

I. Introduction

Decoding host-pathogen interactions is key to understanding the viral lifecycle but presents a complex challenge for experimental studies. This work addresses open questions in picornavirus coxsackievirus B3 (CVB3) replication through integration of experimental and computational modeling methods. This repository contains data and modeling code that support evidence presented in Lopacinski et. al.

The following document provides readers with descriptions of the modeling framework, basic scripts to get readers started using the model, and scripts that regenerate figures and tables presented.

II. CVB3 Viral Lifecycle Model Code

This section provides descriptions of model MATLAB files developed using MATLAB version R2019b. MATLAB versions 2018 or later and Bioinformatics Toolbox are required to generate simulation plots.

1. CVB3ODEfunc.m

This function stores a system of differential equations that represent the CVB3 viral lifecycle and host-pathogen interactions. Viral receptor binding, internalization, genome replication, viral protein translation, and viral progeny assembly are captured by 54 differential equations and 51 parameters. Parameter values are derived from literature or experimental evidence and can be found in Table S1.

2. CVB3ODEEval.m

This file defines a function that takes user supplied multiplicity of infection (MOI) and calls `CVB3ODEfunc` to simulate the viral lifecycle model using MATLAB's `ode15s` stiff differential equation solver. Additional user supplied options define the simulation context including the type of simulation, time span of the simulation, enabling anti-viral interferon response, enabling viral interferon interference, and simulating exogenous interferon stimulation. The model is repeatedly simulated with parameters for each simulation randomly generated from independent log-normal distributions. The distributions are based on the parameter mean and standard deviation. Model simulation outputs tables of the median, upper quartile, lower quartile, and mean of the set of simulations. The table below enumerates all possible options and their default values. All model reaction rate constants and initial conditions are stored in this file. Simulation results are outputted as a table and plotted. For examples on how to use this function, see **Introductory Scripts** section.

Option	Description	Default Value	Option Values
PopulationSetting	Indicates whether or not to use a Poisson distribution for MOI or just a single integer indicating the MOI of a single cell.	'Single Cell'	'Single Cell' or 'Population'
MaxTime	Maximum simulation time in hours	16 hours	any positive real number
IFNSwitch	Indicates if the interferon response is enabled	'on'	'on', 'off', or ''
VirResponse	Indicates if the viral anti-viral response is enabled	'on'	'on', 'off', or ''
IFNSstimulation	Indicates if interferon stimulation is enabled	'off'	'on', 'off', or ''
IFNSstimulationTime	The time of interferon stimulation in hours. Negative values indicate stimulation prior to viral infection.	0	Any real number
EC50_RNAdeg	The half-effective nanomolar concentration of interferon stimulated genes for viral RNA degradation.	5 nM	any positive real number
EC50_DetectorDeg	The half-effective nanomolar concentration of viral protease for viral detector degradation.	0.001 nM	any positive real number
EC50_Protease	The half-effective nanomolar concentration of interferon stimulated genes for viral protease degradation.	20 nM	any positive real number
EC50_Translate	The half-effective nanomolar concentration of interferon stimulated genes for viral translation inhibition.	10 nM	any positive real number
PlotResults	Indicates if plots of simulation results should be automatically generated.	'on'	'on', 'off', or ''
PlotType	Specifies the type of y-axes to plot results on (linear or semilog).	'semilog'	'semilog' or 'linear'
SensitivityAnalysis	Indicates if sensitivity analysis should be simulated.	'off'	'on', 'off', or ''
SensitivityAnalysisOutput	A string that indicates which species should be used for sensitivity analysis. 'Other' will prompt user for input.	'Plus RNA'	'Plus RNA', 'Minus RNA', 'dsRNA', 'RNA Ratio', 'Polyprotein', 'Virion', 'Empty Provirion', 'Other'

ScalingFactor	The factor by which each parameter is scaled during sensitivity analysis.	10	any positive real number
MaxScalingOrder	The integer absolute value of the maximum order of magnitude change to test via sensitivity analysis.	2	any positive integer
ExportData	Indicates if simulation results should be exported.	'off'	'on','off'
DataFile	The file name and type that the simulation results should be written to.	'results.csv'	Any character string following the pattern 'myFile.txt', 'myFile.csv', 'myFile.xls'
RunCount	The number of times the model is simulated with parameters stochastically sampled from independent log-normal distributions.	100	Any positive integer
UpperQuantile	The upper quantile outputted for model species	0.95	Any number between 0 and 1
LowerQuantile	The lower quantile outputted for model species	0.5	Any number between 0 and 1
CV	The coefficient of variation of the log-normal distribution from which the parameters are stochastically determined.	0.05	Any positive number

4. SensitivityAnalysisfunc.m

This function is called by CVB3ODEEval when SensitivityAnalysis option is 'on'. This code examines the sensitivity of model species like total +ssRNA or infectious virions (determined by the SensitivityAnalysisOutput option) to changes in individual model reaction rate constants and initial conditions. Each parameter is scaled by the specified ScalingFactor for the provided MaxScalingOrder and model results are outputted as a heatmap centered around the base model results.

5. CVB3ODEPlots.m

This function plots the model simulation results. It is called automatically by CVB3ODEEval when PlotResults is 'on'. It can be called outside of CVB3ODEEval with customizable plotting options enumerated in the table below.

Option	Description	Default Value	Option Values
PlotType	Specifies whether the results should be plotted on linear or semilog axes.	'Semilog'	'Semilog' or 'Linear'
PlotOutputs	Indicates which species should be plotted.	'All'	a cell array containing any subset of the variable names from the CVB3ODEEval results table

III. Introductory Scripts

`IntroductoryScripts.m` provides introductory scripts to help readers get started using the model and visualizing results.

IV. Model Results

This section provides scripts to regenerate figures and tables presented in Lopacinski et. al.

V. Troubleshooting Contact

Please contact Aaron Lopacinski, Millie Shah, or Kevin Janes for any questions regarding model set-up and simulation. Contact information can be found in the author details of Lopacinski et. al.