

# Investigating the Impact of the Binding Site Barrier on Antibodies: A Comparative Study of ODE and PDE Models

P. Joyce<sup>1\*</sup>, J. Yates<sup>2</sup>, M. J. Chappell<sup>1</sup>.

<sup>1</sup> School of Engineering, University of Warwick, Coventry, CV4 7AL, UK. <sup>2</sup> GSK, Gunnels Wood Road, Stevenage, Hertfordshire, SG1 2NY, United Kingdom.

WARWICK

SCHOOL OF ENGINEERING

GSK



## 1 Introduction

- Antibodies and Antibody-drug conjugates are a developing form of targeted treatment for cancer. However, the **distribution of antibodies** within tumours is limited due to several factors.
- The **Binding Site Barrier** is the phenomenon where antibodies bind rapidly to antigens on the surface of the tumour near blood vessels, causing a reduction in antibody distribution within the tumour.
- Bordeau et al. [1] proposed an **Ordinary Differential Equation** approach (Figure 1a) to model antibody distribution via  $n$  concentric spheres of equal width; Fujimori et al. [2] proposed a **Partial Differential Equation** approach (Figure 1b) which models the distribution continuously throughout the tumour.
- This poster aims to compare the compartmental ODE and continuous PDE approaches for antibody distribution within tumours.

