

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

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Appendix A

A.1 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.1.1. Mathematical form of the 16 models considered.

| 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.2.1. Model group A structural identifiabilities. Model group A uses a logistic form for viral dynamics and does not incorporate direct suppression of viral replication by CD8+ T cells.

| 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.2.2. Group B structural identifiabilities. Model group B uses a target cell limited model for viral dynamics and does not incorporate direct suppression of viral replication by CD8+ T cells.

| 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.2.3. Group C structural identifiabilities. Model group C uses a logistic form for viral dynamics and incorporates direct suppression of viral replication by CD8+ T cells.

| 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.2.4. Group D structural identifiabilities. Model group D uses a target cell limited model for viral dynamics and incorporates direct suppression of viral replication by CD8+ T cells.

14 A.3 All Model Parameter Fits

15 A.3.1 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] | ¹ | - |
| 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] | ² | |
| s_T | Homeostatic CD8+ T cell proliferation rate | $cell \cdot d^{-1}$ | $d_T T(0)$ | $d_T T(0)$ | - | - | From steady state |
| r | CD8+ T cell proliferation rate | d^{-1} | 0.274 | 99.9 | [1e-4,1e2] | ^{1,3} | |
| k_T | CD8+ T cell half saturation constant | (PFU/ml) | 2.48e+3 | 2.50e+7 | [1e1, 1e8] | ⁴ | |
| d_T | Base CD8+ T cell clearance rate | d^{-1} | 0.0775 | 1.00e-4 | [1e-4,1e0] | ^{4,5} | |

Table A.3.1. Summary of MA1 parameters. The mathematical expression for MA1 is presented in [A.1.1](#).

| 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] | ¹ | - |
| 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] | ² | |
| s_T | Homeostatic CD8+ T cell proliferation rate | $cell \cdot d^{-1}$ | $(d_T + c_T)T(0)$ | $(d_T + c_T)T(0)$ | - | - | From steady state |
| r | CD8+ T cell proliferation rate | d^{-1} | 0.273 | 0.157 | [1e-4,1e2] | ^{1,3} | |
| k_T | CD8+ T cell half saturation constant | (PFU/ml) | 2.21e+3 | 1e1 | [1e1, 1e8] | ⁴ | |
| d_T | Base CD8+ T cell clearance rate | d^{-1} | 0.0757 | 1.36e-4 | [1e-4,1e0] | ^{4,5} | |
| c_T | CD8+ T cell downregulation rate | $(PFU/ml)d^{-1}$ | 7.02e-8 | 0.0612 | [0,1e0] | - | Assumed similar to d_T |

Table A.3.2. Summary of MA2 parameters. The mathematical expression for MA2 is presented in [A.1.1](#).

| 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] | ¹ | - |
| 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] | ² | |
| s_T | Homeostatic CD8+ T cell proliferation rate | $cell \cdot d^{-1}$ | $d_T T(0)$ | $d_T T(0)$ | - | - | From steady state |
| r | CD8+ T cell proliferation rate | $d^{-1}(PFU/ml)^{-1}$ | 1.91e-6 | 4.28e-6 | [1e-4/ k_V ,1e2/ k_V] | ^{1,3} | Bounds are scaled. |
| d_T | Base CD8+ T cell clearance rate | d^{-1} | 1.00e-4 | 0.0146 | [1e-4,1e0] | ^{4,5} | |

Table A.3.3. Summary of MA3 parameters. The mathematical expression for MA3 is presented in [A.1.1](#).

| 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] | ¹ | - |
| 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] | ² | |
| s_T | Homeostatic CD8+ T cell proliferation rate | $cell \cdot d^{-1}$ | $(d_T + c_T)T(0)$ | $(d_T + c_T)T(0)$ | - | - | From steady state |
| r | CD8+ T cell proliferation rate | $d^{-1}(PFU/ml)^{-1}$ | 1.12e-6 | 3.43e-6 | [1e-4/ k_V ,1e2/ k_V] | ^{1,3} | Bounds are scaled. |
| d_T | Base CD8+ T cell clearance rate | d^{-1} | 1.00e-4 | 1.00e-4 | [1e-4,1e0] | ^{4,5} | |
| c_T | CD8+ T cell downregulation rate | $(PFU/ml)d^{-1}$ | 0.142 | 0.236 | [0,1e0] | - | Assumed similar to d_T |

Table A.3.4. Summary of MA4 parameters. The mathematical expression for MA4 is presented in [A.1.1](#).

| Model MB1 Parameters | | | | | | | |
|----------------------|--|------------------------------|------------|------------|---------------|---------------------|---------------------------------------|
| Parameter | Description | Units | Adult | Aged | Search Bounds | Reference | Notes |
| β | Infection rate of uninfected cells | $(\text{PFU/ml})^{-1}d^{-1}$ | 2.10e-5 | 1.77e-5 | [1e-8,1e-4] | 2 | - |
| d_I | Clearance rate of infected cells | cells^{-2} | 5.80e-7 | 4.39e-6 | [1e-8,1e-4] | 2 | Fixed for structural identifiability. |
| p | Production rate of virus | d^{-1} | | | 1e0 | 2 | |
| c | Clearance rate of virus | d^{-1} | 2.09 | 1.42 | [1e-2,1e2] | 2 | |
| s_T | Homeostatic CD8+ T cell proliferation rate | $\text{cell} \cdot d^{-1}$ | $d_T T(0)$ | $d_T T(0)$ | - | - | From steady state |
| r | CD8+ T cell proliferation rate | d^{-1} | 0.599 | .197 | [1e-4,1e2] | 1,3 | |
| k_T | CD8+ T cell half saturation constant | (PFU/ml) | 5.48e+4 | 11.6 | [1e1, 1e8] | 4 | |
| d_T | Base CD8+ T cell clearance rate | d^{-1} | 0.0572 | 9.19e-4 | [1e-4,1e0] | 4,5 | |

Table A.3.5. Summary of MB1 parameters. The mathematical expression for MB1 is presented in [A.1.1](#).

