**CTL Dynamics: Insight into a Single Plausible Mathematically Driven Simulation of T-cell Activation**

**Derived from Two Independent Research Papers.**

Thomas E. Perez

\*California State University, Northridge

thomaseperez.perez.311@my.csun.edu

Advisors: Dept.\* of Computer Science - Dr. Kyle Dewey, Dept.\* of Mathematics - Dr. Bruce Shapiro

**Abstract**

**T cell activation is a crucial defense mechanism for virus control, and viruses can cause cancer, among other things. Numerous research papers have been written on the modeling of T cell activation. There exists two lab-proven and completely independent models of T cell activation, where one is based on linear equations and the other on probability. They are also unique in terms of their biological mechanisms, with distinct T cell activation processes. My research combines these models via an animated simulation of the interactions between viruses, healthy host mouse cells, and common lab type virus cells. My observation is that the mechanisms of one model set up the starting conditions for the other model.**

**Introduction**

We rely on protection from foreign invaders of our body by several means and mechanisms that include white blood cells. Lymphocytes, white blood cells, include B cells, plasma cells and T or thymus cells. The thymus is a gland in the throat area that contains these T cells such that once summoned by biological signaling, they form a line of defense against a, antigen, pathogen or virus (an apv, for convenience). Once triggered they recognize the immune response, and react to an antigenic stimulation like a sneeze, or worse, more specialized and more heavily equipped T cells are signaled to confront and attempt to counter more serious viruses, namely retroviruses eg. HIV etcetera. To review, T cells come in a few varieties, so upon commitment, (explained shortly in Related Work†), they can take on new identities. So when they become mature enough to a certain point, (before becoming memory T cells) they commit to what duties are presented to them according to how they are identified, by what is called differentiation. An analogy is that they have graduated, and are now ready for a particular type of work. They work to attack apv’s as required by the immune response and the immune system as a whole both in relation to the particular apv the person is exposed to.

[[Include jpgs of presentation]]

**Related Work**

**Kueh et al**

Hao Kueh et al [2] researched a new process of T cell commitment†. Commitment in this context means more or less what it sounds like, and that is what Wodarz refers to as activation. It’s an enabling, a type of switching-on or promotion of T cells to full functionality. The main takeaway form Kueh et al in relation to this paper and C++ simulation application is what is called Bcl11b. This gene that encodes the protein by the same name has been heavily studied for years and continues to be examined. It is not attempted to be explained here, other that it serves as a type of master electrical switch that is controlled and regulated by a set of four other closely knit proteins that are themselves switches in the behaviors they exhibit. A discussion of these four proteins are out of scope for this paper’s purpose. The Bcl11b protein, is [most likely] subcellular [4], and is an initial factor in the simulation, explained later in the C++ Application Discussion section. As mentioned in the Introduction, this model sets up the starting conditions for the next model discussed, and ie. the Wodarz et al model.

[[INCLUDE JPGS FROM BOOK]]

**Wodarz et al**

Firstly and briefly, a pathway in this context is a set of specific directions from one cell form or type to a different cell form or type via its other directions or paths. (In this context again), it’s analogous to a digital circuit (comprising of various control signals) with one input and at least two outputs such that a single signal starting at a specfic node can end up at one of two different but related nodes. So Wodarz discusses two pathways leading to CTL activation: a 'classical' pathway and a CD4-APC-CTL pathway. The details are out of scope for this venue.

[[INCLUDE JPGS FROM BOOK]]

… END RELATED WORK

**C++ application discussion**

Before describing the cpp program, an argument must be made as to why and how the W→K connection and why it’s.

This can be under the heading, “Wodarz-Kueh correlation”.

Cartogram process:

Input;

Proliferation rates for CTL,

given virus load (placement)

in tissue sample. The CTL

(or NK) counts, is determined

by which Pathway is used.

Output;

a) Relative kinetics between

the above cells.

b) A graphical frame by

frame depiction of the

interactions of the cells.

c) Some useful comparisons

via an Excel spreadsheet.

