

Approaches for Developing Computational Models of Immune System Function & Formation

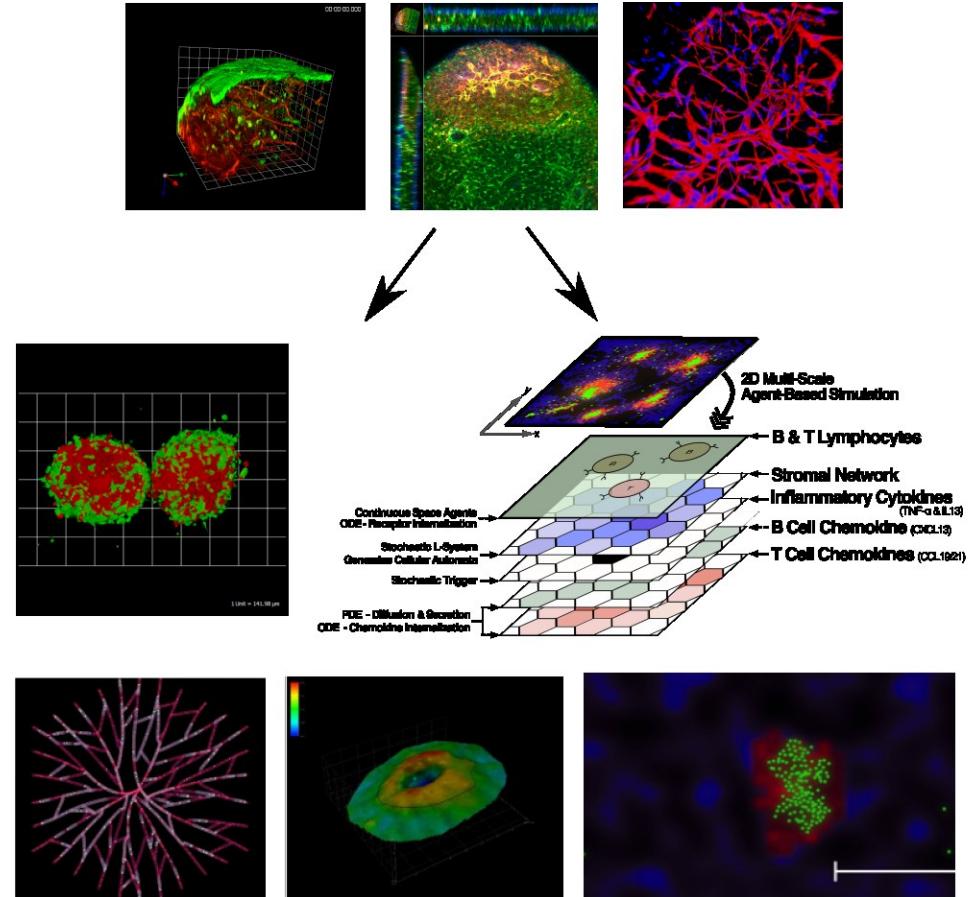
Dr Kieran Alden

York Computational Immunology Lab
Department of Electronics
University of York

York Computational Immunology Lab

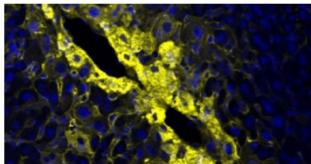
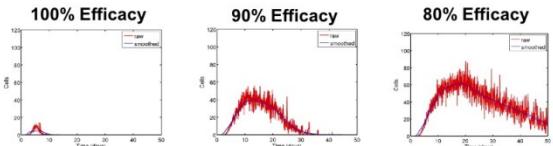
Employs state-of-the-art lab techniques in conjunction with computational & statistical methods to:

- inform the design of future experimentation,
- enhance understanding of the mechanisms of disease
- reduce animal experimentation



Case Studies

Neuronal Damage



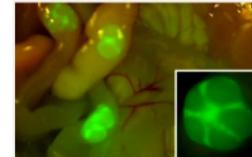
Novel Interventions for Experimental Autoimmune Encephalomyelitis (EAE)



Granuloma Formation in Experimental Visceral Leishmaniasis



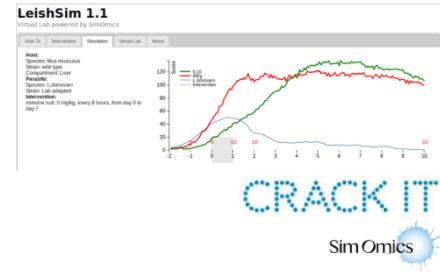
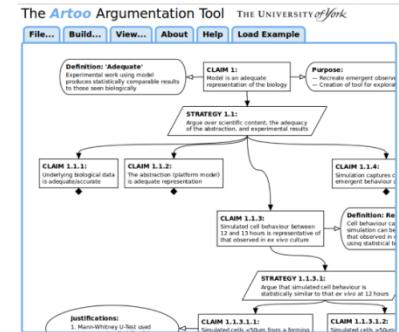
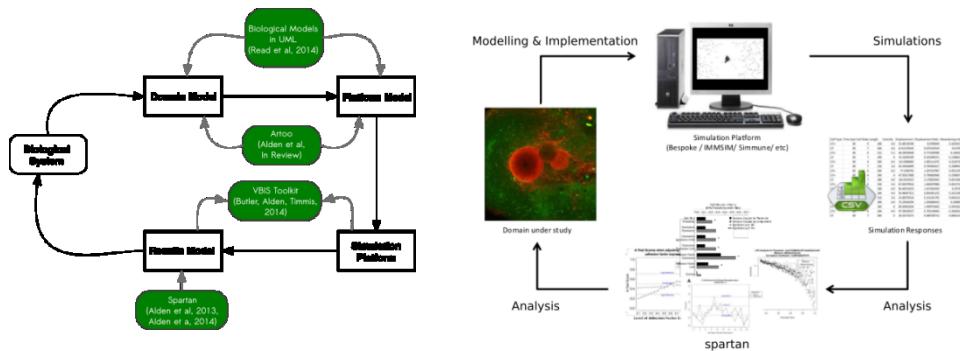
Treatments for Inflammatory Bowel Diseases