| Model MB2 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 | 1.70e-5 | [1e-8,1e-4] | 2 | - |
| d_I | Clearance rate of infected cells | cells^{-2} | 5.72e-7 | 4.74e-7 | [1e-8,1e-4] | 2 | Fixed for structural identifiability. |
| p | Production rate of virus | d^{-1} | | | 1e0 | 2 | |
| c | Clearance rate of virus | d^{-1} | 2.05 | 12.2 | [1e-2,1e2] | 2 | |
| s_T | Homeostatic CD8+ T cell proliferation rate | $\text{cell} \cdot d^{-1}$ | $(d_T + c_T)T(0)$ | $(d_T + c_T)T(0)$ | - | - | From steady state |
| r | CD8+ T cell proliferation rate | d^{-1} | 4.18e-1 | 2.08e-1 | [1e-4,1e2] | 1,3 | |
| k_T | CD8+ T cell half saturation constant | (PFU/ml) | 1.05e4 | 1.31e1 | [1e1, 1e8] | 4 | Assumed similar to d_T |
| d_T | Base CD8+ T cell clearance rate | d^{-1} | 9.47e-2 | 1.00e-4 | [1e-4,1e0] | 4,5 | |
| c_T | CD8+ T cell downregulation rate | $(\text{PFU}/\text{ml})d^{-1}$ | 1.62e-14 | 3.20e-6 | [0,1e0] | - | |

Table A.3.6. Summary of MB2 parameters. The mathematical expression for MB2 is presented in [A.1.1](#).

| 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] | 2 | - |
| d_I | Clearance rate of infected cells | cells^{-2} | 5.77e-7 | 4.31e-7 | [1e-8,1e-4] | 2 | Fixed for structural identifiability. |
| p | Production rate of virus | d^{-1} | | | 1e0 | 2 | |
| c | Clearance rate of virus | d^{-1} | 2.05 | 11.6 | [1e-2,1e2] | 2 | |
| s_T | Homeostatic CD8+ T cell proliferation rate | $\text{cell} \cdot d^{-1}$ | $d_T T(0)$ | $d_T T(0)$ | - | - | From steady state |
| r | CD8+ T cell proliferation rate | $d^{-1}(\text{PFU}/\text{ml})^{-1}$ | 3.13e-6 | 1.15e-5 | [1e-4/ k_V ,1e2/ k_V] | 1,3 | Bounds are scaled. |
| d_T | Base CD8+ T cell clearance rate | d^{-1} | 0.0650 | 1.00e-4 | [1e-4,1e0] | 4,5 | |

Table A.3.7. Summary of MB3 parameters. The mathematical expression for MB3 is presented in [A.1.1](#).

| 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] | ² | - |
| d_I | Clearance rate of infected cells | cells^{-2} | 5.74e-7 | 4.34e-7 | [1e-8,1e-4] | ² | Fixed for structural identifiability. |
| p | Production rate of virus | d^{-1} | | | 1e0 | ² | |
| c | Clearance rate of virus | d^{-1} | 2.05 | 11.3 | [1e-2,1e2] | ² | |
| s_T | Homeostatic CD8+ T cell proliferation rate | $\text{cell} \cdot d^{-1}$ | $(d_T + c_T)T(0)$ | $(d_T + c_T)T(0)$ | - | - | From steady state |
| r | CD8+ T cell proliferation rate | $d^{-1}(\text{PFU/ml})^{-1}$ | 3.13e-6 | 7.22e-6 | [1e-4/ k_V ,1e2/ k_V] | ^{1,3} | Bounds are scaled. |
| d_T | Base CD8+ T cell clearance rate | d^{-1} | 0.0648 | 1.00e-4 | [1e-4,1e0] | ^{4,5} | |
| c_T | CD8+ T cell downregulation rate | $(\text{PFU/ml})d^{-1}$ | 9.95e-12 | 1.61e-1 | [0,1e0] | - | Assumed similar to d_T |

Table A.3.8. Summary of MB4 parameters. The mathematical expression for MB4 is presented in [A.1.1](#).

| 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] | ¹ | - |
| k_V | Carrying capacity of virus | (PFU/ml) | | | 1.2e6 (fixed) | - | Determined from data |
| c_V | Viral clearance rate | $d^{-1} cell^{-1}$ | 1.58e-6 (1.18e-6,2.90e-6) | 6.87e-7 | [1e-8,1e-4] | ² | |
| s_T | Homeostatic CD8+ T cell proliferation rate | $cell \cdot d^{-1}$ | $d_T T(0)$ | $d_T T(0)$ | - | - | From steady state |
| r | CD8+ T cell proliferation rate | d^{-1} | 0.278 (0.199,0.341) | 0.198 | [1e-4,1e2] | ^{1,3} | |
| k_T | CD8+ T cell half saturation constant | (PFU/ml) | 3.19e+3 (1.68e+3,1.29e+4) | 1.08e1 | [1e1, 1e8] | ⁴ | |
| d_T | Base CD8+ T cell clearance rate | d^{-1} | 0.0789 (0.0118,0.0952) | 1.12e-4 | [1e-4,1e0] | ^{4,5} | |
| K | Half saturation constant regulating V replication | $cell^{-1}$ | 2.33e-7 (1.84e-7,2.72e-7) | 1.25e-6 | [0,1e-4] | - | From observed CD8+ T cell range. |

Table A.3.9. Summary of MC1 parameters. The mathematical expression for MC1 is presented in [A.1.1](#).

| 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] | ¹ | - |
| k_V | Carrying capacity of virus | (PFU/ml) | | | 1.2e6 (fixed) | - | Determined from data |
| c_V | Viral clearance rate | $d^{-1} cell^{-1}$ | 1.23e-6 | 5.90e-7 | [1e-8,1e-4] | ² | |
| s_T | Homeostatic CD8+ T cell proliferation rate | $cell \cdot d^{-1}$ | $(d_T + c_T)T(0)$ | $(d_T + c_T)T(0)$ | - | - | From steady state |
| r | CD8+ T cell proliferation rate | d^{-1} | 0.274 | 0.231 | [1e-4,1e2] | ^{1,3} | |
| k_T | CD8+ T cell half saturation constant | (PFU/ml) | 2.73e3 | 1.17e2 | [1e1, 1e8] | ⁴ | |
| d_T | Base CD8+ T cell clearance rate | d^{-1} | 7.70e-2 | 4.03e-4 | [1e-4,1e0] | ^{4,5} | |
| c_T | CD8+ T cell downregulation rate | $(PFU/ml)d^{-1}$ | 2.08e-6 | 3.19e-5 | [0,1e0] | - | Assumed similar to d_T |
| K | Half saturation constant regulating V replication | $cell^{-1}$ | 2.28e-7 | 1.36e-6 | [0,1e-4] | - | From observed CD8+ T cell range. |

Table A.3.10. Summary of MC2 parameters. The mathematical expression for MC2 is presented in [A.1.1](#).

