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A Perturbation Problem Arising from the Modelling of Soluble Fas Ligand in Tumour Immunology

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Abstract—It has been known for many years that immune cells can kill cancer cells by a variety of mechanisms. However, new experimental evidence suggests that cancer cells also express these cell killing mechanisms. This enables the tumour to mount a counterattack against the anticancer immune cells. Based on these observations, we propose an ordinary differential equation model for tumour-immune cell interactions. With initial conditions corresponding to a mixture of cancer and immune cells, numerical solutions of the model show a sharp increase in the level of a chemical regulator associated with the interaction of the two cell types. We investigate this behaviour by constructing an analytical approximation to the solution using singular perturbation analysis. This problem has an unusual asymptotic structure. Instead of the usual solution form, with two outer solutions separated by a single transition layer centred at the point at which the sharp jump in the solution occurs, our solution contains multiple fast time layers, with each layer being necessary to capture the entire dynamics of the sharp transition.

Keywords—Fas/FasL, Immunology, Modelling, Singular perturbation.

1. INTRODUCTION

The Fas ligand (called FasL) is a membrane-bound molecule which plays a crucial role in the immune system's destruction of cancer cells [1,2]. FasL is expressed most prominently in a class of immune cells called T-lymphocytes (also termed T-cells). Binding of FasL to its receptor (Fas) on a tumour cell can transmit a signal which causes cell death in the Fas-receptor expressing tumour cell [3–5]. Until recently, immune cells were thought to be the major source of active FasL molecules, with Fas-induced cell death directed towards the tumour [6]. However, this picture is incomplete, since it is now clear that many tumour cells also express the Fas ligand, and can therefore counterattack and kill Fas-expressing immune cells using their own weapons [7–9].

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Based upon this 'counterattack', we have developed in [10] an ODE model involving tumour-immune cell interaction, and cell surface expression of the Fas ligand and its receptor. The model predicts that an important regulatory event in this counterattack is the production of the soluble form of FasL (called sFasL) via the cleavage of the FasL molecule from the cell surface by metalloproteinase enzymes (MMPs). This soluble Fas ligand can still bind to the Fas receptor, but is unlikely to transmit a death signal, and is shown to inhibit Fas-L killing by acting as a decoy ligand for the receptor. High levels of soluble sFasL have been found in many cancer patients, and our model does indeed reproduce this behaviour. An interesting prediction of our model is that this high level of soluble FasL is obtained via a sharp increase in the sFasL solution. The aim of this present work is to investigate this behaviour in more detail by constructing an analytical approximation to the solution using singular perturbation analysis.

2. MODEL EQUATIONS

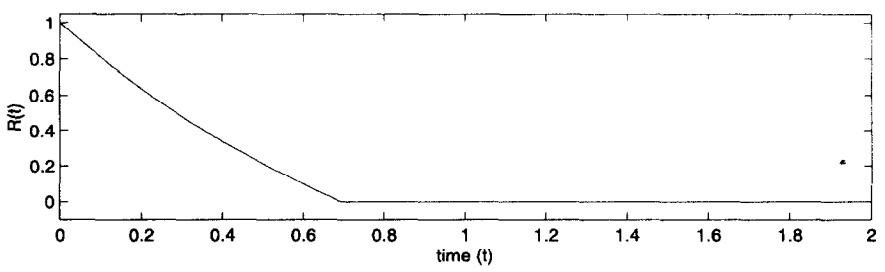
The original model (see [10] for full details) consists of seven ODEs, two conservation equations for tumour and immune cell densities per unit area (m,T), two each for tumour and immune cells for the average numbers of Fas ligand molecules (L_m,L_T) and free Fas receptors (R_m,R_T) on the surface of each cell, and one for the concentration of the soluble Fas ligand (S_L). To facilitate the analysis, we reduce the dimension of this system by making the following assumptions. First, the cell killing occurs on a much slower time scale than that of the ligand and receptor binding, so in the region of the sFasL transition, the cell numbers appear to be constant. Thus, we fix the cell densities at these values. Second, the degradation of Fas ligand is much more rapid than that of the receptor, and thus, we assume that the tumour and immune cell FasL are both in equilibrium. Finally, near the sFasL transition the numbers of tumour and immune cell Fas are approximately the same, so we set $R_T = R_m$. With this, the dimensionless system of ODEs reduces to only two, for $R = R_T = R_m$ and S_L, namely,

$$\frac{dR}{dt} = 1 - R - \frac{1}{\varepsilon^3} R S_L, \tag{1a}$$

$$\frac{dS_L}{dt} = \frac{1}{\varepsilon}(\beta + 1 - \beta S_L) - \frac{1}{\varepsilon^4} R S_L, \tag{1b}$$

