Modeling The Spatiotemporal Distribution Of HIV Infection In The Brain

In standard clinical practice, only plasma viral load and CD4 counts are measured to keep track of disease status and progression in Human Immunodeficiency Virus (HIV)-infected individuals. However, viruses reside in the brain, causing neurocognitive disorders and an obstacle to a cure, despite virus control in plasma with antiretroviral therapy. Therefore, tracking the virus distribution across different brain compartments is essential for disease management in HIV-infected individuals. In this study, we first performed a correlation network analysis of RNA in the brain with plasma and CSF (Cerebrospinal fluid) to identify whether plasma or CSF viral loads can infer the viral burden in the brain. Secondly, we performed a correlation network analysis of viral RNA among different brain regions to identify the brain's essential regions related to viral burden within the brain. Thirdly, we built a mathematical model that explains the spatiotemporal distribution of HIV in the brain using the essential brain regions obtained from our correlation analysis. Our model was validated using data collected from the brain of the simian immunodeficiency virus (SIV)-infected macaques. We analyzed the model and performed parameter sensitivity to get insights into the distribution and replication of HIV throughout the different brain regions.

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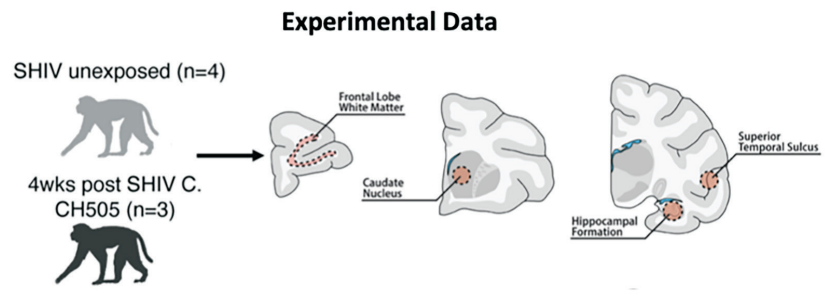


Figure: Schematic of experimental SHIV infection in the brain of rhesus macaque

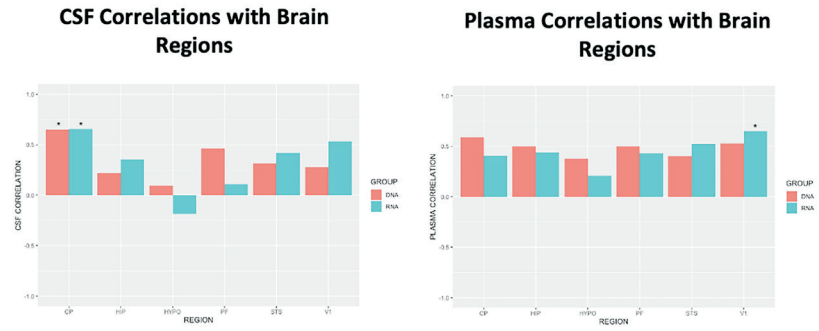


Figure: Correlations of brain regions with CSF (top) and plasma (bottom). Red indicates correlation for DNA copies and blue indicates correlations for RNA copies. * $p < 0.05$

$$\frac{M_{CP}}{dt} = \psi_3 M_{V1} + \psi_1 M_{PF} - \psi_1\psi_3 M_{CP} - \beta_3 V_{CP} M_{CP} - dM_{CP}$$

$$\frac{M^*_{CP}}{dt} = \psi_3 M^*_{V1} + \psi_1 M^*_{PF} - \psi_1\psi_3 M^*_{CP} + \beta_3 V_{CP} M_{CP} - \delta M^*_{CP}$$

$$\frac{V_{CP}}{dt} = \alpha_3 V_{V1} + \alpha_1 V_{PF} - \alpha_1\alpha_3 V_{CP} + pM^*_{CP} - cV_{CP}$$

$$\frac{M_{V1}}{dt} = \psi_3 M_{CP} + \psi_2 M_{PF} - \psi_2\psi_3 M_{V1} - \beta_2 V_{V1} M_{V1} - dM_{V1}$$

$$\frac{M^*_{V1}}{dt} = \psi_3 M^*_{CP} + \psi_2 M^*_{PF} - \psi_2\psi_3 M^*_{V1} + \beta_2 V_{V1} M_{V1} - \delta M^*_{V1}$$

