Building Confidence in Modelling and Simulation

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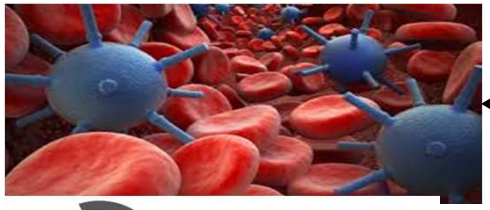
Crossing Boundaries

Immunology



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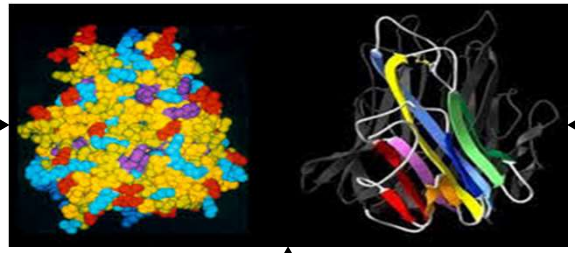
Modelling



Bio-inspired Systems

Environmental Sciences

capacitie

Cutting-Edge Approaches for Pollution Assessment in Cities

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Commercial

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Critical Engineering

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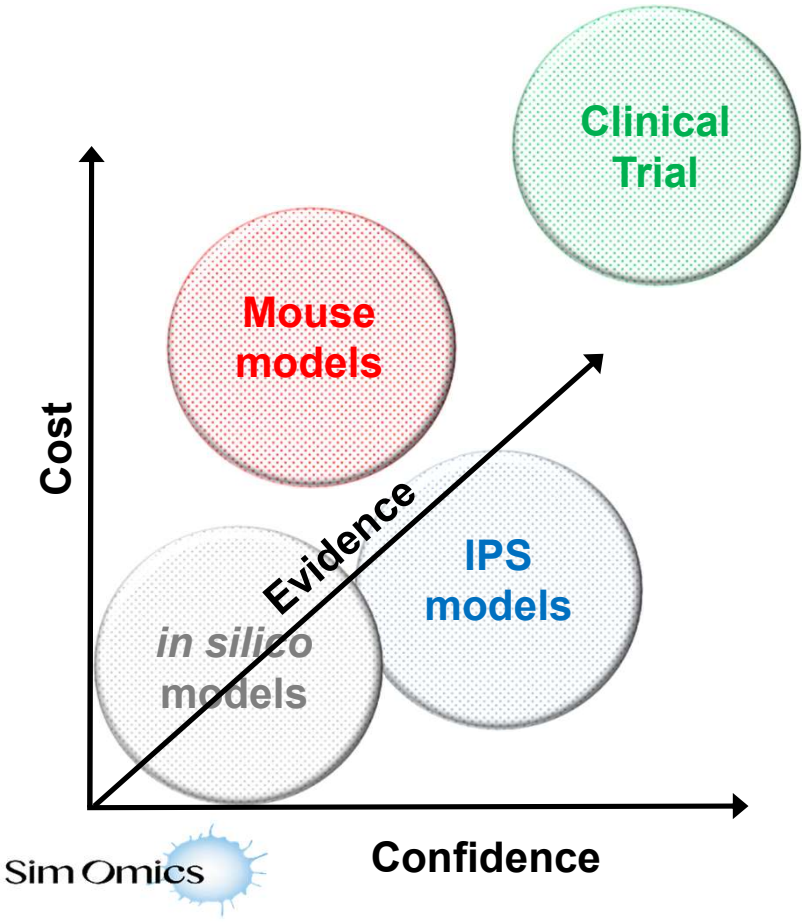
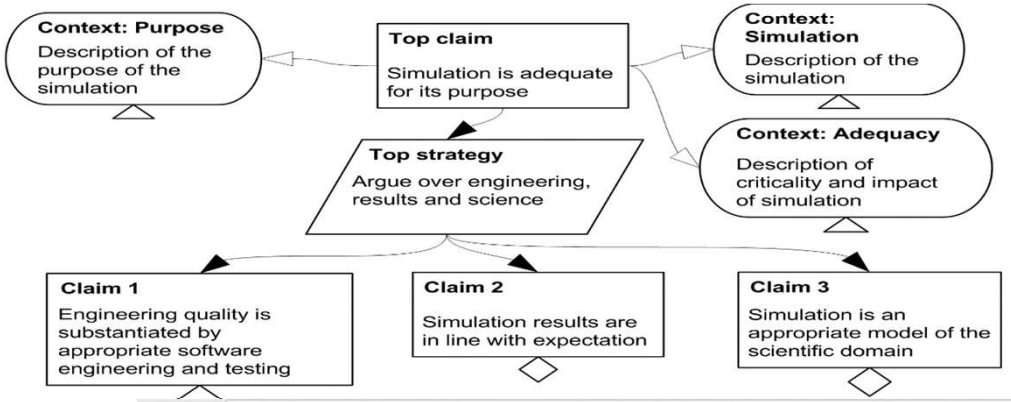
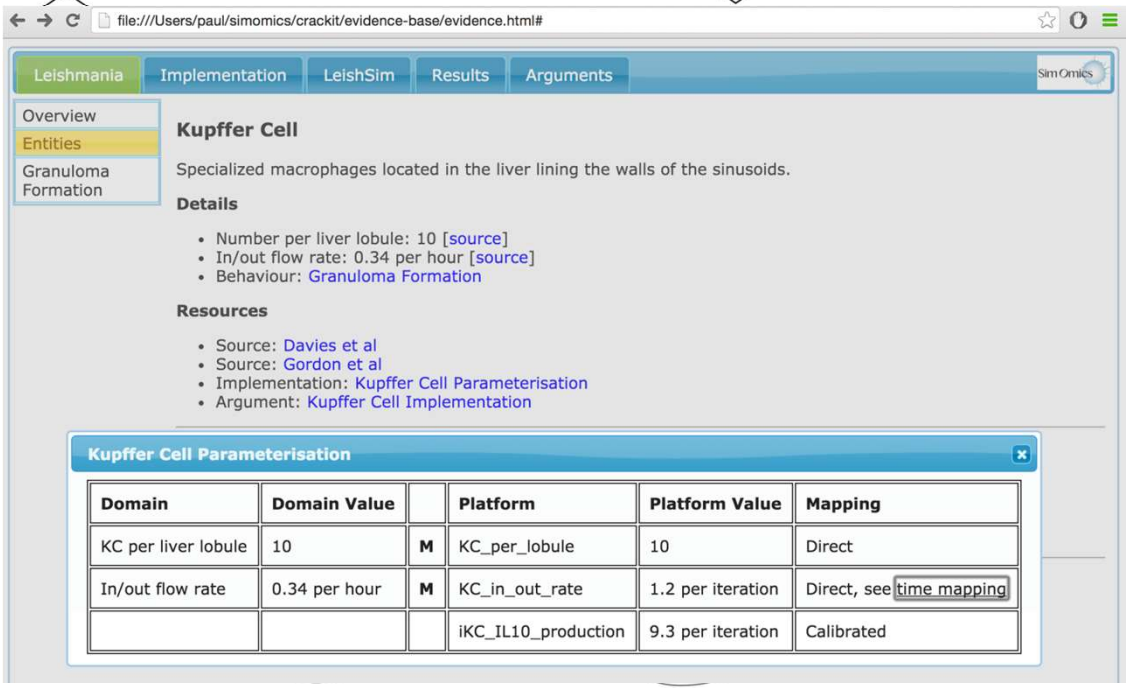
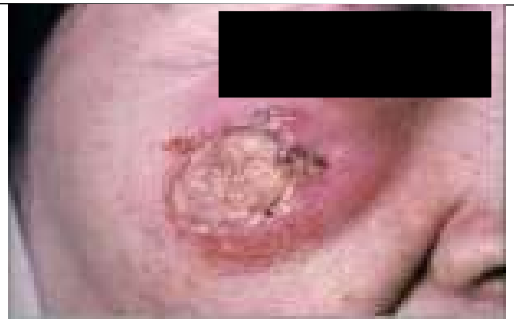
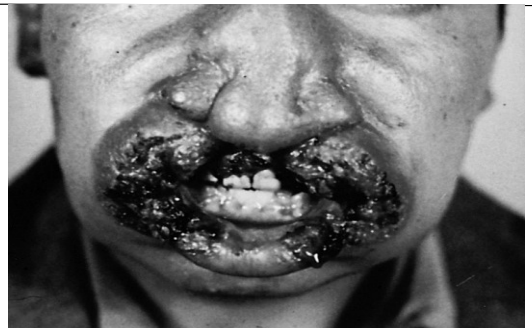
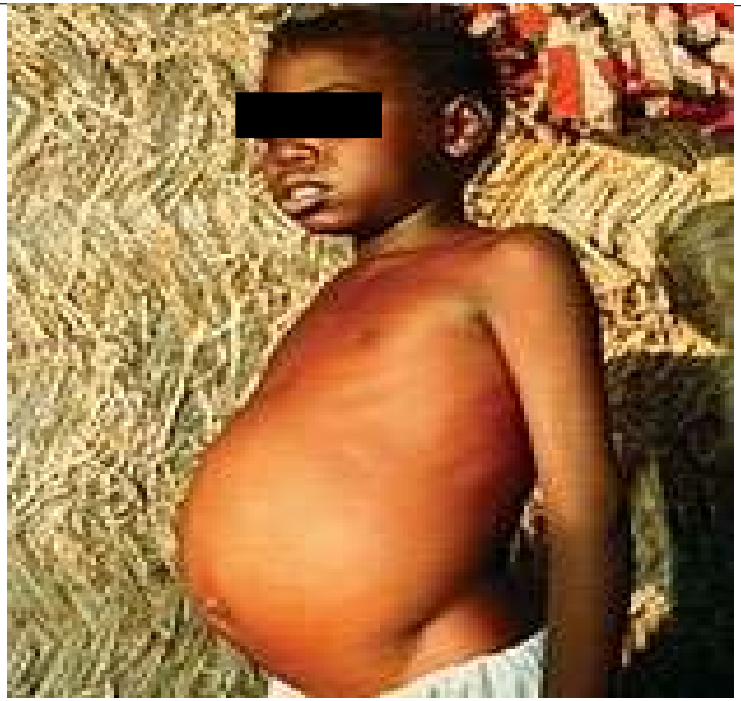
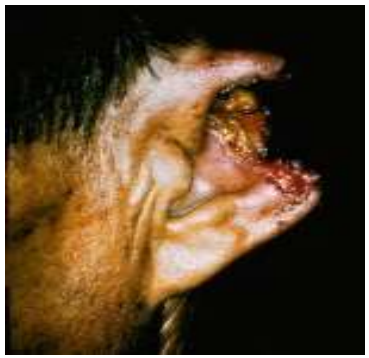
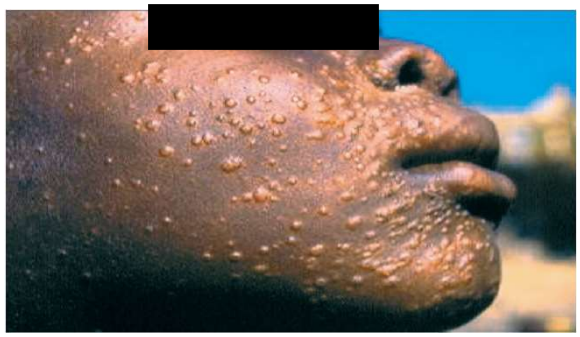
Evidence, Confidence and Transparency
Applying critical systems engineering approaches







