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A Simple Mathematical Model and Alternative Paradigm for Certain Chemotherapeutic Regimens

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Abstract—A simplified two-compartment model for cell-specific chemotherapy is analysed by reformulating the governing system of differential equations as a Schrödinger equation in **time**. With the choice of an exponentially decaying function representing the effects of chemotherapy on cycling tumor cells, the potential function $V(t)$ is a Morse-type potential, well known in the quantum mechanical literature; and the solutions are obtainable in terms of confluent hypergeometric functions (or the related Whittaker functions). Because the chemotherapy is administered periodically, the potential $V(t)$ is periodic also, and use is made of existing theory (Floquet theory) as applied to scattering by periodic potentials in the quantum theory of solids. Corresponding to the existence "forbidden energy bands" in that context, it appears that there are "forbidden" or inappropriate chemotherapeutic regimens also, in the sense that for some combinations of period, dosage, and cell parameters, no real solutions exist for the system of equations describing the time evolution of cancer cells in each compartment. A similar, but less complex phenomenon may occur for simpler mathematical representations of the regimen. The purpose of this paper is to identify the existence of this phenomenon, at least insofar as this model is concerned, and to examine the implications for clinical activities. This new paradigm, if structually stable (in the sense of the phenomenon occurring in more realistic models of chemotherapy) may be of considerable significance in identifying those regimens which *are* appropriate for effective chemotherapy, by providing a rational basis for such decisions, rather than by "trial and error" (see the statement by Skipper [1] at the conclusion of this paper).

Keywords—Chemotherapy, Schrödinger equation, Periodic potential, "Forbidden" regimens.

1. INTRODUCTION

In a recent paper [2], Panetta and Adam analyzed a two-compartment model of cell-specific chemotherapy (see Figure 1). The two compartments represent cycling cells (containing the G1, S, G2, and M phases) and resting cells, respectively. While obviously a simplistic model of the cell cycle (or, equivalently, a simplistic model of the effects of chemotherapy), the mathematical aspects of the model can be investigated in considerable detail, which we set out below. For further details of the chemotherapeutic treatment, the reader is referred to [2].

The governing system of differential equations is

$$\frac{d\mathbf{x}}{dt} = \begin{pmatrix} -a & b \\ \mu & -b \end{pmatrix} \mathbf{x} - \begin{pmatrix} g(t) & 0 \\ 0 & 0 \end{pmatrix} \mathbf{x}, \tag{1}$$

where $\mathbf{x} = (x_1, x_2)^\top$; x_1 and x_2 represent the cycling and resting (or noncycling) tumor cell mass, respectively. The quantity a is the rate at which cycling cells leave the cycling compartment (including natural decay or death) *minus* the cycling cell growth rate, b is the rate at which resting cells enter the cycling compartment, and μ is the rate at which cycling cells enter the

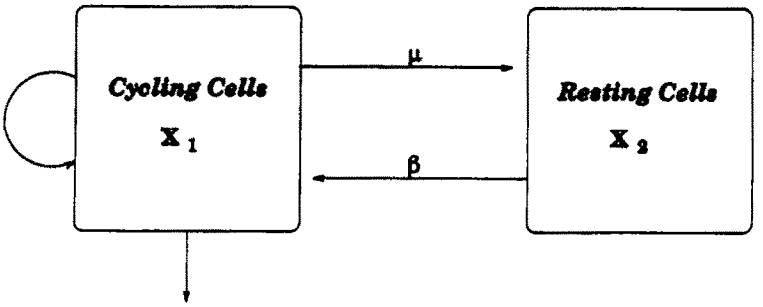

Figure 1. The two-compartment model consisting of cycling cells and resting cells. The terms a, b, and μ are exit/entry rates defined in the introduction.

resting compartment. All the quantities (a, b, and μ) are nonnegative. The function $g(t)$ is continuous in any interval $(n\tau, (n+1)\tau)$, and describes the effects of chemotherapy on the cycling tumor cells. In the first period, it is defined by

$$g(t) = he^{-\alpha t}, \qquad 0 \leq t \leq \tau, \tag{2}$$

where h is the so-called cell-kill parameter, α the drug decay or evacuation rate, τ is the minimal period of the function $g(t)$, and $n+1$ is the period number, $n = 0, 1, 2 \ldots$.

2. SCHRÖDINGER EQUATION FORM FOR (1)

From equation (1), the following homogeneous second-order differential equation may be derived for $x_1(t)$:

$$\frac{d^2x_1}{dt^2} + G_1(t)\frac{dx_1}{dt} + G_2(t)x_1 = 0, \tag{3}$$

in general for $n\tau \leq t \leq (n+1)\tau$, where

$$\begin{aligned} G_1(t) &= a + b + g(t), \\ G_2(t) &= g'(t) + b(a - \mu) + bg(t). \end{aligned} \tag{4}$$

Note also that

$$x_2(t) = b^{-1}\left\{\frac{dx_1}{dt} + (a + g(t))x_1\right\}. \tag{5}$$

Equation (3) may be cast into a variety of forms; in particular, Whittaker's differential equation, which is closely related to the canonical form of the confluent hypergeometric differential equation (see Section 3). For the moment, however, we content ourselves with a reformulation of the equation into linear Schrödinger form.

