Mathematical Institute

Practical parameter identifiability analysis applied to a model of autoimmune myocarditis

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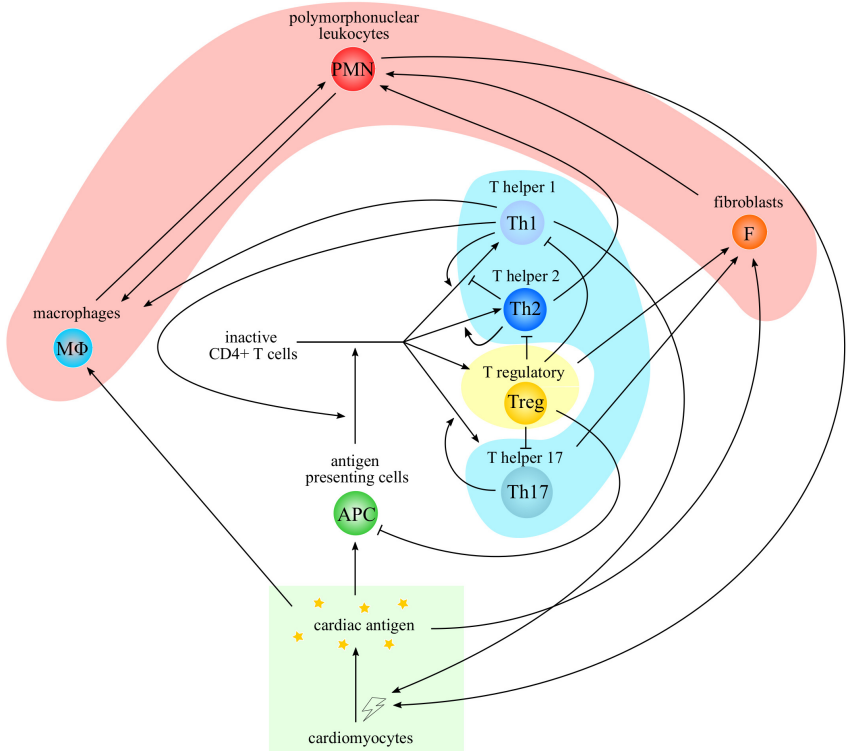
Oxford Mathematics

Introduction to autoimmune myocarditis

- $\sim$ 40% of cancer patients are eligible for treatment with ICIs, such as nivolumab and ipilimumab.
- 0.1–1% of cancer patients treated with ICIs will develop autoimmune myocarditis.
- In 25–50% of the cases, autoimmune myocarditis will be fatal.
- Currently no pre-clinical screening available for cardiotoxicity of new compounds.

Why practical identifiability matters

- To develop an *in vitro* cardiotoxicity assay, a minimum set of immune cell types must be identified.
- A feedback loop between a mathematical model of the *in vitro* set-up and the experimental set-up itself can aid in this.



A mathematical model of autoimmune myocarditis

Dead/damaged cardiomyocytes (C)

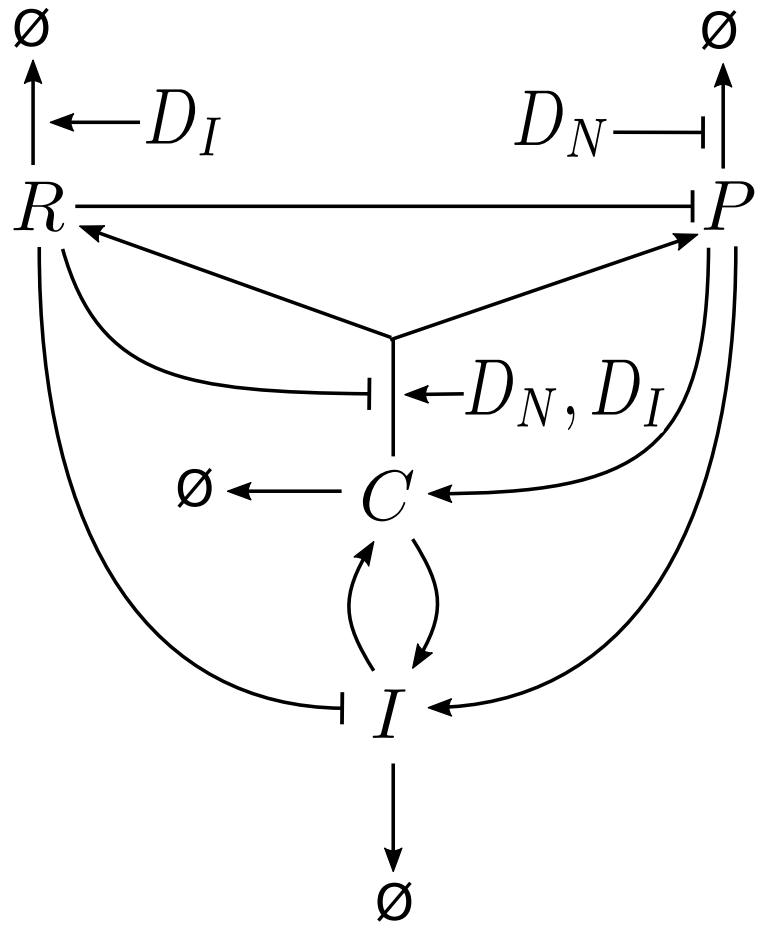
Innate immune cells (I)

