Simulations of candidate vaccine injections

A talk for chemical process systems engineers.

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- Links to articles cited in the study
- Links to data sets and simulations used in cited studies

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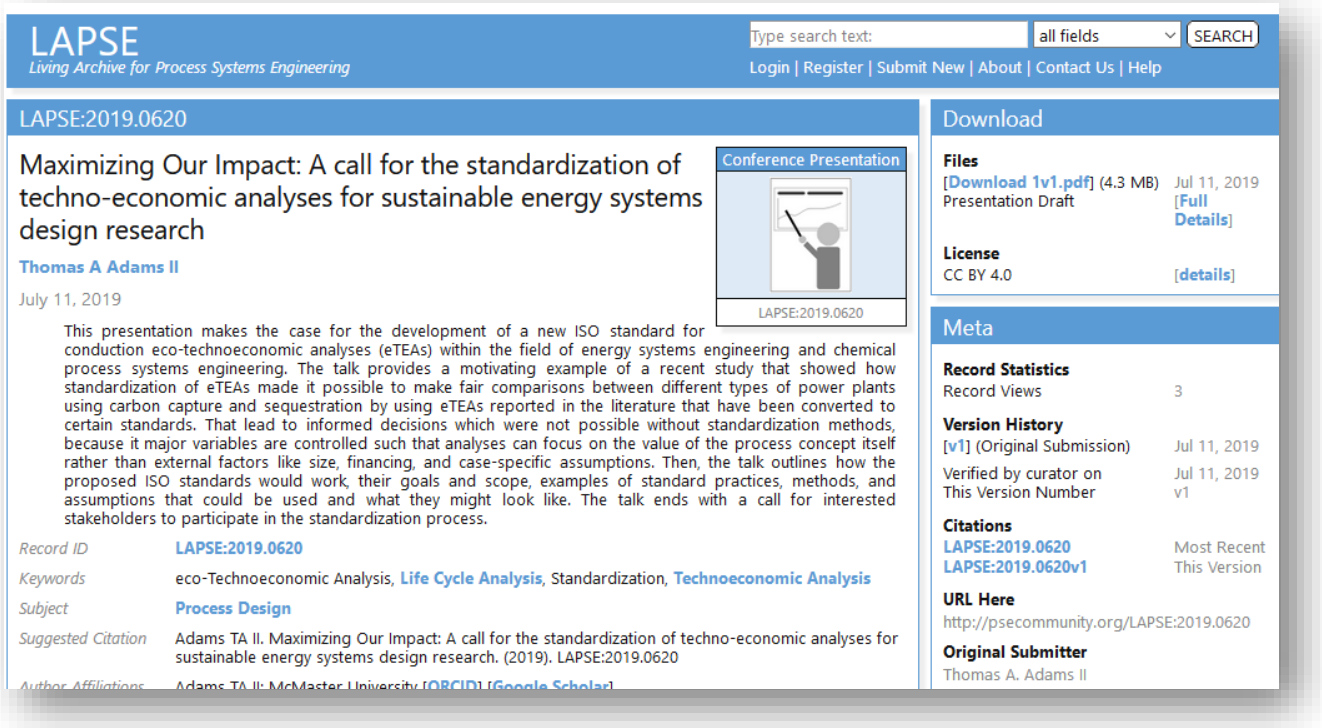

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Background

WHEN WILL WE GET THE VACCINE?

Introduction

… from the literature or are unknown and so are taken as a parameter. The number of cells in the population can vary from 10 to several million depending on the length of the run, the size of the system, and the parameters chosen, with each cell being individually tracked.

… when inside the boundary. For example, cell transitions are only influenced by what exists inside the boundary. Anything that exists in the rest of the body is ignored. Cells that have left the boundary are counted (as type K) but are tracked no …

Simulation Framework

… transitions are described next.

Arrival Rates

… Δt. The analogous equation exists for P. Although not used in this paper, the STORE model allows for the user to choose a quadratic introduction rate for A and P, rather than a linear one (A1). In this case, the following equation is used instead:

A and P …

P_AP=p_(AP,bind) N_A/(N_A+N_P)

Source: Christian DA et al. cDC1 Coordinate Innate and Adaptive Responses in the Omentum required for T cell Priming and Memory. In Review. Preprint: https://doi.org/10.1101/2020.07.21.214809

Vaccination Basics: Antigens and T-Cells

Where is COVID-19?