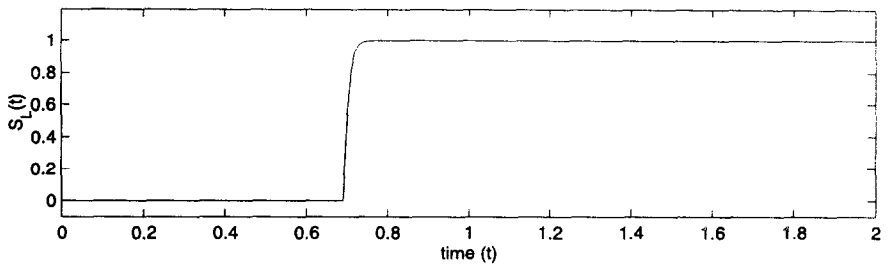
$$R(0) = 1, \qquad S_L(0) = 0,$$

where β and ε are positive constants. The biological interpretation of the model is that Fas receptor and sFasL are supplied at constant rates to the cell surface and extracellular space, respectively, both degrade linearly proportional to their concentrations and both are used up when sFasL binds irreversibly to the cell surface Fas receptor. These are the $-RS_L/\varepsilon^3$ and

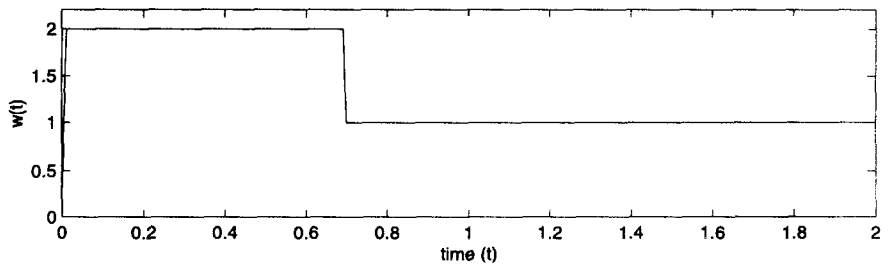


(a)

Figure 1. (a) and (b) are illustrations of the form of $R(t)$ and $S_L(t)$. The $R(t)$ solution gradually decreases from the initial value $R(0) = 1$ to its steady state R^*. After an initial transient, there is a sharp jump in the S_L solution to the steady state $S_L^* = 1$. The solution is calculated by numerical solution of (1a) and (1b), with $\varepsilon = 10^{-2}$ subject to the initial conditions $S_L(0) = 0$, $R(0) = 0$. The parameter β is taken to be 1. (c) is a plot of the solution $w(t) = R(t)S_L(t)/\varepsilon^3$. After an initial increase, $w(t)$ is a simple step function with a jump from $w = \beta + 1$ to $w = 1$ at $t = t^*$.



(b)



(c)

Figure 1. (cont.)

$-RS_L/\varepsilon^4$ terms. The Fas receptor has a long half-life, a turnover time of hours [11] compared to the rate of FasL MMP inactivation, and the decline of sFasL in the blood stream, which are both of the order of minutes [12]. Thus, the three terms involving ε are large; for biologically realistic parameters, ε is in the range 10^{-2}–10^{-5} and $\beta = O(1)$.

Numerical solutions have two key features that are also found in solutions of the full model (see Figures 1a and 1b). First, the R profile gradually decreases from its initial value to its steady state (which we will denote by R^*). Second, after an initial transient, where there is a small relative increase in S_L compared to the decrease in the R solution, there is a sharp jump in the S_L profile to the steady state S_L^*=1.