| 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] | ¹ | - |
| 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] | ² | |
| s_T | Homeostatic CD8+ T cell proliferation rate | $cell \cdot d^{-1}$ | $d_T T(0)$ | $d_T T(0)$ | - | - | From steady state |
| r | CD8+ T cell proliferation rate | $d^{-1}(PFU/ml)^{-1}$ | 1.37e-5 | 1.38e-5 | [1e-4/ k_V ,1e2/ k_V] | ^{1,3} | Bounds are scaled. |
| d_T | Base CD8+ T cell clearance rate | d^{-1} | 1.00e-4 | 1.00e-4 | [1e-4,1e0] | ^{4,5} | |
| K | Half saturation constant regulating V replication | $cell^{-1}$ | 4.03e-7 | 6.07e-6 | [0,1e-4] | - | From observed CD8+ T cell range. |

Table A.3.11. Summary of MC3 parameters. The mathematical expression for MC3 is presented in [A.1.1](#).

| 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] | ¹ | - |
| 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] | ² | |
| s_T | Homeostatic CD8+ T cell proliferation rate | $cell \cdot d^{-1}$ | $(d_T + c_T)T(0)$ | $(d_T + c_T)T(0)$ | - | - | From steady state |
| r | CD8+ T cell proliferation rate | $d^{-1}(PFU/ml)^{-1}$ | 9.27e-7 | 1.06e-5 | [1e-4/ k_V ,1e2/ k_V] | ^{1,3} | Bounds are scaled. |
| d_T | Base CD8+ T cell clearance rate | d^{-1} | 1.00e-4 | 1.00e-4 | [1e-4,1e0] | ^{4,5} | |
| c_T | CD8+ T cell 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 CD8+ T cell range. |

Table A.3.12. Summary of MC4 parameters. The mathematical expression for MC4 is presented in [A.1.1](#).

| Model MD1 Parameters | | | | | | | |
|----------------------|---|------------------------------|------------|----------------------------|---------------|----------------|---------------------------------------|
| Parameter | Description | Units | Adult | Aged | Search Bounds | Reference | Notes |
| β | Infection rate of uninfected cells | $(\text{PFU/ml})^{-1}d^{-1}$ | 2.23e-5 | 4.67e-5 (1.71e-5,6.54e-5) | [1e-8,1e-4] | ² | - |
| 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] | ² | Fixed for structural identifiability. |
| p | Production rate of virus | d^{-1} | | | 1e0 | ² | |
| c | Clearance rate of virus | d^{-1} | 2.17 | 12.3 (1.36,17.8) | [1e-2,1e2] | ² | |
| s_T | Homeostatic CD8+ T cell proliferation rate | $\text{cell} \cdot d^{-1}$ | $d_T T(0)$ | $d_T T(0)$ | - | - | From steady state |
| r | CD8+ T cell proliferation rate | d^{-1} | 4.18e-1 | 0.208 (0.171,0.325) | [1e-4,1e2] | ^{1,3} | From observed CD8+ T cell range. |
| k_T | CD8+ T cell half saturation constant | (PFU/ml) | 1.05e4 | 12.0 (10.0,156) | [1e1, 1e8] | ⁴ | |
| d_T | Base CD8+ T cell clearance rate | d^{-1} | 9.47e-2 | 1.00e-4 (1.00e-4,0.0777) | [1e-4,1e0] | ^{4,5} | |
| K | Half saturation constant regulating V replication | cell^{-1} | 1.29e-14 | 1.66e-7 (8.90e-11,1.54e-6) | [0,1e-4] | - | |

Table A.3.13. Summary of MD1 parameters. The mathematical expression for MD1 is presented in A.1.1.

| Model MD2 Parameters | | | | | | | |
|----------------------|---|-------------------------------|-------------------|-------------------|---------------|----------------|---------------------------------------|
| Parameter | Description | Units | Adult | Aged | Search Bounds | Reference | Notes |
| β | Infection rate of uninfected cells | $(\text{PFU/ml})^{-1} d^{-1}$ | 2.23e-5 | 4.68e-5 | [1e-8,1e-4] | ² | - |
| d_I | Clearance rate of infected cells | $cells^{-2}$ | 5.57e-7 | 4.50e-7 | [1e-8,1e-4] | ² | Fixed for structural identifiability. |
| p | Production rate of virus | d^{-1} | | | 1e0 | ² | |
| c | Clearance rate of virus | d^{-1} | 2.17 | 12.3 | [1e-2,1e2] | ² | |
| s_T | Homeostatic CD8+ T cell proliferation rate | $cell \cdot d^{-1}$ | $(d_T + c_T)T(0)$ | $(d_T + c_T)T(0)$ | - | - | From steady state |
| r | CD8+ T cell proliferation rate | d^{-1} | 4.18e-1 | 0.208 | [1e-4,1e2] | ^{1,3} | From observed CD8+ T cell range. |
| k_T | CD8+ T cell half saturation constant | (PFU/ml) | 1.05e4 | 12.5 | [1e1, 1e8] | ⁴ | |
| d_T | Base CD8+ T cell clearance rate | d^{-1} | 9.47e-2 | 1.12 e-4 | [1e-4,1e0] | ^{4,5} | |
| c_T | CD8+ T cell 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 CD8+ T cell range. |

Table A.3.14. Summary of MD2 parameters. The mathematical expression for MD2 is presented in A.1.1.

| 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] | ² | - |
| d_I | Clearance rate of infected cells | cells^{-2} | 5.86e-7 | 5.57e-7 | [1e-8,1e-4] | ² | Fixed for structural identifiability. |
| p | Production rate of virus | d^{-1} | | | 1e0 | ² | |
| c | Clearance rate of virus | d^{-1} | 2.02 | 1.29 | [1e-2,1e2] | ² | |
| s_T | Homeostatic CD8+ T cell proliferation rate | $\text{cell} \cdot d^{-1}$ | $d_T T(0)$ | $d_T T(0)$ | - | - | From steady state |
| r | CD8+ T cell proliferation rate | $d^{-1}(\text{PFU}/\text{ml})^{-1}$ | 3.12e-6 | 1.20e-5 | [1e-4/ k_V ,1e2/ k_V] | ^{1,3} | Bounds are scaled. |
| d_T | Base CD8+ T cell clearance rate | d^{-1} | 6.52e-2 | 1.00e-4 | [1e-4,1e0] | ^{4,5} | From observed CD8+ T cell range. |
| K | Half saturation constant regulating V replication | cell^{-2} | 2.11e-12 | 2.52e-6 | [0,1e-4] | - | |