Pathogenic CD4+ T cells (P)

Regulatory T cells (R)

Nivolumab (D_N)

Ipilimumab (D_I)



van der Vegt et al., JTB 537: 111002, 2022.

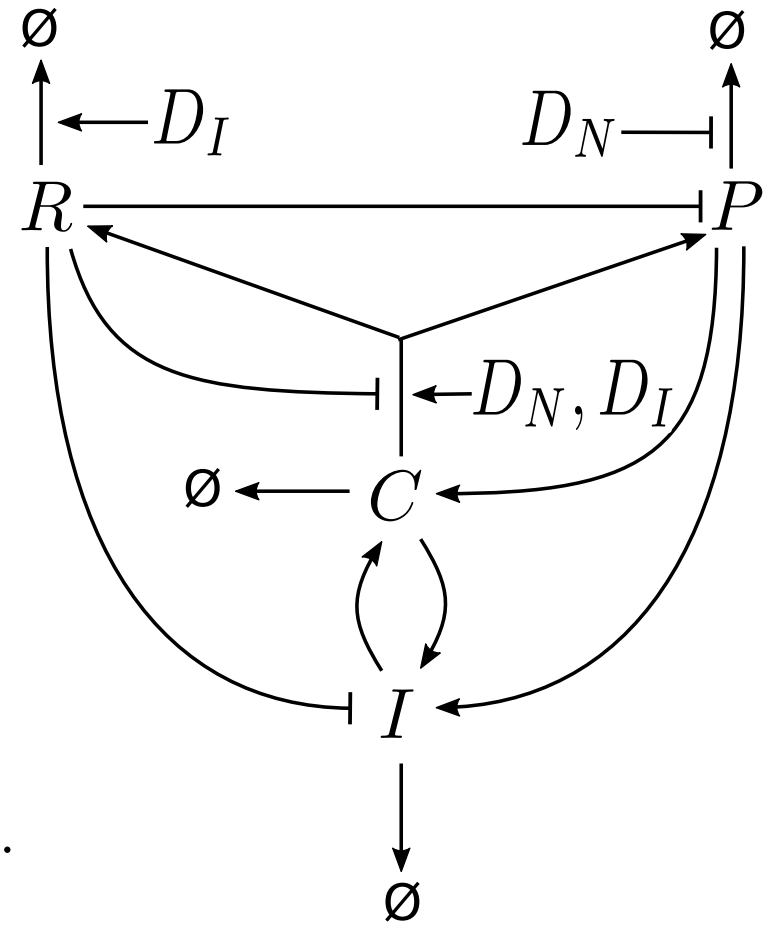
A mathematical model of autoimmune myocarditis

$$\frac{\mathrm{d}C}{\mathrm{d}t} = a_1 \frac{P^2}{R_1 + R} + a_2 \frac{I}{R_2 + R} - d_1 C,$$

$$\frac{\mathrm{d}I}{\mathrm{d}t} = a_4 \frac{P}{R_1 + R} + a_5 C - d_3 I,$$

$$\frac{\mathrm{d}P}{\mathrm{d}t} = a_6(D_N, D_I)\phi \frac{C}{R + R_3} - d_4(D_N)P,$$

$$\frac{\mathrm{d}R}{\mathrm{d}t} = a_6(D_N, D_I)(1-\phi) \frac{C}{R + R_3} - d_5(D_I)R.$$



