

Modeling the CD8+ T cell immune response to influenza infection in adult and aged mice

Benjamin Whipple^{1,2}, Tanya A. Miura^{2,3,4}, and Esteban A. Hernandez-Vargas^{1,2,4,*}

¹Department of Mathematics and Statistical Science, University of Idaho, Moscow, ID, 83844, United States

²Bioinformatics and Computational Biology Program, University of Idaho, Moscow, ID, 83844, United States

³Department of Biological Sciences, University of Idaho, Moscow, ID, 83844, United States

⁴Institute for Modeling Collaboration and Innovation, University of Idaho, Moscow, ID, 83844, United States

*Corresponding author: esteban@uidaho.edu

A Supplemental Material

A.1 Preliminary Analysis of CTL Downregulation

One hypothesis of possible differences between the CTL response in young and aged mice is that adult mice have faster downregulation of CTL post viral clearance than adult mice. This hypothesis may help explain the worsened outcomes against IAV infection with age, as extended presence of CD8+ T cells can contribute to disease¹⁻³. As an initial test of this hypothesis we perform exploratory simple linear regression on the aged and adult CTL data.

We model the downregulation rates by the form $\log(T(t)) = \beta_0 + \beta_1 t$, where t represents days post infection and $T(t)$ represents measured CTL counts at day t . The viral data is below the measured threshold on days 9 and 11 for adult and aged mice respectively, and so is assumed cleared after that time. As such, we restrict t to be greater than or equal to 9 and 11 for adult and aged mice respectively.

It is worth noting that the data is both sparse and unbalanced over the considered range, with there being many more samples in the adult group than the aged group. Specifically, there are 36 total observations for the adult group, balanced at 9 observations per day. However, there are only 7 total for the aged group, distributed as 3, 2, and 2 samples on days 11, 15, and 19 respectively. As such, our data makes our model ill suited to traditional tests of significance.

In order to identify the degree of difference in slopes between the estimated groups, we utilize nonparametric bootstrapping of the data to conduct a nonparametric bayesian analysis. We generate 10000 resamples of the data by sampling with replacement from each time and age group the same number of time points observed originally. We then compute the least squares estimate of our linear model. This process has the effect of sampling the posterior of our parameters using an approximate, noninformative prior distribution of our data⁴. We present the predictions and β_1 posteriors of our bootstrapped models in figures A.1.1 and A.1.2 respectively.

We find evidence for a faster retraction of the CTL response in adults as presented in A.1.1 and A.1.2, as well as through

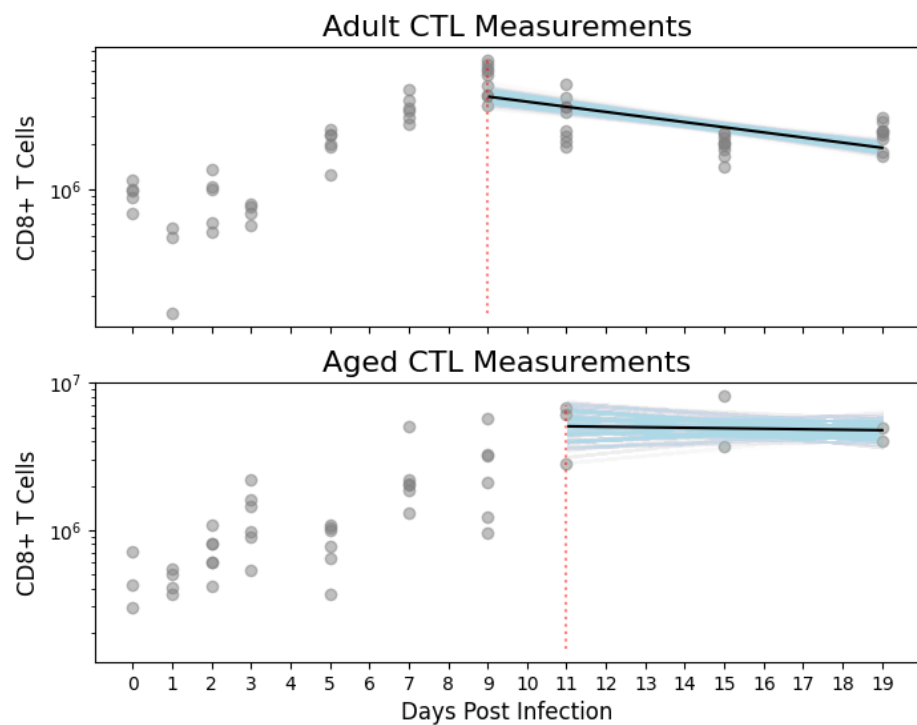


Figure A.1.1

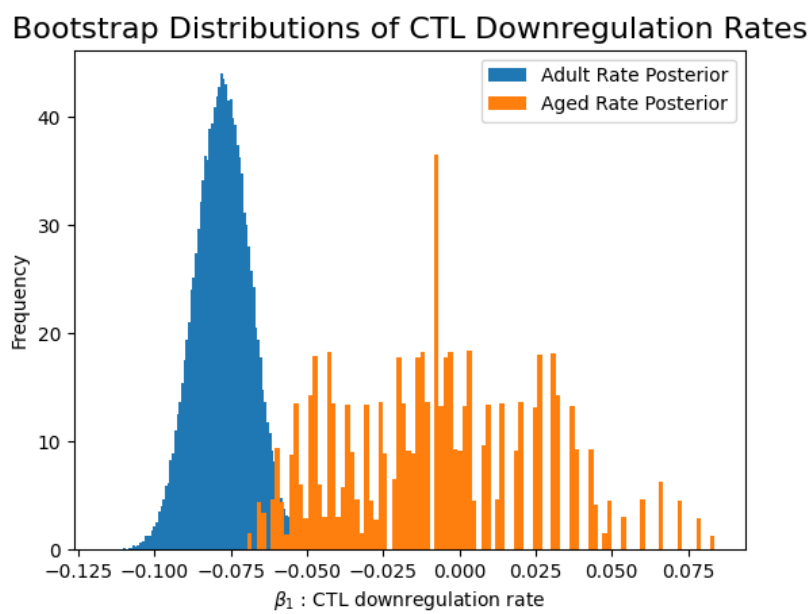


Figure A.1.2

probability computation using the posterior. We can see in figure A.1.1 that the adult bootstrapped models generally have more negative slope than the aged bootstrapped models. Further, the plotted posterior distributions of β_1 shown in figure A.1.2 indicate taht the adult rate posterior is dramatically more negative than the aged rate posterior. Finally, using the bootstrapped samples, we can approximate $\mathbb{P}(\beta_{1,\text{adult}} < \beta_{1,\text{aged}})$, which we find to be 0.997. We take this finding to be indicate that we should consider the possibility that there is a meaningful difference in the rate of CTL downregulation between the aged and adult groups.

A.2 Model Equations

Model	Expressions
MA1	$dV/dt = pV(1 - V/k_V) - c_V VT, dT/dt = s_T + rTV/(V + k_T) - d_T T$
MA2	$dV/dt = pV(1 - V/k_V) - c_V VT, dT/dt = s_T + rTV/(V + k_T) - c_T/(1 + V^2)T - d_T T$
MA3	$dV/dt = pV(1 - V/k_V) - c_V VT, dT/dt = s_T + rTV - d_T T$
MA4	$dV/dt = pV(1 - V/k_V) - c_V VT, dT/dt = s_T + rTV - c_T/(1 + V^2)T - d_T T$
MB1	$dU/dt = -\beta UV, dI/dt = \beta UV - d_I TI, dV/dt = pI - cV, dT/dt = s_T + rTV/(V + k_T) - d_T T$
MB2	$dU/dt = -\beta UV, dI/dt = \beta UV - d_I TI, dV/dt = pI - cV, dT/dt = s_T + rTV/(V + k_T) - c_T/(1 + V^2)T - d_T T$
MB3	$dU/dt = -\beta UV, dI/dt = \beta UV - d_I TI, dV/dt = pI - cV, dT/dt = s_T + rTV - d_T T$
MB4	$dU/dt = -\beta UV, dI/dt = \beta UV - d_I TI, dV/dt = pI - cV, dT/dt = s_T + rTV - c_T/(1 + V^2)T - d_T T$
MC1	$dV/dt = pV(1 - V/k_V)/(1 + (KT)^2) - c_V VT, dT/dt = s_T + rTV/(V + k_T) - d_T T$
MC2	$dV/dt = pV(1 - V/k_V)/(1 + (KT)^2) - c_V VT, dT/dt = s_T + rTV/(V + k_T) - c_T/(1 + V^2)T - d_T T$
MC3	$dV/dt = pV(1 - V/k_V)/(1 + (KT)^2) - c_V VT, dT/dt = s_T + rTV - d_T T$
MC4	$dV/dt = pV(1 - V/k_V)/(1 + (KT)^2) - c_V VT, dT/dt = s_T + rTV - c_T/(1 + V^2)T - d_T T$
MD1	$dU/dt = -\beta UV, dI/dt = \beta UV - d_I TI, dV/dt = pI/(1 + (KT)^2) - cV, dT/dt = s_T + rTV/(V + k_T) - d_T T$
MD2	$dU/dt = -\beta UV, dI/dt = \beta UV - d_I TI, dV/dt = pI/(1 + (KT)^2) - cV, dT/dt = s_T + rTV/(V + k_T) - c_T/(1 + V^2)T - d_T T$
MD3	$dU/dt = -\beta UV, dI/dt = \beta UV - d_I TI, dV/dt = pI/(1 + (KT)^2) - cV, dT/dt = s_T + rTV - d_T T$
MD4	$dU/dt = -\beta UV, dI/dt = \beta UV - d_I TI, dV/dt = pI/(1 + (KT)^2) - cV, dT/dt = s_T + rTV - c_T/(1 + V^2)T - d_T T$

Table A.2.1. Mathematical form of the 16 models considered.

