

**MATHEMATICAL ENGINEERING
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METR 2006-32

May 2006

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WWW page: <http://www.i.u-tokyo.ac.jp/mi/mi-e.htm>

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A Mathematical Model of Intermittent Androgen Suppression Remedy for Prostate Cancer

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May 22th, 2006

Abstract

Androgen suppression has been the principal modality for treatment of advanced prostate cancer for several decades. Although the tumor response rate to androgen deprivation is initially high, almost all patients relapse within several years due to proliferation of androgen-independent tumor cells. Since Bruchovsky *et al.* suggested in animal models that intermittent androgen suppression can prolong the time to relapse compared with continuous androgen suppression, intermittent medication has been expected to enhance clinical efficacy in conjunction with reduction of adverse effects and improvement of patient's quality of life during off-treatment periods. This paper presents a mathematical model that describes growth of prostate tumor under intermittent androgen suppression therapy based on monitoring of serum prostate-specific antigen. Treating the cancerous tumor as an assembly of androgen-dependent and androgen-independent cells, we investigate the difference between continuous and intermittent androgen suppressions in the effects on androgen-independent relapse. Numerical and bifurcation analyses show how the tumor growth is influenced by the proliferation rate of androgen-independent cells, metastatic sites, and the prostate-specific antigen levels to stop and reinstitute the androgen suppression.

1 Introduction

The prostate gland, which is a small chestnut-shaped genital organ found below the bladder in men, manufactures and secretes seminal fluid, which

carries, nourishes, and protects the spermatozoa. These functions are essential for normal urinary health and sexual activity. If cancerous cells are detected in the prostate gland, the patient is diagnosed with adenocarcinoma of prostate. Staging of prostate cancer is currently conducted with serum prostate-specific antigen (PSA) test which enabled early detection of the cancer together with other imaging modalities. The major treatment for prostate cancer is endocrine therapy, which is often combined with surgical, radiational, and chemical therapies according to the stage of the cancer. Although the cause of prostate cancer is not fully understood at present and its effective prevention has not yet been established, aging and fatty foods are regarded as influential factors.

It has been known from a long time ago that prostate cancer growth is stimulated by androgens, or male sex hormones, secreted from organs such as testicles and adrenal glands. Loss of the normal regulation by hormone secretion leads to progress of the disease where initially localized cancer cells turn to be spread by invasion and metastasis. Since Huggins and Hodges [1] demonstrated the benefits of the ablation of testicular function by surgical orchiectomy in the 1940s, androgen deprivation therapy (ADT) has been the common stepping stone for treating advanced prostate cancer. Androgen deprivation can also be achieved by chemical castration, or administration of pharmacological agents such as luteinizing hormone releasing hormone (LHRH) analogues inhibiting the androgen production from its primary source, or the testes. The remaining androgens produced by other sources such as adrenal glands can be eliminated by an additional treatment with antiandrogens. Combination of antiandrogens with castration is known as total androgen blockage (TAB). Both ADT and TAB can facilitate apoptotic death of androgen-dependent (AD) cancer cells and induce regression of cancer tumors temporarily. However, most patients undergo relapse with rise of the serum PSA level within several years after the therapy [2]. Since it is impossible for dividing cells to differentiate and become pro-apoptotic again in absence of androgens, androgen-independent (AI) cells are considered to be responsible for recurrent tumor growth [3]. Bruchofsky *et al.* [4] suggested that AI cells increase in a hormone-depleted environment resulting from an adaptive change of the AD cells. Once the tumor acquires androgen-independence, or ultimately hormone-refractoriness, then androgen deprivation is not able to halt the cancerous tumor growth and the eventual relapse is inevitable. Figure 1 schematically illustrates typical tumor growth under the continuous androgen suppression (CAS) therapy. Therefore, it is an important issue in medical castration to delay the time to relapse as long as possible. It is also clinically significant to reduce economic costs and alleviate adverse effects of prolonged androgen suppression, because many patients survive for years after the PSA relapse.

A possible strategy to postpone the progression to the AI state is intermittent androgen suppression (IAS) remedy, or a form of androgen ablative

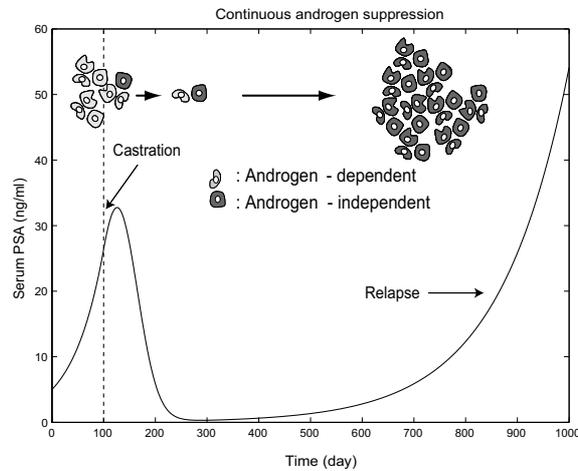


Figure 1: Schematic illustration of tumor growth under continuous hormonal therapy for prostate cancer. Although AD cells are drastically reduced immediately after castration, PSA relapse often takes place within several years due to growth of AI cells.

therapy delivered intermittently. Under successful IAS therapy, cycles of growth and regression of prostatic tumor can be expected under an appropriate control of administration as shown in Figure 2. In order to avoid emergence of AI basal-cell clones and molecular adaptation under androgen depletion, IAS therapy introduces off-administration terms which serve to maintain androgen sensitivity of cancer cells and restore their apoptotic potential induced by androgen withdrawal. Since clinical efficacy of IAS therapy was suggested in animal models [5, 3, 6], a series of phase II studies on IAS has established its safety to some extent as well as provided clinical data helpful for intermittent medication [7]. Most studies have confirmed improvement in quality of life during off-treatment periods and alleviation of adverse reactions such as hot flushes, sexual dysfunction, and osteoporosis. The clinical examples of IAS remedy including phase II and ongoing phase III trials are summarized in the review article [7]. However, it remains unknown how to optimally undertake IAS remedy, i.e., when to stop and reinstitute administration for androgen suppression, under observation of the time course of the PSA level. Thus, the potential of IAS has to be further validated for its practical use in comparison with CAS.

