Lecture 3

Interacting population models

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Two species of organisms can interact in a number of ways, but a broad-brush classification could be as either:

(i) competition (i.e. mutually unbeneficial)

(ii) predator-prey (one benefits by eating the other)

and in other ways such as mutualism (mutually beneficial), parasitism (one benefits, the other can be detrimentally effected), commensalism (one benefits, the other unaffected), amensalism (one unaffected, but the other is detrimentally effected) etc. All of these can be modelled and analysed using the ideas below, however, we will be focussing on competition (this Lecture) and predator-prey (next Lecture) in this module.

1 A competition model: tumour growth

Tumours are communities of mutated cells that do not respond to bodily cues as normal (non-mutated) cells; because of genetic mutation, cancer cells lack the control mechanism of *apoptosis*. Consequently, their growth is uncontrolled. However, **tumour cells** need the same resources as **normal cells** (e.g. glucose, O_2 etc.), so there is competition, and are targets for immune cells that seek to destroy tumour cells (not always effectively).

Question: how strong must the immune response be to destroy the tumour?

Definition: Let R be the rate of change of a population of size X, then the *per capita* rate of change of population is R/X.

Model assumptions:

1. Two cell types:
   - $N(t)$: population density of normal (non-mutant) cells;
   - $M(t)$: population density of tumor (mutant) cells.
2. Both cell types grow at an identical, constant *per capita* growth rate b.
3. Both cell types die due to crowding at an equal *per capita* rate $\propto$ total density $= N + M$.
4. Normal cells die naturally (called apoptosis) at a constant *per capita* rate d.
5. Tumour cells are killed by immune cells (assumed constant in density) at a constant *per capita* rate δ.

Applying these assumptions, we obtain the model

$$\frac{dN}{dt} = bN - cN(N+M) - dN = rN\left(1 - \frac{N+M}{K}\right) \tag{1}$$

$$\frac{dM}{dt} = bM - cM(N+M) - \delta M = rM\left(\phi - \frac{N+M}{K}\right) \tag{2}$$

where $r = b - d > 0$ (assumed positive, otherwise both cells will die out), $K = (b-d)/c$ and

$$\phi = \frac{b-\delta}{b-d},$$

which is a dimensionless parameter. In Eq. (1), the term bN stems from assumption 2 above, the term $cN(N+M)$ from assumption 3, and dN from assumption 4. In Eq. (2), the term bM stems from assumption 2, the term $cN(N+M)$ from assumption 3, and δM from assumption 5. We note that this model does not consider new mutations that could positively contribute to $\frac{dM}{dt}$.
To close the system we impose initial conditions $N(0) = N_0$ and $M(0) = M_0$ (they will play a big part in the analysis below).
We first non-dimensionalise the ODE system, via the 3-step process, using

$$N = K\hat{N}, \quad M = K\hat{M}, \quad t = \frac{\hat{t}}{r} \tag{3}$$

and on dropping the hats for clarity, we get the non-dimensional form of the system

$$\frac{dN}{dt} = N(1-N-M) = f(N,M) \tag{4}$$

$$\frac{dM}{dt} = M(\phi - N - M) = g(N,M), \tag{5}$$

which has the just one parameter ϕ (+2 initial conditions).

Big Note 3.1A: The parameter ϕ is key to this topic's question. Given the definition of ϕ above and assuming b and d are fixed, we can deduce that

$$\text{increasing } \phi \Rightarrow \text{weakening the immune response}$$

We cannot solve the ODE system analytically for general ϕ so, as with the budworm model, we instead analyse the steady-states to better understand the solutions as $t \to \infty$.

1.1 Steady-state analysis

To find all of the steady-states $N = N^*$ and $M = M^*$ that satisfies $f(N^*, M^*) = 0$ and $g(N^*, M^*) = 0$ it is best to be systematic. We will

(1) Find all the possibilities of $f(N^*, M^*) = 0$.
(2) For each possibility in (1), work out when they satisfy $g(N^*, M^*) = 0$.

