Evaluating the B-cell density with various activation functions using White Noise Path Integral Approach

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Abstract. A The White Noise Path Integral Approach is used in evaluating the B-cell density or the number of B-cell per unit volume for a basic type of immune system response based on the modeling done by Perelson and Wiegel. From the scaling principles of Perelson [1], the B-cell density is obtained where antigens and antibodies mutate and activation function \( f(|S-SA|) \) is defined describing the interaction between a specific antigen and a B-cell. If the activation function \( f(|S-SA|) \) is held constant, the major form of the B-cell density evaluated using white noise analysis is similar to the form of the B-cell density obtained by Perelson and Wiegel using a differential approach. A piecewise linear function is also used to describe the activation \( f(|S-SA|) \). If \( f(|S-SA|) = 0 \), the density decreases exponentially. If \( f(|S-SA|) = S-SA-SB \), the B-cell density increases exponentially until it reaches a certain maximum value. For \( f(|S-SA|) = 2SA-SB-S \), the behavior of B-cell density is oscillating and remains to be in small values.

1. Introduction

Since the proposal of an immune network by Jerne in 1955 [3], various attempts have been made to interpret the behavior of the immune system by studying the collective dynamical properties of interacting cellular or molecular species. Deducing macroscopic properties of the immune system from the properties and interactions among elementary components has a similar purpose to that of statistical mechanics [2]. Thus, results in statistical physics describing a large number of interacting particles can now be applied in immunology. Stochasticity is also a dominating phenomenon in immune system. For instance, T and B cell receptors are assembled by a random combination of germ-line genes during the differentiation of hematopoietic stem cells [3]. Therefore mathematical models of immune response inevitable will be stochastic models.

The white noise theory was develop by Takeyuki Hida in 1975 [4] as a novel approach to infinite dimensional analysis. The white noise analysis is an advance stochastic calculus that has been developed extensively for the last three decades. The basic idea in white noise theory was to take a collection of infinitely many independent random variables \( \omega \) and treat this as a coordinate system of an infinite dimensional space [5]. White noise theory analysis is often used as a tool in evaluating the Feynman Path Integral, in quantum mechanical system and in problems related to protein folding, (i.e. [6]) stochastic neurodynamics (i.e. [7]), and polymer science [8,9] among others.

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This study presents calculation of the B-cell density or the number of B-cells per volume using White Noise analysis. The B-cell density represents the population of B-cells at a certain time after it has encountered foreign pathogens. We use as a starting point the model and design principles for immune system recognition done by Perelson and Wiegel [1].

2. A short review on some design principles for antibody-antigen mutations

During an immune response, many B cells will mutate their antigen-binding receptor. As a result, a clone of identical cells will proliferate into a large number of different points in shape space. The shape space is a conceptual and computational framework to view antibody-antigen affinity and its resultant consequences. It is a linear space of all possible sequences of $S_1$, $S_2$, $S_3$, ..., $S_n$, such that, each antibody is characterized by a specific point in S, which is called the shape [1]. The immune response phenomenon is modeled by the Brownian motion or diffusion in shape space. However, in order to escape immune detection, many antigens will also mutate. There are interesting examples, like the trypanosomes causing African sleeping sickness [11], and the HIV virus [12,14] in which the organisms have the ability to change their surface proteins (antigens). Previous modeling of Perelson et al. have the following assumptions for the mutation of antigens [1].

In the modeling of mutations of antigens, it is assumed that the shape $S_A(t)$ of the binding site of a new antigen $A$ at time $t$ is a linear function of time

$$S_A(t) = S_A(0) + v_A t$$

where $S_A(0)$ corresponds to the shape of antigen at time $t = 0$. It is assumed that the shape space of the antigens runs through n-dimensional shape space with a constant velocity $v_A$. The assumption of an antigen moving in a straight-line motion may not be realistic. However, from the point of view of antigen survival, the fastest way to move far from some antibody vicinity is to move in straight line mutations.