The Spectrum of Leishmaniasis

- One of the most neglected tropical diseases, yet ranked 9th in analysis of global burden of disease, with an associated mortality amongst parasitic infections second only to malaria
- 14M people infected, ~40,000 recorded deaths annually (3-4-fold under-reported); 350M at risk in 98 endemic countries (incl. the 15 poorest but also some of the more wealthy).

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The Virtual Infectious Disease Research Challenge

To develop a virtual platform that models infection and the host response to pathogen assault for basic research and enhances new target development in infectious diseases.

CRACK IT

NC 3Rs National Centre for the Replacement Refinement & Reduction of Animals in Research

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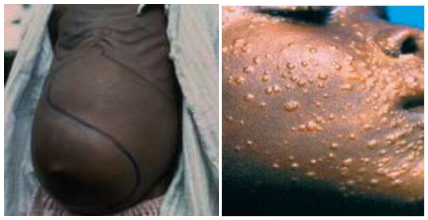
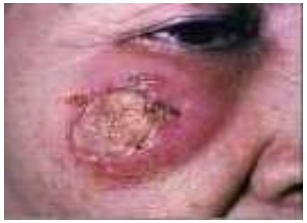
The Challenge of Leishmaniasis Drug Development





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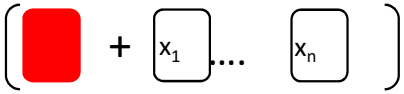
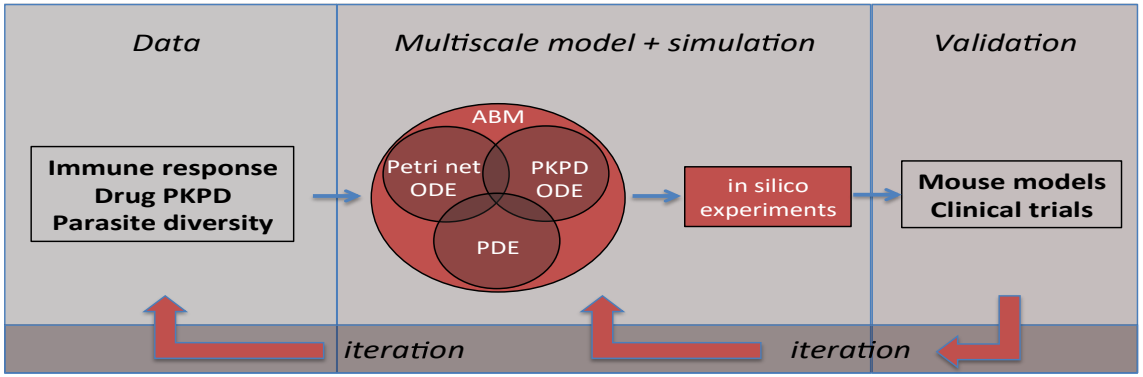
dose, schedule



>1024 combination therapy options

Existing approaches = ***30,000 animals at LSHTM / York in 10 years***
~40,000 animals per year globally



Our goal is to create a virtual laboratory, that:

- allows exploration of the drugable space
- provides new mechanistic understanding
- addresses unmet clinical needs
- has broad application to infectious disease
- is evidenced and free to use

and

delivers maximum 3Rs impact

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An Evidencing “process”?

- Giving a ***structured method*** to have some confidence in the use of models and simulations

- Consider all activities:
  - ***documenting***, ***building***, ***using***, and ***reasoning*** about models and simulations

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Stakeholder Engagement

- What do you simulate?
- When do you need a domain expert?
- How much do you trust a DE's opinion?
- Managing expectations
  - What can models actually do
- Domain differences
- How much time does it take to do something?
- Speaking the same language

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What is your Purpose?