Here, we want (N^*, M^*) satisfying

$$\begin{aligned} f(N^*, M^*) &= N^*(1 - N^* - M^*) = 0 \\ g(N^*, M^*) &= M^*(\phi - N^* - M^*) = 0 \end{aligned}$$

hence,

(1) $f(N^*, M^*) = 0 \implies$ (i) $N^* = 0$
(ii) $1 - N^* - M^* = 0 \quad \Rightarrow \quad M^* = 1 - N^*$
(2) Now to solve $g(N^*, M^*) = 0$ we need to consider cases (i) and (ii) separately

$$\text{Case } (i)\text{: } N^* = 0 \quad \Rightarrow \quad g(N^*, M^*) = 0 \quad \Rightarrow \quad M^*(\phi - M^*) = 0$$

$$\Rightarrow \quad M^* = 0,\, \phi$$

$$\text{hence } (N^*, M^*) = (0,0)\,,\ (0,\phi)$$

(although ϕ can be negative, ϕ should be positive in order for this steady state to be biologically relevant).

$$\text{Case } (ii)\text{: } M^* = 1 - N^* \quad \Rightarrow \quad g(N^*, 1-N^*) = 0$$

$$\Rightarrow \quad (1-N^*)(\phi - N^* - (1-N^*)) = 0$$
$$\Rightarrow \quad (1-N^*)(\phi - 1) = 0$$
$$\Rightarrow \quad N^* = 1\,, \quad \text{when} \quad \phi \neq 1$$

$$\text{hence } (N^*, M^*) = (1,0), \text{ provided that } \phi \neq 1$$

At this stage we should note that the case $\phi = 1$ will be significant. See below.
In the remainder of the module, steady-state values will just be stated without going through the above routine analysis.

In summary: the steady-states of the model and their interpretation are:

- $(0,0)$ $\Rightarrow$ both cell types are extinct (bad!)
- $(1,0)$ $\Rightarrow$ only normal cells are present (good!)
- $(0,\phi)$ $\Rightarrow$ only tumor cells are present ($\phi > 0$) (bad!)

Big Note 3.1B: From the above analysis it is clear that $\phi = 0$ is significant, as it marks the boundary between the biological relevance of the tumor-only steady-state. Furthermore, at $\phi = 1$ there are a family of steady-states lying on the line $N^* + M^* = 1$. Assuming the model is a good description of the interaction between tumour and normal cells, it is extremely unlikely that ϕ will be exactly one of these values, so we will consider separately the three cases such that ϕ lies either side of them, namely

Case 1) $\phi > 1$, (all 3 steady states are biologically relevant)

Case 2) $0 < \phi < 1$, (all 3 steady states are biologically relevant)

Case 3) $\phi < 0$, (only $(0,0)$, $(1,0)$ are biologically relevant)

Very Big Note 3.1C: As with single (scalar) ODE models, the most relevant state will (most often) be the stable steady-states that (N, M) will tend to as $t \to \infty$.

We will now proceed with the two-dimensional version of phase-line analysis to establish the stability of the steady-states.

