Quantitative mathematical modeling of PSA dynamics of prostate cancer patients treated with intermittent androgen suppression

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If a mathematical model is to be used in the diagnosis, treatment, or prognosis of a disease, it must describe the inherent quantitative dynamics of the state. An ideal candidate disease is prostate cancer owing to the fact that it is characterized by an excellent biomarker, prostate-specific antigen (PSA), and also by a predictable response to treatment in the form of androgen suppression therapy. Despite a high initial response rate, the cancer will often relapse to a state of androgen independence which no longer responds to manipulations of the hormonal environment. In this paper, we present relevant background information and a quantitative mathematical model that potentially can be used in the optimal management of patients to cope with biochemical relapse as indicated by a rising PSA.

Keywords: prostate cancer, intermittent androgen suppression, androgen deprivation, biochemical relapse, mathematical model, classification, prediction, optimal scheduling

Introduction
Androgen withdrawal is an option that can be employed in the treatment of all stages of prostate cancer and the response is usually monitored by serial measurements of prostate-specific antigen (PSA). If such therapy is continued, it often results in the emergence of androgen-independent (AI) disease. Intermittent application of androgen withdrawal has been studied in an effort to delay the onset of androgen resistance in addition to improving overall quality of life during off-treatment periods (Bruchovsky et al., 2008). There are various intermittent androgen suppression (IAS) regimens that include an on-treatment period of 6–9 months of androgen withdrawal and a variable off-treatment period determined by the rise in PSA to a pre-determined threshold level. Rather than relying on uniform criteria for starting and stopping such therapy, a personalized mathematical model (Hirata et al., 2010a) has been developed, as described below, from an international PSA database in an attempt to better characterize IAS. The data were obtained from American, Canadian, and Japanese men in biochemical relapse after primary therapy with radiation or prostatectomy. With this model, it is potentially possible not only to improve the outcome of hormone therapy in men with biochemical relapse but also to identify those patients who will benefit from IAS versus those who will not. The model also affords the possibility of classifying patients according to risk of relapse (high, medium, or low), by determining in advance whether IAS will be effective.

Hormone therapy in the treatment of prostate cancer
Huggins and Hodges (1941) showed that the growth of prostate cancer depends on the secretion of testosterone by the testes. Therefore, they proposed surgical castration as treatment for metastatic prostate cancer, the other option being the use of estrogens to suppress the pituitary gland. However, estrogenic agents were associated with major side effects, leading Whitmore to attempt their use on an intermittent basis for reducing morbidity. This experience was reported by Klotz et al. (1986) and the reference was made to the fact that androgens were likely to be suppressed by the treatment, although testosterone was not measured.

The discovery of anti-androgens and luteinizing hormone-releasing hormone (LHRH) agonists made it possible to suppress the testosterone level reversibly and allow for the emergence of IAS as a method of treatment. Since then the combination of an LHRH agonist with an oral anti-androgen on an intermittent basis (Akakura et al., 1993; Akakura, 2005; Bruchovsky et al., 2006, 2007) has been accepted as a standard of care option.
especially for those men suffering biochemical relapse who wish to be treated.

A typical time course of IAS is shown in Figure 1. After the start of hormone therapy, the level of testosterone decreases, followed by a decline in PSA. Hormone therapy is continued for either a specified period of 8–9 months (Canada and USA), or when the PSA decreases to a lower threshold level. After treatment is interrupted, the testosterone level increases, followed by the PSA level. When the value of PSA reaches a higher threshold level, the second cycle of therapy is started. Further cycling follows the same procedure.

Quantitative mathematical model

A mathematical model of prostate cancer during androgen suppression was first proposed by Jackson (2004a, b). Later, the first mathematical model of prostate cancer under IAS was proposed by Ideta et al. (2008). The Ideta model was extended to a model with partial differential equations (Guo et al., 2008; Tao et al., 2009, 2010) and a model with competition between different classes of prostate tumor cells (Shimada and Aihara, 2008). However, these models share a common drawback: they cannot describe the biphasic decline in PSA during the on-treatment periods. Dimonte (2010) evaluated the probability of death by prostate cancer under various treatment options using a cell kinetic model. Kronik et al. (2010) proposed a mathematical model for immunotherapy of prostate cancer.