Upon substituting form (2) for $g(t)$ into equations (3) and (4), we obtain, under the change of dependent variable

$$y(t) = x_1(t) \exp\left\{\frac{1}{2}\int^t G_1(\xi)\,d\xi\right\} \tag{6}$$

the equation

$$\frac{d^2y}{dt^2} + \left\{G_2(t) - \frac{1}{2}G_1'(t) - \frac{1}{4}G_1^2(t)\right\}y = 0, \tag{7}$$

or after some rearrangement

$$\frac{d^2y}{dt^2} + \left\{K + Le^{-\alpha t} + Pe^{-2\alpha t}\right\}y = 0, \tag{8}$$

where

$$K = b(a-\mu) - \frac{1}{4}(a+b)^2,$$
$$L = \frac{h}{2}(2-\alpha-(a+b)), \tag{9}$$
$$P = -\frac{1}{4}h^2 = -\gamma^2.$$

We note the formal similarity between equation (8) and the linear Schrödinger equation with *time* as the independent variable, namely

$$\frac{d^2y}{dt^2} + \left\{\hat{\lambda} - V(t)\right\} y = 0, \tag{10}$$

wherein $\hat{\lambda} = K$ is an "energy" associated with a quantum mechanical "particle" in a potential well, $V(t)$, in **time**, where

$$V(t) = \gamma^2 e^{-2\alpha t} - Le^{-\alpha t}. \tag{11}$$

The application of "boundary conditions" in time enable us, in principle, to identify the parameter $\hat{\lambda}$ (which depends only on the details of the cell compartment entry and exit rates) as an eigenvalue, but let us note first some general features of the time-potential (11). $V(t)$ is in the form of a Morse-type potential for a molecule (see [3] for details), and as defined here, possesses the following properties:

(i) $V(0) = \gamma^2 - L$.
(ii) $\lim_{t\to\infty} V(t) = 0^-$, (though, of course, the potential on $(0,\tau)$ will be periodically translated).
(iii) $V(t_*) = 0$, where $t_* = \alpha^{-1} \ln (2\gamma^2/L)$.
(iv) $V(t_*) = -(L^2/4\gamma^2) < 0$.
(v) $V''(t_*) = L\alpha^2 e^{-\alpha t_*} > 0$ if $L > 0$, i.e., if

$$2 > \alpha + a + b.$$

(vi) $V''(t_i) = 0$, where $t_i = t_* + \alpha^{-1} \ln 2$.
(vii) $V(t_i) = -(3L^2/16\gamma^2)$.
(viii) $V > 0$ for $t < t_0 = \alpha^{-1} \ln (\gamma^2/L)$.

$V(t)$ is sketched in Figure 2.

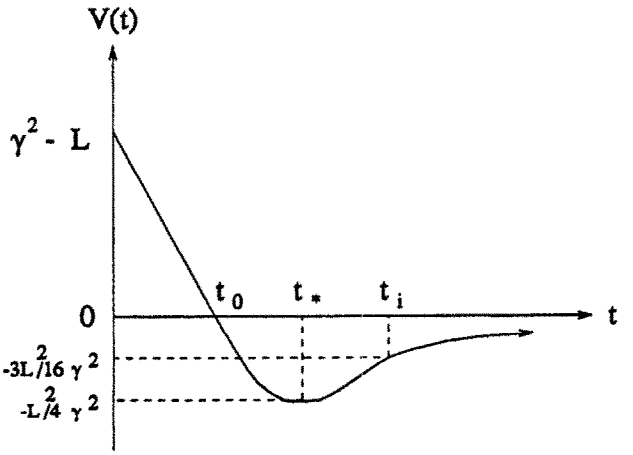

Figure 2. The Morse-type potential $V(t) = \gamma^2 e^{-2\alpha t} - Le^{-\alpha t}$ (see equation (9)) arising from the equation (2) for $g(t)$. This potential on $(0,\tau)$ is periodically repeated in time.

3. ANALYTIC SOLUTIONS FOR (8)

In (8), we define a new independent variable

$$T = \frac{2\gamma}{\alpha} e^{-\alpha t}, \tag{12}$$

and a new dependent variable

$$F(T) = T^{-\beta/\alpha} e^{(1/2)T} y, \tag{13}$$

where $K = -\beta^2$ ($K < 0$ for the choice of parameters used later in Section 5) and $l = L/2\alpha\gamma$.

