Lie Group Analysis of a p53-mdm2 ODE Model

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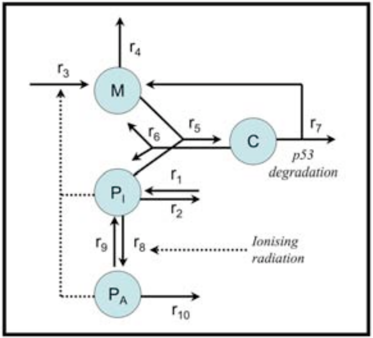
Introduction

- As we saw in the previous presentation, we wish to analyse and understand in depth the dynamical behaviour of the p53-mdm2 pathway.

- In this presentation I will discuss an analytical method that is helping us do that.

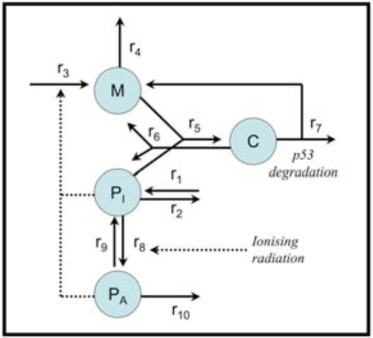
- After explaining the method, I will show how we have applied it to the p53-mdm2 equations, and will conclude by outlining the next steps in this research.

Equations



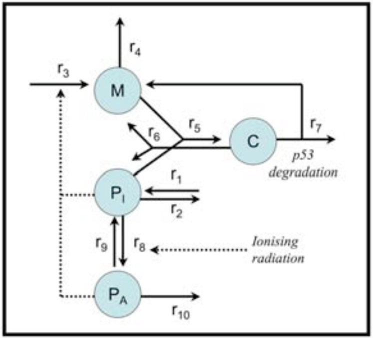
$$
\begin{aligned}
Pi_t &= r_1(t) - r_2(t) - r_5(t) + r_6(t) \\
&\quad - r_8(t) + r_9(t), \\
M_t &= r_3(t) - r_4(t) - r_5(t) \\
&\quad + r_6(t) + r_7(t), \\
C_t &= r_5(t) - r_6(t) - r_7(t), \\
Pa_t &= r_8(t) - r_9(t) - r_{10}(t).
\end{aligned}
$$

Equations



$$
\begin{aligned}
Pi_t &= 1 + \beta_a Pa - (\beta_p + s(t))\, Pi \\
&\quad - \alpha_c PiM + \beta_c C, \\
M_t &= \frac{\alpha'_{m1} Pi + \alpha'_{m2} Pa}{Pi + Pa + \kappa_m} + (1 + \beta_c)\, C \\
&\quad - (\beta_m + \alpha_c Pi)\, M + \alpha_{m0}, \\
C_t &= \alpha_c PiM - (1 + \beta_c)\, C, \\
Pa_t &= s(t)\, Pi - (\beta_a + \beta_p)\, Pa.
\end{aligned}
$$

No Radiation



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C_t &= \alpha_c PiM - (1 + \beta_c)\, C, \\
Pa_t &= s(t)\, Pi - (\beta_a + \beta_p)\, Pa.
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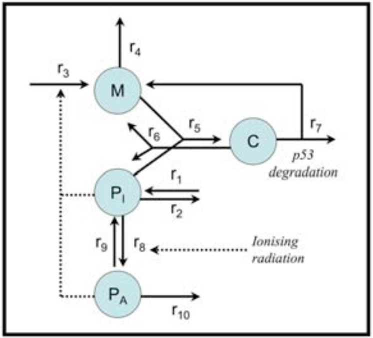
No Radiation



$$Pi_t = 1 - \beta_p Pi - \alpha_c PiM + \beta_c C,$$

$$M_t = \frac{\alpha'_{m1} Pi}{Pi + \kappa_m} + (1 + \beta_c)\, C - (\beta_m + \alpha_c Pi)\, M + \alpha_{m0},$$

$$C_t = \alpha_c PiM - (1 + \beta_c)\, C.$$

Same system if $t \mapsto t + \varepsilon$.

Symmetries

• In the 19th Century the Norwegian mathematician Sophus Lie ('lee') realised that differential equations can be seen as geometrical objects, and that the properties of these geometrical objects could be exploited to find the solutions to these equations.

• In particular, he observed that transformations that leave the differential equation invariant can be used to arrive at the solution.

• A transformation that leaves anything invariant is called a *symmetry*, by definition.

• Thus, a symmetry of a differential equation is a transformation of the independent and dependent variables that leaves the functional form of the differential equation invariant.

• Therefore, the transformation $t \to t + \varepsilon$ is a symmetry of the p53-mdm2 system (without radiation).

Lie Groups

- The set of invertible transformations that leave some feature of a mathematical object invariant form a group.

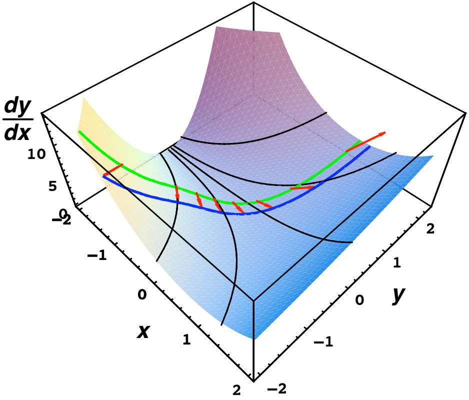
- Because the symmetries devised by Lie leave the functional form of the equation(s) invariant and are invertible, they form a group, called a Lie group.

