Bifurcation Analysis of Tumor-Immune ODE System [*]

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BIFURCATION ANALYSIS

Overview

1. What is a bifurcation analysis?
2. The effect of shifting nullclines.
3. Analytical determination of bifurcation points.
4. Basins of attraction..
5. Bifurcation diagrams.
6. Types of bifurcations.

Bifurcation Analysis

Understanding Qualitative Changes

Simulations and null-cline analyses illuminate the general behavior of the system.

A Bifurcation Analysis gives the bigger picture.

- Question: How do different **QUALITATIVE** behaviors arise as the **PARAMETERS** of the system are varied?

Recall the non-dimensionalized system of Kuznetsov [KMTP94]:

$$\begin{aligned} \frac{dE}{dt} &= \sigma + \frac{\rho E T}{\eta + T} - \mu E T - \delta E \\ \frac{dT}{dt} &= \alpha T(1 - \beta T) - E T \end{aligned}$$

We carry out a bifurcation analysis on this system of equations.

Bifurcation Analysis

Notes for Understanding Qualitative Changes slide:

Answers:

(1) qualitative

(2) parameters

Bifurcation Analysis

Example Question

Question: When is the tumor-free equilibrium *stable*?
Answer: When $\alpha < \dfrac{\sigma}{\delta}$ (using the non-dimensionalized parameters).

The parameters were estimated to be: $\alpha = 1.636, \sigma = .1181$, and $\delta = .3743$.
Therefore, in this case the tumor-free equilibrium is **UNSTABLE**.

Question: In this case, what is the long-term fate of the system?
Before we can answer, we need to see how the number of **EQUILIBRIA** and their **STABILITY** change with the parameters.

Topic for discussion: Why would we be interested?

Bifurcation Analysis

Notes for Example Question slide:

Answers:
(1) unstable. Note:

$$\alpha = 1.636 > \frac{.1181}{.3743} \approx .3144 = \sigma/\delta$$

(2) equilibria
(3) stability.

Notes: In response to the Question: The point to make is that since this tumor-free equilibrium is unstable, we cannot predict anything useful about the behavior of the system until we know the stability and location of the other equilibrium points as well. Once we know the properties of all the equilibria, we can then predict possible long-term behavior of the system, such as whether the tumor will grow indefinitely or whether it will shrink to a negligible size.

Notes: In response to the question Why would we be interested?: This might lead to a short discussion, or some questions to research outside of class.

1. Which parameters might reasonably be changed by treatment?
2. How? (*For example, a bone marrow transplant might increase the value of* σ; *or immunotherapy - stimulation of the immune system by a vaccine, perhaps, might increase* ρ *or* μ.)
3. How might surgery or radiation affect the model? (*These therapies would reduce the number of cells, mainly the tumor cells, but also the immune cells. They may also reduce the immune response of the system to any remaining cancer by weakening the entire system.*)

Bifurcation Analysis

Shape of the Nullclines

In non-dimensional form, we are interested in the intersection of the null-clines:

$$N_E : \left\{ (E,T) : E = \frac{\sigma}{\delta + \mu T - \frac{\rho T}{\eta + T}} = f(T) \right\}$$

$$N_T := \{T = 0\} \cup \{(E,T) : E = \alpha(1 - \beta T) = g(T)\}$$

Determine the qualitative features of these curves:

- The graph of $g(T)$ is always a straight line with slope $-\alpha\beta$.
- The graph of $f(T)$ can have several different forms.

Bifurcation Analysis

Notes for Shape of the Nullclines slide:

Answers:

(1) $-\alpha\beta$.

Notes: The students might try to sketch $f(T)$ and $g(T)$ on the same axes (the positive quadrant only) for various parameter values. The main point is: what features of these graphs will result in a *qualitative* change in the dynamics of the system. Intersections (in the positive quadrant) correspond to (physically relevant) equilibria, and the relative orientation of the two curves at the points of interesection determines the stability of the equilibria. Is it possible to identify parameter values which cause a change in the *number* of intersections, for example?

The next two slides may be omitted, with the information filled in by the students.

Bifurcation Analysis

The Effect of Shifting the T-Nullcline

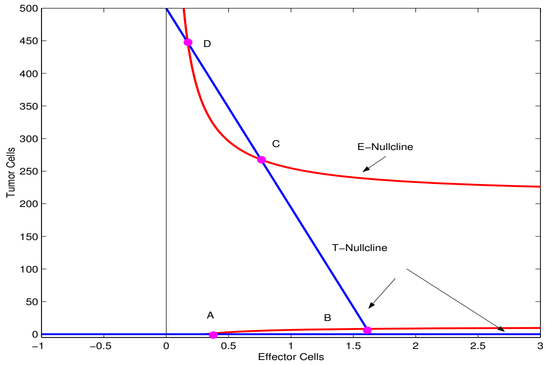

Figure 1: With ‘normal’ parameter values, shifting the T-nullcline by changing α while keeping the product, $\alpha\beta$ constant, has the effect of **SHIFTING THE T-NULLCLINE, WHICH REDUCES THE NUMBER OF EQUILIBRIA (FROM 4 TO 2 TO 1)**

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Bifurcation Analysis

Notes for The Effect of Shifting the T-Nullcline slide:

Answers:

(1) shifting the T-nullcline, which reduces the number of equilibria (from four, to two, to one).

Note: You may want to remind the students that for all the plots in this module, T is plotted on the vertical axis, while E is plotted on the horizontal axis.

