สัญญาเลขที่ MRG5980071

รายงานวิจัยฉบับสมบูรณ์

โครงการการพัฒนาแบบจำลองเชิงเฟ้นสุ่มเซลลูลาร์ ออโตมาตา: กระบวนการกำจัดเชื้อไวรัสเอชไอวี โดยอาศัยระบบภูมิคุ้มกันที่พึ่งเซลล์เป็นฐาน

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สิงหาคม 2563

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สนับสนุนโดยสำนักงานกองทุนสนับสนุนการวิจัยและต้นสังกัด

Abstract (บทคัดย่อ)

Project Code : MRG5980071

Project Title : Medical modeling and simulation to develop a stochastic cellular automaton model: effects of cell-mediated immunity to eradicate HIV-1 infection

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Project Period : 2 years

Abstract

Based on our previous work in Precharattana (2016), we proposed an HIV-CA model which concerned effects of cell-mediated immunities. The model composes of CD4, CD8, CTL, and DC. We found that our proposed model could represent the HIV infection dynamics closer to the typical infection dynamics in clinics than those models in previous works whose concerned such a CD4 cells function. We point out that our proposed model could shows the dynamics of healthy cells at the transient drop during the primary infection approximately 50% of the initial concentration, and at that transient drop the rebounding of the healthy cells is due to effects of cell-mediated immunities we added into the model. Therefore, in this present work, in order to come closer to the mechanic of cells interaction in clinics we propose to (i) add the more kinds of immune cells that play roles in the process of cell-mediated immunities into the system; moreover, (highlight) add the physical characteristics of the immune cells such as sizes and velocities into the model.

In this work, the variation of crucial parameters i.e. the initial number of virus particles and the initial number of $CD4^+$ T cells living in the lymphoid organ are focused. Samples of cell population dynamics for various cases for the infection, which tends to represent an individual patient, are presented.

Keywords : Infectious disease, Cellular automata, Spatial model, HIV-1 infection, Cell-mediated immunity

Executive Summary

Ever since HIV-1 was first diagnosed in human, thousands of scientific works have been undertaken to explore the biological mechanisms involved in infection and progression of the infectious disease. Since the majority of the virus resides in the lymphoid tissue that the interactions of virus-host tend towards locality, cellular automaton (CA) model, mathematical biological modeling taking into account the local interaction, have thus been introduced to understand those interactions and to discover more in-depth knowledge of the infectious disease within the infected host.

In a cellular automaton (CA), the system of interest consists of a collection of cells in which each cell is identified by one of a number of specified states. The progress of the system is tracked by changing the states of the cells. The state of each cell changes according to a set of local rules which depends on the state of that cell and those of its neighbor cells.

Many years ago, several CA models have been developed to explain the dynamics of HIV-1 infection. However, only a few models successfully described the two time scales (short-range in weeks; long-range in years) observed during the course of HIV-1 infection and the entire phases in the progression of the disease. The first CA model that can reproduce the entire dynamics of HIV-1 infection was proposed by Santos *et al.*. They described the dynamics of HIV-1 infection based on the change of states of white blood cells, namely the $CD4^+$ T lymphocytes ($CD4^+$ T cells). The states of those cells could be healthy, infected-stage 1 - the newly infected cells, infected-stage 2 - the infected cells that were interacted by immune response, or dead. Then, other CA research works also have been applied for investigation of dynamics among the virus-host interactions for several aspects including: the robustness of the model against changes in different model parameters, the dynamics features against the different symmetries and dimensionalities of the model lattices, and the dynamics behaviors against several treatments.

Although it was found that the CA models can use to explain the entire dynamics of HIV-1 infection, the studies of spatiotemporal pattern formation revealed that those simulation results are artifacts due to the spatial properties inherent to cellular automata and do not realistically reflect the immune's responses to the viral attack. Therefore, except the role of $CD4^+$ T cells, Precharattana *et al.* thus proposed the roles of other kinds of immune cells, i. e. the cell-mediated immunity, including the mechanisms of cells' mobility into their system. And with the model, it was found that the rebounding of the healthy cells level after the virus' primary attack is due to the effects of HIV-1 specific immune responses, but still the model could be used to describe only the primary phase of HIV-1 infection.

Therefore, in this work, we will again develop a simple, but yet comprehensive and practically useful stochastic CA model to discuss the process of HIV-1 infection in a lymphoid reservoir. With the model the role of HIV-1 target cells, i.e. the $CD4^+$ T cells, the roles of cell-mediated immunity, i.e. the $CD8^+$ cytotoxic T lymphocytes (CTLs) and the $CD4^+$ helper T lymphocytes, and the role of antigen-presenting cells (APCs), i.e. the dendritic cells (DCs), including the mechanisms of cells' mobility and their kinetics associated with the HIV-1 infection, for instance cells' proliferation and cells' differentiation, will be presented and incorporated.

We focus on the dynamics of the cell-mediated immunity because several studies have clearly demonstrated that the CTLs play a key role as the primary effectors in the control of HIV-1

after the primary attack. The $CD4^+$ T cells and their life's cycle are viewed as the major reservoir to be infected by HIV-1 because it was found that the cells are the main source of HIV-1 replication and dissemination in the lymphoid organ, moreover the infected $CD4^+$ T cells produce more than 98% of the newly free virus particles. In addition, among the APCs, we selected the DCs to be the main route of HIV-1 transmission to lymphoid organ since typically the majority of DCs are located in the mucosa and the lymphoid tissue. They are classified as the first cells encountering the virus during sexual transmission. Moreover, it has been suggested that DCs mediate the spread of HIV-1 to $CD4^+$T cells in the lymphoid tissue and also been identified as the most efficient APCs during the course of infection. Thus, we focus our attention on the influence of DCs in the role of trans-infection of $CD4^+$T cells and the initiation of the virus-specific immune response (the $CD4^+$ helper T cells and the CTLs) in our work.

We expected that our proposed model can show the progression of the infection which may guide the improvement of other research works or inspire future knowledge.

Chapter I

Introduction to the research problem and its significance

Ever since HIV-1 was first diagnosed in human, thousands of scientific works [1-3] have been undertaken to explore the biological mechanisms involved in infection and progression of the infectious disease. Since the majority of the virus resides in the lymphoid tissue [4] that the interactions of virus-host tend towards locality, cellular automaton (CA) model, mathematical biological modeling taking into account the local interaction, have thus been introduced to understand those interactions and to discover more in-depth knowledge of the infectious disease within the infected host.

In a cellular automaton (CA), the system of interest consists of a collection of cells in which each cell is identified by one of a number of specified states. The progress of the system is tracked by changing the states of the cells. The state of each cell changes according to a set of local rules which depends on the state of that cell and those of its neighbor cells [5, 6].

Many years ago, several CA models [7, 8] have been developed to explain the dynamics of HIV-1 infection. However, only a few models successfully described the two time scales (short-range in weeks; long-range in years) observed during the course of HIV-1 infection and the entire phases in the progression of the disease. The first CA model that can reproduce the entire dynamics of HIV-1 infection was proposed by Santos *et al*. [9]. They described the dynamics of HIV-1 infection based on the change of states of white blood cells, namely the $CD4^+$ T lymphocytes ($CD4^+$ T cells). The states of those cells could be healthy, infected-stage 1 - the newly infected cells, infected-stage2 - the infected cells that were interacted by immune response, or dead. Then, other CA research works also have been applied for investigation of dynamics among the virus-host interactions for several aspects including: the robustness of the model against changes in different model parameters [10, 11], the dynamics features against the different symmetries and dimensionalities of the model lattices [10-13], and the dynamics behaviors against several treatments [14-16].

Although it was found that the CA models can use to explain the entire dynamics of HIV-1 infection, the studies of spatiotemporal pattern formation revealed that those simulation results are artifacts due to the spatial properties inherent to cellular automata [17, 18] and do not realistically reflect the immune's responses to the viral attack. Therefore, except the role of $CD4^+$ T cells, Precharattana *et al.* [19] thus proposed the roles of other kinds of immune cells, i. e. the cell-mediated immunity, including the mechanisms of cells' mobility into their system. And with the model, it was found that the rebounding of the healthy cells

level after the virus' primary attack is due to the effects of HIV-1 specific immune responses, but still the model could be used to describe only the primary phase of HIV-1 infection.

Therefore, in this work, we will again develop a simple, but yet comprehensive and practically useful stochastic CA model to discuss the process of HIV-1 infection in a lymphoid reservoir. With the model the role of HIV-1 target cells, i.e. the $CD4^+$ T cells, the roles of cell-mediated immunity, i.e. the $CD8^+$ cytotoxic T lymphocytes (CTLs) and the $CD4^+$ helper T lymphocytes, and the role of antigen-presenting cells (APCs), i.e. the dendritic cells (DCs), including the mechanisms of cells' mobility and their kinetics associated with the HIV-1 infection, for instance cells' proliferation and cells' differentiation, will be presented and incorporated.

We focus on the dynamics of the cell-mediated immunity because several studies [20, 21] have clearly demonstrated that the CTLs play a key role as the primary effectors in the control of HIV-1 after the primary attack. The $CD4^+$ T cells and their life's cycle are viewed as the major reservoir to be infected by HIV-1 because it was found that the cells are the main source of HIV-1 replication and dissemination in the lymphoid organ [22, 23], moreover the infected $CD4^+$ T cells produce more than 98% of the newly free virus particles [3, 24, 25]. In addition, among the APCs, we selected the DCs to be the main route of HIV-1 transmission to lymphoid organ since typically the majority of DCs are located in the mucosa and the lymphoid tissue [26]. They are classified as the first cells encountering the virus during sexual transmission [27]. Moreover, it has been suggested that DCs mediate the spread of HIV-1 to $CD4^+$T cells in the lymphoid tissue and also been identified as the most efficient APCs during the course of infection [28-30]. Thus, we focus our attention on the influence of DCs in the role of trans-infection of $CD4^+$T cells and the initiation of the virus-specific immune responses (the $CD4^+$ helper T cells and the CTLs) in our work. While the Ms are not only named to be the APCs, but also be the first cells infected by the virus and be the very source cells of virus production when the $CD4^+$ T cell are markly depleted. Though the productively infected Ms are reported to be not relatively more in lymph node [31] we design the Ms to have function as both the APCs in the role of trans-infection of $CD4^+$T cells and the initiation of the virus-specific immune responses as similar as the CDs, and in the role of cis-infection, be the infected reservoir and producing the virus as $CD4^+$ T cells in ours.

We expected that our proposed model can show the disease's progression which may guide the improvement of other research works or inspire future knowledge.

Chapter II

Literature review

Human Immunodeficiency Virus type 1 (HIV-1)

The infection of **Human Immunodeficiency Virus type 1 (HIV-1)**, causing Acquired Immunodeficiency Syndrome (AIDS), is responsible for millions of deaths worldwide. The features which make HIV-1 very effective in its action against human being includes: (i) its high replication rate; (ii) its high mutation rate; and (iii) its ability in progressive reduction in the number of immune cells, to be specific, $CD4^+$ T cells.

HIV-1 pathogenesis

Like all viruses, HIV-1 cannot grow or reproduce on its own. In order to make new copies of itself, it must infect into the cells of a living organism. Infected by HIV-1 can cause a latent infection in cells of immune system or may activate the cells to produce infectious virus. The virus production leads to death of the infected cells, as well as death of uninfected lymphocytes, subsequent immune deficiencies, and clinical AIDS.

After HIV-1 enters a human body, dendritic cells (DCs) will arrest the virus and then the DCs incorporated with the HIV-1 will move to the lymphoid organs, where the virus are presented and simultaneously infect to the T lymphocytes. The integrated provirus may be activated in infected cells leading to production of viral particles and spread of the infection.

During the course of infection, $CD4^+$ T cells are noted to be the major source that produces viral particles [3, 24, 25]. The result of this event leads to the depletion of the infected $CD4^+$ T cells, as well as death of the uninfected. Although other infected cells, such as DCs, macrophages, and other immune cells may also die during the infectious process, resulting in destruction of the architecture of lymphoid organs; the significance of these functional defects has not been established. Therefore, loss of $CD4^+$ T cells remains the most reliable indicator of disease progression.

In this research work, we thus will focus on the dynamics of CD^+ T cells as they are the source of HIV-1 infection, and will incorporate the life cycle of $CD4^+$ T cells associated with HIV-1 infection, as illustrated in Figure 1, in our model.

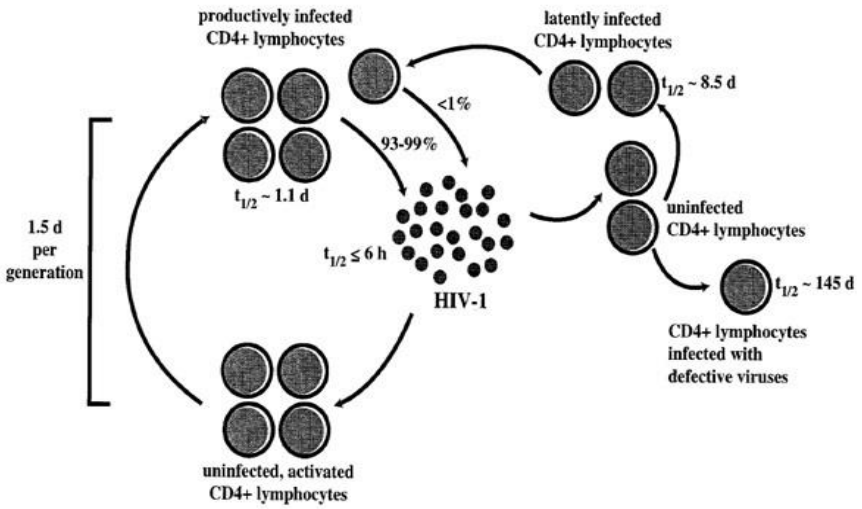

Figure 1 Schematic summary of the $CD4^+$T cells kinetics associated with HIV-1 infection [25].

Clinical features of HIV-1 infection

In order to track evolution of HIV-1 infection, pathogenesis medical professionals use the $CD4^+$ T cells count and viral load in HIV-1 patient blood to refer the stage of disease progression and to decide when to begin treatment. Since the infection start, patients will be able to live proximately 12 years until death. The typically development of HIV-1 infection is divided in three phases as shown in Figure 2:

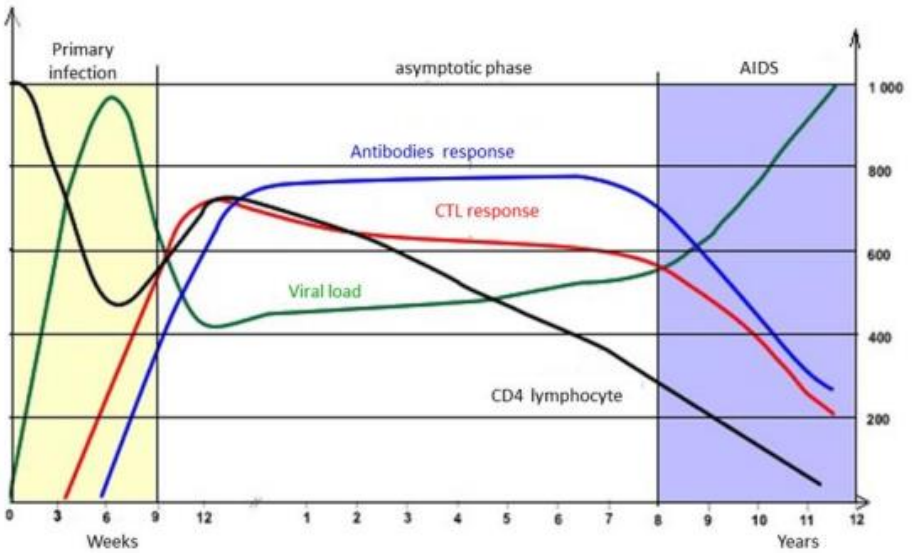

Figure 2 Typical dynamics of HIV-1 infection [32].

(i) *Primary HIV-1 infection*: The immediately increase in plasma viral level leads to the existence of viraemic peak. At the same time the drop in $CD4^+$ T cells level

occurs. Notice that these all develop during just a few weeks (approximately 3-6 weeks) in most patients with the symptoms similar to flu.

(ii) *Chronic asymptomatic HIV-1 infection*: The HIV-specific immune response partially eliminates HIV-1. At this moment, the $CD4^+$ T cells are sufficient to defend against other pathogens. But considering all of this stage, which takes the order of years, the virus replication relates to the depletion of $CD4^+$ T cells level by the patients do not perform any clinical symptoms.

(iii) *Last stage HIV-1 infection*: This period could be determined to be the onset of AIDS. Because of the outbreak of HIV-1 with the rapidly decrease in $CD4^+$ T cells lower than 200 copies per μL, the patients can be attacked by the constitutional symptoms and opportunistic diseases, and then die.

Role of immunity

Immunity is defined as resistance to disease, specifically infectious disease. Immune system is the collection of cells, tissues, and molecules that mediate resistance to infection, and the coordinated reaction of the cells and molecules to infectious microbes is called immune response. Host defense mechanisms which mediate the initial protection against infections is called innate immunity, and those which develop more slowly and mediate later, but even more effective to defense against infections is called adaptive immunity.

Adaptive immune response

The task of the adaptive immune response is to defense against the infectious agents, and this is why defects in the adaptive immune system results in increased susceptibility to infections. The system of adaptive immune consists of lymphocytes and their products, i.e. antibodies. Whereas the mechanisms of the innate immunity recognize structures shared by classes of microbes in epithelia barriers and circulation, the cells of adaptive immunity express receptors that specifically recognize different substances, called antigens, produced by microbes in lymphoid organs.

Two types of adaptive immunity are humoral immunity and cell-mediated immunity. They are mediated by different cells and molecules, and are designed to provide defense against different functions. Humoral immunity has function in defense against extracellular microbes and is mediated by proteins called antibodies which they are secreted by cells called B lymphocytes. In contrast, **cell-mediated immunity** has function in defense against intracellular microbes and is mediated by cells called T lymphocytes.

In this study we are interested in the infection of HIV-1 that are mediated by function of cell-mediated immunity and will incorporate effects of the immunity into our model.

