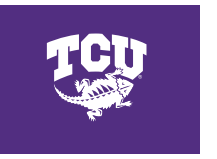




Bootstrap Parameter Estimation of SARS-CoV-2 Viral Dynamics in Favipiravir-Treated Cynomolgus Macaques

Aarush Shetty and Hana M. Dobrovolsky

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



Background

- Viral-dynamics models help interpret longitudinal viral-load data and connect observed trends to underlying biological processes.
- Favipiravir is an antiviral evaluated across multiple dose groups for its effect on viral replication.
- We analyze SARS-CoV-2 viral-load data from cynomolgus macaques.
- Bootstrap resampling quantifies parameter uncertainty and helps assess how stable fitted estimates are across groups.
- Comparing fitted parameters across dose groups helps identify which viral processes are most affected by treatment.

Objective

- Fit an ODE viral-dynamics model to each treatment group.
- Estimate biologically meaningful parameters from the fitted curves.
- Compare groups using bootstrap distributions.
- Determine which parameters show the clearest treatment-associated changes.

Experimental Data

- Four groups were studied: Control, 100, 150, and 180 mg/kg.
- Viral loads were recorded over time as \log_{10} RNA copies/mL.
- Each group was analyzed independently to avoid imposing shared parameters across treatments.
- Best-fit and bootstrap analyses were performed for all groups.
- This design allows groupwise comparison of both model fits and inferred biological parameters.

Mathematical Model

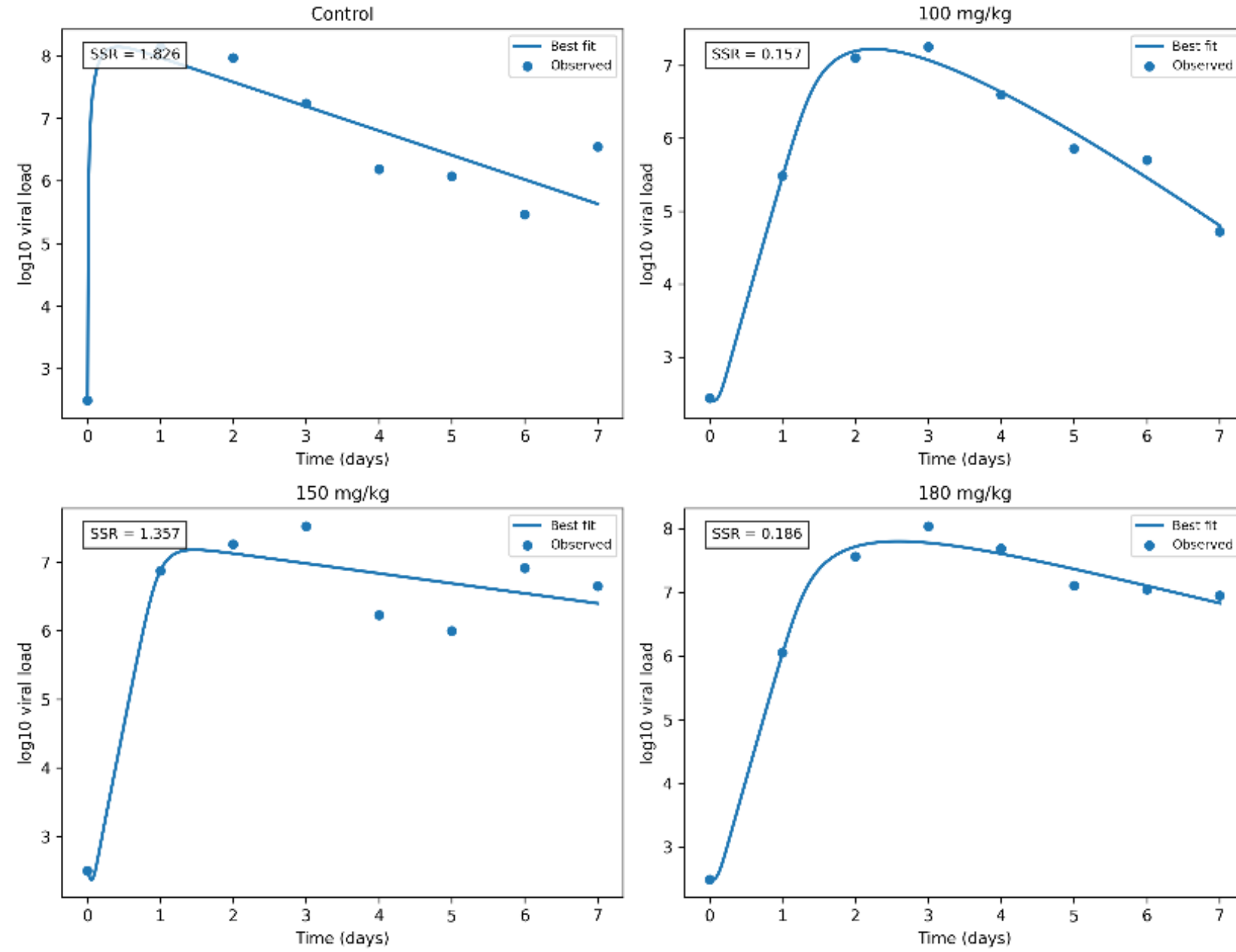
The model contains uninfected target cells (T), eclipse-phase infected cells (I_1), productively infected cells (I_2), and free virus (V). These compartments represent infection, delayed intracellular progression, and virus production.

