.

In an effort to assist in predicting the progression to hormone-refractory prostate cancer and a resulting relapse, a mathematical model was proposed that describes the growth of tumours consisting of AD and AI cells under CAS (Jackson 2004a). This model reproduces the experimentally observed three phases of an evolving tumour, i.e. the exponential pretreatment tumour growth, the transient androgen-sensitive period immediately after treatment and the eventual AI relapse of the tumour. However, the analysis of the model suggests that CAS can only be successful in preventing a relapse for a small range of biological parameters (Jackson 2004b).

Ideta et al. (2008) proposed a mathematical model describing prostate tumour growth under IAS based on the former model for CAS by considering intermittent treatment protocols. The model is formulated as a hybrid dynamical system, in which two different continuous systems for tumour growth in on-treatment and off-treatment periods are switched according to the IAS protocol. The model is capable of replicating three different kinds of qualitative behaviours depending on the parameter values, i.e. a relapse without undergoing an off-treatment period like that in CAS, a relapse after several cycles of on-treatment and off-treatment periods and prevention of a relapse repeating the cycles forever.

Phase transitions between the regimes of relapse and relapse prevention in the IAS therapy model were revealed from a mathematical viewpoint by numerical bifurcation analyses (Tanaka et al. 2008). It is notable that a grazing bifurcation of a limit cycle and a chaotic attractor, which cannot be observed in ordinary smooth dynamical systems, plays a crucial role in the phase transition (Tanaka et al. 2009).

By modifying the IAS therapy model, a competition between AD and AI cells in androgen-poor conditions was considered as a candidate mechanism to enhance the possibility of relapse prevention (Shimada & Aihara 2008). The IAS therapy model represented by switched ordinary differential equations was also developed into a switched partial differential equations version by considering the volume of the tumour (Guo et al. 2008; Tao et al. 2009).

Although these deterministic models are successful in qualitatively reproducing typical tumour growth under IAS therapy, in reality, noise and fluctuations are inevitably involved in the dynamics of cell populations and monitoring of the serum PSA levels. Therefore, it is important to investigate how the IAS therapy model is sensitive to stochastic noise. This is why the first purpose of this article is to develop a stochastic differential equation model with dynamical and observational noise under the protocol of intermittent hormone therapy used in recent clinical study (Bruchovsky et al. 2006, 2007).

Following the developments of the fundamental models of IAS therapy, we have proposed a method to analyse real time-series data of serum PSA concentrations based on a piecewise linear model (Hirata et al. 2010). To complement this study, we explain why the piecewise linear model, instead of conventional models, is necessary for characterizing actual observations of...
clinical PSA data. Moreover, we carry out additional clinical data analysis to further examine the validity of the method. This is the second purpose of this article.

In §2, we present an extended model of switched stochastic differential equations for IAS therapy based on the deterministic model (Ideta et al. 2008) and show how well it reproduces the properties of the real clinical data of the serum PSA level. In §3, using a piecewise linear model, we show time-series analyses of the serum PSA data and classification of patients based on time-series predictions. Finally, discussions are given in §4.

2. Stochastic model

(a) Stochastic hybrid systems

The deterministic model (Ideta et al. 2008) is able to reproduce qualitative behaviour of prostate tumour growth under IAS and tractable in classifications of stationary states. However, some realistic factors should be taken into account to compare with the statistical results of clinical studies. Thus, we extend the former model as follows. First, stochastic noise is introduced to represent intrinsic fluctuations of the tumour dynamics and observation errors related to monitoring of the serum PSA levels. Second, the protocol of IAS is changed to that adopted in the clinical trials (Bruchovsky et al. 2006) with some simplification. The serum PSA level and the androgen level are monitored every 4 weeks. If the serum PSA level is less than \( r_0 = 4 \text{ng ml}^{-1} \) at 36 weeks after the initiation of therapy, the treatment is stopped at that time. Otherwise, the patient is not eligible for interruption of therapy and is withdrawn from the study. In the off-treatment period, therapy is resumed when the serum PSA level increases to \( r_1 = 10 \text{ng ml}^{-1} \).

