# Modeling B cell Dysfunction in HIV infection

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**Abstract**

Progression from infection with the Human Immunodeficiency Virus (HIV) to AIDS is a complex process that remains poorly understood. While mathematical models representing the ongoing battle between HIV and the immune system have been successful, they remain focused on cellular, as opposed to humoral, immunity. This situation remains in spite of the fact that recent evidence has shown the mediators of humoral immunity, the B cells, to represent a significant factor in the progression to AIDS. We propose here a mathematical model of HIV infection, which, in addition to B cells, includes a population of so-called "dysfunctional B cells." These cells are improperly activated by HIV and contribute towards the progression to AIDS as they waste valuable immune resources and promote autoimmunity, which often accompanies HIV infection. By including more relevant aspects of the immune system into our model, we intend to suggest useful experiments as well as gain a more comprehensive picture of HIV infection.

## 1 Introduction

Primary infection with the Human Immunodeficiency Virus (HIV) is characterized by a rapid decrease in the number of $CD4^+$ lymphocytes, otherwise known as T helper cells. These cells are responsible for a wide range of functions regulating the responses of other cells in the immune system. The immune system reacts to the initial, or primary, HIV infection by using both $CD8^+$ cytotoxic T lymphocytes and antibodies produced by B cells to eliminate most of the virus and restore $CD4^+$ numbers in the blood. However, the $CD4^+$ lymphocytes never fully recover and the ensuing chronic infection involves a gradual decrease in $CD4^+$ numbers, culminating in a diagnosis of acquired immune deficiency syndrome (AIDS). Without treatment, AIDS invariably results in opportunistic infections and death.

It is less well known that the B cells of patients with primary HIV infection are also decreased in number and show a number of phenotypic and functional changes, most of which continue throughout chronic infection [1, 2]. A number of these changes occur even before $CD4^+$ numbers begin to decrease [2, 3]. They include abnormal regulation of activation and differentiation as well as an impaired response to vaccinations with T cell-dependent and T cell-independent antigens [1, 4, 5]. This and other evidence suggests the possibility that HIV may act directly on B cells, contributing to disease progression [6].

We propose here a mathematical model simulating the relationship between HIV and the humoral immune system during HIV infection, the aim of which is to provide a system of equations that would suggest experiments based on the assumptions and predictions of the model. The model is unique in that it considers the dynamic between free virus, T cells, and B cells when one assumes HIV acts on immature B cells resulting in a dysfunctional B cell. Recent evidence suggests such a population of cells exists and is responsible for the majority of the B cell dysfunctions in HIV infection [4, 5]. By introducing the dysfunctional B cell, the model aims to provide evidence supporting a more complex view of the causes behind the progression to AIDS. If the mechanism(s) responsible for such effects upon B cells were discovered, new directions towards the treatment of HIV might be possible.

Observations focused on a hormone called B cell activation factor (BAFF) in part inspired the creation of our model. BAFF is a crucial survival factor for many B cells in the body and was found in HIV patients in levels nearly double that of healthy controls [7]. The excess BAFF could be partially responsible for

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the fact that two of the main B cell dysfunctions in HIV infection are autoantibody production and hypergammaglobulemia, an excess of antibodies in the blood [8]. Most of the evidence used in the model relating B cell dysfunctions to BAFF comes from the groups of Moir *et al.* and De Milito textslet al.. Collectively, these researchers have provided evidence that during HIV infection, B cells display an increased turnover rate, decreased binding to BAFF, and a 4 fold increased rate of antibody secretion [4, 9].

## 2 The Presentation of the Model

In oder to illustrate this unusual phenomenon, we will examine the interaction between eleven variables: antigen presenting cells, infected cells, heathy T cells, $CD^+8$ cells,$T_2$ B cells, virus, plasma B cells, B memory cells, dysfunctional B cells, BAFF levels, and antibodies. Here in Figure 1, we introduce a flow diagram between the virus and the immune response .