The basic objective of this paper is to investigate the sharp jump in the concentration of sFasL by singular perturbation analysis.

3. SINGULAR PERTURBATION ANALYSIS

Regular Solution and Initial Singular Layer

We first look for the outer solution of system (1) in the form of a regular series expansion $S_L = \sum_{n=0} S_{Ln}\varepsilon^n$, $R_L = \sum_{n=0} R_{Ln}\varepsilon^n$, which, on substituting into (1) and equating powers of ε, gives two possible solutions:

$$0 < t < t^* : \qquad R(t) = k\exp(-t) - \beta, \quad S_L(t) = \frac{1+\beta}{k\exp(-t)-\beta}\varepsilon^3, \tag{2}$$

where k is a constant of integration and

$$t > t^* : \qquad R(t) = \varepsilon^3, \quad S_L(t) = 1, \tag{3}$$

where we have used t^* to denote the time at which the sharp S_L transition occurs.

Note that, in the first solution (2), we cannot satisfy the initial condition $S_L(0) = 0$. In fact, if $t = 0$, $S_L(0) = (1+\beta)/(k-\beta) \neq 0$. This is because the S_L-equation as $\varepsilon \to 0$ is singular near $t = 0$. We have found that, in order to capture the behaviour of the solution of (1) for times near

$t = 0$, it is necessary to introduce the rescaling $S_L(t) = S(t)\varepsilon^3$ and the fast time scale $\tilde{t} = t/\varepsilon^4$, in which case the O(1) equations, in terms of $S(t;\varepsilon) = \tilde{S}(\tilde{t};\varepsilon)$ and $R(t;\varepsilon) = \tilde{R}(\tilde{t};\varepsilon)$, are

$$\frac{d\tilde{R}}{d\tilde{t}} = 0, \qquad \frac{d\tilde{S}}{d\tilde{t}} = \beta + 1 - \tilde{R}\tilde{S},$$

where tildes denote the inner (singular) solution valid near $t = 0$. Solving these equations with $\tilde{R}(0) = 1$ and $\tilde{S}(0) = 1$ then gives

$$\tilde{R} = 1, \qquad \tilde{S} = (\beta + 1)\left(1 - \exp\left(-\tilde{t}\right)\right). \tag{4}$$

Matching the singular and outer solutions will determine the value of the unknown constant k. The requirement $R(0) = \tilde{R}(\infty)$ implies that $k = 1 + \beta$. Note that, for $t = \ln(k/\beta)$, the outer solution $S_L \to \infty$ (2), and so $\ln(k/\beta)$ is an upper bound for the solution of t^*. Thus, we have obtained matched asymptotic expansions for the solution of (1) for times $0 < t < t^*$. To complete the analysis, we now find solutions for the transition layer near $t = t^*$. To do this, we introduce a change of variables for R and S_L in both of the outer regions.

Change of Variables

With the outer solution (2), in the region $0 < t < t^*$, $S_L(t)$ is of the order $O(\varepsilon^3)$ and $R(t)$ is O(1) while, for $t > t^*$, S_L is O(1) with the outer form $R(t)$ of the order ε^3. We can thus rescale R and S_L in both the outer regions, using the rescaling $R(t) = \bar{R}(t)\varepsilon^3$ in the outer region $t > t^*$ and $S_L(t) = \bar{S}_L(t)\varepsilon^3$ for all $0 < t < t^*$. However, it is more convenient to rewrite (1) using the variables $S_L(t)$ and $w(t) = (1/\varepsilon^3)R(t)S_L(t)$, giving

$$\varepsilon^3\left(w' + w\right)S_L + \varepsilon^2\left(S_L\beta w - w\beta - w + w^2\right) = S_L^2(1 - w), \tag{5a}$$

$$\varepsilon S_L' = \beta + 1 - \beta S_L - w. \tag{5b}$$

The form of the w solution is illustrated in Figure 1c. After an initial increase, the solution $w(t)$ is a step function with a jump from $w(t) = 1 + \beta$ to $w(t) = 1$ at $t = t^*$. Similarly, we can find solutions in each of the two outer regions $0 < t < t^*$ and $t > t^*$:

$$0 < t < t^*: \qquad w(t) = 1 + \beta + \frac{\beta(1+\beta)}{\beta - (1+\beta)\exp(-t)}\varepsilon^3, \tag{6a}$$

$$S_L(t) = \frac{1+\beta}{(1+\beta)\exp(-t) - \beta}\varepsilon^3,$$

$$t > t^*: \qquad w(t) = 1, \quad S_L(t) = 1. \tag{6b}$$

The two parts of the outer solution (6a) and (6b) will be joined by a transition layer centered at $t = t^*$, in which there is a sharp jump in the S_L profile to the steady state $S_L^* = 1$.

Singular Solution to the Problem

We look for a solution valid near $t = t^*$. Since the combination t/ε occurs in the first term in the S_L-equation, we transform t by introducing $\hat{t} = (t - t^*)/\varepsilon$. The purpose of this transformation is to retain the derivative S_L' under the limiting process $\varepsilon \to 0$. Thus, the first order term $\varepsilon\frac{dS_L}{dt}$ contributes to the O(1) solution in the t-domain where the outer solutions are not valid, that is, near $t = t^*$. Note that since the problem is linear in w and S_L, that is, w and S_L have O(1) jumps, rescaling w and S_L is inappropriate. Writing $w(t;\varepsilon) = \hat{w}(\hat{t};\varepsilon)$ and $S_L(t;\varepsilon) = \hat{S}_L(\hat{t};\varepsilon)$, equation (5a) and (5b) becomes

$$\varepsilon^3\hat{w}\hat{S}_L + \varepsilon^2\frac{d\hat{w}}{d\hat{t}}\hat{S}_L + \varepsilon^2\left(\hat{S}_L\hat{w}\beta - \hat{w}\beta - \hat{w} + \hat{w}^2\right) = \hat{S}_L^2\left(1 - \hat{w}\right), \tag{7a}$$

$$\frac{d\hat{S}_L}{d\hat{t}} = \beta + 1 - \beta\hat{S}_L^2 - \hat{w}. \tag{7b}$$

We now set $\varepsilon = 0$ to get the O(1) equations

$$0 = \hat{S}_L^2 (1 - \hat{w}),$$
$$\frac{d\hat{S}_L}{d\hat{t}} = \beta + 1 - \beta \hat{S}_L^2 - \hat{w}.$$

There are two possible solutions of this,

$$\hat{w}(\hat{t}) = 1 + \beta, \qquad \hat{S}_L(\hat{t}) = 0, \tag{8a}$$

and

$$\hat{w}(\hat{t}) = 1, \qquad \hat{S}_L(\hat{t}) = 1 - \alpha_1 \exp(-\beta \hat{t}), \tag{8b}$$

where α_1 is a constant of integration to be determined by matching.

The part of the solution given by (8a) is the singular solution for w and S_L that is valid for $\hat{t} < 0$, which is equivalent to $t < t^*$, while (8b) is the singular solution valid for $\hat{t} > 0$ (the singular region $t > t^*$). These solutions govern w and S_L in the immediate neighbourhood of t^* which corresponds to the $\hat{t}$-domain, $-\infty < \hat{t} < \infty$. However, the jump in $\hat{w}$ at $\hat{t} = 0$ implies that an additional solution component is required. That is, the singular solution (8) has the appropriate form, but fails to be valid in some intermediate region within the $O(\varepsilon)$-domain near t^*.

In this case, we have to use an additional rescaling, giving an 'inner-inner' solution near $t = t^*$ which will join the two parts of the inner solution (8a) and (8b). With the transformation $\tilde{t} = (t - t^*)/\varepsilon$, on letting $\varepsilon \to 0$ in (5), we lose the first-order term $\frac{d\tilde{w}}{d\tilde{t}}$ and the first equation is simply algebraic. Thus, we must look for a transformation in t which involves ε in such a way that, as $\varepsilon \to 0$, $\varepsilon^2 w' S_L$ and $\varepsilon S_L'$ contribute to the O(1) solution where the singular solution (8) is not valid.