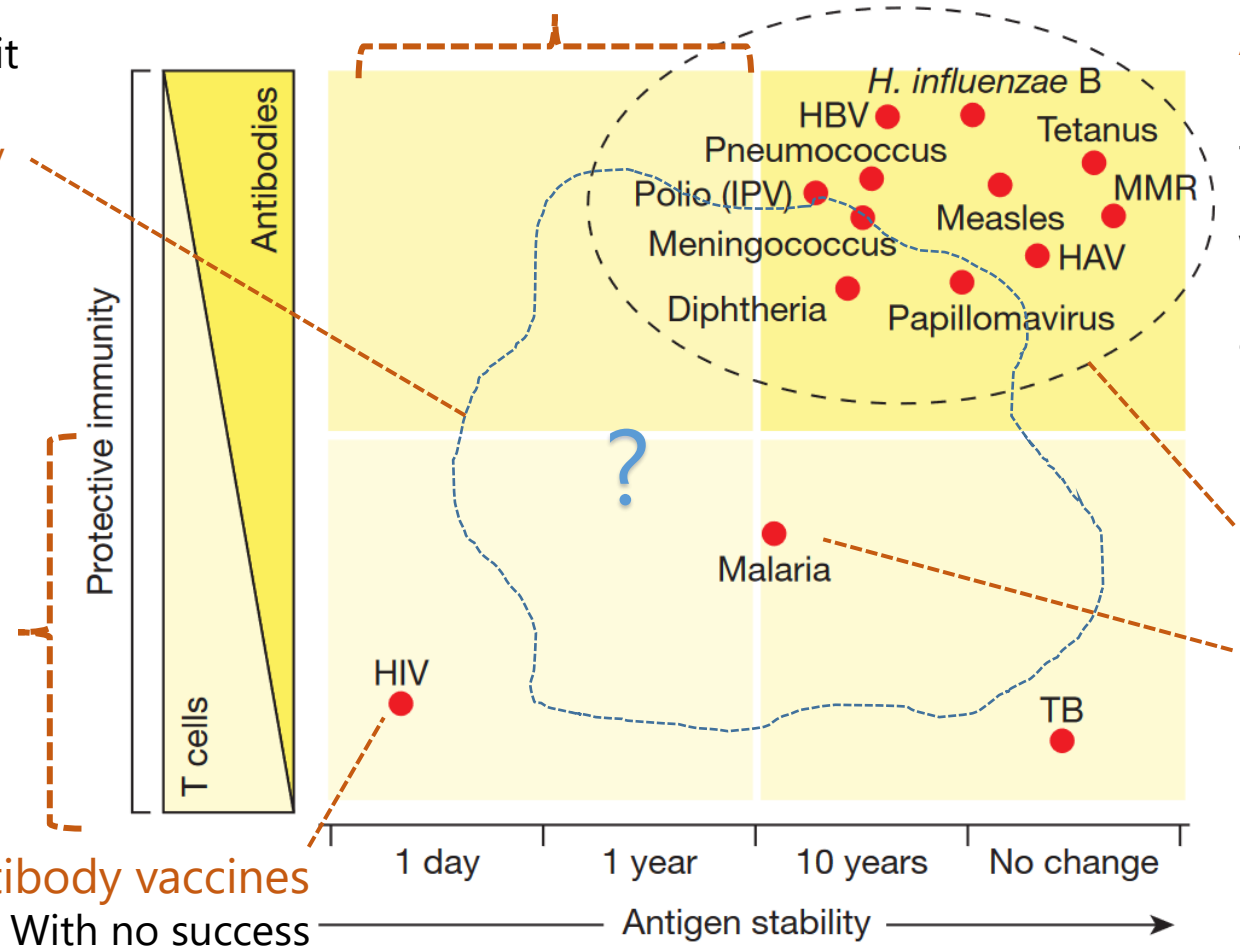
We know antibodies are effective (Trump got them and it worked).

We do not know how long they will remain in the body.

We do not know how fast COVID-19 is mutating.

Other Coronaviruses (e.g. common cold) usually experience rapid mutations

and our antibodies usually don't last more than a year.



Antibody COVID-19 vaccines

may require yearly boosters... forever.

We may need the T-Cell vaccine to provide robust long term protection against COVID-19.

Never been done before.

T-Cells last much longer in the body than antibodies

They are more robust and can be effective against unstable infections (rapid mutations)

Successful Vaccines

415 Million Deaths in 2017

$Billions Spent on HIV antibody vaccines

With no success

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Source: Rappuoli R, Aderem A. A 2020 Vision for vaccines against HIV, tuberculosis, and malaria. *Nature* 473:463-469 (2011)

Vaccine Response Basics: Cellular Responses

STEP 1

Vaccine Injected into Patient
The vaccine is the antigen.

