**Insight into a Mathematically Driven Simulation**

**of T-cell-Activation Enabled Cytotoxic T-cell Dynamics**

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**Abstract**

**T cell activation is a crucial defense mechanism for virus control, and among other things, viruses can cause cancer. 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 logically 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 following model.**

**Introduction**

It is not the intention to delve into the minutia of virology here, since this research is targeted towards a computer science venue. To start,

we rely on protection from foreign invaders of our body by several means and mechanisms that include white blood cells. Lymphocytes, which are 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 an antigen, pathogen or virus, (an “APV”, for convenience). Once triggered, they usually recognize the immune response and react to the antigenic stimulation like a sneeze, cough, vomitus, hives, etcetera. At times, more

specialized and more heavily equipped T cells are signaled to confront and attempt to counter more serious viruses, namely retroviruses eg. HIV, teratogens, etcetera.

To review, T cells come in a few varieties, so upon commitment, (explained shortly in Related Work), they can take on new identities. 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, (among other things). 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, in relation to the particular APV the person is exposed to. Another term is what is called a pathway. In this context it is a set of specific instructions from one cell form or type to a different cell form or type. The term goes hand-in-hand with the term, “mechanism”, and can be viewed as a chain of related mechanisms toward a specific function. Figure 1 shows the models and essence of this research.

![](data:application/pdf;base64,)

**Figure 1** A birds-eye view of this research.

![](data:application/pdf;base64,)

**Figure 2** A relational depiction between the Kueh model and the Wodarz model. “A” refers to the Bcl11b mechanism, while “B” and “C” refer to the classical mechanism and the CD4-APC-CTL mechanism or pathway.

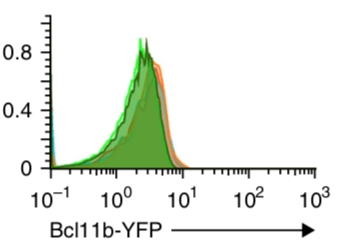
The Abstract implies that I may have found a logical link that gracefully combines Kueh et al., and Wodarz et al., and demonstrate these subsystems as a whole system to run the C++ simulation. Those details are spared here.

**Related Work**

**Kueh et al**

Hao Kueh et al., [2] researched a new process of T cell commitment. Commitment in this context means what it sounds like, and that is what Wodarz refers to as “activation”. It’s an enabling or a type of switching-on or promotion of T cells to full functionality. The main takeaway from Kueh et al., in relation to this paper and the C++ simulation application is based on Bcl11b. This gene, (also described as a transcription factor [5]) that encodes the protein by the same name, has been studied for years and continues to be. The Bcl11b mechanisms are 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 also out of scope for this paper’s purpose, but of course explained in [2]. The Bcl11b protein, is subcellular [4], and is an initial and essential factor in the simulation. It is explained later in the C++ Application Discussion section. Without Bcl11b, an individual is most likely to be a patient with symptoms of various types. A defective Bcl11b or missing one can also be fatal. Of course upon one’s birth, the gene must be coded correctly.

As mentioned in the Introduction, this model sets up the starting conditions for the next model discussed, and ie. the Wodarz et al., model. Numerical information from Kueh et al., is of course taken from [2], and relates to the distribution below in Figure 3.



**Normalized to mode**

**Figure 3** The probability for Bcl11b commitment peaks at ~0.7. This value is used in the simulation. More background information is available in [3], and not elaborated on, in this paper.

**Wodarz et al**

Wodarz discusses two pathways†, a la mechanisms, leading to CTL activation: a classical pathway and a CD4-APC-CTL pathway. (The details are out of scope for this venue.) The Wodarz pathways are a continuation of where the Kueh model or pathway† (or mechanism) terminates. When the simulation starts, the user is presented with an intent (in Java terms) of where to continue, since the program is in a graceful suspension at this moment. (S)he is presented with a choice of pathways†. They are of course, a) classical, or b), CD4-APC-CTL. The program continues as described in the C++ Application Discussion section. Figure 4 shows the concept of a Wodarz abstraction of CTL pathology [1].

