

Simulations of candidate vaccine injections

A talk for chemical process systems engineers.



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Primary 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>

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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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Background

Introduction

The STOchastic Omentum response model is used to simulate the response of the omentum to a parasite Toxoplasma gondii infection. The STORE model tracks the quantitative response of the omentum to the parasite, including phenomena such as cell division, cell migration, and cell death. The model is stochastic, meaning that 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.

The primary purpose of the STORE model is to simulate the overall immune response, explore the effects of different parameters, and understand the system boundary.

The system boundary is defined as the active portion of the omentum, which is the region where activation and expansion of T cells occurs. The system boundary is defined by the arrival rate of the simulation, the boundary duration, and the duration of the simulation. Cells that leave the system boundary through J may leave the system boundary in various ways. Cells are only 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 further. There is no consideration of spatial arrangements of cells or their proximity within the boundary; they are simply lumped together.

Simulation Framework

Time zero of the simulation is the moment the parasite enters the omentum. The simulation runs in steps of length Δt with $\Delta t=0.1$ hours (6 minutes) chosen for the purposes of this paper. The simulation is evaluated to see if a cell undergoes a transition, or not, depending on the probability of the transition occurring against a certain probability. The probabilities depend on user parameters and various model elements. The transitions are described next.

Arrival Rates

and P arrive at the system boundary at rates λ_A and λ_P , respectively, beginning at time t_0 . These cells arrive at the system boundary, which no more than Δt after the system boundary. N_{A0} and N_{P0} are the number of cells that enter the system boundary at time t_0 . The STORE model assumes that the probability of a cell entering the system boundary is p_{AP} , and that exactly N_{A0} and N_{P0} have entered the system boundary at time t_0 . The STORE model assumes that the probability of a cell entering the system boundary is p_{AP} , and that exactly N_{A0} and N_{P0} have entered the system boundary at time t_0 .

where t is the current simulation time and $N_A(t, \text{timestep})$ is the number of A which arrive during the timestep window 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:

$$N_A(t, \text{timestep}) = N_{A0} + \lambda_A \cdot t + \frac{1}{2} \lambda_A \cdot t^2$$

A and P

Each time step, each P has a certain probability that it will bind to an A. The reaction is given by equation (A3):



where $p_{AP} \cdot \text{bind}$ is the probability of a P binding to an A. The STORE model assumes that the probability of a P binding to an A is p_{AP} . The STORE model assumes that the probability of a P binding to an A is p_{AP} . The STORE model assumes that the probability of a P binding to an A is p_{AP} . The STORE model assumes that the probability of a P binding to an A is p_{AP} .

WHEN WILL WE GET THE VACCINE?

Vaccination Basics: Antigens and T-Cells

Where is COVID-19?

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

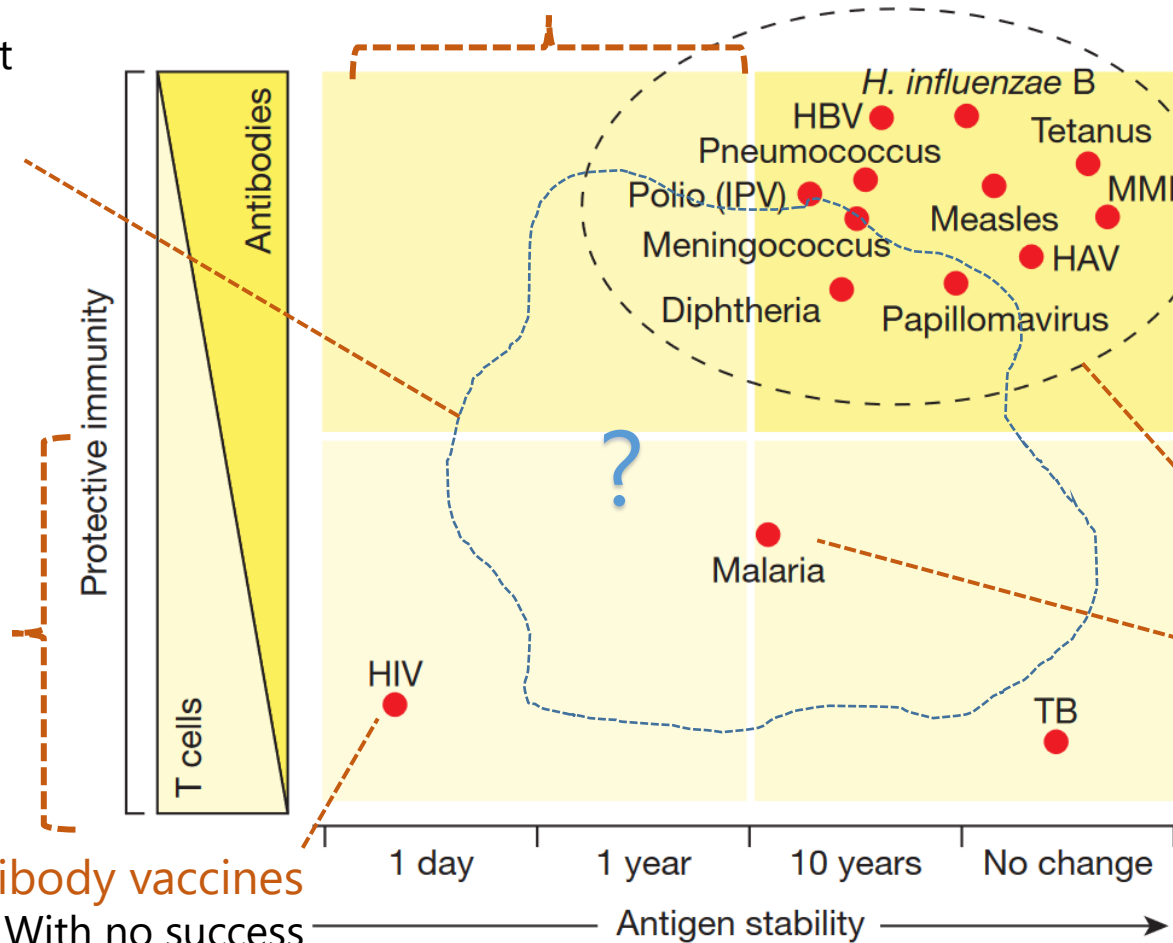
We do not know how long they will remain in the body.