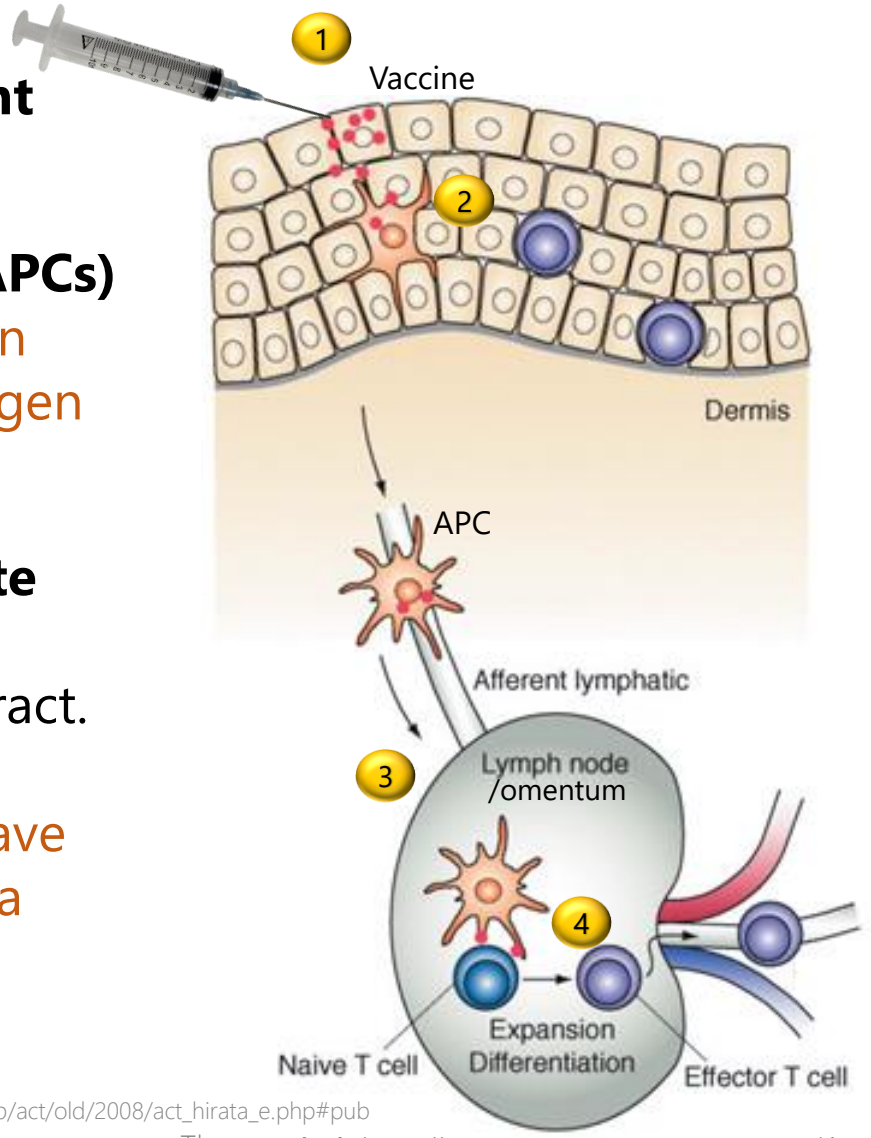
STEP 2

Antigen Presenting Cells (APCs)
A cell that breaks up and then carries some piece of an antigen (the foreign body)

STEP 3

APC cells and T cells migrate into the omentum.
They meet and begin to interact.

Naïve T-Cells are cells that have not yet learned how to fight a pathogen.



STEP 4

The T Cell Begins to Mature

During this process, the T cell learns how to detect cells that carry the antigen fragments. Then the T-cell has been "primed".

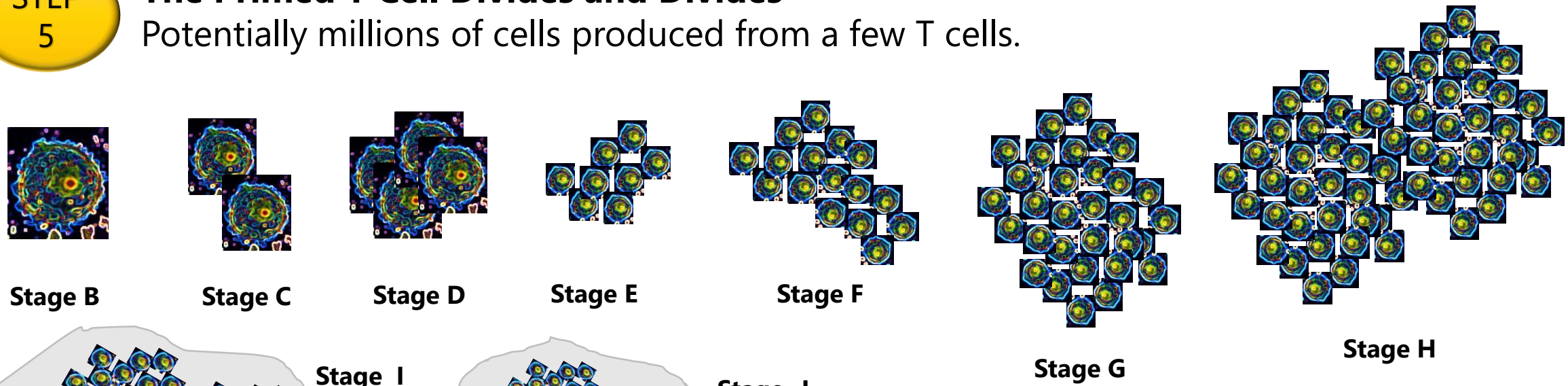
Image: http://www.biken.osaka-u.ac.jp/act/old/2008/act_hirata_e.php#pub

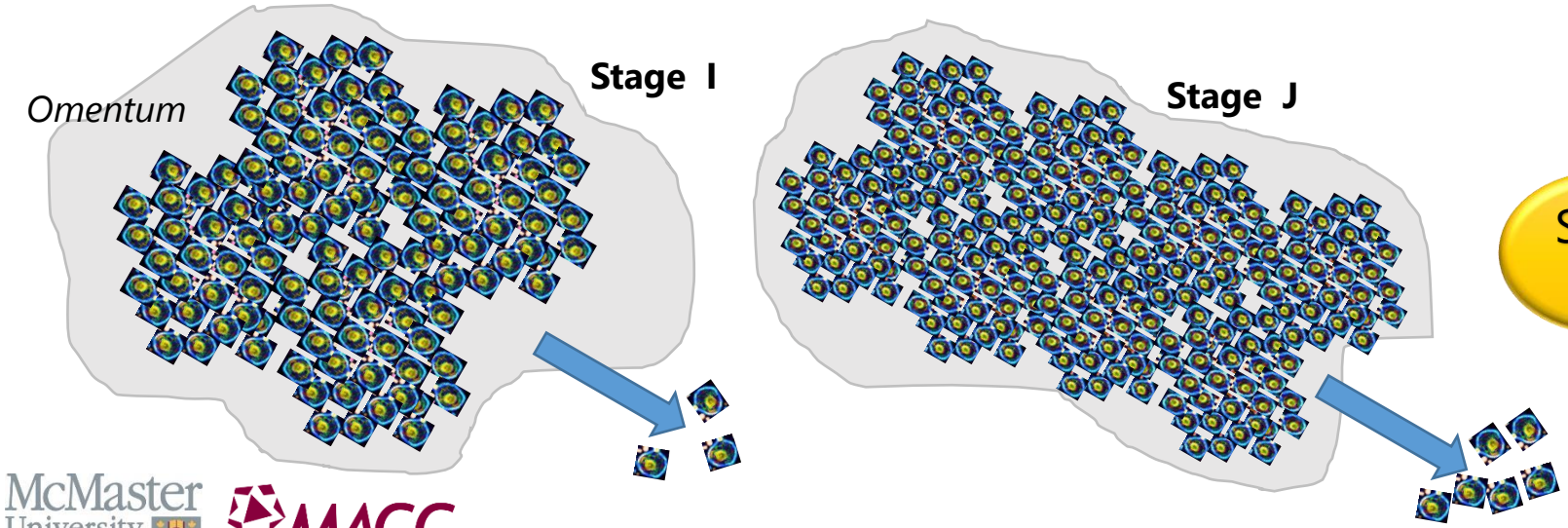
Vaccine Response Basics: T-Cell Replication

STEP 5

The Primed T Cell Divides and Divides

Potentially millions of cells produced from a few T cells.