Table A.3.15. Summary of MD3 parameters. The mathematical expression for MD3 is presented in A.1.1.

| 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] | ² | - |
| d_I | Clearance rate of infected cells | cells^{-2} | 5.86e-7 | 5.63e-6 | [1e-8, 1e-4] | ² | Fixed for structural identifiability. |
| p | Production rate of virus | d^{-1} | | | 1e0 | ² | |
| c | Clearance rate of virus | d^{-1} | 2.02 | 1.43 | [1e-2, 1e2] | ² | |
| s_T | Homeostatic CD8+ T cell proliferation rate | $\text{cell} \cdot d^{-1}$ | $(d_T + c_T)T(0)$ | $(d_T + c_T)T(0)$ | - | - | From steady state |
| r | CD8+ T cell proliferation rate | $d^{-1}(\text{PFU/ml})^{-1}$ | 3.12e-6 | 8.50e-6 | [1e-4/ k_V , 1e2/ k_V] | ^{1,3} | Bounds are scaled. |
| d_T | Base CD8+ T cell clearance rate | d^{-1} | 6.52e-2 | 1.00e-4 | [1e-4, 1e0] | ^{4,5} | Assumed similar to d_T |
| c_T | CD8+ T cell downregulation rate | $(\text{PFU/ml})d^{-1}$ | 5.82e-12 | 1.40e-1 | [0, 1e0] | - | |
| K | Half saturation constant regulating V replication | cell^{-2} | 1.99e-13 | 1.81e-6 | [0, 1e-4] | - | |

Table A.3.16. Summary of MD4 parameters. The mathematical expression for MD4 is presented in A.1.1.

19 A.4 Fit Model Plots

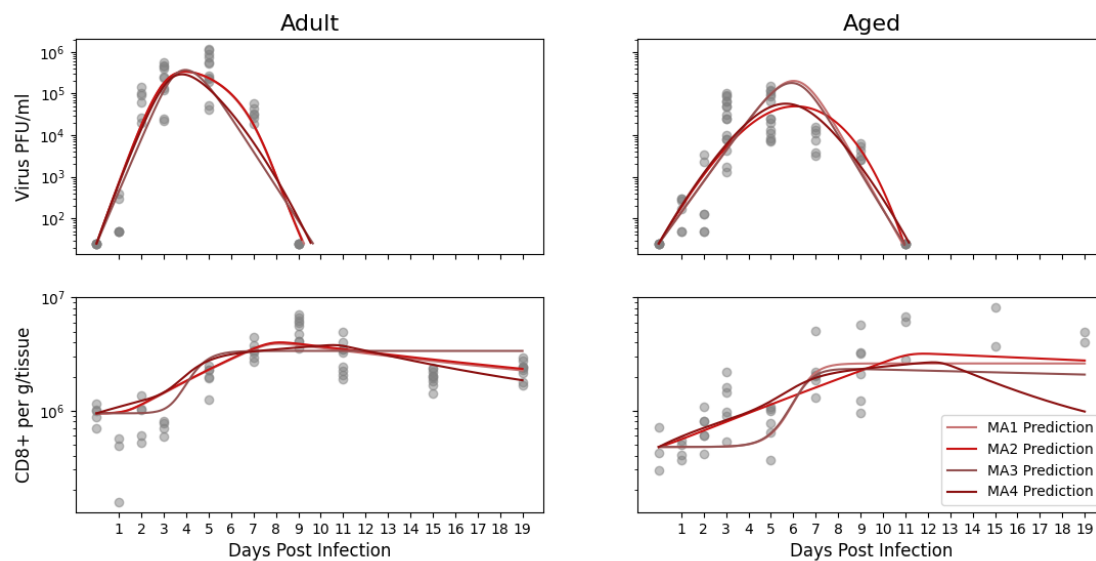


Figure A.4.1. Group A fitted model trajectories alongside the data from Toapanta et al.⁶. We can see that all models are biologically reasonable, though MA4 appears to fit the CD8+ T cell data rather poorly.

