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Large Scale Dynamical Model of Macrophage/HIV Interaction for the Mathematical Analysis of Methamphetamine Emergent/Epigenetic Effects on HIV/AIDS Disease Progression

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Large-scale, complex biological systems have been shown to display emergent properties—epigenetic phenomena that arise in the dynamics of biochemical networks that are not discernable at the individual gene or protein level. To investigate the influence of methamphetamine on the emergent properties of macrophage biochemistry, we introduce a large-scale dynamical model of HIV/macrophage interaction. The model contains 713 components and 1583 edges and is simulatable in response to 38 different external inputs (growth factors, bacteria, viral soluble factors, etc.). The model correctly simulates the dynamics of over 50 different known phenomena, including molecular events associated with viral infection, endocytosis, transport, replication, budding, and cellular release. Further validation comes from mathematical analyses, including Determinative Power and Biological Essentiality, which identified components in the network with significant potential to affect both normal and infected macrophages. The components identified correlate well with known influential proteins (confirmed in the laboratory). With the model's dynamics validated in multiple ways, it now provides a platform for the discovery and investigation of emergent properties of HIV-infected macrophages and determining how those properties are affected by methamphetamine. Using a high-throughput data set we generated in the laboratory from cells with and without HIV infection and/or methamphetamine exposure, we can create model profiles that match the expression data. Using visual statistical inference (an advanced statistical method developed by an investigator in our group), we can then determine how emergent (epigenetic) properties in models that replicate HIV and/or methamphetamine exposure differ from the model that replicates normal cells.