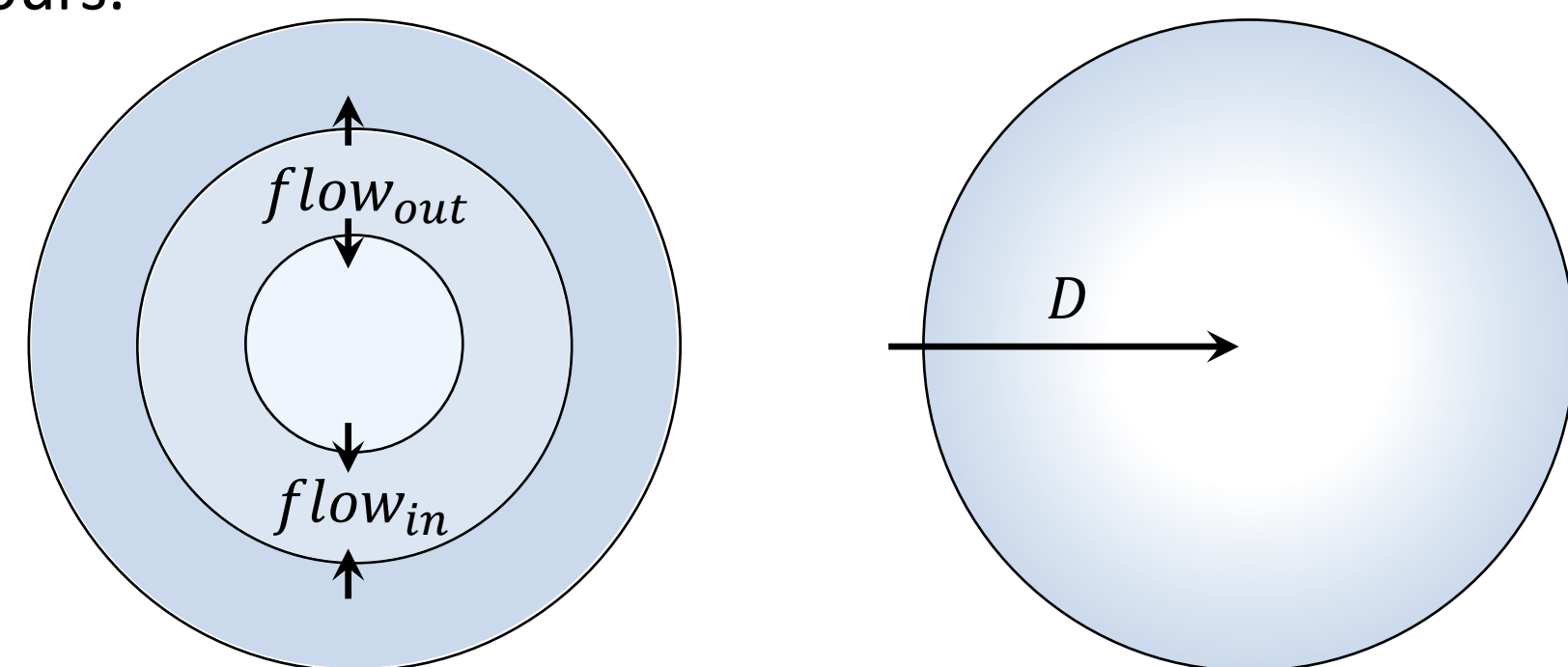


Figure 1: a) Representation of the ODE model, b) Representation of the PDE model with a continuum in terms of tumour volume.

## 2 Model Definitions

Mathematical models have been used to describe antibody distribution within tumours. The **key difference** between the ODE and PDE models are **distribution terms** within the tumour. The ODE Model uses **discrete distribution terms**,  $flow_i$  and  $flow_o$ , that vary depending on the layer radius, whereas the PDE Model uses a **continuous diffusion term** with radial partial derivatives to describe spatial distribution.

ODE Model (for a single layer):

$$\frac{dx(t)}{dt} = flow_i - flow_o - k_{on}xy + k_{off}z - k_{deg,antibody}x$$

$$\frac{dy(t)}{dt} = k_{syn} - k_{on}xy + k_{off}z - k_{int,target}y$$

$$\frac{dz(t)}{dt} = k_{on}xy - k_{off}z - k_{int,complex}z - k_{deg,complex}z$$

PDE Model:

$$\frac{\partial x(t,r)}{\partial t} = D \frac{1}{r^2} \frac{\partial x}{\partial r} \left( r^2 \frac{\partial x}{\partial r} \right) - k_{on}xy + k_{off}z - k_{deg,antibody}x$$

$$\frac{dy(t)}{dt} = k_{syn} - k_{on}xy + k_{off}z - k_{int,target}y$$

$$\frac{dz(t)}{dt} = k_{on}xy - k_{off}z - k_{int,complex}z - k_{deg,complex}z$$

Parameter Values:

$$k_{deg,antibody} = 0.0017/h$$

$$k_{deg,complex} = 0.0017/h$$

$$k_{int,target} = 0.05775/h$$

$$k_{int,complex} = 0.693/h$$

$$k_{on} = 2.6/nM/h$$

$$k_{off} = 1.3/h$$

$$k_{syn} = 5.775/h$$

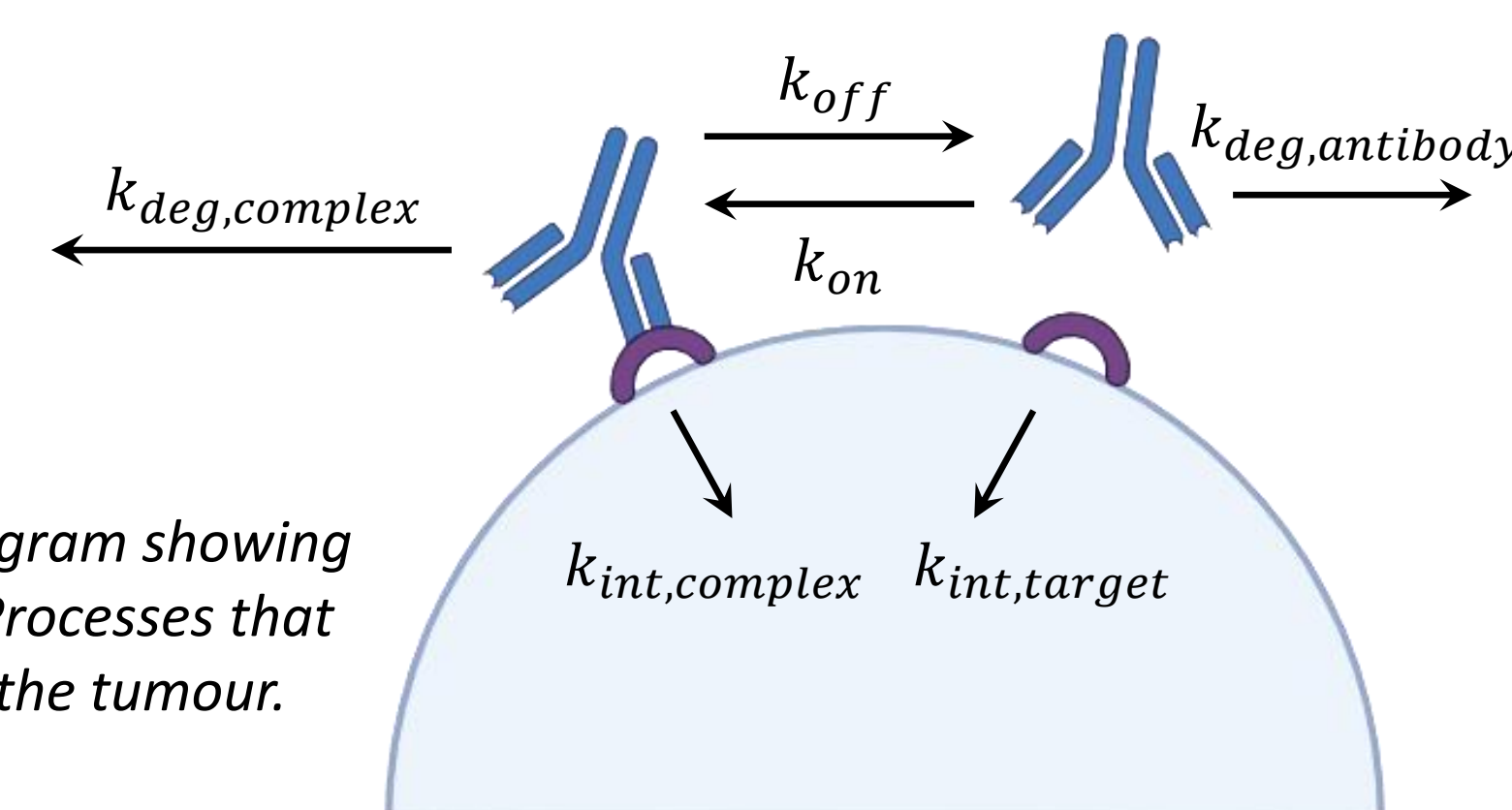


Figure 2: Diagram showing the Binding Processes that occur within the tumour.

## 3 Structural Identifiability Analysis

Structural identifiability analysis determines whether the **unknown parameters** can be **uniquely identified** by the input-output behaviour of a system.

- Globally identifiable:** All unknown model parameters have unique solutions
- Locally identifiable:** At least one unknown model parameter has a finite number of solutions
- Unidentifiable:** At least one unknown model parameter has an infinite number of solutions

The **ODE Model** can be proven at least **locally identifiable** via the **Taylor Series** approach, whereas the **PDE Model cannot currently be proven to be structurally identifiable** due to memory limitations in Maple when using the Input-Output Method.