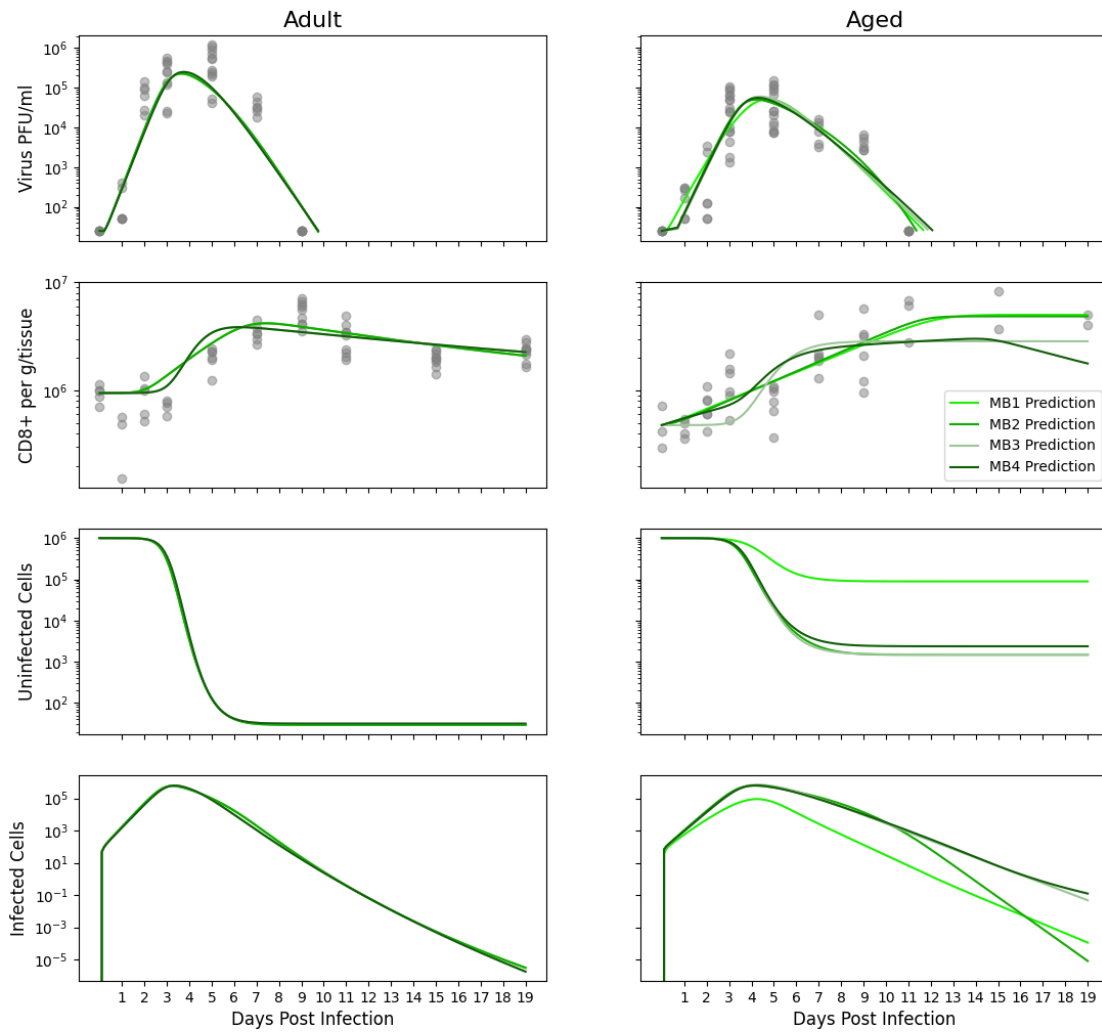


Figure A.4.2. Group B fitted model trajectories alongside the data from Toapanta et al.⁶. We can see that all models are biologically reasonable, though MB4 appears to fit the CD8+ T cell data rather poorly.

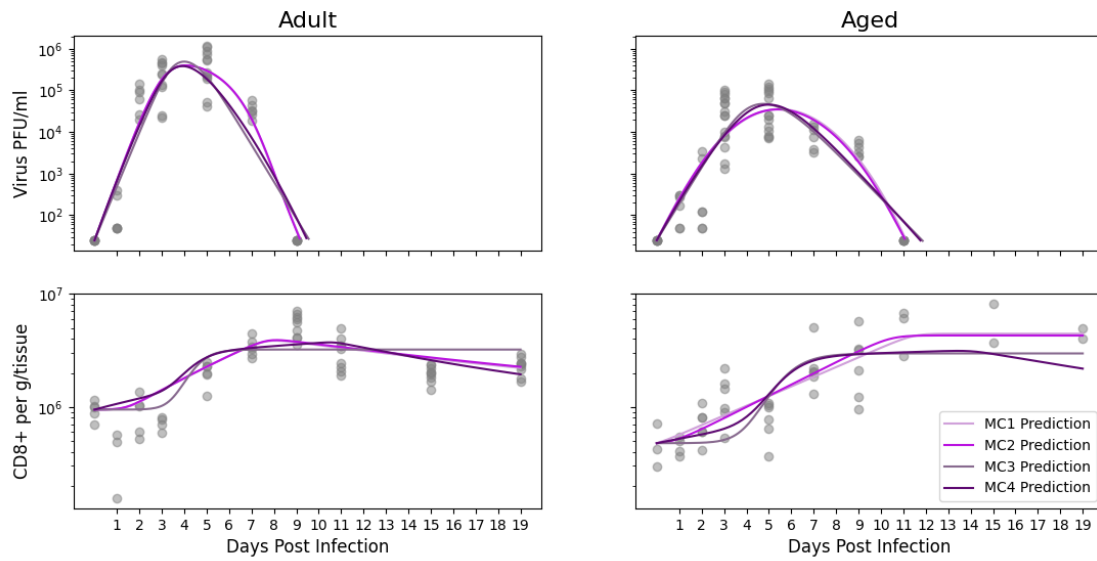


Figure A.4.3. Group C fitted model trajectories alongside the data from Toapanta et al.⁶. We can see that all models are biologically reasonable.

