Qualitative Analysis of Tumor-Immune ODE System *

L.G. de Pillis and A.E. Radunskaya

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QUALITATIVE ANALYSIS

Overview

1. Simplified System of ODEs
2. Solution and Analysis Approaches
3. Graphical Analysis: Finding Nullclines and Equilibria
4. Determining Stability Analytically

Qualitative Analysis

Reduction to Two ODEs

Letting

$$\begin{aligned} p &= fk \\ m &= k(k_{-1}+k_2)-k_1 \\ n &= k(k_{-1}+k_3)-k_1 \end{aligned}$$

the new ODE system becomes

$$\frac{dE}{dt} = \underline{\hspace{8cm}}(1)$$

$$\frac{dT}{dt} = \underline{\hspace{8cm}}(2)$$

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Qualitative Analysis

Notes for Reduction to Two ODEs slide:

Answers:

(1) $s + \frac{pET}{g+T} - mET - dE$

(2) $aT(1-bT) - nET$

See [KMTP94, page 301]. Based on the simplifications given in the Equation Development module, the students should be asked to figure out what these two ODEs should be.

Qualitative Analysis

Solution and Analysis Approaches

Question: What is the next step?

Answer: We want to "solve" this system. There are three main approaches to understanding the solutions of a system of ODEs:

1. Find the ______________________________(1)
2. Do a ______________________________(2)
3. Find a ______________________________(3)

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Qualitative Analysis

Notes for Solution and Analysis Approaches slide:

Answers:

(1) analytical solution

(2) qualitative analysis

(3) numerical solution

Notes:

- Find the **analytical solution**: This can be very challenging, and sometimes impossible, when the system is nonlinear, as it is in our case.
- Do a **qualitative analysis**: A qualitative analysis allows us to understand something about the global and local behavior family of solutions of the system, without actually finding particular solutions.
- Find a **numerical solution**: This is the approach we will eventually take in order to find approximations to particular solutions. But a numerical solution requires that some preparation be done first. We need to carry out a qualitative analysis

continue ⇒

of the system so we know what sort of behavior to expect, and we need to determine realistic values for the system parameters.

In our case, since finding an analytical solution is not tractable, we must begin with a qualitative analysis of the system.

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Qualitative Analysis

Finding Nullclines

Step 1: Find nullclines algebraically.

1. Set

$$\frac{dE}{dt} = \underline{\qquad\qquad}(1)$$
$$\frac{dT}{dt} = \underline{\qquad\qquad}(2)$$

continue ⇒

Notes for Finding Nullclines slide:

Answers:

(1) 0

(2) 0

The first goal in the Qualitative Analysis is to find all the equilibrium points. These are where the nullclines intersect. So the very first step is to find the nullclines.

We are assuming here that the students have had to carry out such a qualitative analysis in their introductory ODEs class. However, for review, we still outline the steps that need to be taken. It may be necessary to recall the following definition.

Definition: Given an n-dimensional system of differential equations $d\vec{\mathbf{x}}/dt = \vec{\mathbf{F}}(\vec{\mathbf{x}})$, the nullcline corresponding to the i^{th} state variable x_i is the set of points where $F_i = 0$, *i.e.* the set of points were $dx_i/dt = 0$.

Qualitative Analysis

Finding Nullclines (continued)

2. Solve for E-nullcline:

$$E = \underline{\hspace{6cm}}\text{(3)}$$

3. Solve for T-nullcline:

$$E = \underline{\hspace{6cm}}\text{(4)}$$

or $$T = \underline{\hspace{1.5cm}}\text{(5)}$$

Qualitative Analysis

Notes for Finding Nullclines(cont) slide:

Answers:

(3) $E = \frac{(g+T)s}{(mT+d)(g+T)-pT}$

Note: Find the nullcline by setting $E(mT + d - \frac{pT}{g+T}) - s = 0$ and solve for E. It would be a good idea to let the students try to work this one out in class. Later we are going to look at graphs of these nullclines. We will call the RHS $f(T)$, so that the nullcline for E is given by $E = f(T)$.

(4) $E = \frac{a(1-bT)}{n}$

Note: Solve by setting $aT(1 - bT) - nET = 0$. In this case we also solve for E (instead of for T) in order to make a *graphical* solve for the equilibrium points easier (seeing where the graphs of the nullclines intersect). However, there are many ways to solve for this. We will call this RHS $g(T)$, so that one component of the T-nullcline is given by $E = g(T)$.