A.3 Structural Identifiability Analysis

MA1		MA2		MA3		MA4	
Parameters	Identifiability	Parameters	Identifiability	Parameters	Identifiability	Parameters	Identifiability
k_T	✓	d_T	✓	s_T	✓	d_T	✓
c_V	✓	k_T	✓	k_V	✓	c_T	✓
d_T	✓	c_V	✓	$T(t)$	✓	c_V	✓
k_V	✓	p	✓	r	✓	k_V	✓
p	✓	r	✓	c_V	✓	p	✓
$T(t)$	✓	s_T	✓	d_T	✓	$T(t)$	✓
$V(t)$	✓	k_V	✓	$V(t)$	✓	$V(t)$	✓
r	✓	$T(t)$	✓	p	✓	r	✓
s_T	✓	$V(t)$	✓			s_T	✓
		c_T	✓				

Table A.3.1. Group A structural identifiability

MB1		MB2		MB3		MB4	
Parameters	Identifiability	Parameters	Identifiability	Parameters	Identifiability	Parameters	Identifiability
d_I	✓	c_T	✓	s_T	✓	c_T	✓
$V(t)$	✓	p	✓	c	✓	$V(t)$	✓
r	✓	$T(t)$	✓	$I(t)$	✓	r	✓
d_T	✓	k_T	✓	$T(t)$	✓	d_I	✓
c	✓	β	✓	β	✓	c	✓
k_T	✓	$V(t)$	✓	d_I	✓	d_T	✓
$U(t)$	✓	d_I	✓	$U(t)$	✓	$U(t)$	✓
β	✓	r	✓	r	✓	$beta$	✓
$T(t)$	✓	s_T	✓	$V(t)$	✓	$T(t)$	✓
p	✓	$U(t)$	✓	p	✓	p	✓
s_T	✓	c	✓	d_T	✓	s_T	✓
$I(t)$	✓	d_T	✓			$I(t)$	✓
		$I(t)$	✓				

Table A.3.2. Group B structural identifiability

MC1		MC2		MC3		MC4	
Parameters	Identifiability	Parameters	Identifiability	Parameters	Identifiability	Parameters	Identifiability
d_T	✓	s_T	✓	d_T	✓	c_V	✓
k_T	✓	c_T	✓	K	✓	d_T	✓
c_V	✓	d_T	✓	c_V	✓	c_T	✓
p	✓	$T(t)$	✓	k_V	✓	p	✓
r	✓	c_V	✓	p	✓	r	✓
s_T	✓	K	✓	$T(t)$	✓	s_T	✓
k_V	✓	k_T	✓	$V(t)$	✓	k_V	✓
$T(t)$	✓	$V(t)$	✓	r	✓	$T(t)$	✓
$V(t)$	✓	r	✓	s_T	✓	$V(t)$	✓
K	✓	p	✓			K	✓
		k_V	✓				

Table A.3.3. Group C structural identifiability

MD1		MD2		MD3		MD4	
Parameters	Identifiability	Parameters	Identifiability	Parameters	Identifiability	Parameters	Identifiability
c	✓	K	✓	c	✓	c	✓
p		β	✓	$V(t)$	✓	p	
$T(t)$	✓	$V(t)$	✓	r	✓	$T(t)$	✓
k_T	✓	c_T	✓	d_I	✓	d_T	✓
K	✓	k_T	✓	β	✓	K	✓
$V(t)$	✓	$I(t)$		d_T	✓	$V(t)$	✓
d_I	✓	d_T	✓	$U(t)$		c_T	✓
r	✓	c	✓	K	✓	r	✓
s_T	✓	$T(t)$	✓	$T(t)$	✓	s_T	✓
$U(t)$		$U(t)$		p		$U(t)$	
β	✓	p		s_T	✓	β	✓
d_T	✓	d_I	✓	$I(t)$		d_I	✓
$I(t)$		s_T	✓			$I(t)$	
		r	✓				

Table A.3.4. Group D structural identifiability

38 A.4 All Model Parameter Fits

39 A.4.1 Model Group A

Model MA1 Parameters							
Parameter	Description	Units	Adult	Aged	Search Bounds	Reference	Notes
p	Viral replication rate	d^{-1}	5.48	2.60	[1e-2,1e2]	5	-
k_V	Carrying capacity of virus	(PFU/ml)			1.2e6 (fixed)	-	Determined from data
c_V	Viral clearance rate	$d^{-1} cell^{-1}$	2.21e-6	1.84e-6	[1e-8,1e-4]	6	
s_T	Homeostatic CTL proliferation rate	$cell \cdot d^{-1}$	$d_T T(0)$	$d_T T(0)$	-	-	From steady state
r	CTL proliferation rate	d^{-1}	0.274	99.9	[1e-4,1e2]	5,7	
k_T	CTL half saturation constant	(PFU/ml)	2.48e+3	2.50e+7	[1e1, 1e8]	8	
d_T	Base CTL clearance rate	d^{-1}	0.0775	1.00e-4	[1e-4,1e0]	8,9	

Table A.4.1. Model MA1 parameters

Model MA2 Parameters							
Parameter	Description	Units	Adult	Aged	Search Bounds	Reference	Notes
p	Viral replication rate	d^{-1}	5.46	3.08	[1e-2,1e2]	5	-
k_V	Carrying capacity of virus	(PFU/ml)			1.2e6 (fixed)	-	Determined from data
c_V	Viral clearance rate	$d^{-1} cell^{-1}$	2.16e-6	1.98e-6	[1e-8,1e-4]	6	
s_T	Homeostatic CTL proliferation rate	$cell \cdot d^{-1}$	$(d_T + c_T)T(0)$	$(d_T + c_T)T(0)$	-	-	From steady state
r	CTL proliferation rate	d^{-1}	0.273	0.157	[1e-4,1e2]	5,7	
k_T	CTL half saturation constant	(PFU/ml)	2.21e+3	1e1	[1e1, 1e8]	8	
d_T	Base CTL clearance rate	d^{-1}	0.0757	1.36e-4	[1e-4,1e0]	8,9	
c_T	CTL downregulation rate	$(PFU/ml)d^{-1}$	7.02e-8	0.0612	[0,1e0]	-	Assumed similar to d_T

Table A.4.2. Model MA2 parameters

Model MA3 Parameters							
Parameter	Description	Units	Adult	Aged	Search Bounds	Reference	Notes
p	Viral replication rate	d^{-1}	4.80	2.71	[1e-2,1e2]	⁵	-
k_V	Carrying capacity of virus	(PFU/ml)			1.2e6 (fixed)	-	Determined from data
c_V	Viral clearance rate	$d^{-1} cell^{-1}$	1.99e-6	2.05e-6	[1e-8,1e-4]	⁶	
s_T	Homeostatic CTL proliferation rate	$cell \cdot d^{-1}$	$d_T T(0)$	$d_T T(0)$	-	-	From steady state
r	CTL proliferation rate	$d^{-1}(PFU/ml)^{-1}$	1.91e-6	4.28e-6	[1e-4/ k_V ,1e2/ k_V]	^{5,7}	Bounds are scaled.
d_T	Base CTL clearance rate	d^{-1}	1.00e-4	0.0146	[1e-4,1e0]	^{8,9}	

Table A.4.3. Model MA3 parameters

Model MA4 Parameters							
Parameter	Description	Units	Adult	Aged	Search Bounds	Reference	Notes
p	Viral replication rate	d^{-1}	5.58	3.19	[1e-2,1e2]	⁵	-
k_V	Carrying capacity of virus	(PFU/ml)			1.2e6 (fixed)	-	Determined from data
c_V	Viral clearance rate	$d^{-1} cell^{-1}$	2.20e-6	2.10e-6	[1e-8,1e-4]	⁶	
s_T	Homeostatic CTL proliferation rate	$cell \cdot d^{-1}$	$(d_T + c_T)T(0)$	$(d_T + c_T)T(0)$	-	-	From steady state
r	CTL proliferation rate	$d^{-1}(PFU/ml)^{-1}$	1.12e-6	3.43e-6	[1e-4/ k_V ,1e2/ k_V]	^{5,7}	Bounds are scaled.
d_T	Base CTL clearance rate	d^{-1}	1.00e-4	1.00e-4	[1e-4,1e0]	^{8,9}	
c_T	CTL downregulation rate	$(PFU/ml)d^{-1}$	0.142	0.236	[0,1e0]	-	Assumed similar to d_T