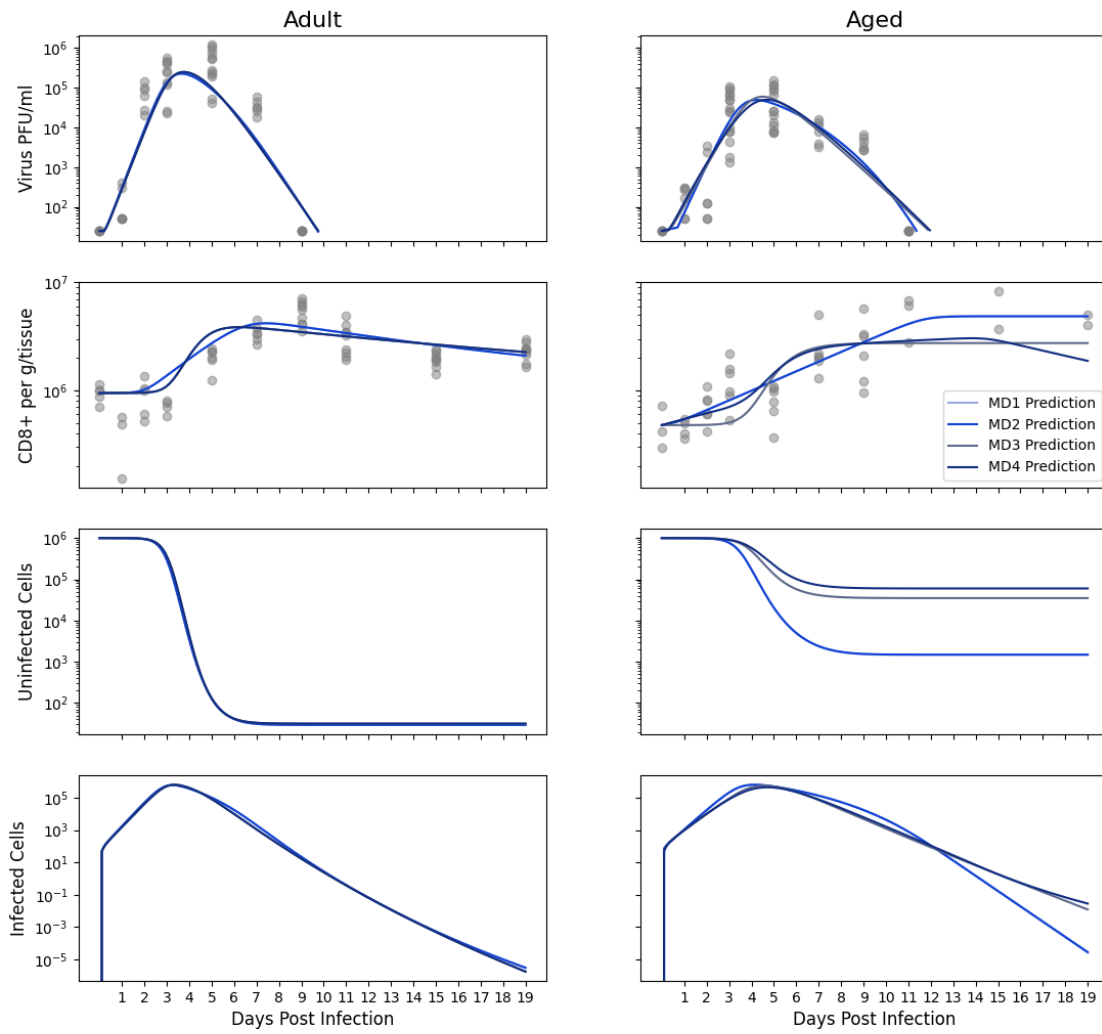


Figure A.4.4. Group D fitted model trajectories alongside the data from Toapanta et al.⁶. We can see that all models are biologically reasonable.

20 **A.5 Bootstrapped Predictions for the Selected Models**

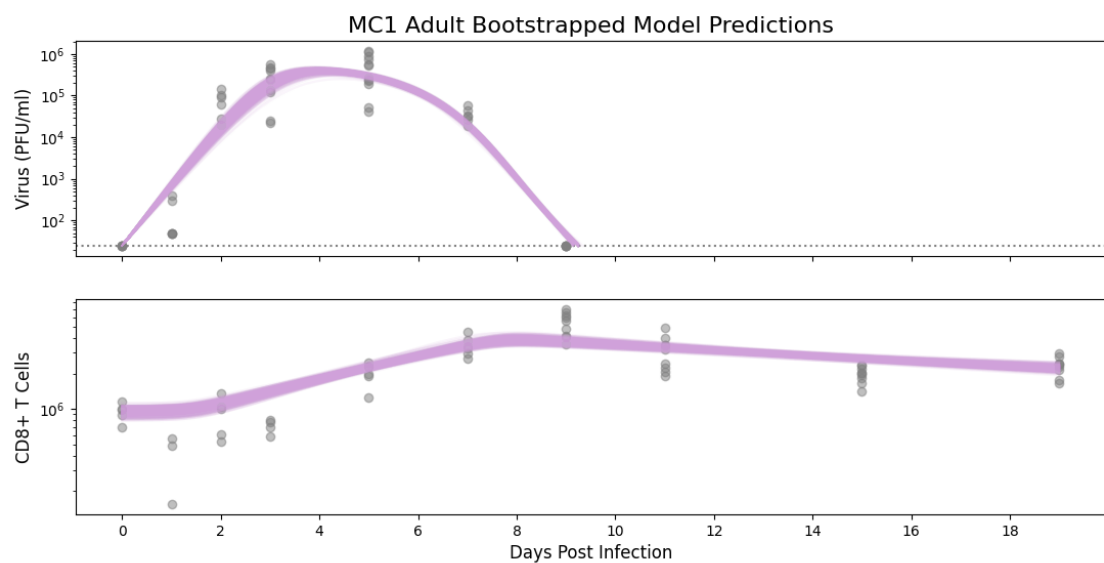


Figure A.5.1. Adult model (MC1) bootstrapped trajectories alongside the data from Toapanta et al.⁶.

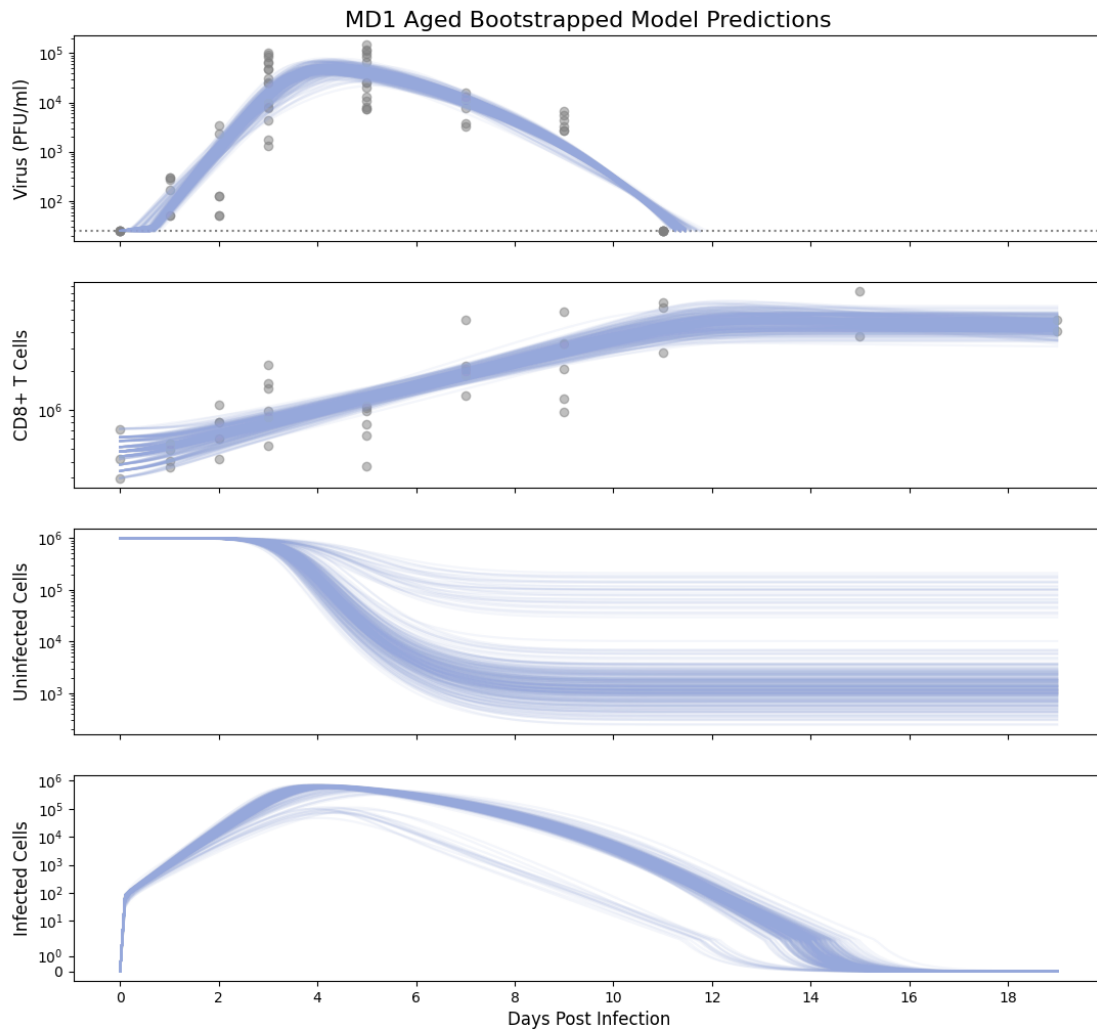


Figure A.5.2. Aged model (MD1) bootstrapped trajectories alongside the data from Toapanta et al.⁶.