- To what extent did you know what you were going to investigate before you started simulating?
- Use simulation to ask a specific question?
  - Or general exploration?
- How do you record/document/communicate purpose?
- Bespoke tools vs generic frameworks

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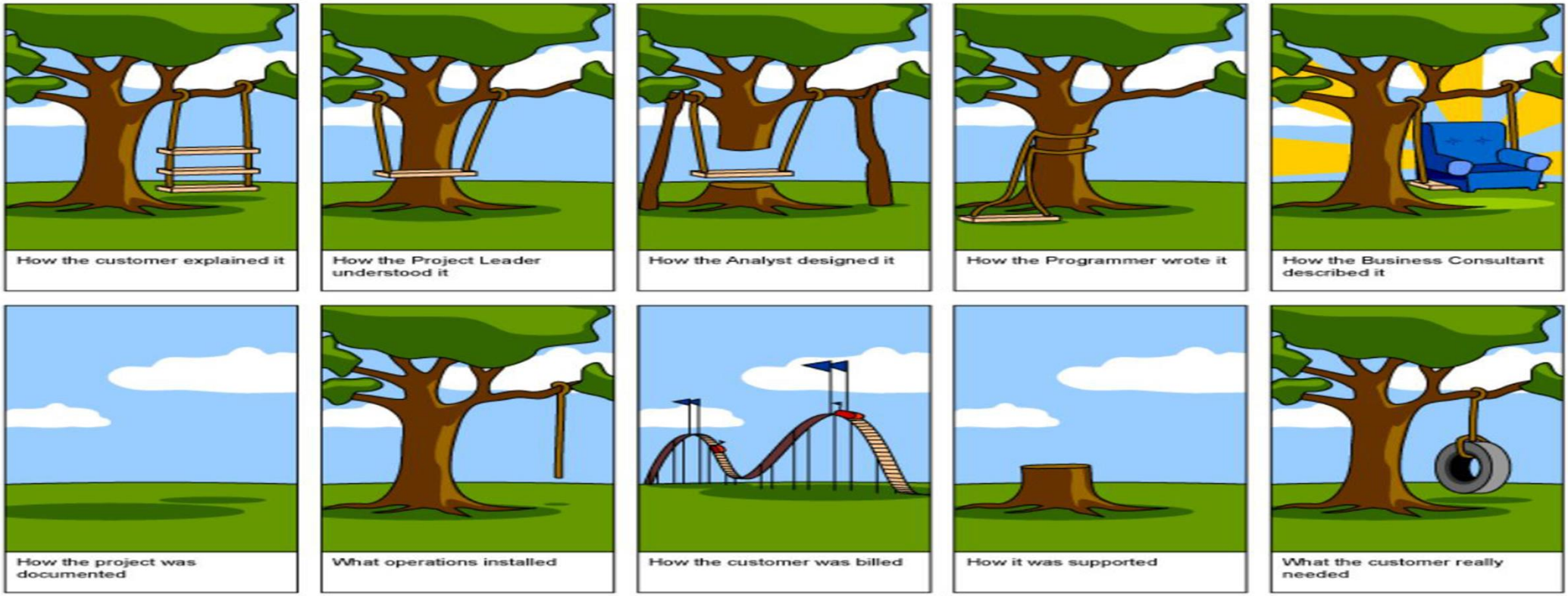
Where can it go wrong?



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Terminology: Confidence

Simulation outputs adequately represent the domain

- Problem and purpose specific
- Not currently quantified
- Not absolute
- Open to interpretation

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Qualifying Confidence

- What is “confidence” to you?
  - how much do you need?
- Do you measure it?
- Impact and criticality
- Use of ***evidencing***

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Some questions to think about

- What constitutes acceptable evidence? (quantitative versus qualitative evidence, role of expert opinion)
- What types of evidence do people deal with?
- How do they find evidence? What sources they use?
- How do they decide whether evidence is generalizable?
- How do they rate confidence in evidence, and deal with uncertainty?
- What are the different needs from your stakeholders?
- Do you care more about the biology or also the structure of the model and how it was built.
- What are the best ways to visualise evidence?
- If you could identify one key piece of evidence to convince you of the value of a model – what would it be?

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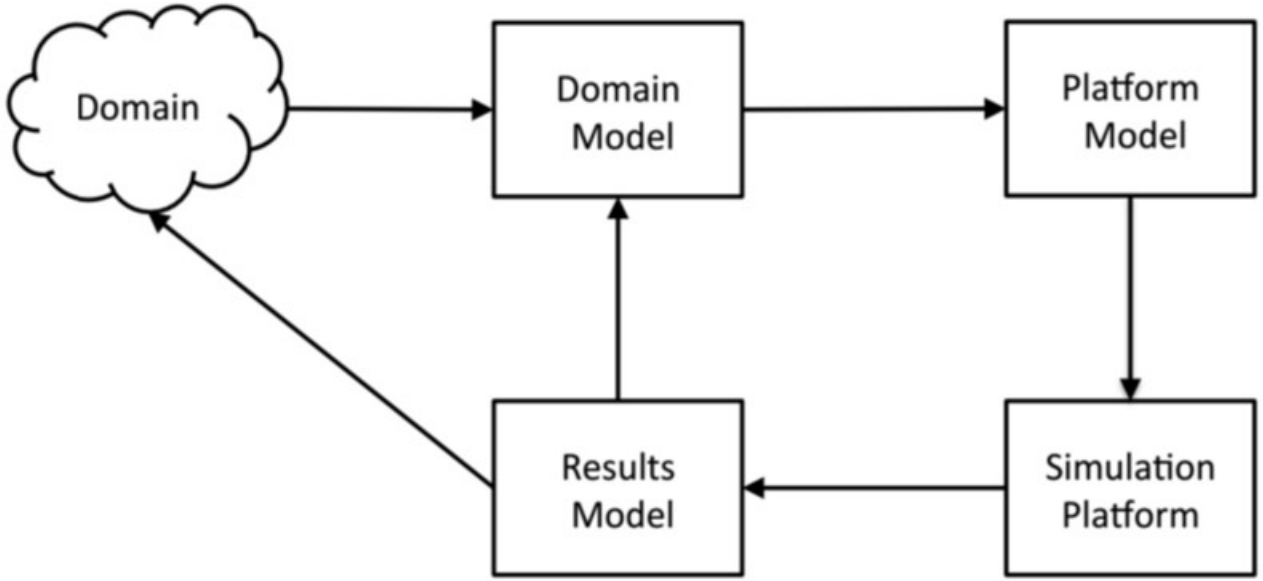
Process for Modelling