Let $b(S_B, t)$ denote the density in shape space of B-cells with shape $S_B$ at time $t$ that have been stimulated by the antigen and stimulated B-cells proliferate at per capita rate $c(S,t)$. Assuming that all the stimulated cells divide at the same constant rate $c$, we have,

$$c(S_B, t) = c.$$  \hspace{1cm} (2.2)

B-cells death is represented by $d(S_B, t)b(S_B, t)$ where $d(S_B, t)$ is the rate of cell death. Within the germinal centers, the location in the body in which most somatic mutation occurs, dividing the B cells appear to be programmed to die [1]. However, they are rescued from dying in an affinity – dependent fashion. Therefore, cells that mutate to be closer in shape space to the antigen are preferably spared from death which gives the following equation

$$d(S_B, t) = d - f(|S_B - S_A|)$$

where $d$ is a constant and the function $f$ increases when the distance $|S_B - S_A|$ is shape space between the particular B-cell and the antigen decreases. Lastly, stimulated B-cells also mutates in shape space which leads to the term $+D \Delta b$, where $D$ is the diffusion coefficient and $\Delta$, the Laplace operator.

Summing up all the cases, Eq. (2.9) represents the mutation of antigens in shape space

$$\frac{\partial b}{\partial t} = D \Delta b + \{ f | S - S_A | - d_o \} b$$

where $d_o = d - c$ and the path integral form of Eq. (2.4) is given by [1]
In ref. [1], Eqn. (2.4), the number, $N_B(t)$, of B-cells was computed for shapes located inside a sphere of radius $\epsilon_1$ around the point that represents the shape of the antigen at time $t$:

$$N_B(t) = \frac{2\pi^{n/2}}{n\Gamma(n/2)} e^{\epsilon_1 b(S_A(t),t)}$$

(2.6)

where the asymptotic behavior of $b(S_A(t),t)$ is given by

$$b(S_A(t),t) \equiv (\text{constant}) \exp \left[ \left( f(0) - d_s \frac{v_s^2}{4D} \right) t \right]$$

(2.7)

3. The White Noise Analysis

White noise calculus was introduced by Hida [4] in 1978 as a novel approach to infinite dimensional analysis and a tool in evaluating the Feynman Path Integral. The basic idea was to take the collection of infinitely many independent random variables, $\{\omega(t); t \in R\}$, and treat this as the coordinate system of infinite dimensional space. The following table shows the correspondence between the finite-dimensional and infinite-dimensional cases [4].

| FINITE DIMENSIONS | INFINITE DIMENSIONS |
|-------------------|---------------------|
| Independent variable: $x_j$ | Independent random variable: $\omega(t)$ |
| Coordinate system: $(x_1, \ldots, x_n)$ | Coordinate System: $\omega(t); t \in R$ |
| Function: $f(x_1, \ldots, x_n)$ | Functional: $\Phi(\omega(t); t \in R)$ |
| Space: $R^n$ | Space of tempered distributions: $S^*$ |
| Lebesgue measure: $dx$ | Gaussian measure: $d\mu(\omega)$ |

3.1. The $T$- and $S$-transform

Each white noise functional is determined by its T-transform defined by [4],

$$T\Phi(\xi) = \int_\xi \exp( i < \omega, \xi > ) \Phi(\omega)d\mu(\omega)$$

(3.1)

which is like a fourier transform analogue in infinite-dimensions. The Gaussian measure $d\mu(\omega)$ has the form

$$d\mu(\omega) = N_\omega \exp \left( -\frac{1}{2} \int \omega(\tau)^2 d\tau \right) d^n\omega$$

(3.2)

The exponential in $d\mu(\omega)$ is responsible for the Gaussian fall-off [4] and the $N_\omega$ is a normalization factor. In order to have correspondence

$$Nd^n\omega \rightarrow N_\omega d^n\omega = \exp \left( \frac{1}{2} \int \omega(\tau)^2 d\tau \right) d\mu(\omega)$$