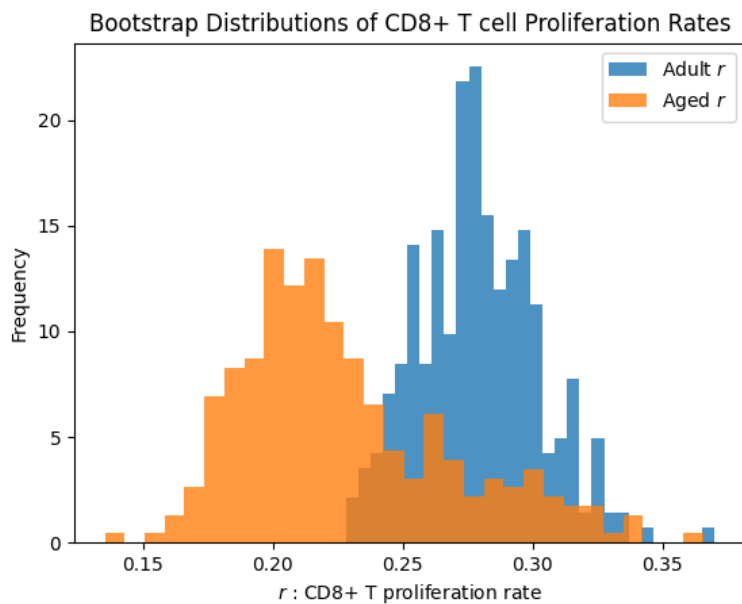


Figure A.6.1. r posterior distributions

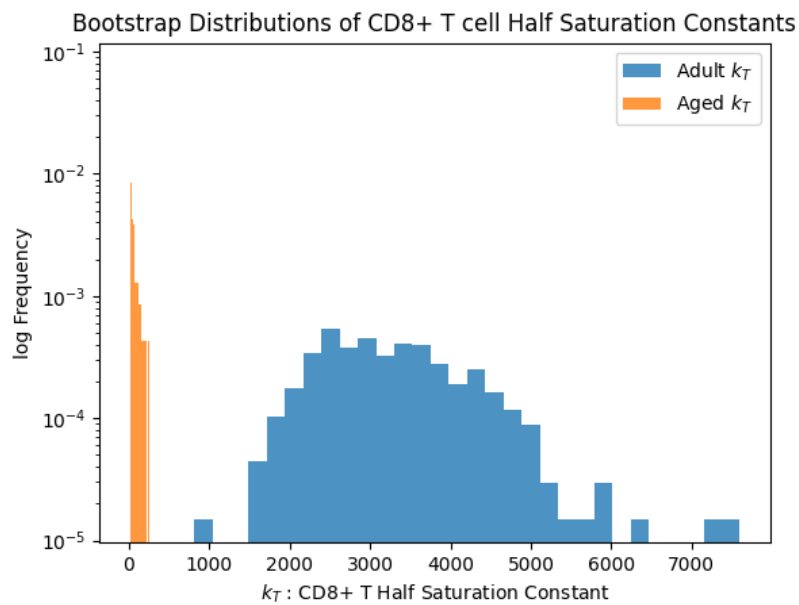


Figure A.6.2. k_T posterior distributions

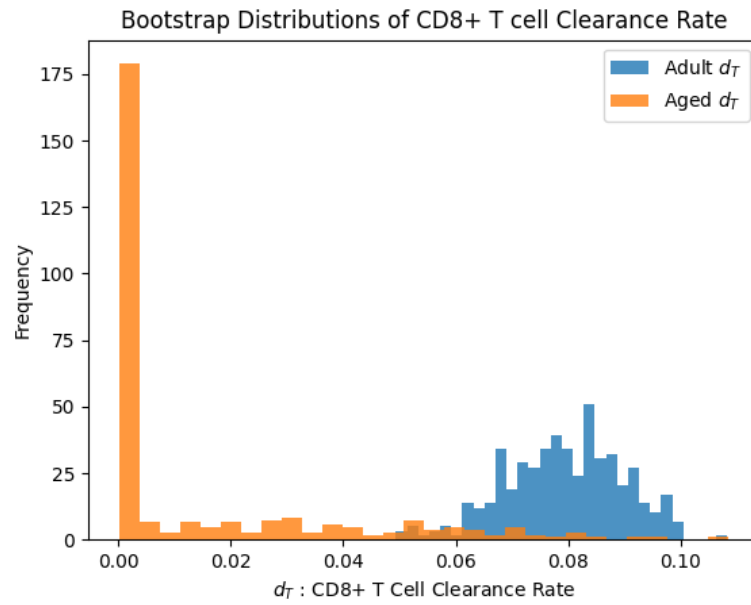


Figure A.6.3. d_T posterior distributions

