**Signal Transduction Pathway Modeling via Block Diagrams and Transfer Functions**

Cell signaling refers to the process by which cells sense their environment, including communication with other cells. Signaling in cells is initiated by extra-cellular molecules that activate an intracellular signaling pathway, which ultimately leads to the formation of proteins involved in basic cellular processes like regulation of cell growth and division or expression of other, secreted proteins. This entire process in which biological information is transferred from extra-cellular signals into changes inside a cell is referred to as signal transduction. As malfunction of signaling pathways can be associated with some diseases, e.g., certain types of cancer, cells usually have regulatory mechanisms built into signal transduction pathways.

The system under investigation deals with signaling pathways involved in a body’s response to burn-injury-induced inflammation. The injured cells release cytokines, one of which is interleukin 6 (IL-6), to the bloodstream. These cytokines are sensed by hepatocytes in the liver, and they activate the acute phase response (APR). The acute phase response up- or down-regulates the expression of certain plasma proteins that take part in the body’s response to the burn-injury-induced inflammation. Investigating cell signaling in hepatocytes stimulated by inflammatory agents is of crucial importance to understanding the mechanisms underlying the APR.

The specific topic of this homework deals with analyzing a transfer function model of the JAK (Janus-Associated Kinases)/STAT (Signal Transducers and Activators of Transcription) signaling pathway in hepatocytes stimulated by IL-6. Signaling through the JAK/STAT pathway is regulated by SOCS3 (Suppressors Of Cytokine Signaling 3) proteins. These proteins are induced by the JAK/STAT signaling pathway once the signal emanating from the cell surface reaches the nucleus of the cell. SOCS3 regulates further signaling from the cell surface to the nucleus of the cell by inhibiting the activation of STAT3, a process that is usually taking place as a result of binding of IL-6 to the receptors on the cell surface.

You are given the Simulink model of the JAK/STAT pathway. Use this model for the following assignments:

1. Simulate an increase in the IL-6 concentration from 3E-4 nM to 3.3E-4 nM. Plot the concentration of the nuclear STAT3 dimer over time.
2. What are the steady state concentrations of the nuclear STAT3 dimer for the original stimulation (3E-4 nM) and the new stimulation (3.3E-4 nM)?
3. Determine the IL-6 concentration that is needed to reach a steady state concentration of 0.13 nM for the nuclear STAT3 dimer.
4. Now create a model of a SOCS3 knockout cell by cutting open the feedback loop. Repeat 1), 2), and 3) for the SOCS3 knockout cell model.
5. What do you conclude when you compare the IL-6 concentration needed to reach a level of 0.13 nM of the nuclear STAT3 dimer for the original model and the SOCS3 knockout model?