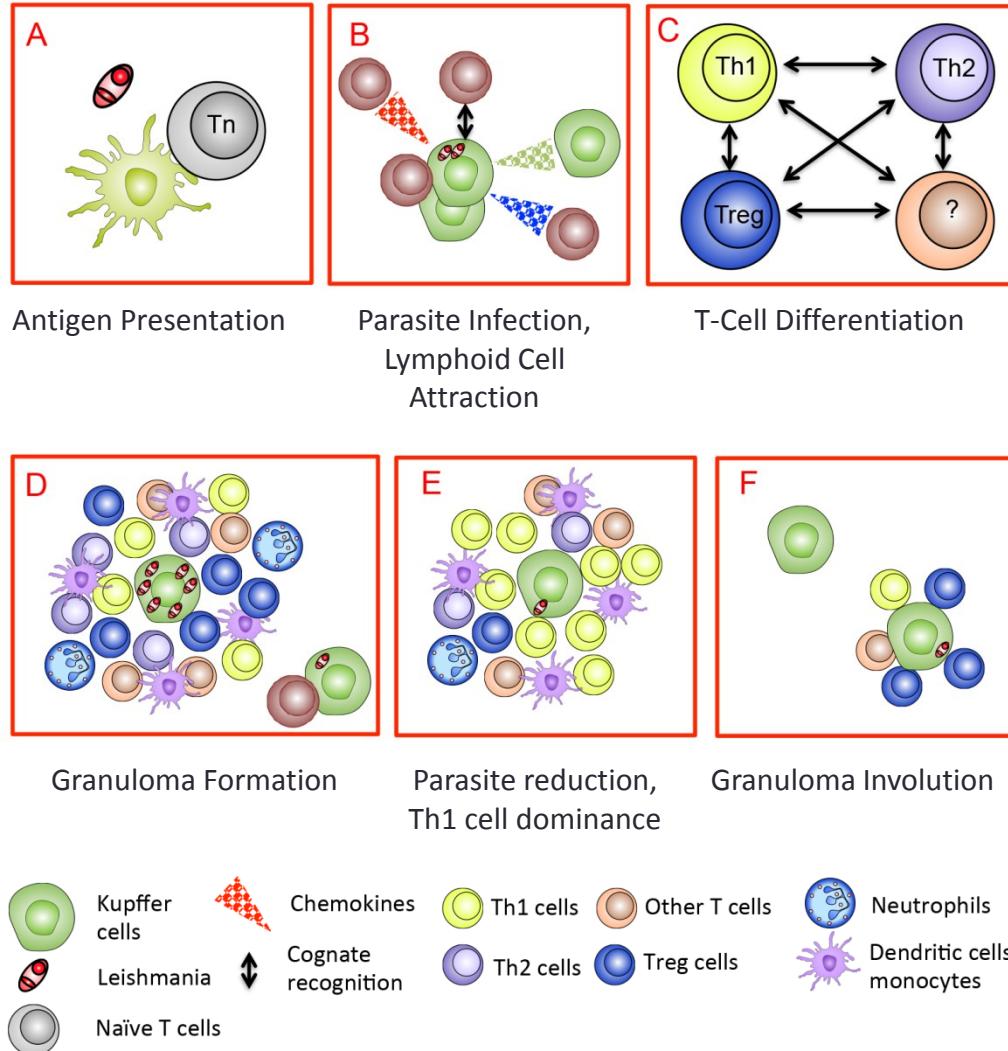
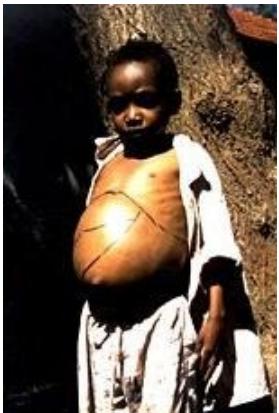
Understanding Wound Healing