Types of Cell-mediated immunity

Types of cell-mediated immunity could be classified according the reaction designed to eliminate different types of intracellular microbes: **$CD4^+$ helper T cells** activate phagocytes to destroy microbes residing in the vesicles of these phagocytes, and **$CD8^+$ cytotoxic T lymphocytes (CTLs)** kill any cell containing microbes or microbial proteins in the cytoplasm.

How T lymphocytes eradicate HIV-1 infection: Activation of Cell-Mediated Immunity and Elimination of Cell-Associated the virus

After HIV-1 enters a human body, dendritic cells (DCs), the antigen presenting cells (APCs) that are the most efficient stimulators of naïve T cells [28-30], would arrest the virus and then process the antigen into their epitopes, binding to a major histocompability complex (MHC) molecule. The resulting complex then incorporates the antigen into the membrane of the DCs. Afterward, these DCs then move to the lymphoid tissue and to the spleen, where they can present the epitopes to various clones of T lymphocytes [33, 34]. Once, naïve T cells enter lymph nodes from the circulation, they will rapidly move around in the nodes, scanning the surfaces of the DCs for the presence of the antigen. When a T cell recognizes antigen, the cell will then transiently stops moving and initiates its activation program.

On activation by the antigen, the antigen-specific T cells begin to secrete cytokines, whose function of them stimulates the proliferation of the antigen-specific T cells, resulting in a rapid increase in the number of antigen-specific lymphocytes. This process is called clonal expansion. A faction of these activated T lymphocytes undergo the process of differentiation, which results in the conversion of naïve T cells, whose function is to recognize microbial antigens, into a population of effector T cells, whose function is to eliminate the virus. Some effector T cells may remain in the lymph node, where they function to eradicate infected cells in the lymphoid organ or to provide signals to B cells that promote antibody responses against the virus. Other effector T cells leave the lymphoid organs where they differentiated from naïve T cells, enter the circulation, and migrate to any site of infection. Some of the progeny of the T cells that have proliferated in response to antigen develop into memory T cells, which are long-lived and functionally inactive and circulated for month or years, ready to rapidly respond to repeat exposures to the same evidence. As effector T cells eliminate the infectious agent, the stimuli that trigger T cell expansion and differentiation also are eliminated. As a result, the greatly expanded clone of antigen-specific lymphocytes dies, thereby the system

returns to its basal resting state [35-37]. Steps in the activation of T cells in response to the antigen-recognition are shown in Figure 3.

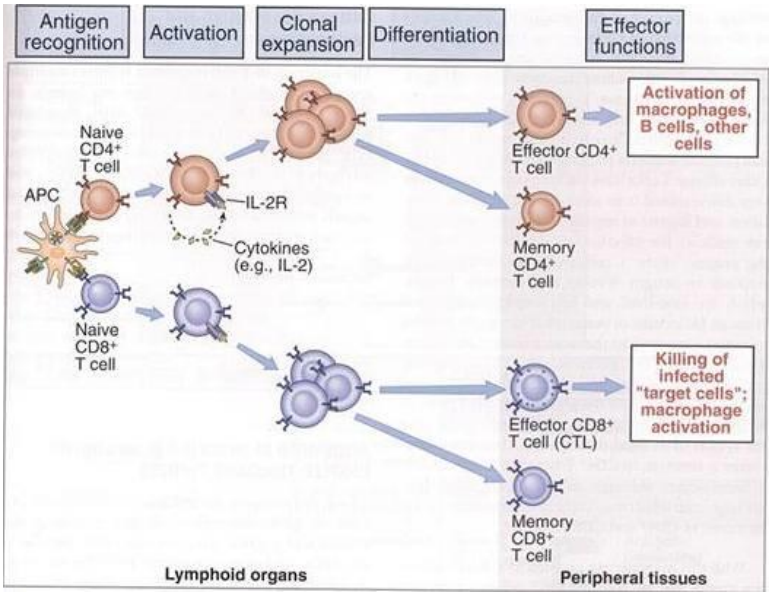

Figure 3 Naïve T cells recognize MHC-associated peptide antigens displayed on antigen-presenting cells (APCs). The T cells respond by producing cytokines, such as IL-2 and expressing receptors for these cytokines, leading to an anticrime pathway of cell proliferation. The result is clonal expansion of the T cells. Some of the progeny differentiate into effector cells, which serve various functions in cell-mediated immunity, and memory cells, which survive for long periods [38].

In this research, we focus on the mechanisms of cell-mediated immunity in which the naive T cells are activated, and then proliferate and differentiate into the effectors. To be specific, dynamics of $CD8^+$ T cells which are directly activated by DCs and then proliferate and differentiate into effector $CD8^+$ T cells)$CD8^+$ cytotoxic T lymphocytes: CTLS (whose function is to kill the infected cells harboring antigens in the cytoplasm, and dynamics of $CD4^+$ T cells that are directly activated by DCs and then proliferate and differentiate into effector $CD4^+$ T cells ($CD4^+$ helper T cells) whose function is, by secreting interleukin 2 (IL-2), to stimulate $CD8^+$ T cells to proliferate and differentiate into $CD8^+$ cytotoxic T lymphocytes (CTLs) [38, 39]. The evidence of these interested interactions may be occurring in lymphoid organ, i.e. the T cell zone called Paracortex in the lymph nodes or Periarteriolar lymphoid sheath (PALS) in the spleen. Figure 4 shows the biological concept that it will be applied for our CA rules in our model.

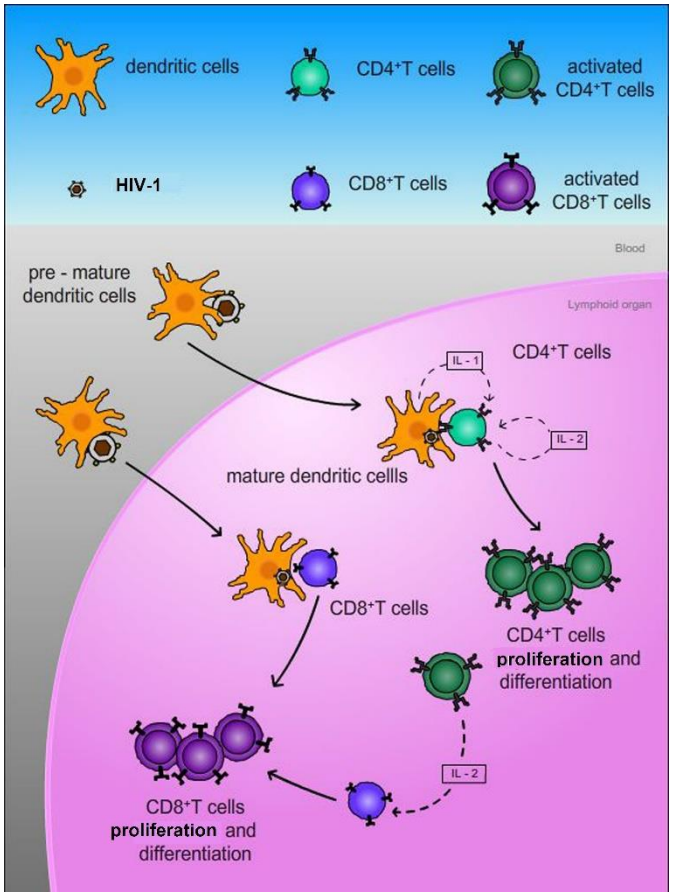

Figure 4 Mechanisms of cell-mediated immunity to eradicate HIV-1 infection in lymphoid tissue of our model. The events that cause T lymphocytes proliferation and differentiation include: (i) if the DCs directly bind to the $CD8^+$T cells, they would result in proliferation and differentiation of the $CD8^+$T cells into effector $CD8^+$T cells known as $CD8^+$ cytotoxic T lymphocytes, CTLs, (ii) if the DCs directly bind to the $CD4^+$T cells, the DCs would secrete interleukin 1 (IL-1) which stimulates the $CD4^+$T cells and causes the particular cells to proliferate and differentiate into effector cells called $CD4^+$ helper T cells. In addition, (iii) the binding of DCs to the $CD4^+$T cells also causes the $CD4^+$ helper T cells to secrete interleukin 2 (IL-2). This compound then would stimulate the $CD8^+$T cells and cause these particular cells to proliferate and differentiate into the CTLs [40].

On the road of using Cellular automaton to study HIV-1 infection dynamics

To date there is neither a prophylaxis which can keep the immunity safety from HIV-1, nor a cure for the disease. Even though several studies [1, 2] have been designed to explain the mechanism between HIV-1 and our immune system, further study is required for completely understanding of the exact mechanism and finding an effective treatment. To that end, studying *in silico* is one of common ways to investigate biological mechanisms for its less time and budget consuming. Also, when studying treatment effects, computational investigation allows researchers to control all factors involving the infection.

Considering studying *in silico*, differential equations [41] seem to be a standard way to describe different aspects of the dynamics of the host and virus interaction. However, these mathematical techniques are limit to describe the spatiotemporal pattern formation and cannot capture the stochastic properties of HIV-1 dynamics. Moreover, supported by the experimental evidence that the majority of HIV-1's target cells ($CD4^+$ T cells) and its infected progression is in the lymphoid tissues [4], including the spread of HIV -1 infection among cell-to-cell is seem to be more important than cell-to-virus transmission [42, 43]. This means that studying the local interaction which a major drives by the cellular automaton (CA) approach thus plays an important role for the HIV-1 infection dynamics.

Cellular automaton

Cellular automaton (CA) [5] are dynamical system which discrete in space and time. It composed of *a collection of cells* (or grids) which we call a lattice whose play a role as a virtual world of cells. Each cell in the lattice can exist in one of a number of k possible states, where k is a finite number ≥ 2, to identify local states of the cells in a current time. In the simple case where each cell can exist in two possible states ($k = 2$), the state of each cell can be labeled by the symbols 0 or 1 and graphically by white or black. In more anthropomorphic terms, we can think of cells in the 0 (white) states as "dead" and those in the 1 (black) state as "alive". *Each state of the cell* can be labeled by a time-dependent variable S_i^t that arrays on the lattice of N sites, $i = 0, 1, 2, \ldots, N - 1$ (for two dimensional CA and three dimensional CA it can be labeled by using indices i, j and i, j, k, respectively). The collection of all local states of the cells is called a configuration.

The progression of the system is tracked by changing the states of those cells which are updated simultaneously at discrete time steps ($t = 1, 2, 3, \ldots$) according to *a set of local rules or local transition function* (F), depending on the current state of that cell and those of its *neighbor cells* - the cells surrounding a specified cell. This alteration of cell states takes place synchronously for all cells in the lattice.

The equation of motion which map a configuration at one time step to the next of the value S of a site at position *i*, for instance, in one dimensional CA with a rule that depends only on nearest neighbors could be written as $S_i^{t+1} = F\left[S_{i-1}^t, S_i^t, S_{i+1}^t\right]$.

For a two dimensional CA and three dimensional CA, there are several possible lattices and neighborhood structures. In this research work, for the two dimensional CA, we consider a square lattice with neighborhood structure as illustrated in Figure 5. A square shaped cellular automaton with Moore neighborhood condition then evolves in analogy according to

$$S_{i,j}^{t+1} = F\left[S_{i,j}^t, S_{i-1,j-1}^t, S_{i-1,j}^t, S_{i-1,j+1}^t, S_{i,j-1}^t, S_{i,j+1}^t, S_{i+1,j-1}^t, S_{i+1,j}^t, S_{i+1,j+1}^t\right] \quad [44]$$

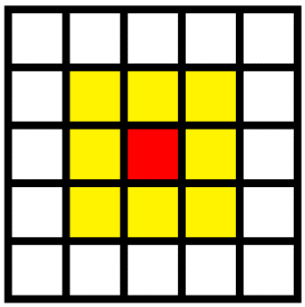

Figure 5 Moore neighborhoods condition (r = 1) for 2-dimensional cellular automaton which consists of a central cell (*i, j*), and its four neighbors, i. e. north (*i, +1j*), west (*i-1, j*), south (*i, j-1*) and east (*i+1, j*), in addition, second nearest neighbors north-east (*i+1, j+1*), north-west (*i-1, j+1*), south-east (*i+1, j-1*) and south-west (*i-1, j-1*), totaling nine cells. The red region indicates the central cell which is updated according to the state of the cells marked in yellow.

For the three dimensional CA, we consider a square cubic with neighborhood structure as illustrated in Figure 6. A cube shaped cellular automaton with Moore neighborhood condition then evolves in analogy according to

$$S_{i,j,k}^{t+1} = F\begin{bmatrix} S_{i,j,k}^t, S_{i,j,k-1}^t, S_{i,j,k+1}^t, S_{i,j-1,k}^t, S_{i,j-1,k-1}^t, S_{i,j-1,k+1}^t, S_{i,j+1,k}^t, S_{i,j+1,k-1}^t, S_{i,j+1,k+1}^t, \ldots \\ S_{i-1,j,k}^t, S_{i-1,j,k-1}^t, S_{i,-1j,k+1}^t, S_{i-1,j-1,k}^t, S_{i-1,j-1,k-1}^t, S_{i-1,j-1,k+1}^t, S_{i-1,j+1,k}^t, S_{i-1,j+1,k-1}^t, S_{i-1,j+1,k+1}^t, \ldots \\ S_{i+1,j,k}^t, S_{i+1,j,k-1}^t, S_{i+1,j,k+1}^t, S_{i+1,j-1,k}^t, S_{i+1,j-1,k-1}^t, S_{i+1,j-1,k+1}^t, S_{i+1,j+1,k}^t, S_{i+1,j+1,k-1}^t, S_{i+1,j+1,k+1}^t \end{bmatrix}$$

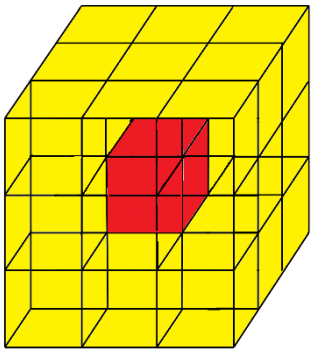

Figure 6 Moore neighborhoods condition (r = 1) for 3-dimensional cellular automaton which consists of a central cell (i, j, k), and its 26 neighbors, i. e. 6 nearest neighbors ($i, j, k-1$), ($i, j, k+1$), ($i, j-1, k$), ($i, j+1, k$), ($i-1, j, k$), ($i+1, j, k$); 12 the second nearest neighbors ($i, j-1, k-1$), ($i, j-1, k+1$), ($i, j+1, k-1$), ($i, j+1, k+1$), ($i-1, j, k-1$), ($i-1, j, k+1$), ($i-1, j-1, k$), ($i-1, j+1, k$), ($i+1, j, k-1$), ($i+1, j, k+1$), ($i+1, j-1, k$), ($i+1, j+1, k$); and 8 the third nearest neighbors ($i-1, j-1, k-1$), ($i-1, j-1, k+1$), ($i-1, j+1, k-1$), ($i-1, j+1, k+1$), ($i+1, j-1, k-1$), ($i+1, j-1, k+1$), ($i+1, j+1, k-1$), ($i+1, j+1, k+1$), totaling 27 cells. The red region indicates the central cube which is updated according to the state of the cubes marked in yellow.

The advantage of cellular automaton is in providing us an ability to model complex dynamical phenomena by reformulating the macroscopic behavior into microscopic and mesoscopic rules. A set of rules specifies the time and space evolution of the system, which is discrete in both variables. These systems have attracted a great deal of interest in recent years because even with very simple rules of CA can show very complex evolution patterns. It is recognized that repeated applications of simple rules can lead to extremely complex behavior that can emulate physical [45, 46], social [47] and biological systems [48].

Studying of HIV-1 infection dynamics using cellular automaton

The first CA model that could reproduce the entire dynamics of HIV-1 infection in a model, was proposed by Santos *et al*. [9]. With the model, an infected lymph node was viewed approximately as a mesh structure with a fractal dimension close to two. Therefore, based on this choice, a two dimensional cellular automaton model was defined to represent configurations using periodic conditions on the boundary in explanation the state changes of $CD4^+$ T cells, occurred in a lymph node. Each lattice site in the system was defined to be the position occupied by a $CD4^+$ T cell which its state could be: Healthy, Infected stage 1 - a newly infected cell, Infected stage 2 - an infected cell that has been already recognized by the immune response, and dead. To update each configuration, the Moore's neighborhood was used according to the set of CA rules. The dynamics of healthy cells, infected cells (stage 1+stage 2), and dead cells simulated by Santos *et al*.'s model which agree closely to the time evolution of the number of $CD4^+$ T cells in the peripheral blood and the plasma vireamia titer shown in clinical experiment are shown in Figure 7.

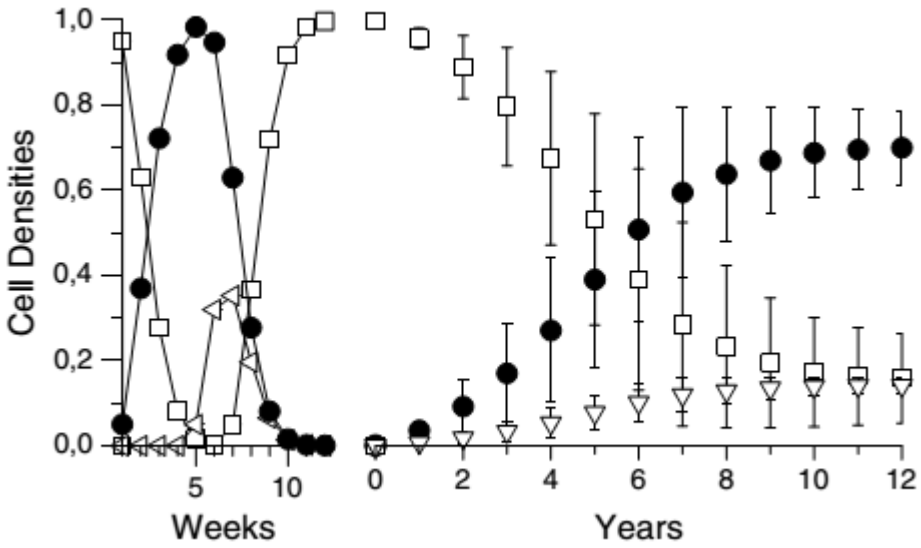

Figure 7 The dynamics of healthy cells, infected cells (stage 1+stage 2), and dead cells simulated by Santos *et al*.'s model.