$$\frac{V_{V1}}{dt} = \alpha_3 V_{CP} + \alpha_2 V_{PF} - \alpha_2\alpha_3 V_{V1} + pM^*_{V1} - cV_{V1}$$

$$\frac{M_{PF}}{dt} = \psi_1 M_{CP} + \psi_2 M_{V1} - \psi_1\psi_2 M_{PF} - \beta_1 V_{PF} M_{PF} - dM_{PF} + \omega plasma - \phi M_{PF}$$

$$\frac{M^*_{PF}}{dt} = \psi_1 M^*_{CP} + \psi_2 M^*_{V1} - \psi_1\psi_2 M^*_{PF} + \beta_1 V_{PF} M_{PF} - \delta M^*_{PF} + \omega\xi plasma - \phi M^*_{PF}$$

$$\frac{V_{PF}}{dt} = \alpha_1 V_{CP} + \alpha_2 V_{V1} - \alpha_1\alpha_2 V_{PF} + pM^*_{PF} - cV_{PF}$$

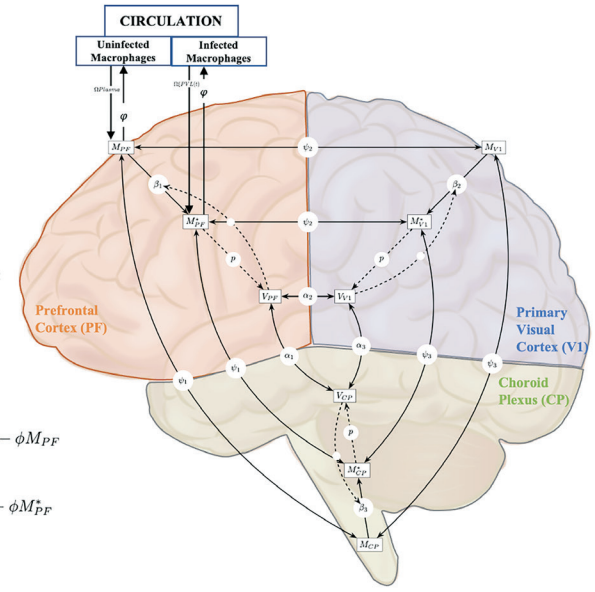
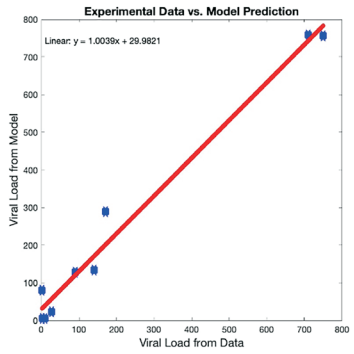


Figure: Schematic diagram of spatiotemporal dynamics of HIV infection in the brain (right) and corresponding ordinary differential equations. Three brain compartments (PF, CF, and V1) are considered based on the correlation network analysis.



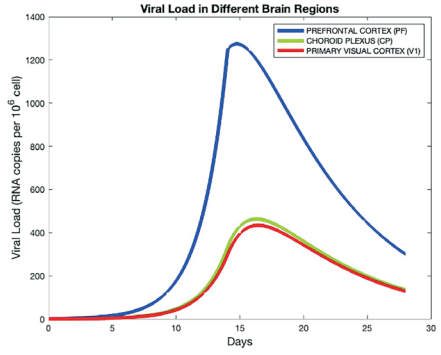


Figure: Viral load of HIV at three brain compartments of three macaques (9 data points) at week 4 post-infection from experimental data versus those predicted by our model along with a line of best fit (left), and model-predicted viral dynamics of HIV in different brain regions over a 4-week period (right).

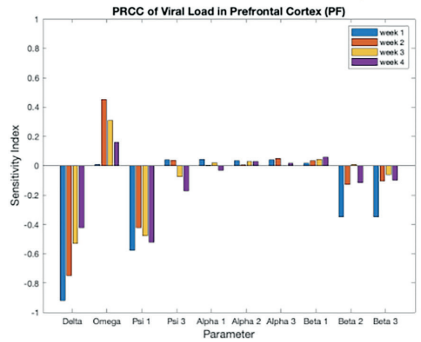


Figure: Partial rank correlation coefficients of the viral load of HIV in the prefrontal cortex (top), choroid plexus (middle), and primary visual cortex (bottom).