(5) $T = 0$

Note: In addition to the set of points $E = g(T)$, the set of points $T = 0$ also satisfies the equation $dT/dt = 0$.

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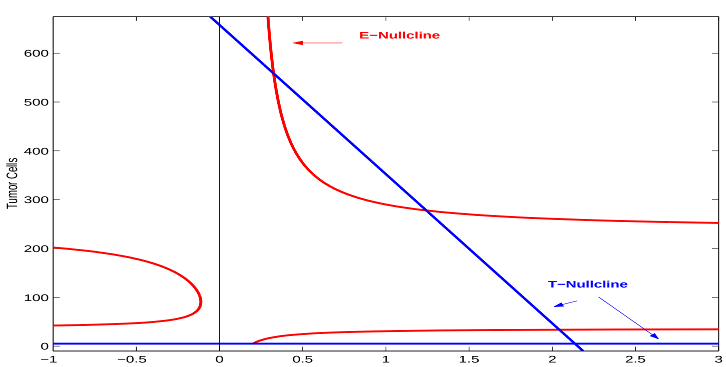
Qualitative Analysis

Finding Equilibria

Step 2: Find ____________________(1) graphically.



Step 3: Determine the ____(2) graphically.

Qualitative Analysis

Notes for Finding Equilibria slide:

Answers:

(1) the equilibria

(2) stability of the equilibria

The equilibria occur where both nullcline equations are solved simultaneously. This will be where the graphs of the nullclines intersect, so we first present from a graphical perspective a way of finding the equilibrium points.

The particular parameter values used to generate this plot are in the range shown in Kuznetsov's paper [KMTP94, p.306,fig.2a], the case in which $\rho \geq \left(\sqrt{n\mu} + \sqrt{\delta}\right)^2$.

We suggest following these steps with this slide:

1. Have students identify the equilibrium points, then draw them onto the plot.

2. Discuss the biological meaning of the equilibrium points, for example:

   (a) Can we ignore points that represent negative population values? (yes)

   (b) Which equilibrium point is tumor free? (point A) See "Letter Labeling" graphic in these notes.

3. Sketch the direction field on the plot. This helps us to determine (qualitatively) the stability of each equilibrium point. Remember to refer to the original ODEs for E and T to help determine in which direction we should be crossing the nullclines.

4. Finally, we should see just from the graphical analysis that

   (a) Point A represents zero tumor, and is a saddle

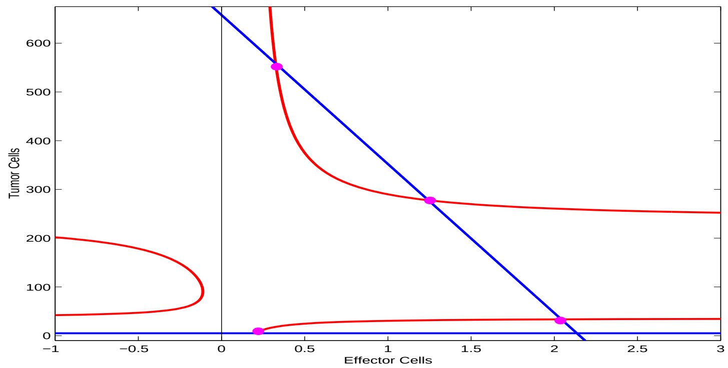
   (b) Point B needs more analysis: it could be a spiral or a center

   (c) Point C is unstable

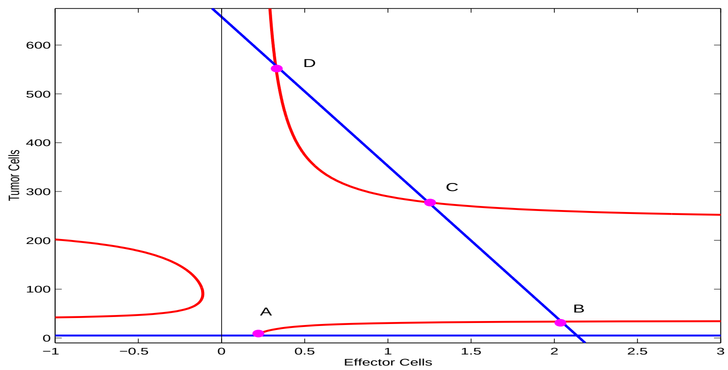
   (d) Point D is stable

Finally, we now include images of the phase portrait as they should be filled in (probably by hand for a nice dynamic effect!) during discussion with the students.