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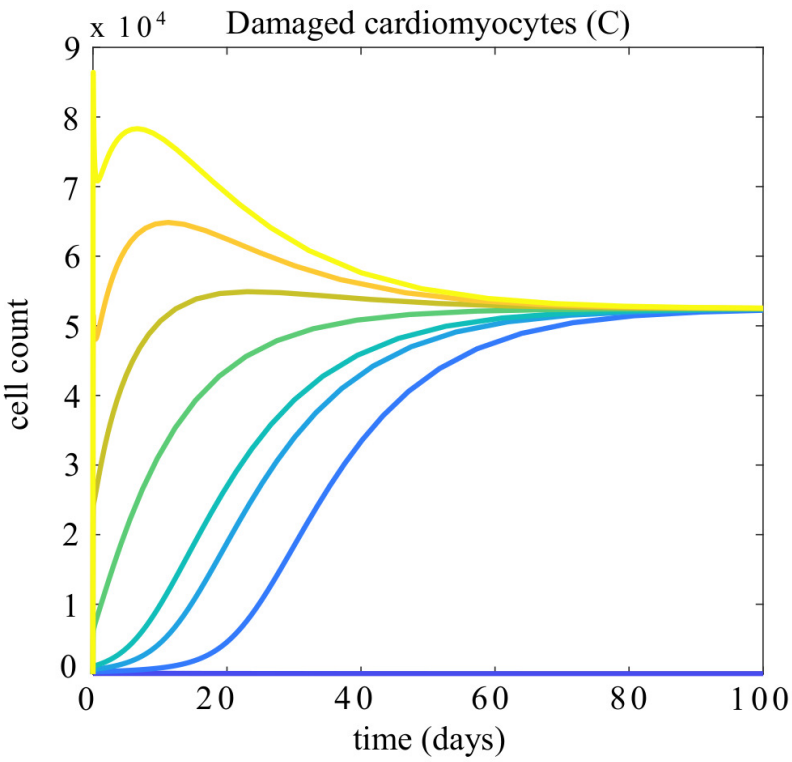
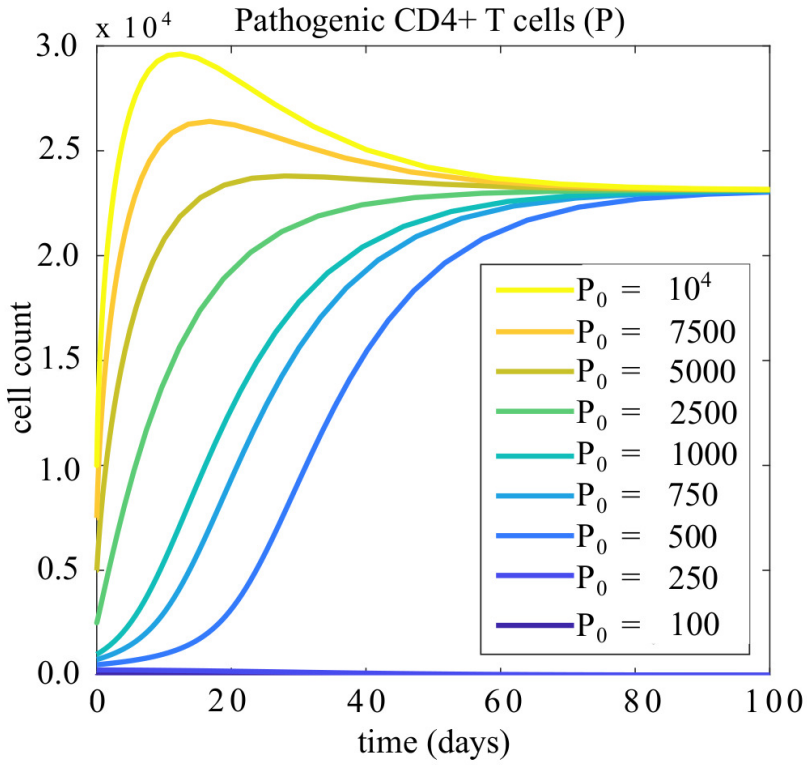
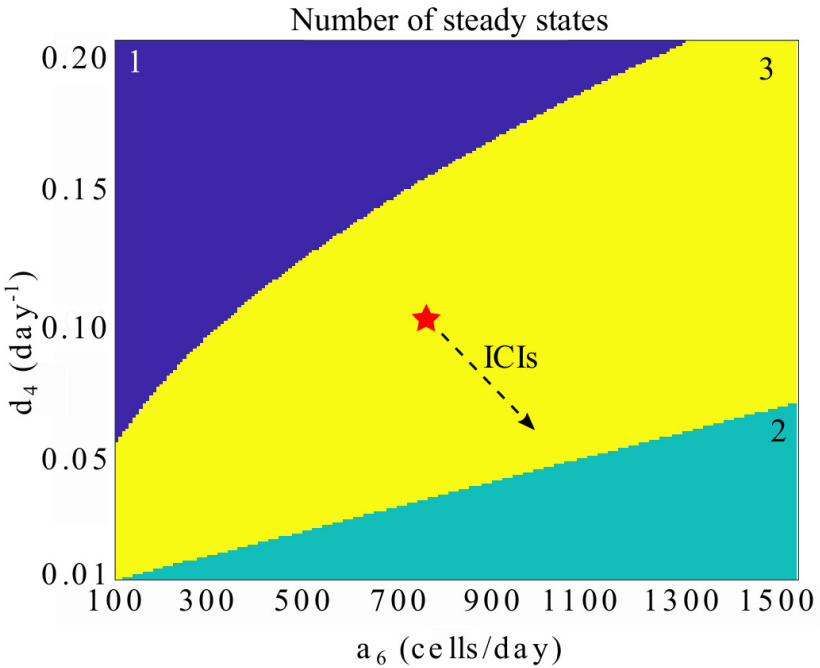
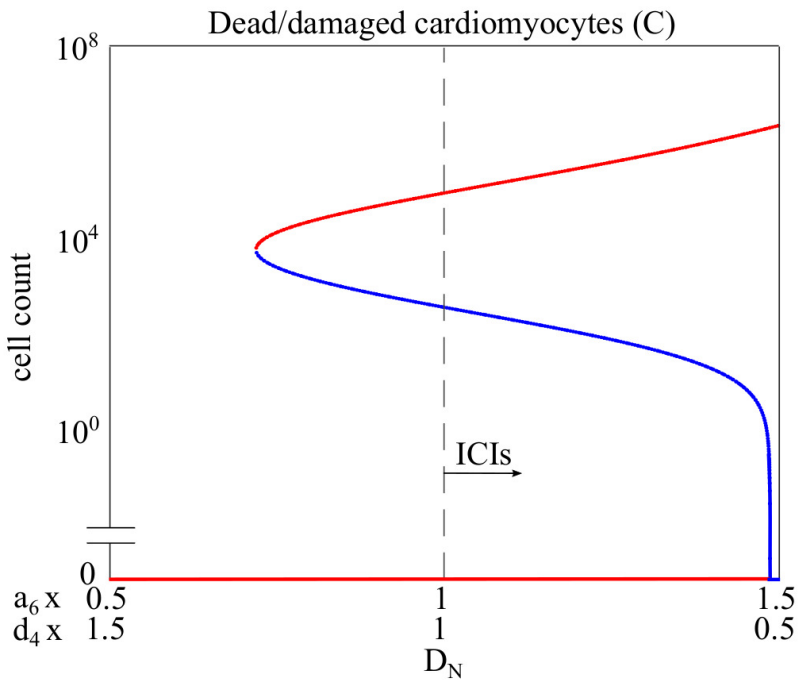
Time traces