The extended model of stochastic differential equations is represented as follows:

\[
\dot{x} = (G_x(z) - M_{xy}(z))x + x\xi_x, \quad (2.1)
\]
\[
\dot{y} = M_{xy}(z)x + G_y(z)y + y\xi_y, \quad (2.2)
\]
\[
\dot{z} = \frac{-z + z_0(1 - u)}{\tau} + z\xi_z, \quad (2.3)
\]
\[
v = x + y + \xi_v \quad (2.4)
\]
and
\[
u = \begin{cases} 
0 & \text{when } v \geq r_1 \text{ and } \dot{v} > 0 \\
1 & \text{when } v < r_0 \text{ and } \Delta t_{on} \geq 36 \times 7, \quad (2.5)
\end{cases}
\]

where \( x, y, z \) and \( v \) denote the population of AD cells, the population of AI cells, the androgen concentration and the serum PSA concentration, respectively. The unit of time \( t \) is assumed to be given by ‘day’. The binary variable \( u \) denotes on-treatment \( (u = 1) \) or off-treatment \( (u = 0) \). The time from the start of each on-treatment term is denoted by \( \Delta t_{on} \). The stochastic noise is given by Gaussian white noise \( \xi_i \ (i = x, y, z, v) \) with \( \langle \xi_i(t) \rangle = 0 \) and \( \langle \xi_i(t)\xi_j(t') \rangle = D_i \delta_{ij} \delta(t - t') \), where \( D_i \) is the noise intensity and \( \langle \cdot \rangle \) means time average.

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The dynamics of tumour growth described in equations (2.1) and (2.2) depends on the androgen concentration \( z \), which exponentially decreases during on-treatment periods and increases to the normal level \( z_0 \) during off-treatment periods following equation (2.3). The growth and mutation rates will be discussed later.

For simplicity, the serum PSA level \( v \) is assumed to be representative of the sum of the populations of AD and AI cells as in equation (2.4). For the most part, serum PSA is correlated with tumour size, although the relationship may differ between groups of patients in different eras (Ochiai et al. 2007). Based on the serum PSA level \( v \), interruption and restart of treatment are determined by the switching rule (2.5). This rule means that the treatment is resumed when an increasing PSA level reaches the upper threshold \( r_1 \) and suspended when a decreasing PSA level falls below the lower threshold \( r_0 \) at 36 weeks after the onset of each cycle. It should be noted that the patient is withdrawn from the study if the PSA level is not less than \( r_0 \) at 36 weeks after resumption of treatment. The values of the clinically controllable parameters \( r_1 \) and \( r_0 \) are fixed in numerical simulations according to the protocol used in clinical trials (Bruchovsky et al. 2006).

(b) Growth and mutation rates of cancer cells

The growth rate \( G_x \) of AD cells, the growth rate \( G_y \) of AI cells and the mutation rate \( M_{xy} \) from AD phenotype to AI phenotype, are, respectively, modelled as follows (Ideta et al. 2008):

\[
G_x(z) = \alpha_x \left( k_1 + (1 - k_1) \frac{z}{z + k_2} \right) - \beta_x \left( k_3 + (1 - k_3) \frac{z}{z + k_4} \right), \tag{2.6}
\]

\[
G_y(z) = \alpha_y \left( 1 - d \frac{z}{z_0} \right) - \beta_y \tag{2.7}
\]

and

\[
M_{xy}(z) = m_1 \left( 1 - \frac{z}{z_0} \right). \tag{2.8}
\]

On the right-hand side of equations (2.6) and (2.7), the first terms correspond to the proliferation rates and the second terms correspond to the apoptosis rates.

Table 1 lists the baseline parameter values for numerical simulations and comments on how they were determined.