Then, (8) becomes

$$T\frac{d^2F}{dT^2} + \left(\frac{2\beta}{\alpha} + 1 - T\right)\frac{dF}{dT} - \left(\frac{\beta}{\alpha} + \frac{1}{2} - l\right)F = 0, \tag{14}$$

which is Kummer's canonical form for the confluent hypergeometric equation in which we make the following identifications:

$$\begin{aligned} \tilde{a} &= \frac{\beta}{\alpha} + \frac{1}{2} - l, \\ \tilde{c} &= \frac{2\beta}{\alpha} + 1, \end{aligned} \tag{15}$$

so $\tilde{a} = (\tilde{c}/2) - l$. Provided $\tilde{c}$ is not an integer [4], there are two linearly independent solutions to (14), namely

$${}_1F_1(\tilde{a}, \tilde{c}; T) \qquad \text{and} \qquad T^{1-\tilde{c}}\,{}_1F_1(\tilde{a} - \tilde{c} + 1, 2 - \tilde{c};\ T),$$

using the standard notation for confluent hypergeometric functions. In terms of $y(T(t))$, the general solution of (8) is

$$y(T(t)) = T^{\beta/\alpha} e^{-(1/2)T}\left\{AF(\tilde{a}, \tilde{c}; T) + \beta T^{1-\tilde{c}} F(\tilde{a} - \tilde{c} + 1, 2 - \tilde{c};\ T)\right\}, \tag{16}$$

where we have now dropped the "${}_1F_1$" notation for simplicity. In terms of the original variables, from (6), (12), and (16)

$$x_1(t) = e^{-(1/2)(a+b)t} e^{(h/2\alpha)e^{-\alpha t}} y(t). \tag{17}$$

From (16), therefore, assimilating constants into A and B, we have two linearly independent solutions (if $\tilde{c}$ is neither zero nor an integer)

$$y_1(t) = e^{-\beta t} e^{-(h/2\alpha)e^{-\alpha t}} F\left(\tilde{a}, \tilde{c}; \frac{h}{\alpha} e^{-\alpha t}\right), \tag{18}$$

and

$$y_2(t) = e^{\beta t} e^{-(h/2\alpha)e^{-\alpha t}} F\left(\tilde{a} - \tilde{c} + 1, 2 - \tilde{c}; \frac{h}{\alpha} e^{-\alpha t}\right), \tag{19}$$

from which (17) yields the corresponding $x_1^{(1)}(t)$, $x^{(2)}(t)$. If required, (5) provides the corresponding expressions for $x_2^{(1)}(t)$ and $x_2^{(2)}(t)$.

An alternative form for the basis solutions (18) and (19) is in terms of Whittaker's confluent hypergeometric functions (Whittaker functions). If in equation (14), we define

$$F = T^{-\tilde{c}/2} e^{(1/2)T} W(T), \tag{20}$$

then it can be shown after some algebra that W satisfies Whittaker's differential equation, which has the advantage of being self-adjoint

$$\frac{d^2W}{dT^2} + \left\{\frac{l}{T} + \frac{(1/4) - m^2}{T^2} - \frac{1}{4}\right\} W = 0, \tag{21}$$

where $m^2 = \beta^2/\alpha^2$. If $2m$ is not an integer, two linearly independent solutions of (21) are

$$W_{l,m}(T) = T^{(1/2)+m}e^{-(1/2)T}F\left(\frac{1}{2} - l + m; 1 + 2m;\ T\right), \tag{22a}$$

and

$$W_{l,-m}(T) = T^{(1/2)-m}e^{-(1/2)T}F\left(\frac{1}{2} - l - m; 1 - 2m;\ T\right). \tag{22b}$$

Whichever form of solution we choose, a necessary condition for effective chemotherapy is, from (17),

$$x_1(t + (n+1)\tau) < x_1(t + n\tau), \qquad n = 0, 1, 2, \ldots, \tag{23}$$

where the $y(t)$ in (17) is based on the linearly independent solutions in (16) or (22).

4. THE CHEMOTHERAPEUTIC REGIMENS AS A PERIODIC POTENTIAL

If the potential $V(t)$ is periodic with minimal period τ, i.e.,

$$V(t + n\tau) = V(t), \qquad n = 0, 1, 2, \ldots, \quad t \geq 0, \tag{24}$$

then the Schrödinger equation (10) is invariant with respect to all translations by integer multiples of τ, $t \to t + n\tau$. If $y_1(t)$ and $y_2(t)$ are two linearly independent solutions of (10), then, in particular so are $y_1(t + \tau)$ and $y_2(t + \tau)$; indeed, these latter two solutions can be written as linear combinations of the former two. From within the solution space spanned by y_1 and y_2, Floquet theory assures us that there are two solutions, $Y_1(t)$ and $Y_2(t)$ say, with the property that

$$Y_i(t + \tau) = \lambda_i Y_i(t), \qquad i = 1, 2, \tag{25}$$

where each λ_i is a constant. It naturally follows that

$$Y_i(t + n\tau) = \lambda_i^n Y_i(t), \qquad i = 1, 2; \quad n = 0, 1, 2, \ldots. \tag{26}$$

Let

$$W(Y_1(t), Y_2(t)) = Y_1(t)Y_2'(t) - Y_1'(t)Y_2(t) \tag{27}$$

denote the Wronskian determinant. From (25), it follows that

$$W(Y_1(t + \tau), Y_2(t + \tau)) = \lambda_1\lambda_2 W(Y_1, (t), Y_2(t)). \tag{28}$$

By a well-known theorem [4], the Wronskian for solutions of (10) is a constant, whence

$$\lambda_1\lambda_2 = 1. \tag{29}$$

At this point in the quantum mechanical literature (see e.g., [3]), it is demonstrated, using (26) and the concept of an "infinite crystal," that λ_1 and λ_2 are complex numbers with modulus unity (Bloch's theorem). However, the independent variable here is time, and the treatment is finite in duration (see comments in [5]), so we are not thus restricted. An obvious constraint is that we discard that solution y_2 (say) for which $\lambda_2 > 1$, and retain y_1 for which $\lambda_1 < 1$. This is merely the constraint noted in Section 3 (equation (23)).

