

On the Existence of Steady Solutions in a Moving Boundary Model of Neurite Morphogenesis with Cellular Autoregulation

DOUGLAS MCLEAN, KAREN LAUHLAN and BRUCE GRAHAM

Department of Computing Science and Mathematics

University of Stirling

Stirling FK9 4LA

SCOTLAND

drm@maths.stir.ac.uk, <http://www.cs.stir.ac.uk/~drm>

Abstract: - We present an enhancement of our partial differential equation model (McLean DR, Graham BP. Mathematical formulation and analysis of a continuum model for tubulin-driven neurite elongation. *Proc. Roy. Soc. Lond. A*, Vol. 460, 2004, pp. 2437-2456) of neurite elongation to include the cellular autoregulatory mechanism responsible for up-(down-)regulation of the tubulin flux. The existence and uniqueness of steady state solutions is then proven in each degenerate case and in the general cases of vanishing and non-zero active tubulin transport and species degradation.

Key-Words: - neuron, neurite growth, tubulin, continuum model, time-dependent domain, cellular autoregulation.

1 Introduction

Mathematical modelling and analysis are the keys to defining and quantifying biophysical systems such as those in neuroscience and further to neuronal development. Hodgkin and Huxley famously derived a system of nonlinear differential equations in 1952 to describe the transmission of electrical impulses in neurons. The field of mathematical *developmental* neuroscience is very new. One focus of the modelling has been to the morphological development of neurons. The chemical most directly responsible for neurite outgrowth is tubulin and this is produced in the soma, or cell body. It is then carried in unpolymerized form by molecular motors to the growth tip. At the growth tip, the oligomer is polymerized onto the ends of long tubulin microtubules which then contribute to the length of the neurite. The temporal evolution of the oligomer tubulin has been studied by numerous ordinary differential equation models of increasing complexity all implemented computationally (see [1],[2], [3] and, for an overview, [4]). These

models have served as important stepping stones in the understanding of neurite growth. A full mathematical analysis of these models is made difficult, however, due to their analytically intractable nature. We have developed a partial differential equation model of unbranched neurite elongation [5]. This model provides an accurate continuum description of the important transport, diffusion and species degradation processes along the entire length of a single, unbranched neurite which has been lacking in previous models. The model [5] is made mathematically interesting by the inclusion of a *moving boundary* at the neurite's growth tip. Briefly, [5] describes the tubulin concentration $c(x, t)$ at a position $x \in [0, l]$ at time $t \geq 0$. The tubulin and neurite length evolution equations are

$$\frac{\partial c}{\partial t} + a \frac{\partial c}{\partial x} = D \frac{\partial^2 c}{\partial x^2} - gc, \quad \frac{dl}{dt} = r \left[c \right]_{x=l} - s$$

where a, D, g, r and s are the active transport, diffusion, species degradation, growth and retraction parameters, respectively. In [5], boundary conditions of constant flux are maintained at

$x = 0$ and of a flux proportional to the tubulin concentration minus a constant disassembly rate at $x = l$:

$$\begin{aligned} -\frac{\partial c}{\partial x} &= \epsilon_0 c_0 \text{ at } x = 0, \\ -\frac{\partial c}{\partial x} &= \epsilon_l c - \zeta_l \text{ at } x = l \end{aligned}$$

with constants ϵ_0, ϵ_l and c_0 . The model was then solved for the steady values of $c(x, t)$ and $l(t)$ using an asymptotic technique. We found that a neurite could easily regulate the extent of its own growth by increasing or decreasing its tubulin production relative to the active transport/species degradation fraction. An important feature not yet included in [5] is the cellular autoregulatory function of tubulin production at the soma. It has been shown, [6], that the mRNA regulates the tubulin production at the soma and that there is evidence that the synthesis of tubulin mRNA is reduced at high tubulin concentrations in the soma by a feedback control mechanism. It is the purpose of this work to introduce the autoregulatory control mechanism and to prove the existence of steady solutions.