The effect of CAS for treatment of prostatic tumor has been studied with a mathematical model based on experimental observations in order to understand biological characteristics of prostate cancer [8, 9]. The previous study intended to examine progression to androgen-independence and consequential AI relapse after a hormonal therapy by treating a tumor as an

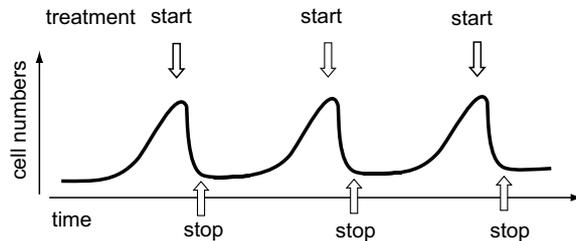


Figure 2: Schematic illustration of cycles of tumor growth and regression under intermittent androgen suppression therapy. Introduction of off-treatment periods aims at preventing the tumor from androgen-refractoriness.

assembly of AD and AI cells. In the model, the prostatic growth is described with proliferative and apoptotic death rates of tumor cells so that plentiful androgens trigger proliferation of both normal and cancerous cells while androgen withdrawal induces apoptosis of them. It tactfully reproduced three phases of prostate cancer progression, including exponential growth prior to treatment, androgen sensitivity immediately after therapy, and the eventual AI relapse of the tumor. Moreover, it was predicted that CAS therapy can only be successful for a small range of biological parameters.

The purpose of this paper is to propose a mathematical model that describes prostatic tumor growth under the IAS remedy, incorporating mutation effects and intermittent medical control into the previous model [8]. The IAS remedy model is formulated as a hybrid system switching the dynamics between medication and non-medication periods. We investigate the dynamics of the tumor growth and the transition of the PSA level, especially putting the focus on how it is influenced by the proliferation rate of AI cells, metastasis sites, and the PSA levels to stop and restart administration. Numerical simulation and bifurcation analysis of the model shows that the IAS therapy utilizing androgen-mediated apoptosis as a cellular nature enables to avert PSA relapse for a certain range of parameter conditions. The validity of the IAS therapy is discussed based on the numerical simulation and the bifurcation analysis.

2 Formulation of prostate tumor growth

2.1 Mathematical descriptions

Prostatic cancer cells, like the normal prostatic cells from which they arise, are sensitive to androgenic stimulation with respect to their growth [10]. Abundant androgens stimulate proliferation of AD cells and inhibit their apoptosis. Therefore, a prostatic tumor keeps growing without successive

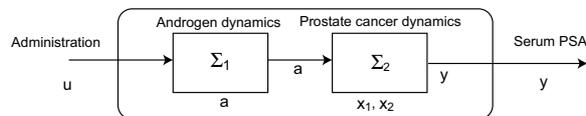


Figure 3: Block diagram representing a hormonal therapy. The androgen dynamics depending on the presence or absence of administration governs the prostate cancer dynamics. The only observable is the serum PSA concentration that reflects the prostate tumor growth.

treatment of androgen suppression. In an advanced prostatic tumor under androgen deprivation therapy, the proliferation rate of AD cells is significantly reduced and their apoptotic rate is increased. The most common hormonal therapy takes advantage of such an androgen sensitivity of the constituent cells, and thereby achieves temporal regression of the prostatic tumor [11]. However, despite the positive effects of androgen deprivation, a relapse often occurs owing to heterogeneous AI tumor cells whose proliferation rate exceeds their apoptotic death rate even after complete androgen blockage. Therefore, the AI regrowth of tumor could possibly be the result of post-therapy decrease in the apoptotic rate of the AI cells. Based on these findings, Jackson [8, 9] presented a mathematical model of tumor growth under successive treatment, and examined conditions for relapse prevention and AI relapse. As in the previous study, we formulate growth of AD and AI cells in a tumor with medication and without medication. We take into consideration the mutational effect of AD cells, which is viewed as one of the factors triggering progression to the AI phenotype. We assume that the time variation of the serum PSA concentration reflecting tumor growth is observable, towards the description of intermittent control of medication in the next section. Figure 3 illustrates the block diagram of a hormonal therapy formulated in this section.

Androgens circulate in the blood and diffuse into the tissue where they stimulate the prostate tumor to grow. We assume that the androgen concentration, which is steady in a normal state, is exponentially decreasing under androgen deprivation therapy. Thus, the androgen dynamics indicated by Σ_1 in Figure 3 is described as follows:

$$\frac{da(t)}{dt} = -\gamma(a(t) - a_0) - \gamma a_0 u(t), \quad (1)$$

where $a(t)$ (nmol/l) represents the androgen concentration [8]. The steady-state value of the androgen concentration is denoted by a_0 (nmol/l) which takes a value of $15 \leq a_0 \leq 30$ for normal male adults. The binary variable $u(t)$ represents the presence or absence of administration, i.e., $u(t) = 1$ for on-administration terms and $u(t) = 0$ for off-administration terms. The

androgen level $a(t)$ exponentially decays to 0 with medication, while exponentially converges to the steady-state value a_0 without medication. The speed of recovery and decay of the androgen concentration is represented by the exponent γ . Thus, equation (1) shows the different dynamics of androgens depending on the binary variable $u(t)$.

The growth of a polyclonal tumor consisting of AD and AI cells are dependent upon the androgen concentration [8]. The tumor dynamics indicated by Σ_2 in Figure 3 is given as follows:

$$\frac{dx_1(t)}{dt} = \{\alpha_1 p_1(a(t)) - \beta_1 q_1(a(t)) - m(a(t))\}x_1(t), \quad (2)$$

$$\frac{dx_2(t)}{dt} = m(a(t))x_1(t) + \{\alpha_2 p_2(a(t)) - \beta_2 q_2(a(t))\}x_2(t), \quad (3)$$

where $x_1(t)$ and $x_2(t)$ represent the numbers of AD and AI cells, respectively. Equation (2) describes the time evolution of the number of the AD cells, whose total growth rate is determined by the proliferation rate $\alpha_1 p_1$, the apoptotic rate $\beta_1 q_1$, and the mutational rate m at which an AD cell mutates into an AI cell. Similarly, in equation (3), $\alpha_2 p_2$ and $\beta_2 q_2$ represent the proliferation and apoptosis rates of AI cells, respectively. The coefficients of the androgen-dependent functions α_1 , α_2 , β_1 , and β_2 are the parameters depending on the metastatic sites. The androgen-dependent functions in equations (2)-(3) are given as follows:

$$p_1(a) = k_1 + \frac{(1 - k_1)a}{a + k_2}, \quad (4)$$

$$q_1(a) = k_3 + \frac{(1 - k_3)a}{a + k_4}, \quad (5)$$

$$p_2(a) = \begin{cases} \text{(i)} & 1 \\ \text{(ii)} & 1 - \left(\frac{1 - \beta_2/\alpha_2}{a_0}\right)a \\ \text{(iii)} & 1 - \frac{a}{a_0} \end{cases}, \quad (6)$$

$$q_2(a) = 1, \quad (7)$$

$$m(a) = -\left(\frac{m_1}{a_0}\right)a + m_1, \quad (8)$$

where the fixed parameters k_i for $i = 1, \dots, 4$ and m_1 depend on the stage of the cancer, especially on its polyclonality. The published data [10] for the *in vivo* daily percentages of cell proliferation and death is adopted in the model parameters. Table 1 lists the related parameter values estimated from cancerous cells in bone and lymph node metastases in untreated and hormonally failing patients.

For advanced prostate cancer, androgen deprivation is usually administered based on monitoring of the serum PSA concentration by which the state of the tumor can be estimated [12]. Since large amounts of PSA are

parameter	bone metastasis	lymph node metastasis
$\alpha_1(\text{days}^{-1})$	0.0204	0.0290
$\alpha_2(\text{days}^{-1})$	0.0242	0.0277
$\beta_1(\text{days}^{-1})$	0.0076	0.0085
$\beta_2(\text{days}^{-1})$	0.0168	0.0222
k_1	0	0
k_2	2	2
k_3	8	8
k_4	0.5	0.5

Table 1: Parameter values estimated from the clinical data [10].

secreted by metastatic cancer cells, the model incorporates the dynamics of the PSA concentration $y(t)$ under the assumption that it has linear relationship with the number of the prostate cancer cells as follows:

$$y(t) = c_1x_1(t) + c_2x_2(t), \quad (9)$$

which is the inner product of an output vector (c_1, c_2) and the state vector $(x_1, x_2)^T$. The PSA concentration is the only observable that reflects prostatic tumor growth as illustrated in Figure 3.

2.2 Proliferation, apoptosis, and mutation rates

The total tumor growth, determined by equations (2)-(3), is virtually governed by the androgen-dependent functions (4)-(8). Figure 4 shows how proliferation, apoptosis, and mutation rates of tumor cells are dependent upon the androgen concentration in the case of the bone metastasis and $a_0 = 30$.

Figure 4(a) plots the proliferative and apoptotic rates of AD cells. These cells, which do not proliferate without androgens, grow more quickly with a larger androgen concentration. The proliferation rate of AD cells approaches α_1 approximately under an androgen-plentiful environment. The apoptotic death rate ranges from β_1 under the steady androgen level to β_1k_3 in an androgen-deprived state.

On the other hand, the proliferative and apoptotic rates of AI cells are shown in Figure 4(b). The apoptotic rate is set at the constant value β_1 independent of the androgen concentration for the sake of simplicity. It is assumed to hold even if the androgen level falls, because a gene product such as Bcl-2 renders AI cells less susceptible to apoptosis. Concerning the proliferation rate of AI cells, which is α_2 when androgen is absent, three possibilities are hypothesized in an androgen-rich condition according to how AI cells coexist under competition with AD cells, as follows.

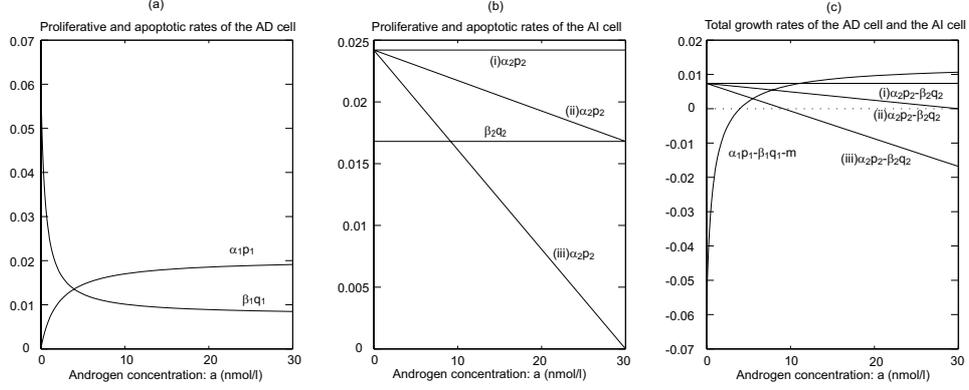


Figure 4: Androgen dependence of tumor cell growth in the bone metastasis case. Proliferative and apoptotic rates of (a) AD cells and (b) AI cells. (c) Total growth rates of AD and AI cells.

- (i) Even if AI cells compete with AD cells, the proliferation rate of the AI cells keeps constant, i.e., $\alpha_2 p_2(a_0) = \alpha_2$.
- (ii) When plenty of androgen is supplied for the proliferation of AD cells, the total number of AI cells does not change, i.e., $\alpha_2 p_2(a_0) = \beta_2 < \alpha_2$.
- (iii) When plenty of androgen is supplied for the proliferation of AD cells, the total number of AI cells decreases, i.e., $\alpha_2 p_2(a_0) = 0$.

The three androgen-dependent functions defined in equation (6) correspond to the above three cases, respectively. The case (i) is plausible because AI cells proliferate independently of the androgen level. However, since AD cells are dominant and AI cells are below detectable levels when androgen is abundant before initiation of androgen suppression therapy, the possibilities (ii)-(iii) can not be denied. It is well known that an original cell can survive longer than a mutated cell under a normal condition. Therefore, AD cells may survive longer than AI cells under an androgen-rich environment. This is the reason why we assume in the case (iii) that the number of the AI cells even decreases during an off-administration period because of the competition between AD and AI cells.