A year later the declaration of the successfulness of Santos *et al.* [9]'s model , Strain and Levine [49] had studied the model of Santos *et al.* and commented that although the model could reproduce the entire phases of HIV-1 infection, it still has some limitation particularly in using some parameters to complete the dynamics of the model. More specifically, the simulation results would agree with the experiments only for the values used in the model. Therefore, more or less during in years 2004-2013, it comes to the trend of using CA model for HIV-1 infection which the research dimensions were the studies of the robustness

of the model in changes of the grid shapes [12], the dimensionalities [10, 11, 13], and the parameters [10, 11] of the model. Followed by an attempt to increase the diversity of virion and its quantity which related to the rate of infection [50, 51] coupled with the presentations on the effect of treatments [14-16]; including, especially, the beginning in task of consideration the model conditions taken into account the pattern formation that affects cell population [18] in which it became to our attention in solving the artifacts and to increasing the more sensibility in immunology by incorporating the other kind of immune cells except the $CD4^+$ T cells into the model [52].

So, based on this choice, we will conduct a stochastic CA model which incorporates effects of cell-mediated immunity, i.e. the $CD8^+$ cytotoxic T lymphocytes (CTLs), and the $CD4^+$ helper T lymphocytes, to discuss the dynamics of HIV-1 infection in a lymphoid reservoir, to be specific, 2-dimensional cellular automaton for a lymphoid tissue. With the model, the role of HIV-1 target cells, i.e. the $CD4^+$ T cells, the roles of cell-mediated immunity, i.e. the $CD8^+$ cytotoxic T lymphocytes (CTLs) and the $CD4^+$ helper T lymphocytes, and the role of antigen-presenting cells, i.e. the dendritic cells (DCs), including the mechanisms of cells' mobility and their kinetics associated with the HIV-1 infection, for instance cells' proliferation and cells' differentiation, will be presented and incorporated. Moreover, the dynamics cell population is noted to be the aspects that will be discussed with the results from clinics.

The process on HIV-1 infection and how the immune cells are changed its state when the infected was infected to our lymphoid tissues

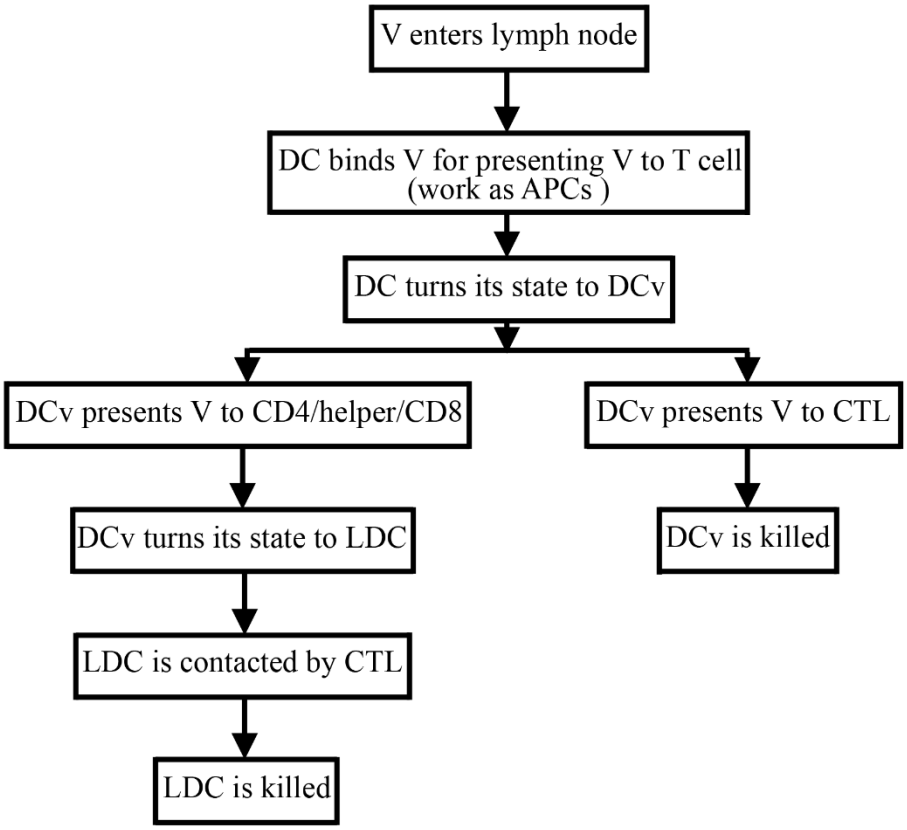

Figure 8 Flowchart of Dendritic cell cycle.

After HIV-1 entries into human body. As function of APCs, Dendritic cells will bind the virus for presenting the virus to the T cells. In the case of a Dendritic cell that is bind with the virus presents the virus to CTL, the Dendritic cell with virus will be killed to get rid of the virus.
In case of the Dendritic cell presents the virus to either $CD4^+$ T cells, helper T cell, or $CD8^+$ T cells, it will be licensed as dendritic cell with virus called Licensed Dendritic cell which the cell would waiting the CTL to kill itself later.

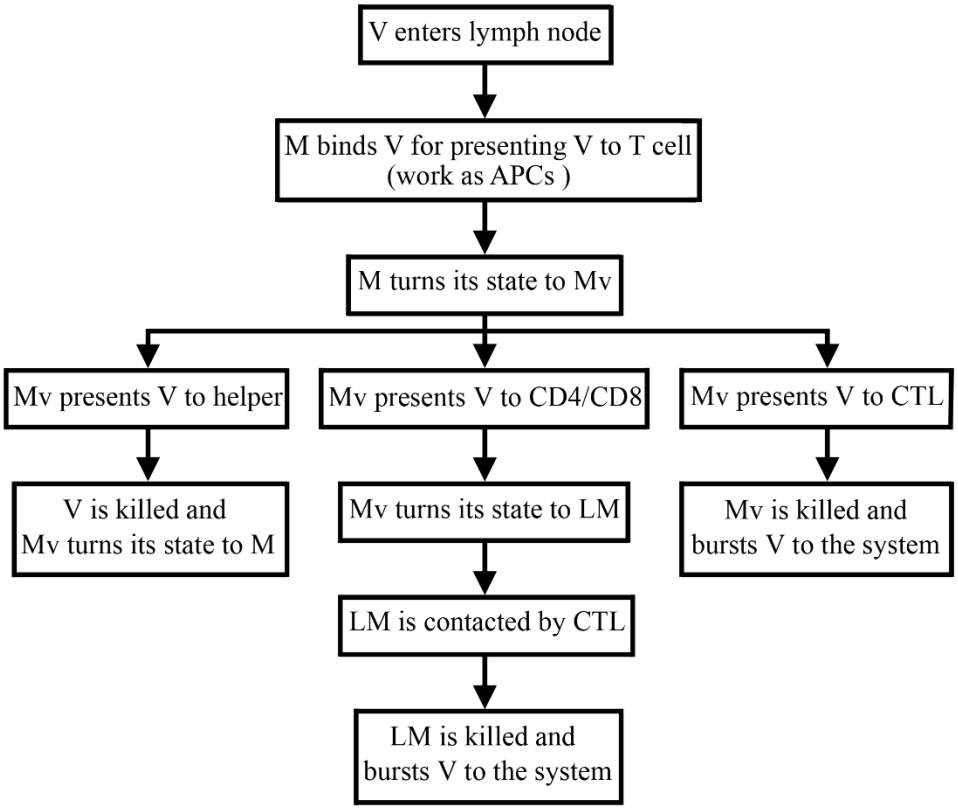

Figure 9 Flowchart of Macrophage cycle.

After HIV-1 entries into human body. As function of APCs, Macrophages will phagocyte the virus for presenting the virus to the T cells. If the Macrophage with the virus (Mv) present the virus to the Helper T cell, the lock and key model will happen. The helper cell will help the Macrophage kill the swallowed virus. However, If the Macrophage with the virus (Mv) present the virus to CD4 cells or CD8 cells. The Macrophage with the virus will be licensed (Licensed Macrophage) as it is the cell with virus. This is a sign that this cell is an infected cell that awaits CTL to eliminate. When the CTL comes it will destroys the infected Macrophage cells. Macrophage will burst the viruses when it is killed.

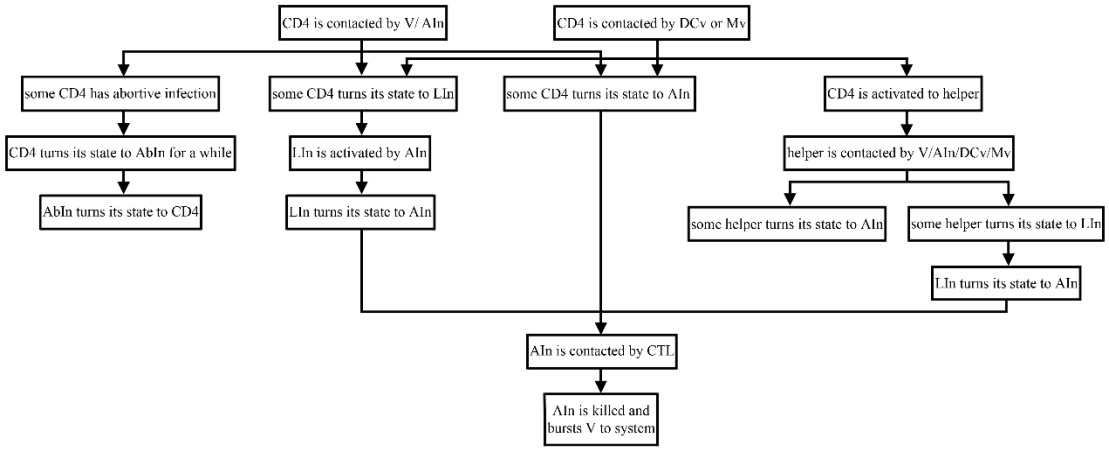

Figure 10 Flowchart of $CD4^+$T cells cycle.

On the other hand, when $CD4^+$ T cell is presented a virus by a Dendritic cell or a Macrophage, the $CD4^+$ T cell itself will have the opportunity either to be activated to a helper T cell that is responsible for helping the Macrophage to get rid of the holed virus, or it could become an infected cells by both from the presenting of the viruses by the Dendritic cells and the Macrophage, and the direct attacks from the virus and the infected $CD4^+$ T cell.

If the infection drives the $CD4^+$ T cell become an actively infected cells, the cell will be able to infect and pass on the virus to other immune cells within the system suddenly. However, in case of the infection drives the $CD4^+$ T cell to the latent state. The virus will be embedded inside the latent cell, do not released or infect to other immune cells. The latent infected cell will disguise the virus for a moment until the right time or until it is stimulated by the environment surrounding itself (here is the actively infected cells). It therefore reinstated itself to a stimulating state, release the virus and later infected to other cells.

Changes the state to actively infected cells or latent infected cells after this infection can occur either within the infection of $CD4^+$ T cells or helper T cells that are directly infected by the virus or from the infected cells i.e. actively infected cells, or from APCs function i.e. Dendritic cells with virus or Macrophage with virus. However, it is also found that the abortive infection that causes the $CD4^+$ T cells to be transiently turned its state to the abortive infected cells could be occurred in the case that $CD4^+$ T cells are infected by the virus directly or the actively infected cells due to the incomplete infection.

Based on the above biological mechanisms. When we understanding how mechanism changes and how the virus-cell mediated immunity interaction is performed. Therefore, we thus adapted the mechanism and used it to create our computational model shown in next chapter as following.

Chapter III

Proposed Model

From the Biological concept to CA components and algorithms

Lattice and cell state

To mimic the interaction among the HIV-1 and the specific immune cell responses residence on a patch of lymphoid tissue at paracortex zone in a lymph node, a 2D cellular automaton with a square lattice sized 100 x 100 grids was developed. Each grid in the lattice is designed to be either a position being a state of an immune cell or a cluster of the viruses, or an empty space in the lymphoid tissues. One cell grid is assigned as a square grid sized 7 x 7 μm^2. This is to compromise between the sizes of the virus, and those of the immune cells (i.e. the T cells whose function is the cell-mediated immunities, and the Dendritic cells and the Macrophages whose function is the antigen representing cells). Each state of the cells and its meaning are:

Table 1 Cell type and its meaning used in our model.

Cell type and symbol	Description
Cluster of virus (V)	HIV-1 cells that entry into the human lymphoid tissue.
$CD4^+$ T cell ($CD4$)	A T cell that presents $CD4^+$ cell receptors on its surface. This state of the cell could be the state of the $CD4$ that turns its state from the $AbIn$, or either a naïve healthy $CD4$ cell that has never been in contacted with the V or the infected cells such as the AIn , the DCv , the Mv , the LCD , or the LM before.
Helper T cell ($helper$)	A differentiate state of the $CD4$ cell that is activated by the DCv or the Mv. The state of this $CD4^+$T cell will provide help to other cells in immune response by recognizing the antigen.
Abortive infected ($AbIn$)	A state of an infected $CD4^+$T cell that has abortive infection in which the virus fails to replicate and no infective virus is produced. The situation may result from an infection with defective viruses or the host cell is non-permissive and prohibits the replication of the virus. Therefore, the state of this infected $CD4^+$T cell cannot neither infect nor release the viruses to other immune cells.
Actively infected (AIn)	An infected state of a $CD4$ that could infect the other immune cells actively.
Latently infected (LIn)	An infected $CD4^+$T cell that stays in latent state. It cannot neither infect other immune cells nor release the viruses.
Express infected (EIn)	An Actively infected $CD4^+$T cell (AIn) or a License Macrophage (LM) that is weakened by the CTL (CTL) or the expiration.
$CD8^+$ T cell ($CD8$)	A T cell that presents $CD8^+$ cell receptors on its surface. This state of the cell is a naïve cell that has never been in contacted with the infected cells such as the , the Mv , the LDC , or the LM before.

CTL (CTL)	A differentiate state of the $CD8$ cell that is activated by either a DCv, an LDC, an Mv, or an LM to turn its function to cytotoxic T lymphocyte for killing the antigen and the infected cells.
DC (DC)	An antigen-presenting cell (APC) whose function is boosting the immune response system by processing the antigen material by using the phagocytosis system and then present it on the surface to the cell mediated immunities i.e. $CD4$, $helper$, and $CD8$. This state of the DC is a naïve healthy cell that has never been in contacted with the V before.
Antigen-bearing DC (DCv)	A DC that binds HIV-1 at its vesicle or swallowed the virus into its cytoplasm.
License DC (LCD)	A DCv that is licensed by the cell mediated immunities i.e. $CD4$, $helper$, and $CD8$.
Macrophage (M)	An antigen-presenting cell (APC) whose function is boosting the immune response system by processing the antigen material by using the phagocytosis system and then present it on the surface to the cell mediated immunities i.e. $CD4$, $helper$, and $CD8$. This state of the M cell could be a naïve healthy cell that has never been in contacted with the V before, or the state of the cell that turns its state from the Mv.
Macrophage with virus (Mv)	An M that binds HIV-1 at its vesicle or swallowed the virus into its cytoplasm.
Licensed macrophage (LM)	An Mv that is licensed by the cell mediated immunities i.e. $CD4$, and $CD8$.
Dead (D)	An immune cell that dies due to the expiration, or it is killed by the immune responses.
Burst cell ($Burst$)	A dead AIn cell or a dead Mv cell that explodes the V cells while it was ding.
Empty space (E)	A gap within the lymphoid tissues that is a pathway for the immune cells interaction.

Cell characters: sizes, lifespan, and velocities

Apart from the various types of immune cells, we also have determined the sizes and the velocities of the cells in this works. Based on the immunological evidences, we have found that the T cells have an average diameter of 7 μm [53] [54] , the DCs have a diameter sizes more or less during 10-16 μm to the biggest size found is 25 μm [55] , and the sizes of the Macrophages are during 15-21 μm [56] [57] which it is seem that the sizes of the APCs might 4 times larger than the T cells. Therefore, we thus compromise between the diameter's size of the APCs and the T cells, and assigned a grid in our model to be 7 μm^2 and use one cell grid in our system to represent a position of the T cell while that of the APCs occupy four cell grids.

However, besides the compromising among the sizes of the immune cells, we also investigate the size of the viruses, and found that size of HIV-1 are diameter around 90-260 *nm* [58, 59] [60] which is very small - approximately 100 times smaller than the white blood cells. So, in

case of virus, we thus assign it to be a cluster of HIV-1 that contains an amount of HIV-1 particles approximately 80 particles at a position of a grid.

Moreover, speaking of the cells' movement, while the velocities of T cells are found more or less during 10-15 $\mu m/min$ [61-63], until as fast as 25 $\mu m/min$ [64], the APCs are very as slow as 1.64-2.7 $\mu m/min$ [61] [65]. Therefore, we thus assign the T cells movement to be a radius $1 \leq r \leq 2$, and the APCs to be r = 1 from a specified position in a time step. In contrast, the velocities of the viruses are very fast i.e. 120-180 $\mu m/min$ [66] when compare to the velocities of the immune cells. Therefore, we thus assign virus' velocities to be $17 \leq r \leq 26$ in ours.

For the more clearly understanding, following are the table that summarize and show how the biological information were transferred to our proposed computational parameters (see Table 2).

Table 2 The comparison between the biological variables and the computational parameters used in our model.