Rescaling in the Inner Region

Motivated by the form of the inner solution (8), we look for a solution valid on a smaller inner-inner domain centered at $t = t^*$. Numerical simulations indicate that it is necessary for S_L to be of the order ε, and so we take $S_L = \varepsilon \bar{S}_L$. We then let $\xi = (t - t^*)/\varepsilon^\alpha$, where α must be determined, and rewrite (8) in terms of $w(t) = \psi(\xi)$ and $\bar{S}_L = \sigma(\xi)$:

$$\varepsilon^{2-\alpha}\sigma \frac{d\psi}{d\xi} + \varepsilon^3 \psi\sigma + \varepsilon^3 \sigma\psi\beta - \psi\beta - \psi + \psi^2 = \sigma^2(1 - \psi),$$
$$\varepsilon^{2-\alpha}\frac{d\sigma}{d\xi} = \beta + 1 - \beta\varepsilon\sigma - \psi.$$

If $\alpha = 2$, then as $\varepsilon \to 0$ with ξ fixed both first-order terms remain in the first approximation. Thus, with $\alpha = 2$, the O(1) equations are

$$\sigma \frac{d\psi}{d\xi} = \psi(\beta + 1 - \psi) + \sigma^2(1 - \psi), \tag{9a}$$
$$\frac{d\sigma}{d\xi} = \beta + 1 - \psi. \tag{9b}$$

Substituting (9b) into (9a) implies

$$\frac{d}{d\xi}\left(\frac{\psi}{\sigma}\right) = \frac{d\sigma}{d\xi} - \beta \Rightarrow \psi = \sigma^2 - \beta\sigma(\xi - \xi_0), \tag{10}$$

where ξ_0 is a constant of integration. Substituting this back into (9b) with $\sigma = (1/y)\frac{dy}{d\xi}$ gives

$$\frac{d^2y}{d\xi^2} - \beta(\xi - \xi_0)\frac{dy}{d\xi} - (\beta + 1)y = 0.$$

If we now change the dependent variable to $\zeta = \beta(\xi - \xi_0)^2/2$ instead of ξ, the problem becomes

$$\zeta \frac{d^2y}{d\zeta^2} + \left(\frac{1}{2} - \zeta\right)\frac{dy}{d\zeta} - \frac{\beta+1}{2\beta}y = 0,$$

which is in a standard form known as a degenerate hypergeometric equation (*Kummer's equation*). The solution is available from standard textbooks, which in terms of the original variables gives a solution for $\sigma(\xi)$ in the inner-inner region as

$$\sigma(\xi) = \begin{cases} a\beta\bar{\xi}\dfrac{[2k_1\Phi(a+1,3/2;\zeta) - \Psi(a+1,3/2;\zeta)]}{[k_1\Phi(a,1/2;\zeta) + \Psi(a,1/2;\zeta)]} & (\bar{\xi} < 0)\,, \\ a\beta\bar{\xi}\dfrac{[2k_2\Phi(a+1,3/2;\zeta) - \Psi(a+1,3/2;\zeta)]}{[k_2\Phi(a,1/2;\zeta) + \Psi(a,1/2;\zeta)]} & (\bar{\xi} > 0)\,, \end{cases} \tag{11}$$

where $\bar{\xi} = \xi - \xi_0$, $a = (\beta+1)/2\beta$, k_1 and k_2 are constants of integration which will be determined by matching, and $\Phi(\cdot)$ and $\Psi(\cdot)$ are hypergeometric functions of the first and second kind, respectively. Substitution of this into (10) gives the inner-inner solution for ψ.