The Wodarz pathways†;

The CD4-APC-CTL pathway [1] used is a shown below. Using this interpretation of CTL vs viral population behavior, ratio is;

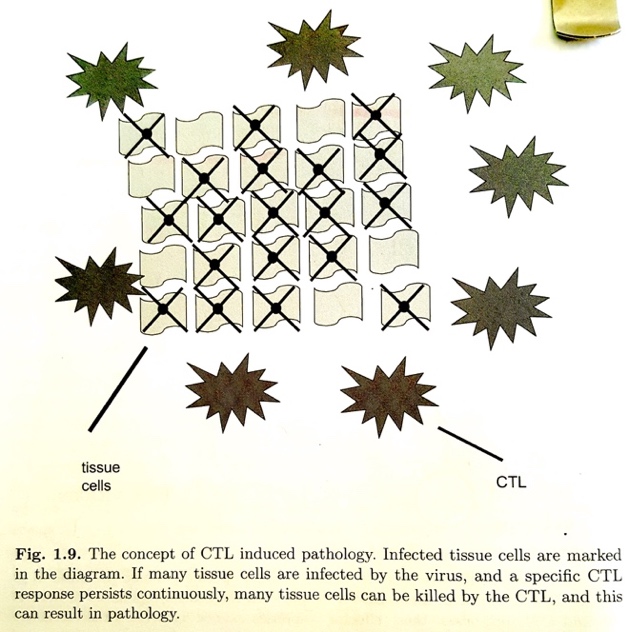
virus:CTL ≈ 3:1

The classical pathway [1] is described by a simplified equation;

CTL proliferation rate ≈ (2 \* v2) / (1 + v)

Figure 8 shows a typical final frame of the simulation. The simulation length is adjustable by the user. If the runtime is > 24 hrs e.g., there would be more K's present, intentionally replacing the v's, since they were eradicated by CTL. On the other hand, if the runtime were set to e.g., 0.1 sec, there would be nearly as many H's as there were initially upon program start,

(t-0+ seconds). Ideally, a healthy individual would have as many v's eradicated ASAP with as many K's present as possible, depending on the type of APV presented to the individual.



**Figure 4** This is a page taken from [1], and shows the concept of CTL pathology.

**Simulation Background Information;**

This section provides a simplified synopsis of CTL. It goes barely beyond the information offered in the Introduction section above. It seemed appropriate to discuss at this time before going any further. It illustrates the life cycle of CTL in an abstracted manner. The arrow means "differentiates into". It is analogous to

a metamorphosis from one type of entity to another. The function and purpose is changed, sometimes quite differently.

• Precursor (naive) CTL [1] ->

• Effector CTL [1][2] (We have heard the

phrase, "White blood cells (eg CTL)

come to the rescue!") ->

• Memory CTL [1], ("I never forget a face"). Eg.,

a subsequent returning strain of an influenza

virus will be recognized by the memory CTL

and will disable it.

• Co-stimulation between is a requirement for

communications between eg., an antigen

presenting cell (ie APC, a cell like a B cell), that

presents an antigen to a T cell upon contact to

an APC.s

• Technically speaking, regarding the last frame

of figure 9, the K's occur if and when a CTL

K\_ills a v\_irus. Eg., where an HIV retrovirus

has progressed, where the immune response

requires that CTL be activated and come into

virus eradication towards what Wodarz

calls "viral clearance". I simulate the

interaction between healthy cells and viruses

on a frame-by-frame basis, ie., the essence of

this research. Their interactions are explained

to gain insight into the following frames.

Upon program launch and normal

continuation, it is assumed that the

initial condition of the tissue sample is

healthy, ie., the person is in relatively good

health and cells are virus-free. For sake of

argument, assume now that the individual

came into contact with a strong enough virus

eg., a flu virus. An immune response then

develops and your body temperature

increases along with other tell-tail signs of influenza. If and when a virus particle comes into contact with a host cell, it will most likely infect it. Once infected, a leukocyte will attempt to disable the virus by various means depending on several factors. This of course occurs upon the leukocyte being as close in proximity as possible to the virus to render it ineffective, also by several means. Success is when these leukocytes are numerous and enough strong enough to eradicate the many virus particles on be on the road to viral clearance and recovery.