STEP 6

Late-stage T cells begin to leave the omentum.

Others stay to continue reproducing. Enters bloodstream to fight pathogen.

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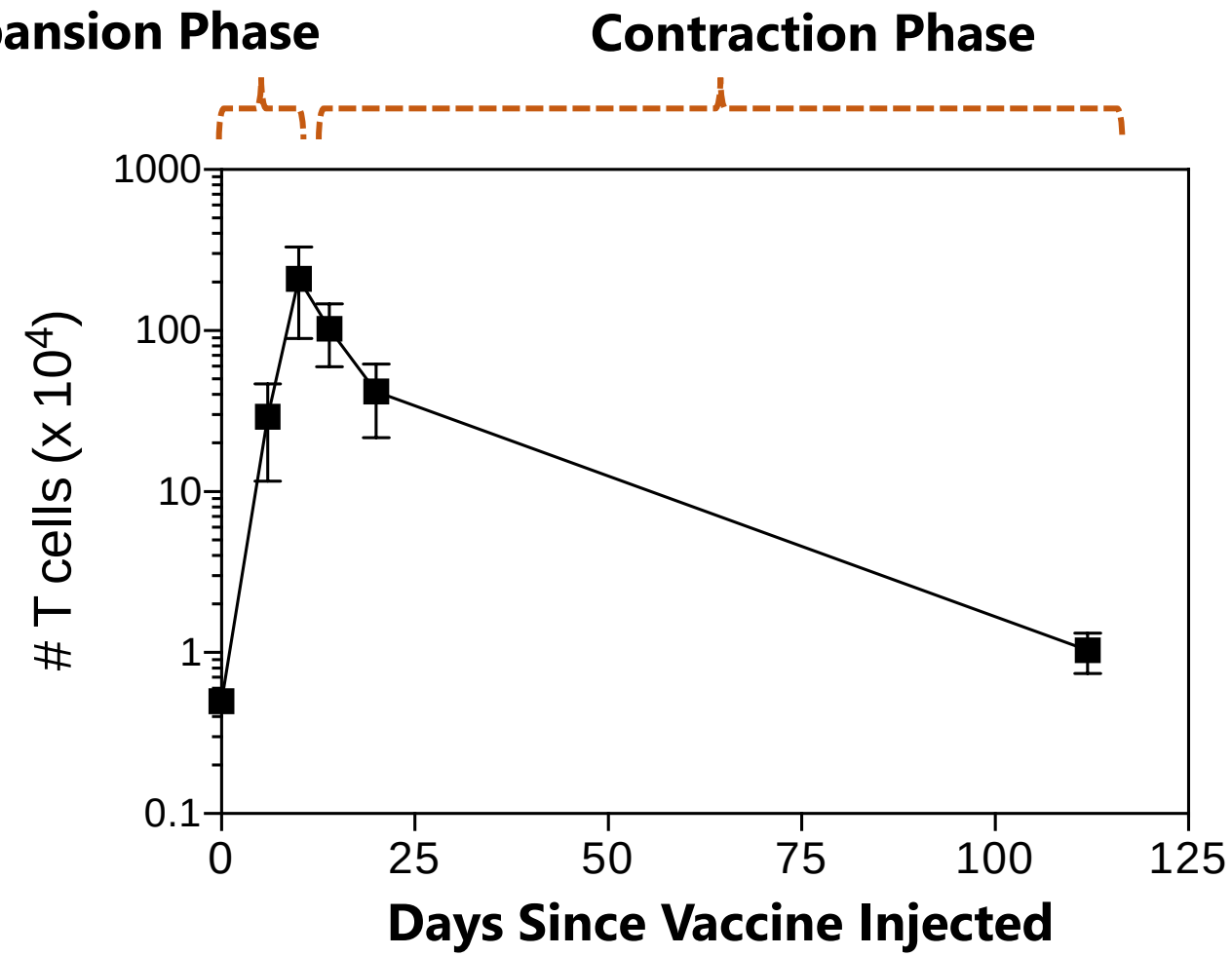
Key Data for Vaccine Assessments