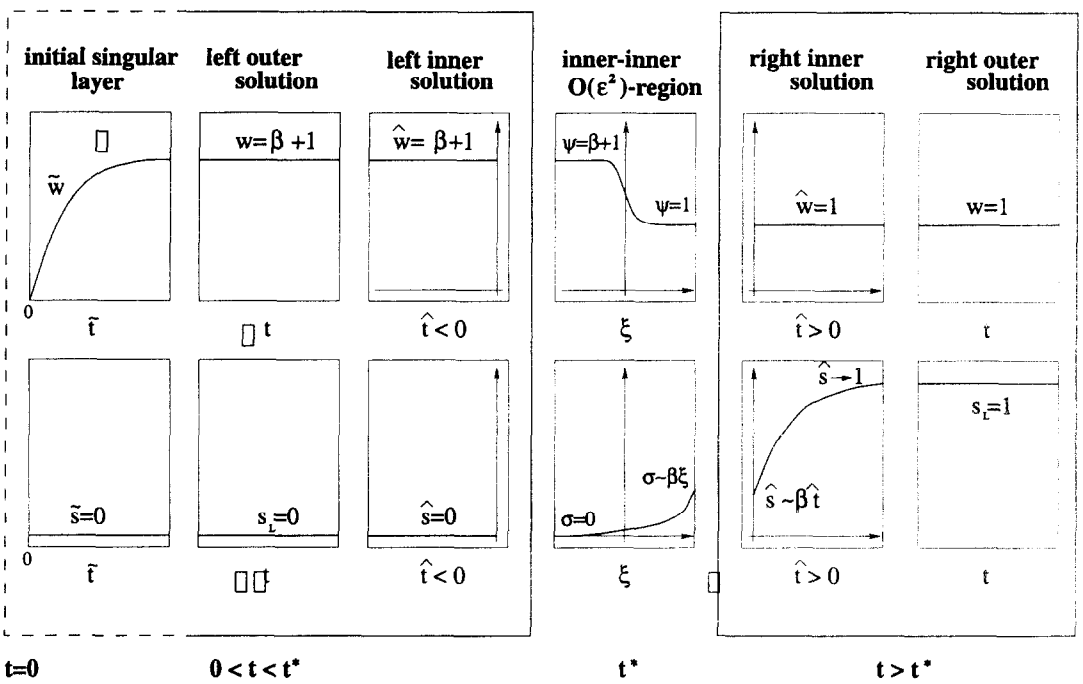
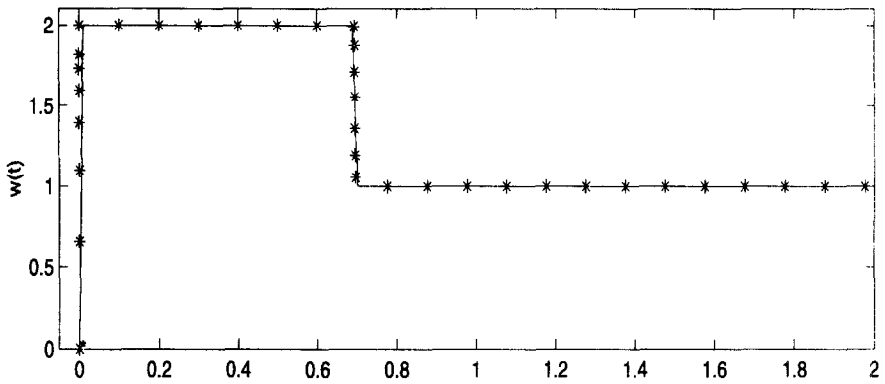


Figure 2. Schematic behaviour of the leading order solutions of the caricature model (7) for $w(t)$ and $S_L(t)$ (see text for full details).

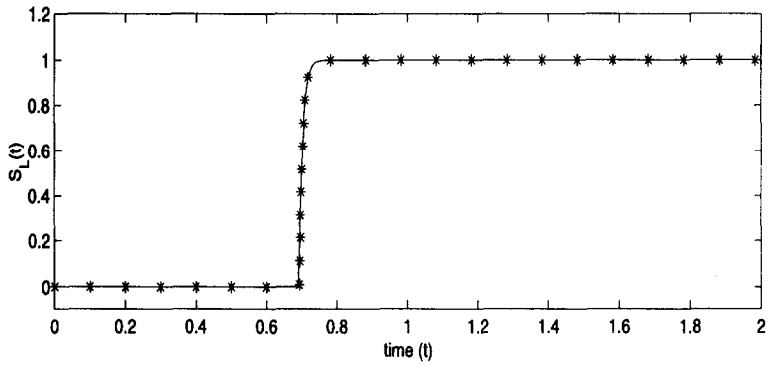
By constraining the solution $\sigma(\xi)$ to be continuous at $\bar{\xi} = 0$, standard formulae for $\Phi(\cdot)$ and $\Psi(\cdot)$ yield a constraint equation in terms of Gamma functions, $\Gamma(\cdot)$, with

$$k_1 + \frac{\Gamma(1/2)}{\Gamma(a+1/2)} = -k_2 - \frac{\Gamma(1/2)}{\Gamma(a+1/2)}. \tag{12}$$

We also need to match the inner-inner solutions with the inner solutions calculated previously.