1.2 Phase-plane analysis

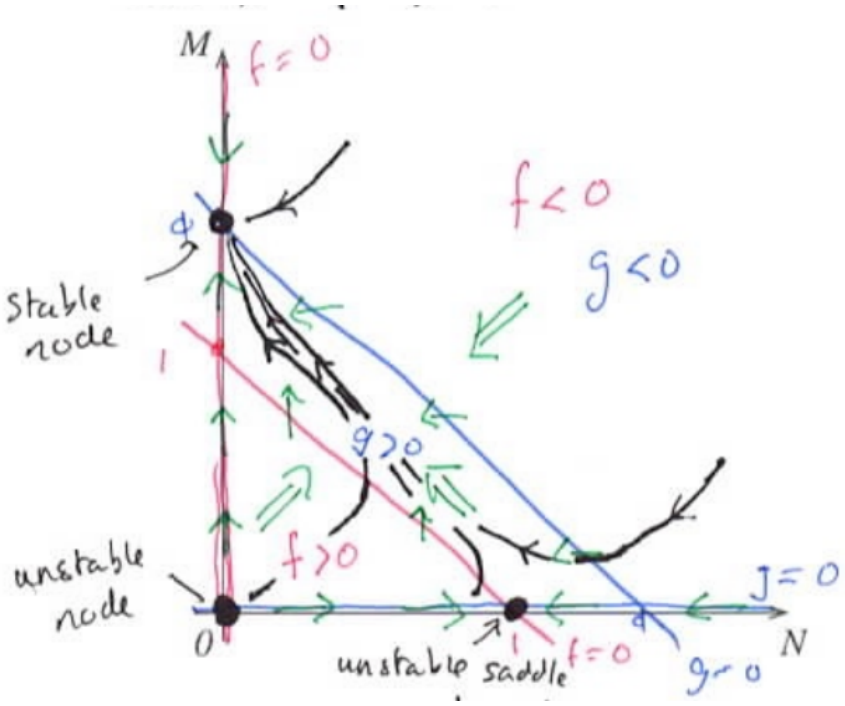
As with a phase-line diagram, a deep understanding of a 2 ODE model solutions can be deduced quickly (with practice) using phase-plane diagrams. These include qualitatively predicting what the solutions $(N(t), M(t))$ of the ODE system look like and, in particular, establish where the solutions go as $t \to \infty$ by identifying the which steady-states are stable and unstable. (**See Appendix in Lecture 2**).

Using the ideas from the Appendix in Lecture 2, the nullclines satisfying $f(N, M) = 0$ and $g(N, M) = 0$ are

- $f(N, M) = 0 \quad \Rightarrow \quad N(1 - N - M) = 0 \quad \Rightarrow$
  1. $N = 0$
  2. $1 - N - M = 0 \quad \Rightarrow \quad M = 1 - N$
- $g(N, M) = 0 \quad \Rightarrow \quad M(\phi - N - M) = 0 \quad \Rightarrow$
  1. $M = 0$
  2. $\phi - N - M = 0 \quad \Rightarrow \quad M = \phi - N$

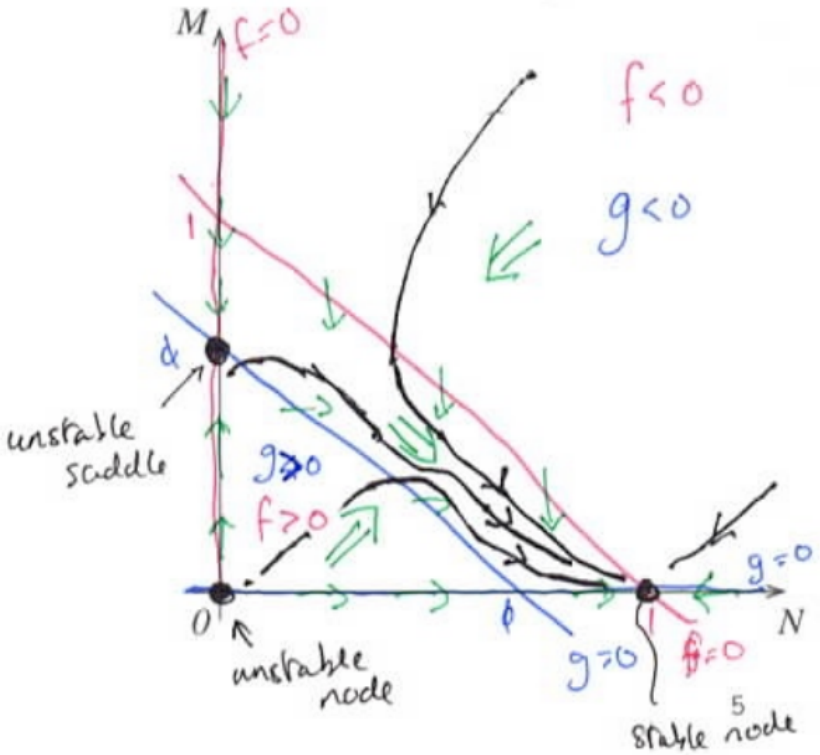
We consider the 3 cases identified in **Big Note 3.1B** in turn.