Figure 2 shows the above functions of the growth and mutation rates of the tumour. The net growth rate of AD cells is positive with a high concentration of androgens but negative with a low concentration of androgens as shown in figure 2a.

The net growth rate of AI cells is assumed to bear a linear relationship with the androgen level for simplicity and the slope parameter \( d \) is introduced as shown in figure 2b, although the relationship can be nonlinear in general (Kokontis et al. 1994). It is unclear whether AI cells decrease in an androgen-rich condition, but there are some experimental results supporting this assumption (Kokontis et al. 1998, 2005; Chuu et al. 2005).

Figure 2c shows that the mutation rate from the AD cell phenotype to the AI cell phenotype is enhanced as androgens are depleted. Although only the irreversible mutational effect is considered in the present model for simplicity,
Figure 2. (a) Net growth rate of AD cells, or $G_x(z)$ in equation (2.6), which is given by the difference between proliferation and apoptosis rates. (b) Net growth rate of AI cells, or $G_y(z)$ in equation (2.7), which depends on the parameter $d$. (c) Mutation rate from AD cell phenotype to AI cell phenotype, or $M_{xy}(z)$ in equation (2.8). This is the case of $z_0 = 30$.

Table 1. List of baseline parameter values used for numerical simulations.

<table>
<thead>
<tr>
<th>parameter</th>
<th>value</th>
<th>note</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\alpha_x$</td>
<td>0.0204 $d^{-1}$</td>
<td>proliferation rate of AD cells at $z = z_0^a$</td>
</tr>
<tr>
<td>$\alpha_y$</td>
<td>0.0242 $d^{-1}$</td>
<td>proliferation rate of AI cells at $z = 0^a$</td>
</tr>
<tr>
<td>$\beta_x$</td>
<td>0.0076 $d^{-1}$</td>
<td>apoptosis rate of AD cells at $z = z_0^a$</td>
</tr>
<tr>
<td>$\beta_y$</td>
<td>0.0168 $d^{-1}$</td>
<td>apoptosis rate of AI cells$^a$</td>
</tr>
<tr>
<td>$k_1$</td>
<td>0</td>
<td>$\alpha_x k_1$ is the proliferation rate of AD cells at $z = 0^b$</td>
</tr>
<tr>
<td>$k_2$</td>
<td>2</td>
<td>plausible proliferation rate curve of AD cells$^b$</td>
</tr>
<tr>
<td>$k_3$</td>
<td>8</td>
<td>$\beta_x k_3$ is the apoptosis rate of AD cells at $z = 0^c$</td>
</tr>
<tr>
<td>$k_4$</td>
<td>0.5</td>
<td>plausible apoptosis rate curve of AD cells$^c$</td>
</tr>
<tr>
<td>$d$</td>
<td>$0 \leq d \leq 1$</td>
<td>slope of the proliferation rate curve of AI cells$^d$</td>
</tr>
<tr>
<td>$m_1$</td>
<td>$5 \times 10^{-5} d^{-1}$</td>
<td>mutation rate from AD to AI cells at $z = 0^e$</td>
</tr>
<tr>
<td>$z_0$</td>
<td>20 nmol$^{-1}$</td>
<td>normal androgen level$^f$</td>
</tr>
<tr>
<td>$\tau$</td>
<td>62.5 day</td>
<td>time constant of the androgen dynamics$^f$</td>
</tr>
<tr>
<td>$r_1$</td>
<td>10 ng ml$^{-1}$</td>
<td>upper threshold of the serum PSA level$^f$</td>
</tr>
<tr>
<td>$r_0$</td>
<td>4 ng ml$^{-1}$</td>
<td>lower threshold of the serum PSA level$^f$</td>
</tr>
</tbody>
</table>

$^a$These parameter values correspond to the case of bone metastasis (Berges et al. 1995). Other values for the lymph node metastasis case are also considered in Ideta et al. (2008).

