

Appendix A – Figure 1.

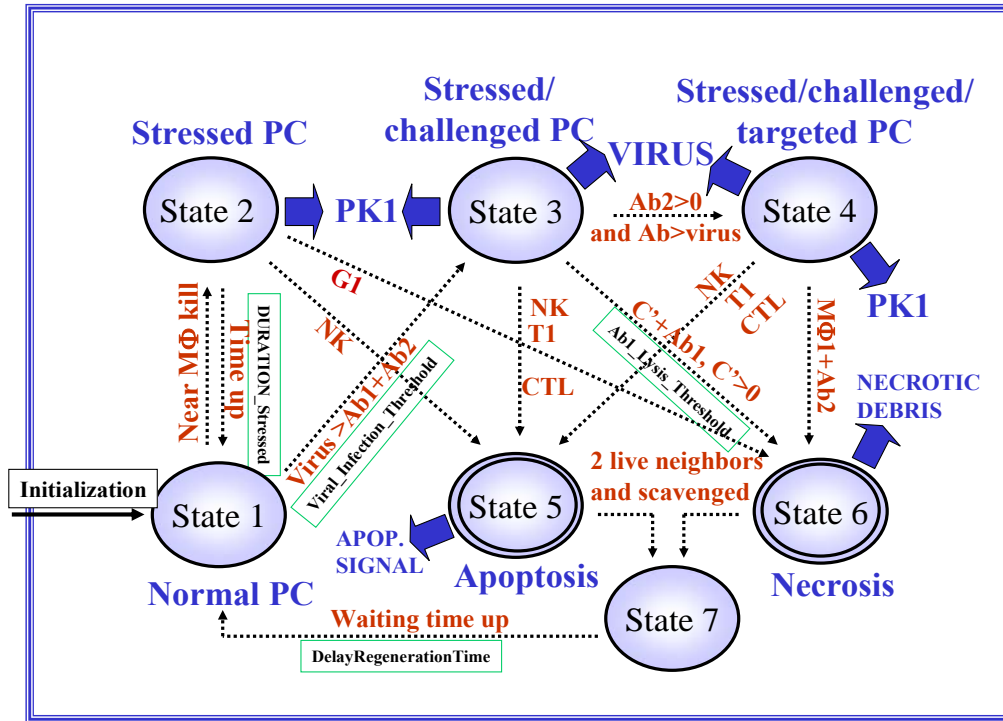


Figure 1 State Diagram: Parenchymal Cell Agents (PCs) in Zone 1.

PCs remain stationary in Zone 1 for the duration of the simulation. They begin as healthy, functional agents (State 1) that become infected with a virus and emit virus signal and Parenchymal-kin 1 (PK1), the stress signal (State 3). PK1 represents mediators such as heat-shock proteins [45], uric acid [46] or chemerin [47] that may be emitted by cells undergoing stress. PCs have two boolean properties or variables that reflect their well-being. One is the property of being stressed, which is true in States 2-4. The other is the property of being challenged, which for the experiments described herein is infection with a virus (true in States 3 and 4). The “challenge” for a simulation run is an input parameter (Table 2) that drives the immune response. Challenged PCs are always stressed, but PCs may be stressed without being challenged (State 2). Virally infected PCs may then transition to one of three fates. They may be killed by Natural Killer agents (NKs), pro-inflammatory T Cell agents (T1s) or Cytotoxic T Lymphocyte agents (CTLs) and undergo apoptosis (State 5). They may be bound by antibody (Ab; State 4) making them a target for recognition by pro-inflammatory Macrophage agents (MΦ1s) [50]. Or, they may be lysed by complement products (C') if Antibody 1 (Ab1) is present [51]. Both of the latter lead to death with release of necrotic debris (State 6). A PC that is in the immediate vicinity of another PC being killed by a MΦ1 will become stressed, representing damage due to reactive oxygen species release by the MΦ1 (State 2)[53]. Such a stressed PC then releases PK1 and may be killed by an NK [49]. PCs stressed for any reason may also be killed by exposure to Degranulation product 1 (G1), the degranulation signal released by Granulocyte agents[52, 53]. This results in the release of the signal for necrotic debris (State 6).

The dead PC debris must be scavenged by a MΦ before any regeneration of the PC may occur[54]. A healthy PC replaces a PC that is dead after the dead PC has been scavenged and if there are at least two healthy PCs in the spaces proximal to the space of the dead PC. This represents the division of one of the healthy PCs. There is a short waiting period once these conditions are met and then the new PC replaces the dead one.

Appendix A - Figure 2 State Diagram: Dendritic Cell Agents (DCs).