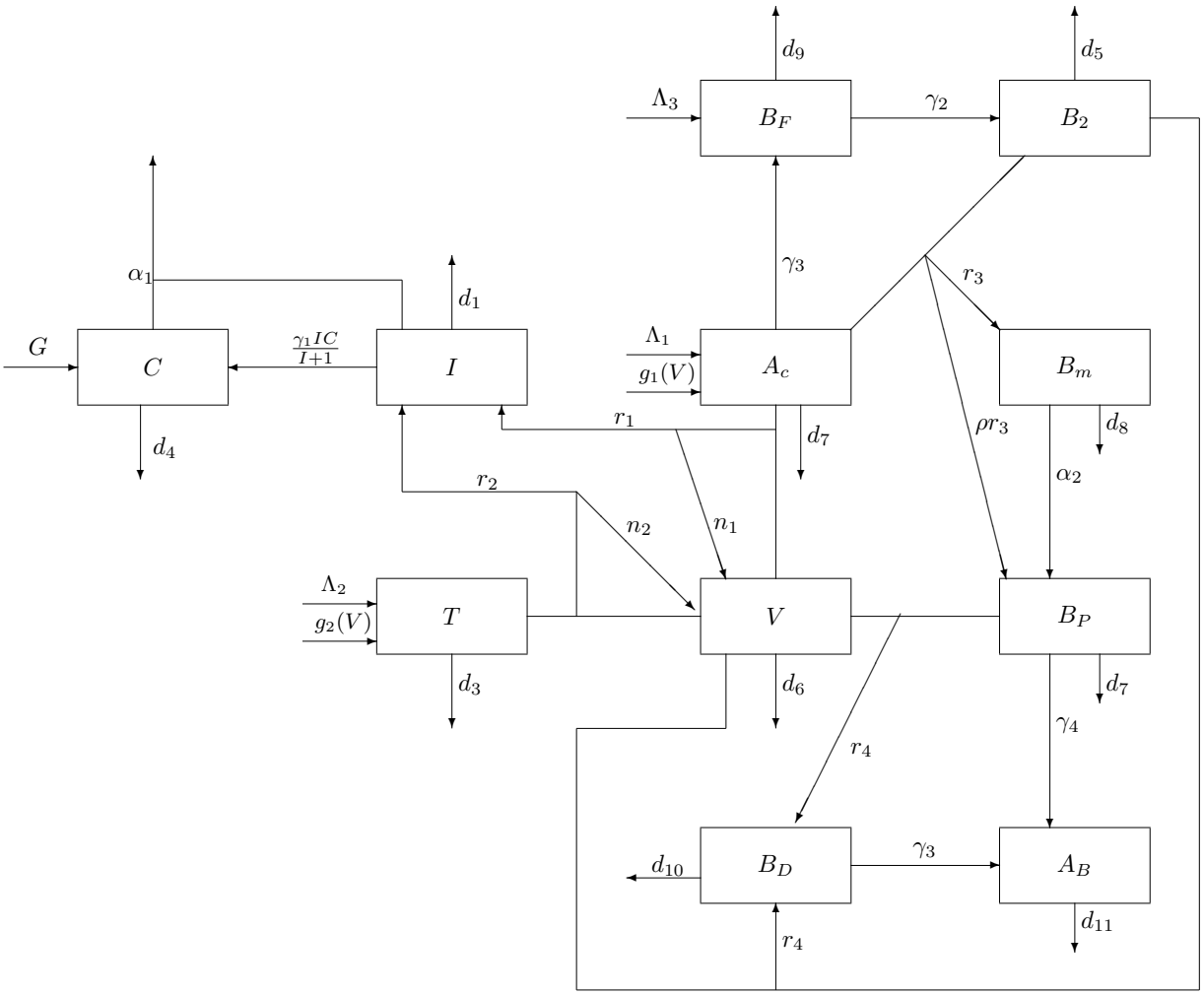


Figure 1: The flow diagram of the HIV model.

From the flow chart, we were able to derive the following system of differential equations:

$$\dot{I} = r_1 A_c V + r_2 V T - d_1 I - c_2 B_p V - \frac{\gamma_1 I C}{1+I} \quad (1)$$

$$\dot{A_c} = \Lambda_1 + g_1(V) - r_1 A_c V - d_2 A_c \quad (2)$$

$$\dot{T} = \Lambda_2 + g_2(V) - r_2 V T - d_3 T \quad (3)$$

$$\dot{C} = \frac{\gamma_1 I C}{1+I} + G - \alpha_1 C I - d_4 C \quad (4)$$

$$\dot{B_2} = \gamma_2 B_F - r_3 B_2 A_c - r_4 B_2 V - d_5 B_2 \quad (5)$$

$$\dot{V} = n_1 r_1 A_c V + n_2 r_2 V T - r_5 B_P V - d_6 V \quad (6)$$

$$\dot{B_P} = \rho r_3 B_2 A_C - d_7 B_P + \alpha_2 B_m \quad (7)$$

$$\dot{B_m} = (1-\rho) r_3 B_2 A_C - d_8 B_m \quad (8)$$

$$\dot{B_D} = r_4 B_2 V - d_{10} B_D \quad (9)$$

$$\dot{B_F} = \Lambda_3 + \gamma_3 A_c - d_9 B_F \quad (10)$$

$$\dot{A_B} = \alpha_3 B_D + \alpha_4 B_P - d_{11} A_B \quad (11)$$

All variables and parameters of the system of differential equations are stated in Table 1 and Table 2. The explanation of these equations follows:

**Table 1.Variables for HIV-1 model.**

| Variable | Definition |
|---|---|
| $A_c$ | activated antigen presenting cells |
| $C$ | CTL |
| $T$ | activated helper T-cells |
| $V$ | virus |
| $B_2$ | $T_2$ B cells |
| $I$ | infected cells (infected activated antigen presenting cells and activated helper T-cells) |
| $B_F$ | BAFF |
| $B_P$ | plasma cells |
| $B_m$ | memory cells |
| $B_D$ | dysfunctional cells |
| $A_B$ | antibodies |

**Table 2. Conditions and parameter values for HIV-1 model.**

| Variable | Definition | Value | Units | References |
|---|---|---|---|---|
| $r_1$ | rate at which $A_c$ become infected by virus | 8.0 x $10^{-12}$ | /day-virion | Bajaria (2003) [10] |
| $r_2$ | rate at which $T$ become infected by virus | 8.0 x $10^{-12}$ | /day-virion | Stafford (2000) [11] |
| $r_3$ | rate of $B_2$ cells becoming plasma $B$ and memory $B$ cells | 0.06 | /day | estimated |
| $r_4$ | rate of $B_2$ cells becoming dysfunctional B cells | No better data | | |
| $r_5$ | rate of which antibodies from plasma B cells clears virus | No better data | | |
| $d_1$ | death rate of $I$ | 0.50 | /day | Stafford (2000) [11] |
| $d_2$ | death rate of $A_c$ | 0.2 | /day | Stafford (2000) [11] |
| $d_3$ | death rate of $T$ | 0.2 | /day | Stafford (2000) [11] |
| $d_4$ | death rate of $CTL$ | 0.015 | /day | |
| $d_5$ | death rate of $B_2$ | 0.1 | /day | Na (2005) [12] |
| $d_6$ | constant clearance rate of virus | 4 | /day | Perelson (1996) [13] |
| $d_7$ | death rate of plasma B cells | 0.08 | /day | De Milito (2004) [9] |
| $d_8$ | death rate of memory B cells | 0.003 | /day | estimated |
| $d_9$ | death rate of dysfunctional B cells | 0.26 | /day | Na (2005) [12] |
| $d_{10}$ | clearance rate of BAFF | 0.5 | /day | estimated |
| $d_{11}$ | clearance rate of antibodies | 0.18 | /day | Na (2005) [12] |
| $c_2$ | the rate at which antibodies from $B_P$ kills infected cells | 4 x $10^{-12}$ | /day-B plasma cell | estimated |
| $g_1(V)$ | function describing $A_C$ increase due to virus | unknown | | |
| $g_2(V)$ | function describing $T$ increase due to virus | unknown | | |
| $n_1$ | rate of virus production by infected $A_c$ | 500 | /day-infected cell | Bajaria (2003) [10] |
| $n_2$ | rate of virus production by infected $T$ | 500 | /day-infected cell | Bajaria (2003) [10] |
| $\alpha_1$ | the rate at which CTL kills infected cells | No better data | | |
| $\alpha_2$ | rate of plasma B increase due to division from memory B cells | No better data | | |
| $\alpha_3$ | rate of antibody production by dysfunctional B cells | 114 | ng/mL/day | De Milito (2004) [9] |
| $\alpha_4$ | rate of antibody production by plasma B cells | 14 | ng/mL/day | De Milito (2004) [9] |
| $\Lambda_1$ | constant rate of $A_c$ production | 0.004 | /day | Stafford (2000) [11] |
| $\Lambda_2$ | constant rate of $T$ production | 0.004 | /day | Stafford (2000) [11] |
| $\Lambda_3$ | constant BAFF production | 0.5 | /day | estimated |
| $\gamma_1$ | rate of CTL increase due to infected cells | No better data | | |
| $\gamma_2$ | rate of $B_2$ cells surviving due to BAFF | 4000 | /mL/day | Na (2005) [12] |
| $\gamma_3$ | BAFF production rate from $A_c$ | No better data | | |
| $\rho$ | proportion of $r_3$ that is plasma B cells | No better data | | |

$$\dot{I} = r_1 A_c V + r_2 V T - d_1 I - c_2 B_p V - \frac{\gamma_1 I C}{1 + I}$$