$^b$Since AD cells do not multiply without androgens, the proliferation rate at $z = 0$, $\alpha_x k_1$, should be zero. $k_2$ is determined in such a way that the proliferation rate of AD cells is larger than the apoptosis rate in an androgen-rich condition. See figure 2a.

$^c$Fitting the serum PSA data under hormone therapy (Bruchovsky et al. 2007) yields an estimated value of the apoptosis rate of AD cells in an androgen-poor condition as $\beta_x k_3 \sim 0.06$. Assuming that the net growth rate of AD cells changes from negative to positive at nearly $z = 5$, we derive the apoptosis rate curve of AD cells. See figure 2a.

$^d$d is the parameter introduced to characterize the proliferation rate of AI cells. Because of the constant apoptosis rate $\beta_y$, the net growth rate of AI cells directly depends upon $d$. See figure 2b.

$^e$Time to a relapse under CAS is usually several years. A feasible range of $m_1$ satisfying this fact is obtained by numerical tests of the model with $\tau = 0$ (Ideta et al. 2008).

$^f$These values were determined in a feasible range consistent with clinical data (Bruchovsky et al. 2007).

Phil. Trans. R. Soc. A (2010)
reversible changes between AD and AI cell phenotypes and other pathways to AI are possible (Feldman & Feldman 2001; Scher et al. 2004; Dehm & Tindall 2005; Edwards & Bartlett 2005). This point will be discussed in §3.

(c) Numerical simulations

The biochemical results from a prospective phase II study of IAS (Bruchovsky et al. 2006, 2007) were analysed for correlations to the onset of hormone-refractory disease. The analyses of time courses of the serum PSA and testosterone levels suggested some statistical trends. Testosterone is an androgen steroid hormone primarily secreted in the testes of males. We examine how well the stochastic model (2.1)–(2.5) is able to reproduce the features of the actual clinical data.

The numerical integration of the stochastic differential equations (2.1)–(2.5) was carried out using the Heun scheme with a time step of 0.005 (Kloeden & Platen 1992). The intensities of the dynamical and observational noise are assumed to be given as $D_x = D_y = D_z = D_d$ and $D_o = D_o$, respectively. These parameter values are set at $D_d = 0.001$ and $D_o = 0.0001$, unless otherwise noted. The maximum observation time is fixed at 2500 days.

Figure 3 shows an example of the time evolutions of the serum PSA and testosterone levels. The therapy is terminated after 4.5 cycles of the on-treatment and off-treatment intervals, because the serum PSA level is not less than 4 ng ml$^{-1}$ at 36 weeks after the beginning of the fifth cycle. The duration of the on-treatment period is 36 weeks for every cycle as specified by the protocol (2.5), while that of the off-treatment period gradually decreases as the cycle number increases. The decrease of the ratio of the off-treatment period gradually decreases as the cycle number increases. The decrease of the off-treatment period may be correlated to the development of early AI. The time course of the serum PSA level also demonstrates that the serum PSA nadir level increases with more cycles of therapy. This tendency was noted in the clinical database of Bruchovsky et al. (2007).
Figure 4. Simulation results of the stochastic model with the initial conditions used in figure 3 for different noise intensities. (a) The mean number of cycles over 20 trials for each value of $d$. (b) The mean time to a relapse or a termination of the therapy over 20 trials for each value of $d$. Filled diamonds, $D_d = 0, D_o = 0$; open inverted triangles, $D_d = 0.001, D_o = 0.0001$; filled circles, $D_d = 0.001, D_o = 0.001$; open triangles, $D_d = 0.01, D_o = 0.0001$.

