BIOMICS

Modelling the Dynamical Stability of Tyson et al.'s Case 2a

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SEVENTH FRAMEWORK PROGRAMME

Overview

- Definition of dynamical systems and stability
- Lyapunov exponents and state transition matrix
- Stability of Case 2a and other examples
- Effective potential and Lyapunov function

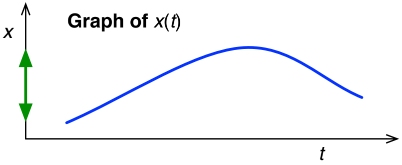
Single Ordinary Differential Equation

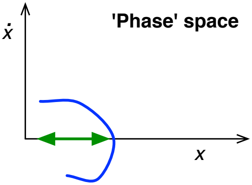
- A single 1st-order ordinary differential equation (ODE) can be written as

$$\frac{dx}{dt} = f(x) \qquad \text{or} \qquad \dot{x} = f(x). \tag{1}$$

- For simplicity we assume autonomous ODEs only, so $f : I \to \mathbb{R}$ is a smooth function defined on some subset $I \subseteq \mathbb{R}$ and does not depend on time.

- The solution is a function $x(t) \colon \mathbb{R} \to \mathbb{R}$





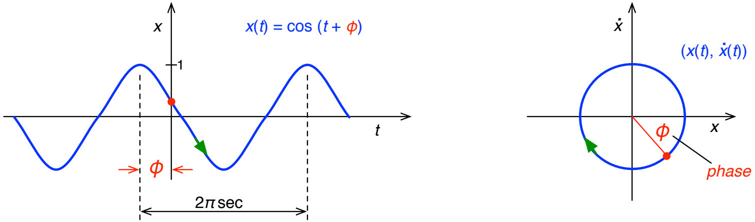
(Note: Zoltán Muzsnay pointed out that the phase curve on the right is not actually a $f(x)$, so this example should be improved.)

Phase Space

- The concept of phase space probably originated from 2nd-order ODEs, and in particular from the simple harmonic oscillator (SHO)

$$\frac{d^2x}{dt^2} + x = 0 \qquad \text{or} \qquad \ddot{x} + x = 0. \tag{2}$$

- The solution is a function $x(t)\colon \mathbb{R} \to \mathbb{R}$



- We can express the original 2nd-order ODE as 2 1st-order ODEs:

$$\text{Letting } u = x, \qquad \dot{u} = v \tag{3}$$

$$\dot{v} = -u \tag{4}$$

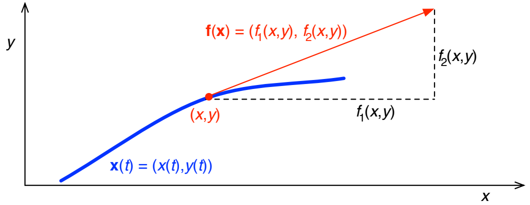
Dynamical Systems and Flows[1]

- More generally, let's define a dynamical system as a set of ODEs

$$\dot{\mathbf{x}} = \mathbf{f}(\mathbf{x}), \quad \text{with} \quad \mathbf{x}(0) = \mathbf{x}_0, \tag{5}$$

where $\mathbf{x}(t) \in \mathbb{R}^n$ is a vector-valued function of time, $\mathbf{f}: U \to \mathbb{R}^n$ is a smooth function defined on some subset $U \subseteq \mathbb{R}^n$, and boldface indicates vector character.

- $\mathbf{f}$ defines a vector field that is everywhere tangent to the solution curves of the ODE when plotted in phase space. E.g., in 2-D:



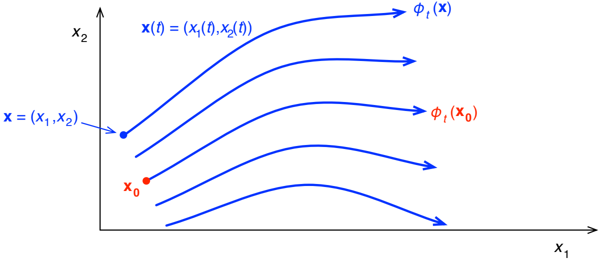
- Thus, the solution vector $\mathbf{x}(t)$ can also be seen as **a map of phase space to itself** – but there is a better notation for that.

