Time-varying production in virus dynamics models

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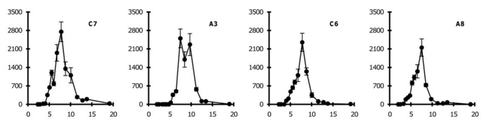
Background

- Mathematical modeling of viral kinetics can be used to gain further insight into the viral replication cycle and virus-host interactions.
- While there is a basic viral kinetics model, several extensions have been proposed to more realistically simulate different aspects of the viral replication cycle (ex: addition of the immune response, symptoms, drug resistance, etc.).
- Experimental studies measuring viral kinetics in single cells have shown that the viral production rate within a host varies over time, unlike the typical assumption of continuous production.
- We identify a model to describe time-varying viral production, then use the model to incorporate time-dependent viral production in a viral kinetics model using an integro-differential equation.

Modeling viral production

- A recent study examined the kinetics of vesicular stomatitis virus production in single BHK cells, Timm and Yin (2012) Virology.



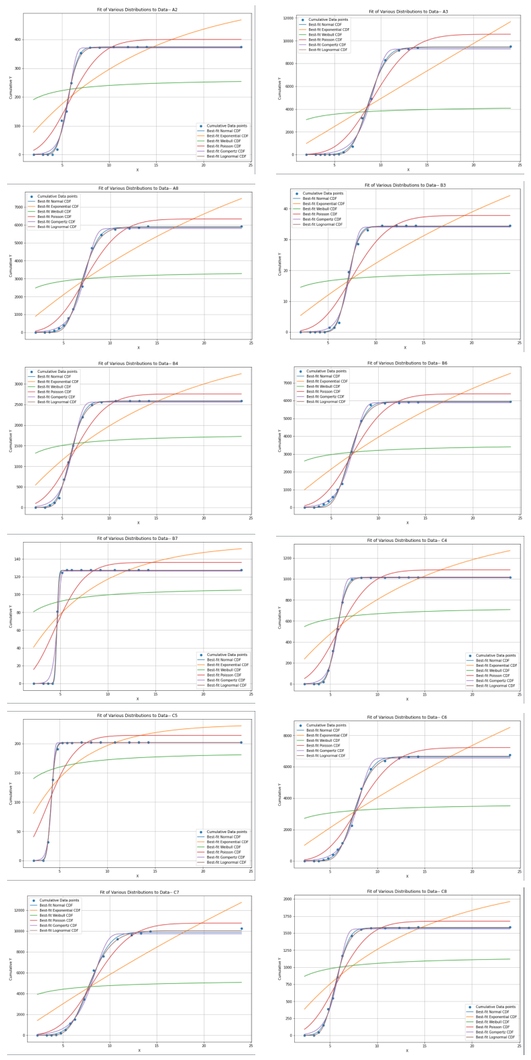
- The most accurate time course for viral production was determined by fitting potential distributions to cumulative viral production by minimizing the sum of squared residuals (SSR).

Distribution	Equation
Exponential	$1 - e^{-\lambda t}$
Normal	$\frac{1}{2}\left(1 + \mathrm{erf}\left(\frac{t-\rho}{\sqrt{2\sigma^2}}\right)\right)$
Weibull	$1 - e^{-\left(\frac{t}{\eta}\right)^{\gamma}}$
Poisson	$e^{-\lambda}\sum_{i=0}^{t}\frac{\lambda^i}{i!}$
Gompertz	$1 - e^{-\eta\left(e^{bt}-1\right)}$
Log-normal	$\frac{1}{2}\left(1 + \mathrm{erf}\left(\frac{\ln t-\mu}{\sqrt{2\sigma^2}}\right)\right)$

- Then, each distribution's Akaike Information Criterion (AIC) score was evaluated and compared to identify the best fit for each cell,

$$\mathrm{AIC}_c = n \ln\left(\frac{SSR}{n}\right) + \frac{2(K+1)n}{n-K-2}.$$

Best-fit Curves



Results

- The log-normal probability distribution had the lowest AIC score for the majority of the cells (7 cells) and was thus selected as the best-fit distribution.
- The normal distribution was the best-fit distribution for 3 cells while the Gompertz distribution was the most ideal for 2 cells.