x 10^4
Damaged cardiomyocytes (C)
cell count
time (days)
0
1
2
3
4
5
6
7
8
9
0
20
40
60
80
100


x 10^4
Pathogenic CD4+ T cells (P)
cell count
time (days)
0.0
0.5
1.0
1.5
2.0
2.5
3.0
0
20
40
60
80
100
P0 = 10^4
P0 = 7500
P0 = 5000
P0 = 2500
P0 = 1000
P0 = 750
P0 = 500
P0 = 250
P0 = 100

Bifurcations





Parameter identifiability

Constructed and characterised the first mathematical model of autoimmune myocarditis.

Further work includes:

- Using the model together with the *in vitro* set-up
- Optimizing treatment schedules of ICIs to prevent autoimmune myocarditis

Must assess under which conditions the model is practically identifiable

Types of identifiability

Structural identifiability: Does every parameter set give rise to a unique distribution of model outputs?

- A property of the model
- Assumes perfectly noise-free and time-continuous data
- A prerequisite for practical identifiability

Types of identifiability

Practical identifiability: Can parameter values be confidently estimated from a given data set?

- A property of the model AND the available data
- Informs what nature of data is required in order to confidently estimate the values of model parameters

Structural identifiability

Two methods:

- DAISY: software tool for determining structural identifiability
- Simple scaling method by Castro and de Boer (2020)

Conclusion: model parameters are only structurally identifiable if all four variables are observed.

Castro and de Boer, PLoS Comp Bio 16(11):e1008248, 2022.
Bellu et al., Comp Methods and Programs in Biomed 88(1): 52-61, 2007.

Practical identifiability: Maximum likelihood profiling

Choose maximum likelihood profiling for computational feasibility.

We require:

- A (sub)set of model parameters for which practical identifiability is to be determined.
- A synthetic data set consisting of a number of measurements with a certain level of noise.
- The loglikelihood function to be maximized.

Practical identifiability: Maximum likelihood profiling

Given a set of parameters of interest $P = [p_1, p_2, p_3, \ldots p_n]$.