The model of Ideta et al. (2008) has been further extended by other groups of researchers, who considered more detailed biochemical dynamics of androgen and androgen receptors, and related effects (Eikenberry et al., 2010; Jain et al., 2011; Portz et al., 2012).

In a somewhat different approach and to quantitatively describe the dynamics of prostate cancer, especially PSA, under IAS, we focus here on a piecewise linear model proposed by Hirata et al. (2010a). In this piecewise linear model, three classes of cancer cells are considered: one class of androgen-dependent (AD cancer cells) and two classes of AI cancer cells (see Figure 2 for the schematic diagram). During an on-treatment period, AD cancer cells can change to two classes of AI cancer cells. During an off-treatment period, AI cancer cells of the first class may become again AD cancer cells. However, AI cancer cells of the second class cannot change back to AD cancer cells or AI cancer cells of the first class. Namely, AI cancer cells of the first class appear by reversible changes such as adaptations, and AI cancer cells of the second class appear by irreversible changes such as mutations. The mathematical model of this piecewise linear model can be written as a hybrid system (Aihara and Suzuki, 2010) as follows:

\[
\frac{dx_0}{dt} = W^{on}_{00} x_0 + W^{on}_{01} x_1 + W^{on}_{02} x_2 = W^{on} x_0 x_1 \tag{1}
\]

for on-treatment periods, and

\[
\frac{dx_0}{dt} = W^{off}_{00} x_0 + W^{off}_{01} x_1 + W^{off}_{02} x_2 = W^{off} x_0 x_1 \tag{2}
\]

for off-treatment periods, where \(x_0\), \(x_1\), and \(x_2\) are variables proportional to the volumes of AD cancer cells, AI cancer cells of the first class, and AI cancer cells of the second class, respectively. Parameters \(W^{on}_{ij}\) and \(W^{off}_{ij}\) show the contribution of cell class \(i\) to the net growth rate of cell class \(j\) during medication \(m\). The PSA level is expressed as the following linear function of \(x_0\), \(x_1\), and \(x_2\) for simplicity:

\[
\begin{pmatrix}
C_0 \\
C_1 \\
C_2
\end{pmatrix}
\begin{pmatrix}
x_0 \\
x_1 \\
x_2
\end{pmatrix},
\]

where we set \(C_0 = C_1 = C_2 = 1\).

Except for the assumption that there are reversible and irreversible changes for cancer cell classes, there are two assumptions related to this piecewise linear model: the first assumption is that the model equation is linear for on- and off-treatment periods, respectively; the second assumption is that the androgen level is not explicitly included in the model. In the paper of Hirata et al. (2010a), we have validated both assumptions by using clinical data sets.