2 Autoregulatory Model

The autoregulatory aspect of the neurite's development can be taken into account by modifying the left-flux boundary condition to

$$-\frac{\partial c}{\partial x} = \epsilon_0 c_0 \left(1 - \frac{c}{c_1}\right) \text{ at } x = 0 \quad (c_1 > 0).$$

Here, the flux either up- or down-regulates itself when $c < c_1$ or when $c > c_1$, respectively, in such a way as to attain $c = c_1$ at $x = 0$. If we then proceed to nondimensionalise the governing equations (the details of which are omitted, see [5]) then we have:

$$\frac{\partial C}{\partial t} + \frac{\alpha}{l} \frac{\partial c}{\partial y} = \frac{1}{l^2} \frac{\partial^2 c}{\partial y^2} - \beta C + \frac{y}{l} \frac{\partial C}{\partial y} ([C]_{y=1} - \gamma) \quad (1)$$

$$\frac{dl}{dt} = [C]_{y=1} - \gamma \quad (2)$$

where α, β and γ are the dimensionless active transport, degradation, and retraction coefficients, respectively, we have introduced a neurite length co-ordinate $y = x/l$ so that $c(x, t) =$

$c(x(y), t) =: C(y, t)$. In [5], boundary conditions of constant flux are maintained at $y = 0$ and of a flux proportional to the tubulin concentration minus a constant disassembly rate at $y = 1$. In the autoregulatory model these are:

$$-\frac{\partial C}{\partial y} = \phi l (1 - \theta C) \text{ at } y = 0, \quad (3)$$

$$-\frac{\partial C}{\partial y} = \phi \rho l (C - \gamma) \text{ at } y = 1 \quad (4)$$

with non-negative constants ϕ, ρ, γ and θ ($:= c_0/c_1$), the dimensionless production, pumping, retraction and autoregulatory coefficients, respectively.

3 Steady State Equations

To save on notation we write $C = C(y)$ and l (also $L := \alpha l$) for the steady state concentration and length. The steady equations are:

$$\text{Tubulin: } 0 = C'' - \alpha l C' - \beta l^2 C, \quad (5)$$

$$\text{Length: } 0 = [C]_{y=1} - \gamma, \quad (6)$$

$$\text{Left bdy: } C'(0, t) = -\phi l + \phi \theta l C, \quad (7)$$

$$\text{Right bdy: } C'(1, t) = 0. \quad (8)$$

3.1 Degenerate Case I: $\alpha := 0, \beta > 0$

Here the auxiliary equation simplifies to $m^2 = \beta l^2$ giving $m = \pm \sqrt{\beta} l$. Let us define, for this subsection only, that $L := \sqrt{\beta} l$. The general solution is then

$$\begin{aligned} C(y) &= A \exp(Ly) + B \exp(-Ly), \\ \Rightarrow C'(y) &= AL \exp(Ly) - BL \exp(-Ly). \end{aligned}$$

($A, B \in \mathbb{R}$). Application of the right bdy condition (8) shows that $B = A \exp(2L)$ so that

$$\begin{aligned} C(y) &= A \{ \exp(Ly) + \exp[L(2 - y)] \} \\ \Rightarrow C'(y) &= AL \{ \exp(Ly) + \exp[L(2 - y)] \}. \end{aligned}$$

The left bdy condition (7) then shows that

$$A = \left\{ \frac{\sqrt{\beta}}{\phi} [e^{2L} - 1] + \theta [e^{2L} + 1] \right\}^{-1}.$$

