BSC6882: Stability Analysis

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1 State space of growth dynamics

Let the number of tumor cells at every point in time be $x(t)$. Consider the following growth models.

1. Exponential: $\dot{x} = rx$
2. Logistic: $\dot{x} = rx(1 - \frac{x}{K})$
3. Logistic with Allee: $\dot{x} = rx(1 - \frac{x}{K})(\frac{x}{A} - 1)$, assuming $0 < A < K$.

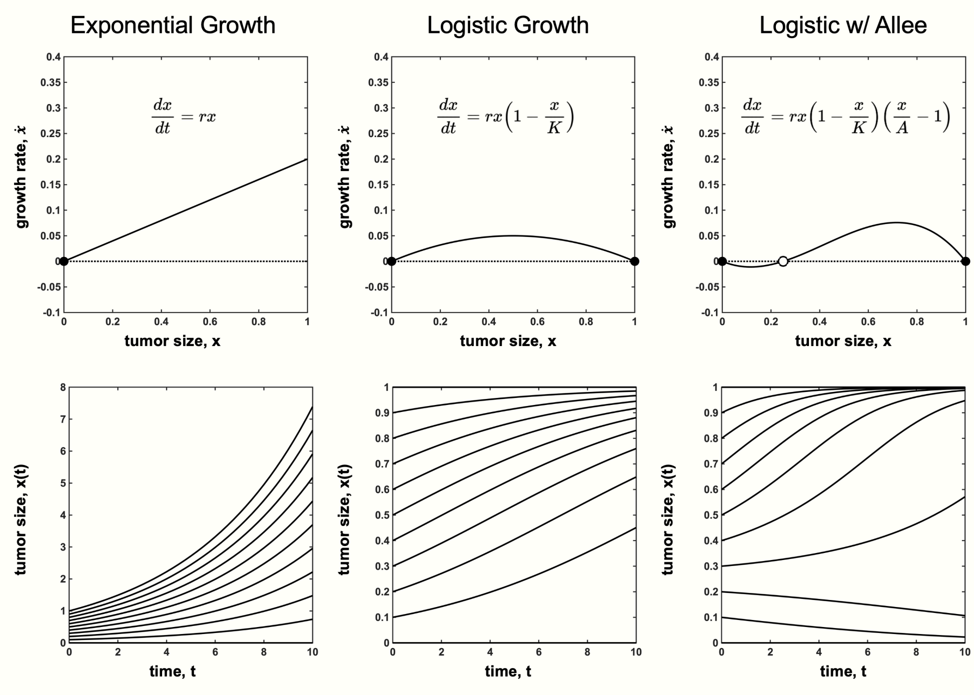

Figure 1. Simple 1-dimensional examples of state-space and trajectories

1.1 Exercise #1: plotting dynamics in state-space

A state space is the set of all possible configurations of a system. In dynamical systems, this is accomplished by plotting the growth dynamic (e.g. $\dot{x}$) for every possible state of the system (e.g. x).

Why is this important? State space representation shows what dynamics are possible in the model. Certain regions of state space are accessible only with a given initial condition. We can provide analytical (or numerical) values to quantify important boundaries. Stability theory can classify these boundaries.

1.2 Defining terms & notation

Stationary points are also referred to as "steady states" or "zeros" or "fixed points." These are defined as states (e.g. $x = x^*$) where dynamics are zero ($\dot{x} = 0$). Exponential growth has a single fixed point ($x^* = 0$), logistic growth has two fixed points ($x^* = 0, K$), logistic growth with Allee effect has three fixed points ($x^* = 0, A, K$).

Every stable point can be classified according to its type of stability (e.g. stable or unstable). Thus far, we have worked in one-dimensional system (a single variable, $x(t)$), but stability analysis theory is most useful in multiple dimensions for a system of n equations (e.g. $\mathbf{x}_n(t) = \{x_1(t), x_2(t), ..., x_n(t)\}$.