[1] Guckenheimer and Holmes, 1983

• We say that the vector field $\mathbf{f}$ generates a *flow* as a vector-valued function $\varphi_t : U \to \mathbb{R}^n$: (note: '$\varphi$' is supposed to be **bold**)

$$\varphi_t(\mathbf{x}) = \varphi(\mathbf{x}, t), \qquad \forall \mathbf{x} \in U \quad \text{and} \quad t \in I = (a, b) \subseteq \mathbb{R}. \qquad (6)$$

The notation $\varphi_t(\mathbf{x})$ refers to a fixed starting point $\mathbf{x} = (x_1, x_2)$:



• The flow solves the original ODE system in the sense that

$$\frac{d}{dt}(\varphi(\mathbf{x}, t))|_\tau = \mathbf{f}(\varphi(\mathbf{x}, \tau)) \qquad \forall \mathbf{x} \in U \quad \text{and} \quad \forall \tau \in I \qquad (7)$$

• For a given initial condition $\mathbf{x}(0) = \mathbf{x}_0 \in U$, we seek a solution such that $\varphi(\mathbf{x}_0, 0) = \varphi_0(\mathbf{x}_0) = \mathbf{x}_0$

Solution Flows = Lie Groups

- Solution flows satisfy the properties of Lie groups:

$$\varphi_0 = id \qquad \varphi_{t+s} = \varphi_t \circ \varphi_s$$

$$\varphi_{t+s} \circ \varphi_r = \varphi_t \circ \varphi_{s+r} \qquad \varphi_t \circ \varphi_{-t} = id$$

- In fact, the solution flow of a system of ODEs can be seen as a 1-parameter Lie group where the parameter is time.

- More generally, a Lie group or Lie symmetry is obtained by integrating its tangent vector field, which is called its *infinitesimal generator*.

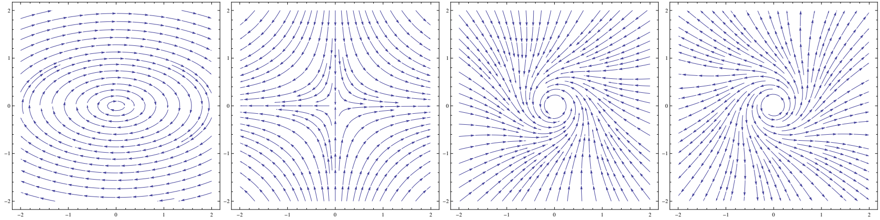
- Although a Lie symmetry is a finite transformation, we tend to call its infinitesimal generator vector field a 'Lie symmetry' as well.

- When the infinitesimal generator is everywhere parallel to $\mathbf{f}(\mathbf{x})$, we call it a 'trivial symmetry'.

Fixed Points, Stability, and Bifurcations

- Points in a solution flow where $\mathbf{f}(\mathbf{x})$ vanishes are called 'fixed points'.

- Fixed points can have different stability properties:



- When the number or character of the fixed points in a solution flow changes – usually in response to a change in a parameter that appears in the ODEs – we say that the system has undergone a *bifurcation*.

- Thus, a bifurcation is a change in the topology of phase space.

Dynamical Stability

- Hopf bifurcation: fixed point becomes a limit cycle
- Grossly oversimplifying, chaos occurs after 3 Hopf bifurcations:

fixed point	$\rightarrow$	limit cycle	$\rightarrow$	flow on torus	$\rightarrow$	chaos
0 *freq*	$\rightarrow$	1 *freq*	$\rightarrow$	2 *freqs*	$\rightarrow$	3^+ *freqs*
		(Case 2a)				

- BIOMICS **assumes** that:
  - systems in the $1f$-$3f$ range can exhibit dynamical stability
  - such systems can be coupled to each other to achieve more complex behaviour
  - their discrete equivalents can give rise to interesting ("self-organizing") computational behaviour
- Problem: still lacking a precise definition of dynamical stability
- Next steps: Lyapunov exponent & Lyapunov function

Lyapunov Exponents and Linear Stability

- Given the simple scalar ODE $\dot{u} = au$, the solution is

$$u(t) = u_0 e^{\lambda t} \qquad \text{so that} \qquad \lambda = \frac{1}{t} \log \left[\frac{u(t)}{u_0} \right].$$

Lyapunov exponents are a generalization of this idea.