Table A.4.4. Model MA4 parameters

40 A.4.2 Model Group B

Model MB1 Parameters							
Parameter	Description	Units	Adult	Aged	Search Bounds	Reference	Notes
β	Infection rate of uninfected cells	$(PFU/ml)^{-1}d^{-1}$	2.10e-5	1.77e-5	[1e-8,1e-4]	⁶	-
d_I	Clearance rate of infected cells	$cells^{-2}$	5.80e-7	4.39e-6	[1e-8,1e-4]	⁶	
p	Production rate of virus	d^{-1}			1e0	⁶	Fixed for structural identifiability.
c	Clearance rate of virus	d^{-1}	2.09	1.42	[1e-2,1e2]	⁶	
s_T	Homeostatic CTL proliferation rate	$cell \cdot d^{-1}$	$d_T T(0)$	$d_T T(0)$	-	-	From steady state
r	CTL proliferation rate	d^{-1}	0.599	.197	[1e-4,1e2]	^{5,7}	
k_T	CTL half saturation constant	(PFU/ml)	5.48e+4	11.6	[1e1, 1e8]	⁸	
d_T	Base CTL clearance rate	d^{-1}	0.0572	9.19e-4	[1e-4,1e0]	^{8,9}	

Table A.4.5. Model MB1 parameters

Model MB2 Parameters							
Parameter	Description	Units	Adult	Aged	Search Bounds	Reference	Notes
β	Infection rate of uninfected cells	$(PFU/ml)^{-1}d^{-1}$	2.08e-5	1.70e-5	[1e-8,1e-4]	⁶	-
d_I	Clearance rate of infected cells	$cells^{-2}$	5.72e-7	4.74e-7	[1e-8,1e-4]	⁶	
p	Production rate of virus	d^{-1}			1e0	⁶	Fixed for structural identifiability.
c	Clearance rate of virus	d^{-1}	2.05	12.2	[1e-2,1e2]	⁶	
s_T	Homeostatic CTL proliferation rate	$cell \cdot d^{-1}$	$(d_T + c_T)T(0)$	$(d_T + c_T)T(0)$	-	-	From steady state
r	CTL proliferation rate	d^{-1}	4.18e-1	2.08e-1	[1e-4,1e2]	^{5,7}	
k_T	CTL half saturation constant	(PFU/ml)	1.05e4	1.31e1	[1e1, 1e8]	⁸	
d_T	Base CTL clearance rate	d^{-1}	9.47e-2	1.00e-4	[1e-4,1e0]	^{8,9}	
c_T	CTL downregulation rate	$(PFU/ml)d^{-1}$	1.62e-14	3.20e-6	[0,1e0]	-	Assumed similar to d_T

Table A.4.6. Model MB2 parameters

Model MB3 Parameters							
Parameter	Description	Units	Adult	Aged	Search Bounds	Reference	Notes
β	Infection rate of uninfected cells	$(\text{PFU/ml})^{-1}d^{-1}$	2.08e-5	4.21e-5	[1e-8,1e-4]	⁶	-
d_I	Clearance rate of infected cells	cells^{-2}	5.77e-7	4.31e-7	[1e-8,1e-4]	⁶	Fixed for structural identifiability.
p	Production rate of virus	d^{-1}			1e0	⁶	
c	Clearance rate of virus	d^{-1}	2.05	11.6	[1e-2,1e2]	⁶	
s_T	Homeostatic CTL proliferation rate	$\text{cell} \cdot d^{-1}$	$d_T T(0)$	$d_T T(0)$	-	-	From steady state
r	CTL proliferation rate	$d^{-1}(\text{PFU/ml})^{-1}$	3.13e-6	1.15e-5	[1e-4/ k_V ,1e2/ k_V]	^{5,7}	Bounds are scaled.
d_T	Base CTL clearance rate	d^{-1}	0.0650	1.00e-4	[1e-4,1e0]	^{8,9}	

Table A.4.7. Model MB3 parameters

Model MB4 Parameters							
Parameter	Description	Units	Adult	Aged	Search Bounds	Reference	Notes
β	Infection rate of uninfected cells	$(\text{PFU/ml})^{-1}d^{-1}$	2.08e-5	4.21e-5	[1e-8,1e-4]	⁶	-
d_I	Clearance rate of infected cells	cells^{-2}	5.74e-7	4.34e-7	[1e-8,1e-4]	⁶	Fixed for structural identifiability.
p	Production rate of virus	d^{-1}			1e0	⁶	
c	Clearance rate of virus	d^{-1}	2.05	11.3	[1e-2,1e2]	⁶	
s_T	Homeostatic CTL proliferation rate	$\text{cell} \cdot d^{-1}$	$(d_T + c_T)T(0)$	$(d_T + c_T)T(0)$	-	-	From steady state
r	CTL proliferation rate	$d^{-1}(\text{PFU/ml})^{-1}$	3.13e-6	7.22e-6	[1e-4/ k_V ,1e2/ k_V]	^{5,7}	Bounds are scaled.
d_T	Base CTL clearance rate	d^{-1}	0.0648	1.00e-4	[1e-4,1e0]	^{8,9}	
c_T	CTL downregulation rate	$(\text{PFU/ml})d^{-1}$	9.95e-12	1.61e-1	[0,1e0]	-	Assumed similar to d_T

Table A.4.8. Model MB4 parameters

41 A.4.3 Model Group C

Model MC1 Parameters							
Parameter	Description	Units	Adult	Aged	Search Bounds	Reference	Notes
p	Viral replication rate	d^{-1}	5.07 (4.31,6.48)	3.84	[1e-2,1e2]	⁵	-
k_V	Carrying capacity of virus	(PFU/ml)			1.2e6 (fixed)	-	Determined from data
c_V	Viral clearance rate	$d^{-1}\text{cell}^{-1}$	1.58e-6 (1.18e-6,2.90e-6)	6.87e-7	[1e-8,1e-4]	⁶	From steady state
s_T	Homeostatic CTL proliferation rate	$\text{cell} \cdot d^{-1}$	$d_T T(0)$	$d_T T(0)$	-	-	
r	CTL proliferation rate	d^{-1}	0.278 (0.199,0.341)	0.198	[1e-4,1e2]	^{5,7}	
k_T	CTL half saturation constant	(PFU/ml)	3.19e+3 (1.68e+3,1.29e+4)	1.08e1	[1e1, 1e8]	⁸	From observed CTL range.
d_T	Base CTL clearance rate	d^{-1}	0.0789 (0.0118,0.0952)	1.12e-4	[1e-4,1e0]	^{8,9}	
K	Half saturation constant regulating V replication	cell^{-1}	2.33e-7 (1.84e-7,2.72e-7)	1.25e-6	[0,1e-4]	-	

Table A.4.9. Model MC1 parameters

Model MC2 Parameters							
Parameter	Description	Units	Adult	Aged	Search Bounds	Reference	Notes
p	Viral replication rate	d^{-1}	4.76	3.78	[1e-2,1e2]	⁵	-
k_V	Carrying capacity of virus	(PFU/ml)			1.2e6 (fixed)	-	Determined from data
c_V	Viral clearance rate	$d^{-1}\text{cell}^{-1}$	1.23e-6	5.90e-7	[1e-8,1e-4]	⁶	From steady state
s_T	Homeostatic CTL proliferation rate	$\text{cell} \cdot d^{-1}$	$(d_T + c_T)T(0)$	$(d_T + c_T)T(0)$	-	-	
r	CTL proliferation rate	d^{-1}	0.274	0.231	[1e-4,1e2]	^{5,7}	
k_T	CTL half saturation constant	(PFU/ml)	2.73e3	1.17e2	[1e1, 1e8]	⁸	From observed CTL range.
d_T	Base CTL clearance rate	d^{-1}	7.70e-2	4.03e-4	[1e-4,1e0]	^{8,9}	
c_T	CTL downregulation rate	$(\text{PFU/ml})d^{-1}$	2.08e-6	3.19e-5	[0,1e0]	-	
K	Half saturation constant regulating V replication	cell^{-1}	2.28e-7	1.36e-6	[0,1e-4]	-	

Table A.4.10. Model MC2 parameters

Model MC3 Parameters							
Parameter	Description	Units	Adult	Aged	Search Bounds	Reference	Notes
p	Viral replication rate	d^{-1}	4.72	21.1	[1e-2,1e2]	5	-
k_V	Carrying capacity of virus	(PFU/ml)			1.2e6 (fixed)	-	Determined from data
c_V	Viral clearance rate	$d^{-1} cell^{-1}$	1.18e-6	4.50e-7	[1e-8,1e-4]	6	
s_T	Homeostatic CTL proliferation rate	$cell \cdot d^{-1}$	$d_T T(0)$	$d_T T(0)$	-	-	From steady state
r	CTL proliferation rate	$d^{-1} (PFU/ml)^{-1}$	1.37e-5	1.38e-5	[1e-4/ k_V ,1e2/ k_V]	5,7	Bounds are scaled.
d_T	Base CTL clearance rate	d^{-1}	1.00e-4	1.00e-4	[1e-4,1e0]	8,9	
K	Half saturation constant regulating V replication	$cell^{-1}$	4.03e-7	6.07e-6	[0,1e-4]	-	From observed CTL range.

Table A.4.11. Model MC3 parameters

Model MC4 Parameters							
Parameter	Description	Units	Adult	Aged	Search Bounds	Reference	Notes
p	Viral replication rate	d^{-1}	5.11	4.47	[1e-2,1e2]	5	-
k_V	Carrying capacity of virus	(PFU/ml)			1.2e6 (fixed)	-	Determined from data
c_V	Viral clearance rate	$d^{-1} cell^{-1}$	1.39e-6	4.98e-7	[1e-8,1e-4]	6	
s_T	Homeostatic CTL proliferation rate	$cell \cdot d^{-1}$	$(d_T + c_T)T(0)$	$(d_T + c_T)T(0)$	-	-	From steady state
r	CTL proliferation rate	$d^{-1} (PFU/ml)^{-1}$	9.27e-7	1.06e-5	[1e-4/ k_V ,1e2/ k_V]	5,7	Bounds are scaled.
d_T	Base CTL clearance rate	d^{-1}	1.00e-4	1.00e-4	[1e-4,1e0]	8,9	
c_T	CTL downregulation rate	$(PFU/ml)d^{-1}$	0.126	9.32e-2	[0,1e0]	-	Assumed similar to d_T
K	Half saturation constant regulating V replication	$cell^{-1}$	2.86e-7	1.84e-6	[0,1e-4]	-	From observed CTL range.