**Infected cells** – Our model considers all antigen presenting cells and helper T cells viable for infection. Some infected cells are killed via the mechanism of antibody dependent cellular cytotoxicity (ADCC). However, this rate is dependent on the number of plasma B cells and not the total antibody levels because the dysfunctional B cells are known to produce unspecific antibodies. There is also infected cell death due to the presence of $CD8^+$ killer cells at a ratio dependent rate.

$$\dot{A_c} = \Lambda_1 + g_1(V) - r_1 A_c V - d_2 A_c$$

**Antigen Presenting cells** – Some APCs are always present in the bloodstream and are responsible for cleaning up debris and introducing antigens to the immune system. APCs in our model are considered to be monocytes, macrophages, and dendritic cells all capable of being infected. Their numbers are increased as a function of virus levels. APCs are the primary cells responsible for BAFF production.

$$\dot{T} = \Lambda_2 + g_2(V) - r_2 V T - d_3 T$$

**$CD4^+$ T helper cells** – The main target of HIV. These regulators of the immune system are essential for activation and proper functioning of $CD8^+$ killer cells as well as B cells. They are assumed to be produced at a constant rate before introduction of the virus. After introduction, the number of $CD4^+$ cells increases as some function of the virus level and decreases as a product of their concentrations.

$$\dot{C} = \frac{\gamma_1 I C}{1 + I} + G - \alpha_1 C I - d_4 C$$

**$CD8^+$ Cytotoxic T lymphocytes**– They play a vital role in fighting viral infections by searching the body for infected cells and killing them. Some $CD8^+$ T cells are produced at a constant rate but are mostly dependent on the number of infected cells in the body.

$$\dot{B_2} = \gamma_2 B_F - r_3 B_2 A_c - r_4 B_2 V - d_5 B_2$$

**$T_2$ B cells** These B cells derive from $B_1$ cells in the bone marrow and are at the first stage of BAFF dependent development. These cells go on to become memory B cells and plasma B cells at a rate dependent on the number of antigen presenting cells in the body. Importantly, our model assumes that $B_2$ cells go on to become dysfunctional B cells at a rate dependent on the level of virus.

$$\dot{V} = n_1 r_1 A_c V + n_2 r_2 V H - r_5 B_P V - d_6 V$$

**Virus** – HIV. Can infect antigen presenting cells and T helper cells. Free virus is cleared non-specifically by constant mechanisms and specifically by the antibodies from functional plasma B cells.

$$\dot{B_P} = \rho r_3 B_2 A_C - d_7 B_P + \alpha_2 B_m$$

**Plasma B cells** – Reside in the bone marrow and secrete large amounts of antibodies. A portion of these cells are specific to HIV. Plasma B cells can be derived either from the $T_2$ B cells or the memory B cells. Rho refers to the portion of maturing $T_2$ cells that become plasma cells instead of memory cells.

$$\dot{B_m} = (1 - \rho) r_3 B_2 A_C - d_8 B_m$$

**Memory B cells** – Memory cells are highly specific for antigen previously encountered in the body and

are the source of long term immunity. Memory B cells derive from $T_2$ cells. The level of memory B cells is cut in half during chronic HIV infection. This fact may be modeled by making the parameter rho a function of viral load.

$$\dot{B_D} = r_4 B_2 V - d_{10} B_D$$

**Dysfunctional B cells** – Characterized by nonspecific antibody secretion, short lifespan, and aberrant markers of activation and differentiation. These cells are produced from $T_2$ B cells at a rate dependent on the level of virus.

$$\dot{B_F} = \Lambda_3 + \gamma_3 A_c - d_9 B_F$$

**B Cell Activation Factor (BAFF)** – An important hormone involved in B cell survival. Some is produced constantly by epithelial cells in areas of immune development and some is produced by antigen presenting cells.

$$\dot{A_B} = \alpha_3 B_D + \alpha_4 B_P - d_{11} A_B$$

**Antibodies** – proteins secreted by plasma B cells as well as dysfunctional B cells. Antibodies made by plasma cells can neutralize the virus by binding it and recruiting other immune cells to destroy it. Antibodies can similarly bind infected cells that display foreign antigen on their surface resulting in their death by ADCC.

# 3 Reformulation

Although we were able to find the majority of the parameters needed for our model in the current literature, there were some parameters - such as the rate of $T_2$ B cells becoming dysfunctional $B$ cells and the rate of BAFF production from the antigen presenting cells - for which there are hardly any experimental data available. This fact, in addition to the number of equations and their complexity led us to simplify the model by reducing the number of equations from 11 to 5. The new model more clearly states the assumptions being made and allows for the removal of a number of parameters unavailable in the literature. The equations eliminated represent the following: antigen presenting cells, T2 immature B-cells, dysfunctional B-cells, the B cell survival factor BAFF and antibodies. How this simplification was done was by getting rid of the antigen presenting cells due to its dynamics were very small as compared to the other variables in the system. In addition, we decided to include five variables and its affects into one variable $B$ using the fact that some variables behave in the same dynamic as others. Thus, we propose a flow chart (Figure 2) to illustrate the relationship between the five variables: $CD4^+$ cells (or T cells), $CD8^+$ cells (or CTL cells), infected cells, the virus, and B cells and their respective parameters stated in Table 3 and Table 4.