- **Simulation based scientific research** based around following components:



- Each model is for one explicit purpose

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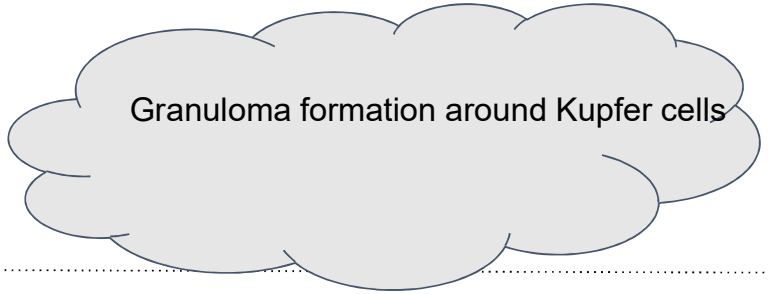
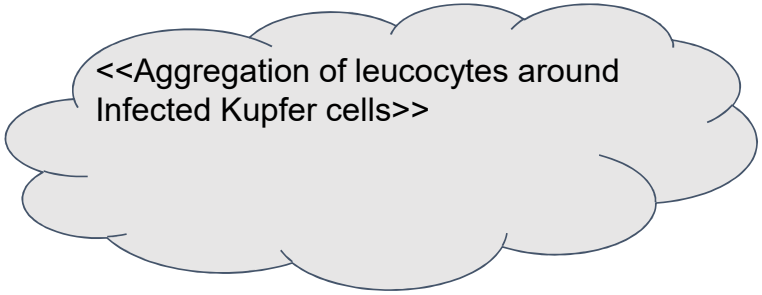
Developing a research context diagram

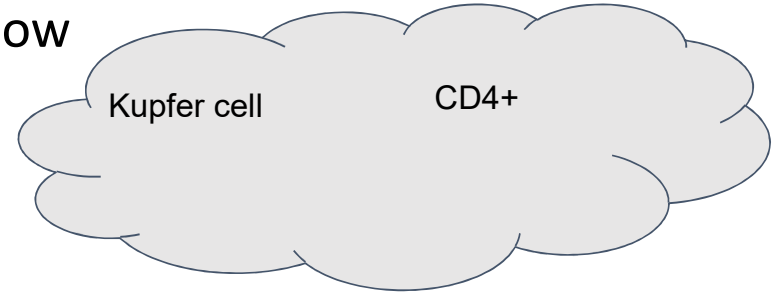
Identify observable phenomena



State hypothesis of how observable phenomena manifest



Identify actors that contribute to hypothesis and how they interact



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Communicating Model and Results

- How do you convince people that your results are representative?
  - **Argumentation**
- Are the traditional research outlets adequate for modern day simulation-based research
  - How do you publish the model? 85 pages of SI?

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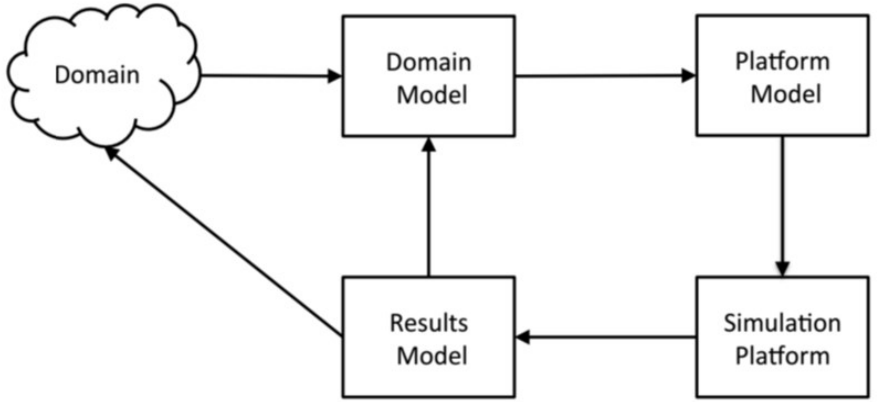
Documentation

- Creating the core model components provides an explicit structure for documentation and communication
- Document
  - What goes into the boxes
  - How you **transition** between the boxes