Bifurcation Analysis

Equilibria Disappear and Change Stability

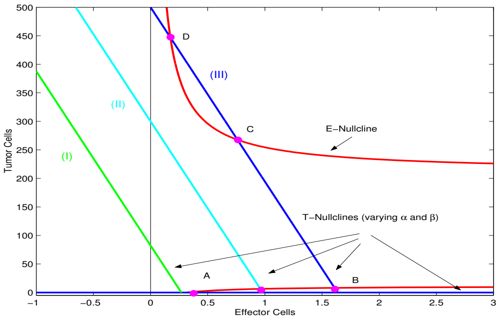


Figure 2: The smallest value of α corresponds to the **GREEN** T-nullcline. Clinically, this means that: **THE PATIENT IS IN REMISSION.**

Question: What happens to the patient? **THEY ARE EVENTUALLY CURED.**

Bifurcation Analysis

Notes for Equilibria Disappear and Change Stability slide:

Answers:

(1) green

(2) The patient is in remission.

Note: Biologically, reducing α corresponds to slowing the rate of tumor growth. The disappearance of the stable equilibrium corresponding to a high tumor burden, the equilibrium labeled "D", is important physically: the system will always tend towards the equilibrium corresponding to a smaller tumor burden, the equilibrium labeled "B", and we might consider a patient in such a situation "in remission".

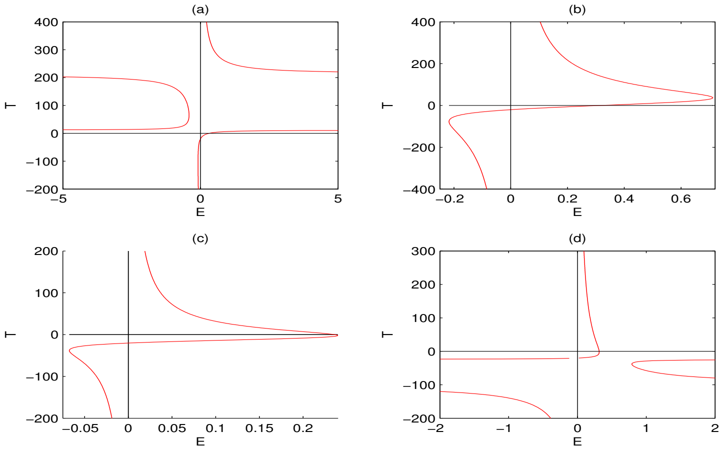
Question: As α is decreased and the T-nullcline is shifted down, the patient is eventually "cured". The first bifurcation occurs when the two equilibria marked D and C coalesce and then disappear. This is called a **saddle-node** or **fold** bifurcation. The tumor-free equilibrium at A, however, remains unstable. This situation corresponds to the T-nullcline labeled (II). As α is decreased further, the two equilibria labeled A and B coalesce and switch relative positions. (For our purposes, the equilibrium at B disappears, since it becomes negative. Mathematically, however, it still exists.) At this

point the two equilibria also switch stability, and the tumor-free equilibrium becomes stable. This type of bifurcation is called a transcritical bifurcation. Graphically, this corresponds to the T-nullcline labeled (I) and *physically* we would consider a patient described by these parameters as "disease free", since the system would move towards the tumor-free state without any outside intervention.

Bifurcation Analysis

The Effect of Varying the E-nullcline

The E-nullcline, *i.e.* the graph of the function $f(T)$, has different forms depending on the parameter values. What are the qualitative differences shown in these four examples?



Bifurcation Analysis

Notes for The Effect of Varying the E-nullcline slide:

Notes: We outline some of the important features that should be highlighted for the students:

Figure (a) These are the “normal” parameter values, already seen in Figure 5. Note that there are two positive horizontal asymptotes, resulting in two separate components of the graph in the positive quadrant.

Figure (b) The asymptotes have disappeared, so there is only one connected component of the graph in the positive quadrant. The function $f(T)$ has one maximum in the positive quadrant.

Figure (c) This is Figure (b) shifted down vertically. The important difference here is that the function is monotonic in the positive quadrant, since the maximum value of $f(T)$ is now below the E-axis.

Figure (d) The function now has two horizontal asymptotes, but they are both negative. As in Figure (c), the function $f(T)$ is monotonic in the positive quadrant.

Bifurcation Analysis

Intersections of the E and T Nullclines

In this example, the graph of $f(T)$ has no **HORIZONTAL ASYMPTOTE**.

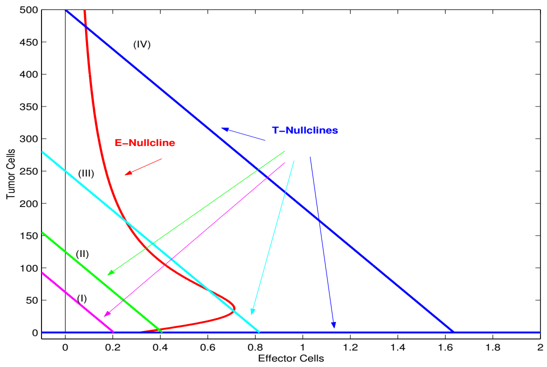


Figure 3: For each of the T-nullclines, determine the number and stability of the equilibria.