$$\dot{T} = \lambda - \beta V T - d_1 T \tag{12}$$

$$\dot{E} = \phi + \frac{b_E I}{I + K_b} E - \frac{d_E I}{I + K_d} E - d_2 E \tag{13}$$

$$\dot{I} = \beta V T - k E I - \delta I \tag{14}$$

$$\dot{V} = N_T \delta I - c B V - d_3 V \tag{15}$$

$$\dot{B} = b_{aff} V B - d_4 B \tag{16}$$

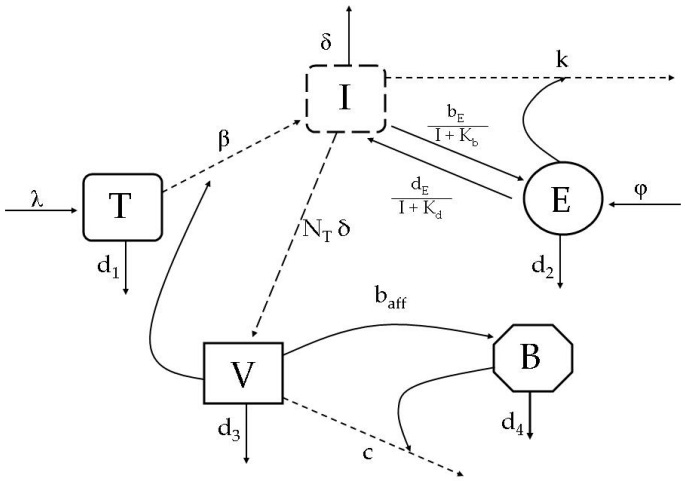


Figure 2: Flow Chart of the Simplified Model

The central assumption of the model remains essentially unchanged and states that HIV infection results in a population of dysfunctional B-cells. The number of normal B-cells becoming dysfunctional is related to the viral load. While the dysfunctional B-cells no longer have their own equation, their numbers can be represented by the term ($b_{aff}VB$) in the B cell equation. A secondary assumption was simplified that allowed for the elimination of 3 equations, $\dot{A}_c$, $\dot{B}_2$, and $\dot{B_F}$. This assumption states that B-cell survival is dependent on BAFF levels, which were found in AIDS patients to be present in levels nearly double that of healthy people. In the original model, BAFF levels were dependent on antigen presenting cell numbers that increased in response to vial load. The T2 B-cells were dependent on BAFF for their survival and the number of plasma B-cells were dependent on the T2 cells. This complicated and indirect mode of virus influencing plasma B cell numbers is now simply stated as the term ($b_{aff}BV$), the parameter $b_{aff}$ representing the increases in B-cell numbers in response to the virus. The fifth equation, antibodies, was easily eliminated by assuming that antibody levels are proportional to B-cell numbers and by representing the effect of antibodies on virus levels with the term ($cBV$) in the Virus equation. In addition to the reduction of our model, we also included two Michealis-Menten saturation nonlinearity terms for the immune response ( $\frac{b_E I}{I+K_b}E$ and $\frac{d_E I}{I+K_d}E$ ) as suggested by Bonhoeffer *et al.* . They describe a saturation of immune stimulation and a saturation of immune impairment at high virus levels [14, 15]. In the B cell equation, we assume B cells are already present in the body and will increase due to the hormone BAFF and decrease due to natural death. Though it makes biological sense to have a clearance rate between the interaction of the CD8$^+$ cells and the virus, to simplify the model we did not consider this.

**Table 3.Variables for second HIV-1 model.**

| Variable | Definition |
|---|---|
| $T$ | healthy CD4$^+$ cells |
| $C$ | CTL or CD8$^+$ |
| $I$ | infected cells |
| $V$ | virus |
| $B$ | B cells |

**Table 4. Conditions and parameter values for the second HIV-1 model.**

| Parameters | Definition | Value | Units | References |
|---|---|---|---|---|
| $\lambda$ | $T$ cell production rate | 10 | | estimated |
| $\beta$ | rate at which T become infected by virus | 0.05 | | Galvani (2005) [16] |
| $d_1$ | death rate of T cells | 0.009 | $\text{day}^{-1}$ | Galvani (2005)) [16] |
| $\phi$ | constant rate of CTL cell production | 9.9085e-03 | $\frac{cells}{mL \cdot day}$ | Adams (2007) [15] |
| $b_E$ | maximum birth rate for CTL cells | 1.0 | $\text{day}^{-1}$ | estimated |
| $K_b$ | saturation constant for CTL birth | 3.9087e-01 | $\frac{cells}{mL}$ | Adams (2007) [15] |
| $d_E$ | maximum death rate for CTL cells | 1.0213e-01 | $\text{day}^{-1}$ | Adams (2007) [15] |
| $K_d$ | saturation constant for CTL death | 8.379e-01 | $\frac{cells}{mL}$ | Adams (2007) [15] |
| $d_2$ | death rate of $CTL$ | 7.0299e-02 | $\text{day}^{-1}$ | Adams (2007) [15] |
| $k$ | immune-induced clearance rate | 3.099e-02 | $\frac{mL}{cells \cdot day}$ | Adams (2007) [15] |
| $N_T$ | virions produced per infected cell | 1.5e10 | $\text{day}^{-1}$ | Adams (2007) [15] |
| $\delta$ | infected cells death rate | 0.003 | $\text{day}^{-1}$ | Adams (2007) [15] |
| $c$ | death rate of virus due to the B cells | 2.5e-05 | | estimated |
| $d_3$ | virus natural death rate | 38.4 | $\text{day}^{-1}$ | Galvani (2005) )[16] |
| $b_{aff}$ | the rate at which B cells are being produced | 100 | | unknown |
| $d_4$ | death rate of B cells | 1.6e-02 | $\text{day}^{-1}$ | Galvani (2005) )[16] |
| $T_0$ | initial T-cell count | 1111.1 | | calculated |
| $E_0$ | initial CTL cell count | 0.14095 | | calculated |
| $I_0$ | initial infected cell count | 0 | | estimated |
| $V_0$ | initial virus count | 10 | | estimated |
| $B_0$ | initial B cell count | 4.0e05 | | calculated |

# 4 Stability and Analysis of the Disease Free Equilibrium

In epidemiology the average number of secondary infections per primary infection in a pathogen-free population is known as the basic reproductive number or $R_0$ [17]. In viral population dynamics, the basic reproductive number is the average number of secondary infected cells arising from a single infected cell in a host that is otherwise free of virus [18]. At the disease-free equilibrium, we can conclude that if $R_0 > 1$, the amount of virus grows through a chain reaction of new infections, and if $R_0 < 1$ the amount of virus (or infected cells) steadily decreases and the infection dies out. The basic reproductive number $R_0$ is calculated as follows: we let $I = 0$ and $V = 0$ in our 5-dimensional model to determine the disease free equilibrium

$$Z_0 = (T_0, E_0, I_0, V_0, B_0) = (\tfrac{\lambda}{d_1}, \tfrac{\phi}{d_2}, 0, 0, 0)$$

where its Jacobian is

$$\mathbf{J} = \begin{pmatrix} -\beta V - d_1 & 0 & 0 & -\beta T & 0 \\ 0 & \frac{b_E I}{I+K_b} - \frac{d_E I}{I+K_d} - d_2 & \frac{b_E E}{I+K_b} - \frac{b_E IE}{(I+K_b)^2} - \frac{d_E E}{I+K_d} + \frac{d_E IE}{(I+K_d)^2} & 0 & 0 \\ \beta V & -kI & -kE - \delta & \beta T & 0 \\ 0 & 0 & N_T \delta & -cB - d_3 & -cV \\ 0 & 0 & 0 & b_{aff} B & b_{aff} V - d_4 \end{pmatrix}. \quad (17)$$