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

T-Cells last much longer in the body than antibodies

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

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.

Successful Vaccines

415 Million Deaths in 2017

\$Billions Spent on HIV antibody vaccines

With no success

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

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Vaccine Response Basics: Cellular Responses

STEP
1

Vaccine Injected into Patient

The vaccine is the antigen.

STEP
2

Antigen Presenting Cells (APCs)

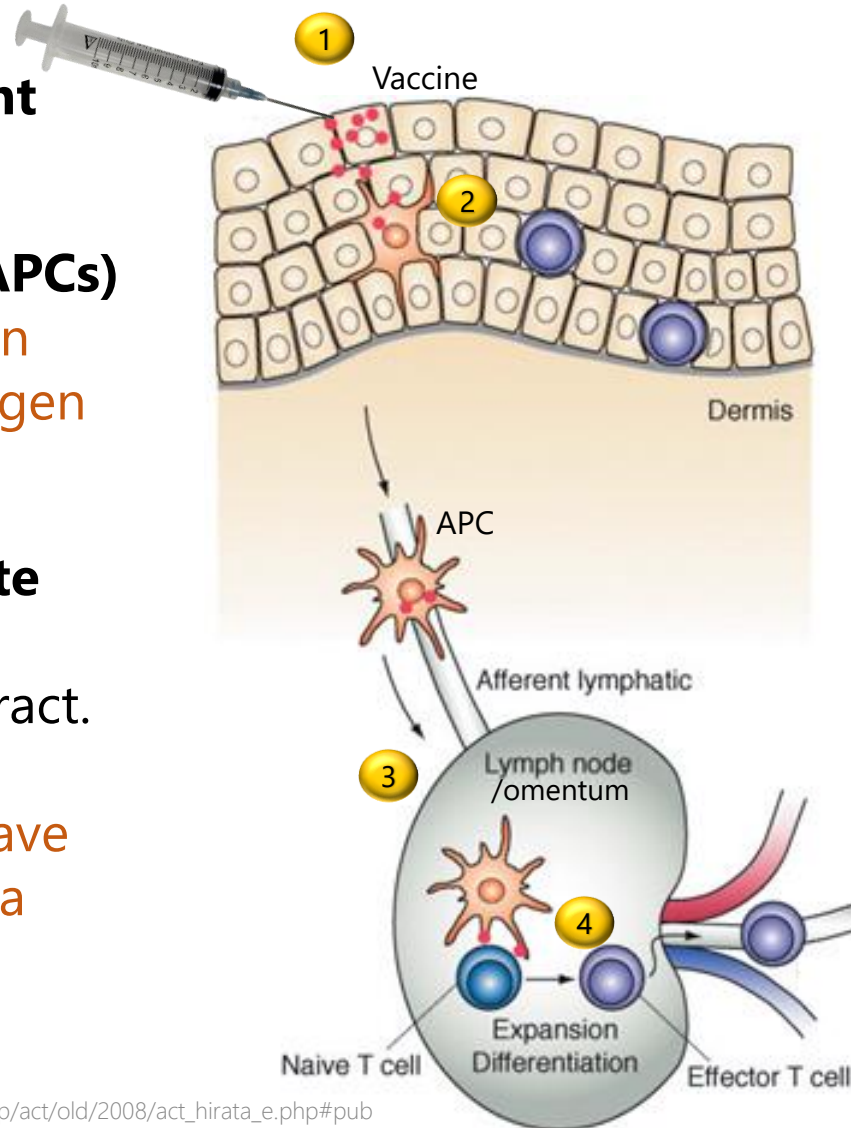
A cell that breaks up and then carries some piece of an antigen (the foreign body)

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

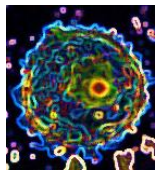
During this process, the T cell learns how to detect cells that carry the antigen fragments. Then the T-cell has been "primed".