Table A.4.12. Model MC4 parameters

42 A.4.4 Model Group D

Model MD1 Parameters							
Parameter	Description	Units	Adult	Aged	Search Bounds	Reference	Notes
β	Infection rate of uninfected cells	$(PFU/ml)^{-1} d^{-1}$	2.23e-5	4.67e-5 (1.71e-5,6.54e-5)	[1e-8,1e-4]	6	-
d_I	Clearance rate of infected cells	$cells^{-2}$	5.57e-7	4.50e-7 (3.51e-7,4.46e-6)	[1e-8,1e-4]	6	
p	Production rate of virus	d^{-1}			1e0	6	Fixed for structural identifiability.
c	Clearance rate of virus	d^{-1}	2.17	12.3 (1.36,17.8)	[1e-2,1e2]	6	
s_T	Homeostatic CTL proliferation rate	$cell \cdot d^{-1}$	$d_T T(0)$	$d_T T(0)$	-	-	From steady state
r	CTL proliferation rate	d^{-1}	4.18e-1	0.208 (0.171,0.325)	[1e-4,1e2]	5,7	
k_T	CTL half saturation constant	(PFU/ml)	1.05e4	12.0 (10.0,156)	[1e1, 1e8]	8	
d_T	Base CTL clearance rate	d^{-1}	9.47e-2	1.00e-4 (1.00e-4,0.0777)	[1e-4,1e0]	8,9	
K	Half saturation constant regulating V replication	$cell^{-1}$	1.29e-14	1.66e-7 (8.90e-11,1.54e-6)	[0,1e-4]	-	From observed CTL range.

Table A.4.13. Model MD1 parameters

Model MD2 Parameters							
Parameter	Description	Units	Adult	Aged	Search Bounds	Reference	Notes
β	Infection rate of uninfected cells	$(PFU/ml)^{-1} d^{-1}$	2.23e-5	4.68e-5	[1e-8,1e-4]	6	-
d_I	Clearance rate of infected cells	$cells^{-2}$	5.57e-7	4.50e-7	[1e-8,1e-4]	6	
p	Production rate of virus	d^{-1}			1e0	6	Fixed for structural identifiability.
c	Clearance rate of virus	d^{-1}	2.17	12.3	[1e-2,1e2]	6	
s_T	Homeostatic CTL proliferation rate	$cell \cdot d^{-1}$	$(d_T + c_T)T(0)$	$(d_T + c_T)T(0)$	-	-	From steady state
r	CTL proliferation rate	d^{-1}	4.18e-1	0.208	[1e-4,1e2]	5,7	
k_T	CTL half saturation constant	(PFU/ml)	1.05e4	12.5	[1e1, 1e8]	8	
d_T	Base CTL clearance rate	d^{-1}	9.47e-2	1.12 e-4	[1e-4,1e0]	8,9	
c_T	CTL downregulation rate	$(PFU/ml)d^{-1}$	1.75e-12	6.04e-6	[0,1e0]	-	Assumed similar to d_T
K	Half saturation constant regulating V replication	$cell^{-1}$	2.99e-12	1.67e-7	[0,1e-4]	-	From observed CTL range.

Table A.4.14. Model MD2 parameters

Model MD3 Parameters							
Parameter	Description	Units	Adult	Aged	Search Bounds	Reference	Notes
β	Infection rate of uninfected cells	$(\text{PFU/ml})^{-1} d^{-1}$	2.09e-5	2.31e-5	[1e-8,1e-4]	6	-
d_I	Clearance rate of infected cells	cells^{-2}	5.86e-7	5.57e-7	[1e-8,1e-4]	6	Fixed for structural identifiability.
p	Production rate of virus	d^{-1}			1e0	6	
c	Clearance rate of virus	d^{-1}	2.02	1.29	[1e-2,1e2]	6	
s_T	Homeostatic CTL proliferation rate	$\text{cell} \cdot d^{-1}$	$d_T T(0)$	$d_T T(0)$	-	-	From steady state
r	CTL proliferation rate	$d^{-1} (\text{PFU/ml})^{-1}$	3.12e-6	1.20e-5	[1e-4/ k_V ,1e2/ k_V]	5,7	Bounds are scaled.
d_T	Base CTL clearance rate	d^{-1}	6.52e-2	1.00e-4	[1e-4,1e0]	8,9	
K	Half saturation constant regulating V replication	cell^{-2}	2.11e-12	2.52e-6	[0,1e-4]	-	From observed CTL range.

Table A.4.15. Model MD3 parameters

Model MD4 Parameters							
Parameter	Description	Units	Adult	Aged	Search Bounds	Reference	Notes
β	Infection rate of uninfected cells	$(\text{PFU/ml})^{-1} d^{-1}$	2.09e-5	2.09e-5	[1e-8,1e-4]	6	-
d_I	Clearance rate of infected cells	cells^{-2}	5.86e-7	5.63e-6	[1e-8,1e-4]	6	Fixed for structural identifiability.
p	Production rate of virus	d^{-1}			1e0	6	
c	Clearance rate of virus	d^{-1}	2.02	1.43	[1e-2,1e2]	6	
s_T	Homeostatic CTL proliferation rate	$\text{cell} \cdot d^{-1}$	$(d_T + c_T)T(0)$	$(d_T + c_T)T(0)$	-	-	From steady state
r	CTL proliferation rate	$d^{-1} (\text{PFU/ml})^{-1}$	3.12e-6	8.50e-6	[1e-4/ k_V ,1e2/ k_V]	5,7	Bounds are scaled.
d_T	Base CTL clearance rate	d^{-1}	6.52e-2	1.00e-4	[1e-4,1e0]	8,9	
c_T	CTL downregulation rate	$(\text{PFU/ml})d^{-1}$	5.82e-12	1.40e-1	[0,1e0]	-	Assumed similar to d_T
K	Half saturation constant regulating V replication	cell^{-2}	1.99e-13	1.81e-6	[0,1e-4]	-	From observed CTL range.