The Jacobian evaluated at the $Z_0$ can be computed as follows

$$J_0 = \begin{pmatrix} -d_1 & 0 & 0 & -\frac{\beta\lambda}{d_1} & 0 \\ 0 & -d_2 & \frac{b_E\phi}{d_2K_b} - \frac{d_E\phi}{d_2K_d} & 0 & 0 \\ 0 & 0 & -\frac{k\phi}{d_2} - \delta & \frac{\beta\lambda}{d_1} & 0 \\ 0 & 0 & N_T\delta & -d_3 & 0 \\ 0 & 0 & 0 & 0 & -d_4 \end{pmatrix}. \tag{18}$$

We know that $Z_0$ is locally asymptotically stable if and only if all eigenvalues of the matrix $J_0$ have a negative real part [19]. From $J_0$, it is easy to obtain three eigenvalues of $J_0$ namely,

$$\begin{aligned} \lambda_1 &= -d_1, \\ \lambda_2 &= -d_2, \\ \lambda_3 &= -d_4, \end{aligned}$$

and leaving us with a $2 \times 2$ matrix, which we will call $A$

$$A = \begin{pmatrix} -\frac{k\phi}{d_2} - \delta & \frac{\beta\lambda}{d_1} \\ N_T\delta & -d_3 \end{pmatrix}. \tag{19}$$

Assuming we do not know the values of the parameters, we still could determine stability from (19). We know that if the trace of a $2 \times 2$ matrix is negative and the determinant is positive, then the system of differential equation is locally asymptotically stable. Here we will apply this theorem

$$tr(A) = tr \begin{pmatrix} -\frac{k\phi}{d_2} - \delta & \frac{\beta\lambda}{d_1} \\ N_T\delta & -d_3 \end{pmatrix} = -\frac{k\phi}{d_2} - \delta - d_3 < 0 \tag{20}$$

$$\begin{aligned} det(A) &= det \begin{pmatrix} -\frac{k\phi}{d_2} - \delta & \frac{\beta\lambda}{d_1} \\ N_T\delta & -d_3 \end{pmatrix} > 0 \\ &\Leftrightarrow -d_3(-\tfrac{k\phi}{d_2} - \delta) - \tfrac{\beta\lambda}{d_1}N_T\delta > 0 \\ &\Leftrightarrow d_3(\tfrac{k\phi}{d_2} + \delta) > \tfrac{\beta\lambda}{d_1}N_T\delta \\ &\Leftrightarrow N_T < \tfrac{d_1d_3k\phi}{d_3\lambda\beta\delta} + \tfrac{d_1d_3}{\lambda\beta} \end{aligned} \tag{21}$$

As a result, we have
**Theorem** $Z_0 = (\frac{\lambda}{d_1}, \frac{\phi}{d_2}, 0, 0, 0)$ *is locally asymptotically stable if and only if the following holds*

$$N_T < \frac{d_1d_3k\phi}{d_3\lambda\beta\delta} + \frac{d_1d_3}{\lambda\beta}. \tag{22}$$

Since the $tr(A) < 0$ and the $det(A) > 0$ is true if the above condition (22) holds, then it could be concluded that our system of differential equations is locally asymptotically stable at the disease free equilibrium. Here $N_T$ is a critical value, which indicates the average number of secondary infections per primary infection, but we can also compute the basic reproductive number $R_0$ from (21) as follows:

$$\begin{aligned} det(A) &= -d_3(-\tfrac{k\phi}{d_2} - \delta) - \tfrac{\beta\lambda}{d_1}N_T\delta > 0 \\ &\Leftrightarrow d_3(\tfrac{k\phi}{d_2} + \delta) > \tfrac{\beta\lambda}{d_1}N_T\delta \\ &\Leftrightarrow R_0 = \tfrac{d_2N_T\lambda\beta\delta}{d_1d_3(k\phi + d_2\delta)} < 1. \end{aligned} \tag{23}$$

If $R_0 < 1$ then the virus will not spread, since every infected cell will on average produce less than one other infected cell. If on the other hand, $R_0 > 1$, then every infected cell on average produces more than one newly infected cell.

The basic reproductive number that was found in (23), holds true for the disease free equilibrium, however, $B_0 = 0$, which gives us no information on the dynamics of B-cells when virus is not introduced into the system. Hence, we will introduce another basic reproductive number based on the level of B cells $R_B$ as follows: each infected cell produces $N_T$ virus particles. The average lifetime of a virus particle is $\frac{1}{cB+d_3}$, so that the infectious potential of an infected cell is given by $\frac{\beta N_T}{cB+d_3}$. The number of $CD4^+$ cells at the onset of the infection is $\hat{T}$, which is equivalent to $T_0$ at the disease-free equilibrium ($\hat{T} \Leftrightarrow T_0 = \frac{\lambda}{d_1}$). Hence, an infected cell at the beginning of an infection can give rise to $R_B = \frac{\beta N_T \hat{T}}{cB+d_3}$ newly infected cell per unit of time. Whether or not an infection takes off depends on the level of the immune response. Protection from infection is provided if the strength of the immune response exceeds the critical level $B_{threshold}$. At this threshold, we find ourselves at the knife's edge between a successful and unsuccessful infection and hence $R_B = 1$. This level can now be calculated from $\frac{\beta N_T \hat{T}}{cB_{threshold}+d_3} = 1$, which is equivalent to

$$B_{threshold} = \frac{\beta N_T \hat{T} - d_3}{c}. \tag{24}$$

We can now work out how long the hormone BAFF will provide protection. As long as the level of immune response exceeds $B_{threshold}$ the infection cannot take off. Therefore, the period of time over which the host is protected can be calculated from $B_v e^{-d_4 t} = B_{threshold}$, where $B_v$ is the immune response generated through BAFF, which gives

$$t = \frac{1}{d_4} \ln \frac{B_v}{B_{threshold}} = \frac{1}{d_4} \ln \frac{cB_v}{\beta N_T \hat{T} - d_3}. \tag{25}$$

This formula tells us that the hormone BAFF provides long protection if the loss of immune cells is slow and the immune system has a long memory ($d_4$ small), if the immune response against the virus is effective (high $c$) or it elicits a strong response (high $B_v$) albeit that the two latter effects only work in the logarithm of the response. Long protection is also associated with a low transmission rate $\beta$, with a scarcity of target cells or with a small burst size, $N_T$.