- As a starting point, let's look at the linear stability of $\dot{\mathbf{x}} = \mathbf{f}(\mathbf{x})$. In particular, let's define linear stability in terms of sensitive dependence on initial conditions.

- We denote the distance at time t between adjacent trajectories that started a small distance $\Delta \mathbf{x}_0$ apart at $t = 0$ by

$$\varphi_t(\mathbf{x}_0 + \Delta \mathbf{x}_0) - \varphi_t(\mathbf{x}_0) = \Delta \varphi_t(\mathbf{x}_0). \tag{8}$$

- We wish to see how this distance depends on variations in $\Delta \mathbf{x}_0$, assuming a linear process.

• In other words, we want to calculate the **derivative** of the distance between the two trajectories at time t with respect to variations in the initial vector $\Delta\mathbf{x}_0$:

$$\lim_{\Delta\mathbf{x}_0 \to 0} \frac{\varphi_t(\mathbf{x}_0 + \Delta\mathbf{x}_0) - \varphi_t(\mathbf{x}_0)}{\Delta\mathbf{x}_0} = \frac{D\varphi_t(\mathbf{x}_0)}{D\mathbf{x}_0} = J_{\mathbf{x}_0}(\varphi_t(\mathbf{x}_0)) \quad (9)$$

The derivative of a vector w.r.t. a vector is a matrix, usually called the Jacobian.

• The distance at time t, therefore, is $\Delta\mathbf{x}_t = J_{\mathbf{x}_0}(\varphi_t(\mathbf{x}_0))\Delta\mathbf{x}_0$

• According to a theorem in ergodic theory (Oseledec, 1968), the largest Lyapunov exponent is given by:[2]

$$\lambda_{max} = \lim_{t\to\infty} \frac{1}{t} \log \frac{\|\Delta\mathbf{x}_t\|}{\|\Delta\mathbf{x}_0\|} = \lim_{t\to\infty} \frac{1}{t} \log \|J_{\mathbf{x}_0}(\varphi_t(\mathbf{x}_0))\Delta\mathbf{x}_0\|, \quad (10)$$

(Note: Zoltán Halasi pointed out that $\Delta\mathbf{x}_0/t \to 0$ as $t \to \infty$.)

[2] Sandri, M (1996). Numerical Calculation of Lyapunov Exponents, *The Mathematica Journal*.

State Transition Matrix

• In control theory $J_{\mathbf{x}_0}(\varphi_t(\mathbf{x}_0))$ is also called the state transition matrix since when multiplied by the initial state vector it gives the current state vector.

• If the solution flow vector field on the RHS of $\dot{\mathbf{x}} = \mathbf{f}(\mathbf{x})$ were a constant matrix times the solution vector, then $J_{\mathbf{x}_0}(\varphi_t(\mathbf{x}_0))$ would be the familiar matrix exponential.

Proof: Let A be a constant $n \times n$ matrix and U an $n \times n$ matrix of unknown functions $\mathbb{R} \to \mathbb{R}$. Then the matrix ODE

$$\dot{U} = AU, \text{ with } U(0) = I, \text{ has solution } U(t) = e^{At}. \tag{11}$$

If $U(0) = B$, the solution is $U(t) = e^{At}B$. Since to each column of U there corresponds a system $\dot{\mathbf{u}} = A\mathbf{u}$, with $\mathbf{u}(0) = \mathbf{b}$ (a column of B), each of the n solution vectors is $\mathbf{u}(t) = e^{At}\mathbf{b}$.
But e^{At} here is acting as a state transition matrix! $\square$