Table A.4.16. Model MD4 parameters

43 A.5 Fit Model Plots

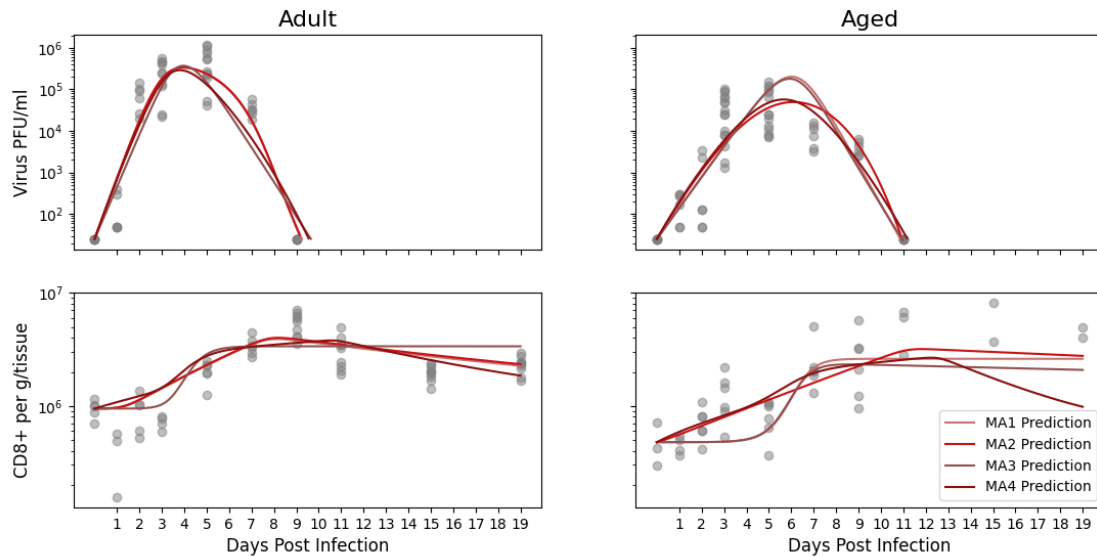


Figure A.5.1. Group A Fits

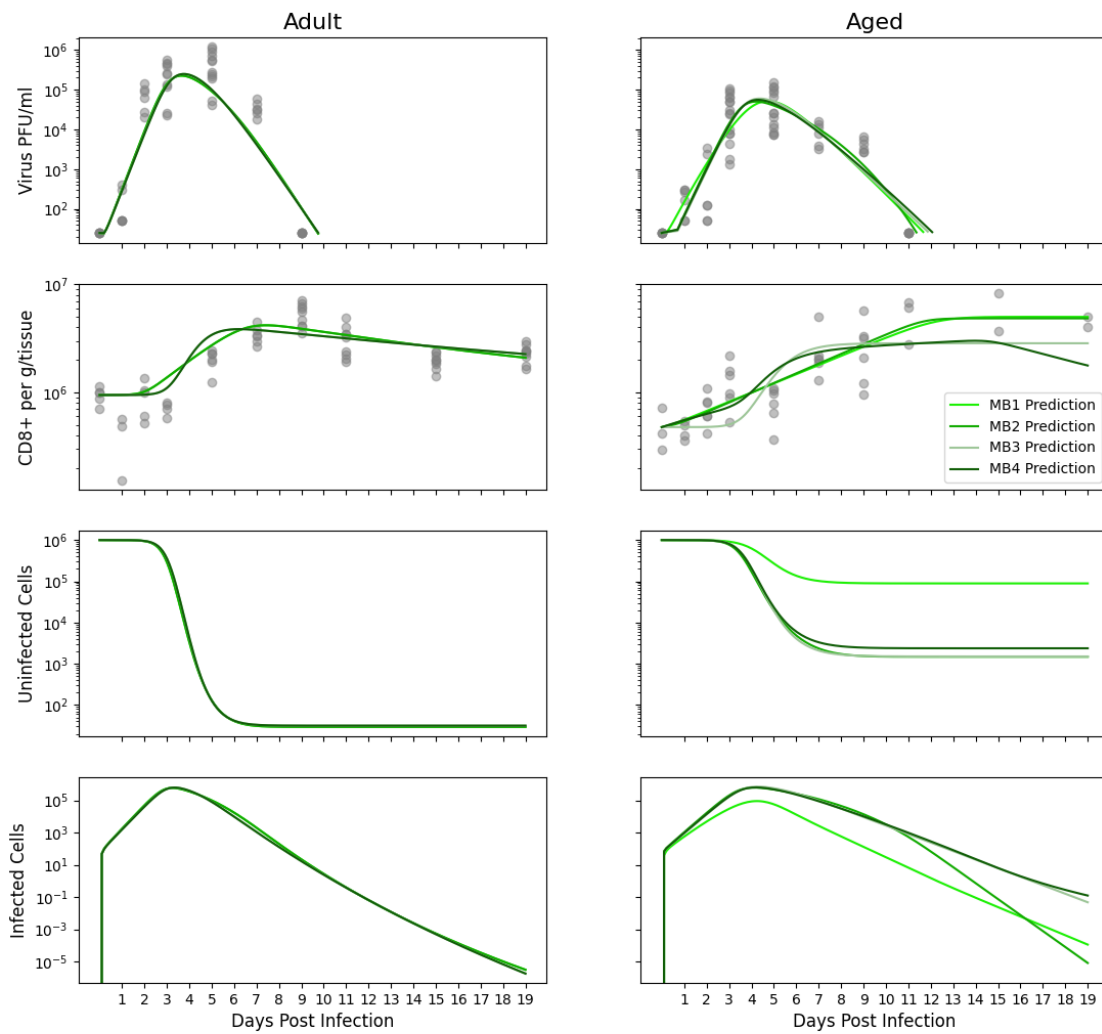


Figure A.5.2. Group B Fits

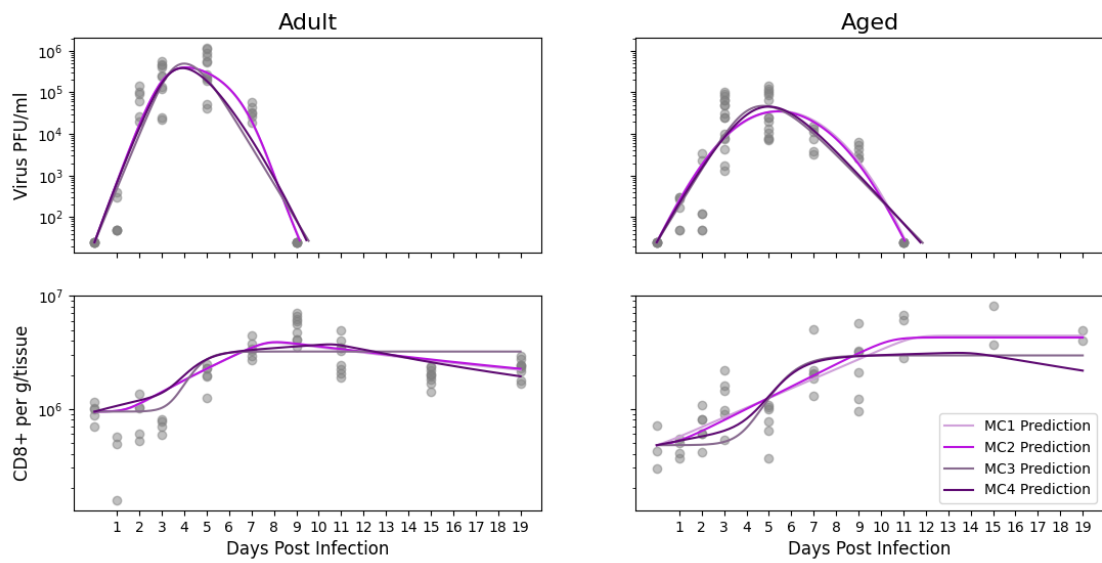


Figure A.5.3. Group C Fits

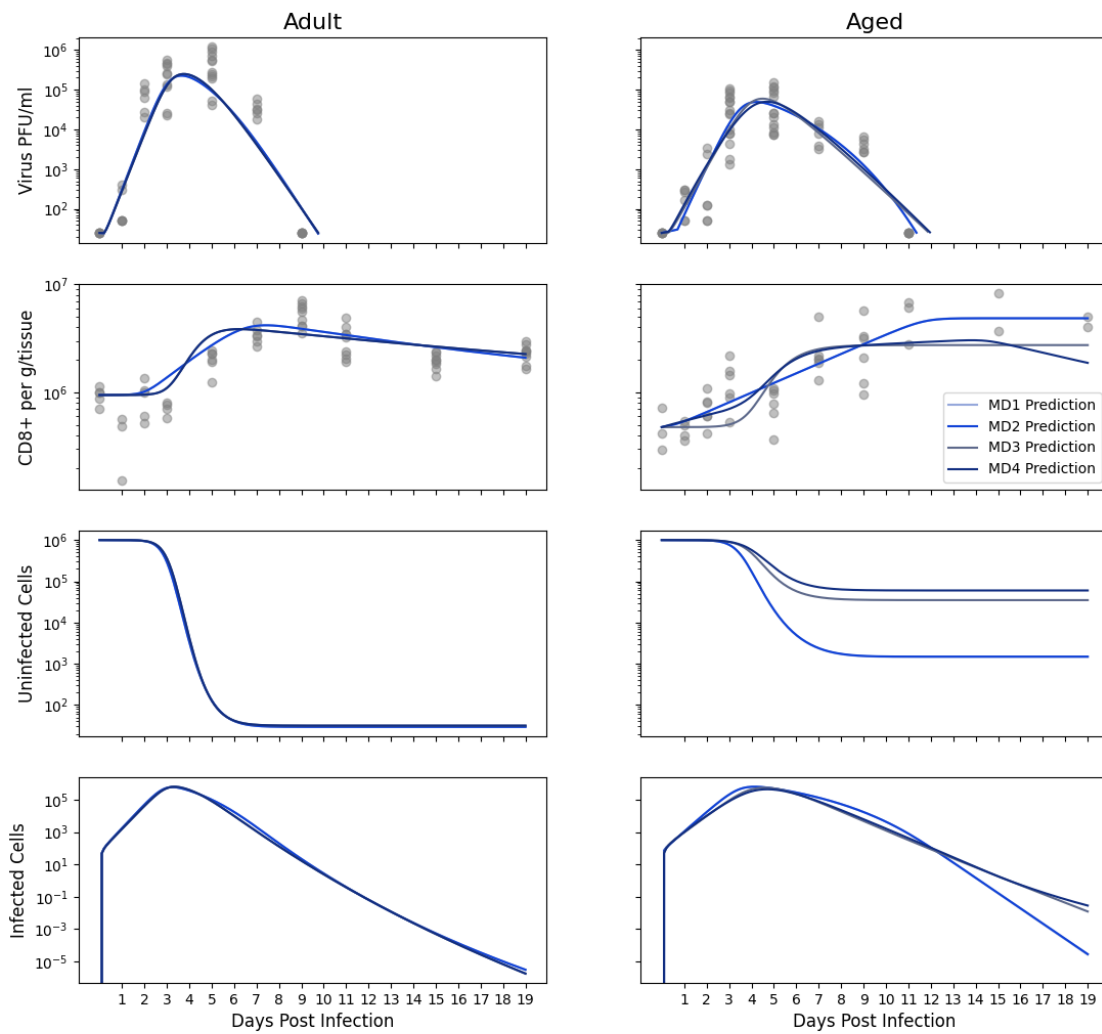


Figure A.5.4. Group D Fits

44 **A.6 Bootstrapped Predictions for the Selected Models**

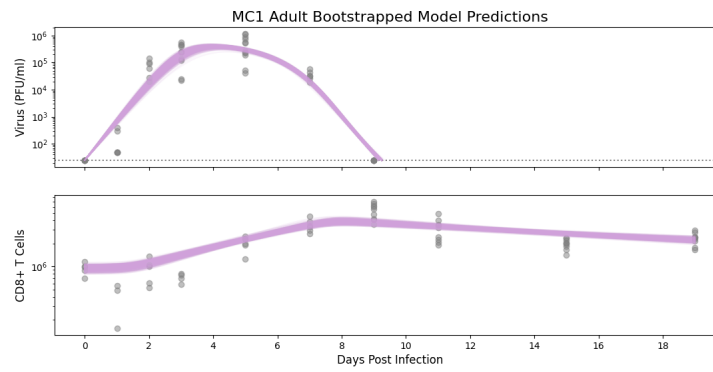


Figure A.6.1. Adult model (MC1) bootstrapped predictions