To take these simplified concepts one step further, amore complete explanation is warranted. (As an added note, according to [6], lymphocytes account for 14% - 47% of leukocytes, and lymphocytes account for 1.1 - 3.5x106 cells/ml, while leukocytes account for 4.1 - 10.9 cells/ml.)

Regarding the previously mentioned leukocyte, in this paper, the cytotoxic T lymphocyte, (CTL) [1] is the focal point of viral clearance. Also along with the previously mentioned virus, (actually an LCMV particle [1]), there is other entity that involved in the "complete" process of viral clearance [1]. This is the Bcl11b gene [2], and must be present from birth, otherwise we incur defects, disease or death [2]. It is in my judgment that at later mature/effector T cell development, Bcl11b is no longer required. This is discussed in the Conclusion. Incidentally, the reason for the quotes around the term, "complete", is because of the simplicity of this simulation, implying the complexity of absolute completeness of all the mechanisms of viral clearance, again, depending on many factors.

Going back to the essence of the application involving the cells just mentioned, the cells migrate within the boundaries of the host's sample tissue, mimicking a natural occurance. They "bounce around" and "bump" into each other. If this occurs within the boundaries of a stochastic domain, a host cell will become infected, and a CTL may kill a virus. (In actuality rather than a predator-prey simulation, we have a predator-prey-prey or a predator-predator-prey simulation.)

**Application Discussion**

A letter followed by an underscore is a means of explaining what the s\_ymbology means. Please refer to the Legend in Runtime

Visual Results.

Input;

• H\_ealthy mouse host cells are imbedded

onto a specified area of tissue in which the

H’s are randomly distributed about the

tissue. At first glance, it appears as though

the H's are spread too far apart. In reality

this is of course true. However for this

simulation, in the interest of effective

runtime and making the point clear, (ie.,

the behavior of CTL vs virus vs host cells)

the spread must be substantial.

• Infection is imminent (H→h). Ie, H\_ost

cells are demoted to h\_ost cells upon

infection by a v\_irus particle. v\_irus

particles invade the system, upon which

an immune response is launched.

• Probabilistic proliferation rates occur for

c\_TL for a given viral load. The initial CTL

counts are probabilistically determined by

which pathway is used and the viral count.

The probability relations are shown in

"The Wodarz pathways"† section above,

and is the essence of the mathematical

analyses of the Wodarz pathways. Full

explanations of most all proliferation and

death rates are meticulously determined

in [1]. On another note, a B\_cl11b gene [2]

codes the Bcl11b protein, in simplistic

terms. This is a very necessary condition

for early T cell commitment, otherwise,

(again) very undesirable health issues can

occur.

Output;

• A graphical frame-by-frame depiction of

the dynamics of the cells, H, h, v, c, and K,

but not B since Bcl11b is usually an

always-conditionº. (Again, s'il vous plait ),

in other words, especially at birth, we

must have this correctly coded gene,

otherwise we may suffer various illnesses,

or not survive at all. With respect to this

simulation, Bcl11b is expectedº to be

present.

• If Bcl11b is not present upon simulation

launch, the program gracefully halts. As

explained, in reality, a host incurs one of

several diseases and may not survive. The

simulation may gracefully halt according

to the probability distribution in [2],

regarding Bcl11b-YFP.

• CTL dynamics (cell movement and

interaction) are easily observable.

Metrics accompany the last tissue sample

status quo depiction. It shows the

resulting entity counts after some or

many v's have been K\_illed off by c\_TL

leukocytes, and some or many H's have

been demoted to h's by infection. Figures

5, 6, 7 and 8 explain these concepts.