From the length equation (6)

$$\begin{aligned}
0 &= [C]_{y=1} - \gamma \\
&= \frac{2e^L}{\frac{\sqrt{\beta}[e^{2L} - 1] + \theta[e^{2L} + 1]}{\tilde{\phi} \pm \sqrt{\tilde{\phi}^2(1 - \gamma^2\theta^2) + 1}}} - \gamma \\
\Leftrightarrow e^L &= \frac{\tilde{\phi} \pm \sqrt{\tilde{\phi}^2(1 - \gamma^2\theta^2) + 1}}{1 + \gamma\theta\tilde{\phi}} \\
\Leftrightarrow l &= \frac{1}{\sqrt{\beta}} \ln \left\{ \frac{\tilde{\phi} \pm \sqrt{\tilde{\phi}^2(1 - \gamma^2\theta^2) + 1}}{1 + \gamma\theta\tilde{\phi}} \right\} \\
&=: l_{\pm} \tag{9}
\end{aligned}$$

where $\tilde{\phi} := \phi/(\gamma\sqrt{\beta})$. Note that for a physical solution, we require $\tilde{\phi}^2(1 - \gamma^2\theta^2) + 1 \geq 0$. This leads to

$$0 \leq \theta \leq \frac{1}{\gamma} \sqrt{1 + \frac{1}{\tilde{\phi}^2}} =: \theta_{max}.$$

The length solution $l_+ > 0$ is always feasible, however the solution l_- arising from the negative path may not always be so. For $l_- > 0$ we require that

$$\begin{aligned}
\frac{\tilde{\phi} - \sqrt{\tilde{\phi}^2(1 - \gamma^2\theta^2) + 1}}{1 + \gamma\theta} &> 1 \\
\Leftrightarrow \tilde{\phi} - \gamma\theta\tilde{\phi} - 1 &> \sqrt{\tilde{\phi}^2(1 - \gamma^2\theta^2) + 1} \tag{10}
\end{aligned}$$

Define functions

$$\begin{aligned}
y_1(x) &:= \tilde{\phi} - 1 - \tilde{\phi}x, \\
y_2(x) &:= \sqrt{1 + \tilde{\phi}^2 - \tilde{\phi}^2x^2}.
\end{aligned}$$

Here, y_1 is a line of gradient -1 with x - and y -intercepts at $x = 1 - \tilde{\phi}^{-1}$ and $y = \tilde{\phi} - 1$, respectively. Function y_2 is an ellipse centred on O whose major and minor axes coincide with the co-ordinate axes and whose x - and y -intercepts are $(1 + \tilde{\phi}^{-2})^{1/2}$ and $(1 + \tilde{\phi}^2)^{1/2}$, respectively. Therefore, in the top-right quadrant, line y_1 can not intersect ellipse y_2 since, $\forall \tilde{\phi} > 0$:

$$\begin{aligned}
y_2(0) &= \sqrt{1 + \tilde{\phi}^2} = \sqrt{(\tilde{\phi} - 1)^2 + 2\tilde{\phi}} \\
&> \sqrt{(\tilde{\phi} - 1)^2} = |\tilde{\phi} - 1| \\
&\geq y_1(0)
\end{aligned}$$

and since the zero of the ellipse in $x > 0$ always exceeds the zero of the straight line y_1 :

$\sqrt{1 + \tilde{\phi}^{-2}} > 1 - \tilde{\phi}^{-1}$. A positive solution to the steady state length equation $l = l_-$ is not possible, the only solution coming from the positive path in (9).

3.2 Degenerate Case II: $\alpha > 0, \beta := 0$

Here the auxiliary equation is $m(m - \alpha l) = 0$ giving roots $m = 0$ or $m = \alpha l =: L$ (for the rest of this work). Hence the general solution is

$$\begin{aligned}
C(y) &= A + B \exp(Ly) \quad (A, B \in \mathbb{R}) \\
\Rightarrow C'(y) &= BL \exp(Ly)
\end{aligned}$$

The right boundary condition (8) requires:

$$C'(1) = 0 \Leftrightarrow B = 0 \text{ or } L = 0.$$

Assuming that $L \neq 0$ then $B = 0$ and $C = A$ (a constant function). The left boundary condition (7) requires:

$$\begin{aligned}
C'(0) &= -\phi l + \phi l \theta C(0) \\
\Leftrightarrow 0 &= -\phi l + \phi l \theta A \\
\Leftrightarrow A &= \frac{1}{\theta}.
\end{aligned}$$