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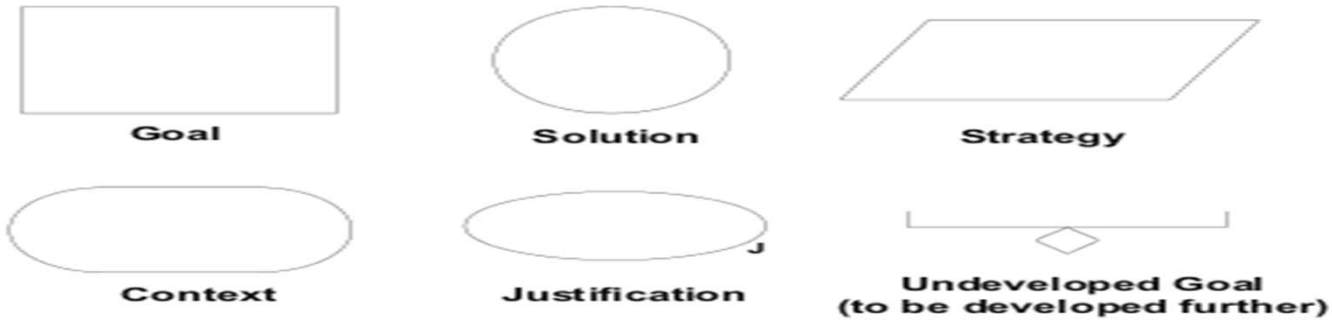
Argument-based Validation

- Inspired by validation of safety-critical systems
- Stringent analysis of compliance to a set of requirements:
  - Each implementation step is validated
  - Reasoning behind inclusion/exclusion of feature/assumption provided
  - Evidence given as to why this conclusion drawn



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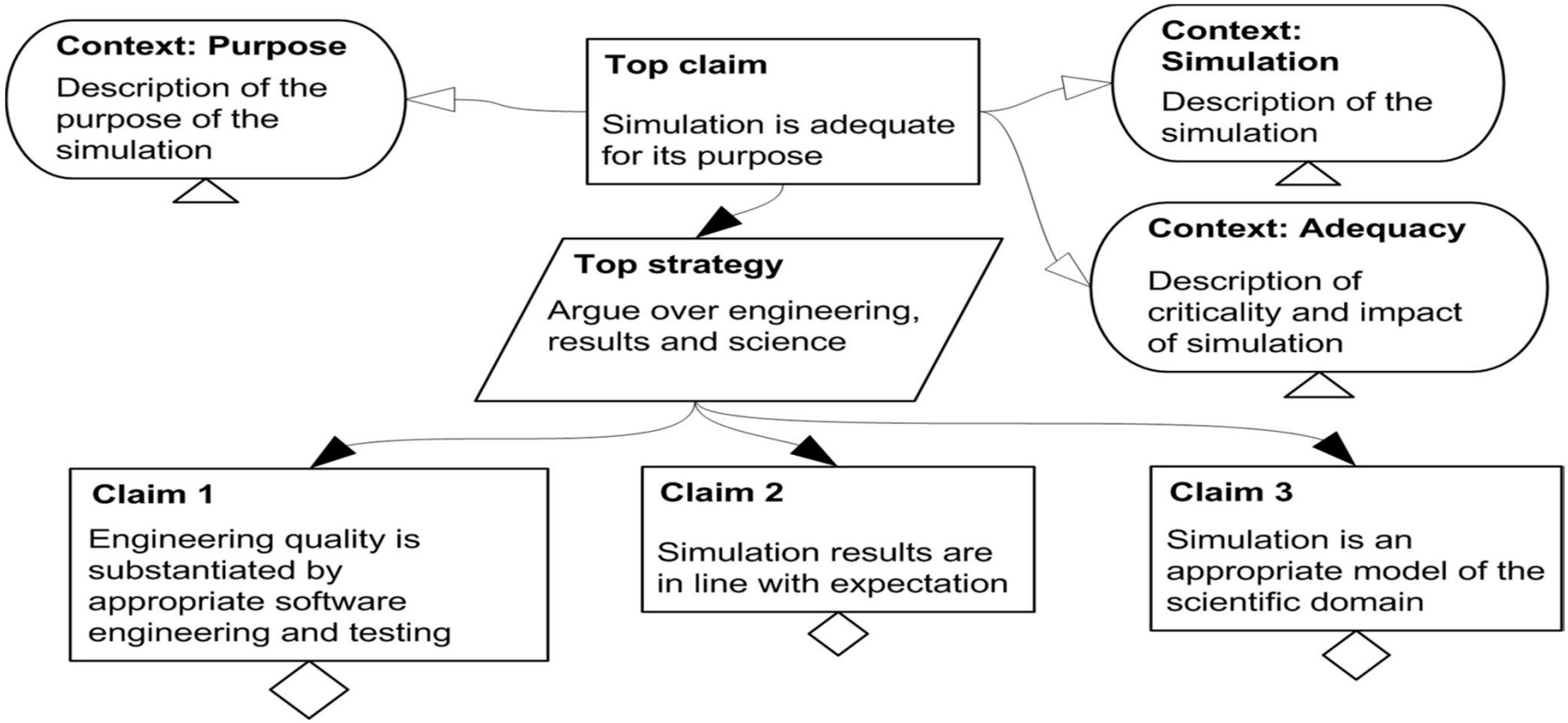
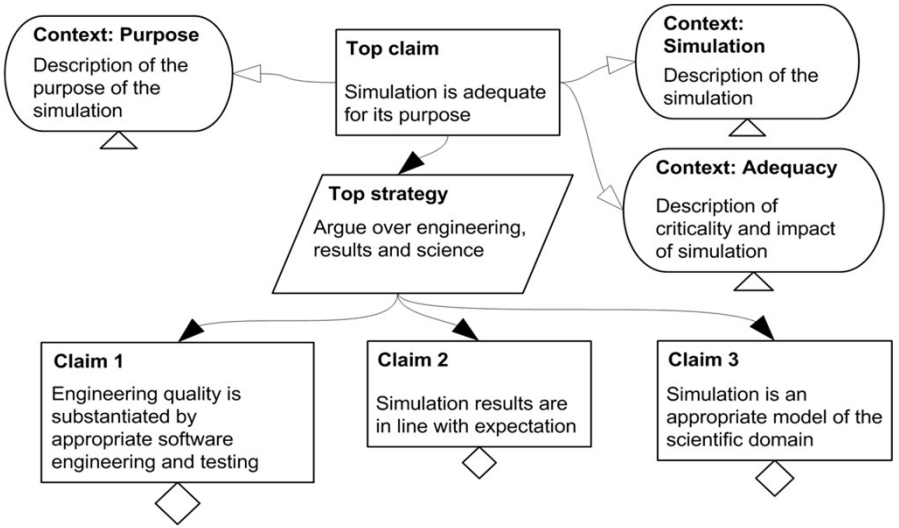
Developing a claim