Vaccine Response Basics: T-Cell Replication

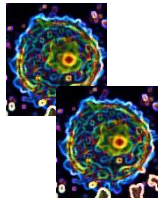
STEP
5

The Primed T Cell Divides and Divides

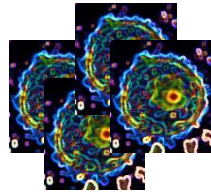
Potentially millions of cells produced from a few T cells.



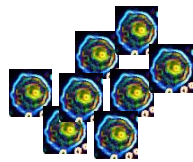
Stage B



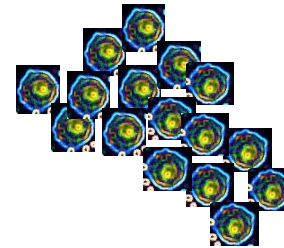
Stage C



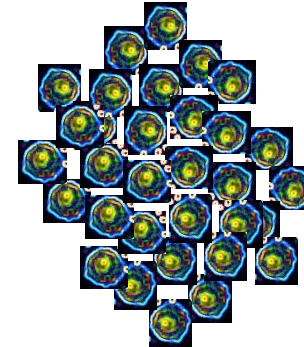
Stage D



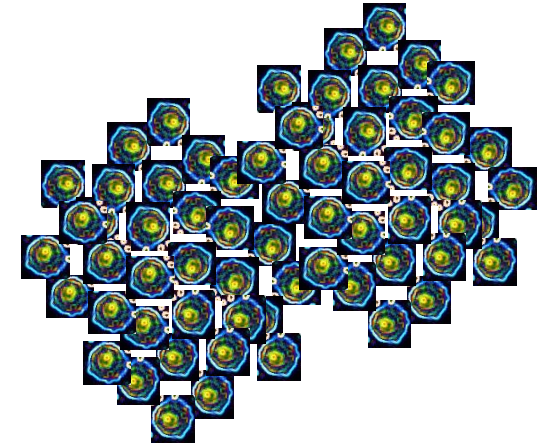
Stage E



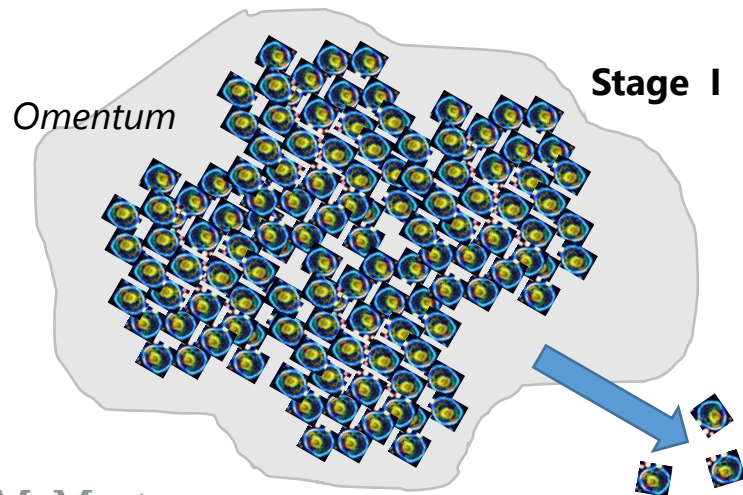
Stage F



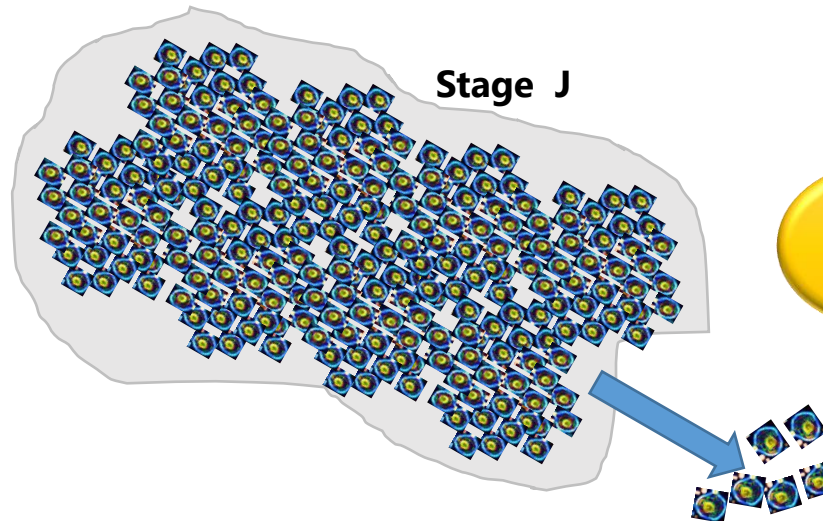
Stage G



Stage H



Stage I



Stage J

STEP
6

Late-stage T cells begin to leave the omentum.