It is a straightforward matter to examine (in principle, at least) what implicit constraints there may be on other parameters within the model. We will now drop the subscript "1" on $Y_1(t)$ and λ_1 and write the former as a linear combination of y_1 and y_2. Thus,

$$Y(t) = Ay_1(t) + By_2(t), \qquad 0 \leq t < \tau. \tag{30}$$

In the next period, $\tau \leq x < 2\tau$, on using (25)

$$Y(t) = \lambda[Ay_1(t-\tau) + By_2(t-\tau)]. \tag{31}$$

By requiring that $Y(t)$ and $Y'(t)$ must be continuous at $t = \tau$, the condition for nontrivial A and B is the standard one, namely

$$\begin{vmatrix} y_1(\tau) - \lambda y_1(0) & y_2(\tau) - \lambda y_2(0) \\ y_1'(\tau) - \lambda y_1'(0) & y_2'(\tau) - \lambda y_2'(0) \end{vmatrix} = 0, \tag{32}$$

or

$$\lambda^2 W(0) + \lambda J(0,\tau) + W(\tau) = 0, \tag{33}$$

where $W(0)$ and $W(\tau)$ refer to the Wronskians of y_1 and y_2 evaluated at $t = 0$ and $t = \tau$, respectively; $J(0,\tau)$ is defined by

$$J(0,\tau) = y_2(0)y_1'(\tau) + y_2(\tau)y_1'(0) - y_1(0)y_2'(\tau) - y_1(\tau)y_2'(0) = J. \tag{34}$$

Note that $W(0) = W(\tau) = W$.

In solving (33) for λ, we will retain the root λ such that $0 \leq Re\lambda \leq 1$. Those parameter values such that $Re\lambda$ falls outside the interval [0,1] will be deemed as corresponding to an "ineffective" regimen. Let us decompose the solutions of (33) in an obvious manner from

$$2W\lambda = -J \pm \left[J^2 - 4W^2\right]^{(1/2)}. \tag{35}$$

Both roots will be real if $J^2 \geq 4W^2$; both will be negative or positive if in addition, J and W have the same or opposite signs, respectively. The roots will be complex conjugates if $J^2 < 4W^2$; in addition, $Re\lambda$ will be negative or positive if J and W have the same or opposite signs accordingly. Since $|J/2W| < 1$ automatically, one root will have $0 \leq Re\lambda < 1$ whenever $J/W < 0$.

Regardless of whether λ is real or complex, an optimal restriction may be obtained by considering $\lambda = e^{i\theta}$ (where θ is a real number which may depend on the model parameters), since for $\lambda = Re^{i\theta}$, $(R > 1)$, one root will be such that $\mid \lambda \mid = R$ and the other (of interest here) will be such that $\mid \lambda \mid = R^{-1} < 1$. Thus, from (35), it follows that

$$\cos\theta = \frac{-J}{2W}. \tag{36}$$

Now if the model parameters were such that $|\frac{J}{2W}| > 1$, it would be clear that (36) could not be satisfied. This is the mathematical basis for the existence of "forbidden energy bands" in solid state physics, and to this end, we examine (33) further by digressing briefly to the physical motivating example of electrons in a periodic square lattice [3,6,7].

5. THE "EIGENVALUE" $\hat{\lambda}$

From equation (9), we have noted that

$$\hat{\lambda} = K = b(a-\mu) - \frac{1}{4}(a+b)^2. \tag{37}$$

It is clear that $\hat{\lambda} < 0$, for we may rewrite this as

$$\hat{\lambda} = -\left[b\mu + \frac{1}{4}(a-b)^2\right] < 0, \tag{38}$$

for a, b, μ all positive, justifying the choice of $K = -\beta^2$ in equation (13).