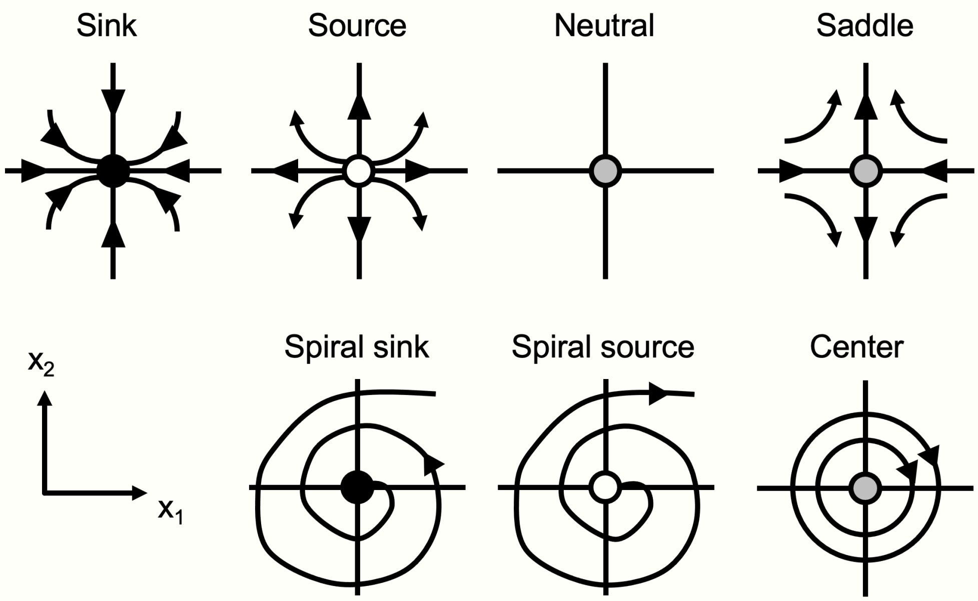

Figure 2. Examples: common types of fixed points.

There are many types of fixed points. Here are some examples:

1. Sink (stable attractor)
2. Source (unstable, repelling)
3. Neutral (neither attracting nor repelling)
4. Saddle
5. Spiral sink

6. Spiral source

7. Center

1.3 How to analyze a dynamic system

1. Find all fixed points ($\dot{x} = 0$)

2. Find the Jacobian matrix of F, $\mathbf{J}(\mathbf{x})$

3. Find Jacobian matrix eigenvalues evaluated at stationary points, $\mathbf{J}(\mathbf{x}^*)$

4. Classify stability type for each zero according to the sign of eigenvalues

2 Application question: is extinction possible?

2.1 Exercise #2

Consider the following mathematical model of treatment-sensitive cells, $x_1(t)$, and treatment-resistant cells, $x_2(t)$:

$$\dot{x}_1 = r_1\left(1 - \frac{x_1 + m_{21}x_2}{K_1}\right)(1-c)x_1 - d_1x_1 \tag{1}$$

$$\dot{x}_2 = r_2\left(1 - \frac{m_{12}x_1 + x_2}{K_2}\right)x_2 - d_2x_2 \tag{2}$$

where intrinsic growth rates are r_1, r_2, the carrying capacities are K_1, K_2, intrinsic death rates are d_1, d_2, and the death rate due to drug is c (targeting sensitive cells only). Competition coefficients m_{ij} quantify the competitive effect of cell type i on cell type j.

2.1.1 Find all fixed points

1. Tumor elimination: $\mathbf{x}^* = \{0, 0\}$

2. Fully resistant: $\mathbf{x}^* = \{0, \frac{r_2 - d_2}{r_2}K_2\}$

3. Fully sensitive: $\mathbf{x}^* = \{\frac{r_1(1-c)-d_2}{r_1(1-c)}K_1, 0\}$

4. Coexistence $\mathbf{x}^* = \left\{\frac{\delta_1 - m_{21}\delta_2}{1-m_{12}m_{21}}, \frac{\delta_2 - m_{12}\delta_1}{1-m_{12}m_{21}}\right\}$, where $\delta_1 = \frac{(r_1(1-c)-d_1)K_1}{r_1(1-c)}$ and $\delta_2 = \frac{(r_2-d_2)K_2}{r_2}$.

2.1.2 Find the Jacobian matrix

For a dynamical system (a set of equations) of the form $\dot{\vec{x}} = F(\vec{x})$, the Jacobian matrix is defined as $\mathbf{J}_{ij} = \frac{\partial \mathbf{F}_i}{\partial x_j}$.