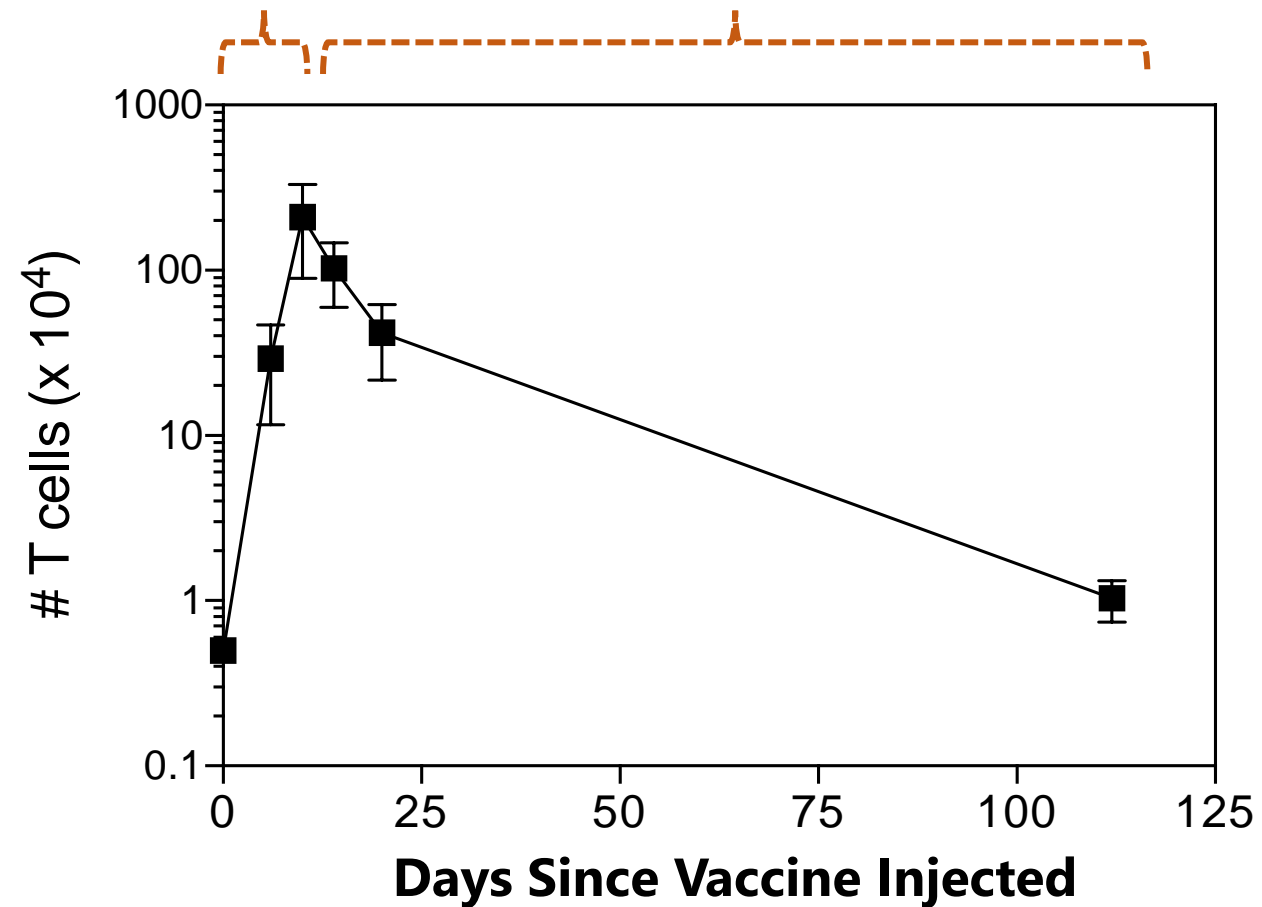
Others stay to continue reproducing. **Enters bloodstream to fight pathogen.**