**Runtime visual results**;

Initially, the vulnerable tissue sample will consist of randomly-placed healthy H\_ost cells. Bcl11b's presence is dependent on a probability from Kueh et al. [2]. Many meticulously derived probability distributions were generated from the bountiful data from many experiments and conclusions in Kueh et al. This of course is especially true for the distribution of Bcl11b, and is inquisitively true (in subtle contrast), for the fluorescent-tracking protein associated with Bcl11b, [viz] Bcl11b-YFP [2]. Figure 5 is sans **B**cl11b, (no ‘**B**’s). It must have this gene to continue the runtime. The simulation program gracefully halts when no B’s are sensed.

Legend;

B = Bcl11b gene, protein [2] or transcription

factor [5]

H = healthy H\_ost cell

h = an infected h\_ost cell

v = v\_irus particle (virion)

c = c\_TL

k = a virus particle has been k\_illed

|--------|

| H |

| H |

|H H |

| H |

| H H  |

|  |

| H |

| H |

|--------|

**Figure 5** Note the absence of "B" in this initial unhealthy host tissue sample upon program launch.

If Bcl11b is present as shown in Figure 6 , the program continues unimpeded, meaning that upon Bcl11b recognition, the user is presented with a choice of Wodarz pathways, classical or CD4-APC-CTL.

|--------|

| H |

| H |

|H H |

| H |

| H H **B** |

|  |

| H |

| H |

|--------|

**Figure 6** Runtime continues unimpeded due to "**B**" being present. Migration of cells start.

Continuing in the runtime environment, a viral attack has occurred and an immune response is launched shown in Figure 7. Referring to letters, rather than, a la "v\_irus" for simplicity, the v's infect, and the c's proliferate the sample tissue. The c’s populate enough to attempt recovery from our illness. As a brief, regarding to Figure 7, if a v\_irus is contiguous to a H\_ost cell, the H becomes an h. Ie., the h\_ost cell has become infected. If a c\_TL is contiguous to a v\_irus, the virus may become a K, denoting that the virus has been K\_illed.

|--------|

|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|

|--------|

**Figure 7** Antigenic stimulation (ie., an immunological response) occurs upon viral infection. Cell migration initiates.

Cell migration commences and is robust as depicted in Figure 8. As in nature, the entities will move about the body or host via several methods, eg., infection by skin contact, and CTL action in the blood and/or tissue.

|--------|

|v c H K |

| v Kc |

| hv h h |

| v |

|h cH v |

| hvKKH K|

| v**B** cv|

|cKh K**B** |

|--------|

**Figure 8** The predator/prey (actually, a predator-predator-prey or predator-prey-prey) migratory activity is active or robust. Ie., is observed that a predator, whether it is the virus or the CTL has behavior such that some 'H's change to 'h's, and likewise, some 'v's change to 'K's'.

**![](data:application/pdf;base64,)Figure 9** An example of the final frame of the simulation. Metrics include all final entity counts except for Bcl11b, which was explained.

**Evaluation**

An evaluation is possible by examining the logic of the code for this simulation in relation to [1]and [2]. As far as evaluating the accuracy of cogency of the link that conforms the two models, Kueh et al., and Wodarz et al., this would have to be examined by entities outside computer science, per se, and would require modern lab equipment and would conceivably include scholars of bioinformatics, statistical biology, computational immunology, virology, oncology, immunology, and microbiology. Such an evaluation can not be done for this paper. We (my advisor and myself) would like to think that yes indeed, a link does exist with a healthy degree of confidence, most likely. Of course proof of the work that explains this would have to be published and/or presented at a top tier venue.

**Conclusion**

For those whom are in the biological sciences, it is 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 nor advanced degree, much less finding funding 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. This is 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 (a sort of "hack") for the next stage of the T cell activation/commitment (a/c) process. That would be the Wodarz et al., T cell process. This produces a complete T cell a/c “story”. “Complete” in no way literally means the entirety of the story, that would be a herculean task. I believe my conclusion to the relation between [1] and [2] gracefully describes a beginning a middle (the link) 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 completely reveal what is happening on a frame-by-frame basis to simulate the predator-prey type behavior of virus versus host cell.

Coding is available in;

https://github.com/citationdude/NK-Cell-Simulator

as well as a seperate .docx that accompanies this paper for submission to Dr. Dewey. A print friendly PDF version of this paper with enumerated pages is available upon request.

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