$$\begin{aligned} \frac{dT}{dt} &= -\beta TV \\ \frac{dI_1}{dt} &= \beta TV - kI_1 \\ \frac{dI_2}{dt} &= kI_1 - \delta I_2 \\ \frac{dV}{dt} &= pI_2 - cV \end{aligned}$$

Parameters

- β : infection rate
- k : eclipse transition rate
- δ : infected-cell loss rate
- p : viral production rate
- c : viral clearance rate

Results: Model Fits to Data



Fitting the Model to Data

- Model fit separately to each group using nonlinear optimization.
- Sum of squared residuals was minimized in \log_{10} space:

$$SSR = \sum_{i=1}^n (\log_{10} V_{data,i} - \log_{10} V_{model,i})^2$$

- Residual bootstrap was performed over 1000 replicates per group.
- Median estimates and 95% confidence intervals were reported from the bootstrap distributions.
- Pairwise Mann-Whitney U tests were used to compare parameter distributions between treatment groups.
- Fits were evaluated both visually and by SSR to assess agreement between observed and modeled viral loads.

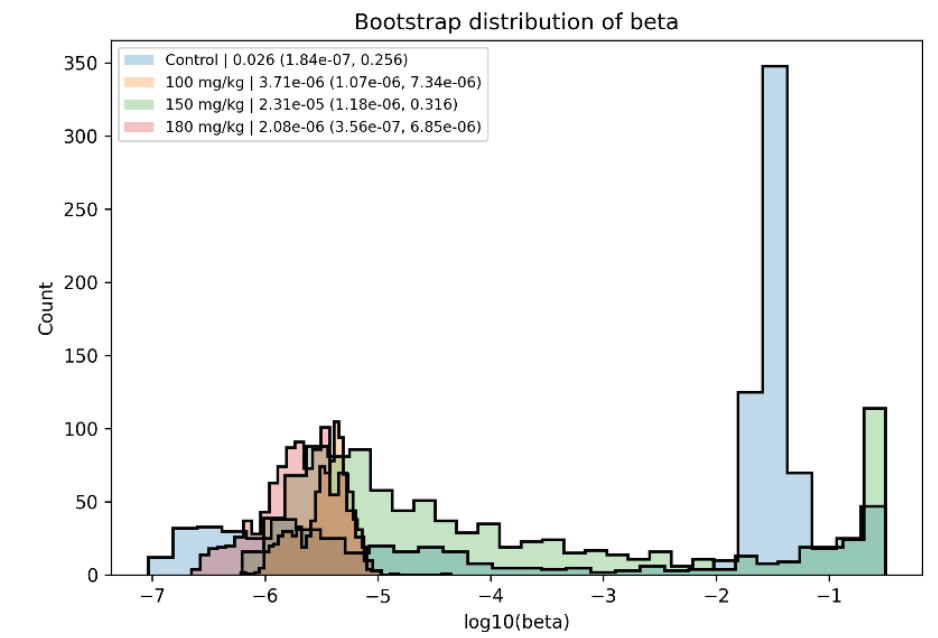
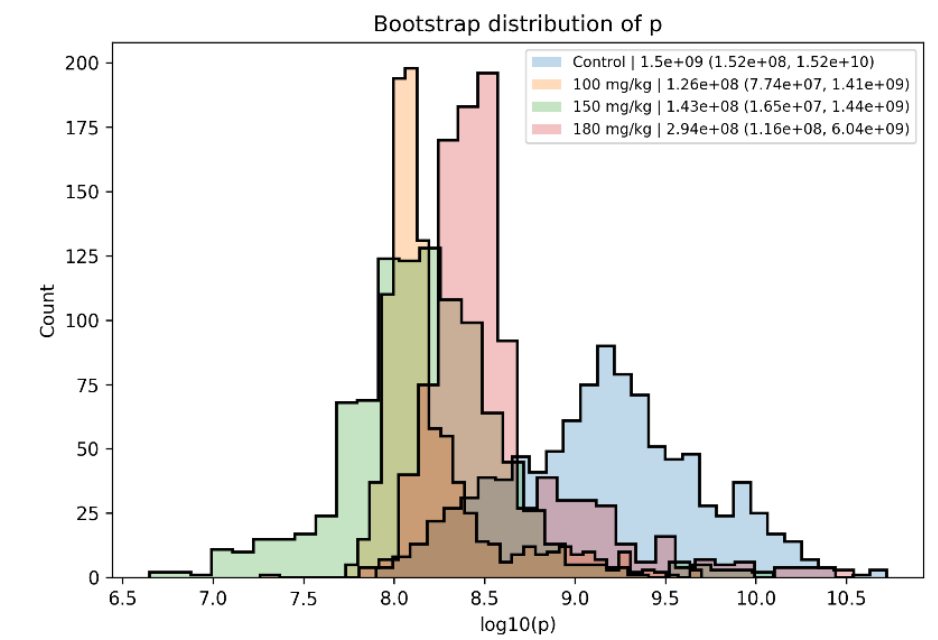
Fit Quality

