# Optimising ADCC with Dynamical Systems and Inference

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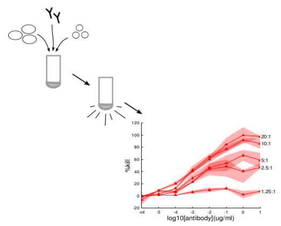
## Background

An important mechanism of action for therapeutic antibodies against cancer is antibody dependent cellular cytotoxicity (ADCC). In ADCC, natural killer (NK) cells kill cancer cells in response to tumour bound antibodies. We aim to use mathematical modeling and inference in order to investigate questions of preclinical and clinical relevance.

- How effective can antibody therapy be in reducing tumour burden in a preclinical setting?
- What level of target expression in a tumour is optimal for ADCC?
- What properties of a therapeutic antibody maximise ADCC?
- How do in vitro results translate to an in vivo setting?
- What is the optimal dosing strategy for an antibody therapy when used in isolation and in combination with other therapies?

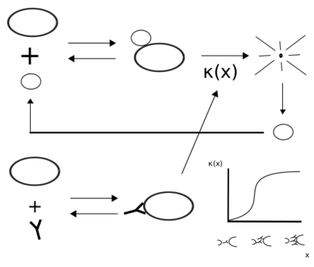
## Data

*In vitro* ADCC lysis assay: tumour cells, antibodies and NK cells are incubated in a microwell and flourescence is measured as proxy for lysis.



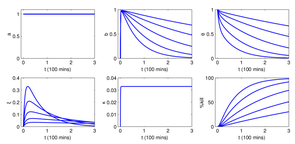

## Model

In order to model *in vitro* ADCC lysis assay data we have developed a system of time-dependent nonlinear ODEs that encode the following schematic:

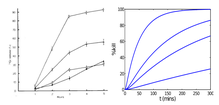



## Model Dynamics

Model simulations give the temporal dynamics of concentrations of antibodies $A$, unbound tumour receptors $T_u$, bound tumour receptors $T_b$, NK cells $N$, tumour cells $T$, NK/tumour conjugates $C$, the kill rate $\kappa(X)$ and percentage lysis %kill.

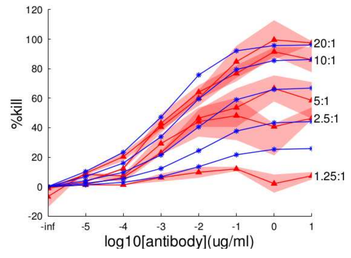


The dynamics of % lysis qualitatively reproduce dynamics in the literature.



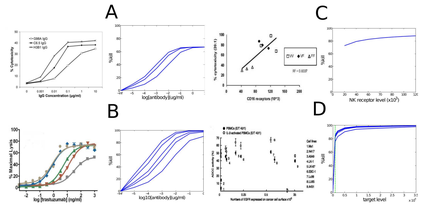
## Model Fit to Data

Model simulation using parameter values that are consistent with experimental estimates produce good fits to ADCC lysis assay data,



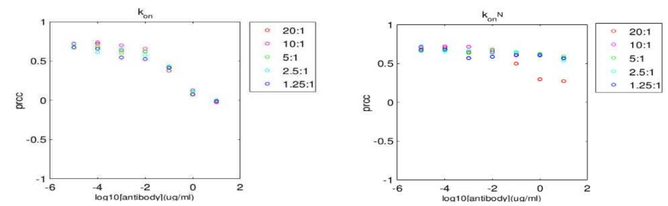

## Comparison with Experimental Literature

The model qualitatively reproduces a large set of system behaviour observed in the experimental literature; (A) changes in antibody target affinity, (B) changes in antibody NK receptor affinity, (C) changes in NK receptor expression, (D) changes in target expression.



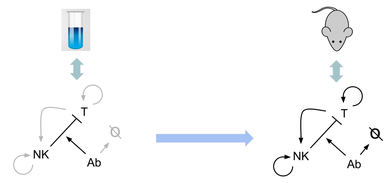

## Sensitivity Analysis

A parameter sensitivity analysis revealed that rates of cell killing depend differently on the affinity of the two ends of an antibody ($k_{on}$ is the antibody target association rate, $k_{on}^N$ is the antibody NK receptor association rate), showing a preference for the end to which NK cells bind. The partial rank correlation coefficient (PRCC) is a measure of parameter sensitivity. It is robust to uncertainty in all other parameters.




## Future Work

Future work will involve further analysis of the model to provide insight into the system and validation of the model's predictive power. The current model will also be extended to predict ADCC and antibody dependent cellular phagocytosis (ADCP) in mice.




## Acknowledgments

We are grateful to Medimmune (Cambridge) for datasets and Astrazeneca/ESPRC for joint funding. For more on ADCC in cancer see [ea07]; and the mathematical modelling of ADCC [J.82].

## References

[ea07] Ben-Kasus T. et al. Cancer therapeutic antibodies come of age: Targeting minimal residual disease. *Mol. Onc.*, pages 42–54, 2007.

[J.82] Merrill S. J. Foundations of the use of an enzyme-kinetic analogy in cell-mediated cytotoxicity. *Math. Biosci.*, 62:219–235, 1982.