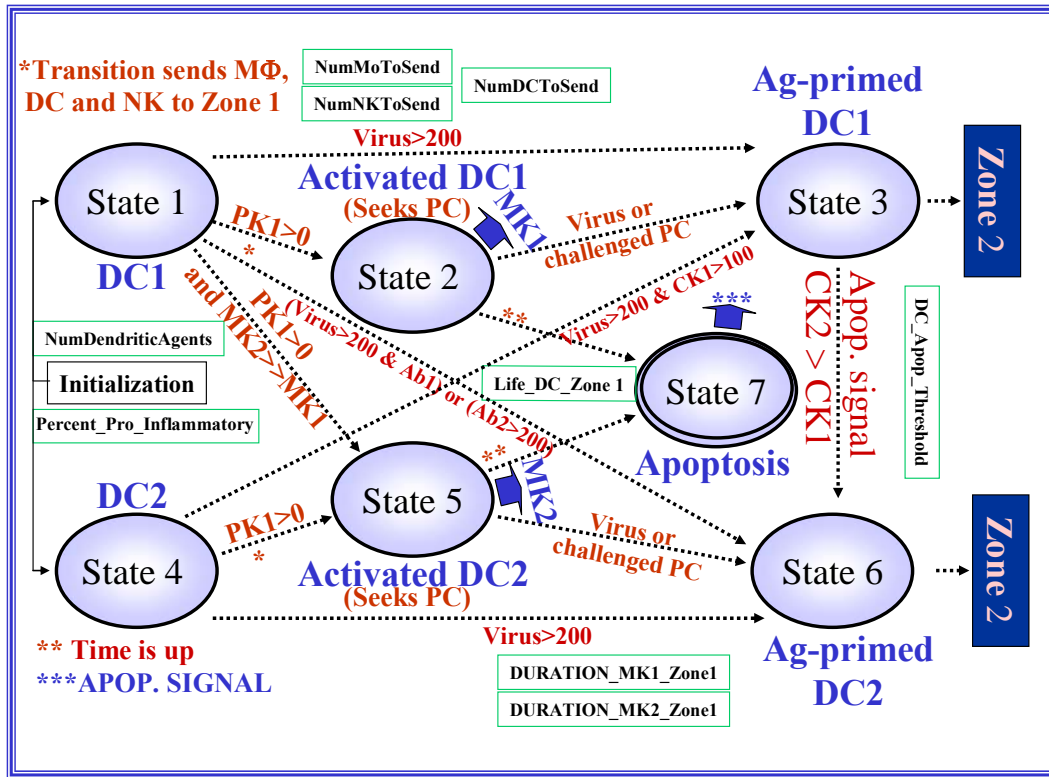


Figure 2a DCs in Zone 1.

DCs begin in Zone 1, where they function in surveillance of the tissue for any disruption of the healthy state of the tissue [27]. At initialization they may be in State 1 or State 4, depending on whether they have the potential to promote inflammation (DC1) or down-regulate it (DC2). The number of DCs and the ratio of DC1:DC2 is controlled by the input parameters “NumDendriticAgents” and “Percent\_Pro\_Inflammatory” (Appendix B). These subsets are meant to represent the ability of dendritic cells to polarize the immune response [59, 60, 65]. The numbers of DCs initially in Zone 1 used in the experiments approximate what may be found in normal dermis [85]. When the simulation begins, the DCs migrate randomly in Zone 1, able to detect soluble stress factor (PK1), virus, antibodies (Ab1 or Ab2), and pro- and anti-inflammatory cytokines [Mono-kine 1 (MK1) and Mono-kine 2 (MK2), Cytokine 1 (CK1) and Cytokine 2 (CK2); see Table 1]. The DCs may transition to another state depending on which signal they encounter first. PK1 causes the DCs to become activated [55] and transition to States 2 or 5. At this time NKs, MΦs and a DC enter Zone 1, as they would in response to chemokines. Once the DCs detect PK1 they follow its concentration gradient, seeking a challenged PC. In the activated state DC1s and DC2s also release signal, MK1 or MK2 (respectively). At this point a DC1 may be induced to convert to the down-regulatory DC2 phenotype by the preponderance of MK2 signal already in the environment [56]. In addition to the transitions to the activated states, the presence of virus in the immediate environment causes the transition to the antigen-primed state (State 3 or 6) [58]. Viral antigen bound by antibody induces the transition of a DC1 to the DC2 type [73] and virus in combination with pro-inflammatory CK1 causes the transition of a DC2 to the pro-inflammatory, antigen-primed DC1 state [57]. Contact with virally infected PCs also causes activated DC1s and DC2s to transition to their respective antigen-primed states [27].

If DC1s or DC2s reach the activated states (States 2 or 5) but do not detect soluble (signal) or PC-bound antigen within a pre-defined number of ticks they undergo apoptosis, or programmed cell death (State 7) [69]. Once the DCs do make contact with antigen, they migrate to Zone 2 to present the antigen to the B Cell agents (Bs), Ts and Cytotoxic T Lymphocyte agents (CTLs) [27]. If the DC1 senses a

preponderance of CK2 or detects apoptotic debris at the tick when the transition to Zone 2 is to be made, it will convert to a DC2 before migrating [55, 56].





Appendix A - Figure 4 State Diagram: Natural Killer Cell agents (NKs) in Zone 1.

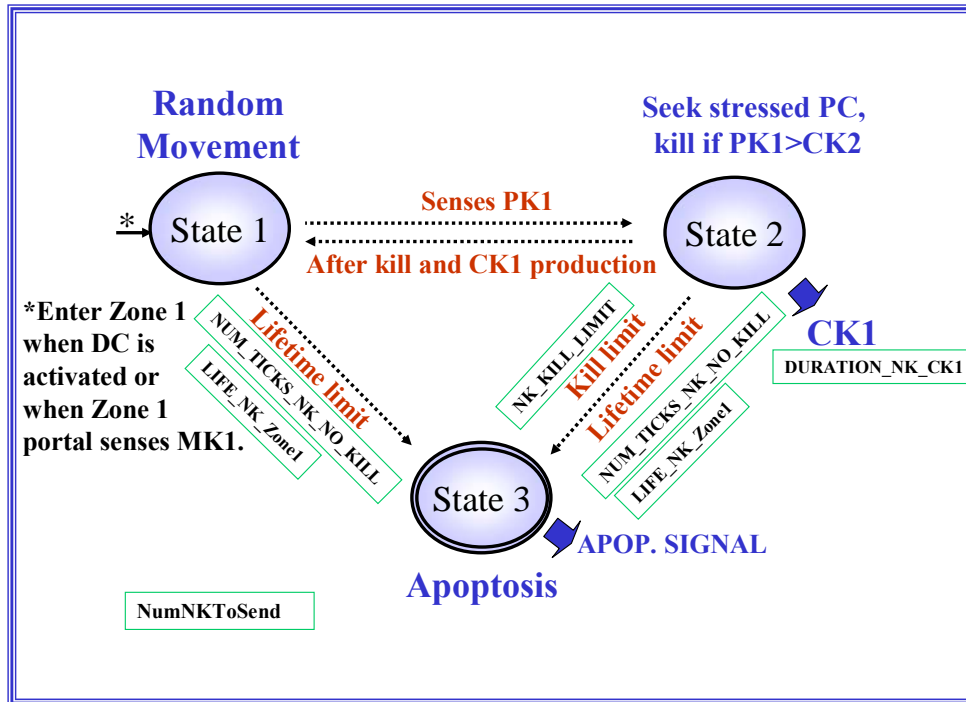


Figure 4. NKs in Zone 1.

