Numerical Study of the Immune Response to Viral Infections with Self-Similar Epitopes

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We use a simple (bit string) model of B-cell clonal specificity to explore the immune response to evolving strains of viruses. We focus on those antigen epitopes that are believed to be similar to the immune system self antigens. The B-cell receptors are edited such that they tolerate self. We study the frequency of receptors which actively interact with the antigen epitopes of the virus. Then, we investigate the development and maturation of these selected B-cells and their influence on decreasing the viral load.

***Keywords* — HIV infection, B-cells, immune response, self-similar epitopes, antigen receptors, auto-immunity, receptor editing, numerical modeling.**

Unsuccessful efforts to induce immunity to fast mutating viral infections, encourages investigation of new vaccination approaches. Examples of such viral infections are HIV and influenza. The development of a completely effective vaccine requires broadly neutralizing antibodies that react with the diverse strains of the virus. It has been observed that a number of these viruses such as the virus of HIV, have epitpopes which are similar to self antigens. Specially, recent studies have revealed the properties of anti-HIV antibodies expressed by HIV infected patients [1]. Interestingly it has been found that these antibodies are polyreactive and bind with low affinity to self-antigens such as cardiolipin. It is hypothesized that the auto-reactivity of these anti HIV antibodies prevents them from acting effectively by the same mechanism that self antigens are tolerated by the immune system. Therefore, making a vaccination strategy for these types of virus antigens is very difficult.

To investigate the humoral immune response to antigens which have self similar epitopes, we study a simplified numerical model. Adaptive immune responses require B-cells to provide antibody. B-cells recognize antigens via antigen receptors displayed on the cell surface. These receptors are composed of two distinct polypeptide chains (light and heavy chains). In our model, strings of binary variables (bits) are used to encode molecular properties of these B-cell light and heavy chain receptors. Similarly, each antigen epitope is specified by a string of binary variables [2,3]. The number of bit matches determines the strength of interaction between two molecules. The specificity of these antigen receptors should be diverse enough to perform protection against a various collection of foreign antigens [4]. Therefore, an initial configuration of a B-cell repertoire is generated randomly. In reality, this diversity is generated by a random process of gene rearrangement.

Among these randomly generated receptors, some are nonfunctional and some may interact with self, which is dangerous. In the model, similar to the real world, in order to regulate the B cell receptors specificity, the receptor genes go through a number of ongoing recombination to edit the receptors which interact strongly with predefined self antigens [5]. The antigen epitope of the virus is simulated as a combination of a highly mutating bit string and a more robust epitope which is similar to a self-antigen. We observe that the frequency of B-cell receptors interacting actively with the self similar segments of the HIV virus depends on: (i) the difference between the active interacting threshold of B-cell receptors with the self antigen and HIV's self similar antigen and (ii) the weighting factor that determines how strongly the antigens bind with the light or heavy chain of the B-cell receptor. Finally, by including B-cell antigen interaction via the influence of helper T-cells and the process, which leads to the development of antibody secreting plasma cells and memory cells, , we numerically investigate the evolutionary dynamics of the HIV viral load.

REFERENCES

[1] Haynes BF et al. (2005), Cardiolipin polyspecific autoreactivity in two broadly neutralizing HIV-1 antibodies. *Science* 308:1906-1908.

[2] Farmer J. D., Packard N. H., and Perelson A. S. (1986), The immune system, adaptation, and machine learning. *Physica* 22D: 187-204

[3] M. Bernaschi and F. Castiglione. (2001) Design and implementation of an Immune System Simulator. *Computers in Biology and Medicine*, 31(5) 303-331

[4] Cohn M. and Langman R. E. (1990), The Protecton: The Unit of Humoral Immunity Selected by Evolution. *Immunological Review* 115*:* 7-147.

[5] Nemazee D. and Weigert M. (2000), Revising B cell receptors. *J. Exp Med*.191:1813-1818.

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