Group	Best-fit SSR	Bootstrap SSR
Control	1.8258	0.8906
100 mg/kg	0.1571	0.0590
150 mg/kg	1.3572	0.6627
180 mg/kg	0.1863	0.0616

Best-fit SSR values were lowest in the 100 mg/kg and 180 mg/kg groups, indicating the strongest agreement between model and observed data. The higher SSR values in the control and 150 mg/kg groups suggest greater residual variability or weaker parameter identifiability in those fits. Overall, the model reproduced the main temporal viral-load trends across all four groups.

Key quantitative result: the strongest treatment-associated shift appeared in the viral production parameter p , which was markedly higher in the control group than in the treated groups.

Results: Model Parameters



The clearest treatment-associated pattern was observed in the viral-production parameter p , with median values decreasing sharply from control to treated groups. Median β values were also generally lower in treated groups, suggesting that treatment may reduce effective infection dynamics in addition to lowering production. In contrast, k , δ , and c showed wider uncertainty ranges, indicating that not all fitted parameters were equally well constrained by the available data.

Summary of Statistical Comparisons

- Most pairwise parameter comparisons were highly significant.
- For p , all control-versus-treatment comparisons were strongly significant.
- The only non-significant comparison for p was between 100 and 150 mg/kg ($p = 0.699$).
- For δ , control versus 180 mg/kg remained significant but was much weaker than most other comparisons ($p \approx 0.033$).

Conclusions

- Bootstrap provided uncertainty estimates for all fitted parameters.
- Most pairwise comparisons were statistically distinct.
- The strongest treatment-associated signal was reduced fitted viral production p .
- Several parameters remained uncertain, indicating partial identifiability limitations.
- Together, the fit plots and bootstrap distributions suggest that treatment most strongly alters viral production dynamics.

Future Directions

- Perform structural and practical identifiability analysis.
- Add immune-response effects to the model.
- Explore joint or hierarchical fitting across groups.
- Compare fitted metrics such as AUC or peak viral load across treatment groups.

This study used bootstrap-based parameter estimation to compare viral-dynamics behavior across favipiravir treatment groups. The model reproduced the main observed viral-load trajectories and identified the clearest treatment-associated effect in the viral-production parameter p , with additional evidence of reduced β in treated groups. These results show how mechanistic modeling and bootstrap uncertainty analysis can be combined to interpret treatment effects beyond visual inspection alone.