NKs enter Zone 1 in response to DC activation by PK1, or when a Portal in Zone 1 initially senses MK1, simulating a chemotactic response [45, 79]. They move randomly until they sense PK1, then they transition to State 2 and follow the PK1 gradient to seek out any stressed PCs that are producing it. They also produce CK1, a pro-inflammatory signal [80]. Although NK cell recognition of self MHC Class I on cells provides an inhibitory signal to prevent killing, in a pro-inflammatory environment the inhibition is overcome [49]. If the NK finds a PC that is stressed and the PK1 signal present is greater than the CK2 signal, the PC is killed and the NK returns to State 1. The NKs have a limited lifetime and they have a limited number of kills that they may execute.

Appendix A - Figure 5 State Diagram: B Cell agents (Bs)

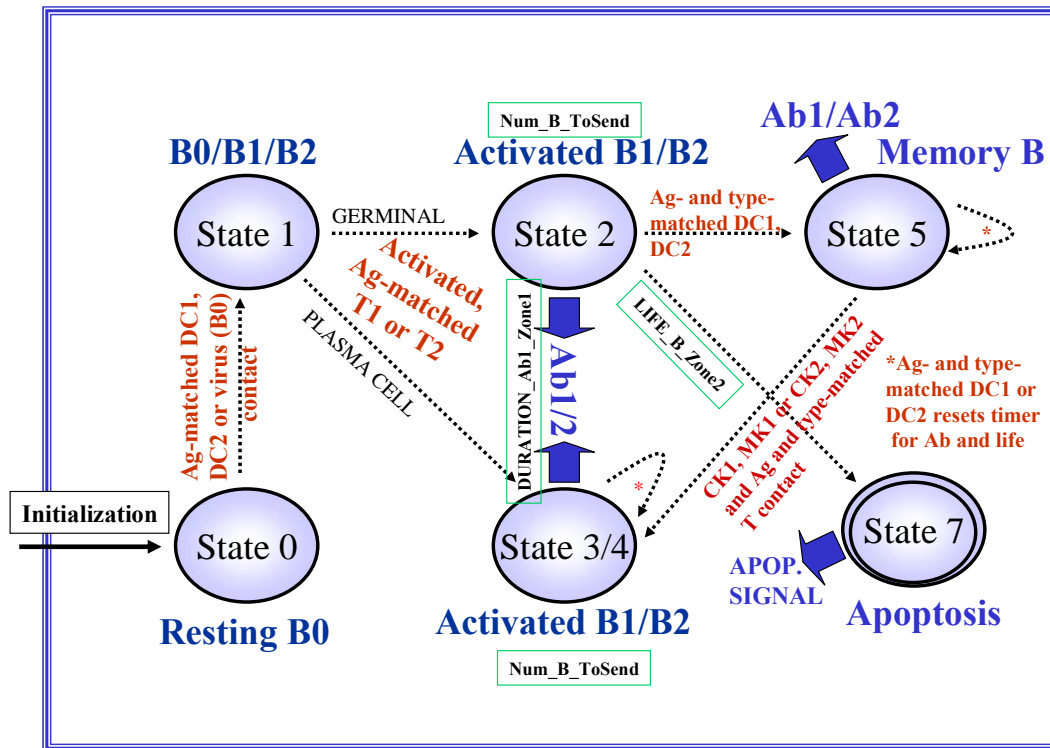


Figure 5a Bs in Zone 2.

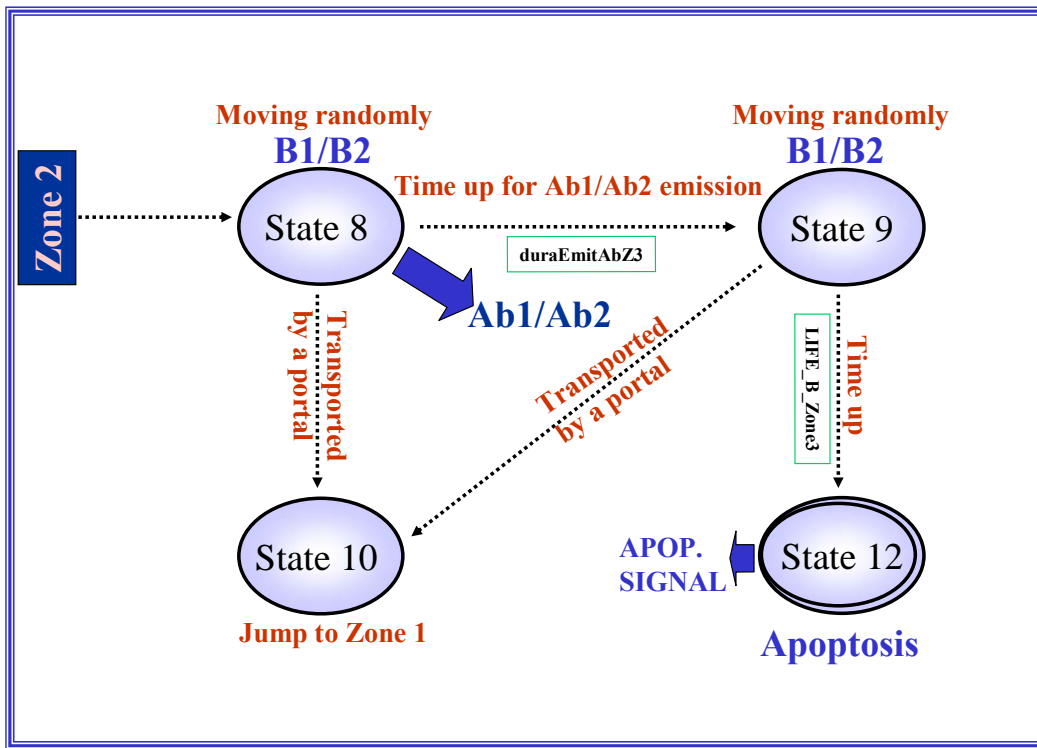
Bs begin in a resting state in Zone 2. They require contact with antigen (Ag) or a DC that is presenting antigen that matches their pre-set specificity [61]. The fraction of Bs that is specific for any particular antigen is an input parameter to the simulation. The default fraction of specific Bs that was used for these experiments was 2% (Table 2).