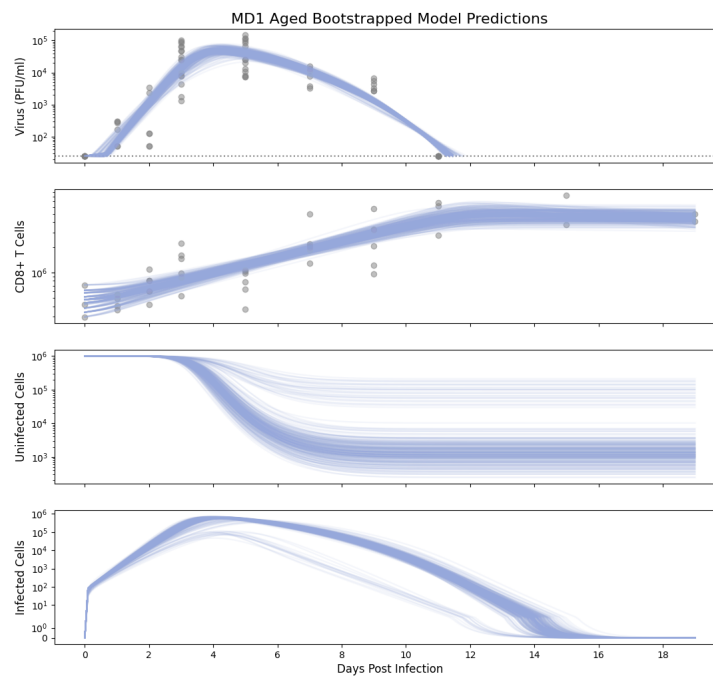


Figure A.6.2. Aged model (MD1) bootstrapped predictions

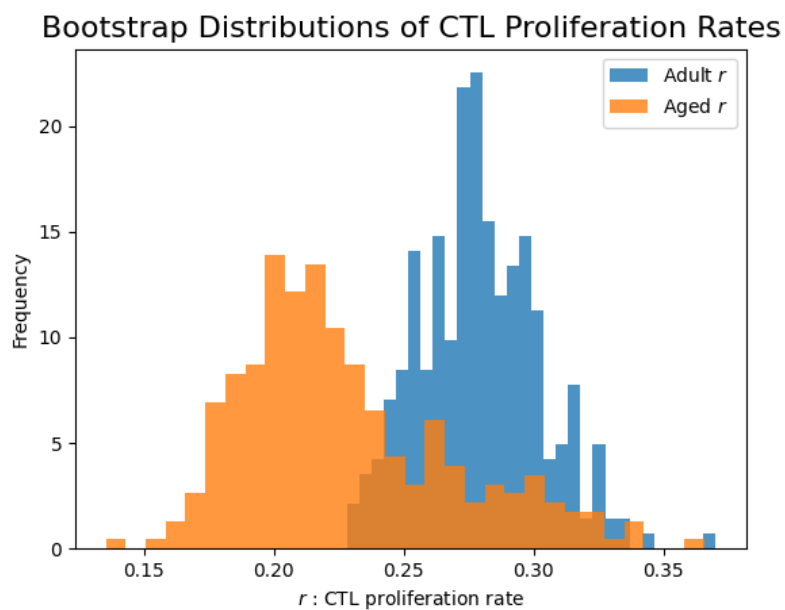


Figure A.7.1. r posterior distributions

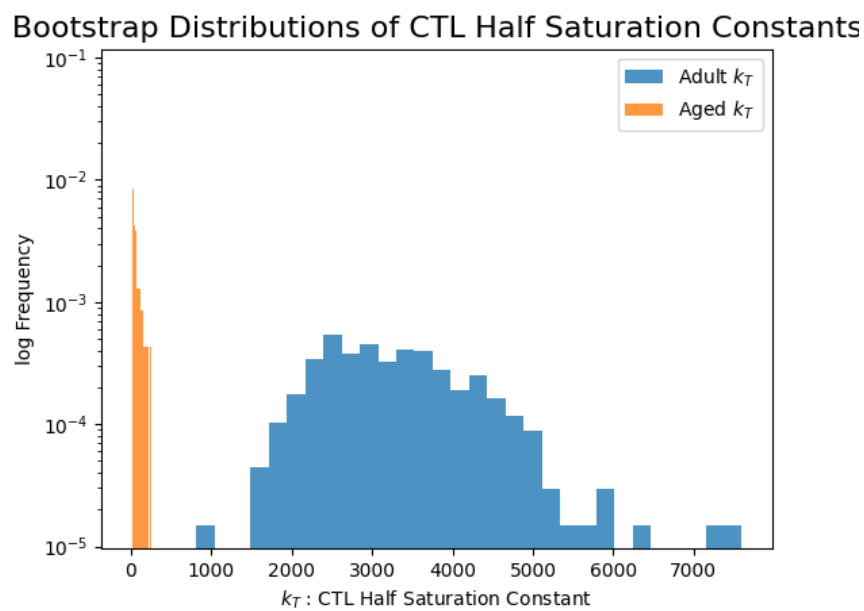


Figure A.7.2. k_T posterior distributions

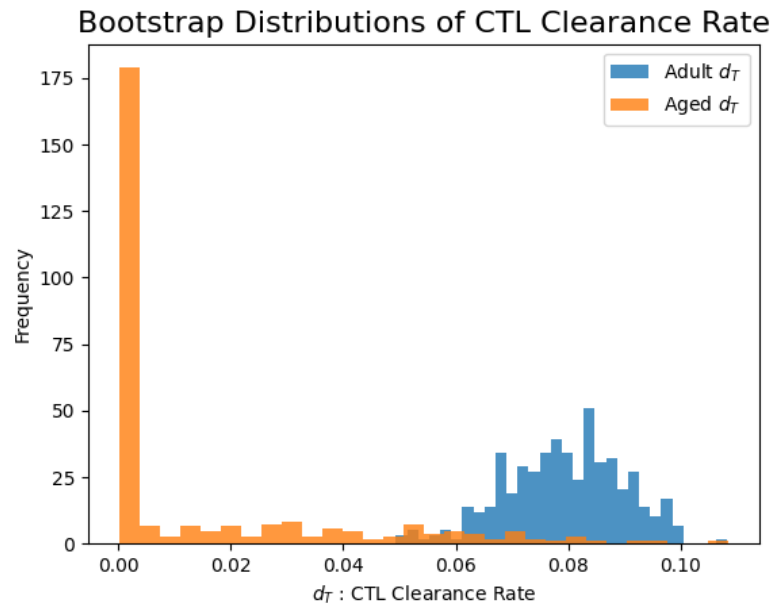


Figure A.7.3. d_T posterior distributions

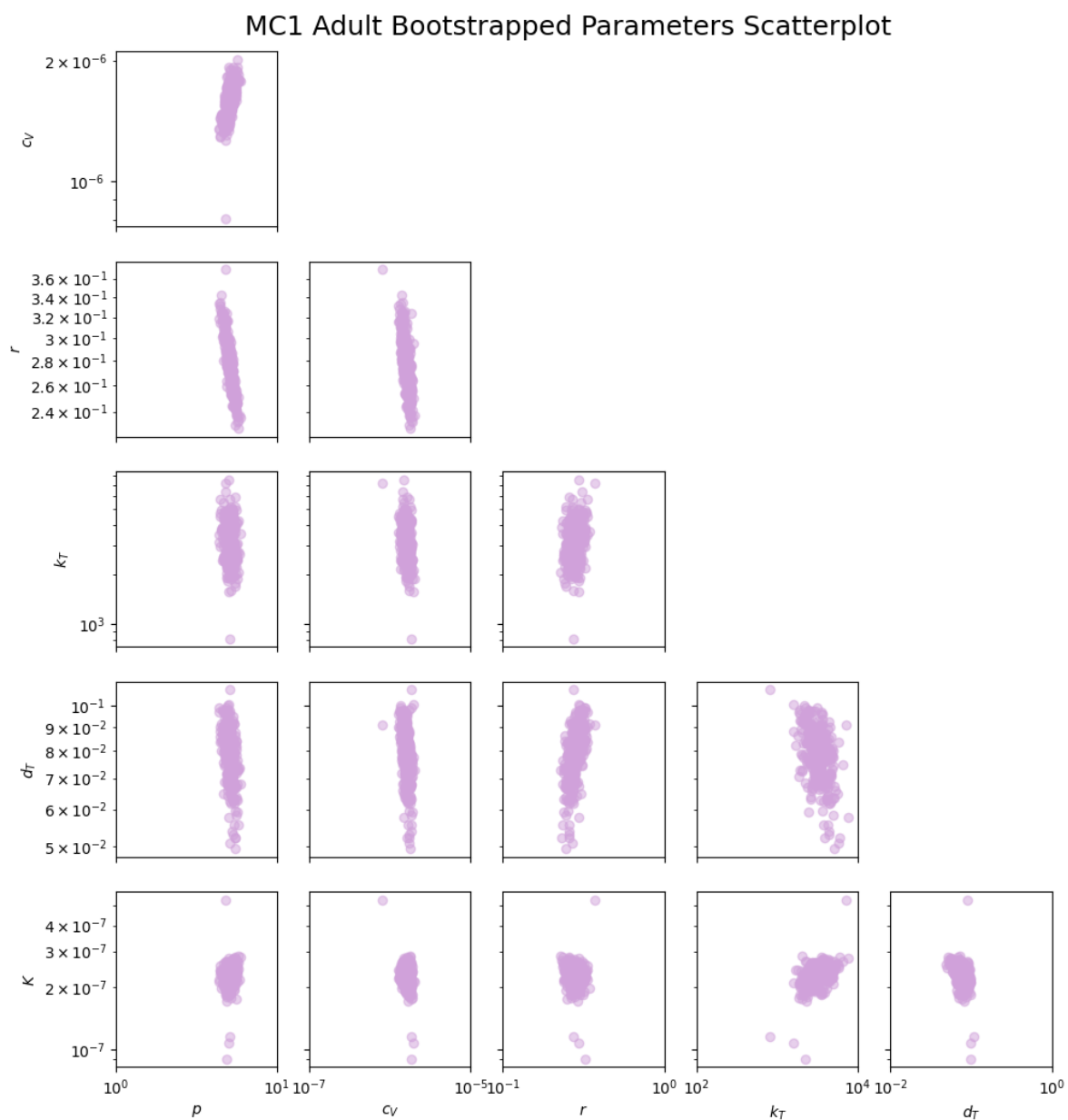


Figure A.8.1. Bootstrapping scatterplot for the adult model (MC1)

