Modelling biological oscillations

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Module 06-23836: Computational Modelling with MATLAB
Outline of Topics

Limit circle oscillation: Van der Pol equation
Van der Pol equation
Van der Pol equation and Hopf bifurcation
Classification of oscillations
The forced Van der Pol oscillator and chaos

Oscillations in biology
Circadian clocks and Van der Pol equation

Modelling neural oscillation
Van der Pol equation

- Discovered by Dutch electrical engineer Balthasar Van der Pol in 1927.
- The first experimental report about chaos.
- The Van der Pol equation has been widely used in the physical and biological sciences.
- The equation:

\[
\frac{d^2x}{dt^2} - \mu(1 - x^2) \frac{dx}{dt} + x = 0
\]

where \(x\) is the position coordinate, which is a dynamical variable, and \(\mu\) is a scalar parameter which controls the nonlinearity and the strength of the damping.
Van der Pol equation: two dimensional form

- We can transform the above second order ODE as a first order system:

\[
\begin{align*}
\frac{dx}{dt} &= y \\
\frac{dy}{dt} &= \mu(1 - x^2)y - x.
\end{align*}
\]

- By Lienard transform, the equation can be also written as:

\[
\begin{align*}
\frac{dx}{dt} &= \mu(x - \frac{1}{3}x^3 - y) \\
\frac{dy}{dt} &= \frac{1}{\mu}x.
\end{align*}
\]
MATLAB implementation

```matlab
18 function dy=vandePolfun(t,y)
19 mu = 1;
20 dy = [mu*(y(1) - 1/3*y(1)^3 - y(2));
21     1/mu*y(1)]
22 end

24 function dy=vandePolfun2(t,y)
25 mu = 1;
26 dy = [y(2); mu*(1-y(1)^2)*y(2)-y(1)]
27 end
29 end
```
MATLAB implementation

```matlab
function VanderPol

clear all; % clear all variables

tspan = [0, 20];
y0 = [20; 0];

[t,Y] = ode45(@vandePolfun,tspan,y0);
```
Bifurcation in the Van der Pol oscillator

- By change the scalar parameter $\mu$, we can observe bifurcation.
- The bifurcation is Hopf bifurcation: a spiral point of a dynamical system switch from stable to unstable, or vice versa, and a periodic solution, e.g., limit circle appears.
- Without any external force, the Van der Pol oscillator will run into limit cycle.
- The limit cycle frequency depends on constant $\mu$. 
Limit cycle oscillation vs harmonic oscillation

- Harmonic oscillator: a system that executes a periodic behaviour, the amplitude of the oscillations depends on the initial conditions.
- The examples of harmonic oscillators: swinging pendulum and the Lotka-Volterra model
- This contrasts with limit cycle oscillators, where the amplitude is not determined by the initial conditions.
- Instead, limit cycle oscillators will automatically come back to a limit cycle after perturbation. In other words, they have a characteristic amplitude.
Limit cycle oscillators

- Limit cycle has an isolated closed trajectory, e.g., its neighbouring trajectories are not closed but spiral either towards or away from the limit cycle.
- Stable limit cycle: it attracts all neighbouring trajectories.
- A system with a stable limit cycle exhibits self-sustained oscillation.
- Self-sustained oscillations can be seen in many biological systems, e.g., electroencephalogram (EEG), mammalian circadian clocks, stem cell differentiation, etc.
- Essentially involves a dissipative mechanism to damp oscillators that grow too large and a source of energy to pump up those that become too small.
The forced Van der Pol oscillator

- By adding a driving function $A \sin(\omega t)$, the new equation is:

\[
\frac{d^2x}{dt^2} - \mu(1 - x^2) \frac{dx}{dt} + x = A \sin(\omega t)
\]

where $A$ is the amplitude (displacement) of the wave function and $\omega$ is its angular frequency.

- There are two frequencies in the oscillator:
  - The frequency of self-oscillation determined by $\mu$;
  - The frequency of the periodic forcing $\omega$.

- We can transform the above second order ODE as a first order system:

\[
\begin{align*}
\frac{dx}{dt} &= y \\
\frac{dy}{dt} &= \mu(1 - x^2)y - x - A \sin(\omega t).
\end{align*}
\]
Chaotic behaviour of the forced Van der Pol oscillator

- By setting the parameters to $\mu = 8.53$, amplitude $A = 1.2$ and angular frequency $\omega = \frac{2\pi}{10}$ we can observe chaotic behaviour
- Source code for the forced Van der Pol oscillator
Oscillations in biology

- We have seen oscillation in predator-prey interaction system, e.g., Lotka-Volterra equations.
- Oscillations are prevalent, e.g., swinging pendulum, Business cycle, AC power, etc.
- Oscillations play an important role in many cellular dynamic process such as cell cycle
### Oscillations in cell biology