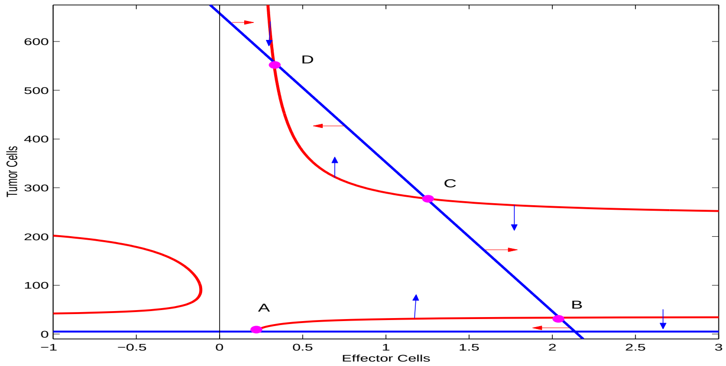
Nullclines and Equilibrium Points



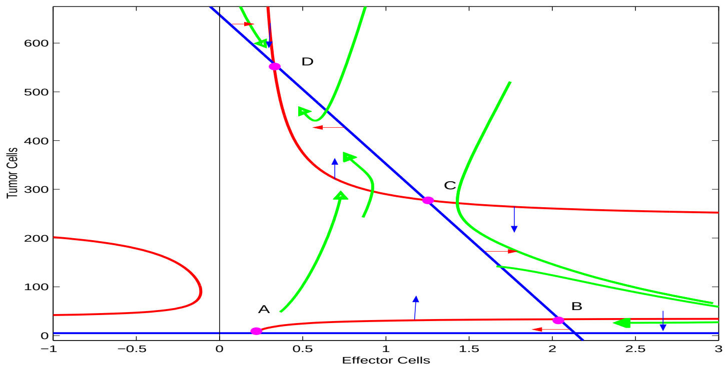
Nullclines and Equilibrium Points and Letter Labeling



Nullclines and Equilibrium Points and Letter Labeling and Arrows



Nullclines and Equilibrium Points and Letter Labeling and Arrows and Phase Portrait Lines



Qualitative Analysis

Summary of Graphical Analysis

From our *graphical* analysis of the equilibria we can conclude that **for the particular parameter set** used in the example:

- Point A (tumor-free) is an ______________________(1).
- Point B (low tumor burden) may be a ______________(2) or a ______________(3), and may be ______________(4) or ______________(5), in which case nearby points might converge to a ______________(6).
- Point C (non-zero tumor burden) is ______________(7) (and may be a ______________(8)).
- Point D (high tumor burden) is ______________(9).

Qualitative Analysis

Notes for Summary of Graphical Analysis slide:

Answers:

(1) unstable saddle
(2) spiral
(3) node
(4) stable
(5) unstable
(6) limit cycle
(7) unstable
(8) saddle
(9) stable

Make sure to highlight for the students that this categorization of the equilibrium points is only valid for a particular parameter set. If the parameters change, the number and type of equilibria will also change. This will be discussed further in the section on bifurcation analysis. This kind of graphical analysis is a good precursor to the analytic determination of the stability of each equilibrium point, which comes on the next slide.

Qualitative Analysis

Analytic Determination of Stability

General Procedure

Step 1: Specify an ________________$_{(1)}$ point to analyze. Call it (x_0, y_0).

Step 2: ________________$_{(2)}$ the system about the equilibrium point by evaluating the Jacobian at that point.

Step 3: Find the ________________$_{(3)}$ of the Jacobian to determine the stability properties of point (x_0, y_0).

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Qualitative Analysis

Notes for Analytic Determination of Stability slide:

Answers:

(1) equilibrium

(2) Linearize

(3) eigenvalues

Note: To get more precise information about equilibria like Points B and C in the previous example, we must analytically determine the stability properties of these points.