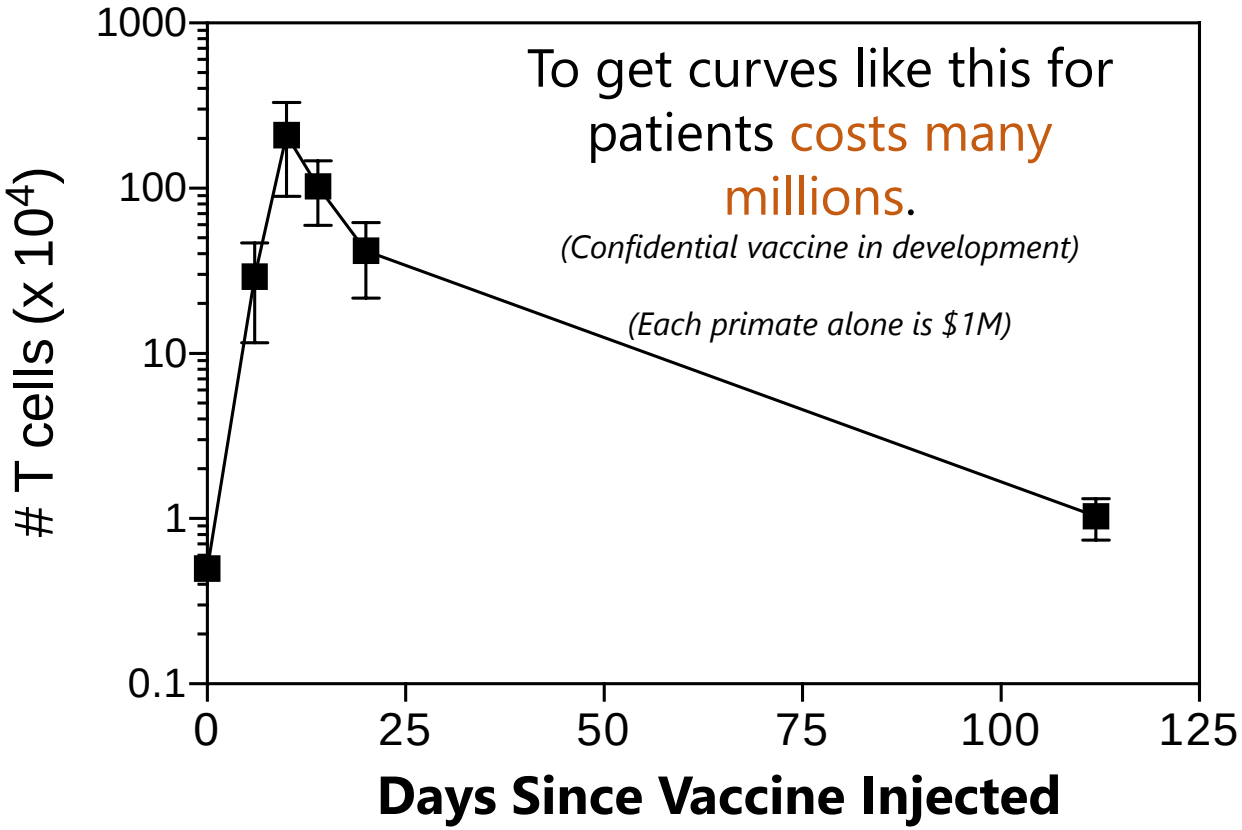
- Actual Patient Data is Key
- Want to track cell counts of each kind over time since vaccine injection
  - Example: the T cell counts being too high during expansion could cause severe fever
  - Example: Counts being too low at the end of contraction will not provide protection
    - Going too high too early may cause the count to drop to zero in the long term.
    - Going too low means it may not end high enough
- With enough understanding, it may be possible to predict end-of-contraction outcomes with just the first 8 days of data



Data: Ross Kedl, study in progress.

Key Challenges

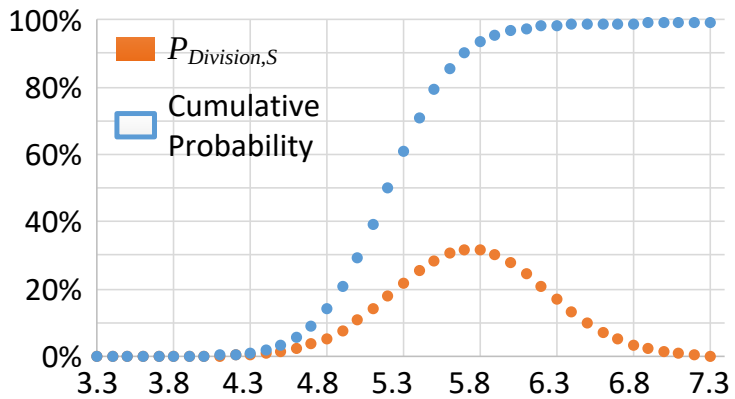
- Can only measure what's in the blood without killing the patient:
  - (We can't see APCs.)
- Stochastic systems
  - A big deal when cell counts are small
- As a result:
  - We normally have to test vaccines by trial and error on human patients
  - We are limited in measurements in human patients during the trial and have to wait for months to find out the result



Data: Ross Kedl, study in progress.

What Can Be Done Well: The Petri Dish

- The petri dish allows us to focus on just one specific "reaction" within the immune system
- Example: C →2D
  - We know it takes about 5.3 hours with some probability distribution



- We can even measure certain things like APCs that we can't measure *in-vivo*

  (Because we put a known amount in the dish)

- Systems Engineers to the Rescue:
  - We can construct a simulation of the immune system response by modelling each of its individual components
  - We can infer variables we cannot measure by including them in the system with those we can measure
  - Test hypothesis about the system structure

