Modeling Influenza A Viral Entry: A Multi-Stage ODE Approach

Ayur Madupur and Hana M. Dobrovolny

Department of Physics and Astronomy, Texas Christian University, Fort Worth, USA

Background

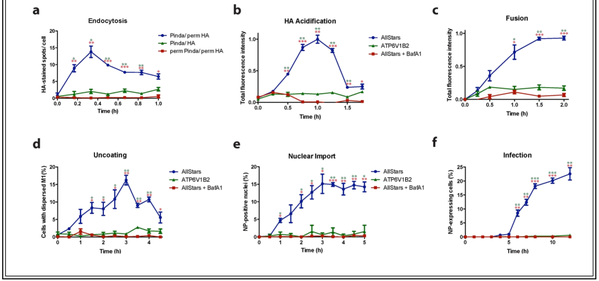
- Influenza A virus (IAV) is a major issue in public health as it mutates at a rapid rate and new strains are constantly emerging, ultimately reducing the effectiveness of vaccines and antiviral drugs.
- Infection occurs over multiple cellular processes, which allow the virus to enter the host cell and start replication.
- Early stages include the virus binding to the cell membrane, endocytosis, acidification within endosomes, membrane fusion, uncoating of the viral capsid, and transport of viral ribonucleoproteins into the nucleus.
- Experimental studies have produced time-course data quantifying the progression of virus particles along the infection pathway using imaging-based assays.
- Treating viral infection as a multi-step process allows for a more detailed understanding of entry dynamics compared with models that treat infection as a single step.

Objective

- Develop a system of ordinary differential equations (ODEs) to represent the stages of influenza viral entry.
- Fit the model to experimental time-series data using nonlinear least squares optimization.
- Estimate biologically significant parameters and perform an analysis of their identifiability.

Experimental Data

- Experimental data came from a set of time-series measurements published by Banerjee et al., 2013, Plos One, which measures the amount of virus at several stages of viral infection: endocytosis, HA acidification, fusion, uncoating, nuclear import, and infection.
- Each stage corresponds to a distinct biological process, beginning with virus binding and endocytosis, and culminating in infection and RNA replication within the host nucleus.



Mathematical Model

The model includes eight compartments describing the transition of virus through each stage of cellular entry.

$$\frac{dV_{ex}}{dt} = -\beta V_{ex} C$$

$$\frac{dV_b}{dt} = \beta V_{ex} C - k_E V_b$$

$$\frac{dV_{end}}{dt} = k_E V_b - k_A(t)\, V_{end}$$

$$\frac{dV_a}{dt} = k_A(t)\, V_{end} - b\, V_a$$

$$\frac{dV_{fus}}{dt} = b\, V_a - k_U V_{fus}$$

$$\frac{dV_{un}}{dt} = k_U V_{fus} - k_N V_{un}$$

$$\frac{dV_{nuc}}{dt} = k_N V_{un}$$

$$\frac{dI}{dt} = p\, V_{nuc}$$

The transitions from one stage to the next are assumed to be exponential with the exception of acidification. The time dependent acidification rate is given by

$$k_A(t) = \frac{Ae^{-\lambda t}}{B + e^{-\lambda t}},$$

arising from the assumptions that pH in the endosome decays exponentially (Lagache et al. (2017)) and the virus responds to changes in pH in a Michaelis-Menton type manner.