Case 1) $\phi > 1$



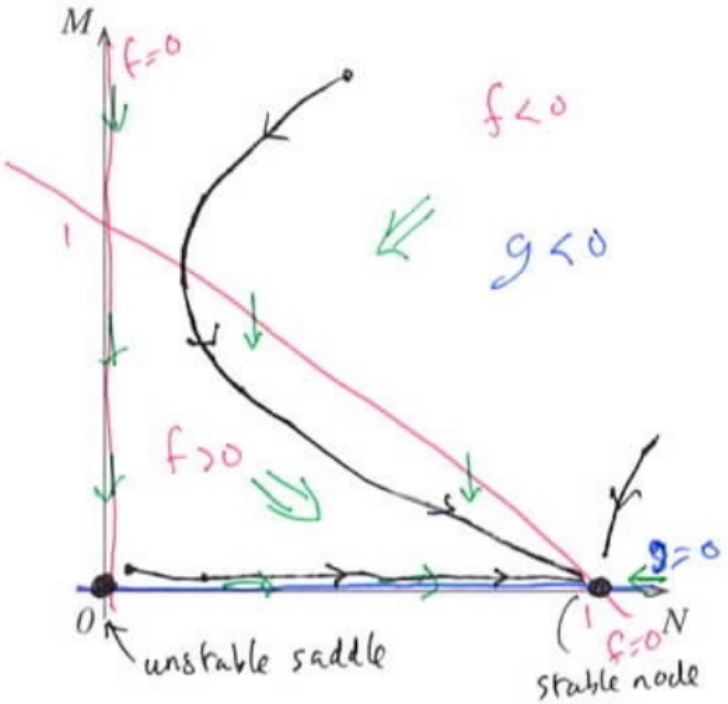
$(N, M) \to (0, \phi)$ from all initial conditions, in the $N > 0$, $M > 0$ quadrant. $(0, \phi)$ is stable (bad!) whereas $(0, 0)$ and $(1, 0)$ are unstable.

Case 2) $0 < \phi < 1$



The steady state $(1, 0)$ is stable, whereas $(0, 0)$ and $(0, \phi)$ are unstable. We expect $(N, M) \to (1, 0)$ at $t \to \infty$, that means that the *tumor dies out* (good!).

Case 3) $\phi < 0$

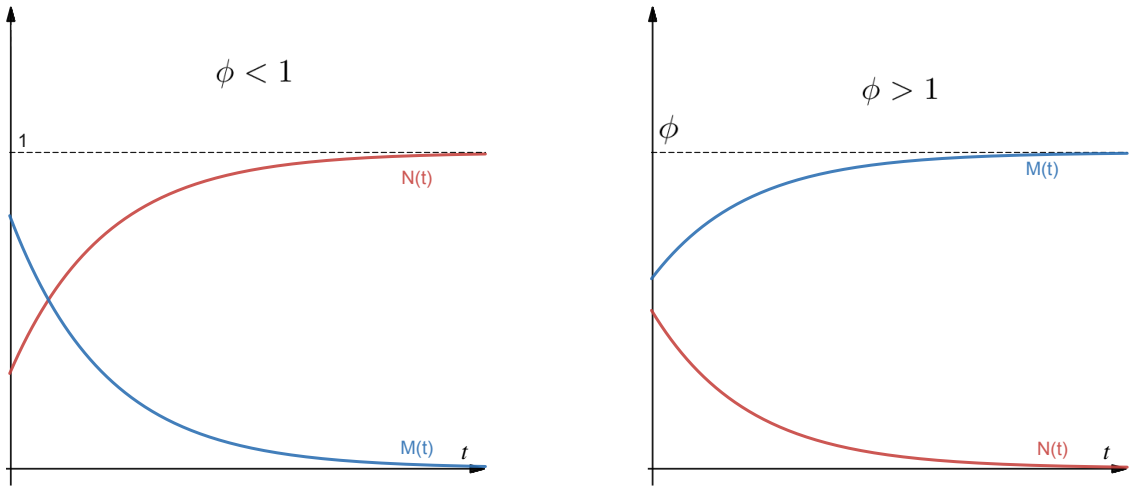


The steady state $(1,0)$ is stable, whereas $(0,0)$ is unstable. We expect $(N,M) \to (1,0)$ at $t \to \infty$, that means the tumor dies out, and normal cells persist (good!).