Process for developing a claim

1. Assessing the biological evidence
2. Justify model engineering decisions
3. Justify model biological assumptions
4. Justifying engineering abstractions
5. Justifying experimental design
6. Justifying the simulation analysis process



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1: Assessing Biological Evidence

- Assess scope of available data
- Expert opinion
- What understanding is currently lacking
- For each, need to establish a “goal”
  - Argue that “the data shows an adequate representation of observed cell behaviour”
  - Strategy to “examine the methodology used to capture the data and the time points the data was collected”
  - Each strategy might be linked to evidence nodes

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2: Justifying Model Engineering Decisions

- Many techniques to implement model could be decided upon
- Need to justify engineering decisions taken
- Could argue that “an agent-based modelling paradigm is most suitable for addressing the key research question”
- A strategy could be “examine the need for heterogeneous populations embedded in a representative space”

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3: Justifying Model Biological Assumptions

- Step 1 will highlight gaps in biological understanding
- Argue that each assumption is an acceptable representation of the biology
  - Need to clearly define what is acceptable

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4: Justifying Engineering Abstractions

- Might not be possible to capture the complete biological system
  - abstractions are necessary that could have a major impact on the model
- Might develop an argument, “it is not necessary to represent an entire lymph node, but only a portion of the lymph node”
- Then a strategy might be to “examine the effect of reducing the amount of represented space on the emergent behaviours of the system”

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5: Justifying Experimental Design

- Prior to any experiments being undertaken establish necessary experiments
- Argue that “in silico experiments being undertaken are necessary to address the research question”
- With a strategy that “examines the use of selected experimental protocol”

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6: Justifying the Simulation Analysis Process

- Results need to be interpreted in light of
  - the scope of the designed simulation
  - the biological system being studied
- Draw conclusions from simulation-derived results, utilising evidence compiled in steps 1 - 5