Bifurcation Analysis

Notes for Intersections of the E and T Nullcline slide:

Answers:

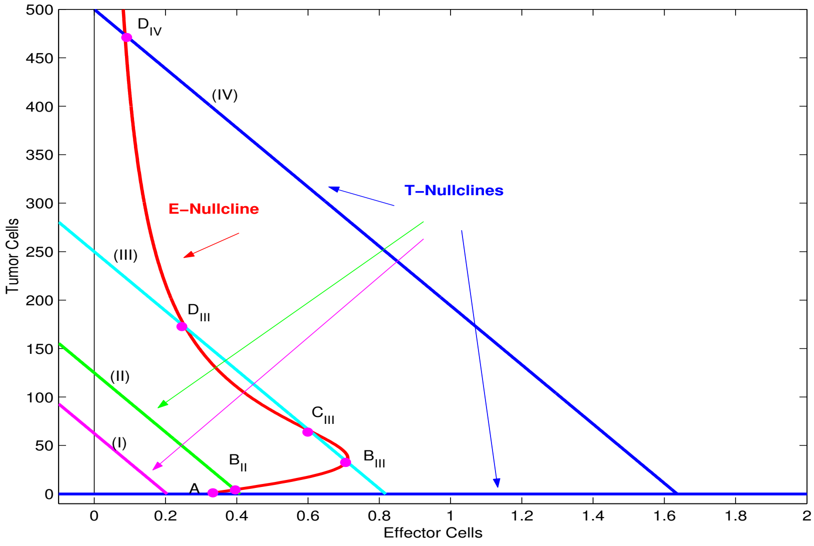
(1) horizontal asymptote.

Number and stability of equilibria:

1. T-Nullcline (IV): Two equilibria: D_{IV}, (stable); and A, (unstable).
2. T-Nullcline (III): Four equilibria: D_{III}, (stable); C_{III}, (unstable); B_{III}, (stable); A, (unstable);
3. T-Nullcline (II): Two equilibria: B_{II}, (stable); and A, (unstable);
4. T-Nullcline (I): One equilibrium: A, (stable).

Bifurcation Analysis

The equilibria are drawn on the graph below:



Notes: The determination of the equilibria and their stability might be a good in-class exercise, or it could be assigned as homework. Students could be asked to sketch by hand representative phase-portraits, or they might solve the systems numerically in each of the different cases to test their conclusions. Parameter sets corresponding to the blue T-nullclines are included in the MATLAB demo code *BifDemo1*.

Bifurcation Analysis

A Further Parameter Change Reduces the Possible Number of Equilibria

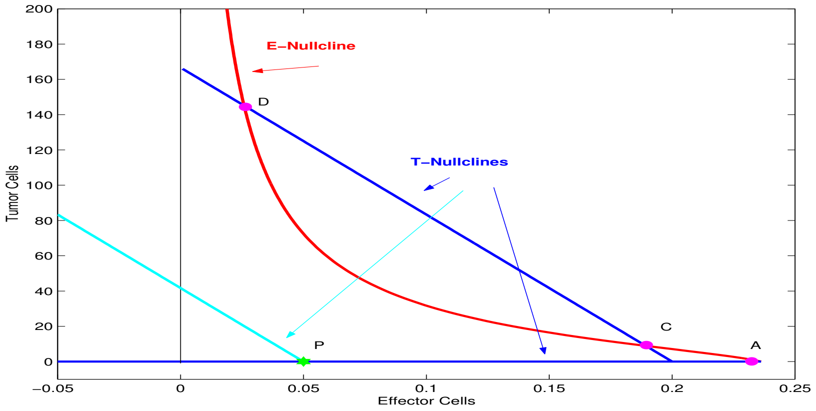


Figure 4: What is the maximum possible number of (positive) equilibria? **3** Is the point P an equilibrium? **NO.**

Bifurcation Analysis

Notes for A Further Parameter Change Reduces the Possible Number of Equilibria slide:

Answers:

(1) Three. Note: The idea here is that the *shape* of the graph of $f(T)$ has not changed, but its unique maximum has shifted, and is attained at a negative value of T. See Figure (c) in slide 7. Hence, the function $f(T)$ is strictly decreasing and concave *up* for $T > 0$. This means that the graph of $g(T)$, no matter what its y-intercept, can intersect the graph of $f(T)$ in at most two points. The third equilibrium, labeled A, is the tumor-free equilibrium which is always present.

(2) No, the point P is not an equilibrium. It is the intersection of the two straight lines making up N_T, the T-nullcline. The tumor-free equilibrium is at the intersection of the horizontal axis, $\{T = 0\}$, and the E-nullcline, N_E.

Bifurcation Analysis

When the Asymptotes of $f(T)$ are Negative

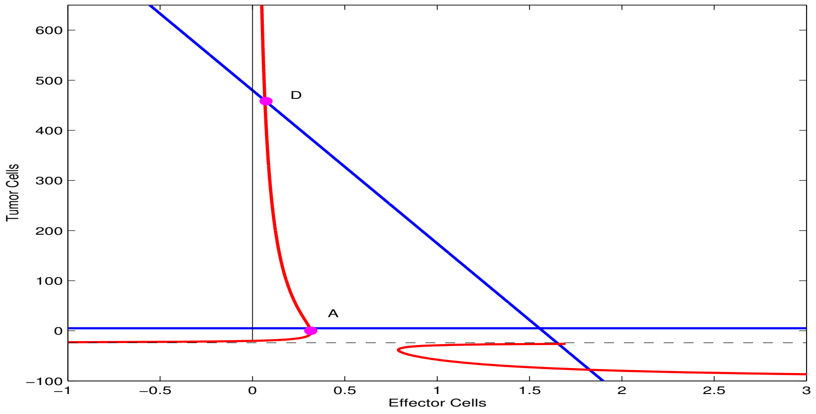


Figure 5: There are **2** equilibria. The equilibrium at **A (tumor-free)** is stable, and the equilibrium at **D** is unstable. Is it possible, by shifting the T-nullcline, to have no equilibria? **NO**.

Bifurcation Analysis

Notes for When the Asymptotes of $f(T)$ are Negative slide:

Answers:

(1) two

(2) A, (the tumor-free equilibrium)

(3) D Note: This situation could be considered a description of a healthy patient. The system's immune cells will invariably kill of any tumor cells.