Initially, the vulnerable tissue sample will of course only be, healthy H\_ost cells, randomly. Bcl11b may or may not be present. If not, it will not be initially, upon birth. That would be unfortunate. The baby will be declared a patient. The frame below is sans **B**cl11b, (no ‘**B**’s). It must have this gene to survive. The simulation program gracefully halts when no B’s are sensed. If at least one B is present “upon birth”, the program continues with the Wodarz et al model.

Assume eg. that a newborn baby is healthy and Bcl11b genes exist as an initial cpp runtime condition.

|--------|

| H |

| H |

|H H |

| H |

| H H **B** |

|  |

| H |

| H |

|--------|

v=virus cells, H=healthy H\_ost cells, c=CTLs. v infects and c proliferate upon antigenic stimulation of our immune system. The c’s populate enough to recover from our viral attack.

|--------|

|v c H v|

|v H c |

|H vH |

| v H**B** v|

| H c H v|

| v v v |

| H v c |

|cvHv v v|

|--------|

Finally, migration occurs. A v next to a H turns the H into an h. A v will be killed by a K.

|--------|

|v c H K |

| v Kc |

| hv h h |

| v |

|h cH v |

| hvKKH K|

| v**B** cv|

|cKh K**B** |

|--------|

The CD4-APC-CTL version† is linear, unlike the classical version. Using this interpretation of CTL vs viral population behavior, the ratio is;

virus : CTL = 3 : 1

This proliferation ratio is simulated frame by frame while the virus particles migrate throughout the tissue sample as appropriate. As the virus gets rendered inactive or destroyed, the particle is replaced by a 'K' symbol. If a virus, v, is contiguous or becomes contiguous to a H\_ost cell, H, the char 'H' becomes a small case char 'h'. This denotes the h\_ost cell has become infected. If a CTL, denoted by a **‘**c’ is contiguous to a virus, the virus (v) becomes a 'K', denoting the virus has been K\_illed off.

More interesting dynamics are open for implementation for this program, and involve much care and minutia. This is just a 'nuts and bolts' visual observation of H, h, v->v, v->K and CTL. CTL proliferation is exponentially distributed and the ranges are theoretically more extreme, and viral clearance is more likely according to Wodarz. The temporal order of the CTL's evolution or "mutation" is;

(The arrow means "differentiates into")

Precursor (naive) CTL ->

Effector CTL (We've heard the colloguialism - "White blood cells come to the rescue!") ->

Memory CTL, ("I never forget a face"). ie eg, the next (nonmutating) strain is mitigated from populating at least robustly.

The simplified equation is;

CTL prolferation = (2 \* v^2) / (1 + v).

The other is the classical pathway as already mentioned. This is also of course simulated on a frame by frame basis. The Classical Pathway, which uses either the CD40 CD40L pair, or the B7 CD28 pair. Others are possible, but out of scope here.

[ End Wodarz – Kueh Discussion ]

**Evaluation**

TBA

**Conclusion**

For those whom are in the biological sciences, it’s known that not all mechanisms of the immune system are described the same. In fact, some are largely divergent. This is especially true in immunology or computational immunology and certainly a possibility here. The reason this is brought up is because though I have no lab to prove my conclusion on what I call the Kueh-Wodarz correlation Model, I believe I have a logical and cogent argument for linking the two researches, by way of how Bcl11b behaves as described in [2]. Kueh et al leads to a “final” T cell status, but provides for a convenient logical step or link for the next stage of the T cell activation/commitment process (a/c for convenience ), and ie. the Wodarz et al T cell a/c process. This produces a complete T cell a/c “story”. (“Complete” in no way literally means the whole story, that would be a herculean task.) My conclusion of the relation between [1] and [2] abstractly and gracefully describes a beginning a middle, and an end to T cell a/c.) Ultimately, memory T cells are produced and armed for services as required for future invasions to our immune system.

The C++ simulation exploits this hack to reveal what is happening on a frame-by-frame basis to basically simulate the preditor-prey type behavior of virus versus host cell.

**References**

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