From the length equation (6) we must have $0 = [C]_{y=1} - \gamma$ which is equivalent to $\theta = 1/\gamma$ and l is completely undetermined. This implies that if an initial condition is set where $C(y, 0) = \gamma$ with $\theta = \theta'_{crit} := 1/\gamma$ and *any* initial length $l = l_0 > 0$ then this configuration will persist $\forall t > 0$. For any other initial condition there can be no steady solution. Interestingly, this result might suggest the existence of an unstable steady state for $0 \leq \beta \ll 1$. Such behaviour in the limiting cases can be investigated by numerical or asymptotic means. In fact, our current asymptotic analysis (unpublished) for the limiting dynamic case of small β gives limit cycle behaviour.

3.3 General Case: $\alpha, \beta > 0$

3.3.1 Nonlinear Length Equation

Consider the most general case, i.e. where neither α nor β are zero. As in MG04, if we momentarily ignore (6) then the a.e. for the reduced system gives roots $m = m_{\pm} = Lf_h^{\pm}$ where $L = \alpha l$

and $f_h^\pm = \frac{1}{2}(1 \pm [1 + 4h]^{1/2})$. The general solution is:

$$C(y) = A \exp(Lf_h^+ y) + B \exp(Lf_h^- y) \quad (11)$$

$$\Rightarrow C'(y) = ALf_h^+ \exp(Lf_h^+ y) + BLf_h^- \exp(Lf_h^- y). \quad (12)$$

for $A, B \in \mathbb{R}$. The right boundary condition (8) shows that

$$A = -\frac{f_h^-}{f_h^+} \exp[L(f_h^- - f_h^+)] B$$

so that

$$\begin{aligned} C(y) &= B \left\{ -\frac{f_h^-}{f_h^+} \exp[L(f_h^- - f_h^+)] \right. \\ &\quad \left. \times \exp(Lf_h^+ y) + \exp(Lf_h^- y) \right\} \\ \& \quad C'(y) = BLf_h^- \left\{ -\exp[L(f_h^- - f_h^+)] \right. \\ &\quad \left. \times \exp(Lf_h^+ y) + \exp(Lf_h^- y) \right\}. \end{aligned}$$

The left bdy condition (7) determines B , and hence A :

$$B = \frac{-\phi l}{Lf_h^- - \phi \theta l - f_h^- \left[L - \frac{\phi \theta l}{f_h^+} \right] \exp(-LH)}$$

where $H := [1 + 4h]^{1/2} = f_h^+ - f_h^- > 0$. This then determines the solution for C up to the (as yet unknown) length l :

$$C(y) = \frac{\phi}{\alpha h} \times \frac{f_h^+ \exp[Lf_h^- (y-1)] - f_h^- \exp[Lf_h^+ (y-1)]}{\left[1 - \frac{\phi \theta}{\alpha f_h^-} \right] \exp(-Lf_h^-) - \left[1 - \frac{\phi \theta}{\alpha f_h^+} \right] \exp(-Lf_h^+)} \quad (13)$$

Now the steady state length equation shows $C(1) = \gamma$ and noting that

$$\begin{aligned} f_h^+ f_h^- &= \frac{1}{4}(1 - [1 + 4h]) = -h, \\ -LH + Lf_h^+ &= L(f_h^- - f_h^+ + f_h^+) = Lf_h^- \end{aligned}$$

gives the nonlinear length equation which must be solved for L (and hence l):

$$\begin{aligned} & \frac{\alpha \gamma h}{\phi} \\ &= \frac{H(f_h^+ - f_h^-)}{\left[1 - \frac{\phi \theta}{\alpha f_h^-} \right] \exp(-Lf_h^-) - \left[1 - \frac{\phi \theta}{\alpha f_h^+} \right] \exp(-Lf_h^+)} \\ &\Leftrightarrow \tilde{\alpha}_h \left[1 - \frac{\phi \theta}{\alpha f_h^-} \right] \exp(-Lf_h^-) \\ &= \tilde{\alpha}_h \left[1 - \frac{\phi \theta}{\alpha f_h^+} \right] \exp(-Lf_h^+) + H. \end{aligned} \quad (14)$$

where $\tilde{\alpha}_h := \beta \gamma / \phi \alpha$. When $\theta = 0$ (14) becomes

$$\tilde{\alpha}_h \exp(-Lf_h^-) = \tilde{\alpha}_h \exp(-Lf_h^+) + H$$

as found in [5].