The DC also controls the response type of the B. If presentation of antigen is made by a DC1, the B will be type B1 and make Ab1. Presentation by a DC2 will cause the B to become a B2 and make Ab2 (Table 1). The abbreviations B1 and B2 indicate different populations present in the simulation and are not meant to correspond to such designations in the literature for B lymphocytes [84]. If the B detects antigen available freely in the lymphatic fluid, the activated T1 or T2 that subsequently contacts the B will determine its response type.

Once the B has either seen soluble antigen (such as virus) or seen antigen presented by a DC, the B requires contact with an antigen matched T1 or T2 before it can produce antibody (States 2-5) [25]. Once the B makes contact with an activated, antigen-matched T, it may take one of two (stochastically determined) paths. It may become a germinal B (State 2), producing antibody and remaining in Zone 2, or a plasma cell (States 3 or 4), producing antibody and traveling to Zone 3. Specific T contact also causes the B to proliferate, the number of progeny produced at each contact is an input parameter to the simulation. A sufficient number of subsequent antigen-specific DC contacts results in the formation of a long-lived memory B (State 5), with each contact

extending the life of the B. A memory B may be reactivated (to States 3 or 4) by the contact of an antigen-specific T and the presence of cytokines in Zone 2.

Appendix A - Figure 5 State Diagram: B Cell agents (Bs)



**Figure 5b Bs in Zone 3.**

Activated Bs in States 3 or 4 represent plasma cells and migrate to Zone 3 where they produce Ab that diffuses into Zone 1, and they may migrate into the actual site of inflammation, Zone 1, from there (State 10) [83]. As long as they remain in Zone 3 they move randomly. Bs have a finite lifetime and a finite period of time to produce antibody in Zone 3 determined by an input parameter.

Appendix A - Figure 5 State Diagram: B Cell agents (Bs)

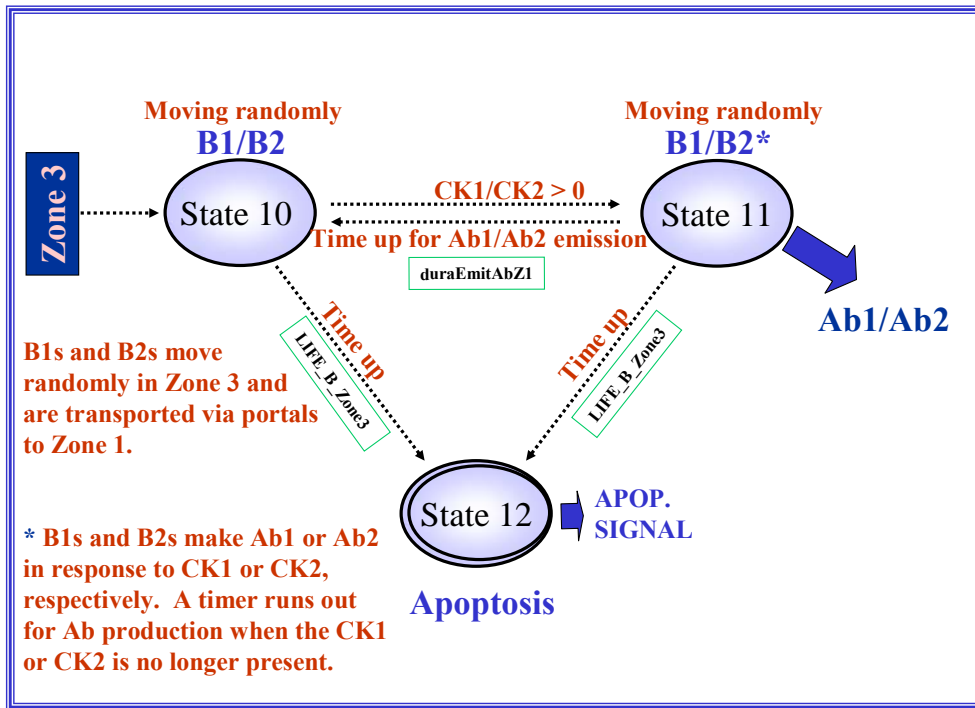


Figure 5c Bs in Zone 1.

In Zone 1 the Bs continue to move randomly and produce Ab if CK1 or CK2 is present (State 11) [82]. Once the signal is no longer present they cease to produce antibody within a period of time (State 10). This represents the behavior of B lymphocytes in immune responses where they may be found in sites of tissue inflammation [83]. Bs have a finite lifetime in Zone 1 determined by an input parameter (Appendix B).