(4) No, it's never possible to eliminate the tumor-free equilibrium, since the graph of $f(T)$ will always intersect the horizontal axis. It is possible, however, for there to be only one equilibrium, (if the graph of $g(T)$ does not intersect the graph of $f(T)$ for $T > 0$), or three equilibria, (if the graph of $g(T)$ intersects the graph of $f(T)$ at two points above the horizontal axis). Terminology Note: The bifurcation which occurs when the graph of $g(T)$ moves *off* of the graph of $f(T)$ is, again, a saddle-node or fold bifurcation, since the two points of intersection approach each other and finally disappear.

Bifurcation Analysis

Determining Bifurcations Analytically

Conditions determining the shape of the graph of $f(T)$:

- The function $f(T)$ has horizontal asymptotes when the parameter, ρ, is: $\rho > (\sqrt{\eta\mu} + \sqrt{\delta})^2$ or $\rho < (\sqrt{\eta\mu} - \sqrt{\delta})^2$
- The function $f(T)$ has a maximum at a positive value of T when $\rho > \eta\mu$
- The condition for the asymptotes to be positive is: $\rho > (\sqrt{\eta\mu} + \sqrt{\delta})^2$

Bifurcation Analysis

Notes for Determining Bifurcations Analytically slide:

Answers:

(1) When

$$\rho > (\sqrt{\eta\mu} + \sqrt{\delta})^2 \quad \text{or} \quad \rho < (\sqrt{\eta\mu} - \sqrt{\delta})^2$$

Details: $f(T)$ will have an asymptote when the denominator is zero, i.e. when

$$\delta + \mu T - \frac{\rho T}{\eta + T} = 0.$$

Solving for T (after rewriting as a quadratic) gives:

$$T_{\text{Asympt}} = \frac{(\rho - \delta - \eta\mu) \pm \sqrt{(\delta + \eta\mu - \rho)^2 - 4\eta\delta\mu}}{2\mu}$$

This equation has two solutions if the radicand is non-negative, i.e. if

$$(\delta + \eta\mu - \rho)^2 > 4\eta\delta\mu.$$

Rearranging this inequality gives the following conditions on the parameters for which asymptotes exist:

$$\rho > (\sqrt{\eta\mu} + \sqrt{\delta})^2 \quad \text{or} \quad \rho < (\sqrt{\eta\mu} - \sqrt{\delta})^2$$

(2) $\rho > \eta\mu$. Details: Taking the derivative of $f(T)$ and setting it equal to zero gives :

$$\mu = \frac{\rho\eta}{(\eta + T)^2}$$

Solving for T gives:

$$T_{\text{max}} = \sqrt{\frac{\rho\eta}{\mu}} - \eta.$$

Setting $T_{\text{max}} > 0$ gives the result.
(3) $\rho > (\sqrt{\eta\mu} + \sqrt{\delta})^2$ Details: In Question (1) we saw that asymptotes will exist only if ρ satisfies one of the two given inequalities. The values T_{Asympt} will be positive only if the expression: $\rho - \delta - \eta\mu > 0$, and hence ρ must satisfy the *first* of the two inequalities given in Answer (1).

Notes:These formulas should be tied back to the graphs on the previous four slides so that the significance of the presence of positive horizontal asymptotes and a positive maximum of $f(T)$ is made clear.

Bifurcation Analysis

A Picture of Parameter Space

The previous calculations can be viewed graphically:

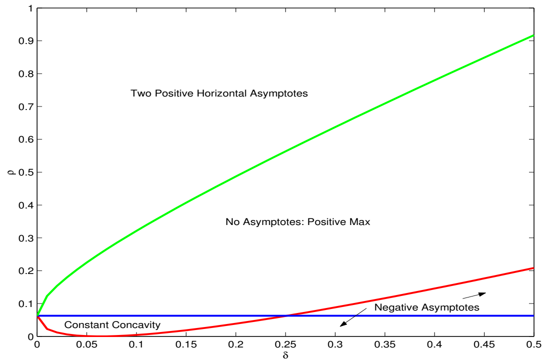


Figure 6: ρ is plotted against δ, delineating the values at which the graph of $f(T)$ changes shape

Bifurcation Analysis

Notes for A Picture of Parameter Space slide:

Notes: The choice of graphing ρ against δ is somewhat arbitrary here. However, it is possible that either of these parameters might be affected by treatment: the value of ρ might be increased by immuno-stimulation, while the value of δ - the death rate of the immune cells - might be increased by cytotoxic chemotherapy.

This parameter space graph is included here as an introduction to this type of graphical display, which students may not have seen before. It may be worth pointing out that the shape of $f(T)$ alone is not enough to determine the number or stability of the equilibria. This will come later.

The MATLAB code used to generate this graph is in *BifDemo2.m*.

Bifurcation Analysis

Finding Equilibria Analytically

To find the equilibria of the system analytically, we can set $f(T) = g(T)$ to get a **THIRD** polynomial whose **ROOTS** are the **EQUILIBRIA**.

$$f(T) = \frac{\sigma}{\delta + \mu T - \frac{\rho T}{\eta + T}} = \alpha(1 - \beta T) = g(T)$$

$$\Rightarrow A_3 T^3 + A_2 T^2 + A_1 T + A_0 = 0$$

where

$A_3 = \beta\mu$

$A_2 = \beta(\mu\eta + \delta - \rho) - \mu$

$A_1 = \beta\delta\eta - \mu\eta - \delta + \rho + \frac{\sigma}{\alpha}$

$A_0 = \frac{\sigma\eta}{\alpha} - \delta\eta$

Bifurcation Analysis

Notes for Finding Equilibria Analytically slide:

Answers:

(1) third

(2) roots

(3) equilibria Note: These intersections do not include the tumor-free equilibrium, which is given by $f(0) = \frac{\sigma}{\delta}$.