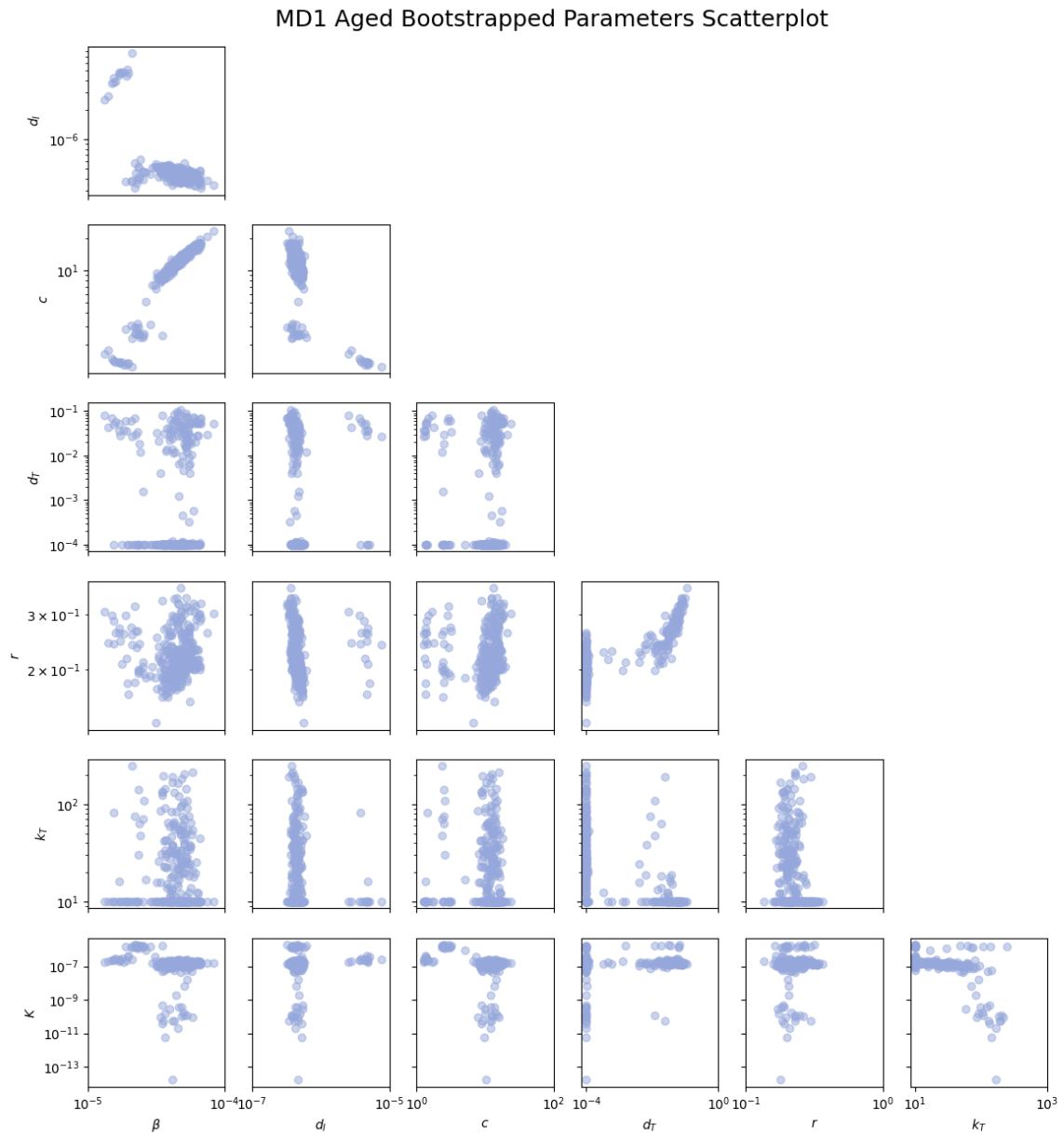


Figure A.8.2. Bootstrapping scatterplot for the adult model (MD1)

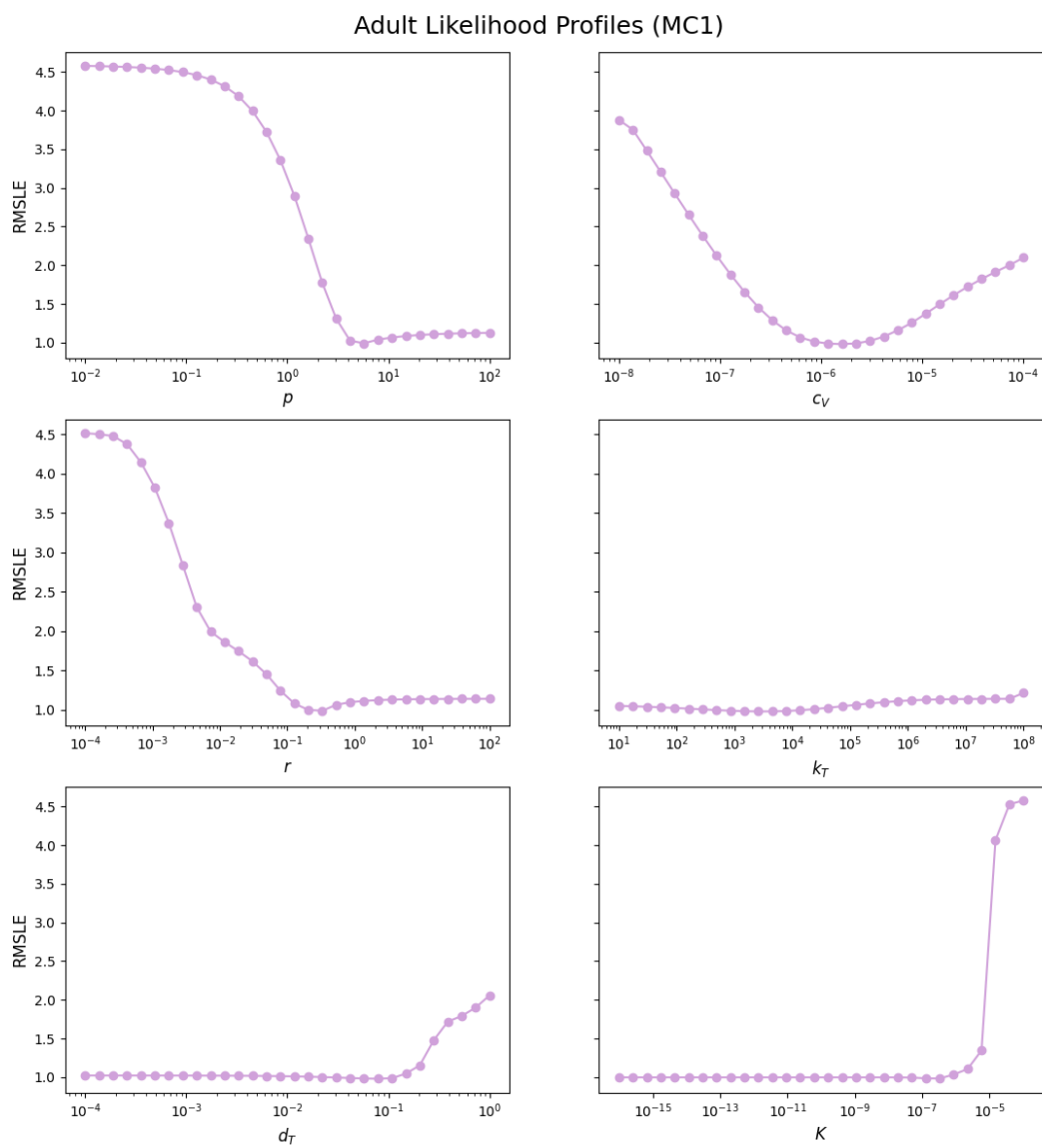


Figure A.9.1

Aged Likelihood Profiles (MD1)