In the quantum mechanical problem for a potential well, such negative eigenvalues correspond to "bound states" of the system. We may also carry over some of the terminology to advantage in the present model. For the Morse potential $V(t)$ described by equation (11), the minimum occurs at $t = t_* = \alpha^{-1} \ln (2\gamma^2/L)$, with value $V(t_*) = -L^2/4\gamma^2$ (see Figure 3). A bound state will be said to occur if

$$\hat{\lambda} \in (- \mid V(t_*) \mid, 0), \tag{39}$$

i.e., if

$$\left[b\mu + \frac{1}{4}(a-b)^2\right]^{(1/2)} < \left|1 - \frac{1}{2}(\alpha + a + b)\right|, \tag{40}$$

which places restrictions on the parameter set $\{a, b, \mu, \alpha\}$—notice this is independent of the dosage h—in particular on α, if the remainder is prescribed, i.e., either

$$0 < \alpha < 2\left\{1 - \left[b\mu + \frac{1}{4}(a-b)^2\right]^{(1/2)}\right\} - (a+b) \tag{41}$$

or

$$\alpha > 2\left\{1 + \left[b\mu + \frac{1}{4}(a-b)^2\right]^{(1/2)}\right\} - (a+b). \tag{42}$$

Note also that $V(0)$ is positive or negative according to whether $\gamma^2 - L$ is positive or negative, i.e., when h is greater than or less than the quantity

$$4 - 2(\alpha + a + b), \tag{43}$$

respectively. The minimum of $V(t)$ is actually attained if $\tau \geq t_*$.

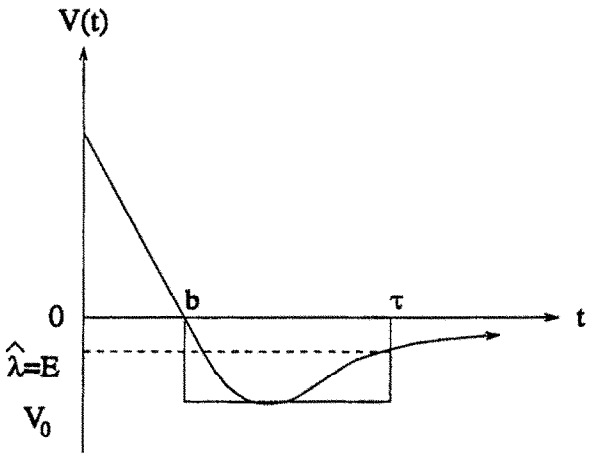

Figure 3. The Morse potential of Figure 2 with a rectangular potential well superimposed upon it. The negative "eigenvalue" parameter $\hat{\lambda}$ is indicated, as are other parameters discussed in Section 5.

In order to simplify the problem enough to illustrate the implications of the model, we replace the Morse potential (drawn in Figure 3 for $V(0) > 0$) by a potential well as shown. The well depth is $V(t_*) = -V_0$, and $c = \tau - b$ measures the width of the well (b may be chosen zero if $V(0) < 0$).

In terms of a periodic rectangular *barrier* of height $V_0 > 0$, E (positive in that problem) $= k_1^2$, $V_0 - E = K_2^2 > 0$, $(K_2 > 0)$.

In terms of the multiplier $\lambda = Re^{i\theta\tau}$ $(R \leq 1)$, we find from (33) or [6]

$$\cos k_1 b \cosh K_2 c - \left(\frac{k_1^2 - K_2^2}{2k_1 K_2}\right) \sin k_1 b \sinh K_2 c = R \cos \theta\tau. \tag{44}$$

For the problem at hand (see Figure 3), $E < 0$ and $V_0 \to -V_0$, so we substitute $E = k_1^2 = -K_1^2$, $K_1 > 0$ into (44), noting that K_2^2 is now $-V_0 + K_1^2 < 0$, so $K_2^2 = -k_2^2 < 0$ for $-V_0 < E < 0$. Under these circumstances, a new form of (44) is obtained, namely

$$\cosh K_1 b \cos k_2 c + \left(\frac{K_1^2 - k_2^2}{2K_1 k_2}\right) \sinh K_1 b \sin k_2 c = R \cos \theta\tau \tag{45}$$

has no real solution (in terms of E or k_1) *for some ranges of* E, viz., if $k_2 c = m\pi, m$ any integer, (45) reduces to

$$(-1)^m \cosh K_1 b = R \cos \theta\tau, \tag{46}$$

which is, of course, impossible for nonzero real values of the parameters and $R \leq 1$. On the other hand, it is clear that, in particular, if $k_2 c = \frac{\pi}{2}$ and K_1 is sufficiently small, there are parameter ranges for θ, k_2, b, τ, etc. for which (45) is satisfied. There will, in general, be some ranges of E, therefore, for which (45) *is* satisfied. This is to be contrasted with the case of a *barrier* with $E < 0$ (as opposed to a *well* with $E < 0$), for which (44) becomes

$$\cosh K_1 b \cosh K_2 c + \left(\frac{K_1^2 + K_2^2}{2K_1 K_2}\right) \sinh k_1 b \sinh K_2 c = R \cos \theta\tau. \tag{47}$$

Since the first term on the left exceeds one for nonzero parameters, and the second term is positive, this criterion is never satisfied for real parameters and $R \leq 1$.

The reason for the existence of forbidden bands in the quantum-mechanical context (which is a boundary value problem for $y(x)$) is that the waves, in traversing the potential $V(x)$ are reflected in phase by the potential and so interfere destructively with an "incoming" wave so that it is effectively annihilated. In the present context, it appears that the "feedback" from the chemotherapy for some ranges of dosage, period and all exit/entry rates is very counterproductive to the succeeding segment of the regimen.