Cell type	Biology			Computer		
	Size (μm)	**Life span (days)**	**Velocity ($\mu m/min$)**	**Size (grid)**	**Time delay; τ (time step)**	**Motion radius; r**
Cluster of virus (V)	90-160 nm [58], 95-175 nm [59], 120-260 nm [60]	6 hr (half-life) [67]	120-180 [66]	1	τ_V=540	$17 \leq r \leq 26$
CD4$^+$ T cell ($CD4$)	7 [53, 54]	165-365 [68]	10 [61, 62], 10.2-12.7,10-15 [63], maximum = 25 [64]	1	τ_{CD4} 237,600-525,600	$1 \leq r \leq 2$
Helper T cell ($helper$)	7 [53, 54]	60 hr [69]	5 [61]	1	τ_{Th} = 3,600	r = 1
Abortive infected ($AbIn$)	7 [53, 54]	145 days (half-life) [67]	NA	1	τ_{AbIn} = 302,400	$1 \leq r \leq 2$ *adhoc*
Actively infected (AIn)	7 [53, 54]	1-2 [70]	NA	1	2 days τ_{AIn} = 2,880	$1 \leq r \leq 2$ *adhoc*
Latently infected (LIn)	7 [53, 54]	8.5 (half-life) [67]	NA	1	τ_{LIn}= 4,320	$1 \leq r \leq 2$ *adhoc*
Express infected (EIn)	7 (T cell) [53, 54] 21(macrophage) [56]	NA	NA	1 (T cell) 4 (macrophage)	τ_{EIn}= 720 *Adhoc*	$1 \leq r \leq 2$ (T cell) r = 1 (macrophage)
CD8$^+$ T cell ($CD8$)	7 [53, 54]	165-365 [68]	10, 10.2-12.7,10-15,	1	τ_{CD8} = 237,600-525,600	$1 \leq r \leq 2$

			maximum = 25			
CTL (CTL)	7 [53, 54]	60 hr [69]	5 [61]	1	τ_{CTL} = 3,600	r = 1
DC (DC)	10-16 (the biggest 25) [55]	1-11 [71]	2.7-1.64, 2-3 [61]	4	τ_{DC} = 1,440-15,840	r = 1
Antigen-bearing DC (DCv)	10-16 (the biggest 25) [55]	60 hr [71]	NA	4	τ_{DCv} = 3,600	r = 1 *adhoc*
License DC (LCD)	10-16 (the biggest 25) [55]	36 hr [72, 73]	NA	4	τ_{LDC} = 2,160	r = 1 *adhoc*
Macrophage (M)	21 [56], 15-18 [57]	25-30 [57]	2.5 [65]	4	τ_{M} = 36,000-43,200	r = 1
Macrophage with virus (Mv)	21 [56], 15-18 [57]	NA	NA	4	τ_{Mv}=10,080 *adhoc*	r = 1
Licensed macrophage (LM)	21 [56], 15-18 [57]	NA	NA	4	τ_{LM}= 5,760 *adhoc*	r = 1
Dead (D)	Depend on cell type	-	-	Depend on cell type	τ_{D} = 1	-
Burst cell (D)	Depend on cell type	-	-	Depend on cell type	τ_{B} = 1	-
Empty space (E)	7	-	-	-	-	-

Model mechanism

Initial condition, flow, and data collection

The initial configuration of HIV-1 infection dynamics begin with the arrival of the viruses at day 0 in a patch of lymphoid tissue within a LN. It is randomly consisting of the fundamental states of immune cells are the $CD4$ cells, the $CD8$ cells, the *DC* cells, and the *M* cells with the probability P_{CD4}, P_{CD8}, P_{DC}, and P_M, respectively mixed with the cluster of *V* with P_v . Figure 11 shows a sample of initial configuration of our proposed model.

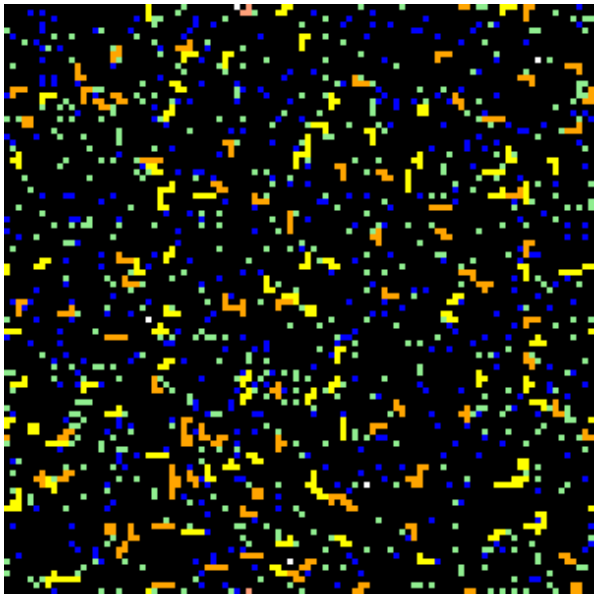

Figure 11 the initial configuration.

The CA lattice is governed by periodic boundary conditions where the cell leaving one side of the lattice reappears on the opposite site. To process each configuration, all states of the cells, except the dead (*D*) and the burst (*Burst*) are randomly moved to an empty space (*E*) (to represent the cells' mobility) with a different radius of the Moore's neighborhood (to represent the cells' velocity). Later, the state of each cell is updated according to the CA rules (to represent the cells' differentiation). Then, the number of each cell type is counted and noted and following by the configuration is announced as one time step which is taken as one minute in real life (see Figure 12).

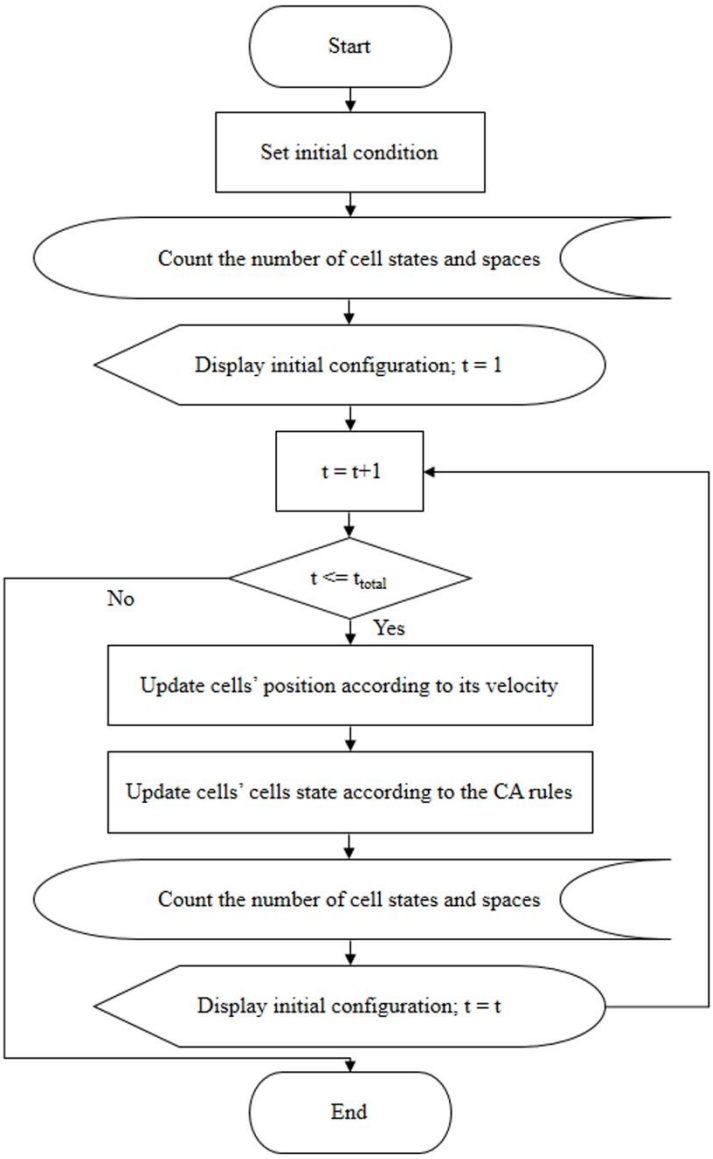

Figure 12 Flow diagram of the algorithm in our CA model.

Transition CA Rules

A set of updating rules for CD4⁺ T cell

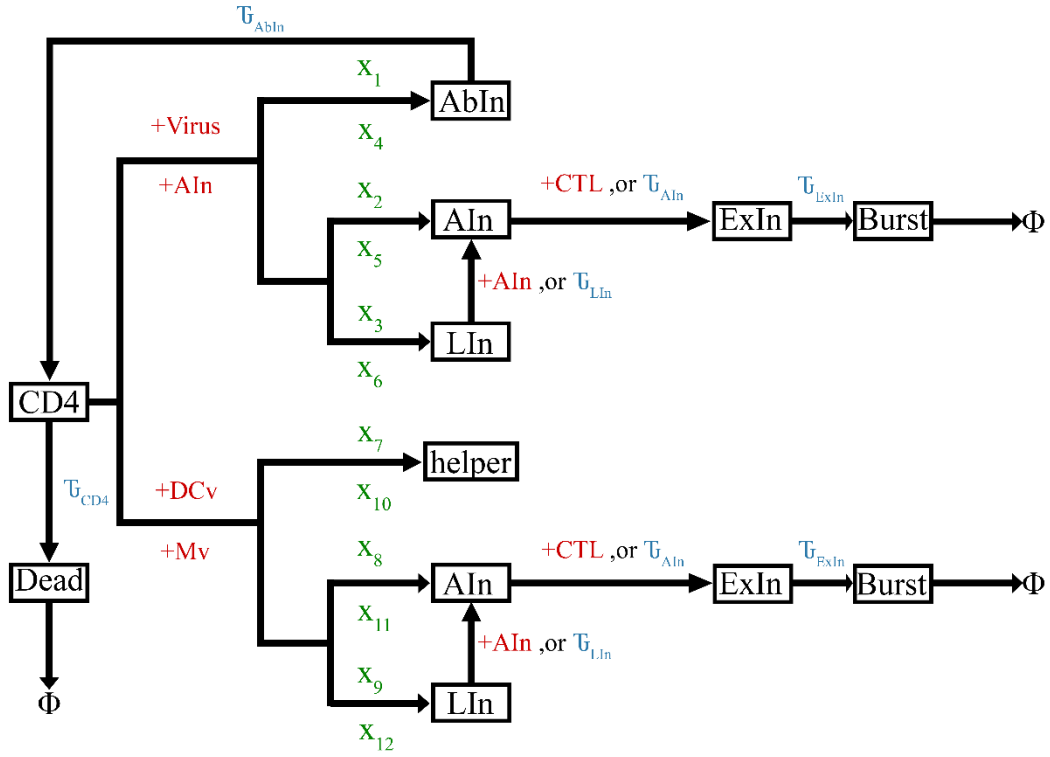

Figure 13 Transition rules for updating a *CD4* cell, an *AbIn* cell, an *LIn* cell, an *AIn* cell, and an *ExIn* cell position.

Rule A:

A *CD4* cell becomes	(A1) either an *AbIn* cell with probability $x_1 = 0.95$, an *AIn* cell with probability $x_2 = 0.99(1-x_1)$, or an *LIn* cell with probability $x_3 = 0.01(1-x_1)$ after contacts with a *Virus* cell.
	(A2) either an *AbIn* cell with probability $x_4 = 0.95$, an *AIn* cell with probability $x_5 = 0.99(1-x_4)$, or an *LIn* cell with probability $x_6 = 0.01(1-x_4)$ after contacts with an *AIn* cell.
	(A3) either a *helper* cell with probability $x_7 = 0.9998$, an *AIn* cell with probability $x_8 = 0.0001$, or an *LIn* cell with probability $x_9 = 0.0001$ after contacts with a *DCv* cell.
	(A4) either a *helper* cell with probability $x_{10} = 0.9998$, an *AIn* cell with probability $x_{11} = 0.0001$, or an *LIn*

	cell with probability x_{12}= 0.0001 after contacts with an *Mv* cell.
	(A5) a *Dead* cell after τ_{CD4} time step.

Rule B: An *AbIn* cell turns its stated to a *CD4* cell after τ_{AbIn} time step.

Rule C: An *LIn* cell becomes an *AIn* cell after τ_{LIn} timestep, or contacts with an *AIn* cell.

Rule D: An *AIn* cell becomes an *ExIn* cell after τ_{AIn} time step, or contacts with a *CTL* cell.

Rule E: An *ExIn* cell becomes a *Burst* cell after τ_{ExIn} time step.

A set of updating rules for helper T cell

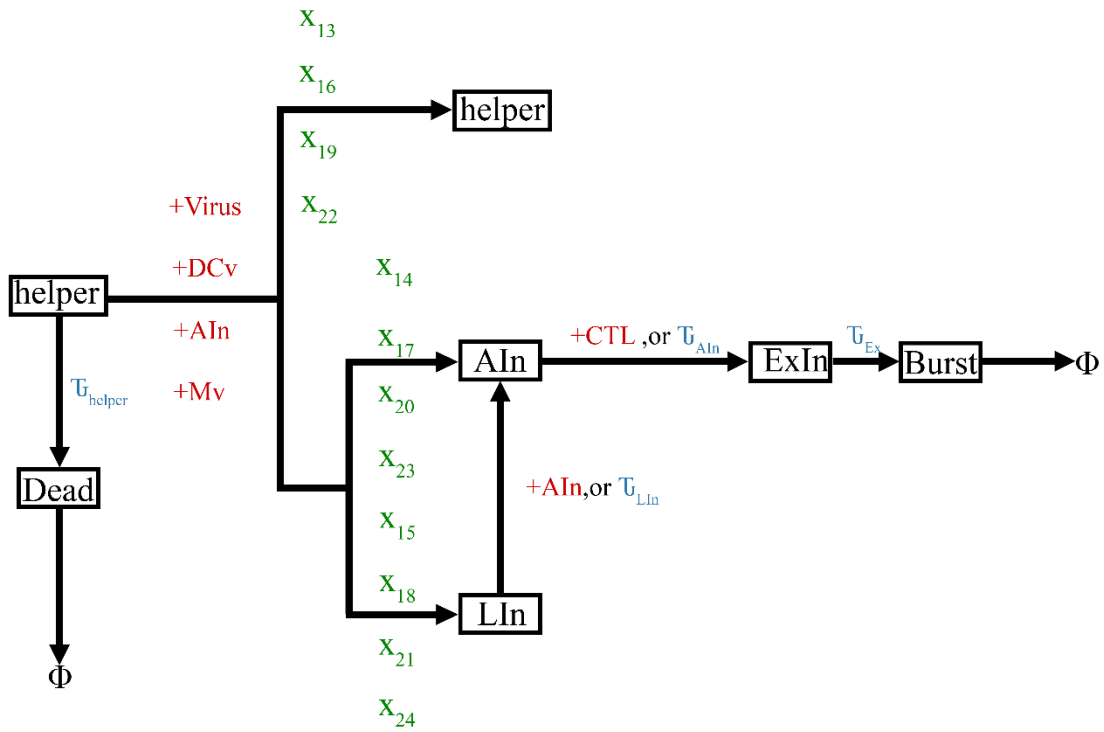

Figure 14 Transition rules for updating a *helper* cell position.

Rule F:

A *helper* cell becomes	(F1) either an *AIn* cell with probability x_{14} = 0.0495, or an *LIn* cell with probability x_{15} = 0.0005 after contacts with a *Virus* cell. Otherwise, its stays unchanged its state with probability x_{13} = 0.95.
	(F2) either an *AIn* cell with probability x_{17} = 0.0495, or an *LIn* cell with probability x_{18} = 0.0005 after

	contacts with a *AIn* cell. Otherwise, its stays unchanged its state with probability $x_{16} = 0.95$.
	(F3) either an *AIn* cell with probability $x_{20} = 0.0001$, or an *LIn* cell with probability $x_{21} = 0.0001$ after contacts with a *DCv* cell. Otherwise, its stays unchanged its state with probability $x_{19} = 0.9998$.
	(F4) either an *AIn* cell with probability $x_{23} = 0.0001$, or an *LIn* cell with probability $x_{24} = 0.0001$ after contacts with a *Mv* cell. Otherwise, its stays unchanged its state with probability $x_{22} = 0.9998$.
	(F5) a *Dead* cell after τ_{helper} time step.

A set of updating rules for CD8$^+$ T cell

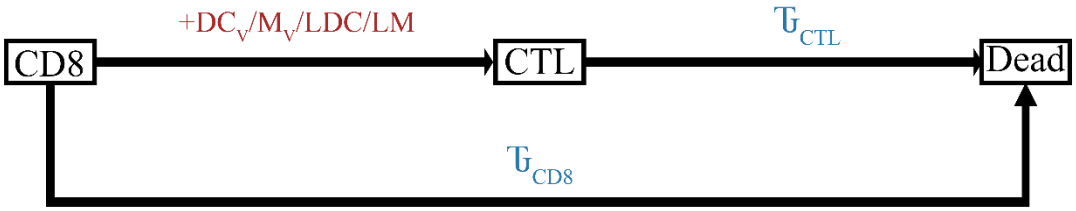

Figure 15 Transition rules for updating a *CD8* cell and a *CTL* cell position.

Rule G:

A *CD8* cell becomes	(G1) a *CTL* cell after contacts with an *DCv* cell, an *LDC* cell, an *Mv* cell, an *LM* cell.
	(G2) a *Dead* cell after τ_{CD8} time step.

Rule H: A *CTL* cell becomes a *Dead* cell after τ_{CTL} time step.

A set of updating rules for DC

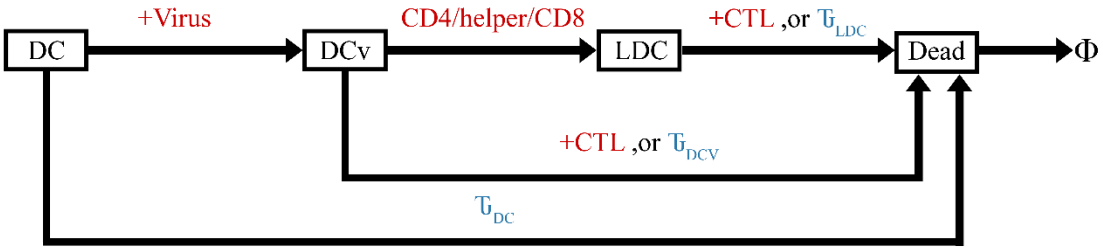

Figure 16 Transition rules for updating a *DC* cell, a *DCv* cell, and an *LDC* cell position.

Rule I:

A *DC* cell becomes	(I1) a *DCv* cell after contacts with a *Virus* cell.
	(I2) a *Dead* cell after τ_{DC} time step.

Rule J:

A *DCv* cell becomes	(J1) an *LDC* cell after contacts with either a *CD4* cell, a *helper* cell, or a *CD8* cell.
	(J2) a *Dead* cell after τ_{DCv} time step, or contacts with a *CTL* cell.

Rule K:

An *LDC* cell becomes	a *Dead* cell after τ_{LDC} time step, or contacts with a *CTL* cell.