The total growth rates of AD and AI cells are plotted in Figure 4(c). The sign of $\alpha_1 p_1(a) - \beta_1 q_1(a) - m(a)$ determines whether AD cells increase or decrease. The sign of $\alpha_2 p_2(a) - \beta_2 q_2(a)$ governs the growth of AI cells with the mutational rate producing polyclonal AI cells. We assume that these two signs are not concurrently negative for excluding the trivial unrealistic case where the androgen level can be regulated so that the tumor is consistently regressing. Figure 4(c) shows that at all androgen concentration levels at least either of the growth rates of AD or AI cells is positive.

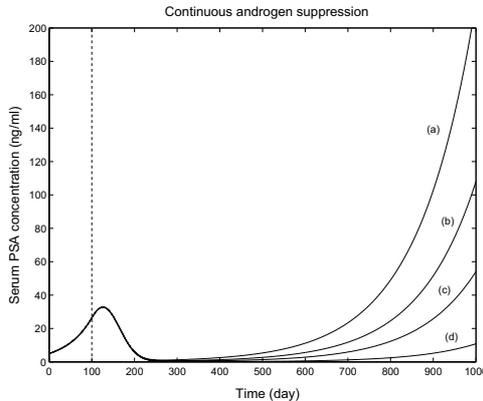


Figure 5: Effect of the mutational rate on the relapse time after the androgen ablation indicated by the dashed line. The time evolution of the PSA concentration is computed with parameter values in the bone metastasis case, $\gamma = 0.8$, and $a_0 = 30$: (a) $m_1 = 0.0002$, (b) $m_1 = 0.0001$, (c) $m_1 = 0.00005$, and (d) $m_1 = 0.00001$.

The maximum mutational rate m_1 significantly influences the time to PSA relapse. As shown in Figure 5, the development of the serum PSA concentration after androgen ablation sensitively depends on the value of m_1 . If we assume that the period before the relapse is about 2.5 years under CAS therapy, then the reasonable value of maximum mutational rate m_1 can be estimated by examining the development of the PSA concentration in numerical trials of the mathematical model with successive medication. Figure 5 shows that m_1 should be taken from the range of $0.00005 \leq m_1 \leq 0.0001$. Here we do not take into account the differences in the mutational rates among individuals, although they may depend on the metastatic site and the grade of malignancy of the cancerous cells.

3 Mathematical Model of Intermittent Androgen Suppression

A mathematical model of IAS therapy is derived from the formulation of the hormonal therapy in the previous section by adding the intermittent administration as shown in Figure 6. As indicated by the hysteresis feedback loop in the block diagram, the administration is switched depending on observations of the serum PSA concentration which provides an indication of tumor growth. That is, the administration is suspended when the PSA concentration falls below r_0 (ng/ml) during on-administration periods and is reinstated when it exceeds r_1 (ng/ml) during off-administration periods. It is a significant issue for clinical practice how to undertake IAS remedy,

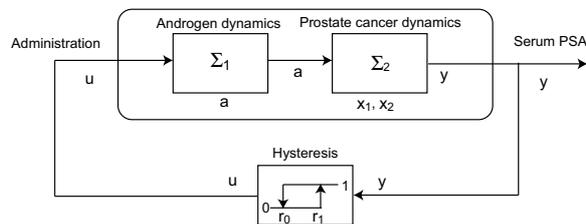


Figure 6: Block diagram representing the IAS remedy. The administration is switched according to the observable PSA concentration.

or how to optimally set the parameters, r_1 and r_0 , under the condition of $r_1 > r_0 > 0$ [7]. One of the purposes of our modelling approach for IAS therapy is to obtain some suggestions on a protocol of intermittent medication.

The total model of IAS remedy for prostate cancer is given as follows:

$$\frac{da(t)}{dt} = -\gamma(a(t) - a_0) - \gamma a_0 u(t), \quad (10)$$

$$\frac{dx_1(t)}{dt} = \{\alpha_1 p_1(a(t)) - \beta_1 q_1(a(t)) - m(a(t))\} x_1(t), \quad (11)$$

$$\frac{dx_2(t)}{dt} = m(a(t)) x_1(t) + \{\alpha_2 p_2(a(t)) - \beta_2 q_2(a(t))\} x_2(t), \quad (12)$$

$$y(t) = c_1 x_1(t) + c_2 x_2(t), \quad (13)$$

$$u(t) = \begin{cases} 0 \rightarrow 1 & \text{when } y(t) = r_1 \text{ and } dy(t)/dt > 0 \\ 1 \rightarrow 0 & \text{when } y(t) = r_0 \text{ and } dy(t)/dt < 0 \end{cases}, \quad (14)$$

where the androgen-dependent functions $p_1(\cdot)$, $p_2(\cdot)$, $q_1(\cdot)$, $q_2(\cdot)$, and $m(\cdot)$ are given in equations (4)-(8). The dynamics of tumor cell growth given in equations (11)-(12) are driven by the androgen dynamics in equation (10) which depends on the discrete variable u representing the presence or absence of administration. Since u is switched based on the PSA concentration by equations (13)-(14), the total model is a hybrid dynamical system [13, 14]. The model is used to investigate the difference in tumor growth among the three cases of the proliferation rate of AI cells as well as the effects of metastasis sites in the next section.

4 Numerical Simulation

Numerical simulations of the IAS remedy model (10)-(14) are performed to investigate the difference among the three cases (i)-(iii) concerning the proliferation rate of AI cells in a prostate tumor. For each case, bone and lymph node metastases, or the corresponding parameter values listed in Table 1, are considered. The exponent related to increase and decrease of