(a)



(b)

Figure 3. A comparison between the approximation ((14a) and (14b) with $\beta = 1$, $\xi_0 = 1$, and $\varepsilon = 10^{-2}$) for $w(t) = (1/\varepsilon^3)R(t)S_L(t)$ and $S_L(t)$ $(*)$ and a numerically calculated form (—), found via numerical solution of the model ODEs (1a) and (1b). The matched asymptotic solution agrees very well with the numerically calculated solutions. The numerical solutions show that t^* is close to the upper bound $t^* < \ln((1+\beta)/\beta)$.

The four matching conditions are

$$\lim_{\xi \to -\infty} \psi(\xi) = \lim_{\hat{t} \to 0} \hat{w}\left(\hat{t}\right) = 1 + \beta, \tag{13a}$$

$$\lim_{\xi \to \infty} \psi(\xi) = \lim_{\hat{t} \to 0} \hat{w}\left(\hat{t}\right) = 1, \tag{13b}$$

$$\lim_{\xi \to -\infty} \varepsilon\sigma(\xi) = \lim_{\hat{t} \to 0} \hat{S}_L\left(\hat{t}\right) = 0, \tag{13c}$$

$$\lim_{\xi \to \infty} \varepsilon\sigma(\xi) = \lim_{\hat{t} \to 0} \hat{S}_L\left(\hat{t}\right) = (1 - \alpha_1) + \beta\alpha_1\hat{t}. \tag{13d}$$

Substituting $\psi = 1$ into (9b) and integrating implies that to leading order as $\xi \to \infty$, $\sigma = \beta\xi$, and so the last condition becomes $\varepsilon\beta\xi = (1 - \alpha_1) + \beta\alpha_1\hat{t}$. Recalling that $\xi = (t - t^*)/\varepsilon^2$ and $\hat{t} = (t - t^*)/\varepsilon$, we get

$$\frac{\varepsilon\beta\,(t - t^*)}{\varepsilon^2} = 1 - \alpha_1 + \frac{\beta\alpha_1\,(t - t^*)}{\varepsilon},$$

and so we must have $\alpha_1 = 1$. Standard asymptotic expansions for the hypergeometric functions $\Phi(\cdot)$ and $\Psi(\cdot)$ show that (12) and matching conditions $\sigma(-\infty) = 0$ and $\sigma(\infty) = \beta\xi$ are satisfied if $k_1 = 0$ and $k_2 = -2\Gamma(1/2)/\Gamma(a + 1/2)$. The remaining two matching conditions (13a),(13b) hold automatically, with no conditions required. The constant ξ_0 is not determined by leading order matching and can thus be chosen arbitrarily at this order. Figure 2 schematically illustrates the matching process.

Composite Solution

The complete composite solution is the sum of the inner solutions near $t = 0$, the outer solutions (6), inner solutions (8), and inner-inner solutions (10),(11) near $t = t^*$, minus the common parts, giving

$$w(t;\varepsilon) = \frac{\beta(1+\beta)}{\beta - (1+\beta)\exp(-t)}\varepsilon^3 + \psi\left(\frac{t-t^*}{\varepsilon^2}\right) - (\beta+1)\exp\left(\frac{-t}{\varepsilon^4}\right), \tag{14a}$$

$$\begin{aligned} S_L(t;\varepsilon) = {} & \frac{1+\beta}{(1+\beta)\exp(-t) - \beta}\varepsilon^3 + \varepsilon\sigma\left(\frac{t-t^*}{\varepsilon^2}\right) + 1 - \exp\left(\frac{-\beta(t-t^*)}{\varepsilon}\right) \\ & - \frac{\beta(t-t^*)}{\varepsilon} - (1+\beta)\exp\left(\frac{-t}{\varepsilon^4}\right). \end{aligned} \tag{14b}$$

With this solution, in the $O(\varepsilon^2)$-region near $t = t^*$, the inner-inner solution is the dominant form while, away from this singular region, the outer form is dominant, the inner solution acts as an intermediate form joining the inner-inner and outer solutions. We also have an inner solution near $t = 0$, which joins the outer solution to the initial data.