For illustrative purposes, we assign some special values to b, c, K_1, and k_2 in equation (45). Firstly, choose $b = \tau/2 = c$. Now

$$K_1^2 = -\hat{\lambda} = -E = |E| \qquad \text{and} \qquad k_2^2 = -K_2^2 = V_0 - |E|.$$

Thus, in terms of the variable $x = |E|/V_0$, $K_1 b = \sqrt{xV_0}(\tau/2)$ and $k_2 c = \sqrt{(1-x)V_0}(\tau/2)$, the left-hand side of equation (45) becomes, upon choosing $V_0 \tau^2 = 4$,

$$\cosh \sqrt{x} \cos \sqrt{1-x} + \left((x - 1/2)/\sqrt{x}\sqrt{1-x}\right) \sinh \sqrt{x} \sin \sqrt{1-x}, \tag{48}$$

for $0 < x < 1$ (the limits exist as x approaches 0^+ and 1^-, respectively). If we were investigating a potential barrier rather than a well, the appropriate domain would be $x \in (0,1) \bigcup (1, \infty)$ (so written because of two different expressions which occur if $E > V_0$ and $E < V_0$). It can be seen from Figure 4 that $f(x) > 1$ (the "forbidden" region) when x exceeds about 0.57, i.e., for the parameters chosen here, $\hat{\lambda}$ should be at most 57% of the "depth of the well in Figure 3."

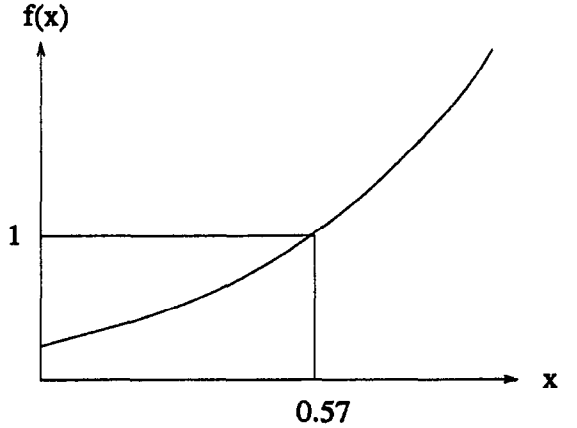

Figure 4. The function $f(x)$ defined by equation (48) for $0 < x < 1$. When this exceeds unity, equation (45) cannot be satisfied for real $\hat{\lambda}$, $R \leq 1$ and for the parameters chosen.

6. PIECEWISE-UNIFORM g(t)

If instead of the form (2), we choose a box-type function for $g(t)$, namely

$$g(t) = \begin{cases} h, & 0 \le t \le T, \\ 0, & T < t \le \tau, \end{cases} \tag{49}$$

then the periodic potential in the Schrödinger equation is correspondingly different. Indeed, in the sense of generalized functions, $g'(t) = -h\delta(t-\tau)$ (see Figure 5), so that from (7)

$$G_2(t) - \frac{1}{2}G_1'(t) - \frac{1}{4}G_1^2(t) = b(a-\mu) + bg + \frac{g'}{2} - \frac{1}{4}(a+b+g)^2$$

(i)
$$= b(a-\mu) + bh - \frac{1}{4}(a+b+h)^2 - \frac{h}{2}\delta(t-\tau), \qquad 0 \le t \le T, \quad \text{or} \tag{50}$$

(ii)
$$= b(a-\mu) - \frac{1}{4}(a+b)^2, \qquad T < t \le \tau. \tag{51}$$

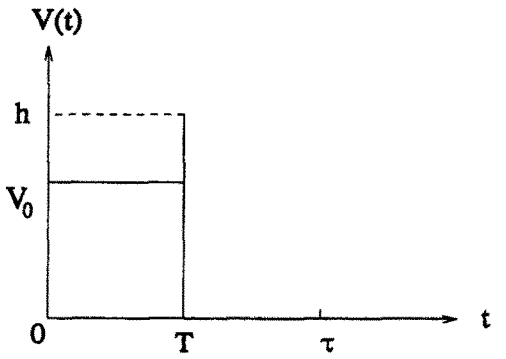

Figure 5. The box function/delta function potential (52) for the piecewise uniform $g(t)$ defined by equation (49).

As in Section 2, we identify the terms in the Schrödinger equation (10) as

$$\hat{\lambda} = b(a-\mu) - \frac{1}{4}(a+b)^2 < 0,$$

and

$$V(t) = \begin{cases} \frac{1}{2}h(a-b) + \frac{1}{4}h^2 + \frac{1}{2}h\delta(t-T), & 0 \le t \le T, \\ 0, & T < t \le \tau. \end{cases} \tag{52}$$

The basic potential on $(0,\tau)$ is thus a rectangular barrier of height $V_0 = (1/2)h(a-b) + (1/4)h^2$ (unless $h < 2(b-a)$ in which case V_0 is the well **depth**) and width T with a delta function "spike" of strength $h/2$ at $t = T$ (see Figure 5). Rather than analyse this model in detail at this point, we merely decompose this problem into two subproblems, each of which represents an extreme: (i) box function potential only, and (ii) delta function potential only.