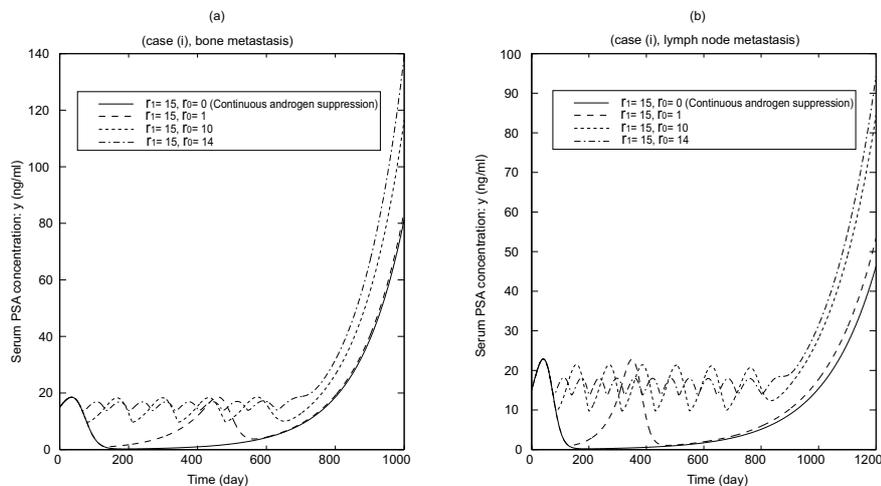


Figure 7: Time evolutions of the serum PSA concentration $y(t)$ in the case (i) for (a) the bone metastasis and (b) the lymph node metastasis. All the trials are computed with $\gamma = 0.08$, $a_0 = 30$, $m_1 = 0.00005$, and $r_1 = 15$. The solid line indicates CAS therapy with $r_0 = 0$, while the dashed lines indicate IAS therapy with different values of r_0 .

the androgen level, the steady-state value of the androgen concentration, and the maximum mutational rate are fixed at $\gamma = 0.08$, $a_0 = 30$, and $m_1 = 0.00005$, respectively, as speculated in the previous section. With regard to medication, we examine how the PSA level r_0 to stop androgen deprivation influences the relapse time when $r_1 = 15$. This assumed value of r_1 is based on the clinical study [15] where androgen suppression is stopped until the serum PSA level increases to a mean value between 10 (ng/ml) and 20 (ng/ml). The value of r_0 is required to be positive and less than r_1 for the model to represent IAS remedy. The model can be viewed to describe CAS remedy if $r_0 = 0$. Additionally, it is assumed that AD and AI cells equivalently secrete PSA, i.e., $c_1 = c_2 = 1$.

Figures 7(a)-(b) show the time evolutions of the serum PSA concentration $y(t)$ in the case (i), where the solid and dashed lines correspond to CAS and IAS, respectively. In Figure 7(a), IAS seems to be more ineffective than CAS in postponing the relapse. However, a relapse occurs within about three years in all the trials with different values of r_0 . Therefore, it is worth treating with IAS because the periods of off-medication introduced by IAS can redress the adverse effects of androgen deprivation. If IAS is adopted, the PSA level repeatedly increases and decreases until the relapse takes place. Since r_0 influences the PSA nadir, a low level of r_0 enables to avoid too much frequently repeated switching between on-medication and off-medication periods at short intervals. The qualitative property of the

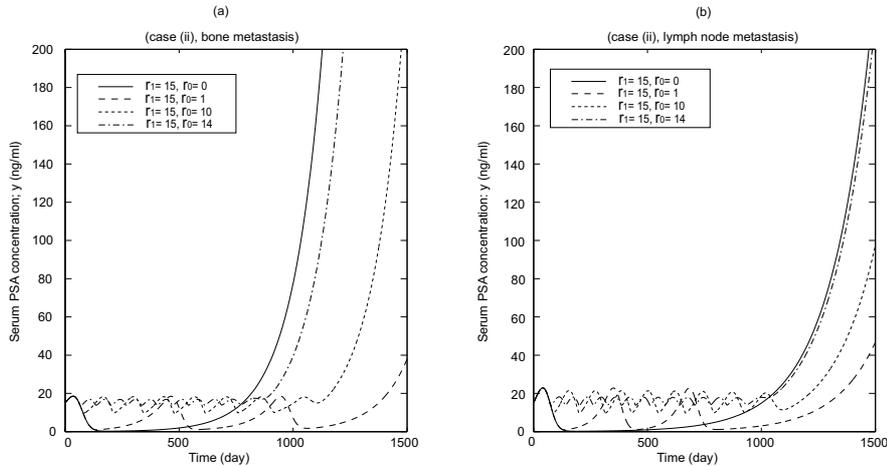


Figure 8: Time evolutions of the serum PSA concentration $y(t)$ in the case (ii) for (a) the bone metastasis and (b) the lymph node metastasis. All the trials are computed with $\gamma = 0.08$, $a_0 = 30$, $m_1 = 0.00005$, and $r_1 = 15$. The solid line indicates CAS therapy with $r_0 = 0$, while the dashed lines indicate IAS therapy with different values of r_0 .

tumor growth in the bone metastasis case described above is also applicable to that in the lymph node metastasis case as shown in Figure 7(b). Before administration is initiated, the tumor grows more quickly in the lymph node metastasis due to larger growth rate of AD cells. Conversely, the relapse is more delayed in the lymph node metastasis because the total growth rate of AI cells, which is responsible for the relapse, is less than that in the bone metastasis. The result, under the assumption that the proliferation rate of AI cells is constant, suggests that IAS may not improve the clinical efficacy of CAS in relapse time but have a potentiality of practical use in terms of reduction of side effects.

The development of the serum PSA concentration $y(t)$ in the case (ii) is depicted in Figure 8(a)-(b). Unlike the previous case, all the trials with IAS indicated by dashed lines remarkably extend the relapse time compared with CAS indicated by solid lines. In particular, IAS therapy can bring about more than one year delay in the relapse time by setting r_0 as small as possible. This is because the PSA nadir immediately before the eventual relapse strongly influences the relapse time as the initial condition of exponential growth of tumor cells. No matter how small the positive value of r_0 is taken, it is impossible to avoid eventual relapse in this case. For fixed values of r_1 and r_0 , the relapse time in the lymph node metastasis case is longer than that in the bone metastasis case due to the difference in the growth rate of AI cells during off-treatment periods. The result, under the assumption