Appendix A - Figure 6 State Diagram: T Cell agents (Ts)

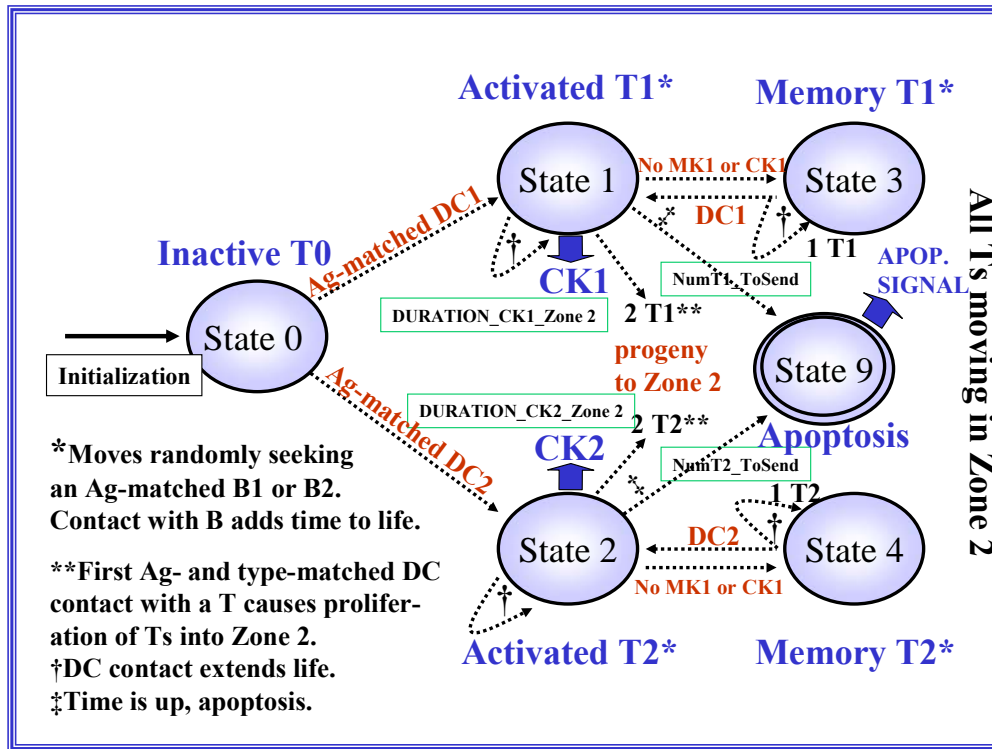


Figure 6a Ts in Zone 2.

The Ts in the simulation represent lymphocytes of the T<sub>-HELPER</sub> type. Like the Bs, the Ts begin in Zone 2 in an inactive state, moving randomly and waiting to make contact with an antigen-matched DC. The pro-inflammatory (DC1) or down-regulatory (DC2) type of the DC that makes first contact with the T determines the type of response that the T will promote in the remainder of the simulation (T1 or T2) [27, 60, 62, 65]. The fraction of Ts that are specific for any given antigen is an input parameter to the simulation, and the default value is 0.4% (Appendix B).

Once contact with an antigen-matched DC is made, the T is activated (States 1 or 2) and produces CK1 or CK2, depending on its response type. Proliferation of the T1 or T2 also occurs at this first contact. Subsequent contacts with antigen-matched DCs extend the life of the T [75]. The Ts also probe any Bs in proximal locations for their antigen specificity. An antigen-matched contact with a B affects the B if it has already been activated by a DC [74]. The contact also extends the life of the T. Ts in State 1 or 2 monitor the presence of CK1 and CK2 in their immediate environment. Absence of cytokines in the environment allows them to transition to long-lived memory Ts. Contact with an antigen- and response type- matched DC brings them back to the activated state [75]. In the absence of DC contact in Zone 2 activated Ts may undergo apoptosis [70]. Ts migrate to Zone 3, where they move randomly until they migrate into Zone 1.

Appendix A - Figure 6 State Diagram: T Cell agents (Ts)