Novel Treatments against Leishmania Parasites

Lymphoid Tissue Development



Leishmania



Mapping a Model to Reality



**Human
Immune System**

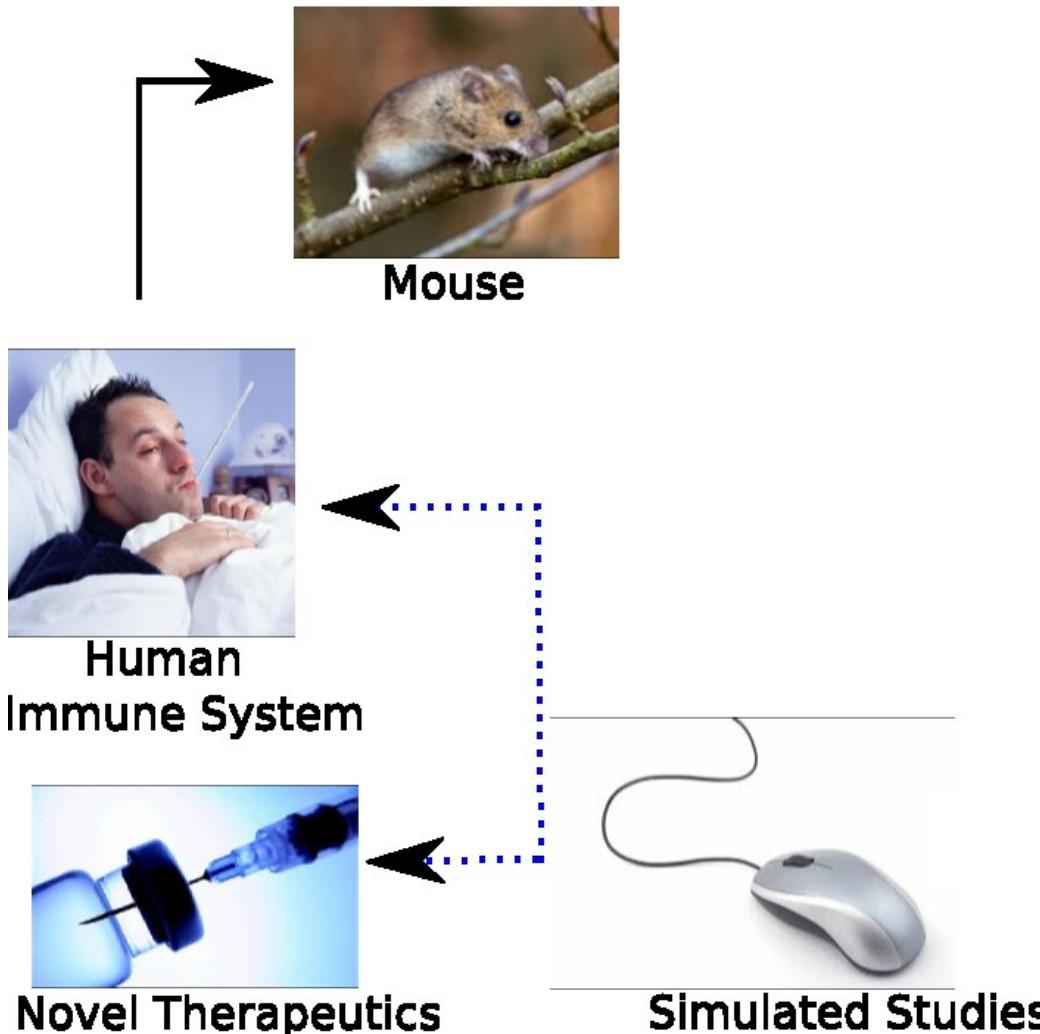


