Syncytia Formation Rate for SARS-CoV-2 Variants

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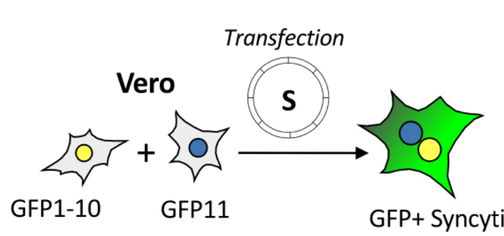
Background

- SARS-CoV-2, more commonly known as COVID-19, led to a global crisis.
- SARS-CoV-2, like some other viruses, can cause neighboring cells to fuse together into large multi-nucleated cells called syncytia.
- The rate of syncytia formation is one factor that might affect the time course of viral infection from SARS-CoV-2.
- Syncytia formation allows viruses to propagate without leaving the host cell, which protects them from exposure to antibodies, but the rate of syncytia formation for any virus is unknown.
- By establishing the rate of syncytia formation for each variant, we can better understand how each variant affects the progression of viral infection.

Cell Fusion Assay



(Taken from Rajah et al. (2021) Plos Pathogens)

- Cell fusion assays use a donor cell expressing the viral surface protein and acceptor cells expressing the cell receptor to observe fusion.
- We used data from cell fusion assays performed by Rajah et al. (2021) Plos Pathogens that examined fusion for 4 SARS-CoV-2 variants.

Cell Fusion Assay Model

- We used a mathematical model to fit data from the cell fusion assay.

$$\begin{aligned}\frac{\mathrm{d}D}{\mathrm{d}t} &= \gamma DA\\ \frac{\mathrm{d}A}{\mathrm{d}t} &= \gamma DA - \gamma SA\\ \frac{\mathrm{d}S}{\mathrm{d}t} &= \gamma DA + \gamma SA.\end{aligned}$$

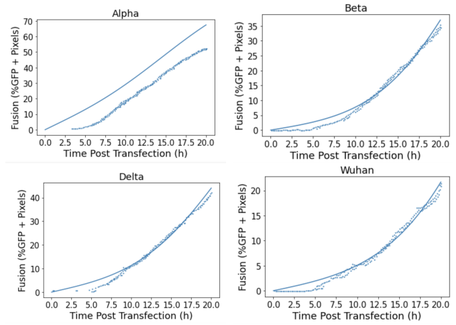
- D are the donor cells, A are the acceptor cells, and S are cells that have fused into syncytia.
- The syncytia formation rate (or fusion rate) is represented by γ,

Methods

- We fit the mathematical model to data using minimization of the sum of squared residuals.
- The fusion rate and the initial number of donor cells were estimated.
- Bootstrapping was used to estimate the posterior distributions of the free parameters.

Original Model Fits

The graphs below show our fits of the data using our original mathematical model.



- The fit of the data here was not very accurate, particularly during the early part of the time course when the model over-estimates the number of syncytia.

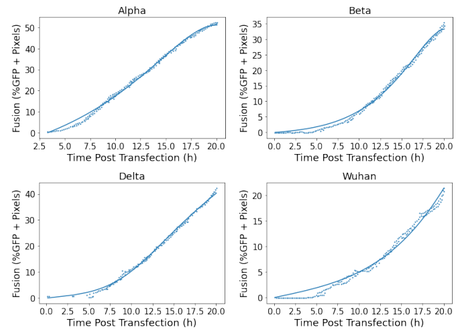
Addition of a Fusing Phase

- The discrepancy between model and data could be due to the assumption that donor and acceptor cells meet and immediately form syncytia.
- In reality, fusion is a process that takes some time since there are a number of biochemical processes that must occur to move from two separate cells to a single cell.
- To include this in the model, we added a fusion phase to the model.

$$\begin{aligned}\frac{\mathrm{d}D}{\mathrm{d}t} &= \gamma DA\\ \frac{\mathrm{d}A}{\mathrm{d}t} &= \gamma DA - \gamma SA\\ \frac{\mathrm{d}F}{\mathrm{d}t} &= \gamma DA + \gamma SA - kF\\ \frac{\mathrm{d}S}{\mathrm{d}t} &= kF.\end{aligned}$$

- This adds a new parameter k where $1/k$ is the average time cells spend in the fusing phase.

Fusing Model Fits



These fits were much improved from the original model fits.

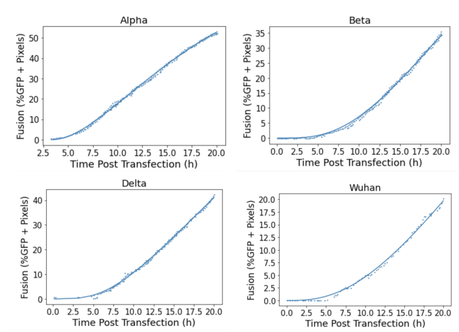
Gamma Distributed Fusion

- The previous model assumes that fusion is essentially a one-step process with a duration that is exponentially distributed.
- A more realistic assumption is to assume that fusion is a multi-step process, which results in a gamma-distributed duration.

$$\begin{aligned}\frac{\mathrm{d}D}{\mathrm{d}t} &= \gamma DA\\ \frac{\mathrm{d}A}{\mathrm{d}t} &= \gamma DA - \gamma SA\\ \frac{\mathrm{d}F_1}{\mathrm{d}t} &= \gamma DA + \gamma SA - kF_1\\ \frac{\mathrm{d}F_2}{\mathrm{d}t} &= kF_1 - kF_2\\ \frac{\mathrm{d}S}{\mathrm{d}t} &= kF_2.\end{aligned}$$

Gamma Distributed Fusion Fits

The graphs below show our fit of the data that used a gamma-distributed fusion phase.



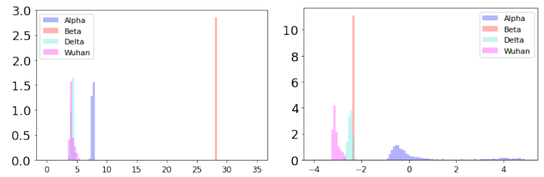
Parameter Estimates

- The table below shows our estimated parameter values using the gamma-distributed fusion model.

—	Fusion Rate (/h)	$D(0)$ %	k (/h)	SSR Value
Alpha	0.358	58.9	0.131	88.1
Beta	4.49×10^{-3}	49.8	0.0354	40.8
D61G	2.80×10^{-3}	28.9	0.245	49.0
Wuhan	6.41×10^{-4}	40.82	0.248	9.62

Differences Between Variants

- From the bootstrapping, we can create distributions for each of the parameter estimates, allowing us to compare parameter estimates from the different variants.
- The histogram on the left shows the amount of time spent in the fusion phase, $1/k$, in hours for the different variants.
- The histogram on the right shows the fusion rate, γ, in /hfor each variant.



Conclusions

- The formation of syncytia cells is a multi-step process best modeled by a gamma distributed fusion phase.
- Delta and Wuhan take a similar amount of time to fuse, but the other two variants take a longer time to fuse.
- The Alpha variant has a much higher fusion rate than the other variants.

Future Directions

- Start running our own experiments so we can apply this analysis method to other data.
- Find fusion rates of different syncytia-forming viruses.
- Determine the temperature dependence of syncytia fusion rate.
- Quantitatively assess the effect of fusion-inhibiting antivirals.