Once again, we assume the students have already seen this linearization and analysis procedure, so we only present a brief review. More review is provided in the exercises. MATLAB routines for finding equilibria and their stability are included in the MATLAB scripts appendix.

Qualitative Analysis

The Stability of a Nearly Linear System

Theorem: from Borrelli and Coleman [BC98] Suppose that $\mathbf{J}$ is an $n \times n$ matrix of real constants. Furthermore, suppose $\vec{\mathbf{P}}(\vec{\mathbf{x}})$ is a vector-valued function that is continuously differentiable in an open ball $B_r(\vec{\mathbf{p}})$, that $\vec{\mathbf{P}}(\vec{\mathbf{p}}) = 0$, and that $\vec{\mathbf{P}}(\vec{\mathbf{x}})$ has order at least 2 at $\vec{\mathbf{p}}$. Then the *nearly linear* system:

$$\frac{d\vec{\mathbf{x}}}{dt} = \mathbf{J}(\vec{\mathbf{x}} - \vec{\mathbf{p}}) + \vec{\mathbf{P}}(\vec{\mathbf{x}})$$

has the following properties:

1. The system is **asymptotically stable** at $\vec{\mathbf{p}}$ if all eigenvalues of $\mathbf{J}$ have negative real parts.
2. The system is **unstable** at $\vec{\mathbf{p}}$ if there is at least one eigenvalue of $\mathbf{J}$ with positive real part.

Qualitative Analysis

The Stability of a Nearly Linear System (continued)

Note: The matrix, $\mathbf{J}$, is the ________________ $_{(1)}$ of the nonlinear system, evaluated at the ________________ $_{(2)}$ $\vec{\mathbf{p}}$.

Unfortunately, this theorem doesn't tell us anything about the equilibrium if all of the eigenvalues of $\mathbf{J}$ have real part ________________ $_{(3)}$, but at least one of them has real part ________________________ $_{(4)}$.

Qualitative Analysis

Notes for The Stability of a Nearly Linear System slide

Answers:

(1) Jacobian

(2) equilibrium

(3) less than or equal to zero

(4) equal to zero

Notes: This is another quick review. You may also need to recall the following definitions:

Definition 1: The system $\dot{\vec{\mathbf{x}}} = \vec{\mathbf{F}}(\vec{\mathbf{x}})$ has an asymptotically stable equilibrium at $\vec{\mathbf{p}}$ if there is a $\delta > 0$ such that,

$$||\vec{\mathbf{x}}(0) - \vec{\mathbf{p}}|| < \delta \Rightarrow \lim_{t\to\infty} \vec{\mathbf{x}}(t) = \vec{\mathbf{p}}$$

Definition 2: The system $\dot{\vec{\mathbf{x}}} = \vec{\mathbf{F}}(\vec{\mathbf{x}})$ has an unstable equilibrium at $\vec{\mathbf{p}}$ if there is a $\delta > 0$ such that $\forall\epsilon > 0$, there is a point $\vec{\mathbf{x}}(0)$ with $||\vec{\mathbf{x}}(0) - \vec{\mathbf{p}}|| < \epsilon$, but $||\vec{\mathbf{x}}(t) - \vec{\mathbf{p}}|| > \delta$ for some $t > 0$.

Qualitative Analysis

Analytic Determination of Stability: General Example

Example: Given the ODE system

$$\begin{aligned} \frac{dx}{dt} &= F_1(x,y) \\ \frac{dy}{dt} &= F_2(x,y) \end{aligned}$$

the linearized system at a point (x_0, y_0) is

$$\begin{bmatrix} \frac{dx}{dt} \\ \frac{dy}{dt} \end{bmatrix} = \mathbf{J} \begin{bmatrix} x \\ y \end{bmatrix}, \quad \text{or with vector notation: } \dot{\vec{\mathbf{x}}} = \mathbf{J}\vec{\mathbf{x}}$$

where $\mathbf{J}$ is the Jacobian of the system evaluated at (x_0, y_0).

continued $\Rightarrow$

Qualitative Analysis

Analytic Determination of Stability: General Example (continued)

The Jacobian matrix $\mathbf{J}$ is given by

$$\mathbf{J} = \begin{bmatrix} \rule{6cm}{0.4pt}(1) & \rule{6cm}{0.4pt}(2) \\ \\ \rule{6cm}{0.4pt}(3) & \rule{6cm}{0.4pt}(4) \end{bmatrix}$$