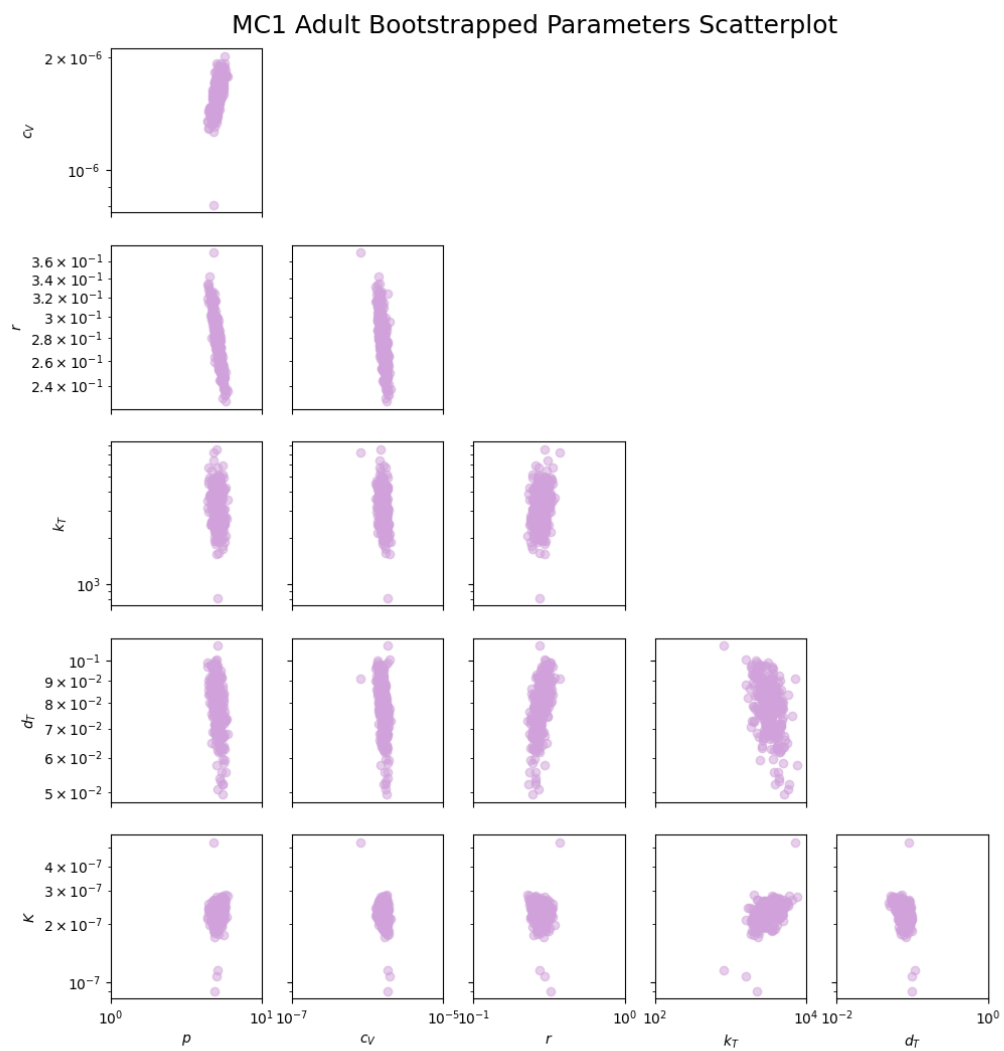


Figure A.7.1. Bootstrapping scatterplot for the adult model (MC1)

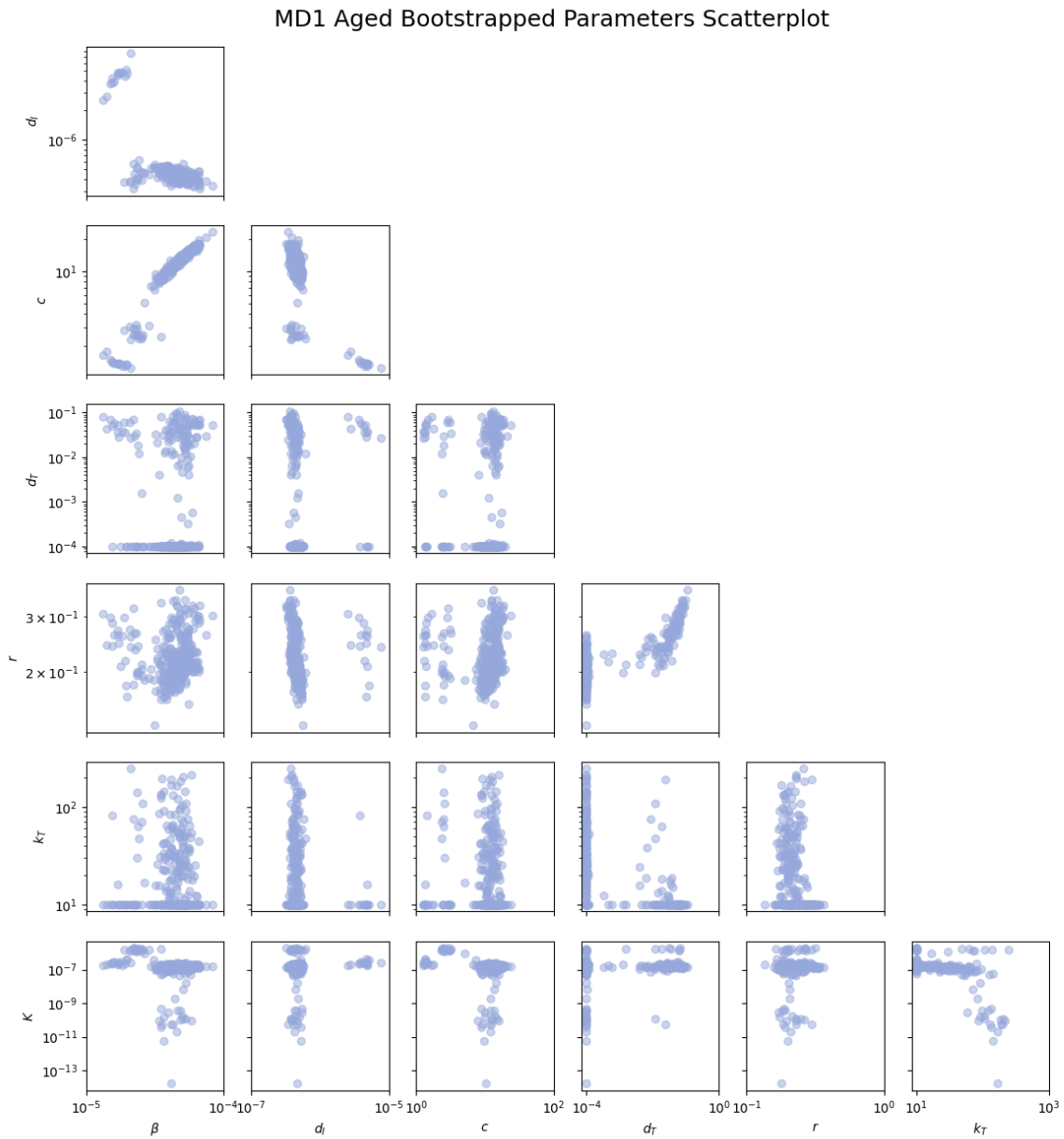


Figure A.7.2. Bootstrapping scatterplot for the adult model (MD1)

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