Variational Equation for $J_{\mathbf{x}_0}(\varphi_t(\mathbf{x}_0))$

- In the general case, the solution vector field may depend in complex ways on the components of the solution vector, implying that the coefficient matrix is a function of time. Given

$$\dot{\mathbf{x}} = \mathbf{f}(\mathbf{x}), \quad \text{with} \quad \mathbf{x}(0) = \mathbf{x}_0, \tag{12}$$

call its solution $\varphi_t(\mathbf{x}_0)$, such that, as we have already seen,

$$\dot{\varphi}_t(\mathbf{x}_0) = \mathbf{f}(\varphi_t(\mathbf{x}_0)), \quad \text{with} \quad \varphi_{t_0}(\mathbf{x}_0) = \mathbf{x}_0. \tag{13}$$

Now take the derivative of both sides w.r.t. $\mathbf{x}_0$, to get (chain rule!)

$$\dot{J}_{\mathbf{x}_0}(\varphi_t(\mathbf{x}_0)) = J_{\mathbf{x}}(\mathbf{f}(\varphi_t(\mathbf{x}_0))) \cdot J_{\mathbf{x}_0}(\varphi_t(\mathbf{x}_0)). \tag{14}$$

Note that $J_{\mathbf{x}_0}(\varphi_{t_0}(\mathbf{x}_0)) = I$. Letting $J_{\mathbf{x}_0}(\varphi_t(\mathbf{x}_0)) = \Phi_t(\mathbf{x}_0)$, a matrix-valued function of t, we finally get

$$\boxed{\dot{\Phi}_t(\mathbf{x}_0) = J_{\mathbf{x}}(\mathbf{f}(\varphi_t(\mathbf{x}_0)))\Phi_t(\mathbf{x}_0), \quad \text{with} \quad \Phi_{t_0}(\mathbf{x}_0) = I.} \tag{15}$$

Numerical Solution

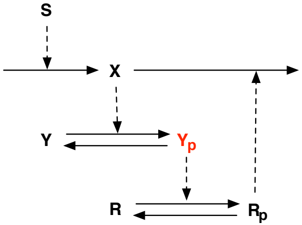
• Note that the *functional form* of each entry in the matrix $J_{\mathbf{x}}(\mathbf{f}(\mathbf{x}))$ is easy to calculate since we know the vector field $\mathbf{f}(\mathbf{x})$ explicitly.

• On the other hand, the *numerical value* of each entry in $J_{\mathbf{x}}(\mathbf{f}(\varphi_t(\mathbf{x}_0)))$ requires knowledge of the solution flow.

• For non-linear problems that we can't solve analytically (e.g. by Lie groups) this means that the variational matrix ODE needs to be solved by numerical integration **simultaneously** with the system being analysed:

$$\begin{bmatrix} \dot{\mathbf{x}} \\ \dot{\Phi}_t(\mathbf{x}_0) \end{bmatrix} = \begin{bmatrix} \mathbf{f}(\mathbf{x}) \\ J_{\mathbf{x}}(\mathbf{f}(\varphi_t(\mathbf{x}_0)))\Phi_t(\mathbf{x}_0) \end{bmatrix}, \quad \text{with} \quad \begin{bmatrix} \mathbf{x}(0) = \mathbf{x}_0 \\ \Phi_{t_0}(\mathbf{x}_0) = I \end{bmatrix}$$

Tyson et al.'s Case 2a[3]



- The governing equations of this negative feedback oscillator are

$$\dot{X} = k_0 + k_1 S - k_2 X - k_{2p} X R_p$$

$$\dot{Y}_p = k_3 X \frac{Y_T - Y_p}{k_{m_3} + Y_T - Y_p} - \frac{k_4 Y_p}{k_{m_4} + Y_p}$$

$$\dot{R}_p = k_5 Y_p \frac{R_T - R_p}{k_{m_5} + R_T - R_p} - \frac{k_6 R_p}{k_{m_6} + R_p}$$

[3] Tyson, J J, Chen, K C and Novak, B (2003). Sniffers, buzzers, toggles and blinkers: dynamics of regulatory and signaling pathways in the cell, *Current Opinion in Cell Biology*, 15:221-231.