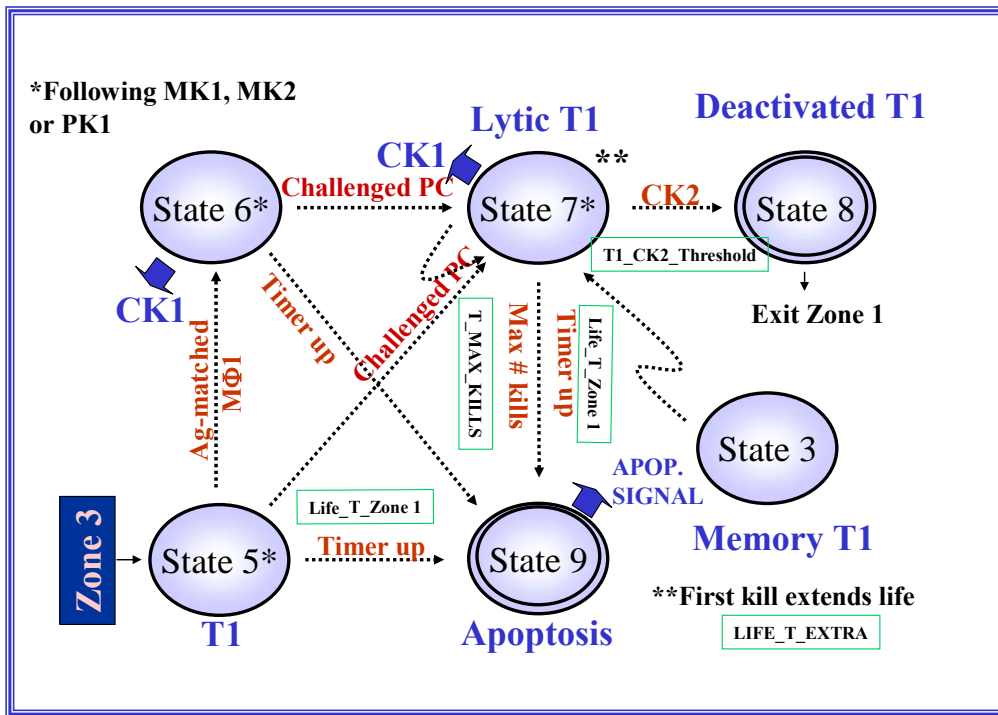
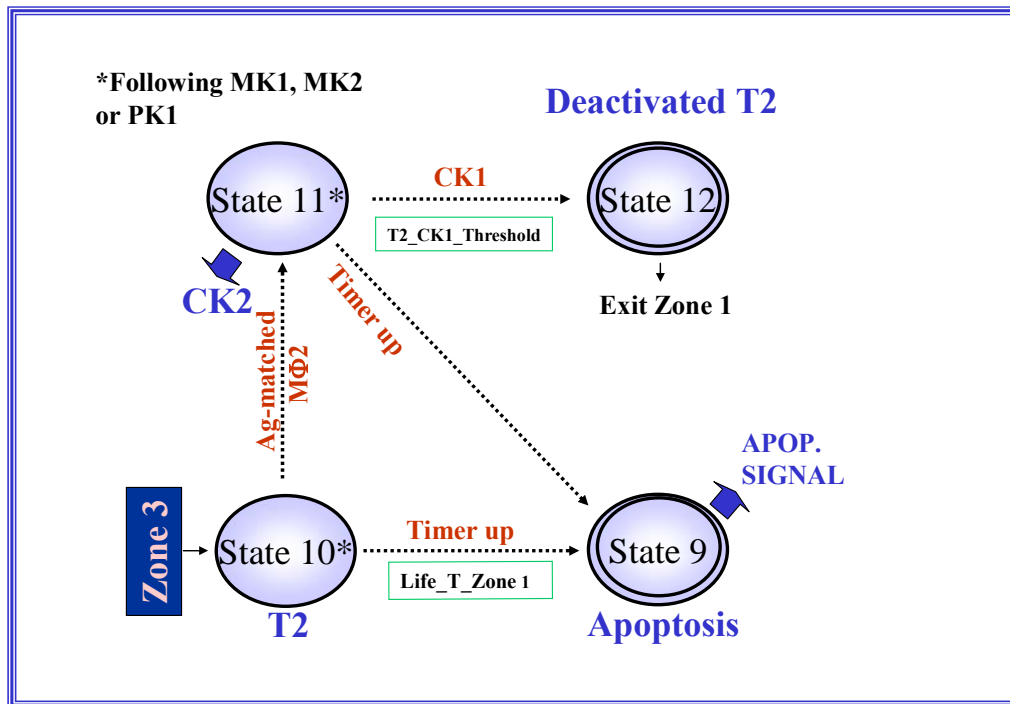


Figure 6b T1s in Zone 1.

When T1s arrive in Zone 1 they may follow MK1, MK2 or PK1, whichever signal they find to be the strongest in their immediate vicinity. If none are present they move randomly until they encounter a signal. They probe their immediate environment for the presence of an antigen-matched MΦ1, and if they encounter one they begin to emit CK1 [64]. They also probe their immediate environment for a virally infected PC, which they kill upon encounter. The T1s count the number of PCs that they kill, because they may only kill a finite number of times before undergoing apoptosis themselves [48]. If they detect CK2 at a level beyond a threshold value they become deactivated and are removed from Zone 1.

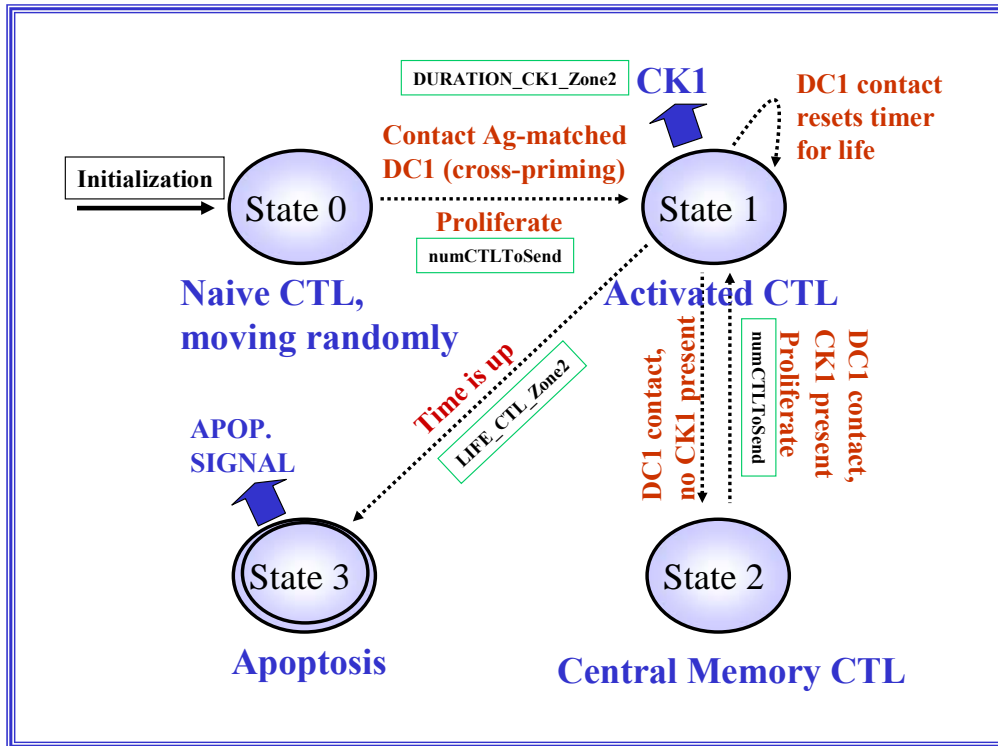
**Figure 6 State Diagram: T Cell agents (Ts)**



**Figure 6c T2s in Zone 1.**

T2s enter Zone 1 and determine the levels of MK1, MK2 and PK1 in their immediate environment. They follow whichever signal is the greatest or move randomly. The T2s look for an antigen-matched MΦ2, and if they encounter one they produce CK2 [64]. If they sense a level of CK1 in their immediate environment that is above a threshold level they are deactivated and exit Zone 1. Otherwise they remain in Zone 1 until they run out of time and undergo apoptosis [48].