3.3.2 Existence

We are interested in the situation where a solution L exists to (14). Define functions $y_1, y_2 \in C^2(\mathbb{R}^+)$:

$$\begin{aligned} y_1(x) &:= \tilde{\alpha}_h \left(1 - \frac{\phi \theta}{\alpha f_h^-} \right) \exp(-f_h^- x), \quad (15) \\ y_2(x) &:= \tilde{\alpha}_h \left(1 - \frac{\phi \theta}{\alpha f_h^+} \right) \exp(-f_h^+ x) + H. \end{aligned} \quad (16)$$

A solution to (14) is then equivalent to solving $y_1(x) = y_2(x)$ for $x \in \mathbb{R}^+$. If curves y_1 and y_2 intersect, a solution $x = L$ exists to the steady state length equation. Given positive system parameters, note that $f_h^- < 0 < f_h^+$ and so $1 - \frac{\phi \theta}{\alpha f_h^-} > 0$. However, $1 - \frac{\phi \theta}{\alpha f_h^+}$ may be of either sign (or zero). Specifically, y_1 is a monotone increasing function of x , bounded below by 0 and tending to ∞ as $x \rightarrow \infty$. However, y_2 is either:

- $$\left\{ \begin{array}{l} \text{(a) monotone increasing} \\ \text{and bounded above by } H \text{ if } \theta < \frac{\alpha f_h^+}{\phi} \\ \text{(b) constant with value } H \\ \text{if } \theta = \frac{\alpha f_h^+}{\phi} \\ \text{(c) monotone decreasing} \\ \text{and bounded below by } H \text{ if } \theta > \frac{\alpha f_h^+}{\phi} \end{array} \right.$$

Furthermore, the y -intercepts for curves y_1 and y_2 are finite and take values:

$$\begin{aligned} y_1(0) &:= \tilde{\alpha}_h \left(1 - \frac{\phi\theta}{\alpha f_h^-} \right), \\ y_2(0) &:= \tilde{\alpha}_h \left(1 - \frac{\phi\theta}{\alpha f_h^+} \right) + H. \end{aligned}$$

Case (a): $\theta < \frac{\alpha f_h^+}{\phi}$

Clearly, for curves y_1 and y_2 to intersect, given that y_1 is monotone increasing and y_2 is monotone decreasing, it is sufficient that $y_1(0) < y_2(0)$ ¹. This is not true for general θ :

$$\begin{aligned} y_1(0) &< y_2(0) \\ \Leftrightarrow \tilde{\alpha}_h \phi \theta \left(\frac{1}{f_h^+} - \frac{1}{f_h^-} \right) &< H \\ \Leftrightarrow \theta < \frac{H}{\tilde{\alpha}_h \phi \left(\frac{1}{f_h^+} - \frac{1}{f_h^-} \right)} &=: \theta_{crit} \end{aligned}$$

Thus, steady-state solutions exist iff $\theta < \theta_{crit}$. Observe that θ_{crit} can be simplified to:

$$\theta_{crit} = \frac{H}{\tilde{\alpha}_h \phi (H/h)} = \frac{h}{\tilde{\alpha}_h \phi} = \frac{1}{\gamma}.$$

Case (b): $\theta = \frac{\alpha f_h^+}{\phi}$

Using a similar argument to that in case (a) except that here y_2 is a constant function with value H , a steady state solution will exist provided

$$\theta < -\frac{\alpha f_h^-}{\phi} \left(\frac{H}{\tilde{\alpha}_h} - 1 \right).$$