(4) $A_3 = \beta\mu$

(5) $A_2 = \beta(\mu\eta + \delta - \rho) - \mu$

(6) $A_1 = \beta\delta\eta - \mu\eta - \delta + \rho + \sigma/\alpha$

(7) $A_0 = \frac{\sigma\eta}{\alpha} - \delta\eta$

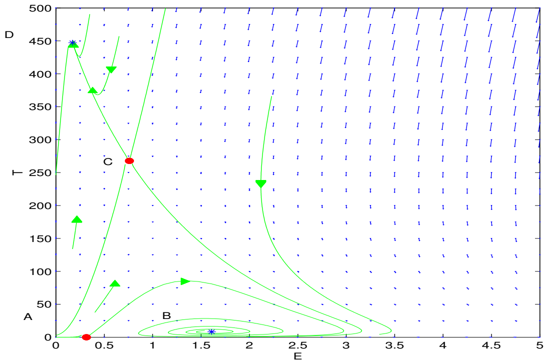
Notes: The actual computation of the coefficients is not very enlightening. The point here is that the T-values at the equilibria must satisfy a third degree polynomial, so there can be at most three of them. We can calculate this roots if we wish, or we could make a chart of the number of positive real roots corresponding to different parameter ranges. Kuznetsov has such a chart in his paper (see page 305 in [KMTP94]). He uses Descarte's rule and Sturm's method ([BC36, pp.448-455]). Descarte's rule is not too complicated, and it is included here for completeness:

Descarte's Rule of Signs: Let $f(x) = a_n x^n + a_{n-1} x^{n-1} + \cdots + a_1 x + a_0$. The number of real positive roots of $f(x) = 0$ is less than or equal to the number of sign changes in the sequence $\{a_n, a_{n-1}, \ldots, a_1, a_0\}$.

Bifurcation Analysis

Determining Stability of the Equilibria

For the estimated parameter values, we get **FOUR** equilibria:



This numerically generated phase protrait suggests that there are **TWO** stable and **TWO** unstable equilibria. We can verify this by calculating the roots of the cubic, and the calculating the **EIGENVALUES** of the **JACOBIAN** at the corresponding equilibria.

Bifurcation Analysis

Notes for Determining Stability of the Equilibria slide:

Answers:

(1) four
(2) two
(3) two
(4) eigenvalues
(5) Jacobian

Notes: The MATLAB code *BifDemo3.m* can be used to find the equilibria and their eigenvalues, and to plot them. This could also be done using other software packages, such as Maple or Mathematica. In the next slide we list the computed equilibria and their associated eigenvalues. A demo of the MATLAB routine, (or some other software) might be appropriate here as well, or the students could be asked to find the equilibria, the Jacobians, and the eigenvalues themselves. (Many hand-held calculators can find roots of polynomials and eigenvalues of matrices as well!)

Bifurcation Analysis

Results of Computations

- A=(.32,0), $\lambda_1 = -.3743, \lambda_2 = 1.3205.$
  This equilibrium is **UNSTABLE (SADDLE)**.
- B=(1.6, 8.19),$\lambda_{1,2} = -.0501 \pm .5763i.$
  This equilibrium is **STABLE (SPIRAL)**.
- C=(.76, 267.80), $\lambda_1 = -1.3565, \lambda_2 = .3248.$
  This equilibrium is **UNSTABLE (SADDLE)**.
- D=(.17, 447.13), $\lambda_1 = -1.6931, \lambda_2 = -.4527.$
  This equilibrium is **STABLE (NODE)**.

Bifurcation Analysis

Notes for Results of Computations slide:

Answers:

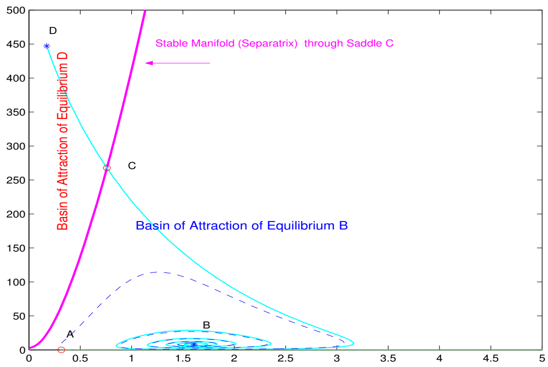
(1) unstable (saddle)
(2) stable (spiral)
(3) unstable (saddle)
(4) stable (node)

Notes: It may be helpful to remind the students here of the different types of equilibria that arise in *linear* systems, along with the associated eigenvalues, either in class or in the exercises. We will be especially concerned with saddle equilibria when we discuss the heteroclinic bifurcation.

Bifurcation Analysis

Basins of Attraction

The two **STABLE** equilibria each have an associated **Basin of ATTRACTION**. The boundaries of these basins contain the **STABLE MANIFOLD** of the unstable equilibrium, C.



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Notes for Basins of Attraction slide:

Answers:

(1) stable
(2) attraction
(3) stable
(4) manifold

Notes: We may need to “recall” the definitions of the stable and unstable manifolds through a point. Some students may have been introduced to these as the *forward* or *backward limit sets* of the point or, alternatively, as the ω or α *limit sets* of the point.

Definition: The *stable manifold* through a point, p in the state space of a system of differential equations is the set of initial values:

$$W_s(p) = \{x_0 | \lim_{n\to\infty} x(t_n) = p\}$$

for some increasing infinite sequence of times, $\{t_1, t_2, \dots\}, \lim_{n\to\infty} t_n = +\infty$, and where $x(t)$ is a solution to the system of differential equations with $x(0) = x_0$.