See Appendix A.1

The upshot: Recall the original question is "how strong must the immune system be to destroy the tumour", from the phase-plane analysis we can deduce

- $\phi < 1 \Rightarrow$ tumor dies out. Recall that $\phi \equiv \dfrac{b-\delta}{b-d}$; so $\phi < 1 \quad \Rightarrow \quad b - \delta < b - d$ that is $\Rightarrow \ \delta > d$, i.e. immune cells' kill rate $>$ natural death rate of cells, for the tumor to die out.
- Obviously a strong immune response will destroy a tumor, but the analysis here provides a simple estimate of "how strong" in comparison to a "known" parameter d.
- The time evolution of N and M for $\phi < 1$ and $\phi > 1$ will look something like



- All of the above, including step-by-step construction of phase-planes is demonstrated in **Maple file 2.1**.

Appendix

A Linear stability analysis of two ODEs: Part 1

Note: You will not be required to derive the theory in the exam, but proficiency in its application is expected. You will be expected to understand Big Note A2 (page 9).

A.1 Linear stability analysis of two coupled ODEs

Suppose

$$\frac{dN}{dt} = f(N,M), \tag{6}$$

$$\frac{dM}{dt} = g(N,M), \tag{7}$$

and let N^* and M^* be steady-states, so $f(N^*,M^*)=0$ and $g(N^*,M^*)=0$. As with the single ODE models (see Lecture 1 Appendix A.3), we investigate the **linear stability** of the steady-state by considering a small perturbation about them of the form

$$N(t) = N^* + n(t), \qquad M(t) = M^* + m(t),$$

where $|n(t)| \ll 1$ and $|m(t)| \ll 1$. On substitution into (6) we get

$$\begin{aligned} \frac{dN}{dt} = \frac{d(N^*+n)}{dt} = \frac{dn}{dt} &= f(N,M) = f(N^*+n, M^*+m) \\ &= f(N^*,M^*) + n\frac{\partial f}{\partial N}(N^*,M^*) + m\frac{\partial f}{\partial M}(N^*,M^*) + \text{h.o.t.} \\ \therefore \quad \frac{dn}{dt} &\approx n\,\frac{\partial f}{\partial N}(N^*,M^*) + m\,\frac{\partial f}{\partial M}(N^*,M^*) \end{aligned} \tag{8}$$

using a 2 variable Taylor's expansion on $f(N,M)$ (h.o.t.= higher-order terms), the expansion was then linearised and $f(N^*,M^*)=0$ was imposed to get the final line. Likewise, from (7),

$$\frac{dm}{dt} \approx n\,\frac{\partial g}{\partial N}(N^*,M^*) + m\,\frac{\partial g}{\partial M}(N^*,M^*). \tag{9}$$

We can write the (8) and (9) in a tidier form

$$\frac{d}{dt}\begin{pmatrix} n \\ m \end{pmatrix} = \boldsymbol{A}\begin{pmatrix} n \\ m \end{pmatrix} \tag{10}$$

where the constant matrix $\boldsymbol{A}$ is the Jacobian of $f(N,M)$ and $g(N,M)$ at (N^*,M^*) and in the context of stability analysis it is call the **stability matrix**, the definition being

$$\boldsymbol{A} = \begin{pmatrix} \dfrac{\partial f}{\partial N} & \dfrac{\partial f}{\partial M} \\ \dfrac{\partial g}{\partial N} & \dfrac{\partial g}{\partial M} \end{pmatrix}_{(N^*,M^*)}. \tag{11}$$

Equation (10) is a linear system of 2 ODEs with constant coefficients. (*It is the 2 equation equivalent to "$\frac{dn}{dt} = f'(N^*)\,n$" in the single ODE case (see Lecture 1 Appendix)*).