Case (c): $\theta > \frac{\alpha f_h^+}{\phi}$

This situation is more delicate than either of case (a) or case (b). Here, both functions y_1 and y_2 are monotone increasing functions of x . The function y_1 is concave-up on all $x \in \mathbb{R}^+$ ($y_1'' > 0$) and y_2 is concave down on all $x \in \mathbb{R}^+$ ($y_2'' < 0$). Therefore, there are possibly none, one or two solutions to the length problem. However, we now show that there can be at most one by observing the following result:

$$\begin{aligned} y_2'(0) &= \tilde{\alpha}_h \left(\frac{\phi\theta}{\alpha} + (-f_h^+) \right) \\ &< \tilde{\alpha}_h \left(\frac{\phi\theta}{\alpha} + (-f_h^-) \right) \\ &= y_1'(0) \end{aligned}$$

since $-f_h^+ < 0 < -f_h^-$. Since both y_1 and y_2 are monotone increasing functions of $x \in \mathbb{R}^+$ with opposing concavity: $y_2''(x) < 0 < y_1''(x) \forall x \in \mathbb{R}^+$; then since $y_2'(0) < y_1'(0)$ [strict] at most one intersection between curves y_1 and y_2 is possible for $x \in \mathbb{R}^+$. For such an intersection to exist, it suffices that $y_1(0) < y_2(0)$. But this is exactly the same condition that we required in case (a) and so exactly one steady-state solution exists for case (c) provided $\theta < \theta_{crit}$.

Refer to Figure 1 for a graphical illustration of the intersection between curves y_1 and y_2 for each of cases (a), (b) and (c).

4 Summary and Future Work

We have extended [5] in developing a cellular autoregulatory model of neurite morphogenesis. The PDE model includes a moving boundary and a feedback control mechanism on the left-most boundary. For the degenerate case of positive decay/tubulin degradation ($\beta > 0$) and vanishing active transport ($\alpha = 0$) we found a steady solution to exist coming from the positive path in (9). In the degenerate case of no decay ($\beta = 0$) but positive active transport only one steady solution exists for a precise initial condition. It is very likely that this steady solution is unstable to infinitesimal perturbations. For the general case of non-trivial active transport and tubulin degradation, we developed a nonlinear length equation for the steady state length (14). Unfortunately, this cannot be solved analytically for L . However, we proved that exactly one steady-state solution exists to (14) when $\theta \neq \alpha f_h^+ / \phi$ provided

$$\theta < \theta_{crit} := \frac{1}{\gamma}.$$

When $\theta = \alpha f_h^+ / \phi$ then we require

$$\theta < -\frac{\alpha f_h^-}{\phi} \left(\frac{H}{\tilde{\alpha}_h} - 1 \right)$$

for a steady-state solution to exist.

The next step in our work is to identify the steady states for the general case and to determine their stability through a perturbation method. Longer term, we seek to model branching behaviour with a development of this model.

¹Strictly speaking, equality is possible here, but it leads to a steady state which has zero length and this is not biologically plausible.

References

- [1] Graham BP & van Ooyen A. Compartmental models of growing neurites. *Neurocomputing*, 38-40, 2001, pp31-36.
- [2] Van Ooyen A, Graham BP, Ramakers GJA. Competition for tubulin between growing neurites during development. *Neurocomputing*, 38-40, 2001, pp73-78.
- [3] Van Veen MP & van Pelt J. Neuritic growth rate described by modeling microtubule dynamics. *Bull. Math. Biol.*, Vol. 56, 1994, pp247-273.
- [4] Kiddie G, McLean D, van Ooyen A and Graham B. Biologically plausible models of neurite outgrowth. *Progress in Brain Research*, Vol. 147, 2004, pp. 67-80.
- [5] McLean DR, Graham BP. Mathematical formulation and analysis of a continuum model for tubulin-driven neurite elongation. *Proc. Roy. Soc. Lond. A*, Vol. 460, 2004, pp. 2437-2456.
- [6] Cleveland DW, Lopata MA, Sherline P & Kirschner MW. Unpolymerized tubulin modulates the level of tubulin mRNAs. *Cell*, Vol 25, 1981, pp537-546