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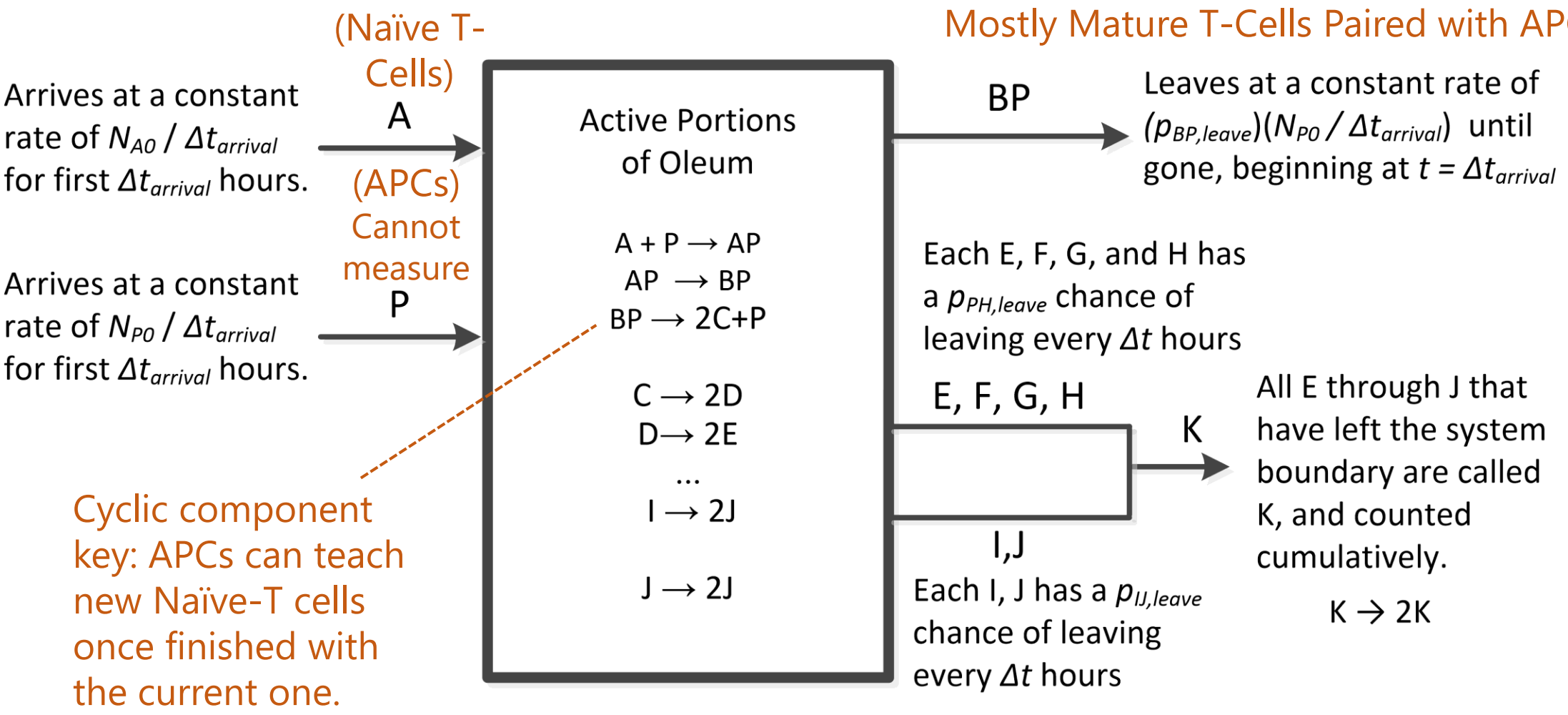
Source: Christian DA et al. cDC1 Coordinate Innate and Adaptive Responses in the Omentum required for T cell Priming and Memory. In Review. Preprint: https://doi.org/10.1101/2020.07.21.214809

Our Immune System Model



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Key Model Traits

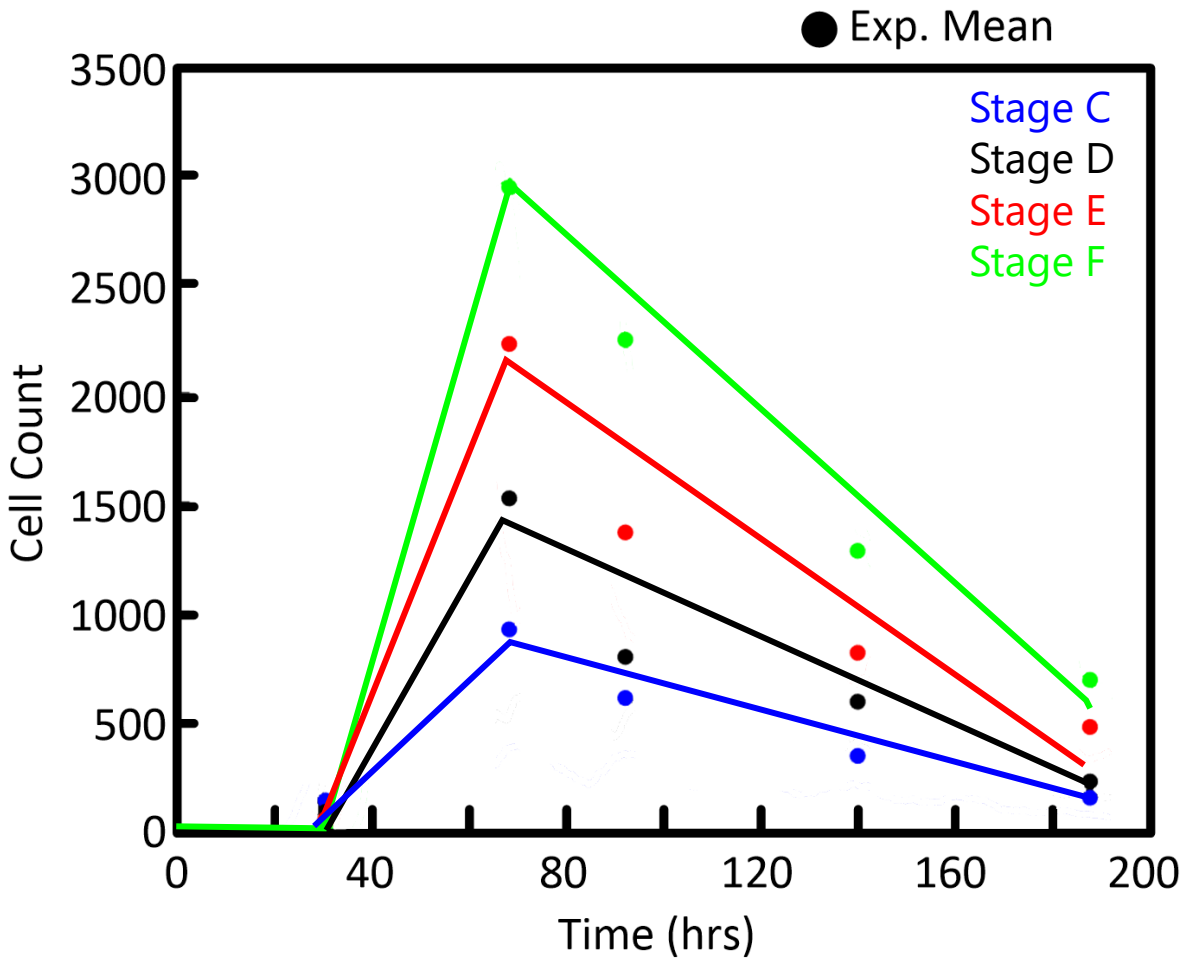
- Only three parameters to fit within small known ranges
  - (Certain rates/probabilities for cells entering/leaving omentum that are not fully studied)
- User supplies initial T cell and APC conditions
  - Correlates directly to vaccine dose, injection methods, and patient age
- All mammalian immune systems
- Stochastic Agent-based modelling
  - Each cell individually tracked
  - From 10s to 1,000,000s of cells
- First model of its kind:
  - Stochasticity
  - Agent based
  - Un-measurable elements
  - Full omentum response
- Started early 2019…