The features of the serum PSA level depend upon the parameter $d$, which characterizes the growth rate of AI cells. As shown in figure 2b, the growth rate of AI cells decreases as the value of $d$ increases. Therefore, both the average number of cycles and the average time to relapse are likely to increase as $d$ itself increases (figure 4). In the deterministic case with $D_d = 0$ and $D_o = 0$, the serum PSA level evolves in the same manner for a fixed value of $d$ without trial-to-trial variations. The low noise case with $D_d = 0.001$ and $D_o = 0.0001$ seems to be reasonable for comparison with the statistics of clinical data, because it produces variable time courses of the serum PSA levels without losing the tendency of the deterministic system. It is remarkable that the number of cycles is variable even for the same value of $d$ owing to the low level of stochastic noise. This is caused by an interplay between the switching dynamics of the system and the stochastic noise. Noise has a great effect particularly on a trajectory near the boundary $(x + y = r_0)$ for switching of dynamics: if a trajectory hits the boundary, then the next cycle follows; otherwise a trajectory diverges and no cycle follows. Therefore, this result suggests that even small stochastic noise can contribute to the diversity of clinical data in different patients. The other two noise levels in figure 4 are too high to mimic a time evolution of the serum PSA level in actual observations. In fact, while the maximum observation time is reached for $d > 0.6$ as shown in figure 4b, the mean number of cycles is much less than that in the deterministic case as shown in figure 4a. Namely, the length of one cycle is very different from the actual data.

Figure 5 shows the effect of the initial testosterone level on the mean off-treatment time. In figure 5a,b, the mean length of the off-treatment periods decreases with each succeeding cycle. This trend can be found in the clinical data (Bruchovsky et al. 2006). However, the trend is not applicable to the case when the initial testosterone level is relatively high as shown in figure 5c. The reason for this is explained as follows. Since a higher initial testosterone level requires more time to be reduced by treatment, a longer delay ensues until the PSA level begins to fall. Therefore, the PSA nadir at 36 weeks after the start of therapy

Phil. Trans. R. Soc. A (2010)
Intermittent hormone therapy

Figure 5. The mean off-treatment time in each cycle, averaged over 20 trials of the stochastic model. The error bar indicates the standard deviation. The initial conditions of the cell populations are fixed at \( x(0) = 15 \) and \( y(0) = 0.1 \), and the initial condition of the testosterone level is varied: (a) \( z(0) = 10 \); (b) \( z(0) = 15 \); (c) \( z(0) = 20 \).

Figure 6. The correlations between the serum PSA nadir level and the length of off-treatment period. For 100 trials of the stochastic model where the value of \( d \) is randomly chosen between 0 and 1, \( x(0) = 15 \), \( y(0) = 0.1 \), and \( z(0) \) is randomly chosen between 10 and 20, the off-treatment times are plotted against the serum PSA nadir level: (a) cycle 1; (b) cycle 2; (c) cycle 3.

tends to be higher, even though it is below the lower threshold \( r_0 \). Consequently, in the following off-treatment period, the time needed for the PSA level to reach the upper threshold \( r_1 \) is shorter. Thus, the length of the off-treatment period is closely related to the testosterone level at the start of therapy in each cycle.

Figure 6 shows correlations between the serum PSA nadir and the duration of the off-treatment period in each cycle. The length of the off-treatment period is longer for a lower nadir level of serum PSA. A high correlation is recognized in cycle 1 (correlation coefficient, \( cc = -0.61 \)) as shown in figure 6a, while not in cycle 2 (\( cc = -0.38 \)) and cycle 3 (\( cc = -0.26 \)) as shown in figure 6b,c. In all cycles, the length of the off-treatment period is related inversely to the serum PSA nadir. This property is consistent with the result of the clinical data analysis (Bruchovsky et al. 2007).
In summary, the proposed stochastic model has generated variable time courses of the serum PSA and testosterone levels. The results demonstrate that stochastic noise can be responsible for the diversity of clinical PSA data in individual patients. The large effect of noise is caused by its interaction with switching properties of the system. Furthermore, we have demonstrated that the model is able to reproduce the characteristics observed in clinical trials, i.e. the shortening of the off-treatment period with more cycles and the inverse relationship between the serum PSA nadir level and the duration of the off-treatment period. Therefore, the stochastic model is considered to be more realistic than the former deterministic model.