Expanded out, the system can be written:

$$F_1 = r_1(1-c)x_1 - d_1x_1 - \frac{r_1(1-c)m_{21}}{K_1}x_1x_2 - \frac{r_1(1-c)}{K_1}x_1^2 \tag{3}$$

$$F_2 = r_2x_2 - d_2x_2 - \frac{r_2m_{12}}{K_2}x_1x_2 - \frac{r_2}{K_2}x_2^2 \tag{4}$$

The Jacobian can be written:

$$\mathbf{J}(\mathbf{x}) = \begin{bmatrix} \frac{\partial \mathbf{F}_1}{\partial \mathbf{x}_1} & \frac{\partial \mathbf{F}_1}{\partial \mathbf{x}_2} \\ \frac{\partial \mathbf{F}_2}{\partial \mathbf{x}_1} & \frac{\partial \mathbf{F}_2}{\partial \mathbf{x}_2} \end{bmatrix} = \begin{bmatrix} r_1(1-c) - d_1 - \frac{r_1(1-c)m_{21}}{K_1}x_2 - \frac{2r_1(1-c)}{K_1}x_1 & -\frac{r_1(1-c)m_{21}}{K_1}x_1 \\ -\frac{r_2m_{12}}{K_2}x_2 & r_2 - d_2 - \frac{r_2m_{12}}{K_2}x_1 - \frac{2r_2}{K_2}x_2 \end{bmatrix} \tag{5}$$

2.1.3 Classification

In order to classify the stability for each fixed point, we find the eigenvalues of the Jacobian (evaluated at each fixed point). An n-dimensional system of equations will have n eigenvalues: $\lambda_1, \lambda_2, ..., \lambda_n$. The fixedpoint at $\mathbf{x}^*$ is (a)...

1. **stable sink** if $Re(\lambda_i) < 0$
2. **semi-stable sink** if $Re(\lambda_i) \leq 0$ (i.e. at least one zero eigenvalue)
3. **neutral** if $Re(\lambda_i) = 0$
4. **unstable source** if $Re(\lambda_i) > 0$
5. **semi-source** if $Re(\lambda_i) \geq 0$ (i.e. at least one zero eigenvalue)

In Matlab, find the eigenvalues of a matrix as follows:

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[eigenvectors, eigenvalues]=eig(J)
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where J is an *nxn* Jacobian matrix, evaluated at a given fixed point.

Figure 3 shows two example parameterizations of the model, with some key observations learned via stability analysis.

3 Brief overview of other tools in dynamical systems

It will be useful to be aware of other techniques and methods that are commonly used in dynamical systems. For example:

1. Basins of attraction
2. Seperatrices (plural form of separatrix)
3. Nullclines / isoclines

To illustrate these examples, consider the Matlab tool "IsoMaTrix," which plots the dynamics of three-player game theory models using the replicator equation[1].