Fitting this piecewise linear model is very difficult when applied to the clinical setting since we need to predict, or prognosticate, relapse of cancer by using a data set which does not include the relapsing part of the data set. To overcome the problem, we
enforce constraints for model fitting. The first constraint is that non-diagonal parameters are non-negative, namely, $W_{0 \rightarrow 1}^{\text{on}} \geq 0$, $W_{1 \rightarrow 2}^{\text{on}} \geq 0$, $W_{1 \rightarrow 2}^{\text{off}} \geq 0$, and $W_{2 \rightarrow 0}^{\text{off}} \geq 0$. These constraints represent the transitions in Figure 2. The second constraint is that each cell class can change its volume by 20% at most within a day, namely, \[
\sum_{j \in \{0, 1, 2\}} W_{i \rightarrow j}^{\text{on}} < 0.2 \text{ for all } i \in \{0, 1, 2\} \text{ and } m \in \{\text{on, off}\}.
\] These second constraints are supported by tumor volume doubling times, which are typically between 60 and 200 days (Klein, 2009). The third constraint is that PSA will relapse if androgen suppression is continued. This constraint is enforced mainly by $W_{2 \rightarrow 0}^{\text{on}} > 0$. The last constraint is applicable to owing to the fact that most prostate cancer patients treated with continuous androgen suppression (CAS) will eventually relapse. Since the piecewise linear model is simple enough, one can classify the patients according to the parameters obtained by fitting each patient’s data in a personalized way (Hirata et al., 2010a, b; see Figure 3 for the algorithm for the classification). There are three types of patients: Type (i) is a patient whose cancer will not relapse during appropriately scheduled IAS. Mathematically, Type (i) patients are defined by the existence of parameter $\alpha \in (0, 1)$ such that the real parts of the all eigenvalues of $aW^{\text{on}} + (1 - a)W^{\text{off}}$ are negative (Liberzon, 2003); roughly each eigenvalue is proportional to the rate of increase in a combination of different classes of cancer cells. Here we have extended the criterion of Hirata et al. (2010a, b) so that the relapses due to $x_0$ and $x_1$ can be taken into account. Type (ii) is a patient in whom the relapse of cancer cannot be prevented but only delayed by IAS. Type (ii) patients are mathematically characterized as patients who are not Type (i) but satisfy $W_{0 \rightarrow 1}^{\text{off}} < W_{0 \rightarrow 0}^{\text{on}}$ or $W_{1 \rightarrow 2}^{\text{off}} < W_{1 \rightarrow 1}^{\text{on}}$ or $W_{2 \rightarrow 2}^{\text{off}} < W_{2 \rightarrow 2}^{\text{on}}$. Under this condition, at least the number of cancer cells for a class decreases during off-treatment periods. Type (iii) is a patient for whom CAS can delay relapse more than IAS over the long term. Type (iii) specifies patients who are neither Type (i) nor Type (ii). Since $W_{0 \rightarrow 0}^{\text{on}} \geq W_{0 \rightarrow 0}^{\text{off}}$ and $W_{1 \rightarrow 1}^{\text{on}} \geq W_{1 \rightarrow 1}^{\text{off}}$ and $W_{2 \rightarrow 2}^{\text{on}} \geq W_{2 \rightarrow 2}^{\text{off}}$ for Type (iii) patients, the net growth rate for cancer cells of every class is not greater during on-treatment periods than during off-treatment periods.

The optimal treatment schedule using the piecewise linear model was considered in Hirata et al. (2010b). In the piecewise linear model, exact solutions can be obtained. The form of exact solutions becomes as follows:

\[
\begin{align*}
\begin{bmatrix} x_0(t) \\ x_1(t) \\ x_2(t) \end{bmatrix} &= W_0^{\text{on}} x_0(0) + W_1^{\text{on}} x_1(0) + W_2^{\text{on}} x_2(0) \\
&= W_0^{\text{on}} x_0(0) + W_1^{\text{on}} x_1(0) + W_2^{\text{on}} x_2(0).
\end{align*}
\]

where $W(W_{0,1})$ is the matrix depending on the treatment scheduling $s_{on}$ for a period between 0 and $t$. Basically, we can delay relapse of cancer more efficiently by minimizing the maximal eigenvalue of $W(W_{0,1})$, which is equivalent to minimizing the fastest net growth rate in a certain combination of different classes of cancer cells. This approach is realized by calculating the maximal eigenvalue for every possible treatment schedule and choosing the schedule that provides the minimum eigenvalue or rate that the number of cancer cells increase. However, the method requires extensive computational time. To reduce the computational cost, Hirata et al. (2010b) considered a simplified periodic treatment schedule of period $T$ and chose the optimal ratio between on- and off-treatment periods. If the treatment schedule is periodic, then $W(W_{0,1})$ can be decomposed into the following form:

\[
W(W_{0,1}) = W_{\text{on}}^{(n)}(W_{\text{off}}^{(n)})^n,
\]

where $n$ is the largest integer such that $nT \leq t$. The behavior of $W(W_{0,1})$ is dominated by that of $W(W_{0,1})$ when $n$ is large. Here $W(W_{0,1})$ corresponds to one cycle of the periodic treatment. In addition, by letting $t_1$ be the length of the on-treatment period, the matrix $W(W_{0,1})$ can be further divided into two parts as follows:

\[
W(W_{0,1}) = W_{\text{off}}^{(n)}W_{\text{on}}^{(n)}.
\]

\[
W_{\text{on}}^{(n)} = \begin{pmatrix} W_{0 \rightarrow 0}^{\text{on}}(S_{0,1}) & 0 & 0 \\ W_{0 \rightarrow 2}^{\text{on}}(S_{0,1}) & W_{2 \rightarrow 0}^{\text{on}}(S_{0,1}) \end{pmatrix},
\]

\[
W_{\text{off}}^{(n)} = \begin{pmatrix} W_{0 \rightarrow 0}^{\text{off}}(S_{1,1}) & W_{0 \rightarrow 2}^{\text{off}}(S_{1,1}) & 0 \\ W_{2 \rightarrow 0}^{\text{off}}(S_{1,1}) & W_{2 \rightarrow 2}^{\text{off}}(S_{1,1}) \end{pmatrix}.
\]

Namely, the matrix $W_{\text{on}}^{(n)}(S_{0,1})$ corresponds to the on-treatment period, and $W_{\text{off}}^{(n)}(S_{1,1})$ corresponds to the off-treatment period. Therefore, we minimize the maximal eigenvalue of $W(W_{0,1})$ over the length of on-treatment period $t_1$. By constraining a set of treatment schedules to be periodic, we can reduce the computational burden.

When the origin is asymptotically stable, then we have

\[
\begin{align*}
\lim_{t \to \infty} x_0(t) &= 0 \\
\lim_{t \to \infty} x_1(t) &= 0 \\
\lim_{t \to \infty} x_2(t) &= 0.
\end{align*}
\]

because the absolute values of all the eigenvalues of $W(S_{0,1})$ are less than 1 in such a case, while non-zero periodic solutions should have the eigenvalue of 1.

**Analysis using a quantitative mathematical model**

Examples of data fitting and prediction are shown in Figure 4, where we use American cases. Here we follow the fitting
procedure of Hirata et al. (2010a), in which we enforce constraints for parameters and initial conditions so that we can reproduce PSA relapse under CAS from data sets that do not include relapse. From these examples, we can imply the following points: in Type (i) patients, IAS can prevent relapse; in Type (ii) patients, IAS does not prevent tumor relapse, rather it delays relapse relative to CAS; in Type (iii) patients, CAS is more effective than IAS in delaying relapse. Fitting the first two and one-half cycles of PSA data under IAS by the piecewise linear model presented herein, the PSA behavior for the following cycles of IAS was quantitatively predicted (Figure 4D).

Initially, we analyzed the data sets from Canadian patients who were treated with IAS. The data sets of Canadian cases were drawn from a Phase II study of IAS (Bruchovsky et al., 2006, 2007, 2008). This Phase II study was approved by the Health Clinical Research Ethics Review Boards of each of the participating treatment centers. All patients provided written informed consent from our model under IAS and the green line shows the simulation by our model under CAS. These examples are taken from American cases.

The results are shown in Table 1. Clearly, there are correlations between judgments by physicians who conducted the clinical trials and the classification afforded by the piecewise linear model \( P = 3.2 \times 10^{-4} \). We used Fisher’s exact test at the homepage of http://aoki2.si.gunma-u.ac.jp/exact/fisher/getpar.html.