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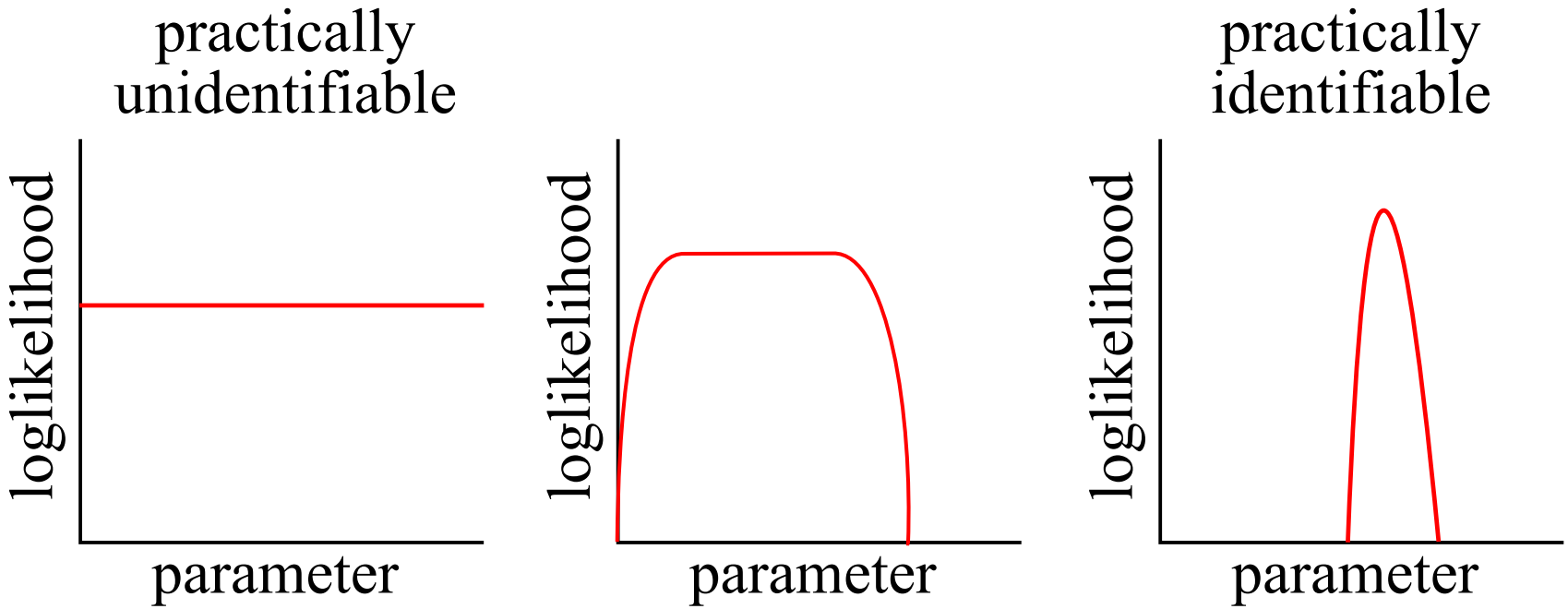
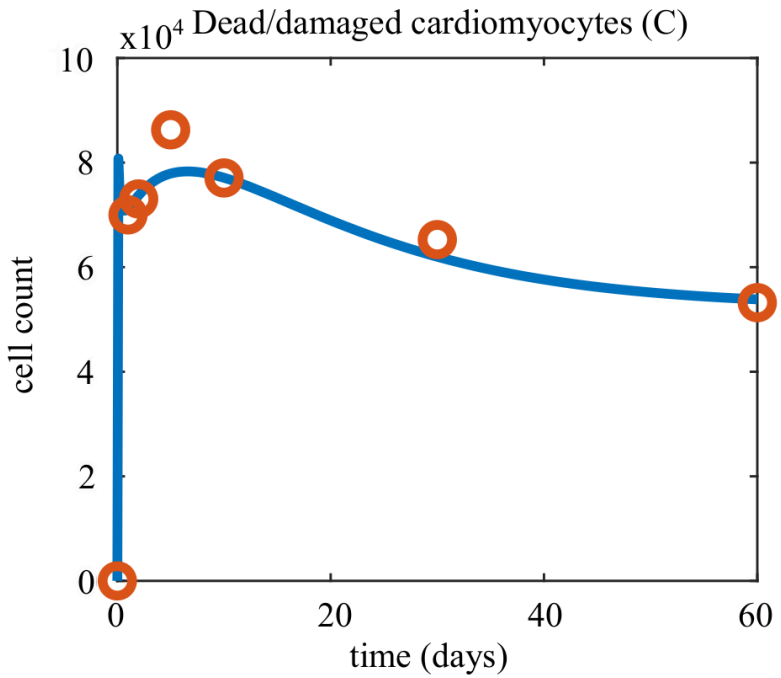
Plot p_i vs. the maximum loglikelihood.