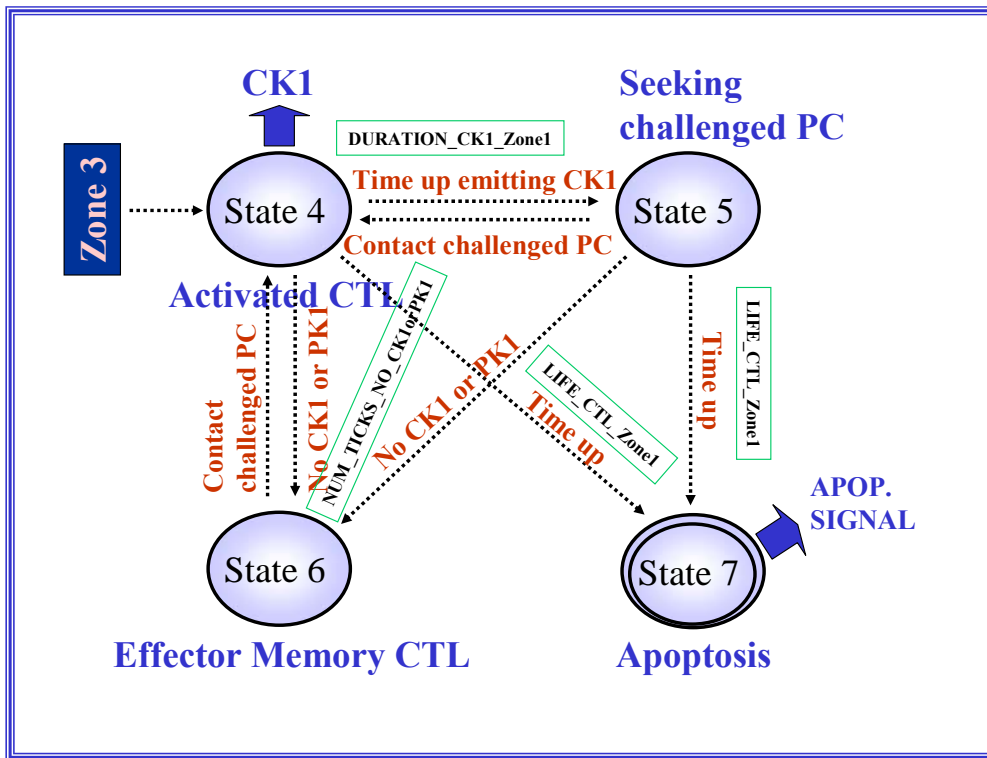
Appendix A - Figure 7 State Diagram: Cytotoxic T Lymphocyte agents (CTLs)



**Figure 7a CTLs in Zone 2.**

The CTLs begin in a resting state in Zone 2. The initial percentage of virus-specific CTLs is 0.4% (Appendix B). They move randomly and wait for contact with an antigen-specific DC1 in order to become activated (State 1). This process is referred to as “cross-priming” or “cross-presentation” [66]. This event also leads to cytokine production and proliferation of the CTLs, and the progeny may migrate into Zone 3. Once the CTL is activated, subsequent contact with a DC1 will cause a transition to a memory CTL (State 2) if there is no CK1 present in the immediate environment [76]. Otherwise the contact extends the life of the CTL in State 1.

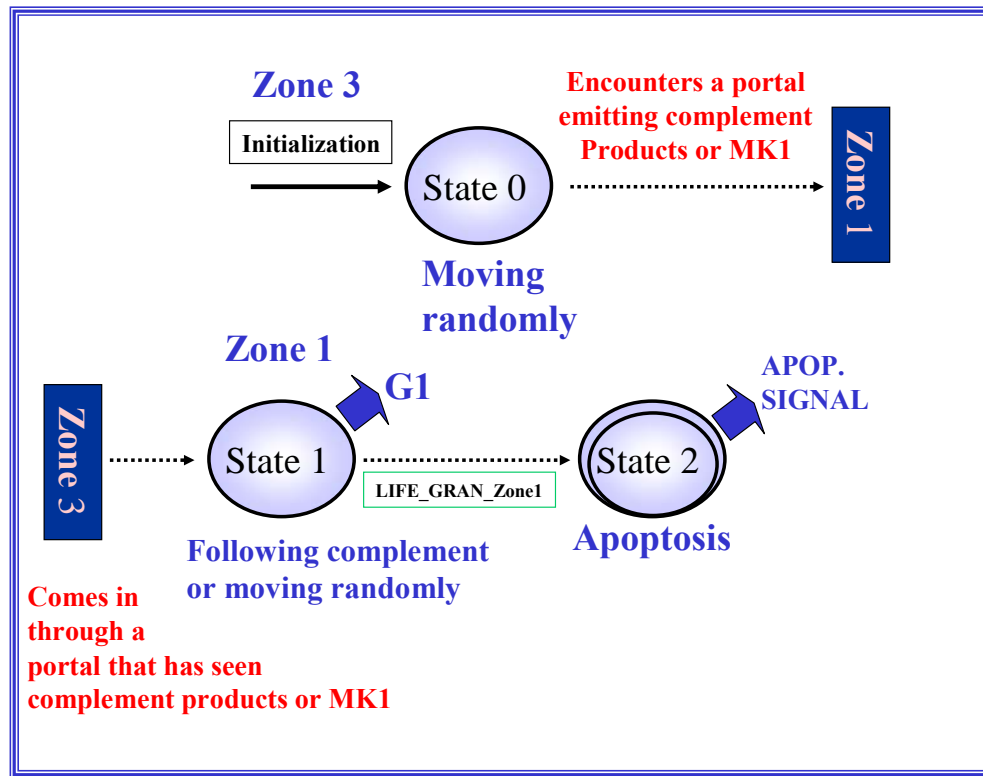
Appendix A - Figure 7 State Diagram: Cytotoxic T Lymphocyte agents (CTLs)