The *unstable manifold* through p, W_u, is defined analagously, with the sequence

of times *decreasing* to $-\infty$:

$$W_u(p) = \{x_0 | \lim_{n\to\infty} x(t_n) = p\}$$

for some decreasing infinite sequence of negative times, $0 > t_1 > t_2 > \dots$, $\lim_{n\to\infty} t_n = -\infty$, with $x(t)$ a solution such that $x(0) = x_0$.

The stable manifold through a saddle equilibrium in a planar system of ODE’s is also called a *separatrix*, precisely because it separates the orbits into two sets. In our case, since there are two stable equilibria, these two sets of orbits actually belong to two different basins of attraction. In higher dimensions the situation can be quite a bit more complicated, but even in two dimensions we can observe some interesting phenomena.

Bifurcation Analysis

Basins of Attraction (Continued)

Definition: Let q be a stable equilibrium point of a system of differential equations, and let B be the set of initial values resulting in solutions which approach q:

$$B = \{x_0 | x(0) = x_0, \text{ and } \lim_{t \to \infty} x(t) = q\}.$$

B is called the *Basin of Attraction of* q.

In our example, the clinical interpretation of the basin of attraction of the stable equilibrium, D, is **THE SET OF STATES OF A PATIENT'S SYSTEM WHICH, IN THE ABSENCE OF THERAPEUTIC INTERVENTION, WILL RESULT IN THE ESTABLISHMENT OF A RELATIVELY LARGE TUMOR**.

Bifurcation Analysis

Notes for Basins of Attraction (Continued) slide:

Answers:

(1) the set of states of a patient's system which, in the absence of therapeutic intervention, will result in the establishment of a relatively large tumor.

Follow-up Discussion Question: What is the clinical interpretation of the basin of attraction of the stable equilibrium labeled B?

If the value of the tumor population at B is small enough, this may correspond to a tumor in remission: i.e. a tumor below the threshold of detection which never goes away, but remains (benignly) small. It is believed that many undetectable tumors do develop, but are kept under control by our immune systems. This model, with its two coexisting stable equilibria, allows for this possibility.

Computational Note: Given a saddle equilibrium, it is relatively easy to numerically approximate the unstable manifold, since almost all initial conditions close to the saddle will approach this set. Thus, by using random perturbations of the saddle equilibrium as initial values for a numerical solution, one can obtain a graph of the unstable manifold. In order to draw the *stable* manifold through a saddle, start with a random perturbation of the equilibrium and solve *backwards* in time, since the backwards limits of almost all nearby points lie on the stable manifold.

A MATLAB file is included which draws the stable and unstable manifolds through the saddle equilibria for a given parameter set. MATLAB demo code: see *BifDemo4*.

Bifurcation Analysis

Bifurcation Points

The next step in the analysis of the system:

- Understand how the **LOCATION**, **NUMBER**, and **STABILITY** of the equilibria change when the parameters of the system are varied. This is done by finding the bifurcation points of the system.

  Definition: A bifurcation point is a **PARAMETER VALUE** at which a qualitative change in the phase portrait occurs.

For example, what is the effect of varying the source rate of immune cells, given by the parameter, σ?

Bifurcation Analysis

Notes for Bifurcation Points slide:

Answers:

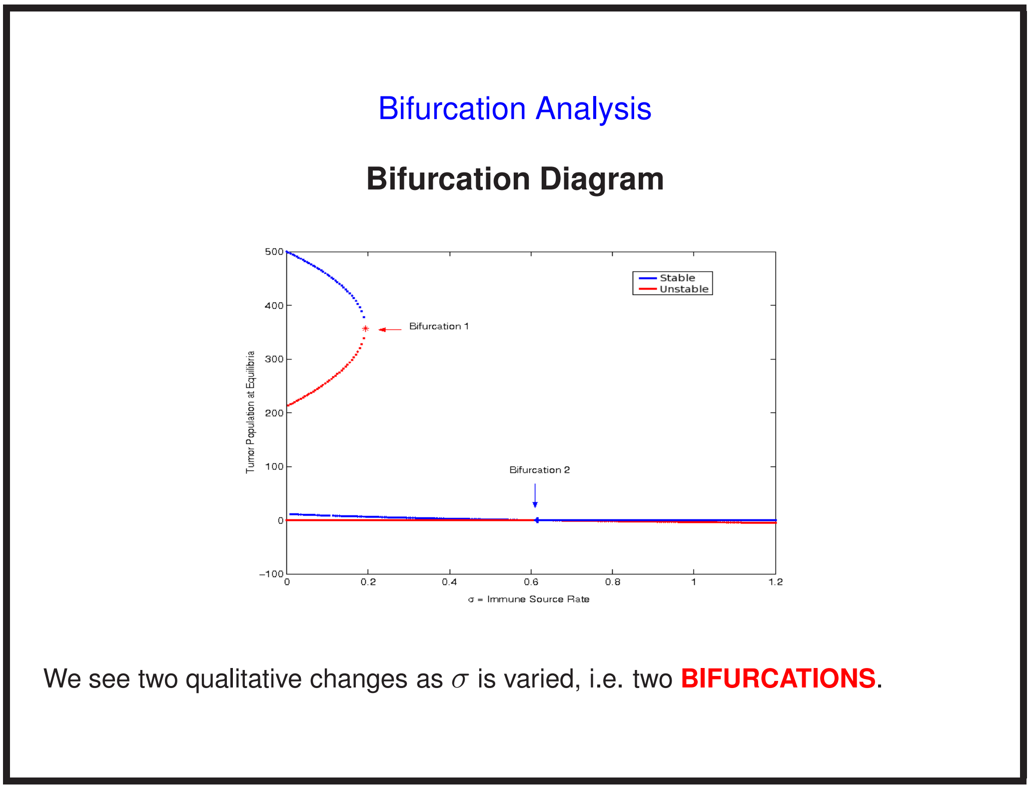
(1) location

(2) number

(3) stability

(4) parameter value

(5) σ. Note: This change in parameter might be accomplished by a bone marrow transplant, for example. This therapy would ideally increase stem-cell production.