(3.3)
S-transform is defined as
\[
S\Phi(\xi) = \exp\left(-\frac{1}{2} \|\xi\|^2\right) \int \exp(<\omega, \xi>) \Phi(\omega) d\mu(\omega)
\] (3.4)
which can also be written in terms of the T-transform as
\[
S\Phi(\xi) = C(\xi) T\Phi(-i\xi)
\] (3.5)
and
\[
T\Phi(\xi) = C(\xi) S\Phi(i\xi)
\] (3.6)

4. B-cell density in immune response: a white noise functional approach

4.1. \(f(|S-SA|)\) is a constant term

The activation function \(f(|SB-SA|)\) defines the degree of activation for the B cell population. It is written in the form \(f(h)\) where \(h\), which is referred as the external field, is the total stimulation that the B-cell population receives from all the other B cell populations in shape space.

The path of the mutating antibodies in shape space is given as [1],
\[
S_b(\tau) = S_A + \sigma(\tau)
\] (4.1)
where \(S_A\) is the position of the antigen and \(\sigma\) is the difference between the position of the B cell and antigen in shape space. Taking the derivative of \(S_b\) with respect to \(\tau\), we obtain;
\[
\frac{dS_b}{d\tau} = v_A + \frac{d\sigma}{d\tau} = \left(v_A + \frac{d\sigma}{d\tau}\right)^2 = \left(2v_A + \frac{d\sigma}{d\tau}\right)
\] (4.2)

With Eq. (4.2), the integrand in (2.5) becomes
\[
\exp\left[-\frac{1}{4D}\int_0^\tau \left(\frac{d\sigma}{d\tau}\right)^2 + 2v_A \frac{d\sigma}{d\tau} + v_A \right] d\tau + \int_0^\tau \omega(\tau) d\tau
\] (4.3)
where \(f(\sigma) = f(|S_B-S_A|)\). We write Eq. (4.3) into the language of white noise through the white noise variable \(\omega\) and is given by
\[
\sigma(\tau) = \sigma_0 - v_A \tau + 2\sqrt{D} \int_0^\tau \omega(\tau) d\tau
\] (4.4)
where the velocity is
\[
\frac{d\sigma(\tau)}{d\tau} = -v_A + 2\sqrt{D} \omega(\tau)
\] (4.5)
Expressing Eq. (4.3) in terms of Eqs. (4.4) and (4.5), the density equation now becomes
\[
b(S_B, t) = \int \exp\left[-\frac{1}{4D}\left(4D\omega(\tau)^2 - 4v_A \sqrt{D}\omega(\tau) + v_A \right) \right] d\tau
\times \exp\left[\int_0^\tau (f(\sigma) - d_0) d\tau + \frac{1}{2} \int_0^\tau \omega(\tau)^2 d\tau \right] d\tau
\] (4.7)

To facilitate the detection of antigens, we fixed the endpoints by introducing a Donsker Delta function from position \(S_B\), the position of antibodies, to \(S_A\), the position of antigens, at a final time \(t\) and expressing it in its Fourier transform, we have
\[
\delta(S_B - S_A) = \frac{1}{2\pi} \int_{-\infty}^{\infty} \exp(i\lambda(S_0 - v_A t + 2\sqrt{D} \int_0^\tau \omega(\tau) d\tau)) d\tau
\] (4.8)
Now, Eq. (4.7) is now written as

\[ b(S, t) = \frac{1}{2\pi} \int_{-\infty}^{\infty} d\lambda \exp(\sigma_0 - \nu_a t + \int_0^t (f(\sigma) - d_0) d\tau \times \]

\[ \int \exp \left( \int_0^t - \frac{1}{2} \omega(\tau)^2 d\tau \right) \exp \left( i\lambda (2\sqrt{D} \int_0^t \omega(\tau) d\tau \right) d\mu(\omega) \]

\[ \tag{4.9} \]

