Model Order Reduction of Cell Signalling Pathways: An Investigation of the Invasive Mechanism of Ebola Virus

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The recent Ebola virus (EBOV) epidemic has claimed over 4000 lives in West Africa. The fatal virus suppresses the host's immune response by inhibiting IFN?-dependent p-STAT1 nuclear import by the Karyopherin transporter protein KPNA5. A comprehensive understanding of EBOV's invasive mechanism hinges on a detailed quantitative investigation of the IFN?-dependent JAK-STAT pathway. Unfortunately, the large number of dynamic variables and bimolecular interactions present in the IFN?-JAK-STAT-EVP24 network makes simulation of this pathway computationally expensive. Existing model order reduction techniques seeking to eliminate slaved species cannot be applied to this network due to the high affinity and stability of the receptor complex. This project proposes a projection-based model reduction algorithm that aims to approximate the state space of the full order system of coupled differential equations describing the molecular interaction network by lower dimensional subspaces, on which the dynamics of the original network are studied. This algorithm (executed at the command-line interface) combines the techniques of proper orthogonal decomposition, trajectory piecewise linearization, and Krylov subspace reduction in an effort to identify a best-fit subspace for the model trajectories that accurately approximates the mapping between the model input and outputs. The command-line tool effectively reduced the dimensionality of a kinetic model of the IFN?-JAK-STAT-EVP24 network from 45 to 5. In addition, implementing the algorithm revealed strong correlations within four disjoint sets of participating species, suggesting the need to monitor the concentration of only one species from each set during a computational or experimental investigation.

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