A Parameter Estimation Method for Multiscale Models of Hepatitis C Virus Dynamics Supplementary Material

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Appendix

In this appendix we briefly show the derivation of the equations that constitute a preparatory step before the optimization procedure for the other seven parameters that were not included in the main text (three were already shown starting from Section 3.3.1). For more details the interested reader is referred to Section 3.3.1).

Parameter d :

The derivative of the general function f (the vector $[T, V]$) with respect to d is:

$$\frac{\partial f}{\partial d}(t, y^d) = \Big[-T - d\frac{\partial T}{\partial d} - \beta\left(\frac{\partial V}{\partial d}T + V\frac{\partial T}{\partial d}\right) \\ (1-\varepsilon_s)\int_0^\infty \rho R(a,t)\frac{\partial I}{\partial d}(a,t)\mathrm{d}a - c\frac{\partial V}{\partial d}\Big]$$

where $y^d = \begin{cases} T \\ V \\ \frac{\partial T}{\partial d} \\ \frac{\partial V}{\partial d} \end{cases}$.

Furthermore:

$$\frac{\partial R(a,t)}{\partial d} = 0,$$

$$\frac{\partial \bar{T}}{\partial d} = 0,$$
$$\frac{\partial \bar{V}}{\partial d} = -1/\beta,$$

$$\frac{\partial I(a,t)}{\partial d} = \begin{cases} \beta\left(\frac{\partial V}{\partial d}(t-a)T(t-a) + V(t-a)\frac{\partial T}{\partial d}(t-a)\right)\mathrm{e}^{-\delta a} & a < t \\ -c/(\beta N)\mathrm{e}^{-\delta a} & a > t \end{cases},$$

The upper right block matrix of the Jacobian is:

$$f'_{d,2\times 2} = \begin{pmatrix} 0 & 0 \\ (1-\varepsilon_s)\int_0^t \rho R(a,t) \times \frac{\partial I(a,t)}{\partial \frac{\partial T}{\partial d}}\mathrm{d}a & (1-\varepsilon_s)\int_0^t \rho R(a,t) \times \frac{\partial I(a,t)}{\partial \frac{\partial V}{\partial d}}\mathrm{d}a \end{pmatrix}$$

and the transposed last two rows of the Jacobian are:

$$\left(\left(f'_{d,3}\right)^{\mathrm{tr}}, \left(f'_{d,4}\right)^{\mathrm{tr}}\right) := \begin{pmatrix} -1-\beta\frac{\partial V}{\partial d} & (1-\varepsilon_s)\int_0^t \rho R(a,t)\frac{\partial \frac{\partial I(a,t)}{\partial d}}{\partial T}\mathrm{d}a \\ -\beta\frac{\partial T}{\partial d} & (1-\varepsilon_s)\int_0^t \rho R(a,t)\frac{\partial \frac{\partial I(a,t)}{\partial d}}{\partial V}\mathrm{d}a \\ -d-\beta V & (1-\varepsilon_s)\int_0^t \rho R(a,t)\frac{\partial \frac{\partial I(a,t)}{\partial d}}{\partial \frac{\partial T}{\partial d}}\mathrm{d}a \\ -\beta T & (1-\varepsilon_s)\int_0^t \rho R(a,t)\frac{\partial \frac{\partial I(a,t)}{\partial d}}{\partial \frac{\partial V}{\partial d}}\mathrm{d}a - c \end{pmatrix},$$

$$\frac{\partial \frac{\partial f}{\partial d}}{\partial t} = \begin{bmatrix} 0, \\ (1-\varepsilon_s)\int_0^\infty \rho\left(\frac{\partial R(a,t)}{\partial t}\frac{\partial I}{\partial d}(a,t) + R(a,t)\frac{\partial \frac{\partial I(a,t)}{\partial d}}{\partial t}\right)\mathrm{d}a \end{bmatrix}.$$

Parameter β:

The derivative of the general function f (the vector $[T, V]$) with respect to β is:

$$\frac{\partial f}{\partial \beta}(t, y^\beta) = \Big[- d\frac{\partial T}{\partial \beta} - (VT + \beta \frac{\partial V}{\partial \beta} T + \beta V \frac{\partial T}{\partial \beta}) \\ (1-\varepsilon_s) \int_0^\infty \rho R(a,t) \frac{\partial I(a,t)}{\partial \beta} \mathrm{d}a - c \frac{\partial V}{\partial \beta} \Big]$$

where $y^\beta = \begin{cases} T \\ V \\ \frac{\partial T}{\partial \beta} \\ \frac{\partial V}{\partial \beta} \end{cases}$.

Furthermore:

$$\frac{\partial R(a,t)}{\partial \beta} = 0,$$

$$\frac{\partial \bar{T}}{\partial \beta} = -c/(\beta^2 N),$$
$$\frac{\partial \bar{V}}{\partial \beta} = d/\beta^2,$$

$$\frac{\partial I(a,t)}{\partial \beta} = \begin{cases} \Big(V(t-a)T(t-a) + \beta \frac{\partial V}{\partial \beta}(t-a)T(t-a) + \beta V(t-a) \frac{\partial T}{\partial \beta}(t-a) \Big) \mathrm{e}^{-\delta a} & a < t \\ dc/(\beta^2 N) \mathrm{e}^{-\delta a} & a > t \end{cases},$$