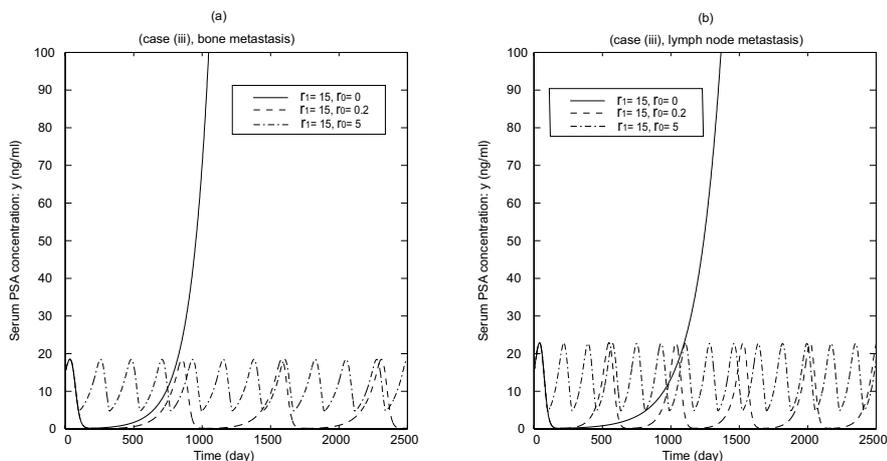


Figure 9: Time evolutions of the serum PSA concentration $y(t)$ in the case (iii) for (a) the bone metastasis and (b) the lymph node metastasis. All the trials are computed with $\gamma = 0.08$, $a_0 = 30$, $m_1 = 0.00005$, and $r_1 = 15$. The solid line indicates CAS therapy with $r_0 = 0$, while the dashed lines indicate IAS therapy with different values of r_0 .

that the number of AI cells holds constant in a rich androgen environment, suggests that IAS substantially contributes to retard the progression to a fatal AI state.

Figure 9(a)-(b) show the time variations of the serum PSA concentration $y(t)$ in the case (iii). The development of the PSA level under CAS indicated by the solid line is almost the same as in the cases (i) and (ii), due to the common proliferation rate of AI cells in an androgen-deprived state. We can see from the simulation that CAS results in a relapse within about three years while IAS leads to repetitive tumor growth and regression without a relapse. As in the previous two cases, a smaller value of r_0 is desirable for reducing the frequency of administration switching. Figure 10 shows an example of cycles in the androgen concentration and the serum PSA concentration under successful IAS therapy. The androgen concentration switches its dynamics at the moments of termination and reinstition of administration. On the other hand, there is a time lag before a decrease in the PSA level follows from a reinstition of administration. This can be interpreted as an expression of the time interval needed for a tumor reaction to a medicine. The result, under the assumption that the number of AI cells decreases in a plentiful androgen environment, suggests that IAS is much more effective than CAS in dealing with an AI relapse.

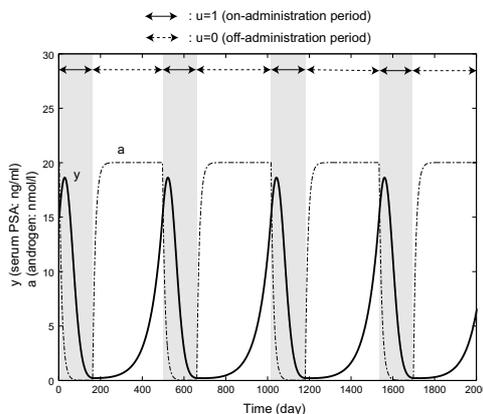


Figure 10: Cycles in the serum PSA concentration $y(t)$ and the androgen concentration $a(t)$ under successful IAS therapy.

5 Bifurcation Analysis

It has been shown in the previous section that the IAS remedy enables to avoid a relapse only in the case (iii). Whether a relapse occurs or not can be differentiated by the final state of the solution orbit of the IAS remedy model. If a relapse is averted successfully, the solution orbit typically converges to a limit cycle. The parameter region where a relapse takes place can be characterized by divergence of the solution orbit. In this section, we further investigate how the proliferation rate of AI cells and the PSA-based administration affect the resulting state after CAS and IAS therapy. The proliferation rate of AI cells given in equation (6) can be parameterized by a non-dimensional parameter d as follows:

$$p_2(a) = 1 - da/a_0, \quad (15)$$

where $d = 0$ for the case (i), $d = 1 - \beta_2/\alpha_2$ for the case (ii), and $d = 1$ for the case (iii). Hence, androgen-dependence of the proliferation rate of AI cells, as shown in Figure 4(b), can be controlled by the parameter d in the range of $0 \leq d \leq 1$.

Figure 11(a)-(b) are the phase diagrams showing how the behavior of the orbit after a transient period is affected by the PSA level r_0 to stop androgen deprivation and the proliferation rate of AI cells. The gray region indicates the parameter conditions with which the prostate tumor growth can be successfully prevented by intermittent medication. In the white region, the AI regrowth leads to a relapse with divergence of the number of AI cells and the PSA concentration. It is feasible that a relapse can not be avoided if d is smaller than the value in the case (ii), because the growth rate of AI cells is positive regardless of the androgen concentration as shown in Figure 4(c).

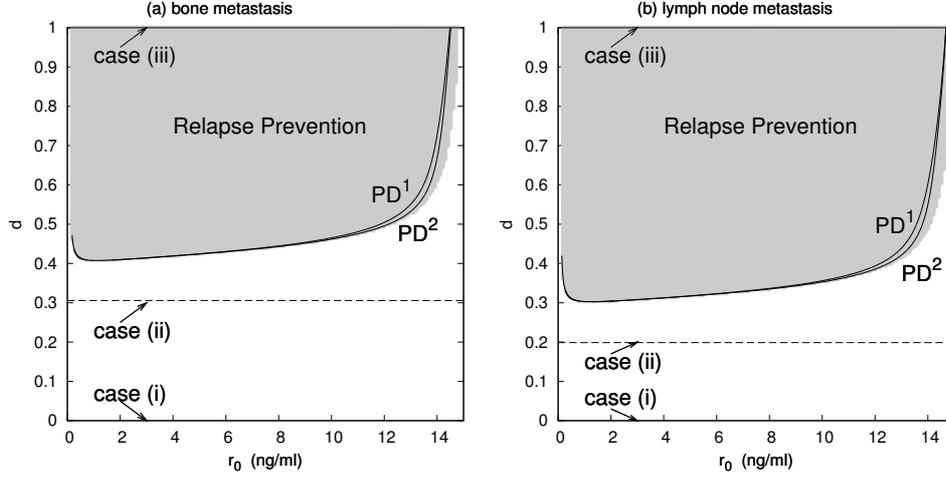


Figure 11: Phase diagram showing the region (gray) where a relapse is averted and the region (white) where a relapse happens, when $\gamma = 0.08$, $a_0 = 30$, $m_1 = 0.00005$, and $r_1 = 15$ for (a) the bone metastasis and (b) the lymph node metastasis. The solid curve denoted by PD^m ($m = 1, 2$) indicates period-doubling bifurcation of a m -folded limit cycle.