The basic reproduction rate $R_0$, found in (23), does not seem to have any correlation with the levels of B cells. However, the correlation between the two could be found through the commonalities of parameters in the $B_{threshold}$ as follows:

**Corollary** $R_0$ (23) is dependent on the levels of B cells, $B_{threshold}$ (24), if and only if

$$R_0 = \frac{d_2}{k\phi + d_2\delta} \left(\frac{B_{threshold}}{d_3 c} + 1\right) \tag{26}$$

(for calculations see Appendix A)

We know if $R_0 < 1$ then the infection dies out, then we know that if

$$\begin{array}{rcl} \frac{B_{threshold}+1}{d_3 c} & < & \frac{k\phi+d_2\delta}{d_2} \\ B_{threshold} & < & \left(\frac{k\phi}{d_2} + \delta - 1\right) d_3 c \end{array}$$

# 5 Coexistence Equilibrium

The coexistence of T cells, CTL cells, infected cells, free virus, and B cells is given by

$$Z^* = (T^*, E^*, I^*, V^*, B^*) \tag{27}$$

*where*

$$\begin{array}{rcl} T^* & = & \frac{\lambda b_{aff}}{\beta d_4 + d_1 b_{aff}}, \\ E^* & = & \frac{\phi}{\frac{d_E}{I+K_d} I - \frac{b_E}{I+K_b} I + d_2}, \\ V^* & = & \frac{d_4}{b_{aff}}, \\ B^* & = & \frac{N_T \delta b_{aff}}{c d_4} I - \frac{d_3}{c}. \end{array}$$

Here $I$ is the solution of the third degree polynomial $P_1 I^3 + P_2 I^2 + P_3 I + P_4 = 0$ (see Appendix B) *where*

$$\begin{aligned}
P_1 &= \delta(b_E - d_E - d_2) - k\phi, \\
P_2 &= \Psi(d_E - b_E + d_2) - \delta(d_E K_b - b_E K_d + d_2 K_d + d_2 K_b) - k\phi(K_b + K_d), \\
P_3 &= \Psi(d_E K_b - b_E K_d + d_2 K_d + d_2 K_b) - K_b K_d(\delta d_2 + k\phi), \\
P_4 &= \Psi(d_2 K_b K_d), \\
\Psi &= \tfrac{\lambda\beta d_4}{\beta d_4 + d_1 b_{aff}}.
\end{aligned}$$

This polynomial could have one, two or three solutions when set equal to 0. Though the equilibrium components $T^*, E^*, V^*, B^*$ were easily calculated, $I^*$ was not. As a result, we decided to plot the third degree polynomial $I^* = 0$ implicitly to observe the dynamics between $I^*$ and one of its parameters. Here in Figure 3, we plot $I^*$ with respect to the hormone BAFF:

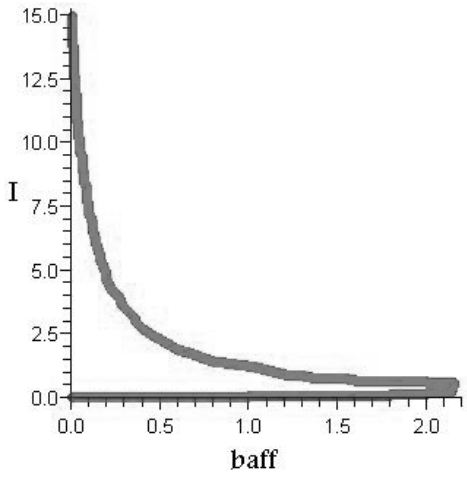


Figure 3: The number of infected cells versus the hormone levels of BAFF given by $I$ with parameters from Table 4. Here the number of infected cells is held at a very low state as the hormone BAFF increase; but at a certain time, the infected cells are not influenced by the hormone, thus increasing its numbers rapidly. Because of the excess level of BAFF in the body, this could lead to the dysfunction of the B cells.

From this graph, we were able to notice the growth rate of the infected cells is held at a very low number by the level of the B cell activation factor hormone initially for some time. However, at a certain point, the affects of the hormone wears off, as a result, the number of infected cells increases rapidly. This result, clearly shows B cells influencing the progression of HIV. Since the hormone BAFF is responsible for the survival of the B cells, the production of antibodies is crucial for suppression of the HIV infection [20]. However, the excess of BAFF has been seen to increase autoantibody levels resulting in a population of dysfunctional B cells. As seen in Figure 3, there exists such a population that results from unproportionately high autoantibody levels in HIV patients due to the affects of BAFF, which impacts the growth of HIV.

# 6 Simulations and Results

One obstacle we encountered with our first model was the number of parameters and their lack of experimental data in the current literature. With several assumptions though, we were able to simplify

our model to consider only five variables resulting in the reduction of the number of parameters. Seen in Table 4, the majority of the parameters were derived from two mathematical papers by Adams *et al.* and Galvani [15, 16]; from these parameters, we were able to estimate and calculate others. However, we were not able to obtain specific levels of BAFF, since there are hardly any experimental value, so we left the parameter to be varied in our simulations. At the level of $b_{aff} = 100$, we were able to acquire the following figure,