Novel Therapeutics

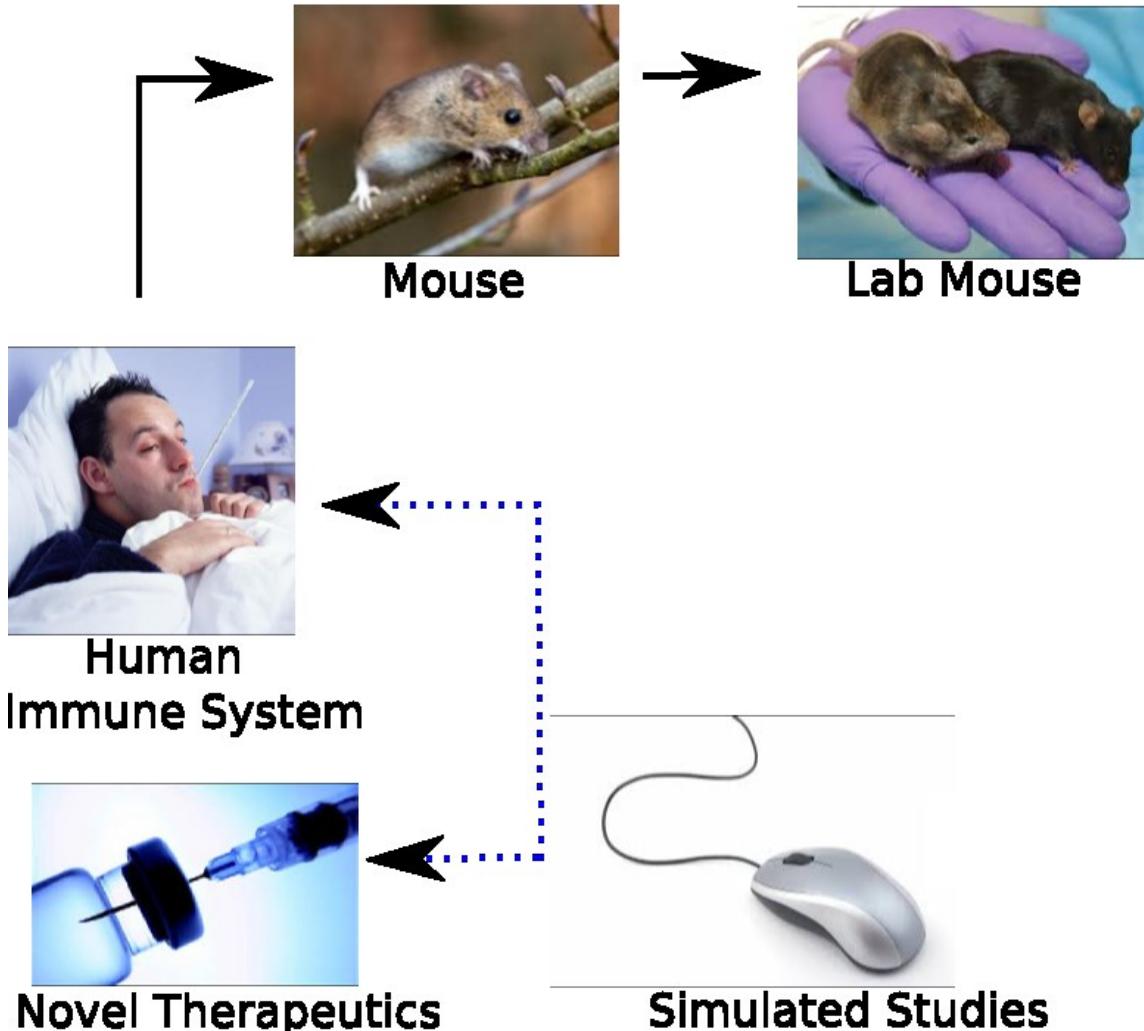


Simulated Studies

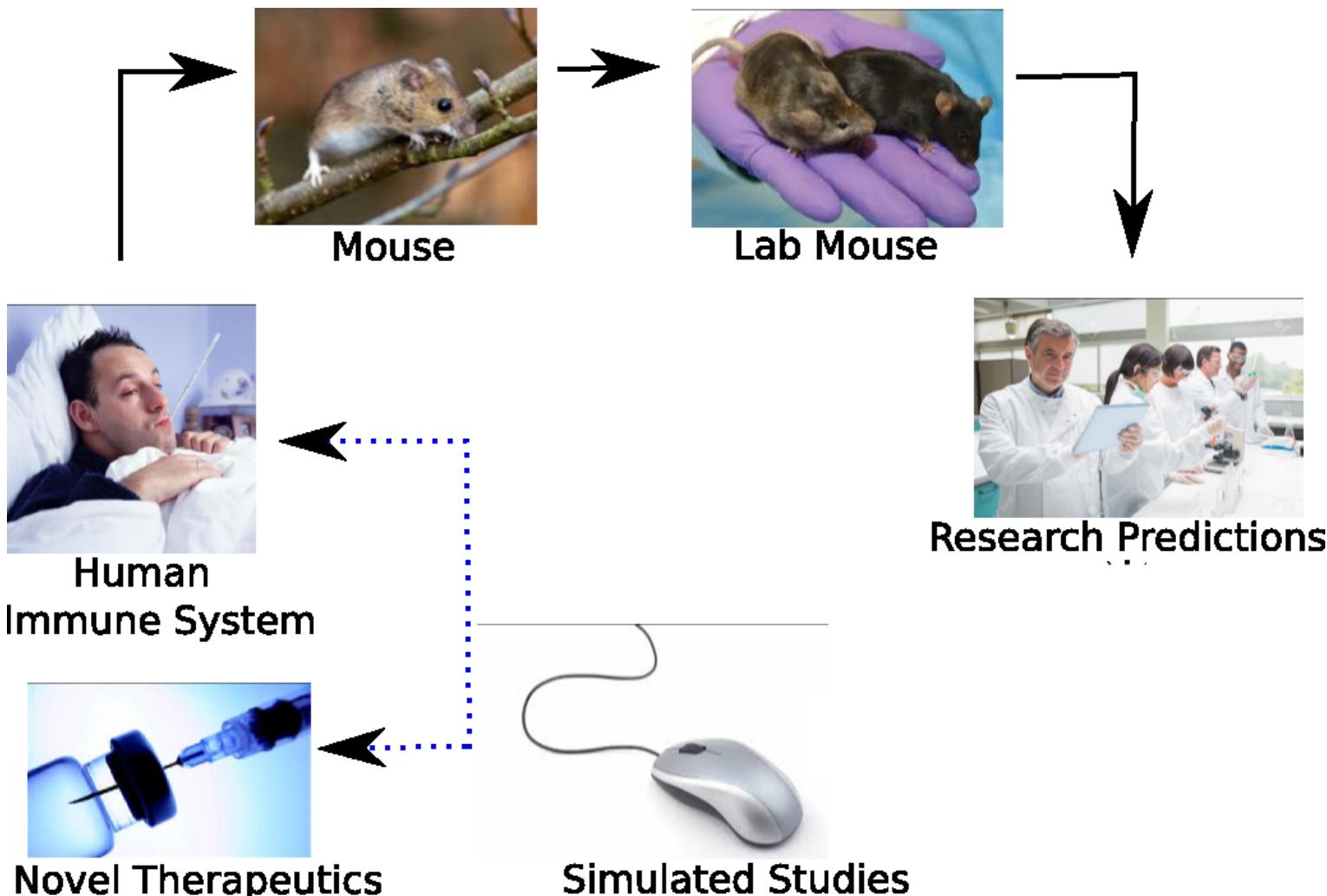
Mapping a Model to Reality



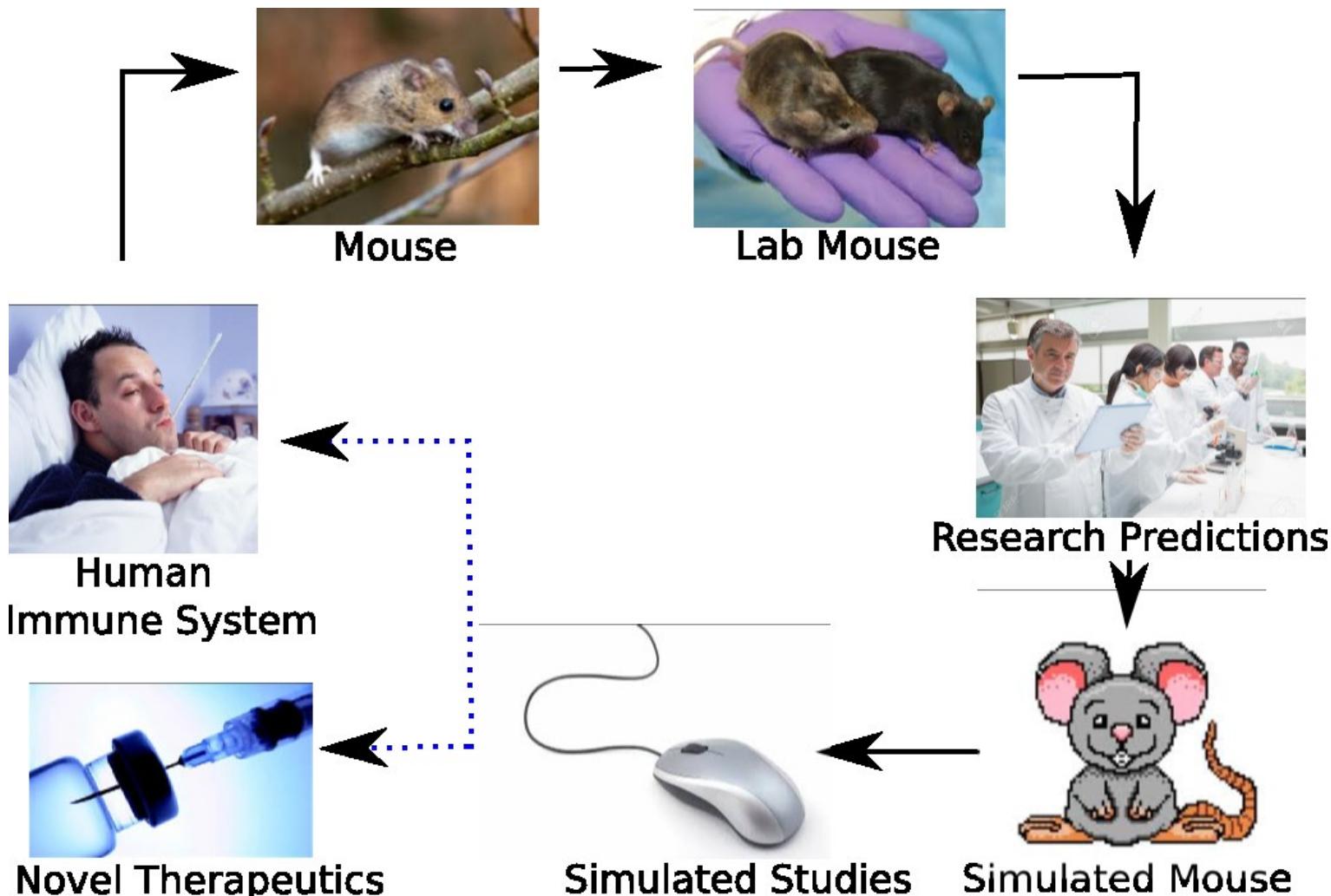