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**

Expansion Phase

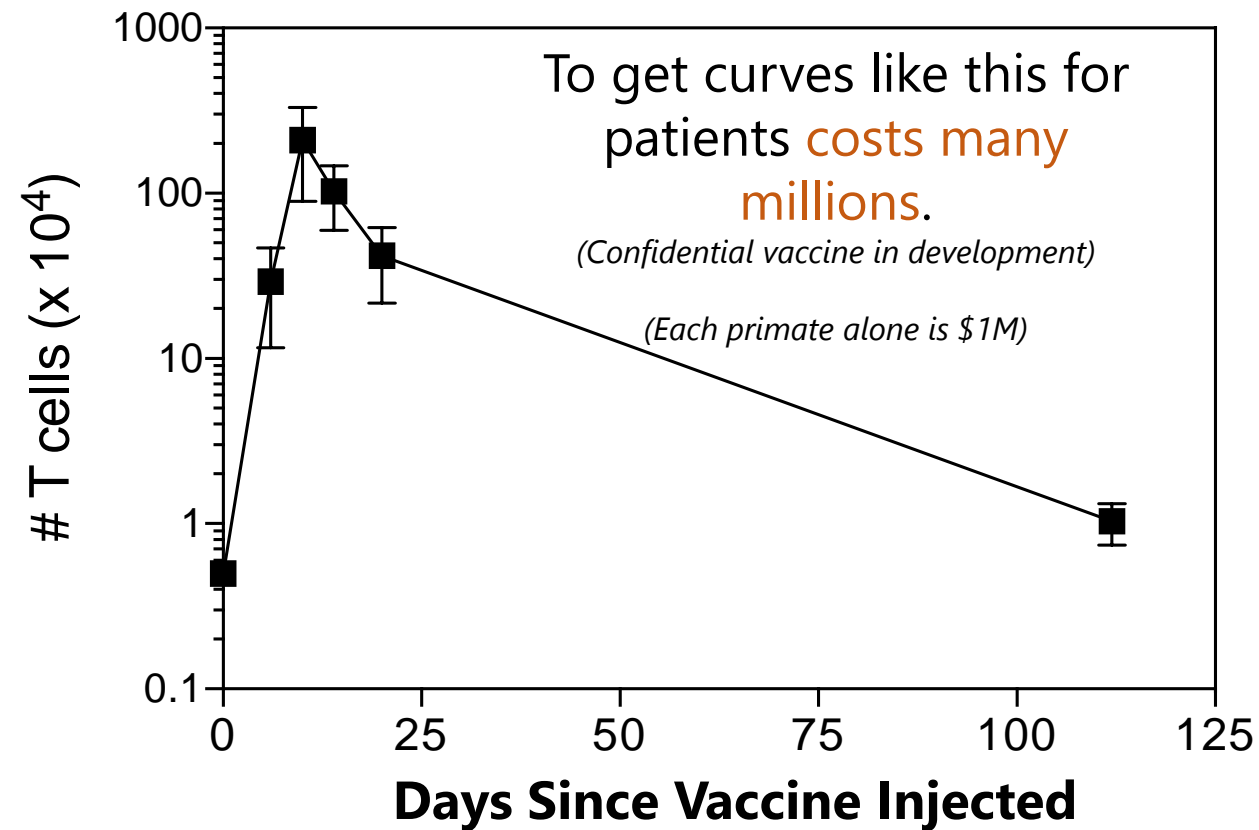
Contraction Phase



Data: Ross Kedl, study in progress.

Key Challenges

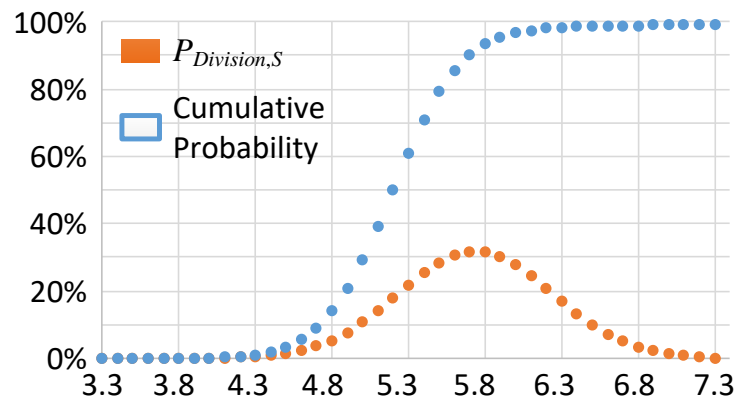
- Can **only measure what's in the blood** without killing the patient:
 - (We can't see APCs.)
- **Stochastic systems**
 - A big deal when cell counts are small
- **As a result:**
 - We normally have to test vaccines by **trial and error on human patients**
 - We are **limited in measurements** in human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



Data: Ross Kedl, study in progress.