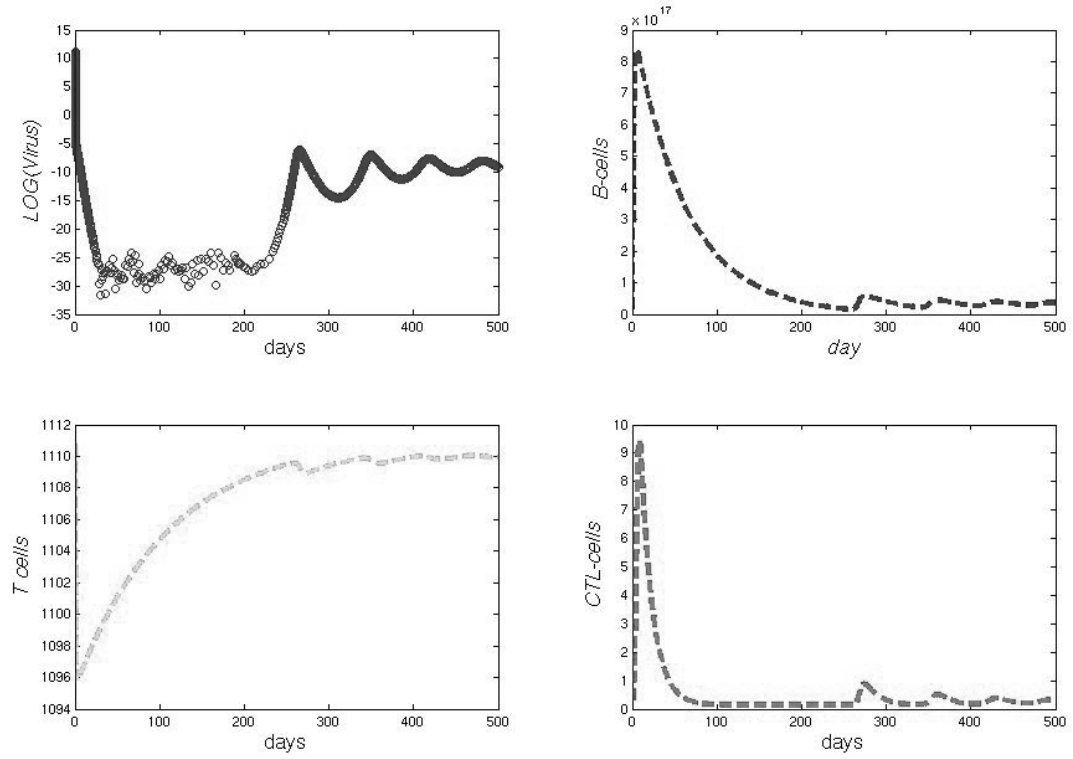


Figure 4: The simulation of the simplified model describing HIV dynamics using various parameters found from current literature and from our own estimations and calculations seen in Table 4.

After running some simulations, we were able to determine, in the acute phase of the disease (in Figure 4), the dynamics of the log of the viral load decreases rapidly initially then fluctuating for about 150 days and then increasing towards a steady state as time increases. As one of the main variables in HIV dynamics, the $CD4^+$ T cells initially decreases quickly, due the increase of virus in the body; but their numbers gradually recovers fluctuating towards a steady state. Along with these two immune elements, the number of $CD^{*+}$ or CTL cells rapidly increases due to the present of HIV, but then decreases to a steady state for the rest of the infected period. In sync with the viral load, T cells and CTL cells, the level of the B cells initially rapidly increases; however, in a few days, their level decreases to a certain level and to a steady state. This demonstrates the effectiveness of the B cells suppressing the viral load at the beginning of the infection; then decreasing and maintaining a level where its affects still remains as the viral load increases. In addition to these graphs, we also considered the progression of the infection with respect to T cells, B cells and log of the viral load in Figure 5.

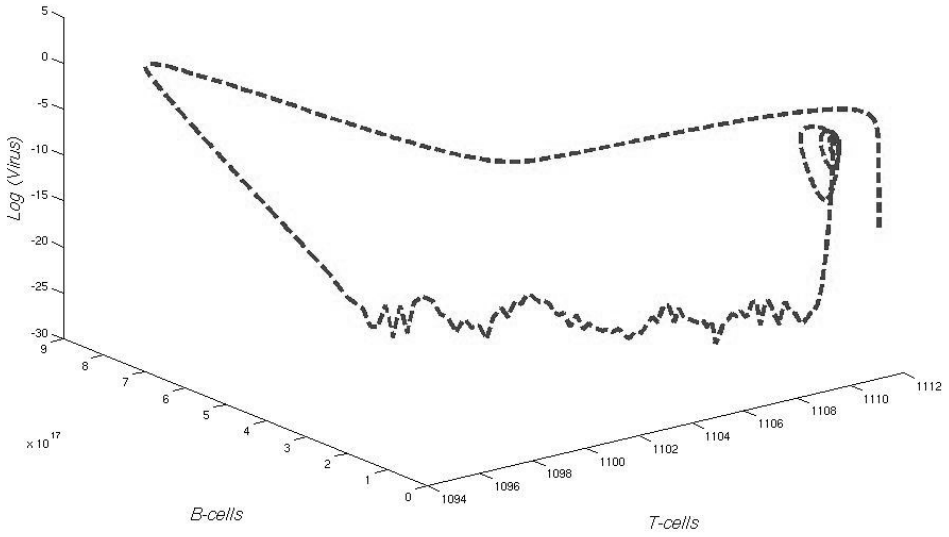


Figure 5: The simulation of the simplified model describing dynamics between the T cells, B cells and the log(viral load) using various parameters seen in Table 4.

In Figure 5, we are able to see these three variable fluctuating over time towards a steady state, thus illustrating the effects of HIV dynamics. In the acute phase of the infection, the dynamics of the T cells, B cells, and CTL cells demonstrates their reliance on one another in order to eliminate as much of the virus before they can reproduce. Especially seen in the B cells, we could see the population of B cells is dependent on the level of BAFF in order to increase its population and produce antibodies to fight off the infection. However, the affects of the B cell wears down as the viral load begins to decrease, concluding the cells have become dysfunctional. As one of the most interesting properties of BAFF is its ability to preferentially increase autoantibody levels, which at abnormally high levels, causes the dysfunction of B cells and the progression of HIV. Though BAFF seems to play a crucial role in both B cell activation and autoantibody production in HIV infection, the case is far from closed. What leads to the increased levels of BAFF in the blood stream? May be BAFF doesn't lead to production of B cells, but follows it. If HIV or autoimmunity were generating B cells through some other mechanism, the body would need to raise the level of BAFF to support the population. There is evidence to suggests that HIV, utilizing unknown mechanisms, activates B cell non-specfically leading to a reduction in the memory B cell response, while at the same time increasing autoantibody levels out of proportion with the observed increase in total antibody levels.

# 7 Conclusion

Despite the numerous significant advancements in the research of the Human Immunodeficiency Virus (HIV), much still needs to be known about virus and its interaction with the immune system in order to develop an adequate treatment and/or vaccine, which has been proven as a difficult obstacle. To study the dynamics of the virus, one must examine *whole* immune systems and its components, not just its main targets (i.e. $CD4^+$ T cells). For reasons not fully known, patients with HIV show a relatively high rate of autoimmune disease and as a result, the B cells usually show signs of abnormal activation, thus leading to a population of dysfunctional B cells. In this paper, we proposed two mathematical models to

showcase the immune system's dependence on B cells during the infection and to investigate the affects of the hormone BAFF towards autoantibody production creating a dysfunctional B cell population and its influence to the progression of HIV.