Mapping a Model to Reality



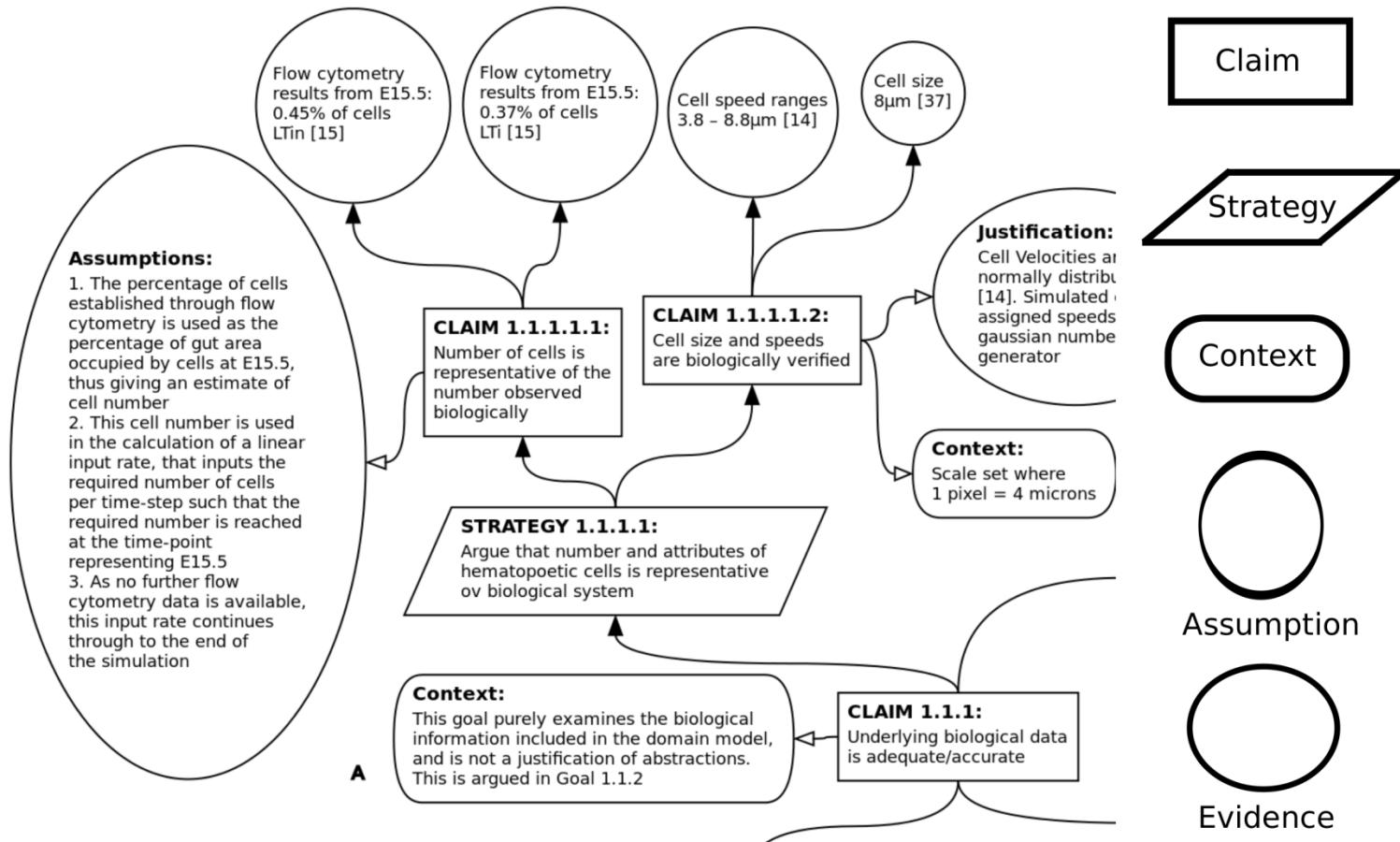
Mapping a Model to Reality



Mapping a Model to Reality

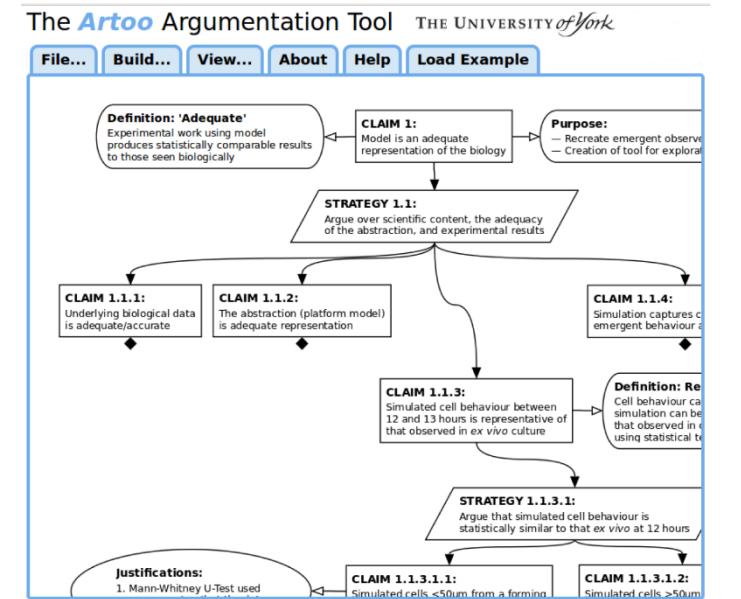
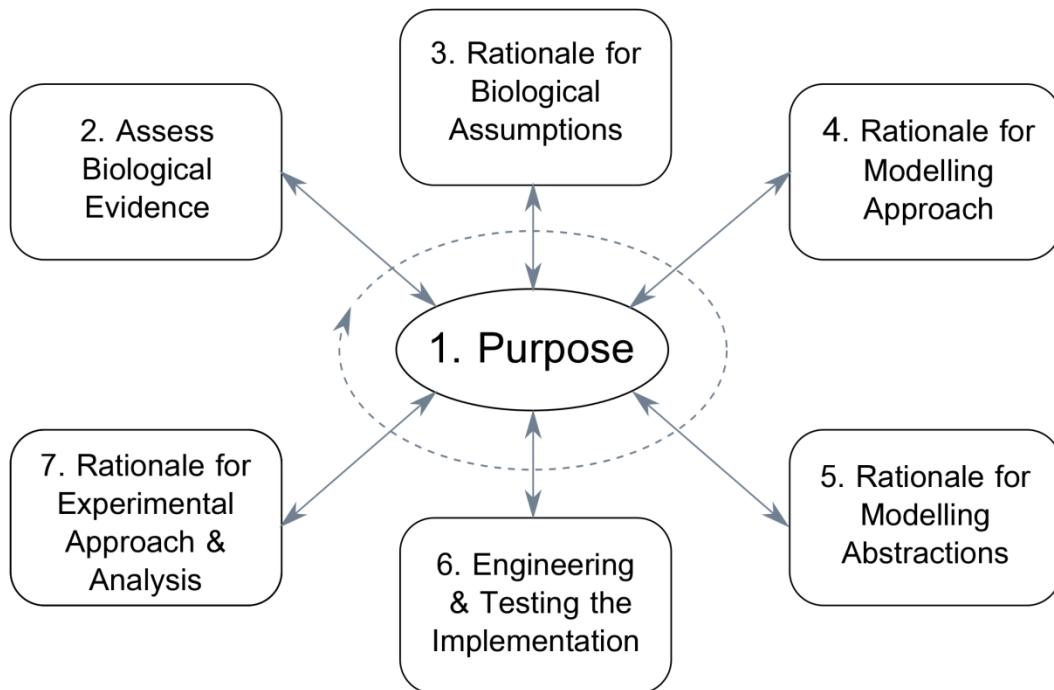