- The method of Lie groups applies equally well to linear and non-linear problems. It is the only analytical technique we have for solving (some) non-linear problems.

Lie Groups

- A 1st-order ordinary differential equation (ODE) can be seen as the equation for a surface:

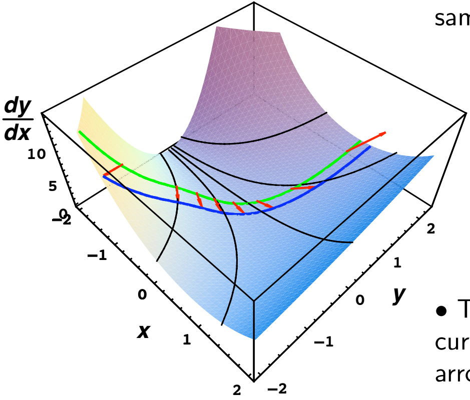
$$\frac{dy}{dx} = e^{-x}y^2 + y + e^x$$



Lie Groups

- A 1st-order ordinary differential equation (ODE) can be seen as the equation for a surface:

$$\frac{dy}{dx} = e^{-x}y^2 + y + e^x$$



- The solution must necessarily lie on this surface (green curve).

- The following symmetry maps the ODE to itself. Thus, the new ODE must lead to another solution on the same surface (blue curve):

$$\begin{aligned} x'(x,y,\varepsilon) &= x + \varepsilon \\ y'(x,y,\varepsilon) &= ye^{\varepsilon}. \end{aligned}$$

- The black curves are the integral curves of this symmetry, and the red arrows are their tangent vectors.

No Radiation Again...

$$
\begin{aligned}
Pi_t &= 1 - \beta_p Pi \\
&\quad - \alpha_c PiM + \beta_c C, \\
M_t &= \frac{\alpha'_{m1} Pi}{Pi + \kappa_m} + (1 + \beta_c)\, C \\
&\quad - (\beta_m + \alpha_c Pi)\, M + \alpha_{m0}, \\
C_t &= \alpha_c PiM - (1 + \beta_c)\, C.
\end{aligned}
$$

$t \mapsto t + \varepsilon$ is a Symmetry.

Reduces to a complicated second-order differential equation:

$$
\begin{aligned}
C_t = \alpha_c C^2 - (1 + \beta_c + \alpha_c(2 + \alpha_{m0} \\
\quad + (c_1 + c_2) \cdot e^{-t} + c_1 \cdot t \cdot e^{-t}))C \\
+ \alpha_c \cdot \left(1 + c_1 \cdot e^{-t}\right) \\
\cdot \left(1 + \alpha_{m0} + c_1 \cdot t \cdot e^{-t} + c_2 \cdot e^{-t}\right).
\end{aligned}
$$

No Radiation, No Oscillations

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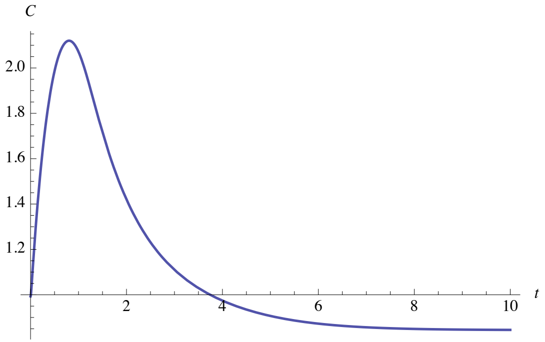
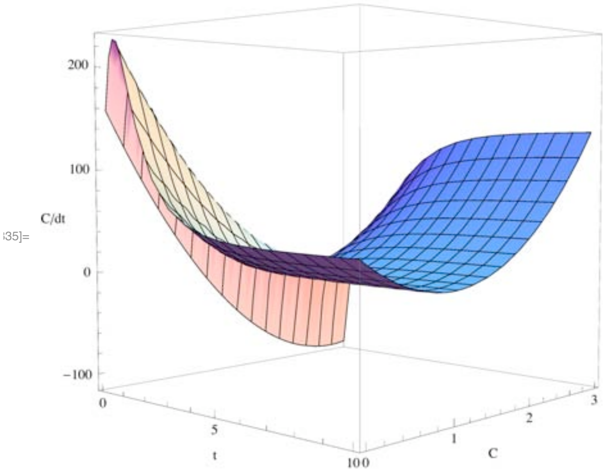


Surface of Riccati Equation (1)



Surface of Riccati Equation (2)

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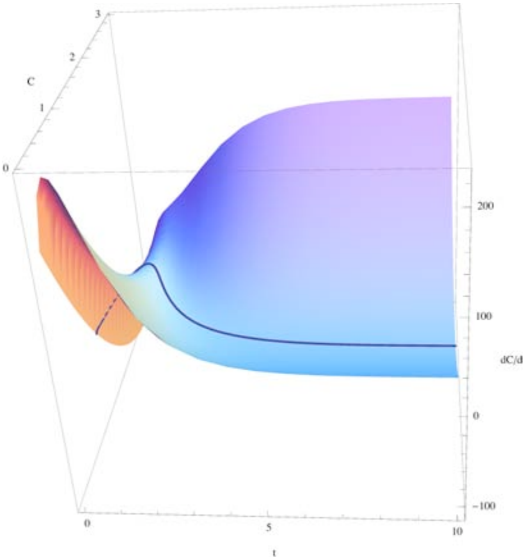

Surface of Riccati Equation (3)