Fitting the Model to Data

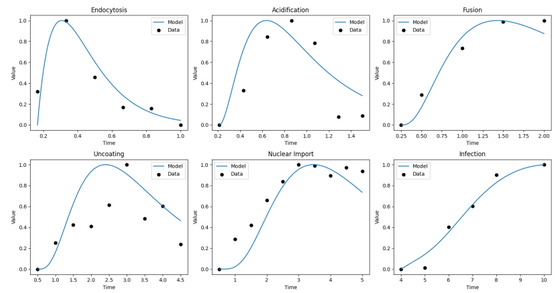
- The datasets were extracted using WebPlotDigitizer from figures included in the original publication and provide the normalized viral concentrations over time for each phase.
- Parameter estimation was done by fitting the ODE model to all six datasets simultaneously by minimizaing the sum of squared residuals (SSR),

$$\mathrm{SSR} = \sum_{i=1}^{n} \left(y_i - f(t_i;\theta)\right)^2,$$

- The `scipy.optimize.minimize` function in Python was used for parameter fitting, with the SSR between the model output and experimental data as the objective function.
- The Nelder-Mead method was used in the initial fitting, while BFGS was used for bootstrapping. Bounds were applied to ensure non-negative parameter values.
- Bootstrapping was done by resampling the data and re-optimizing the parameters over 1000 iterations.

Results: Model Fits to Data

- The fitted ODE model highlights the dynamics of each stage of viral entry.
- The solid lines (simulated trajectories) closely match the points (experimental data) for the phases of endocytosis, HA acidification, fusion, uncoating, nuclear import, and infection.



The model captures the trajectories of each of the steps well.

Results: Model Parameters

Model fits to the data allow us to estimate values of the model parameters.

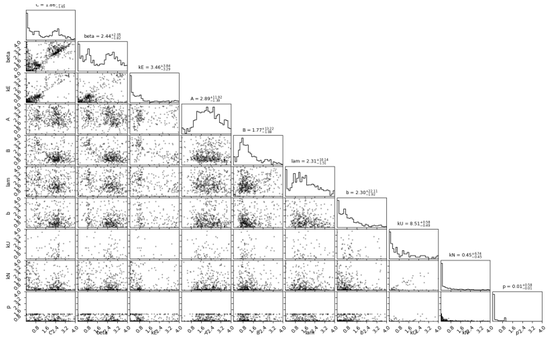
Parameter	Value	95% CI
β (/hour · virus)	0.45	0.0076–16
C (virus)	1.0	0.0017–11
k_E (/hour)	0.88	0.0014–15
A (/hour)	1.1	0.53–90
λ (h)	0.72	0.0024–54
B	0.97	0.15–70
b (/hour)	0.50	3.7×10^{-6}–120
k_U (/hour)	8.5	0.25–46
k_N (h)	0.048	0–34
p (cell/hour · virus)	0.020	0–1.0

The parameters have physical meaning. In this case, values of the model parameters give an estimate of the average durations of each of these steps:

- virus remains bound to the surface for 66 minutes,
- virus spends at most 54 minutes undergoing endocytosis,
- acidification takes on average 30 minutes,
- fusion takes about 7 minutes,
- uncoating is the slowest process at 21 hours,

Results: Identifiability Analysis

To analyze parameter identifiability, 1000 bootstraps were performed using refits of the model to surrogate data sets that were generated by resampling the residuals of the best-fit solution. The resulting parameter distributions were visualized using corner plots.



- Several parameters show narrow distributions, which indicate that the data is reasonably constraining them.
- Others display broad, right-skewed distributions with extended upper tails, which suggest weak identifiability.
- Pairwise scatter plots reveal elongated clouds that are consistent with trade-offs between parameters.

Conclusions

- Despite some parameters not being estimated precisely, the model was able to capture the overall patterns observed in the data.
- With even more refinement and experimental measurement, the model could provide greater insights into the dynamics of viral infection and aid the evaluation of antiviral strategies.

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Influenza virus cell entry is a multistep process that initiates viral replication. In this study, we developed a mathematical model that captures distinct stages of this process: endocytosis, acidification, fusion, uncoating, nuclear import, and infection. The model was fitted to experimental data to elucidate how the virus progresses through each step. Our results demonstrate that the model accurately replicates overall trends in the data, providing estimates of the timing for each stage. This model can enhance our understanding of infection kinetics and aid researchers in designing antiviral drugs targeting specific steps of the process.