**Figure 7b CTLs in Zone 1.**

The CTLs migrate from Zone 3 into Zone 1 where they enter as activated, CK1-producing agents. They produce CK1 for a finite period of time that may be extended by contact with a virally infected PC. They continually sense CK1 and PK1 in their immediate environment and follow PK1 to seek infected PCs, that they kill upon contact. In the absence of any cytokine for a defined period of time they become effector memory CTLs (State 6), a state that allows them to persist for a long period of time and from which they may become activated (back to State 4) by an encounter with a virally infected PC [76, 77].

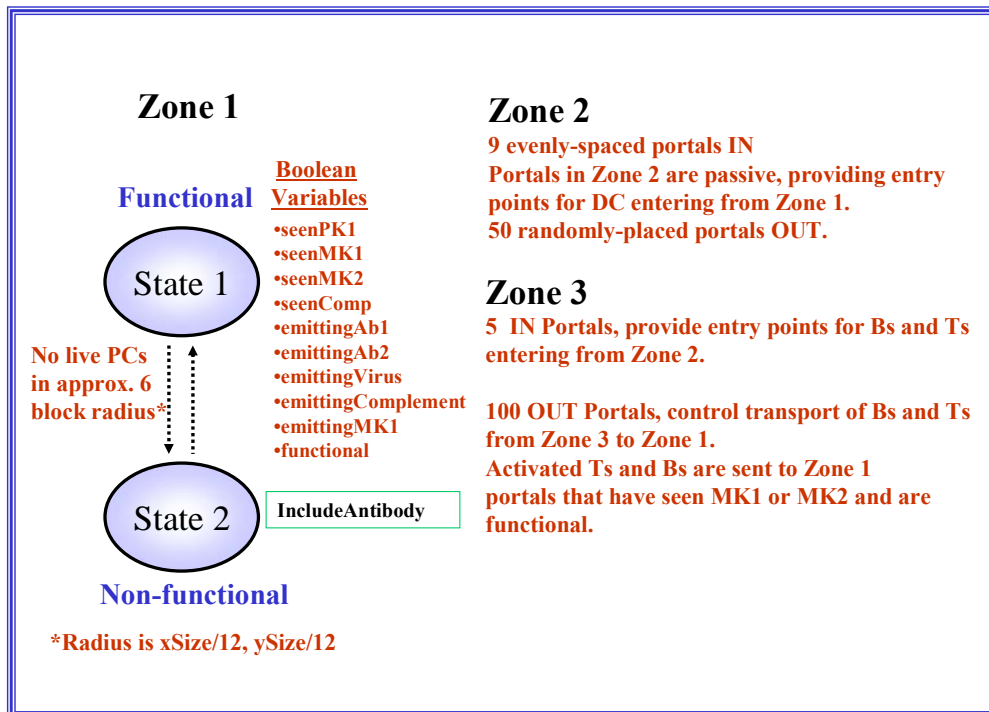
## Appendix A - Figure 8 State Diagram: Granulocyte agents



**Figure 8 Granulocyte agents in Zones 1 and 3.**

Granulocyte agents begin in Zone 3, moving randomly until they detect a portal emitting complement products [51] or MK1. At the detection of this signal they migrate into Zone 1 where they may follow the complement product signal or move randomly. They have a short lifetime in Zone 1, during which they emit a degranulation signal that is lethal for any stressed PC that encounters it [52].

## Appendix A - Figure 9 State Diagram: Portal agents (Portals).



**Figure 9 Portals.**

Portals are stationary agents present in all of the zones that control the migration of all of the other agent types that move from one zone to another. The Portals do not represent any immune cell type. They mark the locations in the zones that agents may use to migrate, representing the endothelium and the lymphatic vessels and blood vessels that the cells of the immune system must travel through. Portals also mark the places that signal produced in one zone may diffuse through to enter another zone. Portals in all of the zones sense the signals that are present near to them and they record this information for inquiry by other agents.

There are 36 portals in Zone 1 that have two states, functional or non-functional, controlled by the state of the PCs in the tissue that surrounds them. If all of the PCs within a particular radius surrounding them have died, they are not functional (State 2). They return to a functional state when the PCs surrounding them are regenerated. Zone 2 contains portals that allow the migration of DCs into the zone, and the migration of the Bs, Ts and CTLs that have proliferated out of Zone 2 into Zone 3.

Zone 3 has 5 portals that mark the locations that agents may enter, and 100 portals that mark the spaces that the randomly moving agents may exit from to migrate to Zone 1. The agents need only land on the coordinates with portals in Zone 3 for the transport to occur. Some agents have rules about the conditions of the portals in Zone 1 where they may enter. For some agents, certain signals must be present at the portal of entry in Zone 1 in order for them to use it. Migration is delayed for agents that cannot find the proper conditions for entry into Zone 1.

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