A.2 Eigenvalue solutions of linear ODE systems

As with **all** *homogeneous, linear ODEs with constant coefficients* the solutions are exponential. We therefore seek solutions of the form

$$n \;=\; n_0\, e^{\lambda t}, \qquad m = m_0\, e^{\lambda t}$$

where n_0 and m_0 are constants (*at least one being non-zero*), gives on substitution into (10),

$$\text{Left-hand side:} \qquad \frac{d}{dt}\begin{pmatrix} n_0\, e^{\lambda t} \\ m_0\, e^{\lambda t} \end{pmatrix} = \begin{pmatrix} \dfrac{d\, n_0\, e^{\lambda t}}{dt} \\ \dfrac{d\, m_0\, e^{\lambda t}}{dt} \end{pmatrix} = \begin{pmatrix} n_0\, \lambda\, e^{\lambda t} \\ m_0\, \lambda\, e^{\lambda t} \end{pmatrix} = \lambda \begin{pmatrix} n_0 \\ m_0 \end{pmatrix} e^{\lambda t},$$

$$\text{Right-hand side:} \qquad \boldsymbol{A}\begin{pmatrix} n_0\, e^{\lambda t} \\ m_0\, e^{\lambda t} \end{pmatrix} \;=\; \boldsymbol{A}\begin{pmatrix} n_0 \\ m_0 \end{pmatrix} e^{\lambda t}.$$

Combining these, and dividing through by $e^{\lambda t}$, yields

$$\lambda \begin{pmatrix} n_0 \\ m_0 \end{pmatrix} = \boldsymbol{A}\begin{pmatrix} n_0 \\ m_0 \end{pmatrix} \Rightarrow \boldsymbol{A}\begin{pmatrix} n_0 \\ m_0 \end{pmatrix} - \lambda \begin{pmatrix} n_0 \\ m_0 \end{pmatrix} = \mathbf{0} \quad \Longrightarrow \quad (\boldsymbol{A} - \boldsymbol{\lambda}\, \boldsymbol{I}) \begin{pmatrix} \boldsymbol{n_0} \\ \boldsymbol{m_0} \end{pmatrix} \;=\; \mathbf{0},$$

where $\boldsymbol{I} = \begin{pmatrix} 1 & 0 \\ 0 & 1 \end{pmatrix}$. Hence, by definition

- $\boldsymbol{\lambda}$ is the **eigenvalue** of the stability matrix $\boldsymbol{A}$.
- $\begin{pmatrix} n_0 \\ m_0 \end{pmatrix}$ is the **eigenvector** corresponding to each eigenvalue of $\boldsymbol{A}$.

So by the routine process of finding *both* eigenvalues of the 2×2 stability matrix $\boldsymbol{A}$ (solving $\det(\boldsymbol{A} - \lambda \boldsymbol{I}) = 0$ etc), the exponents of the exponential solutions of (10) and (11) can be found.

A.3 The Upshot

The signs of the two eigenvalues informs us of the stability of the steady-states:

1. If **BOTH eigenvalues have NEGATIVE real parts** $\Rightarrow (N^*, M^*)$ is **stable**.
   (both exponential solutions of the perturbations $n(t), m(t)$ will vanish as $t \to \infty$).
2. If **at least ONE eigenvalue has a POSITIVE real part** $\Rightarrow (N^*, M^*)$ is **unstable**.
   (a perturbation(s) will grow, so the solution moves away from the steady-state).
3. If **at least ONE eigenvalue is 0 and the other non-positive** $\Rightarrow$ need more information.
   (either consider the "h.o.t."s or use phase-plane analysis).

What the eigenvalues say about the type of steady-state (node, focus, saddle point etc.) is summarised in Fig 1. The significance of the eigenvectors is also shown, but will not be discussed further in this module.