3. Application to clinical data analysis

In this section, we apply our theoretical model to clinical data and show that it can approximate the behaviour of a tumour. To make predictions, a mathematical model should be accurate enough to reproduce growth and regression of prostate cancer under IAS. However, the variations of the serum PSA levels generated by system (2.1)–(2.5) appear to be different from the actual observations in figure 7. In system (2.1)–(2.5), the PSA level decreases sharply to a nadir during the on-treatment period as shown in figure 3. In reality, however, the PSA decline is biphasic with an initial steep slope followed by a more shallow one. Therefore, additional factors in system (2.1)–(2.5) need to be considered to reproduce the biphasic kinetics; moreover, redundant factors should be removed to limit the number of parameters to be estimated for modelling so as to avoid overfitting.

First, we observe that the androgen dynamics in equation (2.3) does not contribute much to the form of the reproduced PSA data sequence. Therefore, this property can be eliminated for the purpose of data-fitting by assuming that the androgen level instantaneously switches between the minimum level 0 and the normal level $z_0$ at the moments of restart and suspension of treatment, i.e. $\tau \to \infty$ in equation (2.3). At this stage, the model has been reduced to a two-dimensional system. Second, one additional dimension is needed to mimic the biphasic decline of the actual serum PSA level during the on-treatment period.
Interruption hormone therapy

Figure 8. A mathematical model consisting of three phenotypes of prostate cancer cells, which is used for clinical data analysis. Nodes 1, 2 and 3 correspond to AD cells, AI cells of the first phenotype and AI cells of the second phenotype, respectively. (a) Under on-treatment; (b) under off-treatment.

We could reasonably increase the dimensions of the system to three by considering a population of AI cells that undergo reversible changes. This would be in line with the idea that there are reversible pathways based on epigenetic mechanisms that lead to AI (Rennie et al. 2005).

Following the above consideration, we proposed a modified model that contains three phenotypes of cancer cells as illustrated in figure 8 (Hirata et al. 2010). One phenotype corresponds to AD cells and the other two correspond to AI cells. During the on-treatment period, AD cells may change to AI cells of the first or the second phenotype. During the off-treatment period, AI cells of the first phenotype may return to AD cells, while AI cells of the second phenotype enter an irreversible state and cannot revert to AI cells of the first phenotype or AD cells. We also showed that a piecewise linear model that omits testosterone is adequate enough for the modelling of prostate cancer under IAS.

Thus, we consider the following mathematical model for clinical data analysis. Let $x_1$, $x_2$ and $x_3$ be the populations of AD cells, AI cells of the first phenotype and AI cells of the second phenotype, respectively. Letting $w_{m}^{i,j}$ be the contribution of cell population $x_j$ to cell population $x_i$ when the treatment is $m$, the dynamics under the on-treatment period is written as

$$
\begin{pmatrix}
\dot{x}_1 \\
\dot{x}_2 \\
\dot{x}_3
\end{pmatrix} =
\begin{pmatrix}
w_{1,1}^{1} & w_{1,2}^{1} & w_{1,3}^{1} \\
w_{2,1}^{1} & w_{2,2}^{1} & w_{2,3}^{1} \\
w_{3,1}^{1} & w_{3,2}^{1} & w_{3,3}^{1}
\end{pmatrix}
\begin{pmatrix}
x_1 \\
x_2 \\
x_3
\end{pmatrix}.
$$

(3.1)

Similarly, the dynamics under the off-treatment period is written as

$$
\begin{pmatrix}
\dot{x}_1 \\
\dot{x}_2 \\
\dot{x}_3
\end{pmatrix} =
\begin{pmatrix}
w_{1,1}^{0} & w_{1,2}^{0} & w_{1,3}^{0} \\
w_{2,1}^{0} & w_{2,2}^{0} & w_{2,3}^{0} \\
w_{3,1}^{0} & w_{3,2}^{0} & w_{3,3}^{0}
\end{pmatrix}
\begin{pmatrix}
x_1 \\
x_2 \\
x_3
\end{pmatrix}.
$$

(3.2)

The PSA level is given by $x_1 + x_2 + x_3$ for simplicity.