A set of updating rules for Macrophage

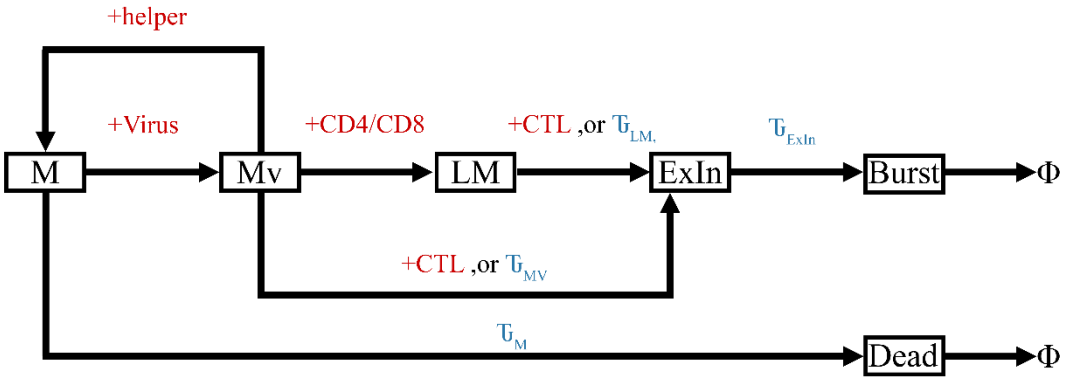

Figure 17 Transition rules for updating an *M* cell, an *Mv* cell, and an *LM* cell position.

Rule L:

A *M* cell becomes	(L1) an *Mv* cell after contacts with a *Virus* cell.
	(L2) an *Dead* cell after τ_M time step.

Rule M:

A *Mv* cell becomes	(M1) an *LM* cell after contacts with either a *CD4* cell, or a *CD8* cell.
	(M2) turns its state to an *M* cell after contacts with a *helper* cell.
	(M3) an *ExIn* cell after τ_{Mv} time step, or contacts with a *CTL* cell.

Rule N:

An *LM* cell becomes	an *ExIn* cell after τ_{LM} time step, or contacts with a *CTL* cell.

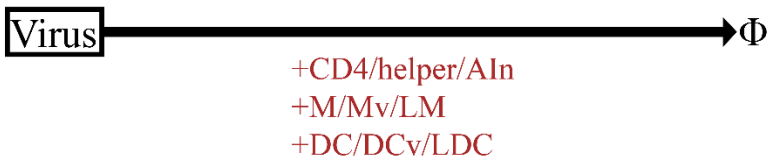

Figure 18 Transition rules for updating a *Virus* cluster position.

Rule O:

A *Virus* cluster position becomes	an *Empty space* after contacts with either a *CD4* cell, a *helper* cell, an *AIn* cell, an *M* cell, an *Mv* cell, an *LM* cell, *DC* cell, a *DCv* cell, or an *LDC* cell.

Rule P:

A *Dead* cell becomes	an *Empty* space.

Rule Q:

A *Burst* cell becomes	an *Empty* space.

A set of updating rules for Empty space

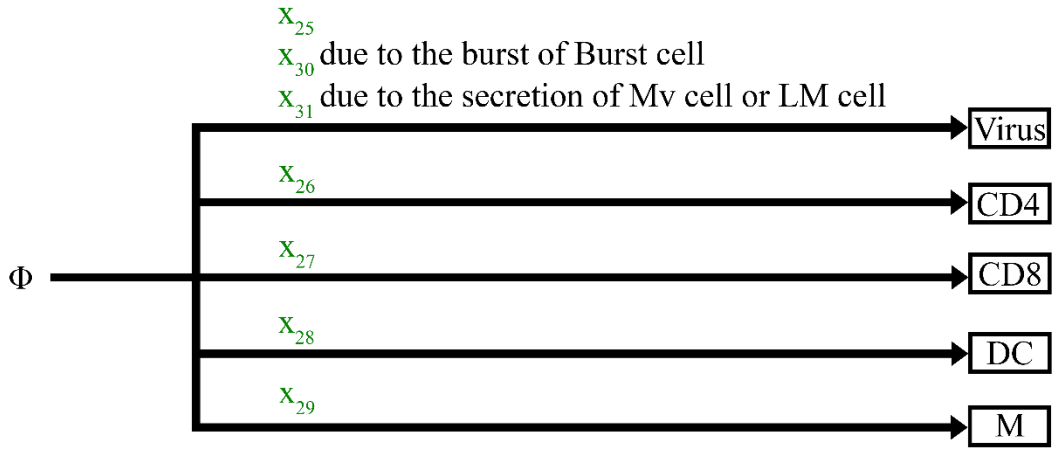

Figure 19 Transition rules for updating an *Empty* space position.

Rule R:

An Empty space is replenished by	(R1) a *Virus* cluster, *a CD4* cell, a *CD8* cell, a *DC* cell, an *M* cell with probability x_{25}, x_{26} x_{27}, x_{28}, and x_{29}, respectively randomly. This is to represent the filling in either the movement of immune cells or virus cell from other systems.
	(R2) a *Virus* cluster more or less during $r \leq 2$ among the *Burst cell* position with probability x_{30} due to the infected cell's explode.
	(R3) a *Virus* cell more or less during $r \leq 2$ among the *Mv cell and LM cell* position with probability x_{31} due to viral secretion of *Mv cell* and *LM cell* during the infection lifetime.

Used parameters, meaning and values

Table 3 the parameters, their meaning, and the assigned values used in our model.

Used parameters	Meanings	Values
x_1	Probability that a $CD4$ cell becomes an $AbIn$ cell after contacts with a V cell 95%-99% and x_1 >> $(x_2 + x_3)$ [25]	0.95 (95% of $x_1 + x_2 + x_3$)
x_2	Probability that a $CD4$ cell becomes an AIn cell after contacts with a V cell [25]	0.99(1-x_1)
x_3	Probability that a $CD4$ cell becomes an LIn cell after contacts with a V cell 0.1%-1% of x_2 [31]	0.01(1-x_1) (1% of x_2)
x_4	Probability that a $CD4$ cell becomes an $AbIn$ cell after contacts with an AIn cell 95%-99% and x_4 >> $(x_5 + x_6)$ [25]	0.95 (95% of $x_4 + x_5 + x_6$)
x_5	Probability that a $CD4$ cell becomes an AIn cell after contacts with an AIn cell [25]	0.0495
x_6	Probability that a $CD4$ cell becomes an LIn cell after contacts with an AIn cell 0.1%-1% of x_5 [31]	0.0005 (1% of x_5)
x_7	Probability that a $CD4$ cell becomes a Th cell after contacts with a DCv cell	0.9998 *adhoc*

x_8	Probability that a $CD4$ cell becomes an AIn cell after contacts with a DCv cell $x_8 + x_9 \rightarrow 0$	0.0001 *adhoc*
x_9	Probability that a $CD4$ cell becomes an LIn cell after contacts with a DCv cell $x_8 + x_9 \rightarrow 0$	0.0001 *adhoc*
x_{10}	Probability that a $CD4$ cell becomes a Th cell after contacts with an Mv cell	0.9998 *adhoc*
x_{11}	Probability that a $CD4$ cell becomes an AIn cell after contacts with an Mv cell	0.0001 *adhoc*
x_{12}	Probability that a $CD4$ cell becomes an LIn cell after contacts with an Mv cell	0.0001 *adhoc*
x_{13}	Probability that a Th cell stays unchanged after contacts with a V cell 95%-99% and x_{13} >> $(x_{14} + x_{15})$ [25]	0.95 (95% of $x_{13} + x_{14} + x_{15}$)
x_{14}	Probability that a Th cell becomes an AIn cell after contacts with a V cell	0.0495 x_{14} = 0.99(1 – x_{13}) *adhoc*
x_{15}	Probability that a Th cell becomes an LIn cell after contacts with a V cell 0.1%-1% of x_{14} [31]	0.0005 (1% of x_{14}) x_{15} = 0.01(1 – x_{13})
x_{16}	Probability that a Th cell stays unchanged after contacts with an AIn cell 95%-99% and x_{16} >> $(x_{17} + x_{18})$ [25]	x_{16} = 0.95 $(x_{16} + x_{17} + x_{18})$ (95% of$x_{16} + x_{17} + x_{18}$)

x_{17}	Probability that a Th cell becomes an AIn cell after contacts with an AIn cell	0.0495 $x_{17} = 0.99(1 - x_{16})$ *adhoc*
x_{18}	Probability that a Th cell becomes an LIn cell after contacts with an AIn cell 0.1%-1% of x_{17} [31]	0.0005 (1% of x_{17}) $x_{18} = 0.01(1 - x_{16})$
x_{19}	Probability that a Th cell stays unchanged after contacts with a DCv cell 95%-99% and $x_{19} >> (x_{20} + x_{21})$ [25]	0.9998 $x_{19} = 0.95\ (x_{19} + x_{20} + x_{21})$ (95% of $x_{19} + x_{20} + x_{21}$)
x_{20}	Probability that a Th cell becomes an AIn cell after contacts with a DCv cell	0.0001 $x_{20} = 0.99(1 - x_{19})$
x_{21}	Probability that a Th cell becomes an LIn cell after contacts with a DCv cell	0.0001 $x_{21} = 0.01(1 - x_{19})$
x_{22}	Probability that a Th cell stays unchanged after contacts with a Mv cell 95%-99% and $x_{22} >> (x_{23} + x_{324})$ [25]	0.9998
x_{23}	Probability that a Th cell becomes an AIn cell after contacts with a Mv cell	0.0001 *adhoc*
x_{24}	Probability that a Th cell becomes an LIn cell after contacts with a Mv cell	0.0001 *adhoc*
x_{25}	Probability that an $Empt$ cell is replenished by a V cell	0.5 *adhoc*
x_{26}	Probability that an $Empt$ cell is replenished by a $CD4$ cell	0.2 *adhoc*
x_{27}	Probability that an $Empt$ cell is replenished by a $CD8$ cell	0.2 *adhoc*
x_{28}	Probability that an $Empt$ cell is replenished by a DC cell	0.05 *adhoc*
x_{29}	Probability that an $Empt$ cell is replenished by an M cell	0.05 *adhoc*

x_{30}	Probability that an $Empt$ cell is replenished by a V cell due to the infected cell combrustion (r<=2)	0.05 *adhoc*
x_{31}	Probability that an $Empt$ cell is replenished by a V cell due to the viral released from an infected cell $x_{31} < x_{30}$	0.1 *adhoc*

Chapter IV
Results and Discussion

Following are samples of our simulation results cases when P_{CD8}, P_{DC} , and P_M are set to be zero (case when there is no initial $CD8^+$ T cells, DC, and M cells in LN), and the (i) ratio between P_v *and* P_{CD4} and (ii) maximum density of cell population in LN are varied. The simulation results would show how our CA model could represent how differences of the cell dynamics when the initial condition is difference (which mimics an individual patient). Moreover, because one time step in our model is equal to one minute in real life, therefore, for the sake of understanding, only the first 60 days after the infection thus presented due to the highly disease progression.

Cell density in LN	100%
P_v	1
P_{CD4}	0

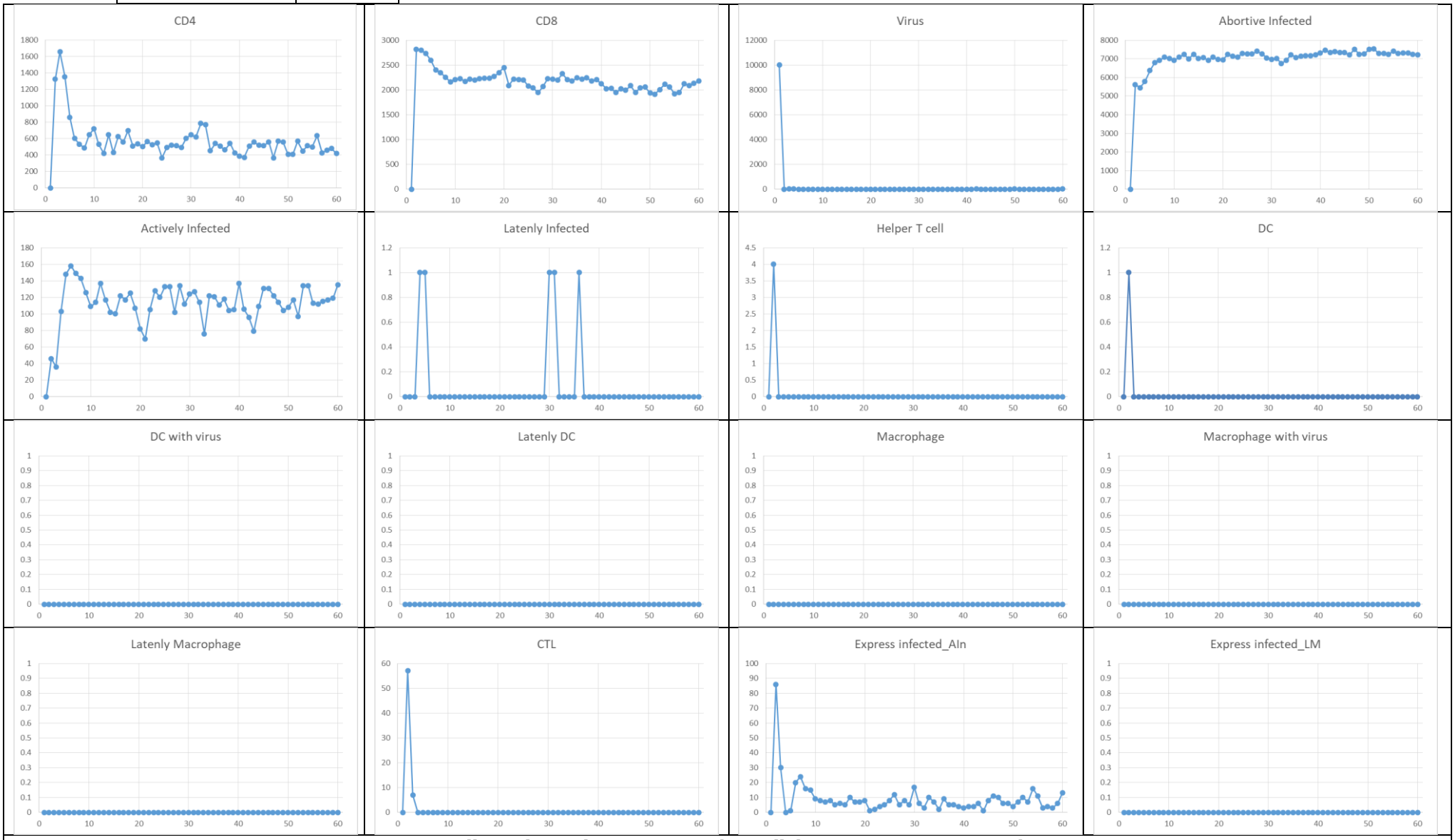

Figure 20 Cell population dynamics case when cell density = 100%, P_v = 1, and P_{CD4} =0.
X-axis is days of infection. Y-axis is number of cell population.

Cell density in LN	100%
P_v	0.8
P_{CD4}	0.2

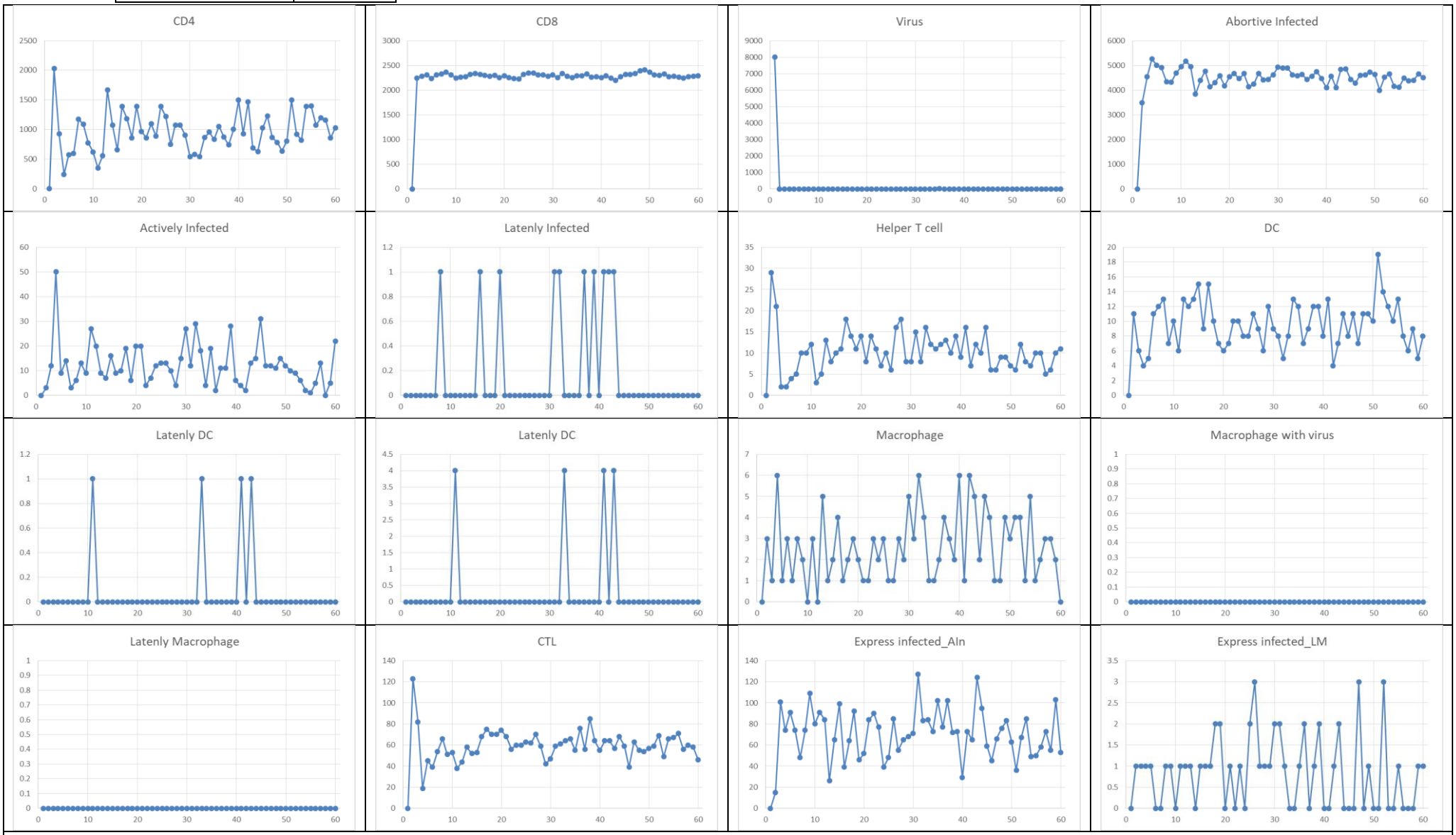

Figure 21 Cell population dynamics case when cell density = 100%, P_v = 0.8, and P_{CD4} =0.2.
X-axis is days of infection. Y-axis is number of cell population.