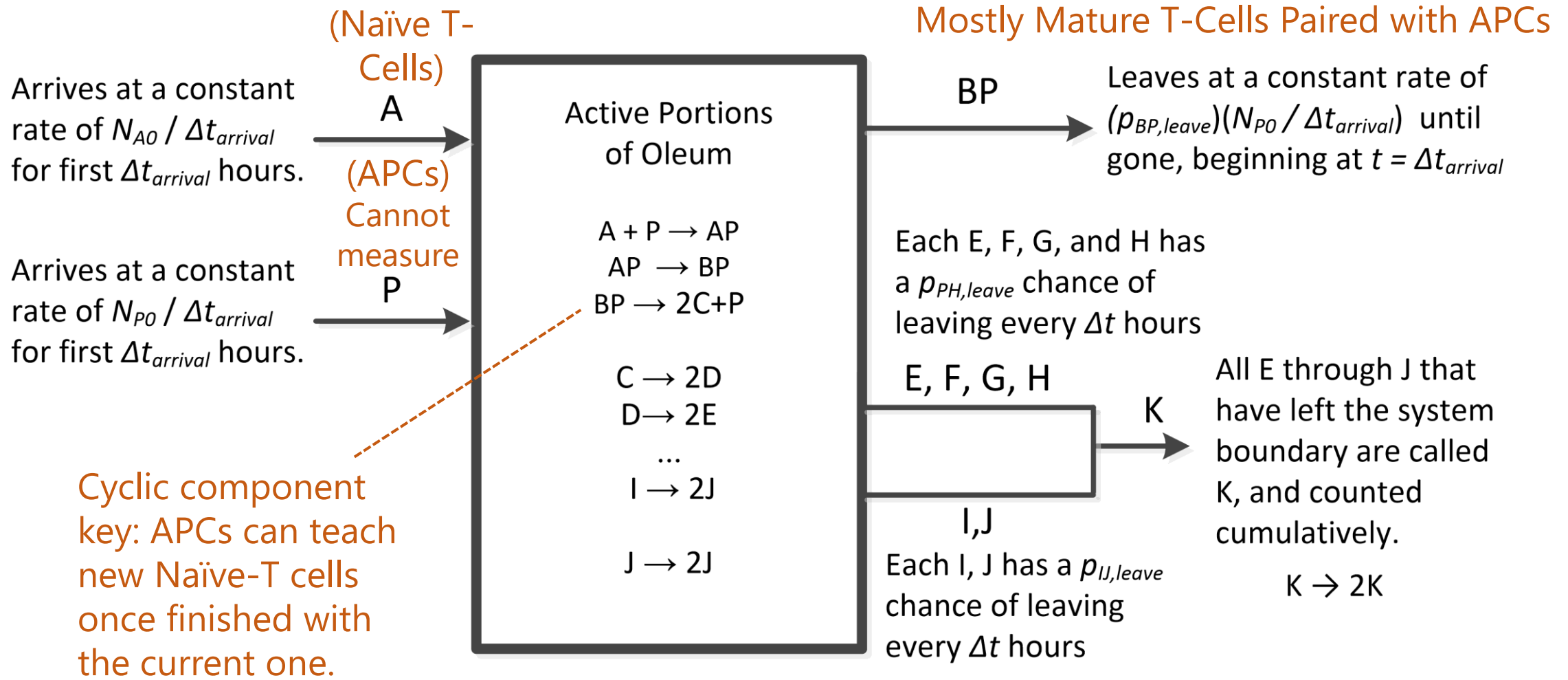
What Can Be Done Well: The Petri Dish

- The petri dish allows us to focus on just **one specific "reaction"** within the immune system
- **Example: C \rightarrow 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