Evidence: A Documented Thought Process



Adapted from Alden et al, Royal Society Interface, 2015

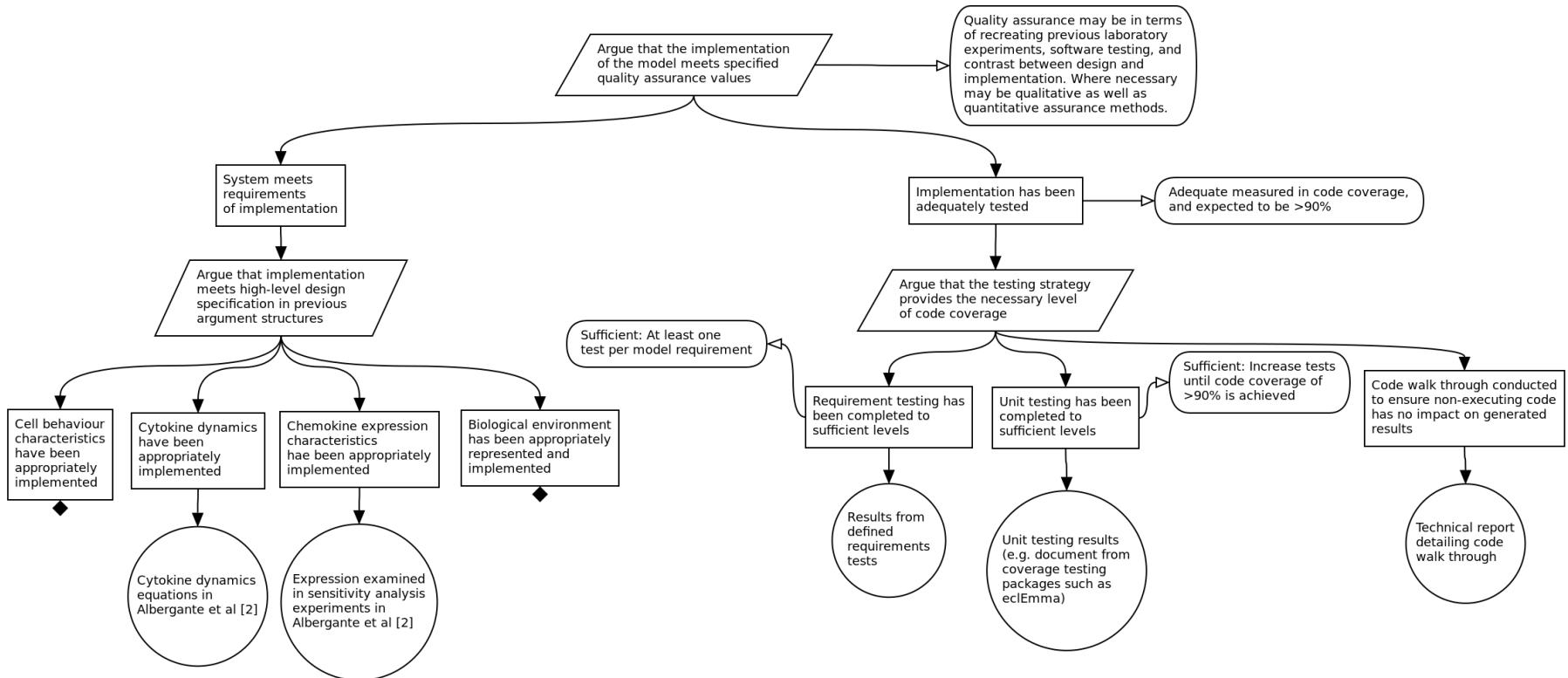
Argumentation & Artoo



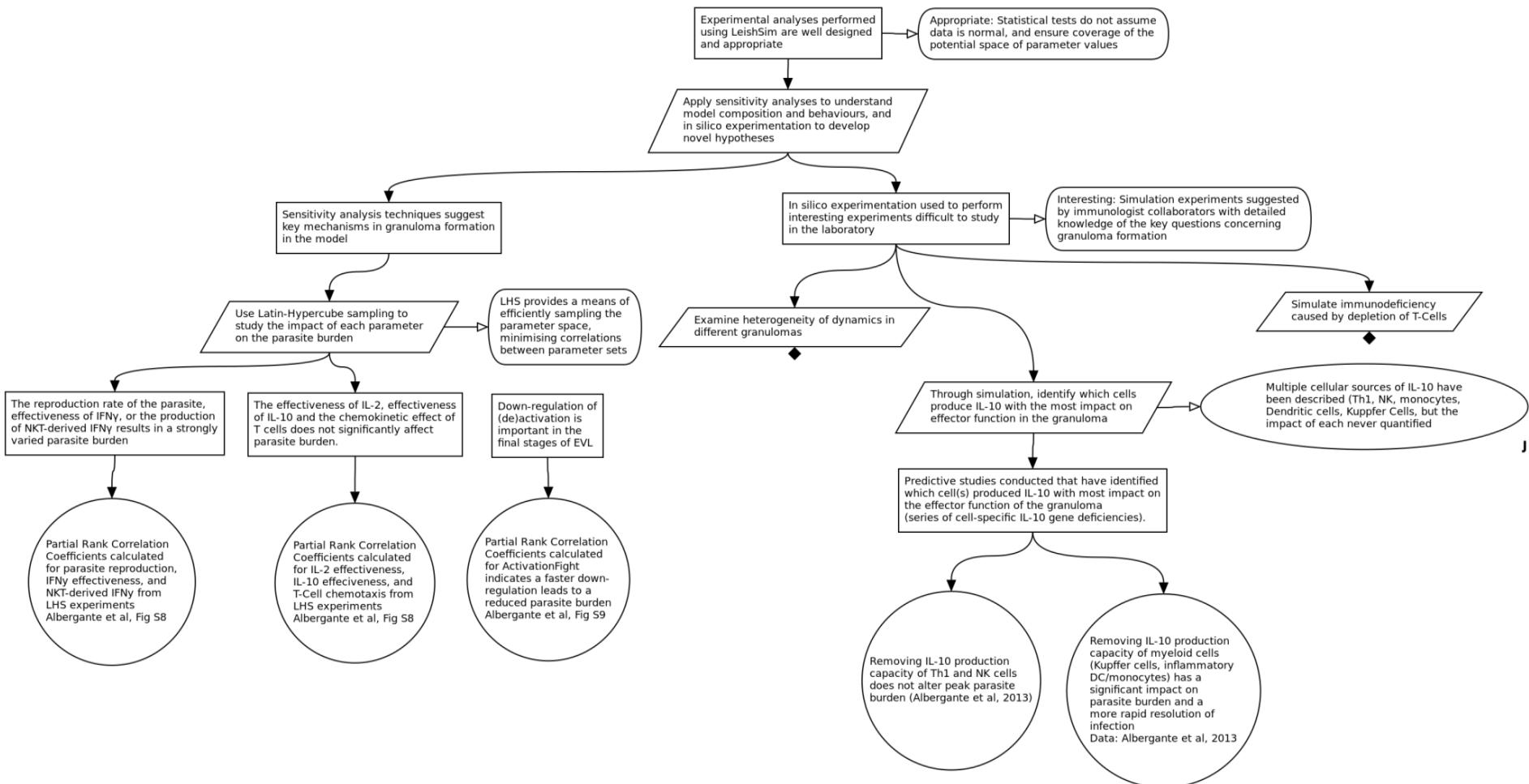
www.york.ac.uk/y cil/software

Timmis et al, CPT Sys. Pharmacol, In Print

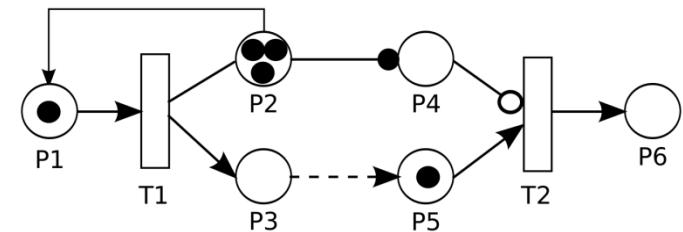
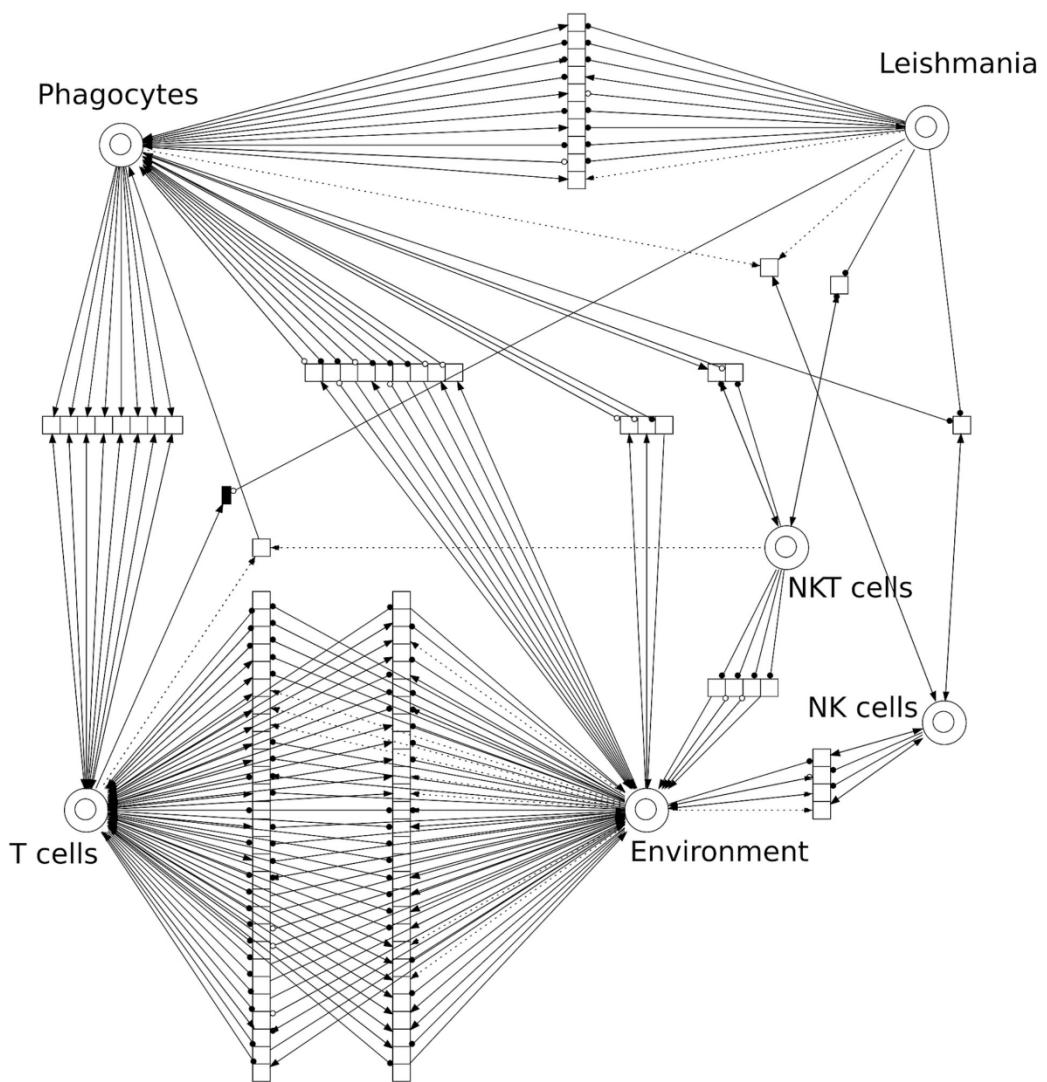
Argumentation: Engineering



Argumentation: Analyses



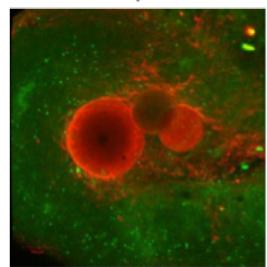
LeishSim SBML Petri-Net



○ Place (P1-P6)
□ Transition (T1&T2)
● Token

Sensitivity Analysis & Spartan

Modelling & Implementation



Domain under study

Analysis

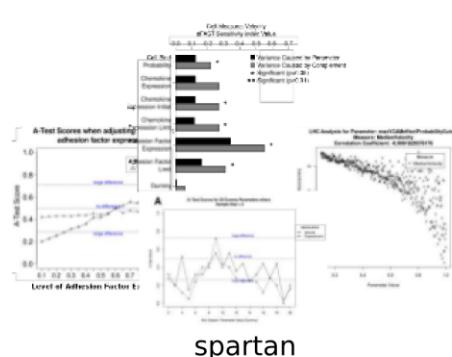


Simulation Platform
(Bespoke / IMMSIM / Simmune / etc)

Simulations

Cell Type	Time Step	Cell State Length	Velocity	Displacement	Displacement Rate	Neighbouring Index
c1v1	80	4	4.6	33.40303008	0.35700000	0.02310302
c1v1	80	7	284	4.6	4.331131610	0.0130002
c1v1	80	4	5.2	46.2959548	0.37700000	0.14800072
c1v1	80	7	4	4.6	4.331131610	0.0130002
c1v1	80	7	284	4.6	121.8900000	2.00111470
c1v1	80	7	284	3.6	41.35004889	0.30900010
c1v1	80	4	4.6	77.23001972	3.28700007	0.02122990
c1v1	80	4	4.6	33.40303008	0.35700000	0.02310302
c1v1	80	7	284	4.6	120.30104513	2.13000002
c1v1	80	7	284	4.6	87.83007098	3.00311000
c1v1	80	7	284	4.6	85.44103010	3.42700000
c1v1	80	7	284	4.6	85.44103010	0.71900000
c1v1	80	7	284	4.6	85.44103010	0.04011100
c1v1	80	7	284	3.6	33.40303008	0.35700000
c1v1	80	7	284	4.6	72.29002059	2.20500003
c1v1	80	7	284	4.6	72.29002059	0.20000000
c1v1	80	7	284	4.6	24.53203272	0.00070072