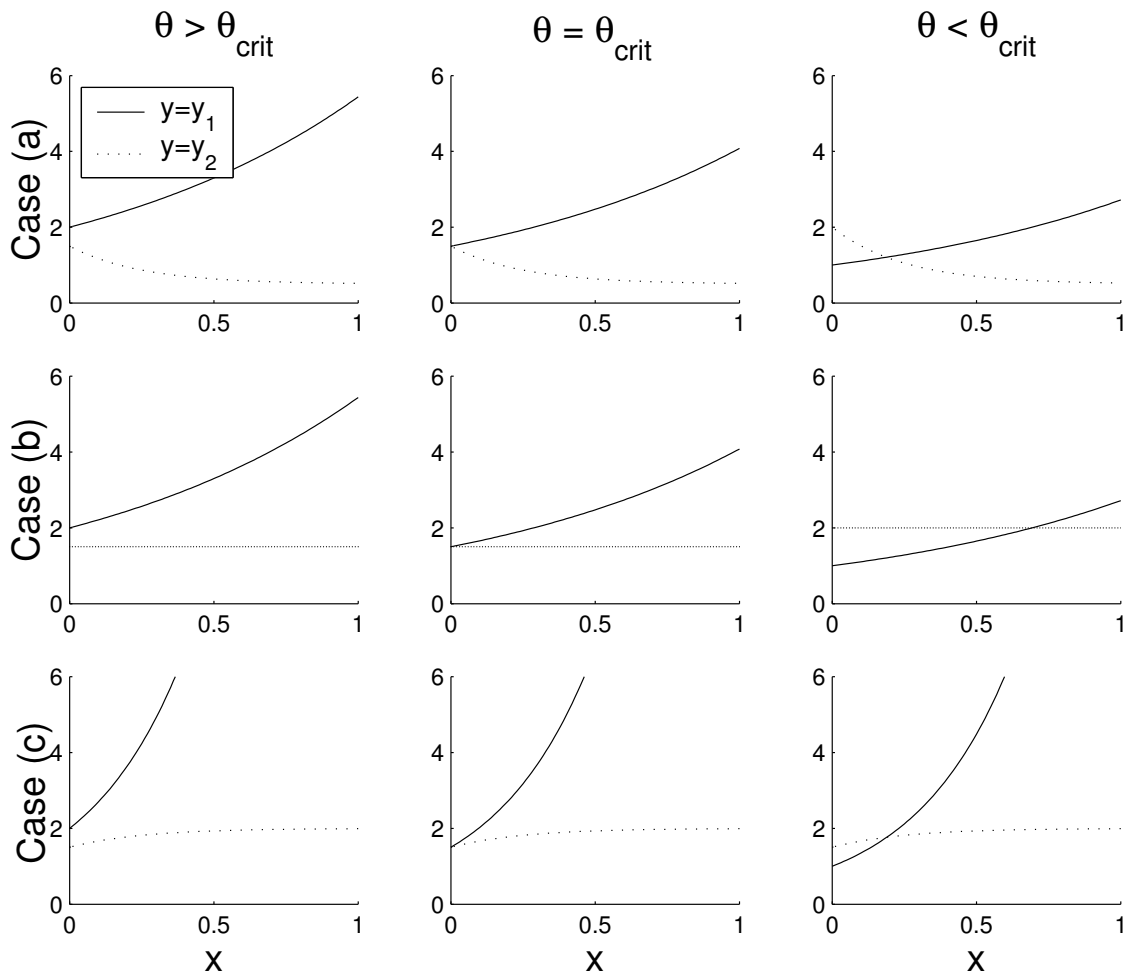


Figure 1: The various possibilities for intersection between curves $y_1(x)$ and $y_2(x)$. Each row corresponds to each of the cases (a), (b) or (c) and each column corresponds to the regimes for θ : $\theta > \theta_{crit}$, $\theta = \theta_{crit}$ or $\theta < \theta_{crit}$.