The fitting of the above model to the serum PSA data faces some difficulties. Although the model needs to be able to reproduce a relapse to make a prognosis and/or personalize the treatment schedule, the relapsing part is not available for fitting the model. Therefore, simple phenomenological approaches will fail in this application.

Phil. Trans. R. Soc. A (2010)
Figure 9. Fitting and prediction for clinical data of a patient. The models (3.1) and (3.2) are fitted as described in the main text. Using the obtained parameters from the first 2.5 cycles, the future change in the serum PSA levels was predicted relatively well. The solid line indicates the fitting and prediction of IAS, the crosses indicate the actual data under IAS and the dashed line shows the simulation result of the fitted model under the assumption of CAS.

To overcome this problem, three realistic constraints during the fitting are considered. The first constraint is that all non-diagonal parameters are non-negative. The second constraint is that each phenotype will change its volume by 20 per cent at most in a day and that at most 10 per cent of each phenotype may change to other phenotype within a day. The third constraint is that under CAS, the PSA level decreases at the beginning of the treatment but starts to increase within 5 years. We enforced these constraints using the penalty method (Price et al. 2005). The two subsystems (3.1) and (3.2) are switched according to the switching between on-treatment and off-treatment periods indicated in clinical data.

By using the above method, the actual data were well approximated by our mathematical model as shown in figure 9. Further, based on system (3.1) and (3.2), we can classify patients of clinical trials (Goldenberg 1995; Hurtado-Coll et al. 2002; Pether & Goldenberg 2004; Bruchovsky et al. 2006, 2007; Shaw et al. 2007) into three types.

The first criterion for classification is whether AI cells of the second phenotype will proliferate or not during an on-treatment period. If $w_{3,3}^1 < 0$, the AI cells of the second phenotype can be diminished by treatment, and thus a relapse may be prevented; on the other hand, if $w_{3,3}^1 \geq 0$, then the AI cells of the second phenotype will always increase and a relapse cannot be avoided. Therefore, if $w_{3,3}^1 < 0$, we classify the patients to be type (i).

The second criterion is whether the relapse can be delayed or not. If $w_{1,1}^1 \leq w_{1,1}^0$ and $w_{2,2}^1 \leq w_{2,2}^0$ and $w_{3,3}^1 \leq w_{3,3}^0$, CAS is the method of choice to reduce PSA to the lowest possible level. If $w_{1,1}^1 > w_{1,1}^0$ or $w_{2,2}^1 > w_{2,2}^0$ or $w_{3,3}^1 > w_{3,3}^0$, IAS may delay the increase in PSA level, and thus IAS may be the better treatment strategy for these patients when compared with CAS. Therefore, if $w_{1,1}^1 > w_{1,1}^0$ or $w_{2,2}^1 > w_{2,2}^0$ or $w_{3,3}^1 > w_{3,3}^0$, we classify patients as type (ii). Otherwise, they are classified as type (iii).
Intermittent hormone therapy

Table 2. Classification of patients based on parameters of models (3.1) and (3.2). Patients without a relapse include those who died from causes other than prostate cancer. In this table, we combined the results obtained from the following two clinical trials (http://www.nicholasbruchovsky.com/clinicalResearch.html). The trial of Bruchovsky et al. (2006) was approved by the Health Protection Branch of the Ministry of Health of Canada and by the Clinical Research Ethics Review Boards of the participating centres. For this trial, all patients provided written informed consent in accordance with institutional guidelines. In the second Vancouver database that was included in Shaw et al. (2007), all patients signed general consent forms for care, which included use of their data for research.