If we let \( I_0 = \exp \left( \int_0^t - \frac{1}{2} \omega(\tau)^2 d\tau \right) \), then the integral with respect to \( d\mu(\omega) \) in Eq. (4.9) is equivalent to the T-transform of \( I_0 \), thus,

\[ TI_0 = \int \exp \left( \int_0^t \omega(\tau) \xi d\tau \right) I_0 d\mu(\omega) = \exp \left( -\frac{1}{4} \int_0^t \xi^2 d\tau \right) \]

\[ \tag{4.10} \]

where \( \xi = 2\lambda \sqrt{D} \), hence the B cell density is now

\[ b(s, t) = \frac{1}{2\pi} \int_{-\infty}^{\infty} d\lambda \exp \left( i\lambda (\sigma_0 - \nu_a t) + \int_0^t (f(\sigma) - d_0) d\tau \right) \times \int_0^t \omega(\tau) \xi d\tau \]

\[ = \frac{1}{2\pi} \int_{-\infty}^{\infty} d\lambda \exp \left( i\lambda (\sigma_0 - \nu_a t) + \int_0^t (f(\sigma) - d_0) d\tau \right) \times \exp \left( -\frac{1}{4} \int_0^t \xi^2 d\tau \right) d\lambda \]

\[ \tag{4.11} \]

Now, provided that \( t \) is large and value of \( \sigma_0 \) is fixed \([1]\), we have

\[ \int_0^t (f(\sigma) - d_0) d\tau \approx (f(0) - d_0) t \]

\[ \tag{4.12} \]

with Eqs. (4.12), the B-cell density is now given as

\[ b(S, t) = \frac{1}{2\pi} \int_{-\infty}^{\infty} d\lambda \exp \left( i\lambda (\sigma_0 - \nu_a t) + (f(0) - d_0) t \right) \times \exp \left( -D \lambda^2 t \right) d\lambda \]

\[ = \frac{1}{2\pi} \int_{-\infty}^{\infty} \exp \left( -D \lambda^2 t + i\lambda (\sigma_0 - \nu_a t) + (f(0) - d_0) t \right) d\lambda \]

\[ \tag{4.13} \]

To evaluate Eq. (4.13), we use the Gaussian integral given by \([10]\)

\[ \int_{-\infty}^{\infty} \exp \left( -ax^2 + bx + c \right) dx = \frac{\pi}{\sqrt{a}} \exp \left( \frac{b^2}{4a} + c \right) \]

\[ \tag{4.14} \]

where \( a, b \) and \( c \) are constants. Using Eq. (4.14), we obtain the form of the B-cell density as

\[ b(S, t) = \frac{1}{4\pi D t} \exp \left( -\frac{(\sigma_0 - \nu_a t)^2}{4D t} + (f(0) - d_0) t \right) \]

\[ = \frac{1}{4\pi D t} \exp \left( -\frac{\sigma_0^2}{4D t} + (S'_{b0} - S'_{d0}) - \frac{\nu_a^2}{4D} t + (f(0) - d_0) t \right) \]

\[ \tag{4.15} \]

\[ = C \exp \left( (f(0) - d_0 - \frac{\nu_a^2}{4D}) t \right) \]

where the constant term \( C \) is

\[ C = \frac{1}{4\pi D t} \exp \left( \frac{\nu_a^2}{2D} (S'_{b0} - S'_{d0}) - \frac{\sigma_0^2}{4D} \right) \]

\[ \tag{4.16} \]

We note that given in Eq. (4.15), the B-cell density has the same form with that obtained by Perelson and Wiegel using differential approach \([2]\).
In Figure 1, the minimal density of the B cells which settled asymptotically from 0, the plot exponentially increased (B cells 1 and B cells 2). When the velocity is changed from 10 to $v_A = 0.025$, the B cell density still increases exponentially. However, the density for the B cells 1 with $v_A = 10$ has slower increase when compared to the B cell density of B cells 2 with $v_A = 0.025$. A smaller value of the linear velocity of antigens indicates a rapid increase of the B cells since B cells are being activated easily when the antigen is within reach. Antigens that moves slower and too close to antibodies would be quickly recognized and eliminated [8]. Thus, the antigen would move away from regions of high B cell density, and in the extreme case one might envision this as a straight line movement. Fast moving antigens are harder to detect in the shape space by the B cells, where proliferation depends on the activation of the population of B cells. After staying of the mutated antigens in the vicinity of the shape space, the B cells detect these antigens and then activate. Soon after it activate, B cells then proliferate. By the time high-affinity antibodies are generated, the antigens are soon eliminated [8].