Cell density in LN	100%
P_v	0.6
P_{CD4}	0.4

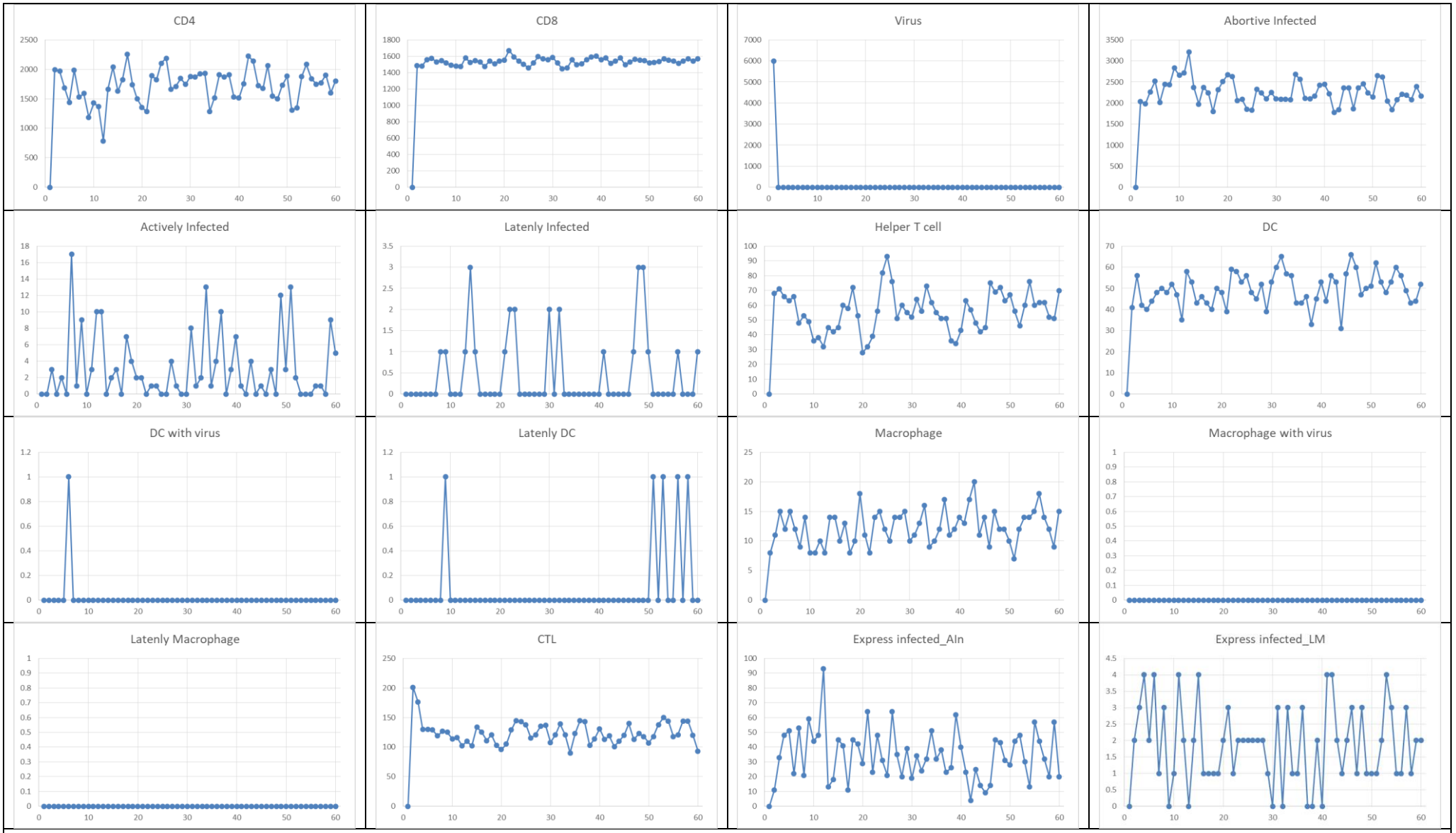

Figure 22 Cell population dynamics case when cell density = 100%, P_v = 0.6, and P_{CD4} =0.4.
X-axis is days of infection. Y-axis is number of cell population.

Cell density in LN	80%
P_v	1
P_{CD4}	0

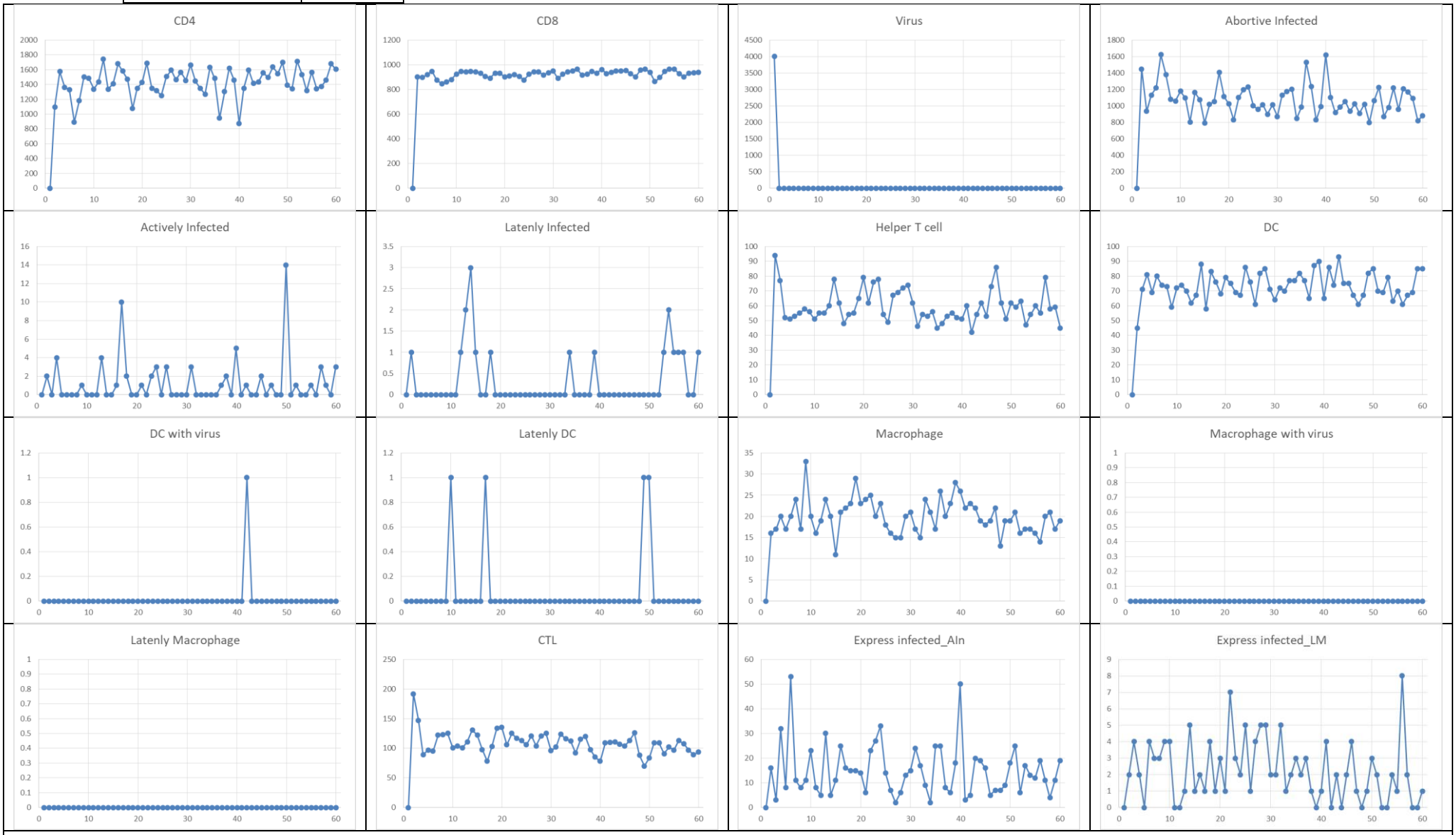

Figure 23 Cell population dynamics case when cell density = 80%, P_v = 1, and P_{CD4} =0.
X-axis is days of infection. Y-axis is number of cell population.

Cell density in LN	80%
P_v	0.8
P_{CD4}	0.2

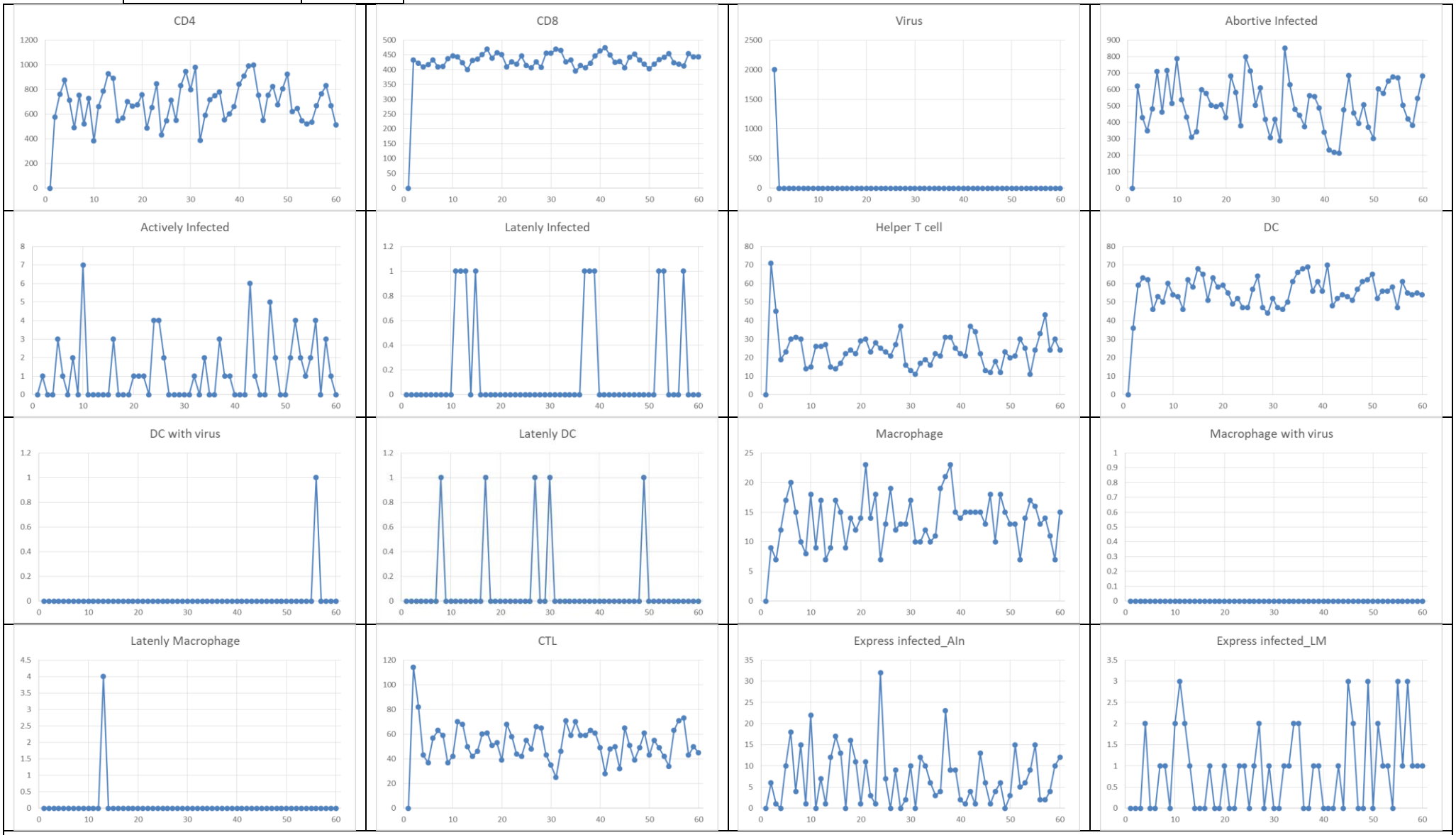

Figure 24 Cell population dynamics case when cell density = 80%, P_v = 0.8, and P_{CD4} =0.2.
X-axis is days of infection. Y-axis is number of cell population.

Cell density in LN	80%
P_v	0.6
P_{CD4}	0.4

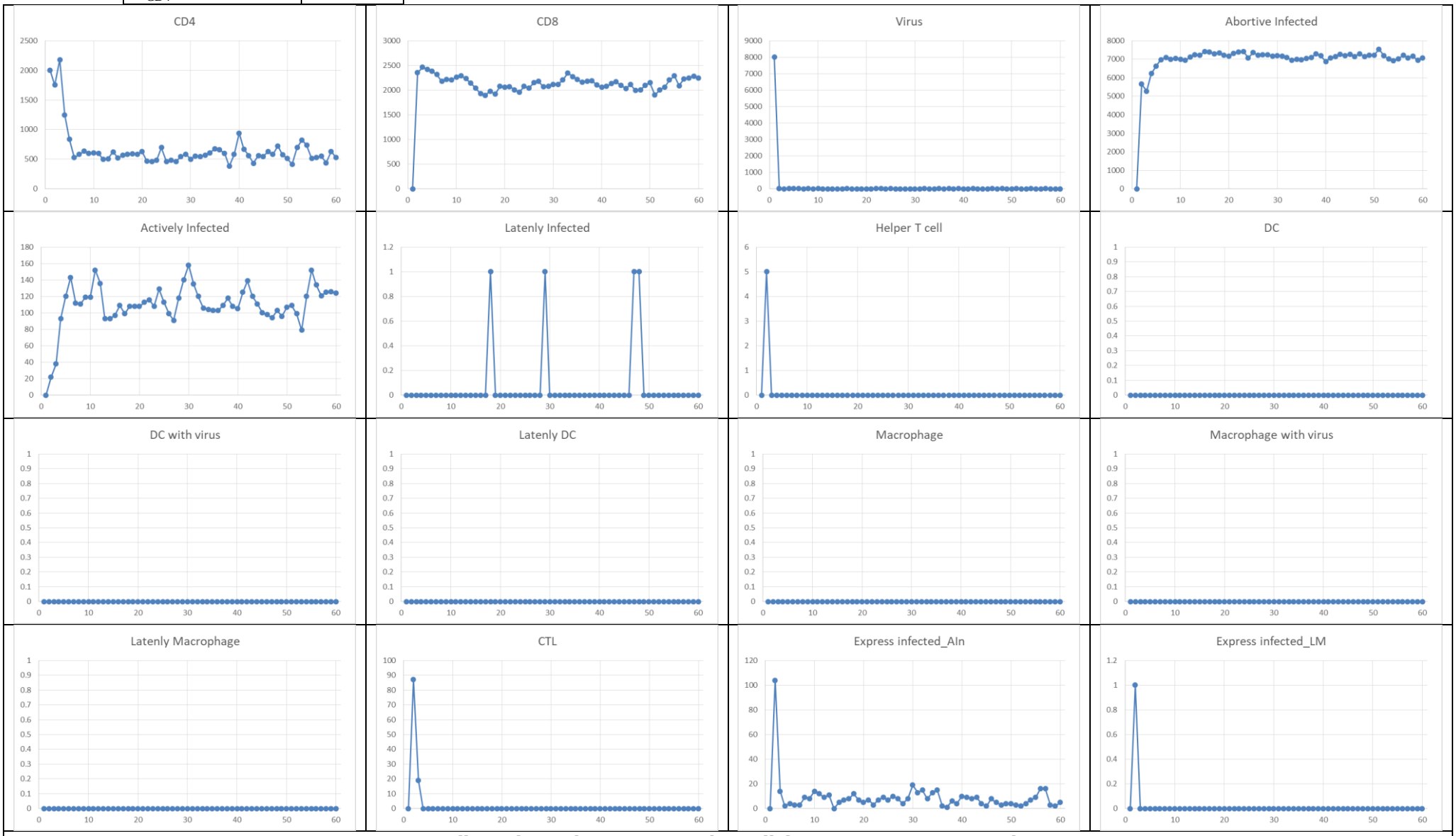

Figure 24 Cell population dynamics case when cell density = 80%, P_v = 0.6, and P_{CD4} =0.4.
X-axis is days of infection. Y-axis is number of cell population.