<table>
<thead>
<tr>
<th>model prediction</th>
<th>patients without a relapse</th>
<th>patients with androgen independence</th>
</tr>
</thead>
<tbody>
<tr>
<td>type (i): no relapse</td>
<td>52</td>
<td>1</td>
</tr>
<tr>
<td>type (ii): relapse delayed</td>
<td>17</td>
<td>15</td>
</tr>
<tr>
<td>type (iii): relapse</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>total no. of patients</td>
<td>71</td>
<td>19</td>
</tr>
<tr>
<td>no. affected</td>
<td>52</td>
<td>18</td>
</tr>
<tr>
<td>accuracy (%)</td>
<td>73</td>
<td>95</td>
</tr>
</tbody>
</table>

In summary, if patients are type (i), IAS may prevent a relapse of malignancy. If type (ii), IAS may delay a relapse. If type (iii), CAS is better than IAS. For details of the derivations of these criteria, see Hirata et al. (2010).

Using the model including irreversible and reversible changes and whole datasets, we have classified 90 patients into three types as shown in table 2. Most patients who experienced a relapse were classified as type (ii) or (iii). The majority of the patients without a relapse were classified as type (i). Therefore, the classification by the proposed model is consistent with judgements made by medical doctors of patient responses in the clinical setting.

4. Discussion

After reviewing mathematical modelling of IAS for prostate cancer, we have presented a stochastic model and shown that it is successful in reproducing statistical features of the time course of serum PSA in clinical trials (Bruchovsky et al. 2006, 2007), such as the shortening of the off-treatment periods with more on- and off-treatment cycles and the inverse relationship between the serum PSA nadir level and the length of the off-treatment interval. However, the stochastic model is not able to replicate the biphasic decrease of the serum PSA level. The model could be further extended by taking into account new findings on the possible pathways to AI in addition to irreversible changes from the AD cell phenotype to the AI cell phenotype. Another possible improvement is to model the growth of both normal and cancer cells.

For time-series analysis of clinical data of the serum PSA concentrations, we have presented a three-dimensional piecewise linear model. By fitting this model to actual data and estimating the model parameters, we have obtained criteria.
for classification of patients. The classification provides an objective guide for a prognosis and a better choice of treatments for individual patients. The results of predictions were almost consistent with judgements made by medical doctors.

Currently, we require the first 2.5 cycles to obtain a good fit such as the one shown in figure 9. Although it is desirable to estimate the parameter values from as short a time series as possible, we need at least the first 1.5 cycles to make predictions. If the time series does not contain the off-treatment period, we cannot obtain the information related to the dynamics under the off-treatment period. Even if the length of time series of the serum PSA level is long enough to determine a set of parameters, the estimation error can be large since the available time series of the PSA determinations would still be too short. To make a correct diagnosis, we have to overcome this estimation error. One of the ideas is to use past datasets of other patients as a priori knowledge for constructing the prior distribution for the parameters and initial conditions. Parameter estimation and overcoming the estimation error are two important topics to make our mathematical analysis standard practice.

Our final goal is to tailor and individualize hormone therapy for prostate cancer using a mathematical approach with hybrid systems modelling as described in this article. We infer that such an approach will be of diagnostic and prognostic benefit in a clinical setting. For this purpose, the optimal control method would help to provide insight into the best scheduling of hormone therapy (Suzuki et al. 2010).

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References


Correction

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Mathematical modelling of prostate cancer growth and its application to hormone therapy

By Gouhei Tanaka, Yoshito Hirata, S. Larry Goldenberg, Nicholas Bruchovsky and Kazuyuki Aihara

In the third paragraph of p. 5040, there are two typographical errors, which should be corrected as follows:

1. In lines 2, 4 and 5 ‘$w_{3,3}^1$’ should be ‘$w_{3,3}^0$’.
2. In lines 2 and 3 ‘on-treatment’ and ‘treatment’ should be ‘off-treatment’.

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