Bifurcation Analysis

Bifurcation Diagram

We see two qualitative changes as σ is varied, i.e. two **BIFURCATIONS**.

Bifurcation Analysis

Notes for Bifurcation Diagram slide:

Answers:

(1) bifurcations.

Notes: This graph may need a few minutes of discussion, to make sure that its meaning is clear. The phase portraits on the following slides should help tie the bifurcations to qualitative changes in the dynamics. The students should make the connection here with the previous discussions about the different equilibria and their stability, i.e. the points previously labeled A,B,C and D. Which point on this graph corresponds to the 'normal' parameter values? ($\sigma = .118$). Do the qualitative changes which occur as σ is increased make sense physically? (*Yes: we would expect to see improvement in the situation if there were more immune cells. At the higher values of* σ*, there is only one (positive) equilibrium left: the tumor-free equilibrium at A, which is stable.*)

The MATLAB code for generating this bifurcation diagram is given in *BifDemo5.m*.

Bifurcation Analysis

Changes in Phase Portraits (1)

The bifurcations on the previous slide correspond to the following changes in the phase portraits:

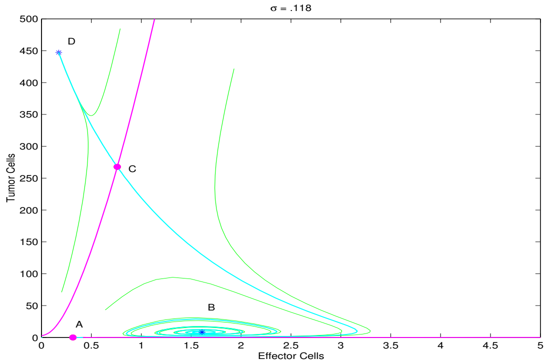


Figure 7: Before Bifurcation 1

Bifurcation Analysis

Changes in Phase Portraits (2)

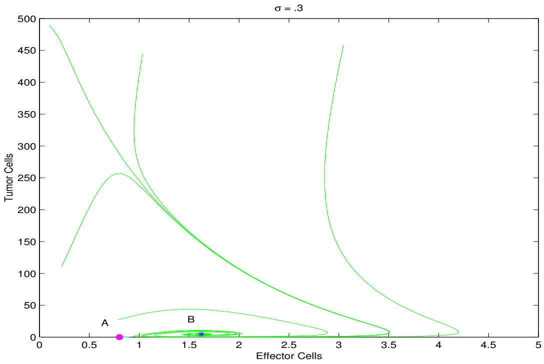


Figure 8: After Bifurcation 1, before Bifurcation 2

Bifurcation Analysis

Changes in Phase Portraits (3)

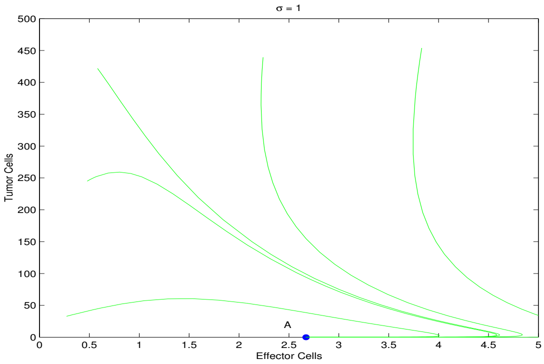


Figure 9: After Bifurcation 2

Bifurcation Analysis

Types of Bifurcations

Each bifurcation has a name. In this model we have three types:

- Transcritical when equilibria change **STABILITY**
- Saddle-node when equilibria **APPEAR** or **DISAPPEAR**
- Heteroclinic when the basins of attraction dramatically **CHANGE SHAPE**

Bifurcation Analysis

Notes for Types of Bifurcations slide:

Answers:

(1) stability
(2) appear
(3) disappear
(4) change shape

Question: Which type occurs at which range of σ-values?

- for a $\sigma \in [.1, .3]$ there is a Saddle-node bifurcation (at $\sigma \approx .19375$)
- for a $\sigma \in [.3, 1]$ there is a Transcritical bifurcation (at $\sigma \approx .6150$)

Note: These bifurcations can be computed by numerically calculating the equilibria and their stability for a range of parameter values, and then refining the search for changes. An analytical approach could also be used. For example, the saddle-node bifurcations occur in this system when the graphs of $f(T)$ and $g(T)$ become tangent, which can be computed analytically. This might make a good project.

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Heteroclinic Bifurcations

A Heteroclinic Bifurcation occurs when boundaries of basins change, i.e. when the stable and unstable manifolds of saddle equilibria change their relative orientation.

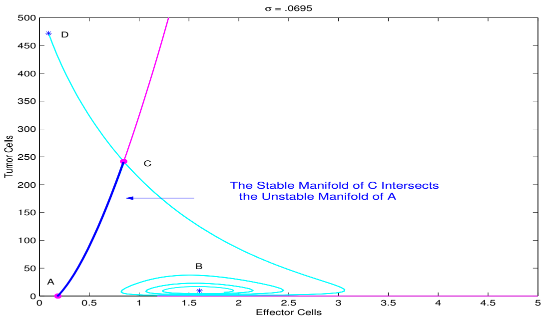

Figure 10: At this bifurcation, the **UNSTABLE MANIFOLD** of A and the **STABLE MANIFOLD** of C intersect.