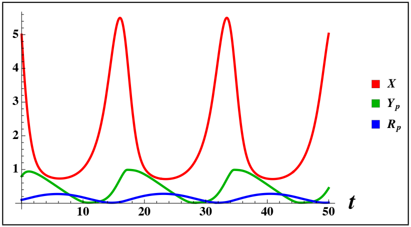
Stability of Case 2a

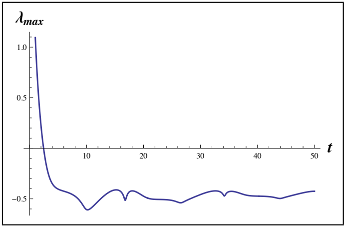
$$\dot{X} = k_0 + k_1 S - k_2 X - k_{2p} X R_p$$
$$\dot{Y}_p = k_3 X \frac{Y_T - Y_p}{k_{m_3} + Y_T - Y_p} - \frac{k_4 Y_p}{k_{m_4} + Y_p}$$
$$\dot{R}_p = k_5 Y_p \frac{R_T - R_p}{k_{m_5} + R_T - R_p} - \frac{k_6 R_p}{k_{m_6} + R_p}$$

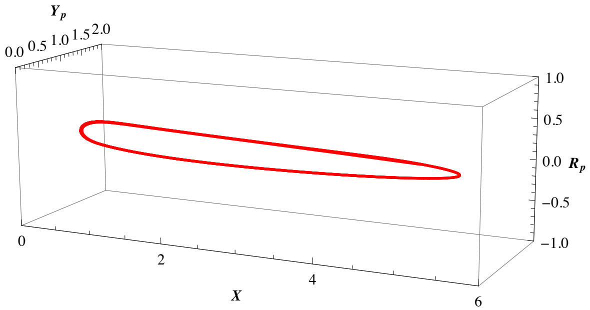
- $\mathbf{x} = (X, Y_p, R_p)$, and the Jacobian $J_{\mathbf{x}}(\mathbf{f}(\mathbf{x}))$ is

$$\begin{bmatrix} -k_2 - k_{2p} R_p & 0 & -k_{2p} X \\ \frac{k_3 (Y_T - Y_p)}{k_{m_3} + Y_T - Y_p} & \frac{-k_3 k_{m_3} X}{(k_{m_3} + Y_T - Y_p)^2} - \frac{k_4 k_{m_4}}{(k_{m_4} + Y_p)^2} & 0 \\ 0 & \frac{k_5 (R_T - R_p)}{k_{m_5} + R_T - R_p} & \frac{-k_5 k_{m_5} Y_p}{(k_{m_5} + R_T - R_p)^2} - \frac{k_6 k_{m_6}}{(k_{m_6} + R_p)^2} \end{bmatrix}$$

Behaviour of Case 2a[4]







[4] $S = 2,\ k_0 = 0,\ k_1 = 1,\ k_2 = 0.01,\ k_{2p} = 10,\ k_3 = 0.1,\ k_4 = 0.2,\ k_5 = 0.1,\ k_6 = 0.05,$ $k_{m_3} = k_{m_4} = k_{m_5} = k_{m_6} = 0.01,\ Y_T = R_T = 1,\ X_0 = 5,\ (Y_P)_0 = 0.8,\ (R_P)_0 = 0.1$

Conclusion: Lyapunov Exponents of Lie Symmetries?

- We have seen that all we require to estimate numerically the max. Lyapunov exponent of a flow (Eq. (10)) is its vector field.

- We have also seen that a Lie group or Lie symmetry of a given system is mathematically identical to its solution flow.

- Since a Lie symmetry flow is determined by its infinitesimal generator, which is a vector field like $\mathbf{f}(\mathbf{x})$, the question naturally arises as to how the stability of a dynamical system compares to the stability of one or more of the Lie groups it admits.

- In other words, can the dynamical stability of a given system be related in any way to the stability of the Lie symmetries corresponding to its Lie algebra?

- As a separate line of inquiry, the Lyapunov function seems worth investigating: no time for that in this talk, unfortunately, but that's what we will turn to next!