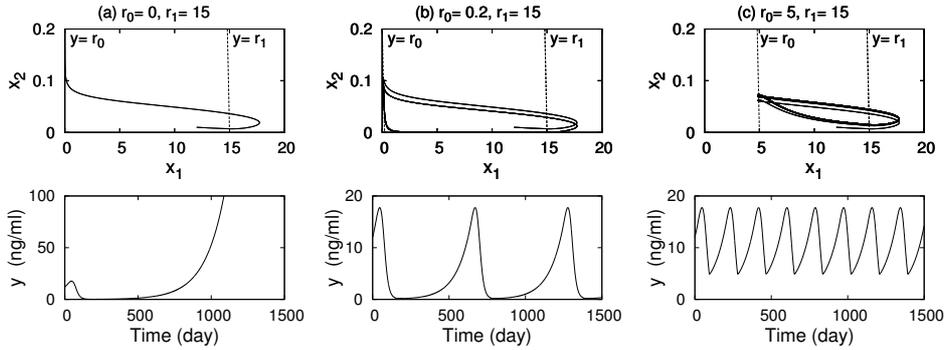


Figure 12: Orbital motion (upper) and time series of the PSA concentration (lower), computed with $\gamma = 0.08$, $a_0 = 30$, $m_1 = 0.00005$, $d = 1$, and the parameter values for the bone metastasis: (a) $(r_1, r_0) = (15, 0)$; (b) $(r_1, r_0) = (15, 0.2)$; (c) $(r_1, r_0) = (15, 5)$.

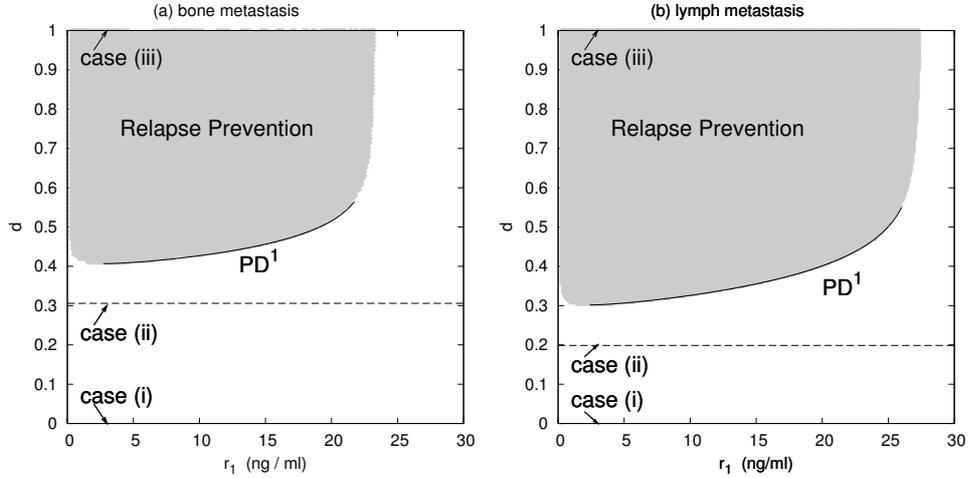


Figure 13: Phase diagram showing the region (gray) where a relapse is averted and the region (white) where a relapse happens, when $\gamma = 0.08$, $a_0 = 30$, $m_1 = 0.00005$, and $r_0 = 0.2$ for (a) the bone metastasis and (b) the lymph node metastasis. The solid curve denoted by PD^1 indicates a set of period-doubling bifurcations of a limit cycle.

Namely, an AI relapse is inevitable unless the proliferation rate of AI cells takes a negative value for a certain range of the androgen concentration. The solid curves indicating period-doubling bifurcations of a stable limit cycle reflecting successful IAS therapy are drawn along the boundary between the two regions with qualitatively different solutions. They are obtained by tracing the bifurcation points by a shooting method [16]. In addition to a one-folded limit cycle, multiple-folded limit cycles and even chaotic motions can be found outside the bifurcation curve indicated by PD^1 . These solutions are also classified into the case of relapse prevention, because they are confined in a finite region in the phase space. Figure 12 depicts examples of the orbital motions. Figure 12(a) corresponds to the CAS therapy case with $r_0 = 0$, where the number of AD cells almost vanishes but the number of AI cells increases to infinity. If r_0 is not too small, the orbit can intersect with the dashed line satisfying $c_1x_1 + c_2x_2 = r_0$, i.e., the criteria for suspension of administration, as shown in Figure 12(b). The intersection is maintained with increase of r_0 as shown in Figure 12(c), although the off-administration periods are totally shortened.

Figure 13(a)-(b) show similar bifurcation diagrams where the horizontal axis represents the PSA level r_1 to reinstitute administration. In these diagrams, r_0 is fixed at a sufficiently small value, assuming that administration is stopped if androgen is almost completely deprived by medical castration. A relapse can be prevented if the proliferation rate of AI cells take negative

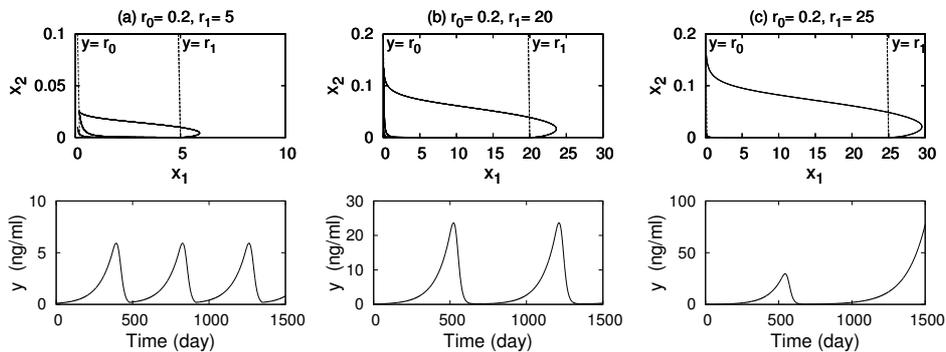


Figure 14: Orbital motion (upper) and time series of the PSA concentration (lower), computed with parameter values for the bone metastasis and $d = 1$: (a) $(r_1, r_0) = (0.5, 0.2)$; (b) $(r_1, r_0) = (5, 0.2)$; (c) $(r_1, r_0) = (20, 0.2)$.