Simulation Responses



PLoS Comp. Bio, 2013

R Journal, 2014

IEEE Trans Comp. Bio & BioInf., 2016

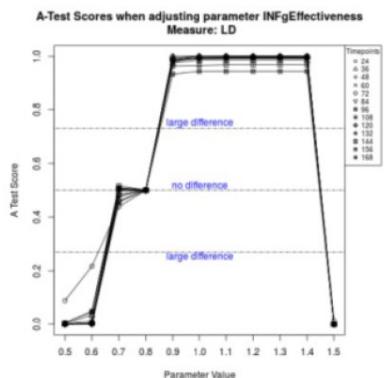
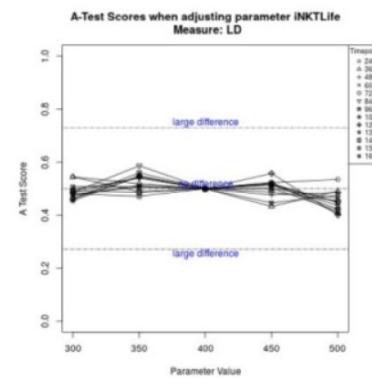
Package of statistical techniques designed to understand the relationship between a simulation and the real-world system

- Stochasticity Analysis
- Local Sensitivity Analysis
- Global Sensitivity Analysis

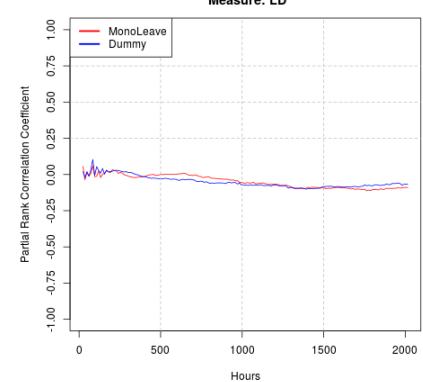
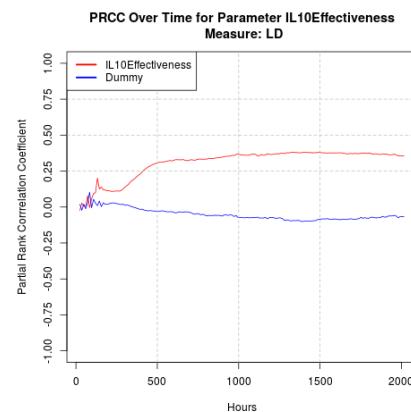
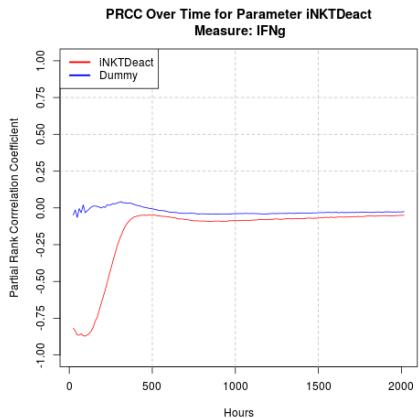
4 Publications, ~3,000 downloads, full tutorial & examples online

Sensitivity Analysis & Spartan

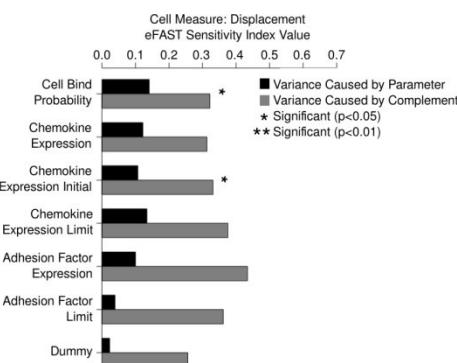
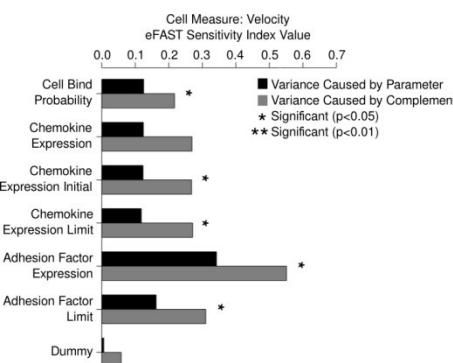
Robustness
Analysis:



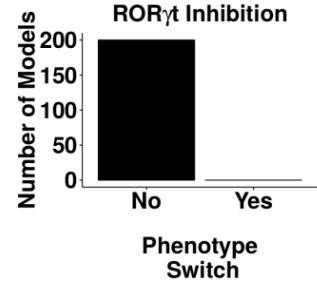
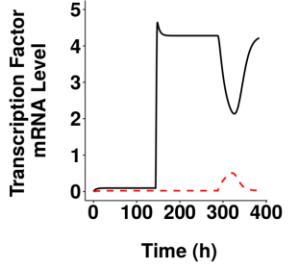
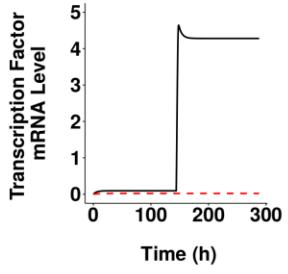
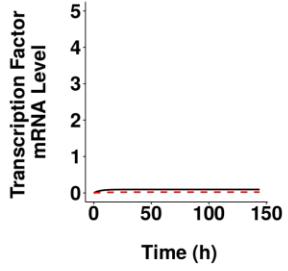
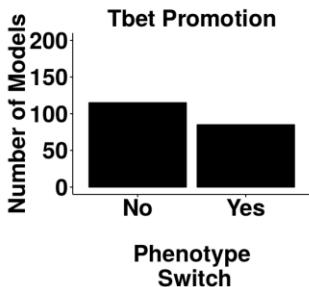
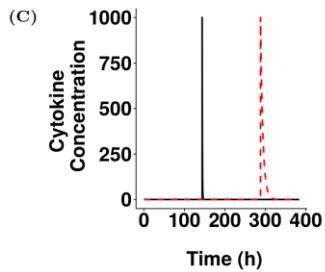
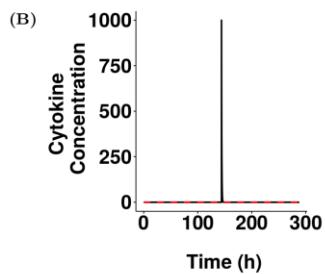
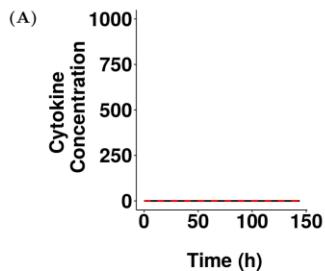
Correlation
Coefficient
Analysis:



Variance
Decomposition
Analysis:



Interventions Using ASPASIA



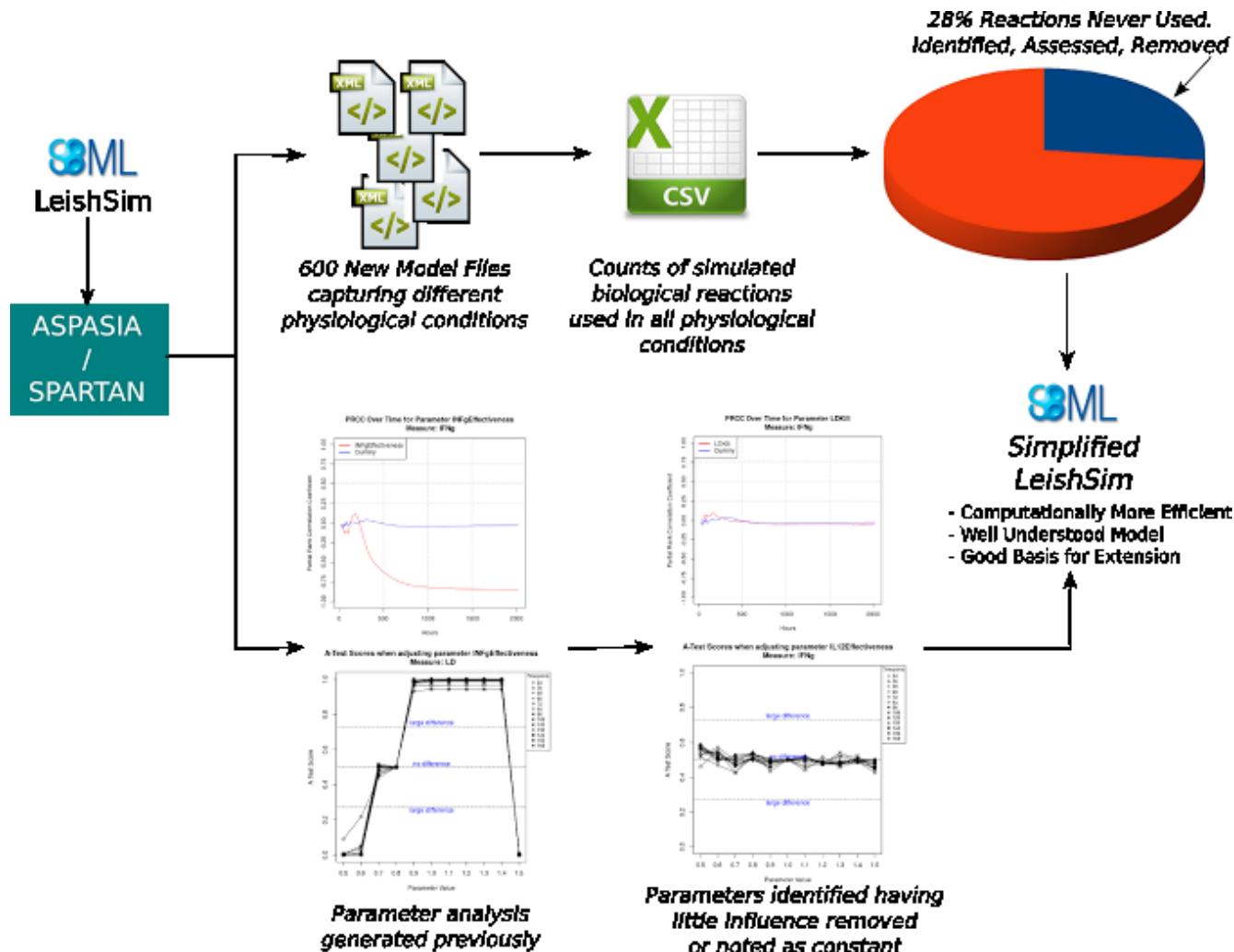
Eases SBML Model Calibration for Intervention-Dependent Behaviours:

- Response may be dependent upon conditions at intervention
- Addresses difficulty in determining extent alteration is intervention attributable

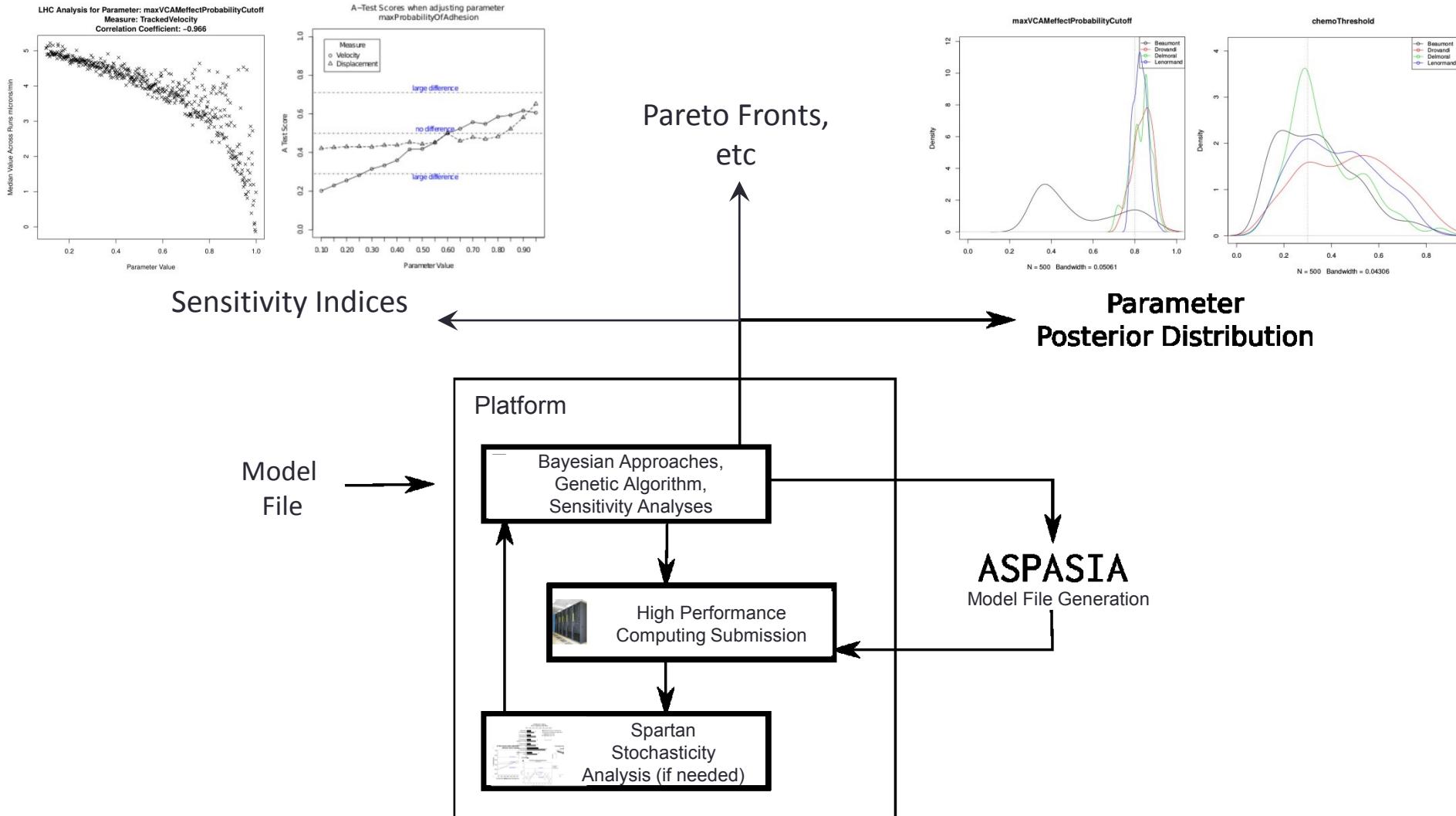
Complements SBML solvers, by generating and modifying models using solver output

Experiments generate SED-ML, with plans to integrate SED-ML into sensitivity analyses

Model Composition Analysis



Uncertainty Analysis



Thoughts & Conclusions

- Where a model informs further work, it is critical that the simulation/real-world relationship is understood
- Argumentation, Statistical Analyses, and Uncertainty Analysis could provide some methods
- Interested in taking the specification of and output of these approaches forward in using and developing simulation experiment standards.

Acknowledgements



Spartan:

Dr Mark Read (Sydney)

ASPASIA:

Dr Marika Kullberg (HYMS)
Stephanie Evans (York, Imperial)

AR TOO:

Dr Paul Andrews (SimOmics Ltd)
Dr Becky Naylor (SimOmics Ltd)

Leishmaniasis:

Prof Paul Kaye (HYMS)
Dr Daniel Moyo (York)
Dr Luca Albergante (Dundee)
Dr Simon Hickinbotham (York)

York Computational Immunology Lab:

Prof Jon Timmis
Prof Mark Coles