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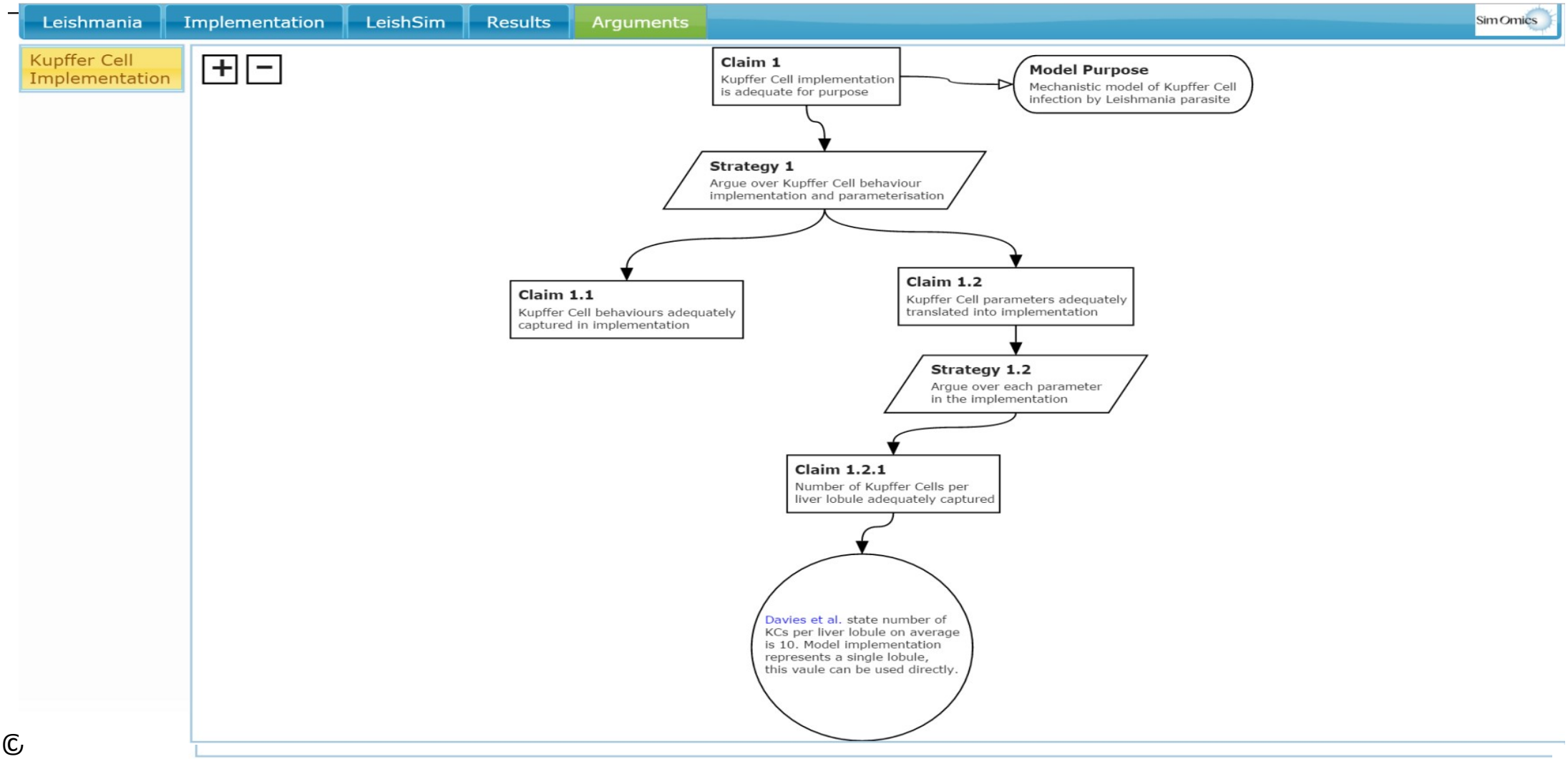
Integrated tools to explore evidence



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Summary

- Transparency of rationale, design and implementation is important
- Better ways of exploring such rationale can be developed
- Potential for better stakeholder engagement and understanding

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More information

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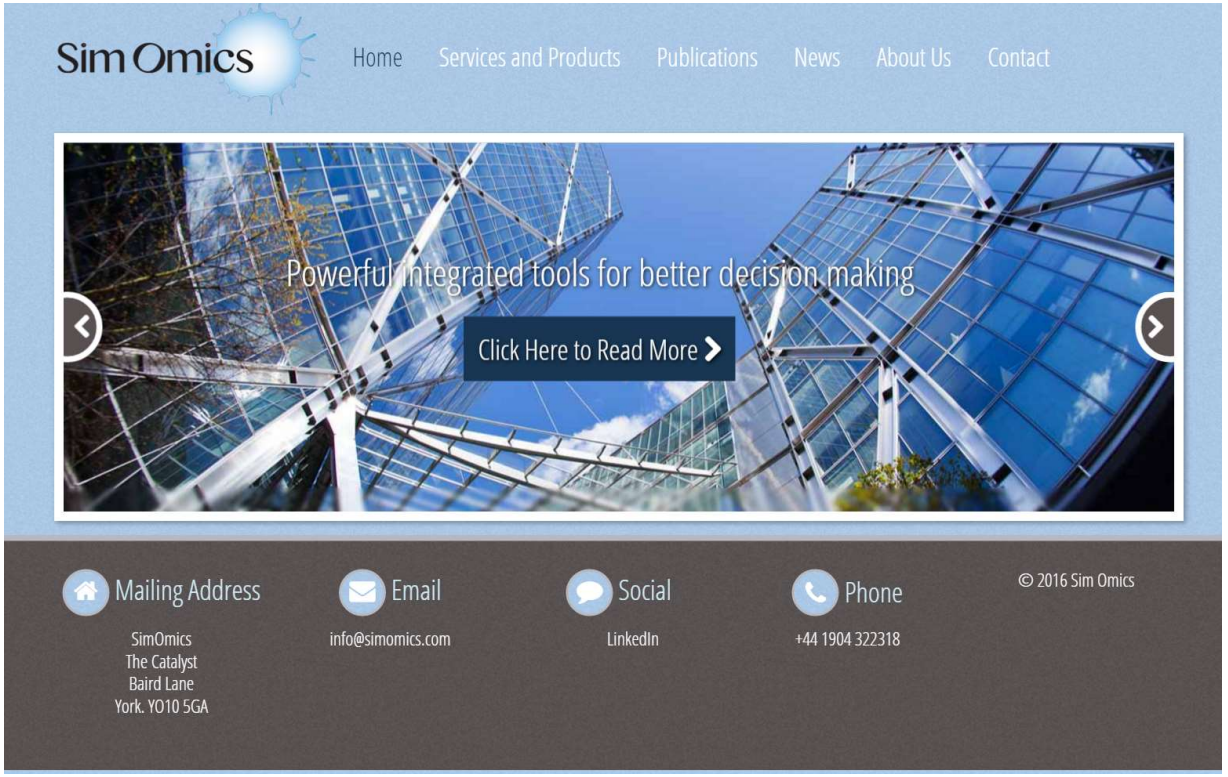

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