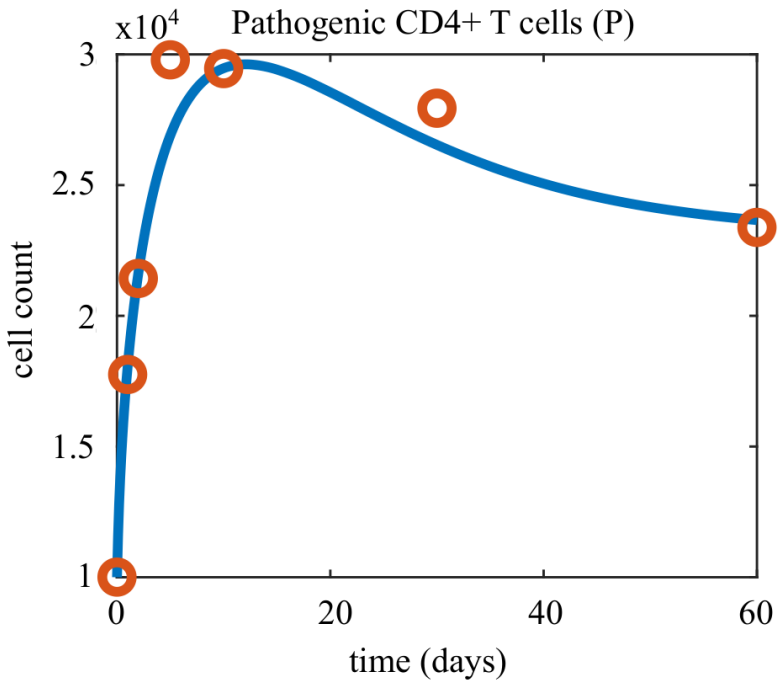
Practical identifiability: Maximum likelihood profiling