Bifurcation Analysis

Notes for Heteroclinic Bifurcations slide:

Answers:

(1) unstable manifold

(2) stable manifold

Note: How could one compute this bifurcation value? Again, the value of σ can be gradually increased, each time determining numerically whether the unstable manifold of A is connected to the stable equilibrium D or the stable equilibrium B. The value of σ at which this changes is the bifurcation value.

It is worth pointing out that in two dimensions there are not many possible long-term behaviors for orbits: they must either go to infinity, go towards an equilibrium, or move towards a limit cycle. In this particular example, limit cycles can be ruled out (see Kuznetsov's paper for details) but we do not discuss this here. However, the fact that the unstable manifold of A must converge to one of the equilibria allows the determination of the bifurcation point by the long-term behavior of a point on $W_u(A)$.

The students could be asked to compute representative phase portraits of the system just before and just after the heteroclinic bifurcation in order to understand its significance. (These phase portraits are given on the next slides, but could be omitted).

Computing tip: If this is done in MATLAB, the function “ginput” is useful for selecting various initial conditions graphically. Also, the ‘Events’ option in the MATLAB ODE solvers is helpful to avoid the solutions running off to inifinity. The use of this option is illustrated in MATLAB demo code *BifDemo4.m*, using the Events function *OutOfRange.m*.

Bifurcation Analysis

Phase Portrait Before the Heteroclinic Bifurcation

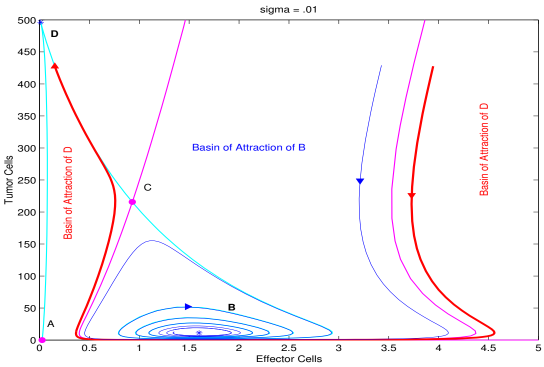

Figure 11: Just before the heteroclinic bifurcation, the unstable manifold through A is connected to **D**.

Bifurcation Analysis

Phase Portrait At the Heteroclinic Bifurcation

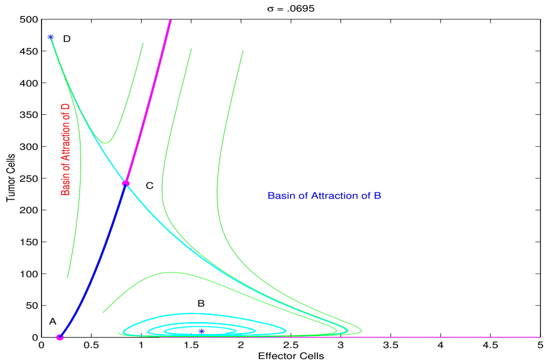

Figure 12: At the heteroclinic bifurcation, the unstable manifold of A is connected to **C**.

Bifurcation Analysis

Phase Portrait After the Heteroclinic Bifurcation

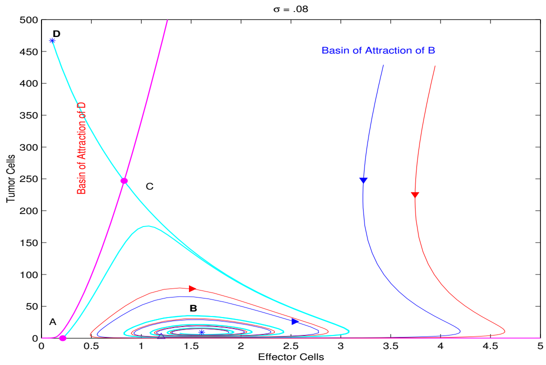

Figure 13: Just after the heteroclinic bifurcation, the unstable manifold through A is connected to **B**.

Bifurcation Analysis

For *Phase Portraits Before and After the Heteroclinic Bifurcations* slides.

Answers:

(1) D
(2) C
(3) B

Notes: These phase portraits illustrate an important clinically observed phenomenon known as “creeping through”. This describes the situation when a tumor seems to have disappeared, i.e. it shrinks below the detectable threshold, remains small for some time, (dormant), and then begins to proliferate. The phase portrait for $\sigma = .01$, *before* the heteroclinic bifurcation, shows to orbits which start close to each other. The orbit graphed in red ends up at the equilibrium, D, which corresponds to a dangerously high tumor burden.. The orbit graphed in blue ends up at the (possibly benign) equilibrium, B. What’s curious is that the initial condition corresponding to a *higher* level of immune cells results in a worse outcome for the patient. This can be explained, perhaps, by the fact that the higher immune levels causes more of the tumor to die out initially. While the tumor burden is low, the immune response decreases (there is not enough antigen present to recruit proliferation of cytotoxic T-cells), until the tumor is allowed to grow

swiftly.

Assignment: Find other parameter regimes in which “creeping through” can occur.

Notes on Periodic Solutions (or a lack thereof): Since this model does not admit limit cycles, we have chosen *not* to discuss Hopf bifurcations here. However, oscillatory behavior is very important to physicians: if the size of a population is osciallating naturally, then therapy which reduces the size initially may have no long term effect. Although it seemed unatural to introduce limit cycles artifically into this particular model, we have provided a separate Project which guides the students through an exploration of Hopf bifurcations and limit cycles. It might be worthwhile to point out that observations of, say, tumor volume along an orbit which is spiraling towards the stable equilibrium, B, would appear to be cycling for quite some time.

Question: Are there parameter values for which the periods of these observed oscillations would match those observed clinically? A literature search would be in order here.

References

[BC36] S. Barnard and J. M. Child. *Higher Algebra*. MacMillan and Company, 1936.

[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.