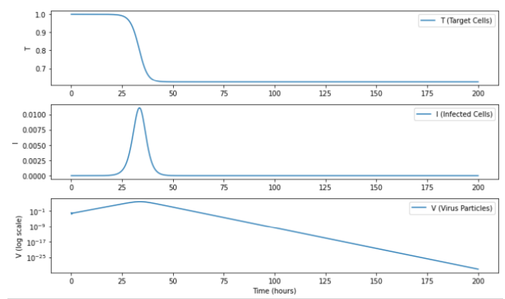
Time-adjusted Model

The distribution that best described time-dependent viral replication was incorporated into a standard constant production model of viral kinetics. The set of mathematical equations that describe the model are shown below. The total amount of virus produced by one cell during an infection will be represented by V, which is the infectious viral titer as detected by plaque assays. We modeled V with an integral equation that incorporates the probability distribution function for production found in the first part of this project. The integro-differential equations for the model are as follows,

$$\begin{aligned}
\frac{dT}{dt} &= -\beta TV, \\
\frac{dE}{dt} &= \beta TV - kE, \\
\frac{dI}{dt} &= kE - \delta I, \\
V(t) &= pI(0)P(t) + p\int_0^t P(t-s)I(s)\,ds \\
&\quad - cp\int_0^t I(0)P(t-s)f(s)\,ds \\
&\quad - cp\int_0^t\int_0^{s_2} P(t-s_2)f(s_2-s_1)I(s_1)\,ds_1\,ds_2.
\end{aligned}$$

Constant production

Constant viral production simulations of target cells (top), infected cells (center) and viral titer (bottom).

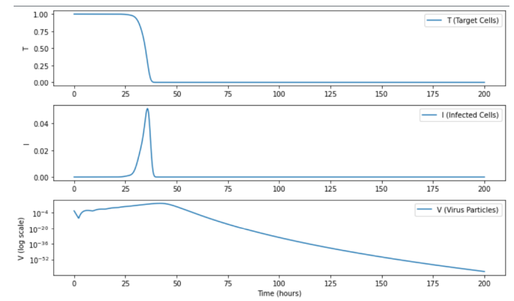


Constant production simulation metrics:

Metric	Value
Time of viral peak (hours)	33.83
Viral peak value (particles)	5.53×10^3
Upslope (particles/hour)	3.80×10^1
Downslope (particles/hour)	-8.46×10^1
AUC (particles $\times$ hours)	4.71×10^4

Time-varying production

Time-dependent viral production simulations of target cells (top), infected cells (center), and viral titer (bottom)

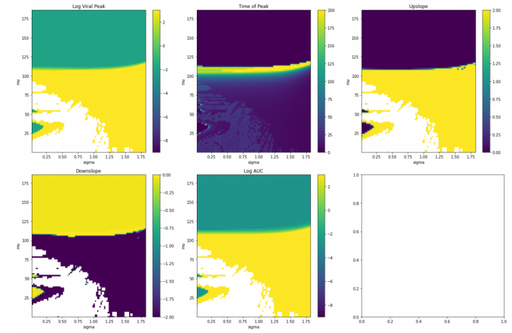


Log-normal production simulation metrics

Metric	Value
Time of viral peak (hours)	41.84
Viral peak value (particles)	5.25×10^5
Upslope (particles/hour)	1.95×10^4
Downslope (particles/hour)	-4.96×10^3
AUC (particles $\times$ hours)	3.12×10^6

Dependence of viral load on distribution parameters

The following graphs demonstrate how a variety of graph metrics change with the parameters of the log-normal distribution. Mu represents the mean while sigma is the standard deviation of the distribution.



Conclusions

Overall, the log-normal distribution provides the best fit for most of the cells, and the time-varying production metrics have more extreme values compared to constant production.