Similar to the Canadian cases, we classified American and Japanese patients. The American data sets were obtained from an on-going Phase II study of IAS (Higano et al., 2004; Yu et al., 2010) approved by the University of Washington Institutional Review Board. The study of Japanese cases was approved by the ethics committees of Tokyo Kosei Nenkin Hospital and University of Tokyo. For both studies, we obtained informed consent from all patients. The additional analysis of American cases was approved by the ethics committee of University of Tokyo.

The results comparing patient types by the country of origin are summarized in Table 2. American and Japanese patients show a similar tendency to Canadian patients (Fisher’s exact test; \( P = 0.30 \)). Therefore, although the patients included in the present study had been selected by the physicians’ assumption that IAS would be suitable treatment, the country of origin for a patient does not influence the ratio of patient types significantly; thus IAS will be also effective for most North American and Japanese patients as well.

In addition, we gained interesting insight into Type (iii) patients. In some of these men, a long period of observation without therapy may help to delay relapse of prostate cancer. This phenomenon seems to happen when \( w_{00}^{\text{on}} \) and \( w_{00}^{\text{off}} \) are far smaller than \( w_{22}^{\text{on}} \) and \( w_{22}^{\text{off}} \), the initial condition is heavily weighted on \( X_0(t) \), and \( X_1(t) \) is very small. An example of this special case is shown in Figure 5. It indicates a possible benefit for some Type (iii) patients, for whom an observation period before starting the hormone treatment might prolong the time to relapse.

The above analysis shows that the choice of a treatment schedule is not difficult, but an apparent optimal periodic schedule does not necessarily provide the best treatment for a finite time. Optimizing the treatment schedule for use in the clinic will demand extensive further analysis, and this will be the focus of our future modeling.

### Table 1 Comparison between classifications by medical doctors and those by the mathematical model for Canadian patients.

<table>
<thead>
<tr>
<th>Classifications</th>
<th>By medical doctors</th>
<th>By mathematical model</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Type (i)</td>
<td>Type (ii)</td>
<td>Type (iii)</td>
</tr>
<tr>
<td>Without relapse</td>
<td>28 (52%)</td>
<td>24 (44%)</td>
<td>2 (4%)</td>
</tr>
<tr>
<td>With relapse</td>
<td>0 (0%)</td>
<td>10 (77%)</td>
<td>3 (23%)</td>
</tr>
<tr>
<td>Total</td>
<td>28 (42%)</td>
<td>34 (51%)</td>
<td>5 (7%)</td>
</tr>
</tbody>
</table>

### Table 2 Comparison of ratios of patient types among Canadian, American, and Japanese patients.

<table>
<thead>
<tr>
<th>Type (i)</th>
<th>Type (ii)</th>
<th>Type (iii)</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Canadian</td>
<td>31 (43%)</td>
<td>36 (50%)</td>
<td>5 (7%)</td>
</tr>
<tr>
<td>American</td>
<td>29 (37%)</td>
<td>38 (48%)</td>
<td>12 (15%)</td>
</tr>
<tr>
<td>Japanese</td>
<td>14 (54%)</td>
<td>11 (42%)</td>
<td>1 (4%)</td>
</tr>
<tr>
<td>Total</td>
<td>74 (42%)</td>
<td>85 (48%)</td>
<td>18 (10%)</td>
</tr>
</tbody>
</table>

Discussion

Numerous molecular hypotheses have been proposed and been examined to explain the mechanisms of AI (Feldman and Feldman, 2001; Rennie et al., 2005; Hu et al., 2008; Attar et al., 2009). These include insufficient decrease in the intraprostatic androgen concentration, amplification and/or overexpression of the androgen receptor gene, point mutation in the androgen receptor gene, splicing variant of the androgen receptor gene, ligand-independent activation of the androgen receptor by growth factors or cytokines, alteration of co-factors of the androgen receptor, and changes in signal transduction pathway related to cell growth or apoptosis. Based on these molecular mechanisms of progression, we hypothesized the existence of three types of prostate cancer cells: AD cells, AI cells generated by reversible changes, and AI cells generated by irreversible changes.
Quantitative mathematical model of PSA dynamics