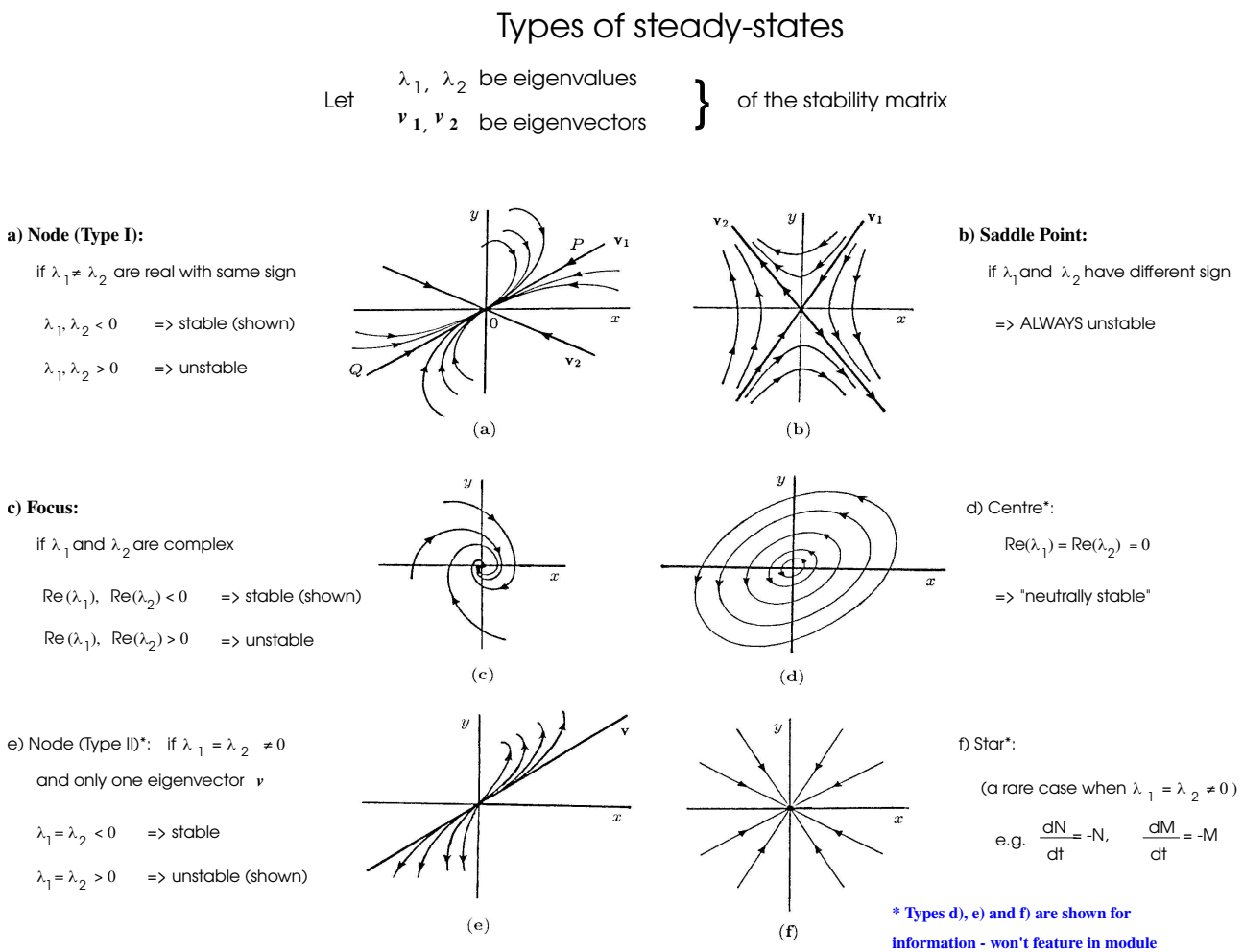


Figure 1: Types of steady states in two dimensions.

Big Note A1: Phase-planes vs. linear stability analysis

- **Phase-plane analysis:** is good for establishing "global behaviour" of solutions, i.e. qualitatively how the solution evolves from any starting point. Stability and type of steady-states can often be identified. However, it is less applicable when there are 3+ differential equations.
- **Linear stability analysis:** is good for establishing "local behaviour" of solutions in the vicinity of a steady-state. Tells you nothing about how the solutions evolve starting far from a steady-state. Stability and type of steady-states can often be identified. Its main advantage is that the ideas extend easily to problems involving 3+ differential equations.