Our Immune System Model



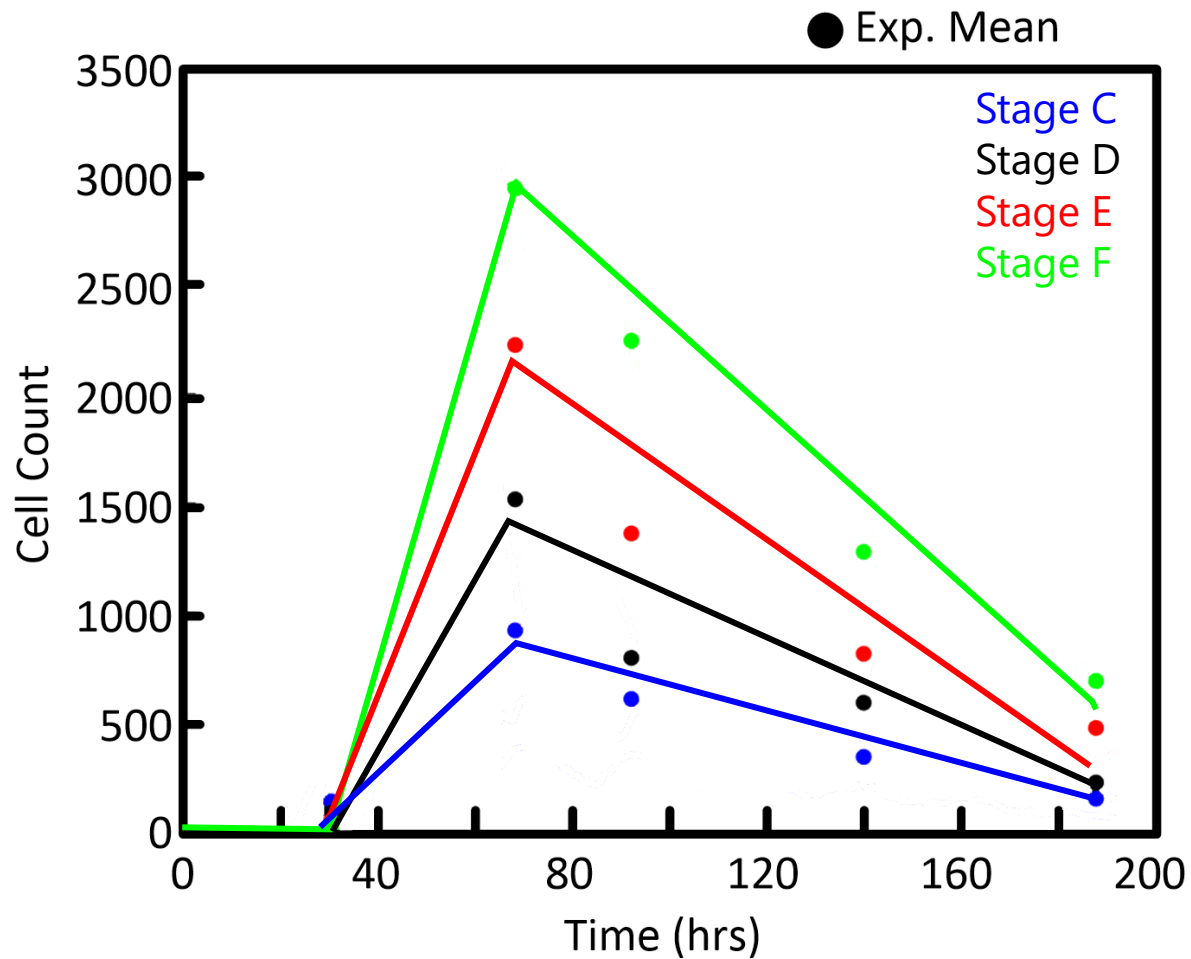
Key Model Traits

- 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...

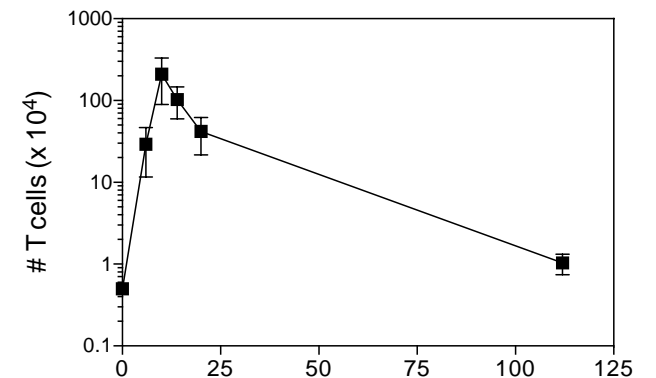
Basic Implementation

- “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)
 - $Prob_{Transition} = f(\text{cell age})$