(i) Box Function Potential

This case is easily dealt with if $V_0 > 0$ (i.e., a barrier) because $\hat{\lambda} = E < 0$ reduces the problem to one previously discussed in Section 5. The relation (44) is *never* satisfied. In quantum mechanical terms, all energies are forbidden; in chemotherapeutic terms (according to this model) no regimen works. If $V_0 < 0$ and $|E| < |V_0|$, then the situation reduces to that defined by equation (45), namely there exists some range of E for which the regimen will not work effectively.

(ii) Delta-function Potential (Shifted to $t = \tau$)

The analysis for this situation is less algebraically intensive than for a piecewise-continuous function. In the quantum theoretical literature, a periodic potential of this type is referred to as a "Dirac comb" [3,8].

From (30) and (31), we obtain, for the equation

$$\frac{d^2y}{dt^2} - |\hat{\lambda}|y = 0, \qquad 0 < t < \tau, \tag{53}$$

$$Y(t) = Ae^{Kt} + Be^{-Kt}, \qquad 0 < t < \tau, \tag{54}$$

$K = |\hat{\lambda}|^{(1/2)}$, and

$$Y(t) = \lambda\left[Ae^{K(t-\tau)} + Be^{-K(t-\tau)}\right], \qquad \tau < t < 2\tau. \tag{55}$$

At $t = \tau$, we must have (i)

$$\lim_{\epsilon \to 0}\{Y(\tau+\epsilon) - Y(\tau-\epsilon)\} = 0, \tag{56}$$

and

$$\lim_{\epsilon \to 0}\{Y'(\tau+\epsilon) - Y'(\tau-\epsilon)\} = \lim_{\epsilon \to 0}\int_{\tau-\epsilon}^{\tau+\epsilon} \frac{h}{2}\delta(t-\tau)Y(t)\,dt,$$

i.e., (ii)

$$\lim_{\epsilon \to 0}\{Y'(\tau+\epsilon) - Y'(\tau-\epsilon)\} = \frac{h}{2}Y(\tau). \tag{57}$$

Thus,

$$Ae^{K\tau} + Be^{-K\tau} = \lambda(A+B), \tag{58}$$

and

$$\lambda K(A-B) - K\left(Ae^{K\tau} - Be^{-K\tau}\right) = \frac{h}{2}\left(Ae^{K\tau} + Be^{-K\tau}\right). \tag{59}$$

It is easily shown, directly or using (33), that

$$\lambda^2 - \left(2\cosh K\tau + \frac{h}{2K}\sinh K\tau\right)\lambda + 1 = 0. \tag{60}$$

Since

$$\eta = \cosh K\tau + \frac{h}{4K}\sinh K\tau \geq 1, \tag{61}$$

we take the smallest real root

$$\lambda = \eta - \left(\eta^2 - 1\right)^{(1/2)} \leq 1. \tag{62}$$

This λ is a monotone function of η, decreasing from one as η increases. Since a general requirement for effective chemotherapy is that λ is as small as possible, this corresponds to making η as large as practical constraints on the parameters will permit. (Note that (62) is valid for all $\eta \geq 1$, in contrast to subproblem (i) which is never satisfied for $V_0 > 0$.) This can be accomplished for given τ by increasing $K = [b\mu + (1/4)(a-b)^2]^{(1/2)}$; in particular, increasing a and b by the same amount would increase K and leave V_0 (assumed small here to suppress the box function contributions) unchanged. Changing a, b, and μ may be possible in real terms through the use of growth factors (see the discussion in Section 7). Another choice, apparently, to decrease λ is to increase the period τ for given K. This permits more resting cells to move to the cycling compartment, and thus, be exposed to the chemotherapeutic regimen, but the submodel is not sophisticated enough to incorporate an implicit restriction on the optimal value of τ (clearly $\tau \to \infty$ is inappropriate!).

What may we infer, in the light of these two submodels, about the full box/delta function potential? Recalling that the first submodel implies no regimen is valid, and the second implies that all regimens are valid (though differing in efficacy), it seems reasonable to suggest that the full potential may exhibit regimes of validity, as does the more realistic potential based on exponential decay discussed in Section 2.

7. DISCUSSION

In this article, we have identified (via several variable rearrangements) a system of ordinary differential equations arising in a model of cell-specific chemotherapy, with the linear Schrödinger equation of quantum mechanics. However, the independent variable in this equation is *time*, for obvious reasons. Furthermore, reflecting the fact that the chemotherapeutic regimen is periodically administered leads to the consideration of a periodic potential $V(t)$. Much work has been carried out for periodic spatial potentials $V(x)$ (in solid state physics, for example), and some of this material has been adapted for use in the present context.

