Temperature dependence of syncytia formation

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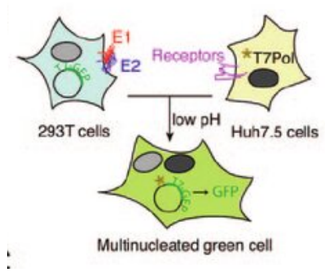
Background

- Several viruses have the ability to cause cells to fuse together into large multinucleated cells called Syncytia.
- Syncytia help the virus propagate without leaving the cell.
- Currently, it is not known how temperature affects syncytia formation rates.
- We use mathematical modeling to investigate the rate of syncytia formation in the HIV virus as temperature varies.

Cell to Cell Fusion in HIV

In the HIV virus, the viral envelope glycoprotein gp120 binds to the CD4+ receptor and a co-receptor on host cells, leading to the fusion of infected and uninfected cells to form multinucleated syncytia. This contributes to the depletion of CD4+ T cells and the weakening of the immune system.



Cell to cell fusion can be studied with a cell-cell fusion assay. In this assay, one cell expresses the envelope protein while the other expresses the cell receptor. Each cell contains part of the green fluorescent protein; when the two cells fuse, the resulting multi-nucleated cell fluoresces in green.

Mathematical model

In this model donor cells, D, bind with acceptor cells, A, and then move to fusing states F_1 and F_2. Once fused after time $1/k$, they form Syncytia S. S represents the number of cells in the syncytia not the number of syncytia. The syncytia formation rate is γ.

$$\frac{dD}{dt} = -\gamma DA$$
$$\frac{dA}{dt} = -\gamma DA - \gamma SA$$
$$\frac{dF_1}{dt} = 2\gamma DA + \gamma SA - kF_1$$
$$\frac{dF_2}{dt} = kF_1 - kF_2$$
$$\frac{dS}{dt} = kF_2$$

Data Fitting

- In our study we use data fitting to adjust the parameters of our mathematical model so the predictions from our mathematical model better align with the data.
- We assume there is 100% coverage of the experimental well so $A + D + F_1 + F_2 + S = 100\%$.
- We measure the difference between model predictions and experimental data using the sum of squared residuals or SSR,

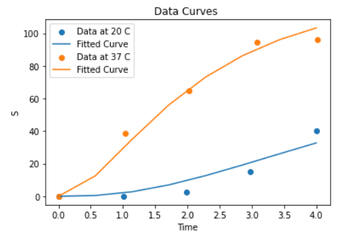
$$\text{SSR} = \sum_{i=1}^{n} (ym_i - y_i)^2,$$

where n is the number of data points, ym_i is the predicted model value, and y_i is the experimental data.

- The system of ordinary differential equations is numerically integrated using `scipy.odeint`.
- We next use the optimization algorithm `scipy.optimize.minimize` to adjust the model parameters to minimize the SSR.

Results

Data is taken from Jiang et al. (2000) Proceedings of SPIE. Experimental data and model best fit curves are shown below.



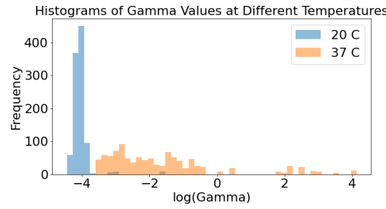
Model best fit curves are given when the following parameters are used.

Parameter	Best Fit	95% Confidence Interval
	20 °C	
γ (/h)	1.55×10^{-2}	$(1.23–4.28)\times10^{-2}$
D_0 (%)	49.7	49.7–49.7
k (/h)	0.527	0.371–0.583
	37 °C	
γ (/h)	3.02×10^{-2}	.03-18.2
D_0 (%)	5.00×10^{-2}	$(4.18–5.79)\times10^{-2}$
k (/h)	742	7.41–7.42

Bootstrapping

- Bootstrapping is a tool used to estimate the distribution of a statistic.
- Bootstrapping randomly resamples data creating many new data sets.
- These new data sets are then refitted giving a distribution of parameter estimates.
- Parameter distributions allow for comparison of parameter values measured at different temperatures.

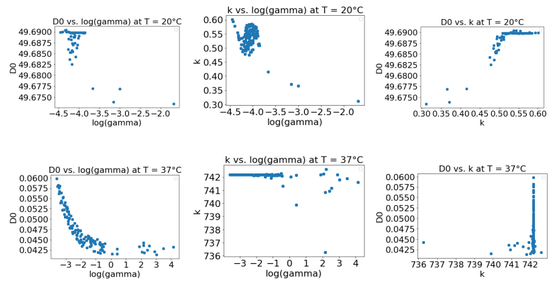
Syncytia Formation Rate



- At 37 °C the γ values tends to be higher when compared to the γ value at 20 °C.
- This suggests that syncytia form more easily at 37 °C than at 20 °C.

Parameter Correlations

Bootstrapping results can also be used to check for parameter correlations.



- D_O vs. $\log(\gamma)$ at 20 °C shows a cluster while at 37 °C there is a negative trend between D_O and $\log(\gamma)$.
- k vs. $\log(\gamma)$ at 20 °C shows a cluster however at 37 °C shows a wide range of values.
- D_0 vs. k at 20 °C and at 37 °C suggest a positive correlation.

Conclusions

- We fit a mathematical model of syncytia formation to HIV cell-cell fusion assays at two different temperatures.
- Syncytia has a higher formation rate in the HIV virus at 37 °C when compared to 20 °C.
- While more data at different temperatures is needed, higher temperatures in the HIV appear to increase syncytia formation.
- The increase in syncytia formation at higher temperatures suggests a greater effect on the host immune response at higher temperatures.

Future Directions

- We are setting up to run cell-cell fusion assays at TCU, which will allow us to control experimental parameters.
- Collect data for longer time frames and sampled more frequently to help with parameter identifiability.
- Examine a wider range of temperatures.
- Apply the Arrhenius equation in order to analyze the effect of temperature on reaction rates.
- Study the effect of pH on syncytia formation rate and fusion rate.
- Study the effect of temperature and pH on syncytia formation of other syncytia-forming viruses.

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Synctyia are formed by individual cells fusing together to create a multinucleated cell. The formation of synctyia can help the virus by enhancing its infectivity and ability to spread within the host. However the effect of temperature on syncytia formation rate is unknown. In our study, we used a mathematical model to estimate the syncytia formation rate for HIV at two different temperatures. We find that a lower temperature lowers the syncytia formation rate. We can use these findings to help develop strategies to control HIV viral spread.