Big Note A2: Solution evolution near steady-states

The eigenvalue analysis tells us that **the predominant behaviour of the solutions** of equations (6) and (7), **local to the steady state (N^*, M^*), are**

$$\begin{pmatrix} N \\ M \end{pmatrix} \sim \begin{pmatrix} N^* \\ M^* \end{pmatrix} + A_1 \begin{pmatrix} n_1 \\ m_1 \end{pmatrix} e^{\lambda_1 t} + A_2 \begin{pmatrix} n_2 \\ m_2 \end{pmatrix} e^{\lambda_2 t}, \tag{12}$$

where (n_1, m_1) and (n_2, m_2) are the eigenvectors associated with eigenvalues λ_1 and λ_2, respectively, and A_1 and A_2 are constants of integration that can be calculated from the initial condition $(N(0), M(0)) = (N_0, M_0)$.

[To determine A_1 and A_2 we substitute $t = 0$ into (12) and impose $(N(0), M(0)) = (N_0, M_0)$ to get the simultaneous linear equations,

$$\begin{pmatrix} N_0 \\ M_0 \end{pmatrix} \sim \begin{pmatrix} N^* \\ M^* \end{pmatrix} + A_1 \begin{pmatrix} n_1 \\ m_1 \end{pmatrix} + A_2 \begin{pmatrix} n_2 \\ m_2 \end{pmatrix}.$$

Typically, we choose the eigenvectors to be of unit length (with no loss to generality), so that the the above analysis requires $|A_1| \ll 1$ and $|A_2| \ll 1$.]

Note A3: Validity of linearised solutions near steady-states

Assuming the eigenvectors are of unit length then

- if (N^*, M^*) is a stable steady-state, then the approximation (12) will be reasonable $\forall\, t > 0$.
- if (N^*, M^*) is unstable then the approximation will eventually become poor; usually on a timescale $t = O\left(\frac{1}{\lambda_1} \ln(\frac{1}{|A_1|})\right)$ and/or $t = O\left(\frac{1}{\lambda_2} \ln(\frac{1}{|A_2|})\right)$.

A.4 * Link between eigenvalues and complementary functions

(The * is to indicate that this section is *for information only*).

- Consider the linear system of coupled ODEs

$$\frac{du}{dt} \;=\; a\,u \;+\; b\,v, \qquad \frac{dv}{dt} \;=\; c\,u \;+\; d\,v, \tag{13}$$

then the stability matrix $\boldsymbol{A}$ is

$$\boldsymbol{A} \;=\; \begin{pmatrix} a & b \\ c & d \end{pmatrix}, \tag{14}$$

which has eigenvalues satisfying the following characteristic polynomial

$$\lambda^2 \;-\; (a+d)\,\lambda \;+\; (ad-bc) \;=\; 0, \tag{15}$$

the solutions λ being the exponents of the exponential solutions of (13).

- From the first equation of (13) we get, provided $b \neq 0$,

$$v \;=\; \frac{1}{b}\left(\frac{du}{dt} - au\right),$$

which on substitution into the second gives

$$\frac{1}{b}\frac{d}{dt}\left(\frac{du}{dt} - au\right) \;=\; cu \;+\; \frac{d}{b}\left(\frac{du}{dt} - au\right)$$

$$\Rightarrow \qquad \frac{d^2u}{dt^2} \;-\; (a+d)\,\frac{du}{dt} \;+\; (ad-bc)\,u \;=\; 0, \tag{16}$$

which is a homogeneous, linear 2nd-order ODE with constant coefficients. (*In fact, any system of n linear, 1st-order ODEs can be rewritten as a single nth-order linear ODE*).

Looking for the complementary function $u_c(t)$, we write $u(t) = u_c(t) = e^{\sigma t}$, which on substitution into (16) yields

$$\sigma^2 \;-\; (a+d)\,\sigma \;+\; (ad-bc) \;=\; 0. \tag{17}$$

The conclusion: The exponents λ via the eigenvalue analysis and σ via the complementary function method are solutions to identical quadratic Eq. (15) and (17), and hence have the same values. The two methods for solving linear ODE systems are entirely equivalent.