The models suggests that the hormone BAFF *does* play a crucial role in both B cell activation and autoantibody production in HIV infection. For a certain amount of time, BAFF, and other factors, are able to hold the number of infected cells at a very low level; however, at a certain time, the affects of the hormone wears off and the growth rate of infected cells rapidly increases. This illustrates the immune system's dependency on the B cells to fight of the infection, however, with the excess of antibodies in the body B cells are improperly activated thus creating a population of dysfunctional B cells, which leads to the progression and persistence of HIV in the body and the death of many. For future experiments towards the development of treatments and/or vaccines and mathematical models, consideration of B cells should also be observed as an important component in the fight against HIV.

For future work, we would like to do more mathematical analysis to further support this hypothesis. We would also like to model the same problem using delay differential equations to consider the effects of time delay in the HIV infection to get a better understanding of this interesting story. In addition, we would so like to consider the affects of nutrition deficiency and its affects on the infection. Hopefully in considering such topics as these we could suggest ways to eradicate this disease.

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## Appendix

## A Appendix

To determine the correlation between $R_0$ and the level of B cells the following calculation was necessary

$$R_0 = \frac{d_2 N_T \lambda \beta \delta}{d_1 d_3 (k\phi + d_2\delta)} \qquad B_{threshold} = \frac{\beta N_T \hat{T} - d_3}{c}$$

$$\begin{aligned} \frac{B_{threshold}}{d_3 c} &= \frac{\beta N_T \lambda}{d_1 d_3} - 1 \\ \frac{B_{threshold}}{d_3 c} + 1 &= \frac{\beta N_T \lambda}{d_1 d_3} \\ R_0 &= \frac{d_2}{k_2\phi + d_2\delta} \left( \frac{B_{threshold}}{d_3 c} + 1 \right) \end{aligned}$$

Here we are able to see there is the level of B cells do influence the basic reproduction rate.

# B Appendix

To derive the coexistence equilibrium we set (12), (13), (14), (15), (16) equal to zero and solve for each variable. From equation (16) we can solve for $V^*$ as follows:

$$\begin{aligned} \dot{B} &= b_{aff}VB - d_4B &&= 0 \\ b_{aff}VB &&&= d_4B \\ V^* &&&= \tfrac{d_4}{b_{aff}} \end{aligned}$$

Next we will solve for $T^*$ from (12)

$$\begin{aligned} \dot{T} &= \lambda - \beta VT - d_1T &&= 0 \\ \lambda &&&= T(\beta V - d_1) \\ T^* &&&= \tfrac{\lambda}{\beta V^* + d_1} \\ T^* &&&= \tfrac{\lambda b_{aff}}{\beta d_4 + d_1 b_{aff}} \end{aligned}$$

Now we will solve for $E^*$ from equation (13)

$$\begin{aligned} \dot{E} &= \phi + \tfrac{b_E I}{I+K_b}E - \tfrac{d_E I}{I+K_d}E - d_2E &&= 0 \\ \phi &&&= E(\tfrac{d_E I}{I+K_d} - \tfrac{b_E I}{I+K_b} + d_2) \\ E^* &&&= \tfrac{\phi}{\frac{d_E I}{I+K_d} - \frac{b_E I}{I+K_b} + d_2} \end{aligned}$$

To find $B^*$ we solve equation (15) as follows

$$\begin{aligned} \dot{V} &= N_T\delta I - cBV - d_3V &&= 0 \\ N_T\delta I &&&= V(cB + d_3) \\ B^* &&&= \tfrac{N_T\delta}{cV^*}I - \tfrac{d_3}{c} \\ B^* &&&= \tfrac{N_T\delta b_{aff}}{cd_4}I - \tfrac{d_3}{c} \end{aligned}$$

To find the $I$ component of the equilibrium, we set (14) equal to zero and solve as follows:

$$\begin{aligned} \dot{I} = \beta VT - kEI - \delta I &= 0 \\ \dot{I} = \beta V^*T^* - kE^*I - \delta I &= 0 \\ 0 &= \beta\tfrac{d_4}{b_{aff}} \cdot \tfrac{\lambda b_{aff}}{\beta d_4 + d_1 b_{aff}} - k\tfrac{\phi}{\frac{d_E I}{I+K_d} - \frac{b_E I}{I+K_b} + d_2}I - \delta I \\ 0 &= \tfrac{\lambda\beta d_4}{\beta d_4 + d_1 b_{aff}} - \tfrac{k\phi I}{\frac{d_E I}{I+K_d} - \frac{b_E I}{I+K_b} + d_2} - \delta I \\ Let\ \ \Psi &= \tfrac{\lambda\beta d_4}{\beta d_4 + d_1 b_{aff}} \\ then\ \ 0 &= \Psi - \tfrac{k\phi I}{\frac{d_E I}{I+K_d} - \frac{b_E I}{I+K_b} + d_2} - \delta I \\ \Psi - \delta I &= \tfrac{I^3(k\phi) + I^2(k\phi K_b + k\phi K_d) + I(k\phi K_b K_d)}{I^2(d_E - b_E + d_2) + I(d_E K_b - b_E K_d + d_2 K_b + d_2 K_d) + K_b K_d d_2} \\ I^3(k\phi) + I^2(k\phi K_b + k\phi K_d) + I(k\phi K_b K_d) &= (\Psi - \delta I)[I^2(d_E - b_E + d_2) + I(d_E K_b - b_E K_d + d_2 K_b + d_2 K_d) + K_b K_d d_2] \\ 0 &= I^3[\delta(b_E - d_E - d_2) - k\phi] + I^2[\Psi(d_E - b_E + d_2) - \delta(d_E K_b - b_E K_d + d_2 K_b + d_2 K_d) - \\ &\quad k\phi(K_b + K_d)] + I[\Psi(d_E K_b - b_E K_d + d_2 K_b + d_2 K_d) - K_b K_d(\delta d_2 + k\phi)] + \Psi K_b K_d d_2 \\ 0 &= AI^3 + BI^2 + CI + D \end{aligned}$$

*where*

$$
\begin{aligned}
A &= \delta(b_E - d_E - d_2) - k\phi, \\
B &= \Psi(d_E - b_E + d_2) - \delta(d_E K_b - b_E K_d + d_2 K_d + d_2 K_b) - k\phi(K_b + K_d), \\
C &= \Psi(d_E K_b - b_E K_d + d_2 K_d + d_2 K_b) - K_b K_d(\delta d_2 - k\phi), \\
D &= \Psi(d_2 K_b K_d), \\
\Psi &= \tfrac{\lambda\beta d_4}{\beta d_4 + d_1 b_{aff}}.
\end{aligned}
$$

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