Hence, death from prostate cancer corresponds to, at the cellular level, an uncontrollable increase in the number of cancer cells, which is generally represented by an increase in the level of PSA. Such mortality might be prevented if the net growth rate $\dot{w}_2^{on}$ of $x_2$ during off-treatment periods is negative, and such effects might be explained by apoptosis and competitions (Shimada and Aihara, 2008; Jain et al., 2011), and experimentally supported by Kokontis et al. (1998, 2005) and Chuu et al. (2005). Because patients from different countries are classified with similar ratios into the three patient types, pathways to AI are probably common among the patients of different nationalities.

In this paper, we used the criterion of Type (i) such that the origin is asymptotically stabilized. We might be able to relax the criterion so that Type (i) can also include stable periodic solutions and chaotic solutions, which are constrained within bounded regions as discussed in Tanaka et al. (2008). Such relaxation is a possible topic of future research.

Given the great heterogeneity of prostate cancer, it is important to develop more individualized approaches to optimally treat patients. Improving the mathematical tools that can be applied in the clinical setting is one approach to accomplishing this goal. For patients treated with IAS, it is now necessary to observe two and one-half cycles of on- and off-treatment to confidently infer a set of parameters for each patient. However, a shorter period of observation would be more desirable for obtaining such parametric information. We are attempting to solve this problem of inferring a set of states and parameters from a shorter time series (Kuramae et al., 2011) by taking advantage of a bootstrap method to approximate parameters and initial conditions where there is uncertainty due to finite and noisy observations.

Another challenge is to develop a strongly reliable method for optimizing an ideal treatment schedule in a personalized way. If we try to estimate a set of parameters and initial conditions from a short time series obtained from a patient’s PSA observations, there is some uncertainty related to the estimation of parameters and initial conditions. Therefore, we would like to design an optimal schedule by taking into account this uncertainty related to parameters and initial conditions. Such an approach will make the mathematical optimization of treatment schedules more robust. Further, the other optimization method of IAS with piecewise affine systems modeling and model predictive control has been also proposed (Suzuki et al., 2010).

Conclusions

A quantitative mathematical model for clinical use must accurately predict the behavior of the cancer in an individual patient. The piecewise linear model described herein fits well with clinical data sets from three countries and affords a method of classifying patients that, in retrospect, appears to match physician judgment. This suggests that this mathematical model can be useful to guide how IAS is administered in an individual patient, although it requires further confirmation in a prospective study.

In this paper, we have chiefly reviewed a quantitative mathematical model of prostate cancer under IAS. After reviewing the basics of prostate cancer, we have introduced the mathematical model. This model is a piecewise linear model, meaning that for on- and off-treatment periods, the model follows different linear differential equations, respectively. We have discussed how to classify the patients according to the fitted parameter values. Type (i) patients are those whose relapse can be prevented by appropriately scheduled IAS. Type (ii) patients are those whose relapse can be delayed by IAS. Type (iii) patients are those for whom CAS is better than IAS over the long term. We have also considered optimal treatment scheduling for IAS. By using these mathematical tools, we analyzed clinical data sets obtained in Canada, USA, and Japan. In the three countries, we have observed a similar tendency for the distribution of patients among the three types. In addition, we have found that there are some Type (iii) patients for whom an off-treatment period can delay PSA relapse within a finite time. This finding might help to prolong the survival times for patients with prostate cancer that has progressed to early AI. In this and other applications, our model affords the possibility of achieving personalized medicine for each patient (Hirata et al., 2010a, 2012; Tanaka et al., 2010).

Our approach might find wide applications to other diseases if a reliable biomarker of disease is available as well as an effective treatment that is eventually overcome by drug resistance (Hirata et al., 2012). Therefore, our approach might help to improve survival and quality of life for other diseases as well.

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