Example Results



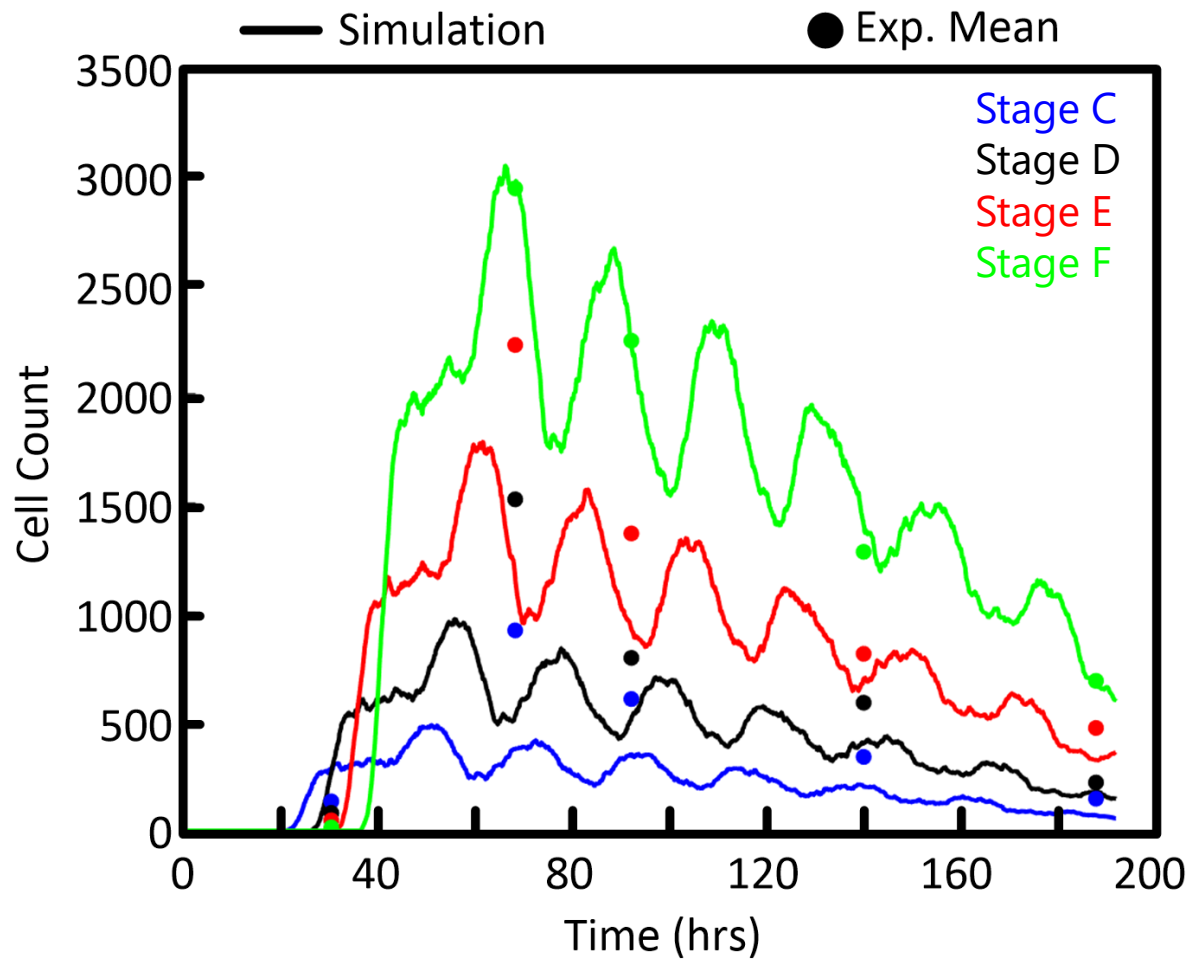
- Five mice were “**harvested**” to collect this data (one at each time point)
- Hundreds of mice needed for the initial data collection...
- Lines here are a **typical understanding** of the immune response before the study. **Recall:**



Data: Ross Kedl, study in progress.

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>

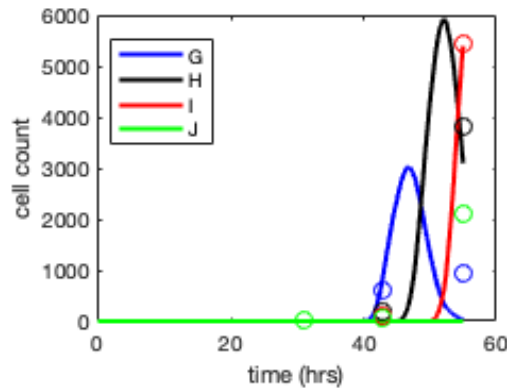
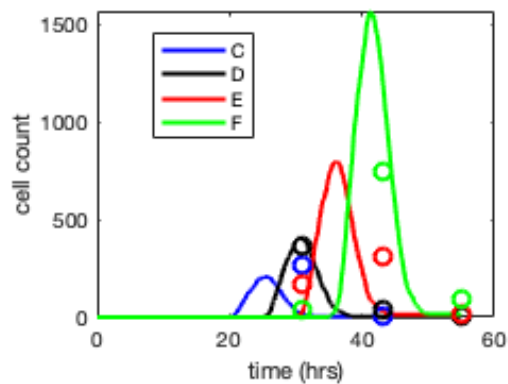
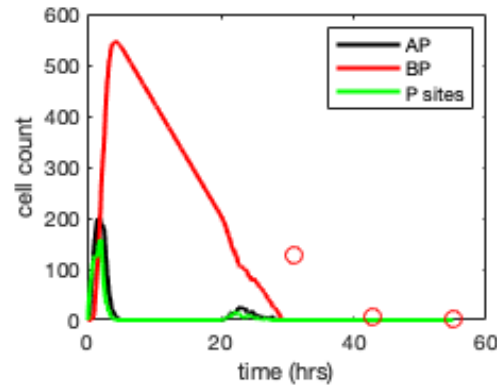
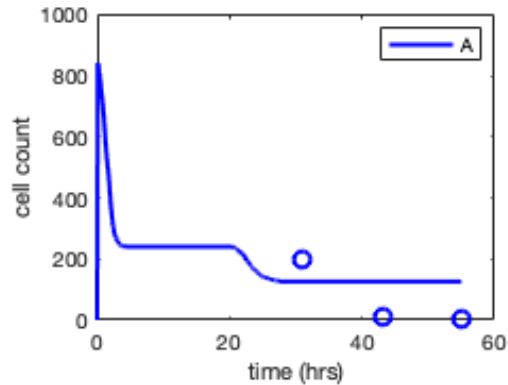
STORE Model Results



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

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