4.2. $f(\sigma)$ is a piecewise linear function

Now we consider the case for the B-cell density when we use a piecewise non-negative linear function for the $f(\sigma)$, which is divided into four regions with a stimulatory and suppressive part. Within the stimulatory part, increasing the field will increase the proliferation rate and within the suppressive part, increasing the field decreases proliferation [7].
The four regions of the piecewise linear functions are given as:

$$f(\sigma) = \begin{cases} 0 & \text{if } \sigma \leq S_B \\ \sigma - S_B & \text{if } S_B < \sigma \leq \frac{S_A}{2} \\ S_A - S_B - \sigma & \text{if } \frac{S_A}{2} < \sigma \leq S_A - S_B \\ 0 & \text{if } \sigma > S_A - S_B \end{cases}$$

where $\sigma = S(t) - S_A$. The piecewise linear function incorporates both stimulatory and suppressive part. Within the stimulatory part increasing the field $f(\sigma)$ increases proliferation and within the suppressive part increasing the field decreases proliferation [4].

4.2.1. Piecewise Linear function with $f(\sigma) = 0$

The stimulated B-cells proliferate, divide with the same constant rate and mutates with a diffusion coefficient D. The B-cell density is given by

$$b(S,t) = \int_{S_A}^{S_B} \exp \left[ -\frac{1}{4} \int_0^t \left( \frac{dS}{d\tau} \right)^2 d\tau - \int_0^t \{d_s\} d\tau \right] d[S(\tau)]$$

(4.17)

We parametrize the path $S(t)$ of a particle, which starts from an initial point $S_0$ in terms of the Brownian motion $B(t)$ such that

$$S(t) = S_0 + 2\sqrt{D} \int_0^t \omega(\tau) d\tau$$

(4.18)

where the velocity is given by

$$\frac{dS}{dt} = 2\sqrt{D} \omega(\tau)$$

(4.19)

The integration over all paths ($\lim_{N\to\infty} \prod d[S_j]$ or $d^\infty S$) leads to an integration over the Gaussian white noise measure $d\mu(\omega) = N_\omega \exp \left( -\frac{1}{2} \int \omega(\tau)^2 d\tau \right) d\omega$. We multiply $d\mu(\omega)$ by a factor $\exp \left( \frac{1}{2} \int \omega(\tau)^2 d\tau \right)$ to obtain the correspondence $d^\infty S \to d^\infty \omega$. The B-cell density expressed in terms of the random white noise variable $\omega(\tau)$ is now written as

$$b(S,t) = \int \exp \left[ -\frac{1}{4} \int_0^t \left( 2\sqrt{D} \omega \right)^2 d\tau - \int_0^t \{d_s\} d\tau \right] \times \exp \left( \frac{1}{2} \int_0^t \omega^2 d\tau \right) \times d\mu(\omega)$$

(4.20)

To facilitate the detection of antigens, we let the endpoints fixed by introducing a Donsker Delta function $\delta(S - S_A)$;

$$b(s,t) = \int \exp \left[ -\frac{1}{2} \int_0^t \omega^2 d\tau \right] - \int_0^t \{d_s\} d\tau \right] d\mu(\omega) \delta(S - S_A)$$

(4.21)

$$= \int e^{2\lambda} \sqrt{2\pi} \int \exp \left( i\lambda(S_B - S_A) - \int_0^t \{d_s\} d\tau \right) \times d\mu(\omega) d\lambda$$

(4.22)

where

$$\varepsilon = 2\lambda \sqrt{D}$$

(4.22)
and
\[
I_0 = \exp\left(-\frac{1}{2} \int_0^\infty \omega(\tau)^2 d\tau\right) \tag{4.23}
\]