## 4 Software Used

Structural Identifiability Analysis – ODE: Taylor Series in Mathematica

Structural Identifiability Analysis – PDE: Input Output Method in Maple

ODE Solver: ode15s in MATLAB

PDE Solver: pdepe in MATLAB

## 5 PK Model & Simulations

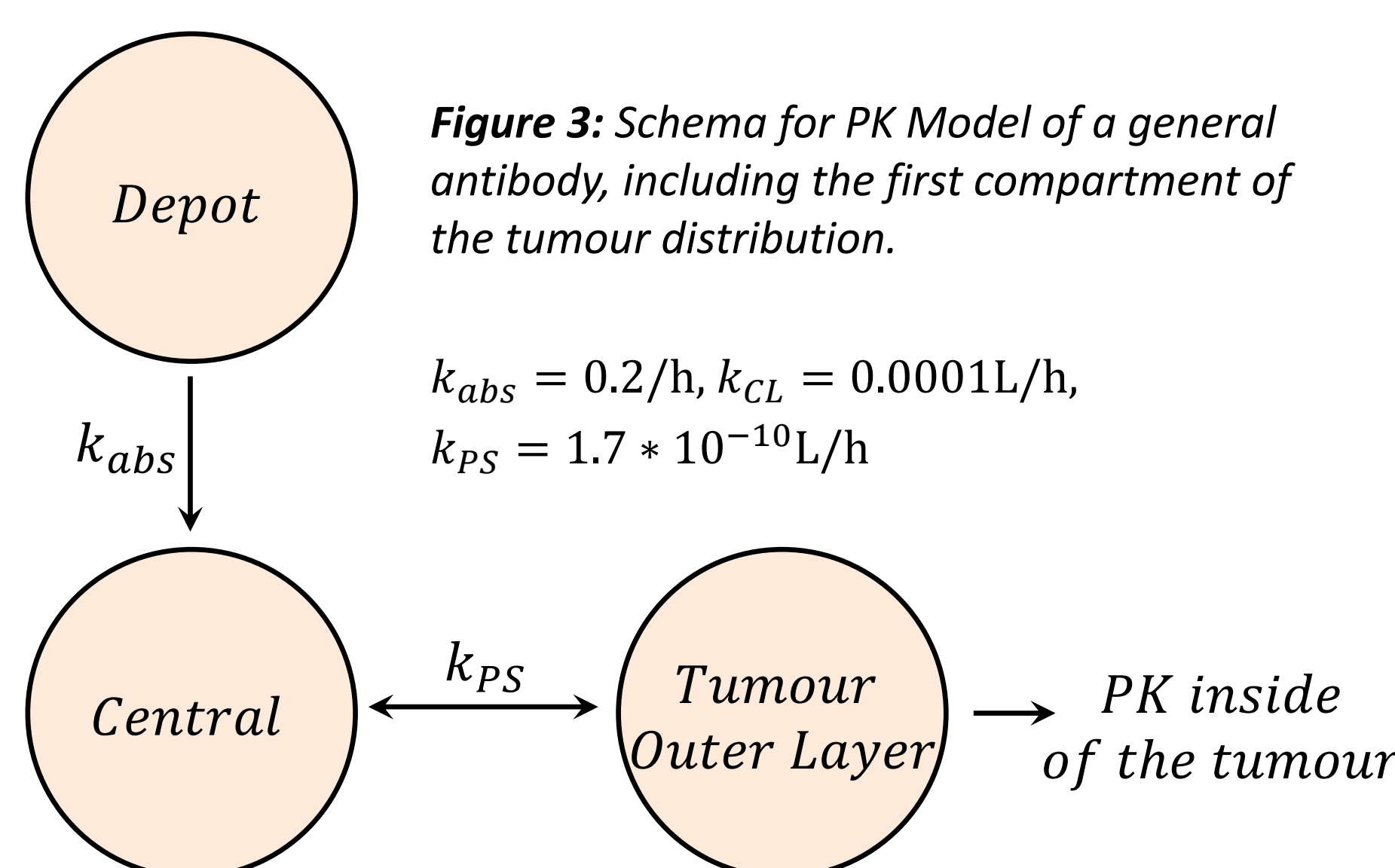


Figure 3: Schema for PK Model of a general antibody, including the first compartment of the tumour distribution.

$$k_{abs} = 0.2/h, k_{CL} = 0.0001L/h, k_{PS} = 1.7 \times 10^{-10}L/h$$

$k_{abs}$ : Rate of Absorption,  $k_{CL}$ : Rate of Clearance,  $k_{PS}$ : Vascular Permeability Coefficient,  $V_C$ : Central Volume of Distribution,  $V_{Tumour}$ : Outer Layer of the Tumour Volume.