values for a wide range of the androgen concentration and r_1 is not too large. The range of r_1 to avoid a relapse is more restricted in the bone metastasis case than in the lymph node metastasis case because of the difference in the total growth rates of AD and AI cells. The bifurcation curve ends halfway without fully following the boundary of the separated regions. This implies that a stable limit cycle loses its stability via a global bifurcation before undergoing a period-doubling bifurcation for r_1 values beyond the middle range. The qualitative change of the solution orbit with increase of r_1 is shown in Figure 14. Figure 14(a)-(b) demonstrate that the maximum value of the PSA concentration is controlled by r_1 if the tumor growth exhibits a repetitive cycle. Setting r_1 at a larger value enhances the fraction of the off-administration periods to the total period. For a too large value of r_1 , however, the orbit fails to touch the criteria line for suspension of administration and escapes to the infinity along the x_2 axis as indicated by Figure 14(c).

The parameter conditions for relapse prevention, which have been revealed by the bifurcation analysis, suggest that both r_1 and r_0 are jointly responsible for the efficacy of IAS therapy. While a small positive value of r_0 is desirable for holding down the PSA nadir and postponing a relapse, it should not be too small because otherwise IAS will result in CAS without stopping medication. The value of r_1 should be not too large in order to reduce the risk of an AI relapse resulting from the increase of the number of AI cells during on-administration periods. These suggestions obtained by the mathematical modelling would be helpful for at least postponing the relapse even if it eventually happens.

6 Discussion

A number of experimental and clinical studies on prostate cancer remedy have shown that continuous hormonal therapy as a normal treatment for advanced prostate cancer often results in recurrent tumor growth despite its beneficial short-term effect. A mathematical model describing the AI relapse under ADT and TAB was presented by Jackson [8, 9] in the form of partial differential equations. The model reproduced well a recurrent tumor growth during therapy by treating a tumor as a group of AD and AI cells and its analysis provided a condition for an AI relapse. Based on the formulation similar to the previous model, we have proposed a hybrid dynamical system describing tumor growth under IAS therapy which is currently evaluated as a potent strategy for delaying or evading an AI relapse [17, 7]. In addition to cellular proliferative and apoptotic effects driven by androgens, the proposed model has taken into consideration the adaptation of AD cells by mutational effects in an androgen-deprived state. Intermittent medication performed with monitoring of the serum PSA concentration has been modelled by the hysteretic feedback loop in the hybrid system where a discrete variable representing presence or absence of medication works as a control variable. The issue of how to optimally undertake intermittent treatment for relapse prevention has been reduced to the problem of how to appropriately choose the criteria for switching the control variable in the mathematical model.

Although AI cells are supposed to be responsible for a prostatic cancer relapse in applying IAS, it is still unknown how the amount of androgens influences AI cell growth. Thus, we have simulated the IAS remedy model under three possible hypotheses on the proliferation rate of AI cells. If the total growth rate of AI cells is positive for any androgen level, a relapse necessarily results regardless of the protocol of intermittent medication. The lower the assumed growth rate of AI cells is, the more possible the relapse is delayed by IAS therapy. If IAS is better than or comparable to CAS in clinical efficacy as in the simulation results, it would take advantage of the merits such as reduction of side effects and rise of life quality during off-treatment periods as well as delaying a relapse. If it is hypothesized that the number of AI cells decreases in competition with AD cells under an androgen-rich condition, relapse can be avoided depending on the manner of intermittent medication. The important problem arising from the numerical simulations is how to optimally determine the fixed PSA levels to suspend and reinstitute administration in a clinically feasible range.

The bifurcation analysis has revealed the parameter region for relapse prevention, where the solution orbit of the system is not divergent but bounded in a finite region as typically a stable limit cycle in the phase space. The observation of the orbital motion has shown that its divergence occurs if the decreasing PSA concentration in on-administration periods fails to reach the criteria for administration suspension. Regarding this criteria,

there is a trade-off between reducing the risk of relapse and reducing the frequency of administration switching. Moreover, administration should be reinstated at an appropriate PSA level so as to keep on-administration periods from being too long. Otherwise, the development of AI cells during on-treatment periods would enhance the risk of a cancer recurrence. The numerical results have indicated the importance of setting together the two adjustable parameters of the intermittent medication.

The bifurcation analysis has focused on the qualitative difference in the attractor, i.e., the final state of the solution orbit. What should be addressed in this point is to clarify the boundary between the two regimes by a detailed bifurcation analysis of the hybrid system. However, even if relapse can not be avoided, it is essential to prolong relapse as long as possible in practical clinics. As regards this, another possible strategy is, instead of stabilizing the solution into a limit cycle, confining the orbit in a bounded region as a transient state with a more flexible feedback control based on monitoring of the PSA concentration. Further, it is interesting to examine the effects of the parameters that are fixed in the numerical simulation. In particular, the steady-state value of the androgen concentration is likely to be deeply related to tumor growth.

This first model of IAS remedy for prostate cancer has provided an insight into the optimal intermittent medication for preventing an AI relapse. The results suggested a possibility that IAS therapy can be superior to CAS therapy in clinical efficacy. IAS remedy needs informed consent for the suspension of medication in exchange for the merits including reduction of medical expense, alleviation of side effects, and improvement of life quality in off-administration periods as well as delaying or evading a relapse. The theoretical approach could be helpful in phase III studies [7] that might be able to enhance patient's confidence in intermittent medical treatment. It is our important future problem to consider nonlinear competition between AD and AI cells and optimize the control strategy for the IAS therapy.

acknowledgments

The authors would like to thank Prof. P. Holmes of Princeton University, Prof. N. Bruchovsky of the Prostate Centre at Vancouver General Hospital, University of British Columbia, and Dr. T. Shimada of Graduate School of Engineering, University of Tokyo for their valuable comments.

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