**Table 1 | Survey of biochemical oscillators**

<table>
<thead>
<tr>
<th>Function</th>
<th>Components</th>
<th>Period</th>
<th>Class*</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metabolism</td>
<td>Glucose, ATP, phospho-fructokinase</td>
<td>2 min</td>
<td>3</td>
<td>52–54</td>
</tr>
<tr>
<td>Signalling</td>
<td>Cyclic AMP, receptor, adenylate cyclase</td>
<td>5 min</td>
<td>3</td>
<td>55,64</td>
</tr>
<tr>
<td>Signalling</td>
<td>Ca²⁺, Ins(1,4,5)P₃</td>
<td>&gt; 1 s</td>
<td>3</td>
<td>65</td>
</tr>
<tr>
<td>Signalling</td>
<td>NF-κB, IκB, IKK</td>
<td>~2 h</td>
<td>1</td>
<td>41,43</td>
</tr>
<tr>
<td>Signalling</td>
<td>p53, MDM2</td>
<td>5 h</td>
<td>1</td>
<td>39,40</td>
</tr>
<tr>
<td>Signalling</td>
<td>Msn2, adenylate cyclase, cAMP, PKA</td>
<td>~10 min</td>
<td>1</td>
<td>66,67</td>
</tr>
<tr>
<td>Somitogenesis</td>
<td>Her1, Her7, Notch</td>
<td>30–90 min</td>
<td>1</td>
<td>40,68</td>
</tr>
<tr>
<td>Yeast endoreplication cycles</td>
<td>Cig2, Cdc10, Rum1</td>
<td>1–2 h</td>
<td>2</td>
<td>49</td>
</tr>
<tr>
<td>Frog egg cycles</td>
<td>CycB, Wee1, Cdc25, Cdc20</td>
<td>30 min</td>
<td>2</td>
<td>47,48</td>
</tr>
<tr>
<td>Circadian rhythm</td>
<td>PER, TIM, CLOCK, CYC</td>
<td>24 h</td>
<td>1</td>
<td>26</td>
</tr>
</tbody>
</table>

*See FIG. 5. Class 1 represents delayed negative-feedback loops; class 2 represents amplified negative-feedback loops; class 3 represents incoherently amplified negative-feedback loops. IκB, inhibitor of NF-κB; IKK, IκB kinase; Ins(1,4,5)P₃, inositol-1,4,5-triphosphate; NF-κB, nuclear factor κB.

Circadian clock

- Circadian clock: or circadian rhythm, is an endogenously driven, roughly 24-hour cycle in biochemical, physiological, or behavioural processes.

Source: wikipedia
Circadian clock

- Circadian clock had been widely observed in bacteria, fungi, plants and animals.
- Biological mechanism partially understood, used mathematical models to piece together diverse experimental data and guide future research.
- Applications: jet lag countermeasures, schedules of shift workers, treat circadian disorders.
- Circadian clock acts as a limit cycle oscillator.
Circadian clock and Van der Pol oscillator

- Only has one nonlinear term, Van der Pol oscillator is the simplest possible two-dimensional limit cycle oscillator.
- Many studies of circadian clock used Van der Pol oscillator for simulation.

Dynamics of three coupled van der Pol oscillators with application to circadian rhythms

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Circadian clock of Drosophila

- Van der Pol oscillator cannot accurately describe the internal mechanism of the circadian clock
- Goldbeter model of circadian clock of Drosophila:

$$\frac{dM}{dt} = v_s \frac{K_l^n}{K_l^n + P_N^n} - v_m \frac{M}{K_m + M},$$

$$\frac{dP_0}{dt} = k_s M - V_1 \frac{P_0}{K_1 + P_0} + V_2 \frac{P_1}{K_2 + P_1},$$

$$\frac{dP_1}{dt} = V_1 \frac{P_0}{K_1 + P_0} - V_2 \frac{P_1}{K_2 + P_1} - V_3 \frac{P_1}{K_3 + P_1} + V_4 \frac{P_2}{K_4 + P_2},$$

$$\frac{dP_2}{dt} = V_3 \frac{P_1}{K_3 + P_1} - V_4 \frac{P_2}{K_4 + P_2} - k_1 P_2 + k_2 P_N - v_d \frac{P_2}{K_d + P_2},$$

$$\frac{dP_N}{dt} = k_1 P_2 - k_2 P_N,$$

FitzHugh–Nagumo oscillators

- Used to describes how action potentials in neurons are initiated and propagated.
- FitzHugh–Nagumo model is a simplified version of the famous Hodgkin–Huxley model, which won a Nobel Prize.
- FitzHugh–Nagumo model equation:

\[
\frac{dv}{dt} = v - \frac{v^3}{3} - w + I_{\text{ext}}
\]

\[
\frac{dw}{dt} = \epsilon (v - a - bw)
\]

where \(v\) is the membrane potential, \(w\) is a recovery variable, \(I_{\text{ext}}\) is the magnitude of stimulus current, and \(a, b\) and \(\epsilon\) are constants.
Assignment

- Search literature for the parameters $a$, $b$ and $\epsilon$.
- Implement the model in MATLAB.
- Try different value of $I_{\text{ext}}$ and observe output $v$ of the neuron.
- If you have more time, try to find the chaotic behaviour and bifurcation of the model.