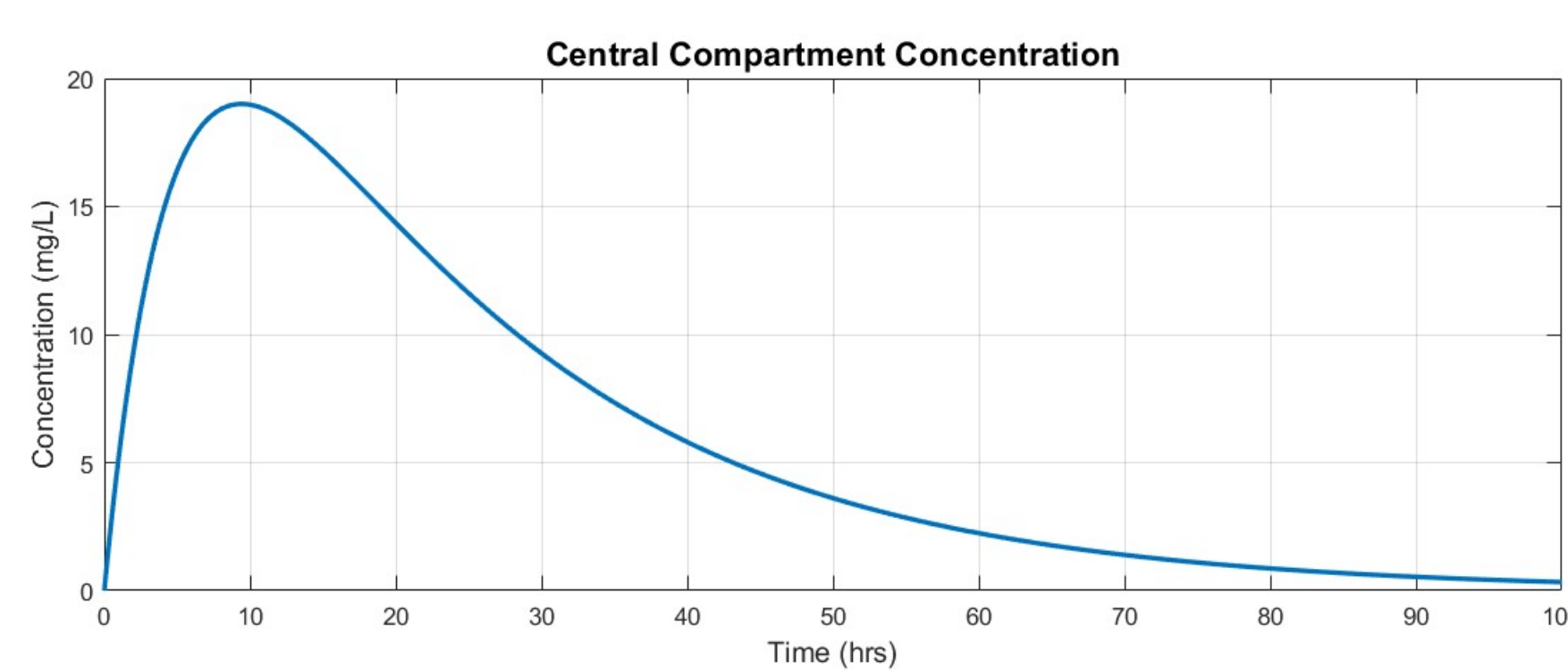