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Qualitative Analysis

Notes for Analytic Determination of Stability Example slide:

Answers:

(1) $\frac{\partial F_1}{\partial x}(x_0, y_0)$

(2) $\frac{\partial F_1}{\partial y}(x_0, y_0)$

(3) $\frac{\partial F_2}{\partial x}(x_0, y_0)$

(4) $\frac{\partial F_2}{\partial y}(x_0, y_0)$

Note: We can use the same general Jacobian matrix for each equilibrium point, just plug in a different (x_0, y_0) each time.

Qualitative Analysis

Example: Jacobian for Point A

- Plug $T = 0$ into E-nullcline equation $\Rightarrow E = s/d$. Therefore, $(x_0, y_0) = (s/d, 0)$.
- Determine the Jacobian.

$$\mathbf{J} = \begin{bmatrix} \underline{\hspace{3cm}}(1) & \underline{\hspace{3cm}}(2) \\ & \\ \underline{\hspace{3cm}}(3) & \underline{\hspace{3cm}}(4) \end{bmatrix}$$

Qualitative Analysis

Notes for Example: Jacobian for Point A slide:

Answers:

(1) $-d$

(2) $ps/dg - ms/d$

(3) 0

(4) $a - ns/d$

Note: This analysis will tell us what parameter ranges make the node stable or unstable.

The steps to working out the Jacobian $\mathbf{J}$ are as follows:

$$F_1(E,T) = s + pET/(g+T) - mET - dE,$$

and

$$F_2(E,T) = aT(1-bT) - nET$$

...so...

$$\left.\frac{\partial F_1}{\partial E}\right|_{(s/d,0)} = [pT/(g+T) - mT - d]_{(s/d,0)} = -d$$

$$\left.\frac{\partial F_1}{\partial T}\right|_{(s/d,0)} = [(pE(g+T) - pET)/(g+T)^2 - mE]_{(s/d,0)} = ps/dg - ms/d$$

$$\left.\frac{\partial F_2}{\partial E}\right|_{(s/d,0)} = [-nT]_{(s/d,0)} = 0$$

$$\left.\frac{\partial F_2}{\partial T}\right|_{(s/d,0)} = [(a(1-bT) - baT - nE)]_{(s/d,0)} = a - ns/d$$

Qualitative Analysis

Example: Eigenvalues of Jacobian for Point A

Because $\mathbf{J}$ is a ________________$_{(1)}$ matrix, the eigenvalues are on the ________________$_{(2)}$. Therefore, eigenvalues λ_1 and λ_2 are

$$\lambda_1 = \underline{\hspace{4cm}}_{(3)}$$
$$\lambda_2 = \underline{\hspace{4cm}}_{(4)}$$

Note:

- λ_1 is always ________________$_{(5)}$.
- λ_2 is ________________$_{(6)}$ if and only if ________________$_{(7)}$

Qualitative Analysis

Notes for Example: Eigenvalues of Jacobian for Point A slide:

Answers:

(1) triangular

(2) diagonal

(3) $-d$

(4) $a - ns/d$

(5) negative Note: For health reasons, we want this zero-tumor point to be stable, so we want the eigenvalues to be negative if we can make them so.

(6) negative

(7) $ad < ns$ Note: Recall that a is the growth rate of tumor cells, d is the death rate of immune cells, n measures how effectively E-cells kill T-cells, and s is the immune source term. From this, you can guide the students to discuss the biological interpretation of this requirement for making λ_2 negative. One possible observation is that in the form we give here, we see that the growth rate of tumor cells should be less than ns/d as a condition for health. That is, the rate of tumor growth is slower than the rate at which available immune cells can kill tumor cells.

References

[BC98] Robert L. Borrelli and Courtney S. Coleman. *Differential Equations: A Modeling Perspective*. John Wiley and Sons, Inc., 1998.

[KMTP94] Vladmir A. Kuznetsov, Iliya A. Makalkin, Mark A. Taylor, and Alan S. Perelson. Nonlinear dynamics of immunogenic tumors: Parameter estimation and global bifurcation analysis. *Bulletin of Mathematical Biology*, 56(2), 1994.