Cell density in LN	60%
P_v	1
P_{CD4}	0

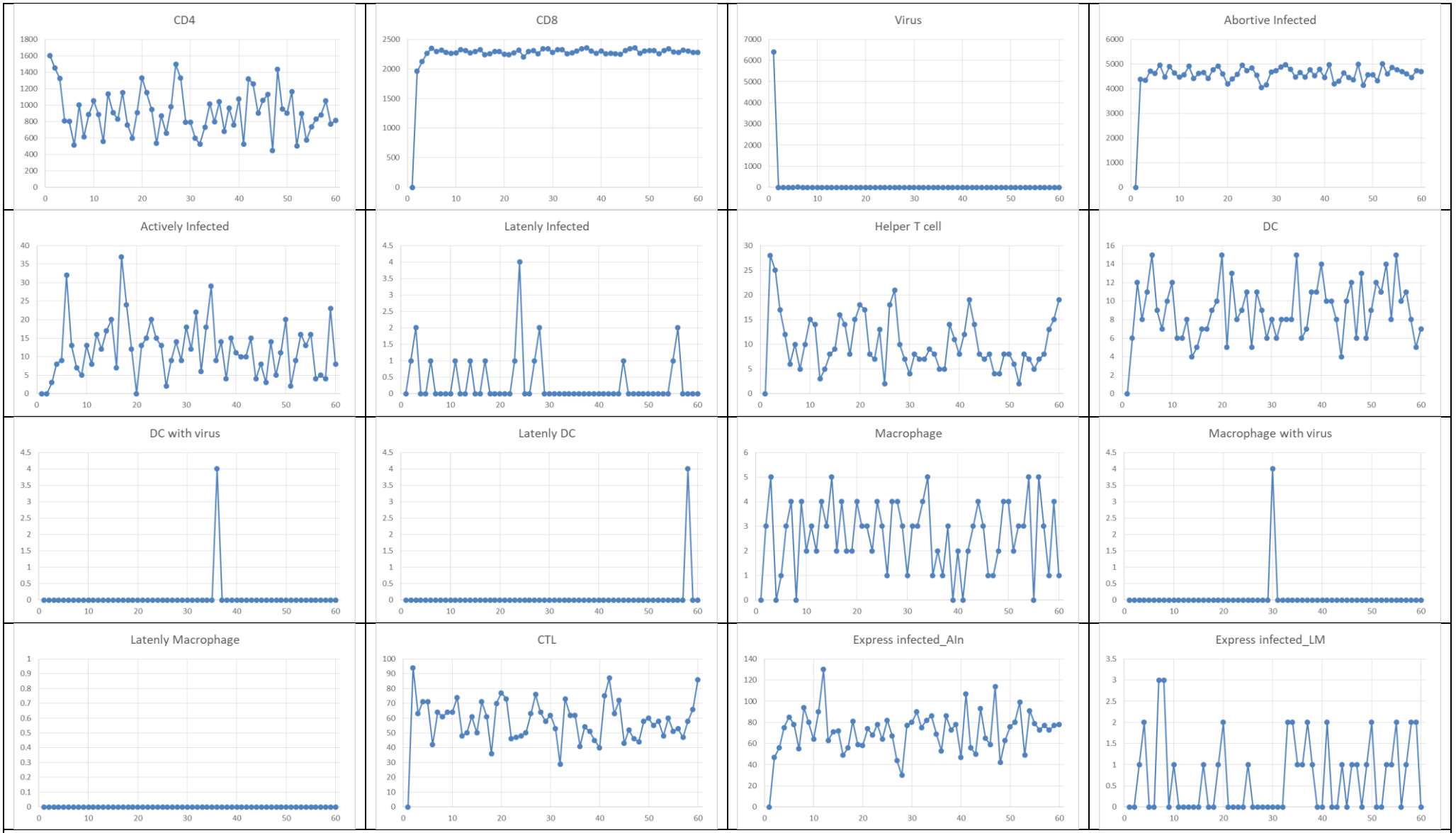

Figure 25 Cell population dynamics case when cell density = 60%, P_v = 1, and P_{CD4} =0.
X-axis is days of infection. Y-axis is number of cell population.

Cell density in LN	60%
P_v	0.8
P_{CD4}	0.2

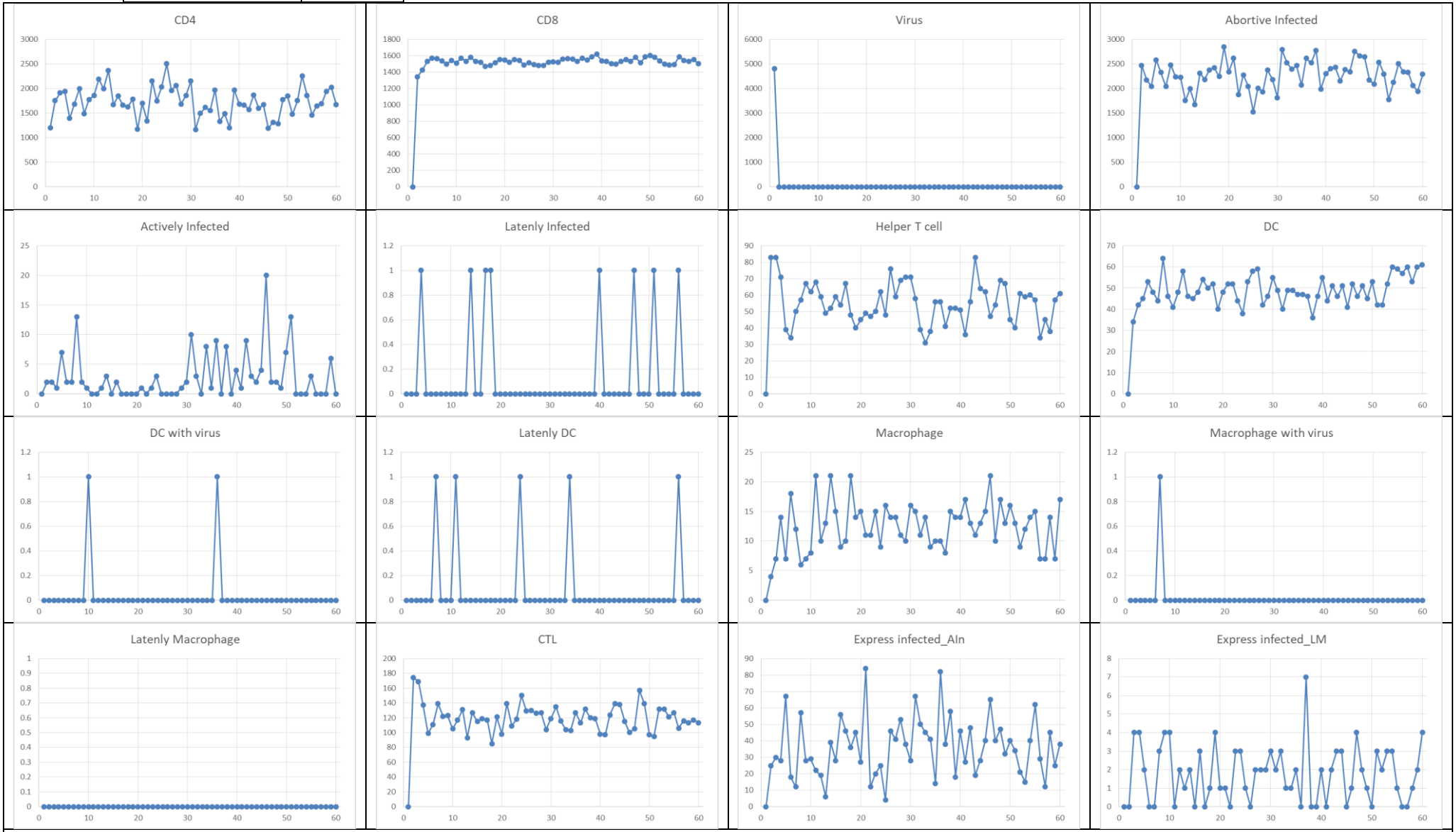

Figure 26 Cell population dynamics case when cell density = 60%, P_v = 0.8, and P_{CD4} =0.2.
X-axis is days of infection. Y-axis is number of cell population.

Cell density in LN	60%
P_v	0.6
P_{CD4}	0.4

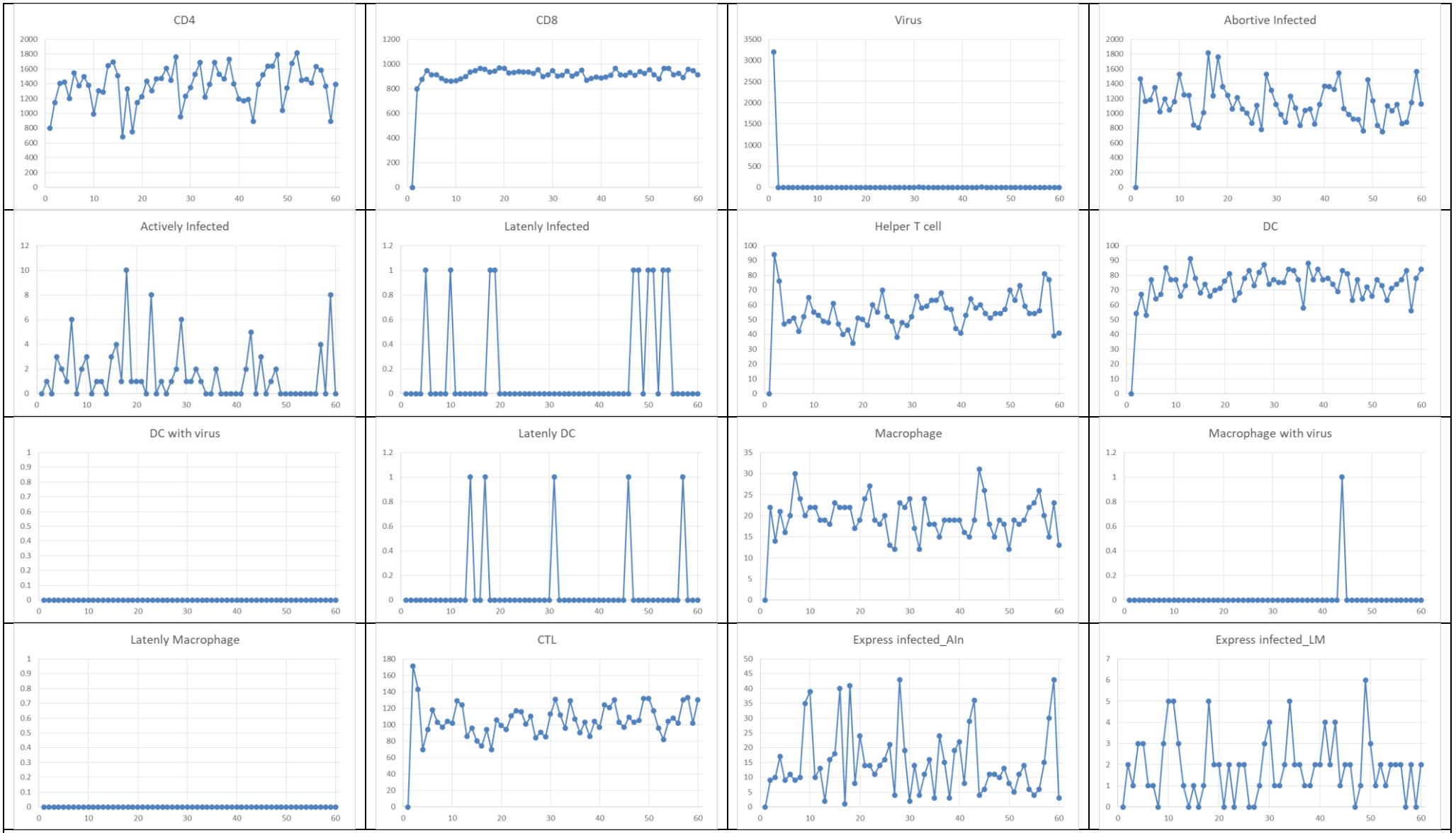

Figure 27 Cell population dynamics case when cell density = 60%, P_v = 0.6, and P_{CD4} =0.4.
X-axis is days of infection. Y-axis is number of cell population.

Cell density in LN	40%
P_v	1
P_{CD4}	0

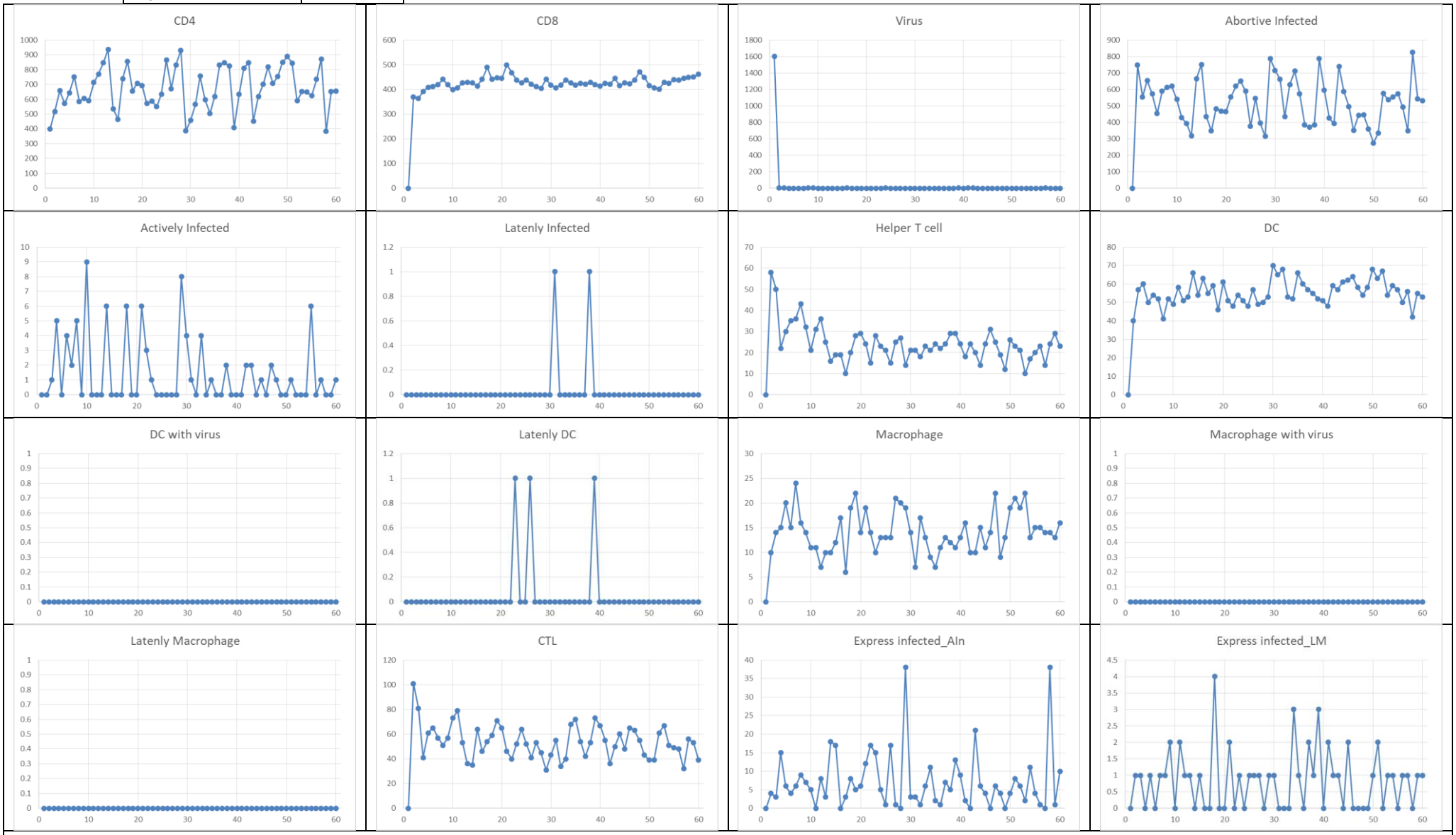

Figure 28 Cell population dynamics case when cell density = 40%, P_v = 1, and P_{CD4} =0.
X-axis is days of infection. Y-axis is number of cell population.

Cell density in LN	40%
P_v	0.8
P_{CD4}	0.2

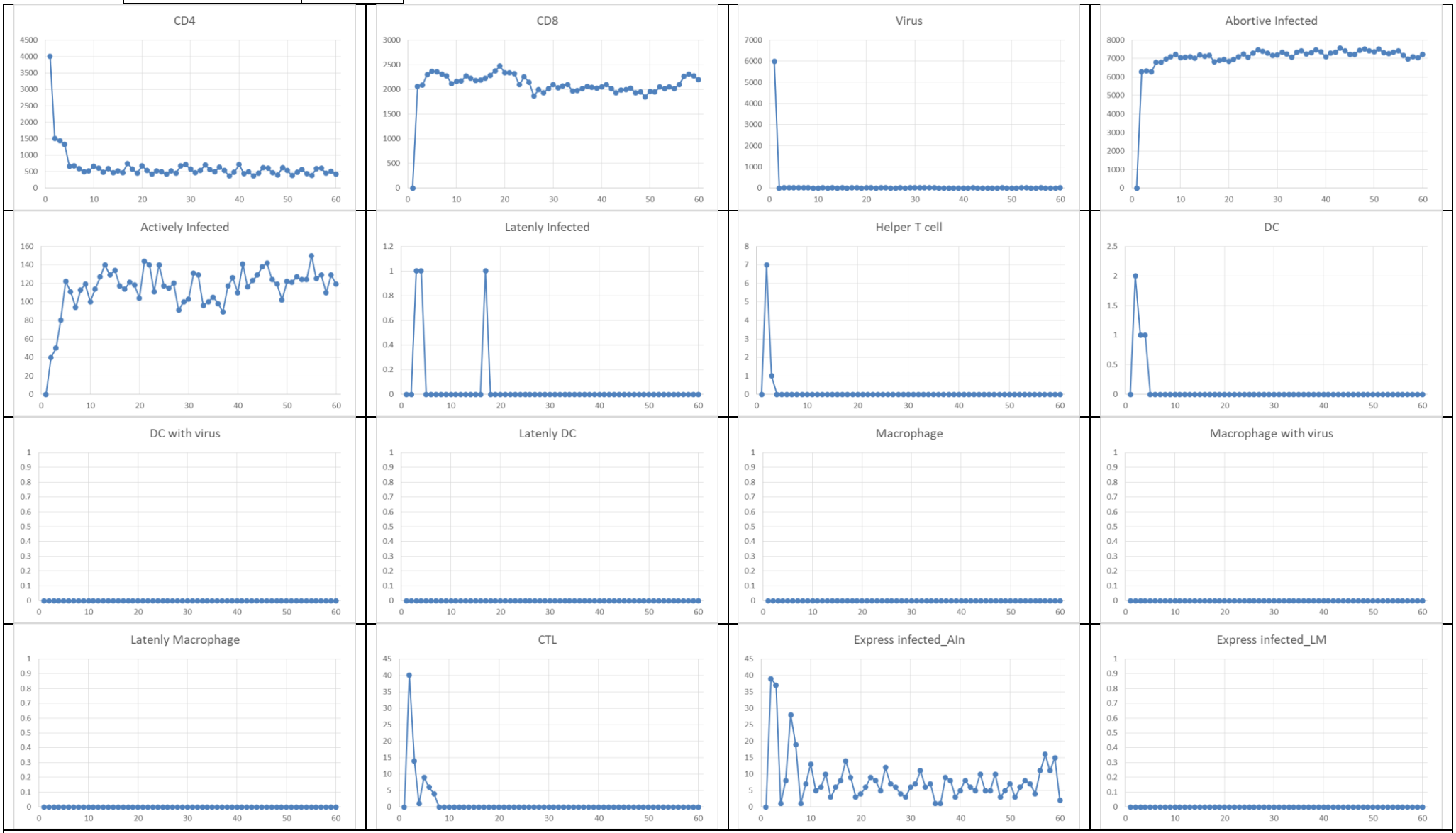

Figure 29 Cell population dynamics case when cell density = 40%, P_v = 0.8, and P_{CD4} =0.2.
X-axis is days of infection. Y-axis is number of cell population.