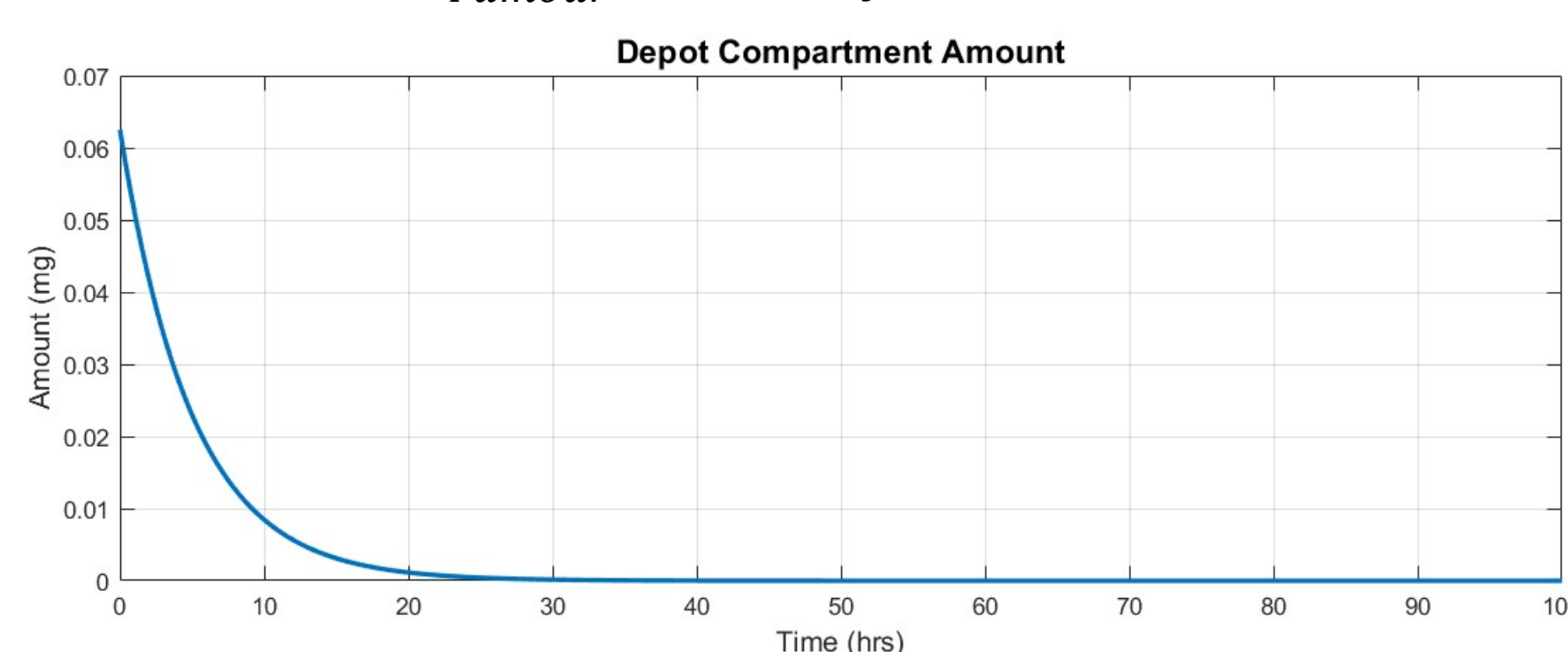