Exact analytical calculation of t^* would require matching the inner solution (8) with higher-order terms in the inner-inner solution, which we have not attempted. However, we have already demonstrated that $\ln((1+\beta)/\beta)$ is an upper bound for t^*: the outer and inner solutions will never match if the outer solution $S_L \to \infty$, and so from (2), we must have $t^* < \ln((1+\beta)/\beta)$. Numerically calculated solutions of the model equations (1) indicate that $t^* \approx \ln((1+\beta)/\beta)$. Figure 3 illustrates the very good fit of this approximation to the numerical solution, with t^* close to this upper bound.

4. DISCUSSION

Summary

The problem studied in this paper is more complex than a standard singular perturbation problem. A standard problem of this type matched asymptotic expansions would contain two outer solutions separated by a single transition layer centred at $t = t^*$. However, with the example presented in this work, there can be no uniformly valid asymptotic solution with a single transition layer. In this problem, near $t = t^*$ there are in effect two fast time scales, the fast time in which t is of $O(\varepsilon^2)$ and the w solution changes very rapidly, and a slower time of $O(\varepsilon)$ during which the S_L solution increases to its steady-state value $S_L^* = 1$. So, near $t = t^*$, both solutions w and S_L change very rapidly, but the change in the w solution is very fast compared with the change in S_L. Thus, to extract the main features of both solutions, we require an inner expansion which approximates S_L near $t = t^*$ and an inner-inner expansion to capture the faster change in the w solution. Away from the singular (inner) regions near $t = t^*$, the nonsingular part of the solution is the dominant form. For a complete description of the solution, we also require an inner solution near $t = 0$ which joins the outer solutions onto the initial values $w(0) = 0$ and $S_L(0) = 0$. This solution form compares very well with the numerical results (see Figure 3). With this process, we have been unable to calculate an exact analytical form for t^*. Nevertheless, the analysis does give an upper bound for t^*, namely $t^* < \ln((1+\beta)/\beta)$, and numerical simulations show that t^* is close to this upper bound.

Implications for the Full Model

We now discuss the extent to which our results for the caricature system (1) can be extended to the full model.

In the full model (described in [10]), numerical simulations show that, after an initial transient, the number of soluble FasL molecules increases sharply to its steady state S_L^*. To study this

behaviour in more detail, we have considered a simplified caricature model. Numerical simulations show that the caricature model also exhibits the sharp transition in the S_L solution. Investigation of the caricature model using singular perturbation analysis has given considerable insight into the behaviour of the solution, and has provided a good analytical approximation to the solutions of the simpler system. These solutions compare very well with the numerical simulations, and capture the interesting transition in the S_L solution that was observed in the full model.

The perturbation approach also yields insight into the mechanism by which the sharp transition in the S_L solution is generated; we have shown that the level of S_L is closely related to R, and the jump in S_L is initiated when R falls to very low values, that is, near $t = \ln((1+\beta)/\beta)$. The caricature model is highly analogous to the full model. This analogy suggests that soluble FasL will increase rapidly to very high levels when the number of membrane-bound Fas receptor molecules becomes small. This makes sense intuitively, since a low number of free Fas receptors will not be able to bind with the large amounts of sFasL shed from the surface of the cells, resulting in the accumulation of high levels of extracellular soluble ligand.

Elevated levels of sFasL have been reported in a wide range of human tumours and are associated with poor patient prognosis [13,14]. In general, this activity is thought to occur as a result of the rapid cleavage of FasL by MMPs. Here, we show that sFasL interaction with its cell surface receptor Fas is also a key regulatory step in this process.

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