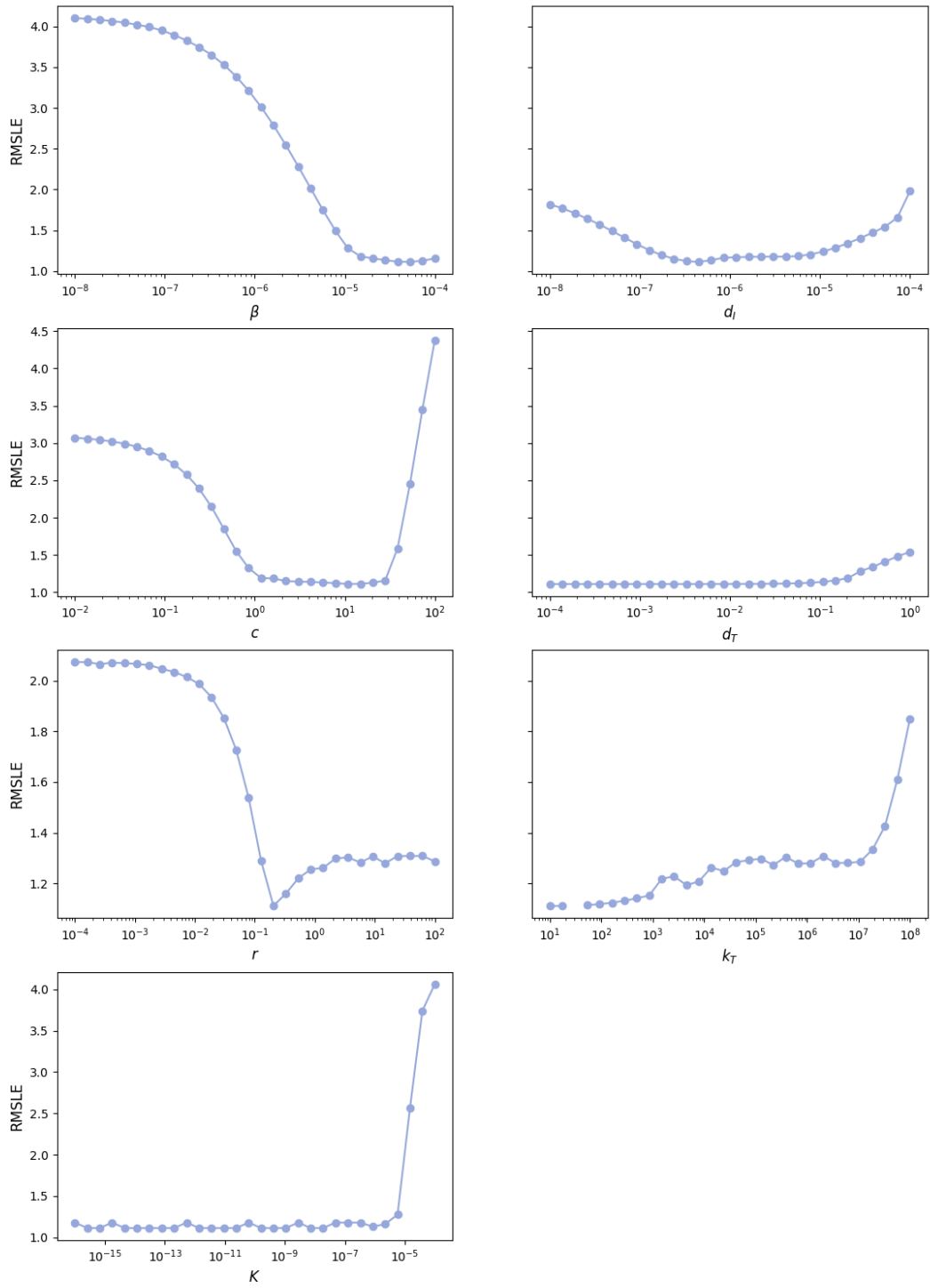
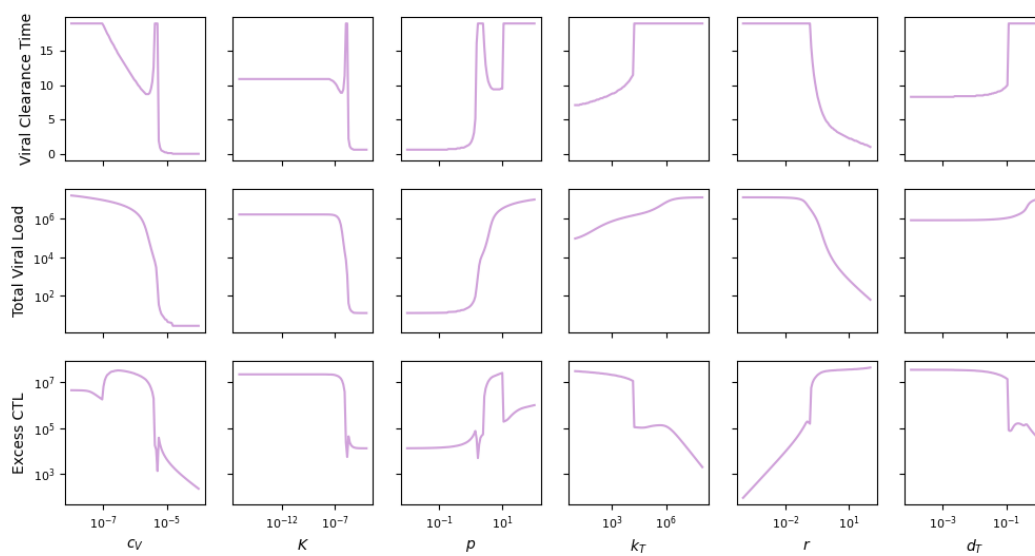
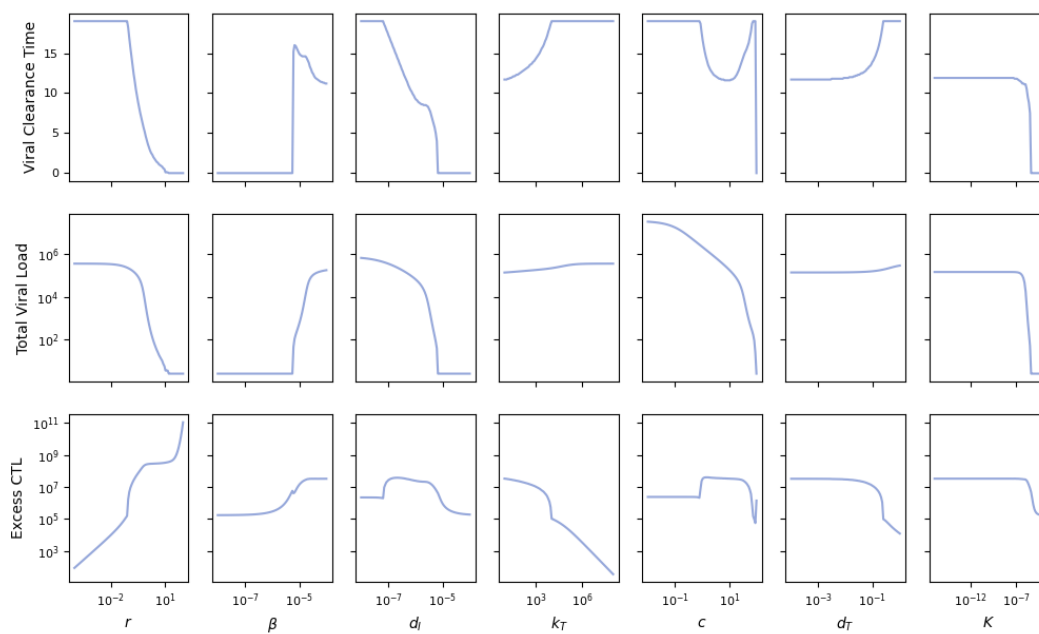


Figure A.9.2

Model MC1 adult fit local sensitivity**Figure A.10.1****Model MD1 aged fit local sensitivity****Figure A.10.2**

References

1. Zhou, J., Matsuoka, M., Cantor, H., Homer, R. & Enelow, R. I. Cutting edge: engagement of NKG2A on CD8+ effector T cells limits immunopathology in influenza pneumonia. *The J. Immunol.* **180**, 25–29 (2008).
2. Van De Sandt, C. E. *et al.* Human CD8+ T cells damage noninfected epithelial cells during influenza virus infection in vitro. *Am. J. Respir. Cell Mol. Biol.* **57**, 536–546 (2017).
3. Xu, L. *et al.* Cutting edge: pulmonary immunopathology mediated by antigen-specific expression of TNF- α by antiviral CD8+ T cells. *The J. Immunol.* **173**, 721–725 (2004).
4. Hastie, T., Tibshirani, R., Friedman, J. H. & Friedman, J. H. *The elements of statistical learning: data mining, inference, and prediction*, vol. 2 (Springer, 2009).
5. Boianelli, A. *et al.* Modeling influenza virus infection: a roadmap for influenza research. *Viruses* **7**, 5274–5304 (2015).
6. Hernandez-Vargas, E. A. *et al.* Effects of aging on influenza virus infection dynamics. *J. Virol.* **88**, 4123–4131 (2014).
7. Zarnitsyna, V. I. *et al.* Mathematical model reveals the role of memory cd8 t cell populations in recall responses to influenza. *Front. immunology* **7**, 165 (2016).
8. Myers, M. A. *et al.* Dynamically linking influenza virus infection kinetics, lung injury, inflammation, and disease severity. *Elife* **10**, e68864 (2021).
9. McDonagh, M. & Bell, E. The survival and turnover of mature and immature CD8 T cells. *Immunology* **84**, 514 (1995).