A Stochastic Model of the Interleukin (IL)-1β Network

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Abstract. The interleukin-1β network is a primary mediator of the inflammatory response and plays an important role in many immunological processes. A Markov chain model of the network is presented, along with results from iteration over the stochastic matrix. The stationary distribution of the model is analysed.

Keywords: IL-1β; interleukin-1β; Markov process; cytokine network; stochastic matrix.

1 Introduction

Interleukin-1β (IL-1β) is a cytokine, a polypeptide mediator used by the immune system to communicate between cells. IL-1 has been described as the most potent and multifunctional cell activator in immunology and cell biology [8]; it plays many essential roles in the immune system. The complexity of the IL-1 network has been noted by many researchers [3], [10]. IL-1 has two forms, IL-1α and IL-1β. There are two receptors which bind IL-1. A receptor accessory protein is necessary to form a signalling complex; many inhibitory factors are part of the network. We shall examine a subset of the IL-1β network using stochastic techniques to find out whether or not a stationary distribution exists over signalling and nonsignalling states.

2 The IL-1β Network

We shall focus on the IL-1β form of IL-1. IL-1β binds to two receptors on the cell membrane, the type-I and type-II receptor: the type-I receptor can cause a signal transduction event; the type-II receptor is a decoy receptor, lacking the transmembrane apparatus to initiate a signalling event [8].

When IL-1β binds to the type-I receptor, a signalling binary complex is formed. Signal transduction does not occur, however, until a receptor accessory protein binds to the signalling binary complex, forming a signalling ternary complex.

The type-II receptor can also bind to IL-1β to form a nonsignalling binary complex. The nonsignalling binary complex can also bind the receptor accessory
protein to form a **nonsignalling ternary complex**. Thus, the type-II receptor competes both for IL-1β and the receptor accessory protein; it is a key inhibitory component in the network.

The type-I receptor is not abundant, but evokes a powerful response without a high level of receptor occupancy [2], as the receptor activates many pathways which operate in parallel. Unlike most other cytokines, it is thought that as few as ten occupied receptors are sufficient to evoke a strong response [20]. Since IL-1β typically acts at very low concentrations, the population sizes of signalling and nonsignalling complexes will be small, and random fluctuations will have a disproportionate effect. The use of stochastic methods is indicated to model such a system.

The interactions we model in this paper are as follows:

- IL-1β + type-I receptor: IL-1β associates with the signalling receptor to form a signalling binary complex
- signalling binary complex + receptor accessory protein: promotion of the receptor accessory forms a signalling ternary complex, and signalling occurs
- IL-1β + type-II receptor: IL-1β associates with the nonsignalling receptor to form a nonsignalling binary complex
- nonsignalling binary complex + receptor accessory protein: promotion of the receptor accessory forms a nonsignalling ternary complex

As in any reaction, the binding event is reversible; the complexes can both associate and dissociate. The association and dissociation rates for the binary and ternary signalling and nonsignalling complexes are given in Table 1.

We use the following notation: L is the free (unbound) IL-1β, R1 is the type-I signalling receptor, R2 is the type-II nonsignalling receptor, S is the signalling binary complex, NS is the nonsignalling binary complex, R is the receptor accessory protein, T is the signalling ternary complex, NT is the nonsignalling ternary complex. Association rates are given as $k_u^+$ for a arbitrary component $u$, and dissociation rates are $k_u^-$. In the notation of chemical reactions, the interactions are:

\[
L + R1 \xleftrightarrow{k_S^+}{k_S^-} S 
\] (1)

\[
L + R2 \xleftrightarrow{k_{NS}^+}{k_{NS}^-} NS 
\] (2)

\[
S + R \xleftrightarrow{k_T^+}{k_T^-} T 
\] (3)

\[
NS + R \xleftrightarrow{k_{NT}^+}{k_{NT}^-} NT 
\] (4)