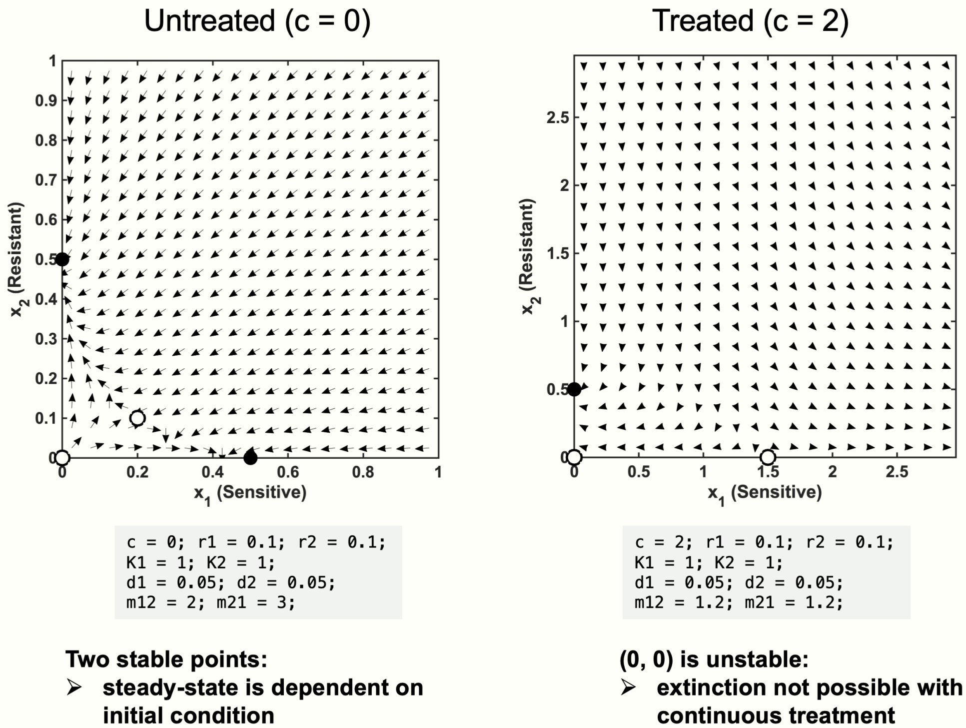

Figure 3. Example parameterizations of the competitive Lotka-Volterra model. (A) shows untreated dynamics ($c = 0$). There are two stable fixed points (solid black dots). Which stable point the tumor goes to is dependent on the initial condition. (B) shows treated dynamics. By stability analysis, we can classify the point of tumor extinction ($x_1 = x_2 = 0$) as an unstable fixed point, indicating that tumor extinction is not possible in this treatment scenario.

4 Availability of code

All the Matlab code used to generate the plots in these lecture notes can be found online[2].

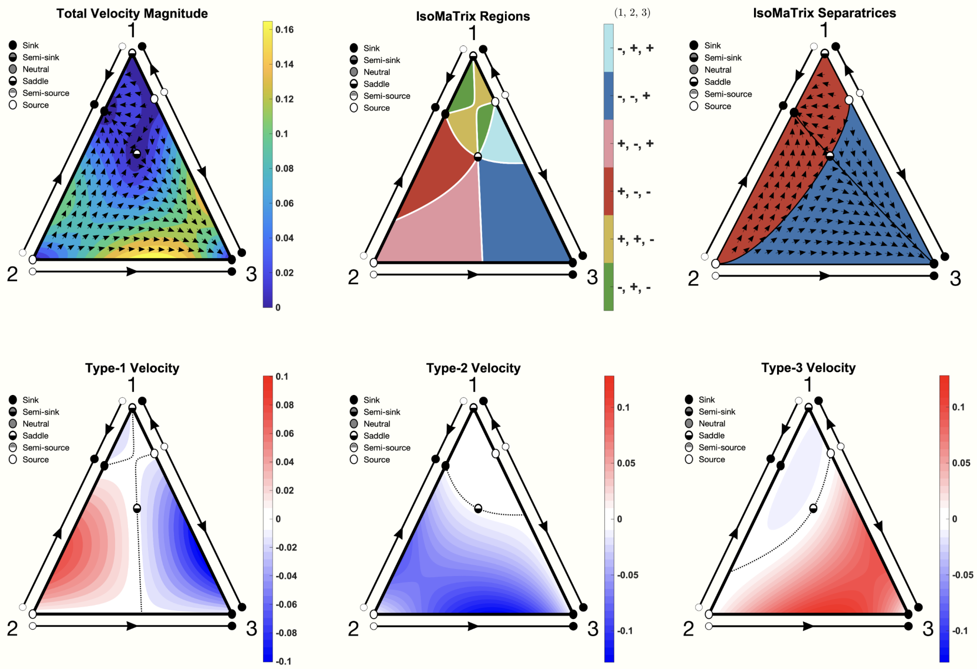

Figure 4. Example from isomatrix software package. (A) shows the dynamics using a quiver plot, with fixed points according to classification. (B) plots all nullclines (isoclines), which divide the state space into regions of positive/negative growth for each subpopulation. (C) shows the separatrices, which divide the state space into regions that lead to the same absorbing state (i.e. an attractor / sink). (D,E,F) show the subpopulation velocity ($\dot{x}_i$) with corresponding nullclines.

References

1. West, J., Ma, Y., Kaznatcheev, A. & Anderson, A. R. Isomatrix: a framework to visualize the isoclines of matrix games and quantify uncertainty in structured populations. *Bioinformatics* **36**, 5542–5544 (2020).

2. West, J. BSC-6882 and BSC-6883 lecture notes. https://github.com/jeffreywest/IMO-lecture-notes (2023).