Simplifying the above expression, we obtain the form of the density as
\[
b(s,t) = \frac{1}{2\pi} \int_{-\infty}^\infty \exp\left(i \lambda (S_B - S_A) - \int_0^t d_\omega d\lambda\right) Tl_0 d\lambda \tag{4.24}
\]

where the T-transform of the Gauss Kernel \(I_0\) is
\[
Tl_0 = \int \exp\left(i \left(\int_0^\infty \omega d\tau\right) I_0 d\mu(\omega) = \exp\left(-\frac{1}{4} \int_0^\infty e^2 d\tau\right) \right. \tag{4.25}
\]

Using the above transform and substituting it to the density equation, the B-cell density with \(f(\sigma) = 0\) is,
\[
b(s,t) = \frac{1}{2\pi} \sqrt{\frac{\pi}{D_t}} \exp\left(\frac{(S_B - S_A)^2}{4D_t} - d_\omega t\right) \tag{4.26}
\]

In Figure 3, which is the region where \(f(\sigma) = 0\), the value of the B-cell density from Equation (4.26) is graphed versus time. We choose \(S_A = 100\) and \(S_B = 10\) following the values used in reference [7], \(D = 100\), \(d_\omega = 1.0\) and \(t = 72\) which is equivalent to three days since the antigen encounter. In appendix B, several values of \(S_A, S_B, D, d_\omega\) and \(t\) are also being plotted and the same pattern is seen for all the values used. It is observed that the initial values of the B-cell density decreases in time until it reaches a stable low value.

### Table 1

| Entries | 71 |
|---------|----|
| Mean y  | 0.005702 |
| RMS x   | 19.63 |
| RMS y   | 0.0309 |

**Figure 3.** B-cell density behaviour when the activation function is \(f(\sigma) = 0\).

#### 4.2.2. Piecewise Linear function with \(f(\sigma) = S_S x S_B\)

This region is considered to be a stimulatory region in which increasing the field \(f(\sigma)\) will increase the rate of proliferation of the stimulated B-cells. The B-cell density is given by
\[
b(s,t) = \int_{S_A}^{S_B} \exp\left(-\int_0^t (S_A + S_B + d_\omega) d\tau\right) \times \exp\left[-\frac{1}{4} \int_0^t \left(\frac{dS}{d\tau}\right)^2 d\tau + \int_0^t S d\tau\right] d[S(t)] \tag{4.27}
\]
Converting it again into the language of white noise by parametrizing the path $S$ into white noise variable $\omega$:

$$s(\tau) = s_0 + 2\sqrt{D} \int_0^\tau \omega(\tau) d\tau$$

(4.28)

where the velocity is given by:

$$\frac{dS}{d\tau} = 2\sqrt{D} \omega(\tau)$$

(4.29)

and

$$d[s(\tau)] = N_\omega d^\omega \omega = \exp\left(\frac{1}{2} \int_0^\tau \omega(\tau)^2 d\tau \right) du(\omega)$$

(4.30)

the B-cell density equation has the form,

$$b(s, t) = \int \exp\left(-\int_0^t (S_\alpha + d_\alpha) dt\right) \times \exp\left(-\int_0^\tau \int_0^\tau \omega(\tau)^2 d\tau + \int_0^\tau \left(2\sqrt{D} \int_0^\tau \omega d\tau \right) d\mu(\omega)\right)$$

(4.31)

To fixed the endpoints for the antigen detection, we introduced a Donsker-delta function $\delta(S - S_\alpha)$

$$b(s, t) = \int S_\alpha^\omega \exp\left(-\int_0^t (S_\alpha + d_\alpha) dt\right) \times \exp\left(-\int_0^\tau \int_0^\tau \omega(\tau)^2 d\tau + \int_0^\tau \left(2\sqrt{D} \int_0^\tau \omega d\tau \right) d\mu(\omega)\right) \times \delta(S - S_\alpha)$$

(4.32)

$$= \frac{1}{2\pi} \int S_\alpha^\omega \exp\left(i\lambda(S_\alpha - S_\alpha) - \int_0^t (S_\alpha + d_\alpha) dt\right) \times \exp\left(-\int_0^\tau \int_0^\tau \omega(\tau)^2 d\tau\right) \times \exp\left(\int_0^\tau \left(2\sqrt{D} \int_0^\tau \omega d\tau \right) d\tau + i\lambda 2\sqrt{D} \int_0^\tau \omega d\tau \right) d\mu(\omega) d\lambda$$