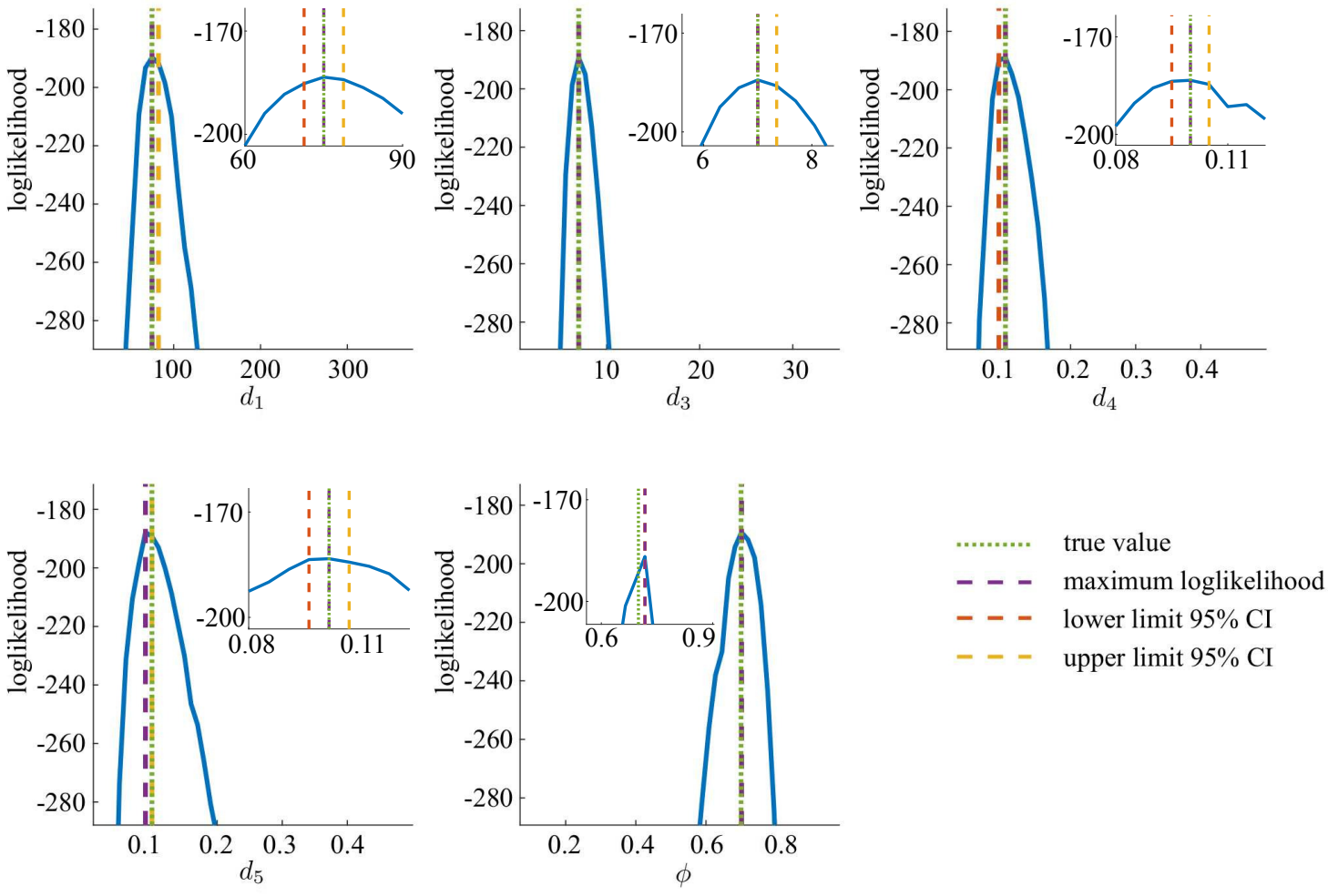
Synthetic data

Use practical identifiability analysis to determine requirements on nature of data