Basic Implementation

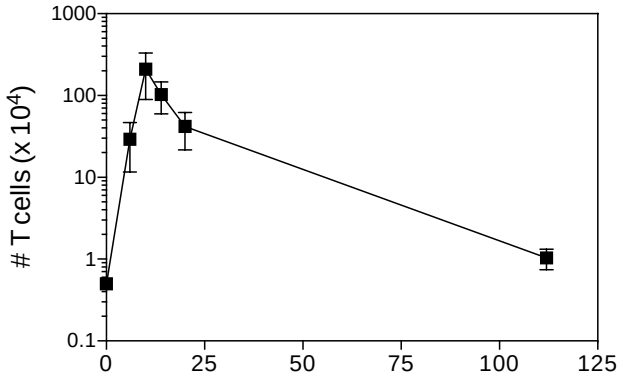
- "Probabilistic finite state machine"
- For each Time Step (6 mins)
  - For each cell
    - Cells may undergo a transition or "reaction" depending on current state, age, or concentration
    - Transitions occur based on state and parameter dependent probabilities

- Example:
  - $A + P \rightarrow AP$ (Naïve T Cell meets APC)
  - $Prob_{Transition} = k \frac{N_A}{N_A + N_P}$
  - k found through parameter fitting range of k is small
- Example:
  - $F \rightarrow 2G$ (Stage F cell divides)
  - $Prob_{Transition} = f(cell\ age)$

Example Results



- Five mice were "harvested" to collect this data (one at each time point)
- Hundreds of mice needed for the initial data collection…
- Lines here are a typical understanding of the immune response before the study. Recall:



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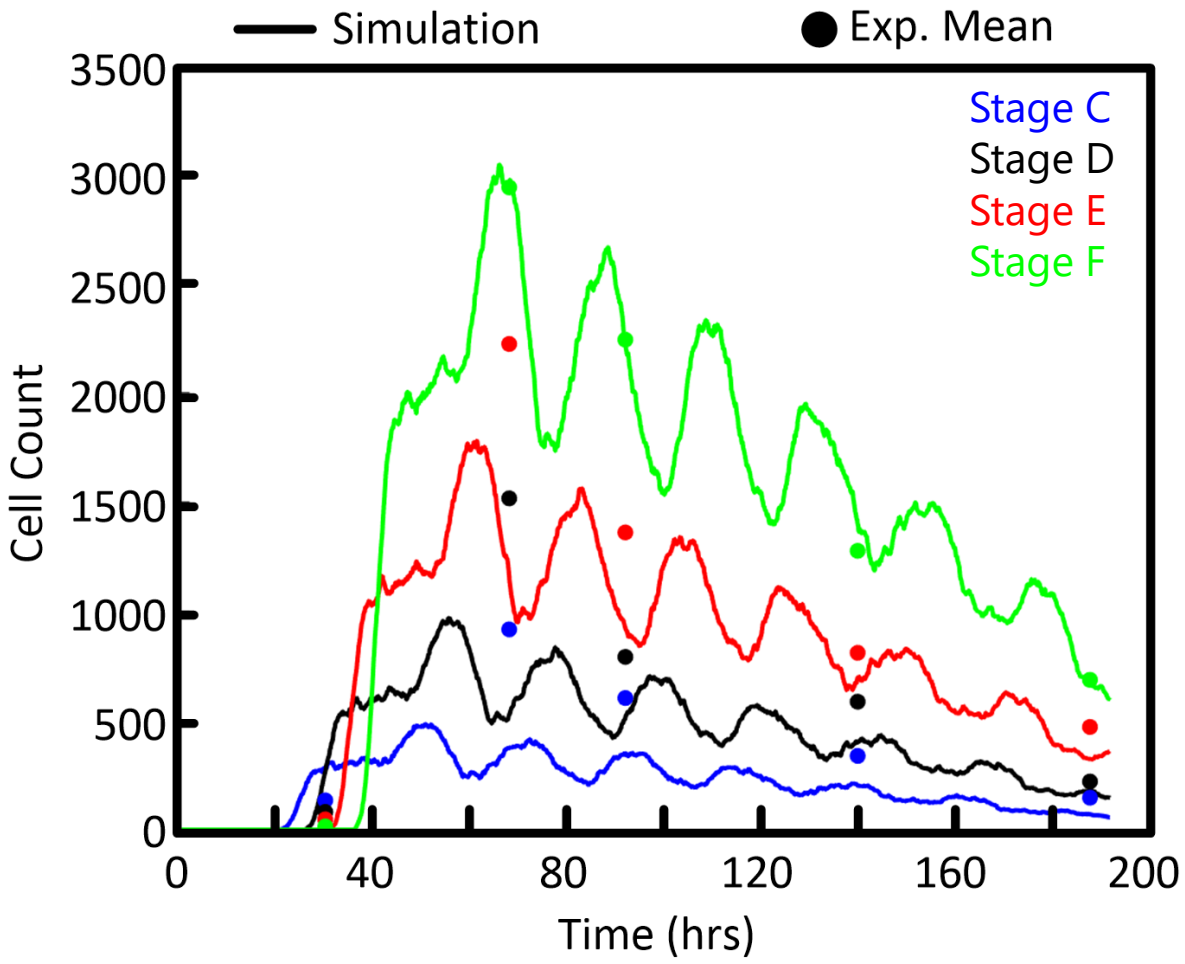
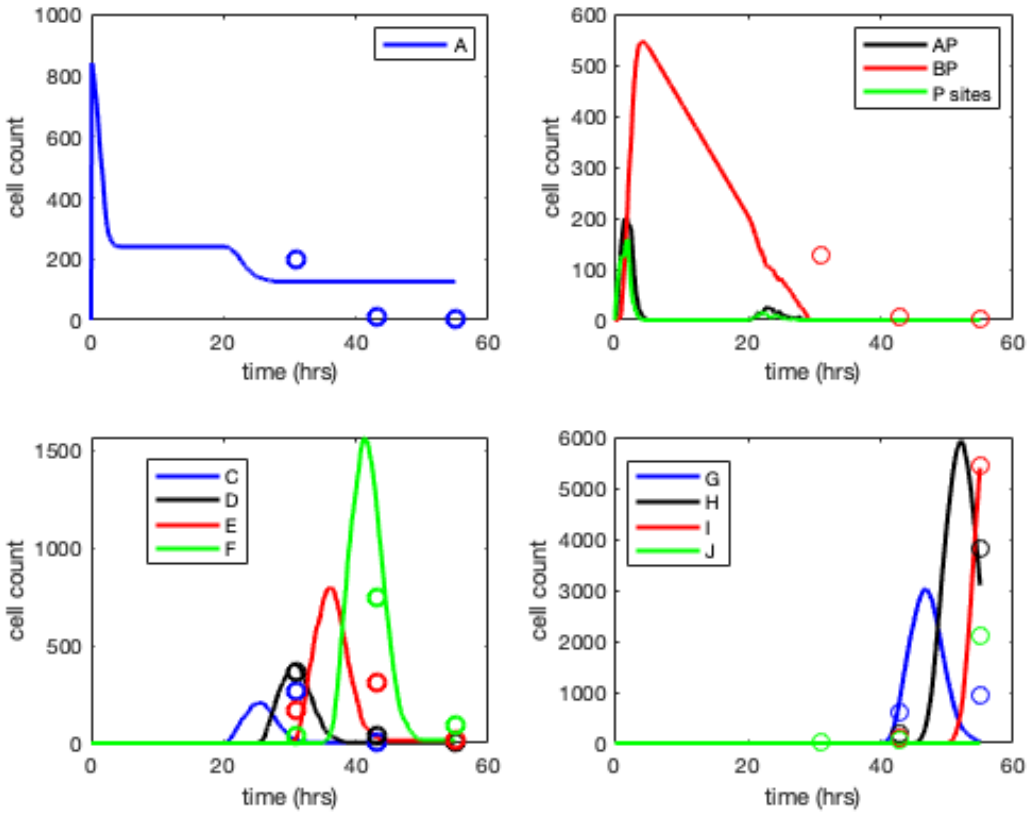
STORE Model Results



- Periodic behaviour explains what was is usually treated as experimental noise
- Remarkable consistency with the data
- Constructed from simple system elements that explain the true nature of the immune response

Source: Christian DA et al. cDC1 Coordinate Innate and Adaptive Responses in the Omentum required for T cell Priming and Memory. In Review. Preprint: https://doi.org/10.1101/2020.07.21.214809

The same system model works in very different vaccine scenarios without modification



- The same model on a completely different vaccine
  - In clinical trials now
- Different injection / dosage schedule
  - Injected directly into the bloodstream instead of the belly
- Completely different system dynamics obtained by a few parameter changes

How this helps with rapid vaccine development

- Only about 4 parameters are vaccine dependent.
  - These parameters can be determined in mouse trials and then in primate trials but are valid in humans
- Data collected in first 8 days in human trials used to predict cell counts out to 5 months
  - We can help predict long term vaccine success after just 8 days of data!
  - Start new human trial groups every 8 days with new dosages and schedules
  - Predict whether boosters are required and when, using only early stage data

Future Work

- Need to collect data (in mice) to extend the model for the contraction phase
- Need access to COVID-19 data for model application
  - As antibody vaccine trials continue, the data will become available.
- May need to add more system elements
  - The model is imperfect, meaning that we don't have full comprehension yet