Cell density in LN	40%
P_v	0.6
P_{CD4}	0.4

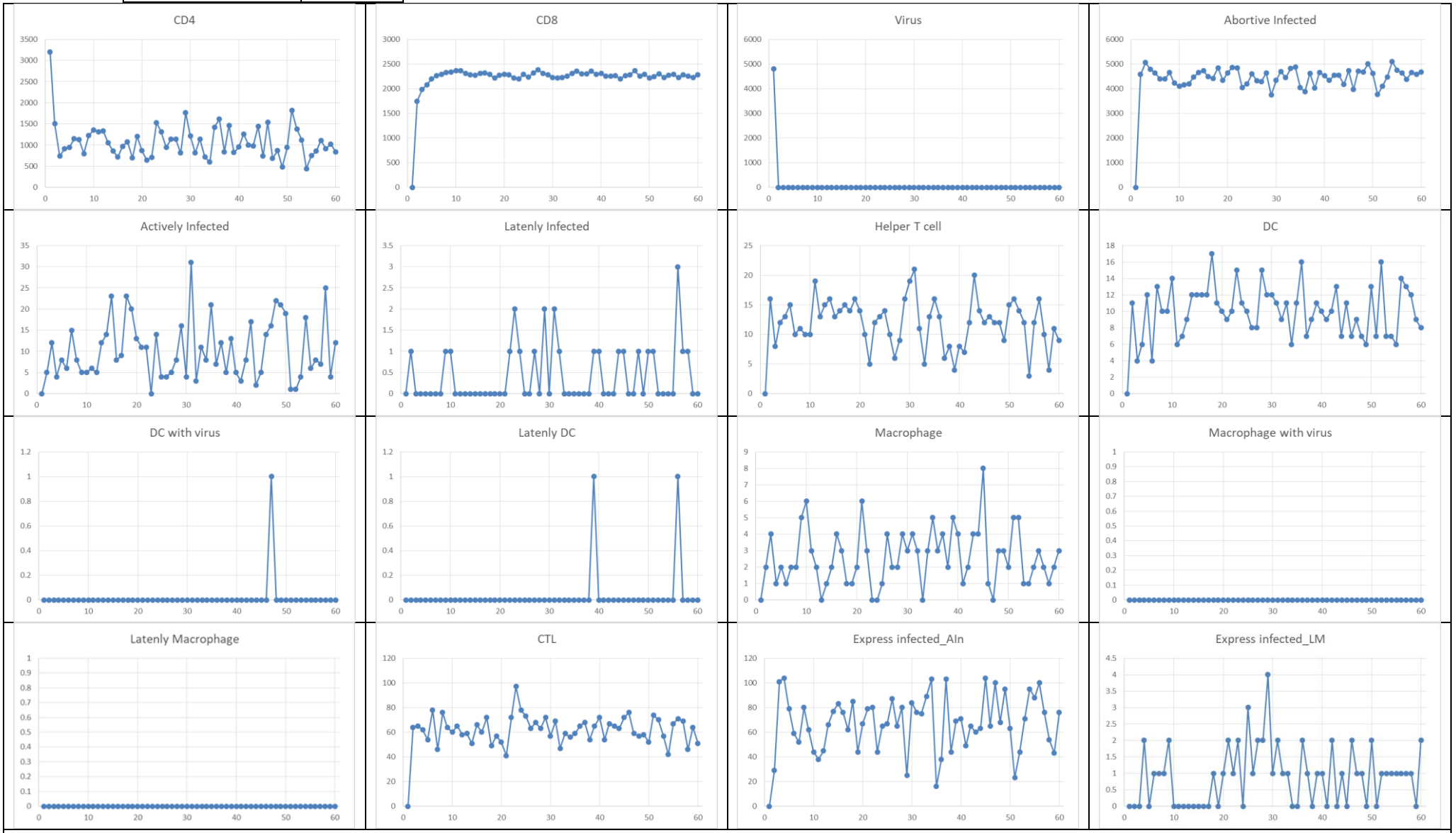

Figure 30 Cell population dynamics case when cell density = 40%, P_v = 0.6, and P_{CD4} =0.4.
X-axis is days of infection. Y-axis is number of cell population.

Cell density in LN	20%
P_v	1
P_{CD4}	0

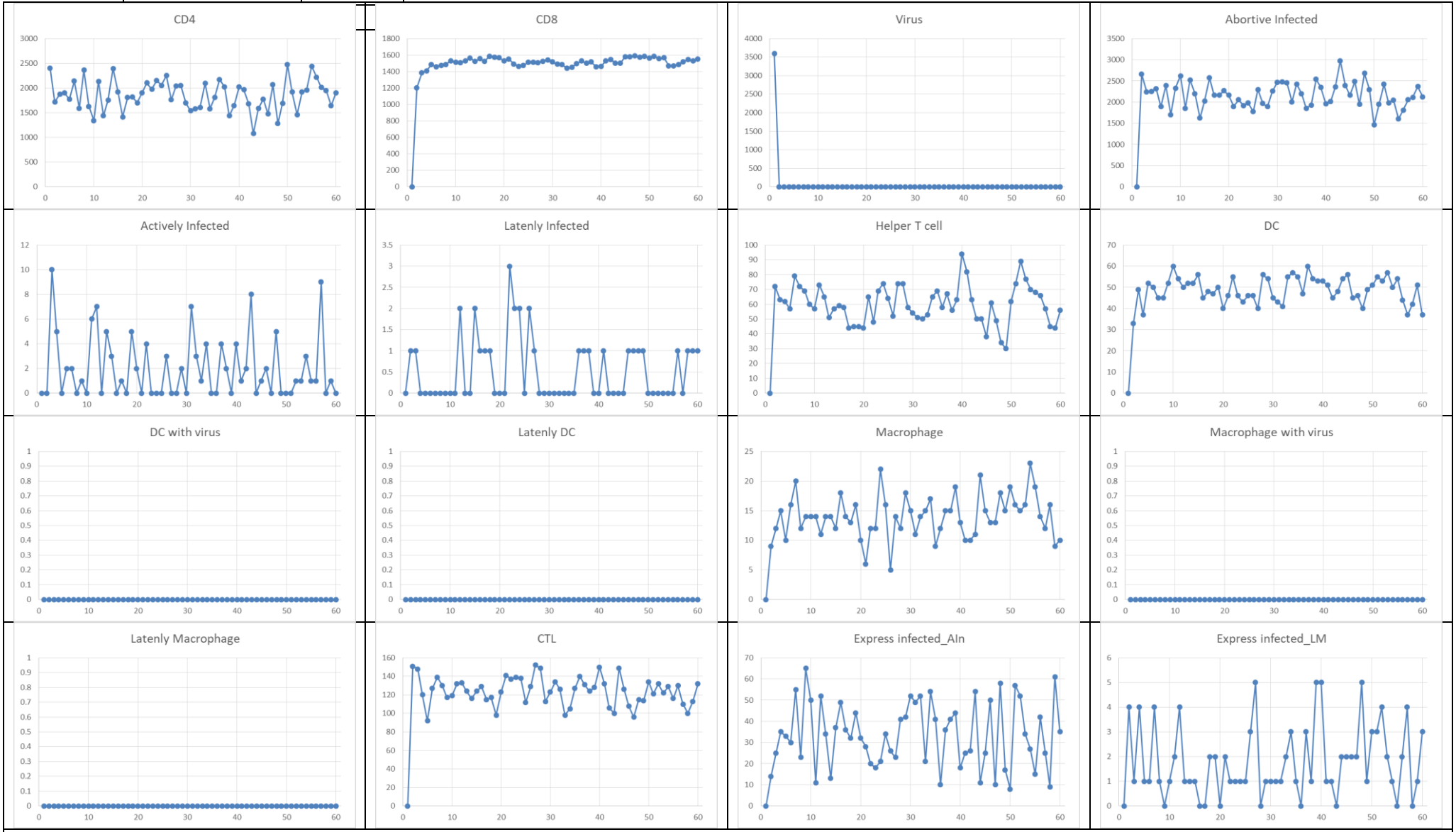

Figure 31 Cell population dynamics case when cell density = 20%, P_v = 1, and P_{CD4} =0.
X-axis is days of infection. Y-axis is number of cell population.

Cell density in LN	20%
P_v	0.8
P_{CD4}	0.2

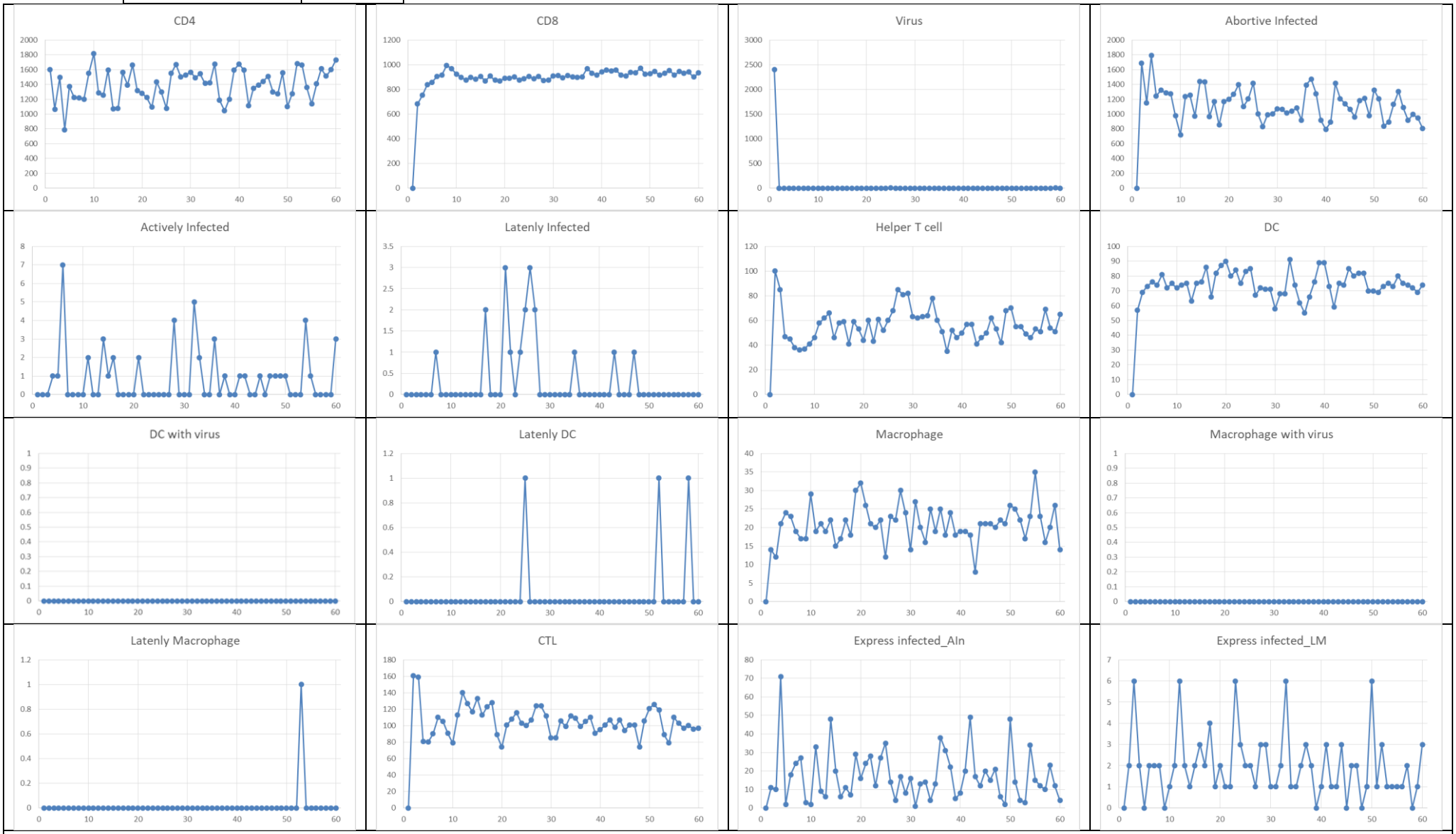

Figure 32 Cell population dynamics case when cell density = 20%, P_v = 0.8, and P_{CD4} =0.2.
X-axis is days of infection. Y-axis is number of cell population.

Cell density in LN	20%
P_v	0.6
P_{CD4}	0.4

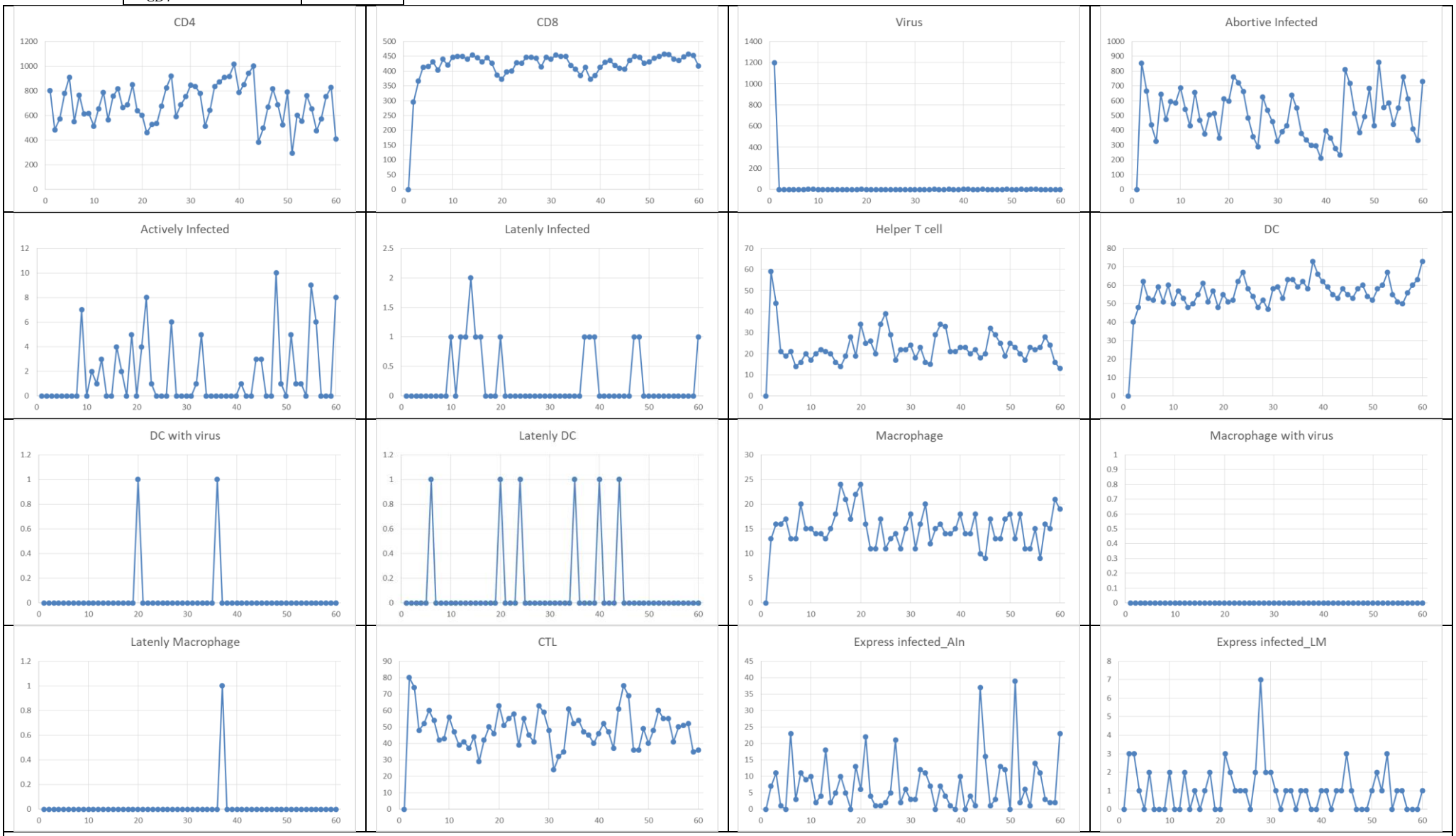

Figure 33 Cell population dynamics case when cell density = 20%, P_v = 0.6, and P_{CD4} =0.4.
X-axis is days of infection. Y-axis is number of cell population.

Chapter V
Conclusion

In this work, an HIV-CA model which concerned effects of cell-mediated immunities is presented. The role of HIV-1 target cells, i.e. the $CD4^+$ T cells, the roles of cell-mediated immunities, i.e. the $CD8^+$ cytotoxic T lymphocytes (CTLs) and the $CD4^+$ helper T lymphocytes, and the role of antigen-presenting cells (APCs), i.e. the dendritic cells (DCs) and the macrophages, including the mechanisms of cells' mobility and their kinetics associated with the HIV-1 infection, for instance cells' proliferation and cells' differentiation, are incorporated onto the model.

By using the proposed model according the proposed CA rules and kinetics, it found that our model could represent the dynamics of cell population related the HIV-specific immune responses. With this report, our simulation results shows how the variations in the cell initial concentration, i.e. the initial number of virus particles and the initial number of $CD4^+$ T cells in lymphoid tissue here, could affect the HIV infection dynamics. Noted that, for the sake of understanding, only the first 60 days simulation results after the infection are presented due to the frequency of our set configurations and the highly disease progression.

Chapter VI

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