In order to simply the integral, we used the following relationship

$$\int\left(2\sqrt{D} \int_0^\tau \omega d\tau \right) d\tau = 2\sqrt{D} \int B(\tau) d\tau$$

$$= 2\sqrt{D} (B(t) - B(0)) = 2\sqrt{D}\left(\int_0^t \omega(\tau) d\tau - \int_0^0 \omega(0) dt\right)$$

(4.33)

$$\approx 2\sqrt{D}\int_0^t \omega d\tau$$

Thus, the density would now be written as:

$$b(s, t) = \frac{1}{2\pi} \int S_\alpha^\omega \exp\left(i\lambda(S_\alpha - S_\alpha) - \int_0^t (S_\alpha + d_\alpha) dt\right) \times \exp\left(-\int_0^\tau \int_0^\tau \omega(\tau)^2 d\tau\right) \times \exp\left(\int_0^\tau \left(2\sqrt{D} \int_0^\tau \omega d\tau \right) d\tau + i\lambda 2\sqrt{D} \int_0^\tau \omega d\tau \right) d\mu(\omega) d\lambda$$

(4.34)

The T-transform gives,

$$TI_0 = \exp\left(-\int_0^\tau \omega d\tau \right) I_0 d\mu(\omega) = \exp\left(-\int_0^\tau e^\tau d\tau\right) = \exp\left(-\frac{1}{4} e^{\tau} t\right)$$

$$= \exp\left(-\frac{1}{4} \left(2\sqrt{D} \lambda - 2i\sqrt{D}\right)^2 t\right) = \exp\left(-\frac{1}{4} \left(2\sqrt{D} \lambda - 2i\sqrt{D}\right)^2 t\right)$$

(4.35)
Thus, we have obtained the value of the density as

\[
\begin{align*}
  b(s,t) &= \frac{1}{2\pi} \int_{\infty}^{\infty} \exp\left(i\lambda(S_B - S_A) - \int_{0}^t (S_A + d_0) d\tau \right) d\lambda \\
  &= \frac{1}{2\pi} \sqrt{\frac{\pi}{Dt}} \exp\left(\frac{(S_B - S_A)^2 + 2\sqrt{D}t}{4Dt} + (D - S_A - d_0)t\right) 
\end{align*}
\]

Figure 4 shows the graph of the B-cell density in equation 4.40 versus time in hours with the field given by \( f(\sigma) = S - S_A - S_B \). The values \( S_A = 100, S_B = 10, D = 100, d_0 = 0.5 \) and \( t = 72 \) is the same as the values used in the first region. It has been observed from the graph that the B-cell density increases from up to 24 hour and then stop. The immune system produces only limited number of cells, it would be difficult for the body to produce many antibodies to pair with all the antigens encountered by the body every day. Thus, for the immune system to detect many possible antigens it must produced high-affinity antibodies from the general antibodies.

\[\text{Figure 4.} \quad \text{B-cell density behaviour when the activation function is} \quad f(\sigma) = S - S_A - S_B.\]

### 4.2.3. Piecewise Linear function with \( f(\sigma) = 2S_A - S_B - S \)

The third region represents as the suppressive region, in this region, increasing the field \( f(\sigma) = 2S_A - S_B - S \), will decrease proliferation. At longer times, the B-cell will stop mutating and will start to convert generalist antibodies to high-affinity antibodies. In this region also, the B-cell density will cease to increase its value. Following equation for the B-cell density is given by,

\[
  b(s,t) = \int_{S_A}^{S_B} \exp\left(\int_{0}^t (2S_A - S_B - d_0) d\tau \right) \times \exp\left(-\frac{1}{4} \int_{0}^t \left(\frac{dS}{d\tau}\right)^2 d\tau - \int_{0}^t S d\tau \right) d[s(\tau)] 
\]