Specifically, the exponentially decreasing function $g(t)$ describing the effect of chemotherapy on cycling tumor cells in one period gives rise to a Morse-type potential, well known in the quantum mechanical literature (see [3] for further references). Solutions to the governing equation can be given in terms of confluent hypergeometric functions (equations (18) and (19)) or Whittaker functions (equations (22)). By regarding the potential $V(t)$ as periodic, we are led in a standard fashion to examine so-called characteristic multipliers $\lambda_i, \quad i = 1, 2$ (defined by equation (25)). In a spatial boundary-value problem, these λ_i are sometimes referred to as eigenvalues, but we retain that term for the parameter $\hat{\lambda}$ which appears in the Schrödinger equation (10). Constraints exist for these multipliers λ_i (see equations (33), (35), for example); there is an obvious biological requirement that the appropriate λ_i has modulus less than one (so that the cell population will decrease after each treatment). The constraints discussed in Section 4 are completely general, and utilize any appropriate pair of linearly independent solutions of the Schrödinger equation. Thus, the sets (18), (19), and (22) are both candidates for detailed examination of parameter space. This is not carried out in the present article because only limited information is available on the parameters (see [2,9] and below.). Instead, we choose to illustrate here the fundamental implications of the model by fitting a "rectangular well" to the Morse potential $V(t)$ (see Figure 3). This has the decided advantage that the constraints on the multipliers λ_i can be obtained with relative ease. (For a very different application of potential wells and barriers, see [10]).

It is shown in Section 5 that the "eigenvalue" $\hat{\lambda}$ is always negative for the model (1), and that the governing constraint equation for the rectangular well is equation (45). This equation cannot be satisfied for some ranges of $\hat{\lambda}$ (or energy E in quantum mechanical terminology). Figure 4 illustrates a specific example of this feature. In the literature of solid state physics, such regions of $\hat{\lambda}$-space are referred to as forbidden bands, and arise physically because of coherent reflections of "waves" from the potential that destructively interfere with those "waves." In the present context, an appropriate interpretation appears to be that for certain choices of the cell exit/entry rates a, b, and μ (and hence $\hat{\lambda}$, via (37)) the chosen dosage and period are such that some type of negative feedback arises between a given period of administration and the subsequent one.

As mentioned above, the information on a, b, and μ is sparse. Birkhead *et al.* [9] give a set of parameter values from breast cancer data. For this model, the set corresponds to

$$a = 0.195, \qquad \mu = 0.218, \qquad b = 0.050,$$

whence from (37) $\hat{\lambda} = -0.016$.

If for this value of $\hat{\lambda}$ (or other values depending on a, b, or μ) and corresponding values of V_0, τ and t_0 in Figure 3, equation (45) cannot be satisfied, we have an inappropriate, and therefore ineffective regimen. Note that while $\hat{\lambda}$ depends only on the set $\{a, b, \mu\}$, $t_0 = \alpha^{-1} \ln(\gamma^2/L)$ and $V_0 = L^2/4\gamma^2$, both depend on the set $\{\alpha, h, a, b\}$. Thus, in principle, the "external" variables α, h, and τ may be varied easily to place $\hat{\lambda}$ in a chemotherapeutically acceptable region such that equation (45) (or its analogue for the Morse potential in terms of confluent hypergeometric or Whittaker functions) *is* satisfied.

However, there is another intriguing possibility regarding the "internal" variables a, b, and μ. Growth factors increasingly are being used to help make chemotherapeutic drugs more effective. Growth factors (or inhibitors) are hormones that can stimulate (or inhibit) the normal cellular

proliferation processes. Further information may be found in [11,12] (and also [2] for specifically chemotherapeutic applications). They can be used to modify the entry/exit rates from one cell compartment to another in order to optimize the cell kill rate. This corresponds to varying the "eigenvalue" $\hat{\lambda}$, and again could be used to place the regimen (i.e., the full set $\{\alpha, h, \tau, a, b, \mu\}$) in an acceptable region of parameter space. Conversely, the use of growth factors to enhance or optimize the cell kill rate may on occasion render the chemotherapy *ineffective* by modifying some parameters in such a way that equation (45) or its more realistic analogue may no longer be satisfied.

In Section 6, a still simpler form of $g(t)$ is investigated. This does not provide as rich a structure as the exponential decay model, as might be expected, but it does contain a feature that may be expected to be present in more general models of the type discussed in this paper, especially if a discontinuity in $g(t)$ occurs for $t \in (0, \tau)$; i.e., in the fundamental domain. The two submodels considered represent extremes in the sense that any more realistic model (such as that considered in the main body of this paper, based on equation (2)) can be expected to exhibit a wide range of behavior, in that some regimens (or parameter sets) are effective (i.e., "allowed" by the system) and others are not. This is indeed the case for the exponential decay model discussed here. Having established the possibility of such a paradigm, or way of viewing the periodic administration of drugs to destroy tumor cells, it will be of great interest to examine more detailed models and their domains of parameter validity as more experimental and clinical information becomes available. This may eventually provide a rational basis for the "trial and error" method so clearly described by Skipper [1]:

> Over 20 years of experimental and clinical experience has demonstrated that intuitive or trial-and-error manipulations of doses, schedules, and combination of drugs—without guidance as to the effects of each manipulation—are apt to provide little or no improvement in combination chemotherapy designs.

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