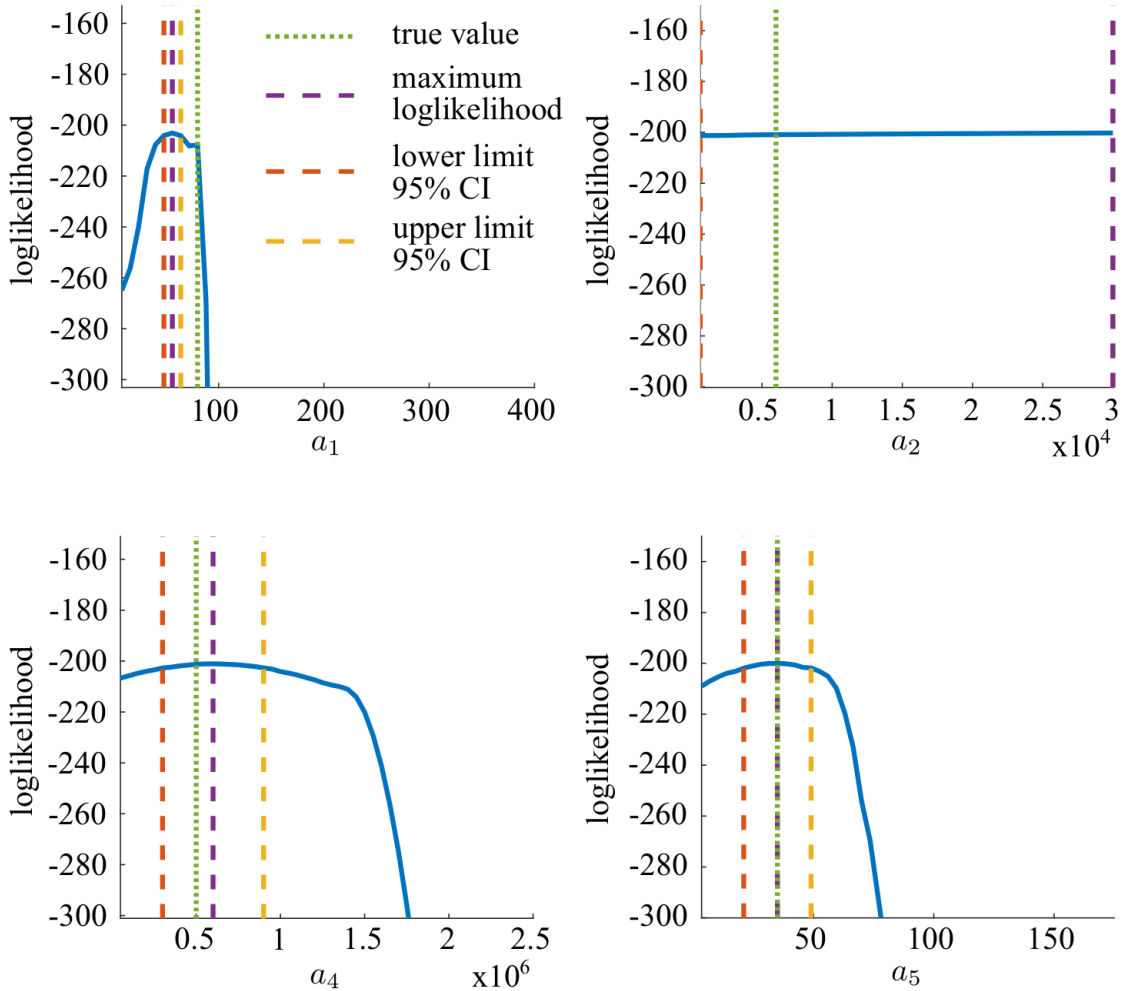




Practical identifiability of deactivation/death rates

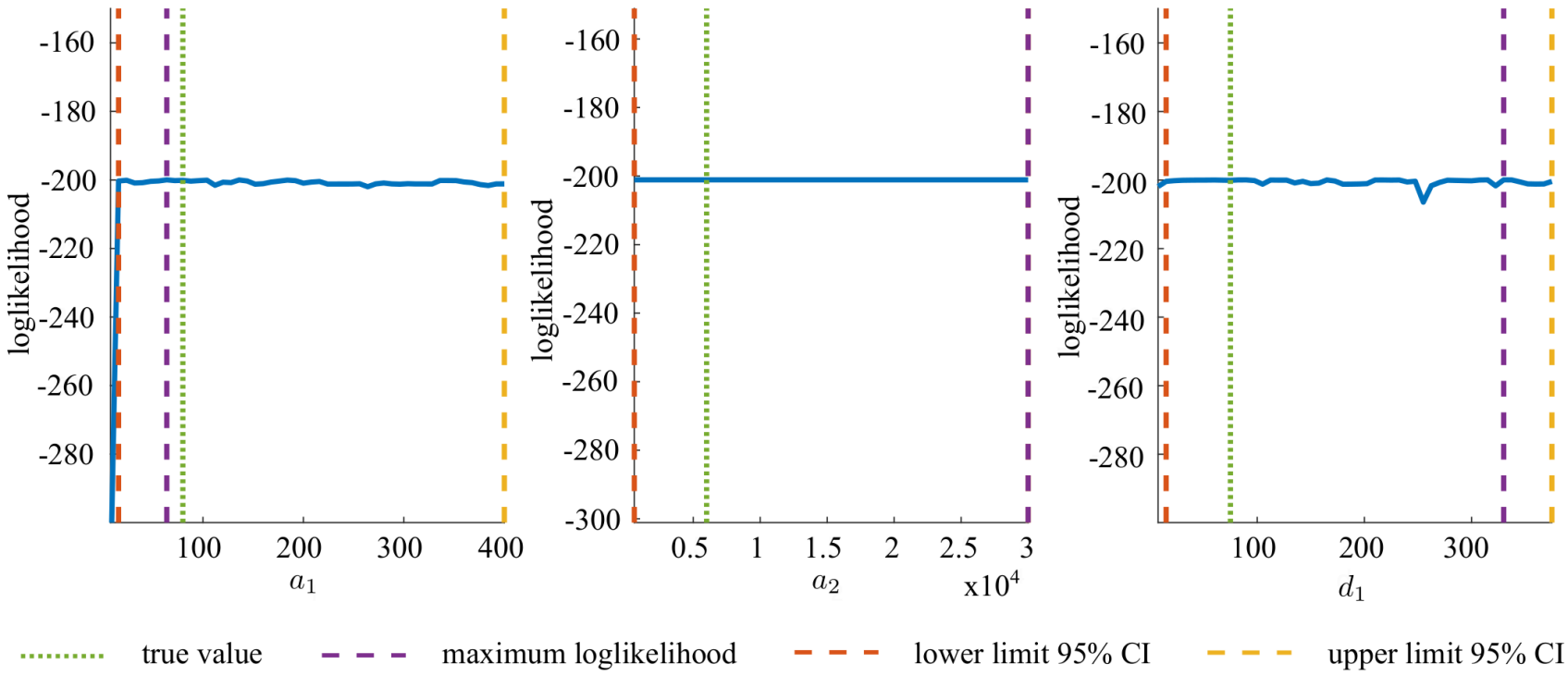


Practical identifiability of activation rates



Practical identifiability by ODE

$$\frac{\mathrm{d}C}{\mathrm{d}t} = a_1 \frac{P^2}{R_1 + R} + a_2 \frac{I}{R_2 + R} - d_1 C,$$



Summary

- Developed the first mathematical model of autoimmune myocarditis.
- Characterized steady state behaviour.
- Future work with this model includes linking to in *in vitro* set-ups or clinics.
- Practical identifiability analysis of the full parameter set is not computationally feasible.

Improvements to numerical methods for optimization are required to allow complete identifiability analysis.

Challenges

Main challenges for maximum likelihood profiling:

- Optimizing over high dimensional parameter spaces
- Finding a global maximum for the loglikelihood.

Thank you for your attention!

Supervisors:
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Prof. Sarah Waters (Oxford)
Dr. Ken Wang (Roche)
Dr. Liudmila Polonchuk (Roche)

Reference:
van der Vegt et al., Mathematical modelling of autoimmune myocarditis and the effects of immune checkpoint inhibitors. JTB 537: 111002, 2022. doi: 10.1016/j.jtbi.2021.111002.

Engineering and Physical Sciences Research Council