Following the procedure done in the previous region, in white noise form is,

\[
  b(s,t) = \exp\left(\int_{0}^t (2S_A - 2S_B - d_0) d\tau \right) \times \exp\left(-\frac{1}{2} \int_{0}^t (\omega)^2 d\tau - \int_{0}^t (2\sqrt{D} \int_{0}^t \omega d\tau) d\tau \right) d\mu(\omega)
\]

Fixing the endpoints by introducing a Donsker-delta function \( \delta(S - S_A) \);
\[ b(s,t) = \int \exp \left[ \int \exp \left( \frac{1}{2} \int_0^\infty \omega^2 \, d\tau - \frac{1}{2} \int_0^\infty \exp \left( 2\sqrt{D} \int_0^\tau \omega \, d\tau \right) \right. \right. \] 
\[ \times \delta(S-S_\delta) \right. \right. \] 
\[ = \frac{1}{2\pi} \int_0^\infty \exp \left( i\lambda (S_\delta - S_\delta) - \int_0^\infty \left( 2S_\delta - 2S_\delta - d_\delta \right) d\tau \right) \] 
\[ \times \exp \left( -\frac{1}{4} \int_0^\infty \omega^2 \, d\tau \right) \times \exp \left( -2\sqrt{D} \int_0^\tau \omega \, d\tau + i\lambda \sqrt{D} \int_0^\tau \omega \, d\tau \right) \right. \right. \] 
\[ \left. \left. \int_0^\infty \delta(S-S_\delta) \right) \right. \right. \] 
\[ = \frac{1}{2\pi} \int_0^\infty \exp \left( i\lambda (S_\delta - S_\delta) - \int_0^\infty \left( 2S_\delta - 2S_\delta - d_\delta \right) d\tau \right) \int_0^\infty \delta(S-S_\delta) \] 
\[ \text{where the T-transform of } b_0 \text{ is given by;} \] 
\[ TI_0 = \int \exp \left( i \left( \int_0^\infty \omega \, d\tau \right) \right) I_0 \, d\mu(\omega) = \exp \left( -\frac{1}{4} \int_0^\infty e^2 \, d\tau \right) \] 
\[ = \exp \left( -\frac{1}{4} \left( i2\sqrt{D} + 2\lambda \sqrt{D} \right)^2 t \right) \] 
\[ = \exp \left( -\frac{1}{4} \left( i2\sqrt{D} + 2\lambda \sqrt{D} \right)^2 t \right) \] 
\[ \text{So, the density is now written as;} \] 
\[ b(s,t) = \frac{1}{2\pi} \int_0^\infty \exp \left( i\lambda (S_\delta - S_\delta) + \int_0^\infty \left( 2S_\delta - 2S_\delta - d_\delta \right) d\tau \right) \int_0^\infty \delta(S-S_\delta) \] 
\[ = \frac{1}{2\pi} \sqrt{\frac{\pi}{Dt}} \exp \left( \frac{(S_\delta - S_\delta)^2 - 2\sqrt{D} \int_0^\infty \omega \, d\tau}{4Dt} \right) \] 
\[ \left. \left. + (2S_\delta - 2S_\delta + d_\delta - D)t \right) \right. \right. \] 
\[ \text{In this region as stated in [3], increasing the activation function should decrease the proliferation rate, however, the behavior of Eq.(4.41) shows an oscillating behavior. Verification from other studies are being done however as suggested in [2], a log-bell shape should be used for the activation function.} \] 

5. Summary and Recommendations

This study is an approach of using white noise theory in evaluating the B-cell density based from the immune response modeling of Perelson and Wiegel. In the framework of white noise analysis, when the activation is held constant, a somehow similar form is observe but with slight difference in the constant. We also used a piecewise linear function to define the B-cell density and its proliferation behavior. An increase in the B-cell density is observed in the second region since it is believed that in this region, B-cell should proliferate. The piecewise linear function is only a useful mathematical approximation of the B-cell density. However, there are features that are a bit unrealistic, thus, a more appropriate log-bell shape functions should be used in future studies.

6. References

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