Figure 4: Simulations of the PK in a mouse in the Depot and Central Compartments following a 2.5mg/kg IP injection, assuming an average animal body weight of 25g.

## 6 Comparison Model Results

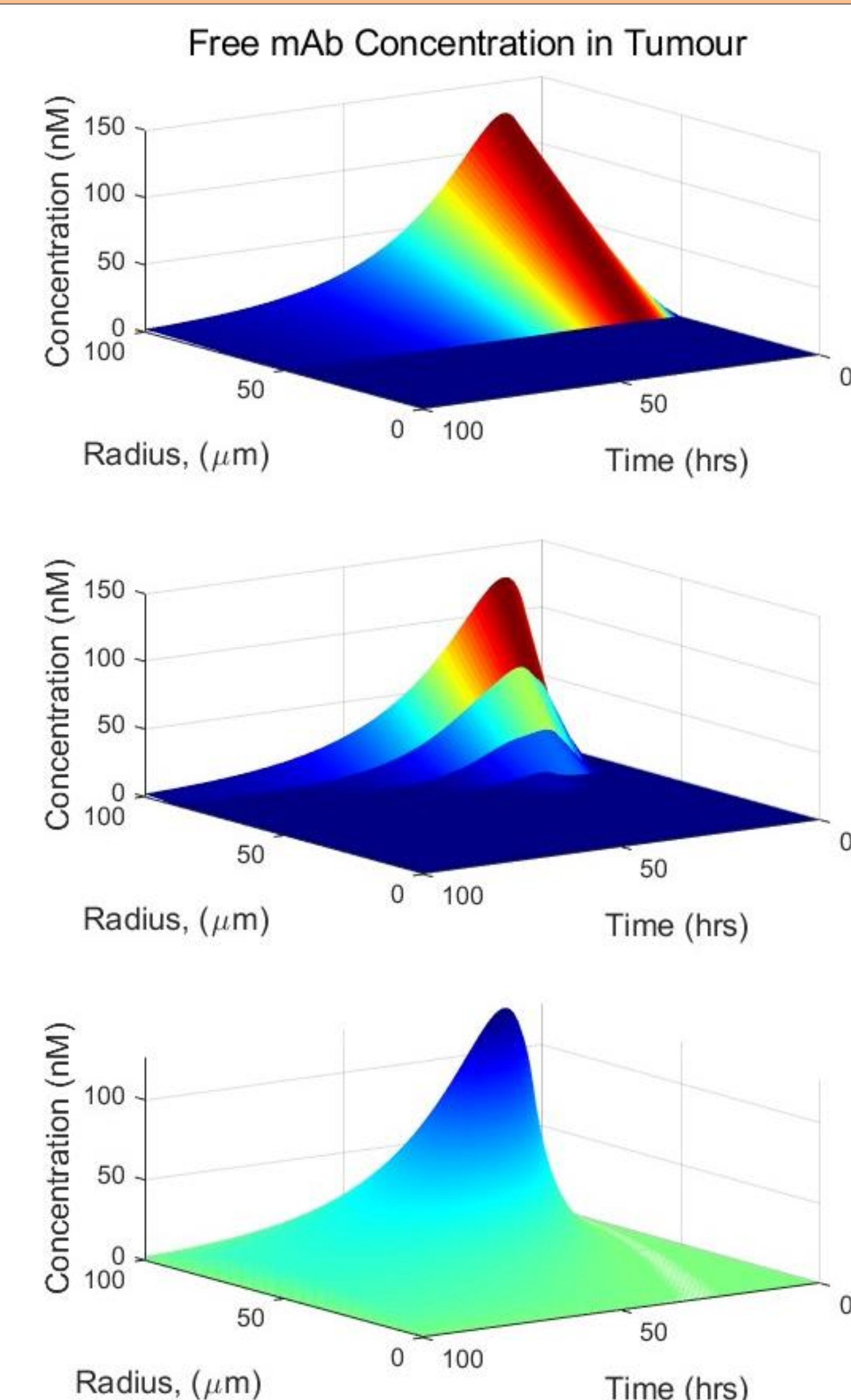


Figure 5: Surf Plots of the antibody distribution within a tumour with a diameter of 200µm. The outer surface of the tumour is defined as 100µm. a) ODE Model with 3 layers, b) ODE Model with 10 layers, c) PDE Model with a continuum of layers.

As the number of layers increases in the ODE model, its distribution more closely approximates the PDE model, but with greater model complexity.

## 7 Conclusions and Future Work

- The antibody distribution within a tumour can be characterised by both models, and the difference between the models decreases as the number of layer increases.

- Differences in the models are due to how the diffusion processes are defined in the ODE model.
- Future work will consider varying dose size, the dosing regimen, the number of receptors, and investigate bivalent bonding.

### References:

- Bordeau, B.M. et al. (2022) 'Development and evaluation of competitive inhibitors of Trastuzumab-HER2 binding to bypass the binding-site barrier', Frontiers in Pharmacology, 13. doi:10.3389/fphar.2022.837744.
- Fujimori, K. et al. (1990) 'A Modeling Analysis of Monoclonal Antibody Percolation Through Tumors: A Binding-Site Barrier', The Journal of Nuclear Medicine, 31(7).

\*Patrick.Joyce@warwick.ac.uk