

# Modelling the immune response to co-infection of Helminths and Malaria: very preliminary work!

E. Scott<sup>1</sup>   T. Spencer<sup>1</sup>  
R. Norman<sup>1</sup>   C. Shankland<sup>1</sup>   A. Graham<sup>2</sup>

<sup>1</sup>University of Stirling,  
Department of Computing Science & Mathematics

<sup>2</sup>Princeton University  
School of Biological Sciences

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# Computing in Biology

The rise of “Systems Biology”:

*“The reductionist approach has successfully identified most of the components and many of the interactions but, unfortunately, offers no convincing concepts or methods to understand how system properties emerge...the pluralism of causes and effects in biological networks is better addressed by observing, through quantitative measures, multiple components simultaneously and by rigorous data integration with mathematical models”*

(Sauer et al, Getting closer to the whole picture, Science Apr 2007)

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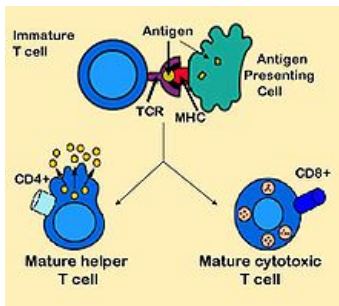
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# Benefits of Modelling Biology?

- Formalisation!
- Gaining a different perspective
- Analysis (computational and algebraic)
- “In silico” hypothesis testing to guide and explain “in vivo” experimentation

# Immunology for non-biologists

Adaptive immunity: the ability to recognise a pathogen, generate a response, and remember that pathogen (for a better response next time).



National Institute of Allergy and Infectious Diseases booklet *Understanding the Immune System*.

Helper T cells (CD4+) are immune response mediators.  
Cytotoxic T cells (CD8+) induce death of infected cells.

# The role of Th1 and Th2

Two kinds of T helper cells (CD4+) are of interest:

## Th1:

(broadly) deals with intracellular pathogens

such as malaria:

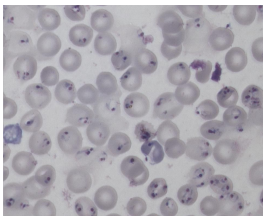


Figure courtesy of Richard Culleton at Malaria Genetics and Epidemiology.

## Th2:

deals with extracellular parasites (also bacteria and toxins)

such as Helminths (parasitic worms):



Figure courtesy of the Centers for Disease Control and Prevention.

# Co-infection

What if we have both? Worms and malaria together.


Questions:

- Is the response different from the single parasite case?
- Is the response to each parasite better or worse than in the single parasite case?
- Is the response equal or unequal (does the immune system favour dealing with one parasite over the other)?

# The experiment

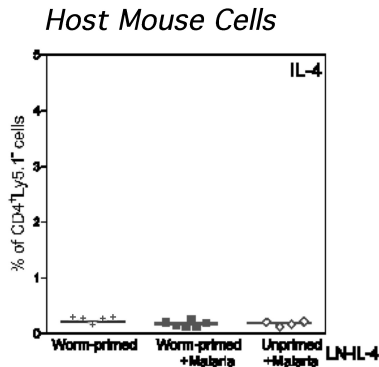
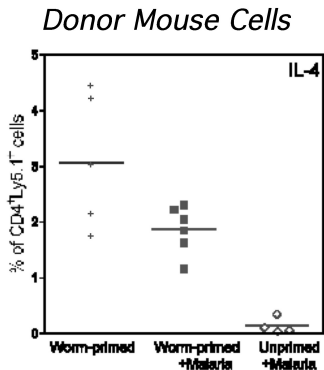
Special mice,  
worms and  
malaria.



day -7 Imm.	day 0 Transfer T cells	day 3 Malaria	day 16 Worm Ag	day 19 cultures
✓		×	✓	worm-primed
✓		✓	✓	worm-primed + Malaria
×		✓	✓	unprimed + Malaria
×		✓	×	Malaria

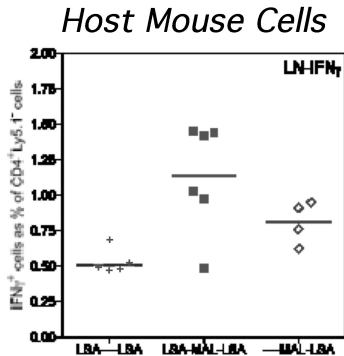
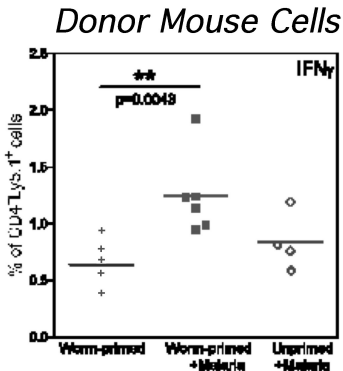
# A surprising experimental result: Th2

The graph shows the measurements at the end of the experiment for IL-4 (a marker for Th2 cells).



# A surprising experimental result: Th1

The graph shows the measurements at the end of the experiment for IFN- $\gamma$  (a marker for Th1 cells).



# Two Proposed Mechanisms

**Outgrowth of Th1** The rate of growth of Th1 cells is increased because of the presence of Th2 cells.

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**Switching of Th2** Th2 cells stop regulating the worm response and change to regulate malaria response.

# Process Algebra

- PEPA - Performance Evaluation Process Algebra
  - Rigorous (mathematical) semantics
  - Actions, Probabilistic choices, Processes
- Individual interactions translate to Population behaviour
  - Describe rules for the behaviour of an individual
  - Put many individuals together in parallel to make a population
  - Gives an automatic and rigorous translation from scale of individual to scale of population
- Associated analytical techniques

# Hypothesis I: Division and Recruitment

Components of the model:

- Naïve T cells: ready for action
- Th1 cells: can divide, and recruit from Naïve pool
- Th2 cells: can divide, and recruit from Naïve pool
- APC: antigen presenting cells stimulate recruitment of Naïve to Th1 or Th2 after some initial delay (3 days and 16 days respectively)

The model focuses only on cells from the first mouse.

Is it possible to match the experimental data by appropriate selection of parameters?

# Hypothesis II: Switching

In addition to the basic model:

- Th1 cells: can switch from Th1 to Th2
- Th2 cells: can switch from Th2 to Th1

Cells are known to be plastic; but rates are not known. Nor are limitations (can a cell switch once? Twice? Infinitely?)

# Simulation Results



Problems:

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- And how do they relate to measurements of IL-4 and IFN- $\gamma$ ?
- What rates are appropriate for division and recruitment?
- And should they vary over time?

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- Matching models to data is hard

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Other factors conveniently ignored (abstracted!):

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Other factors conveniently ignored (abstracted!):

- Regulatory T cells may also be affecting the balance of Th1 and Th2.
- Th cells secrete cytokines - that's what we use to measure their presence. This may be misleading because
  - it is not true that one kind of Tcell leads to one kind of cytokine, and
  - cytokines have a role to play in boosting and suppressing activity.

A more realistic model would include cytokines.