The upper right block matrix of the Jacobian is:

$$f'_{\beta,2\times 2} = \begin{pmatrix} 0 & 0 \\ (1-\varepsilon_s) \int_0^t \rho R(a,t) \times \frac{\partial I(a,t)}{\partial \frac{\partial T}{\partial \beta}} \mathrm{d}a & (1-\varepsilon_s) \int_0^t \rho R(a,t) \times \frac{\partial I(a,t)}{\partial \frac{\partial V}{\partial \beta}} \mathrm{d}a \end{pmatrix}$$

and the transposed last two rows of the Jacobian are:

$$\left(\left(f'_{\beta,3} \right)^{\mathrm{tr}}, \left(f'_{\beta,4} \right)^{\mathrm{tr}} \right) := \begin{pmatrix} -\left(V + \beta \frac{\partial V}{\partial \beta} \right) & (1-\varepsilon_s) \int_0^t \rho R(a,t) \frac{\partial \frac{\partial I(a,t)}{\partial \beta}}{\partial T} \mathrm{d}a \\ -\left(T + \beta \frac{\partial T}{\partial \beta} \right) & (1-\varepsilon_s) \int_0^t \rho R(a,t) \frac{\partial \frac{\partial I(a,t)}{\partial \beta}}{\partial V} \mathrm{d}a \\ -d - \beta V & (1-\varepsilon_s) \int_0^t \rho R(a,t) \frac{\partial \frac{\partial I(a,t)}{\partial \beta}}{\partial \frac{\partial T}{\partial \beta}} \mathrm{d}a \\ -\beta T & (1-\varepsilon_s) \int_0^t \rho R(a,t) \frac{\partial \frac{\partial I(a,t)}{\partial \beta}}{\partial \frac{\partial V}{\partial \beta}} \mathrm{d}a - c \end{pmatrix},$$

$$\frac{\partial \frac{\partial f}{\partial \beta}}{\partial t} = \begin{bmatrix} 0, \\ (1-\varepsilon_s)\int_0^\infty \rho \left(\frac{\partial R(a,t)}{\partial t} \frac{\partial I}{\partial \beta}(a,t) + R(a,t) \frac{\partial \frac{\partial I(a,t)}{\partial \beta}}{\partial t} \right) \mathrm{d}a \end{bmatrix}.$$

Parameter ε_s:

The derivative of the general function f (the vector $[T, V]$) with respect to ε_s is:

$$\begin{aligned}\frac{\partial f}{\partial \varepsilon_s}(t, y^{\varepsilon_s}) = \Big[& -d\frac{\partial T}{\partial \varepsilon_s} - \beta\left(\frac{\partial V}{\partial \varepsilon_s}T + V\frac{\partial T}{\partial \varepsilon_s}\right), \\ & -\int_0^\infty \rho R(a,t)I(a,t)\mathrm{d}a + (1-\varepsilon_s)\int_0^\infty \rho\frac{\partial R(a,t)}{\partial \varepsilon_s}I(a,t)\mathrm{d}a \\ & +(1-\varepsilon_s)\int_0^t \rho R(a,t)\frac{\partial I}{\partial \varepsilon_s}(a,t)\mathrm{d}a - c\frac{\partial V}{\partial \varepsilon_s}\Big]\end{aligned}$$

where $y^{\varepsilon_s} = \begin{cases} T \\ V \\ \frac{\partial T}{\partial \varepsilon_s} \\ \frac{\partial V}{\partial \varepsilon_s} \end{cases}$.

Furthermore:

$$\frac{\partial R(a,t)}{\partial \varepsilon_s} = \begin{cases} \rho\frac{(1-\varepsilon_\alpha)\alpha \mathrm{e}^{-\gamma t}}{\left((1-\varepsilon_s)\rho+\kappa\mu-\gamma\right)^2} \\ -\rho\frac{(1-\varepsilon_\alpha)\alpha \mathrm{e}^{-\gamma(t-a)}}{\left((1-\varepsilon_s)\rho+\kappa\mu-\gamma\right)^2}\mathrm{e}^{-((1-\varepsilon_s)\rho+\kappa\mu)a} & a<t \\ +\rho a\left(1-\frac{(1-\varepsilon_\alpha)\alpha \mathrm{e}^{-\gamma(t-a)}}{(1-\varepsilon_s)\rho+\kappa\mu-\gamma}\right)\mathrm{e}^{-((1-\varepsilon_s)\rho+\kappa\mu)a} \\ \\ \rho\frac{(1-\varepsilon_\alpha)\alpha \mathrm{e}^{-\gamma t}}{\left((1-\varepsilon_s)\rho+\kappa\mu-\gamma\right)^2} \\ -\rho\frac{(1-\varepsilon_\alpha)\alpha}{\left((1-\varepsilon_s)\rho+\kappa\mu-\gamma\right)^2}\mathrm{e}^{-((1-\varepsilon_s)\rho+\kappa\mu)t} & a>t \\ +\rho t\left(\frac{\alpha}{\rho+\mu}+\left(1-\frac{\alpha}{\rho+\mu}\right)\mathrm{e}^{-(\rho+\mu)(a-t)}-\frac{(1-\varepsilon_\alpha)\alpha}{(1-\varepsilon_s)\rho+\kappa\mu-\gamma}\right)\mathrm{e}^{-((1-\varepsilon_s)\rho+\kappa\mu)t} \end{cases},$$

$$\begin{aligned}\frac{\partial \bar{T}}{\partial \varepsilon_s} &= 0, \\ \frac{\partial \bar{V}}{\partial \varepsilon_s} &= 0,\end{aligned}$$

$$\frac{\partial I(a,t)}{\partial \varepsilon_s} = \begin{cases} \beta\left(\frac{\partial V}{\partial \varepsilon_s}(t-a)T(t-a) + V(t-a)\frac{\partial T}{\partial \varepsilon_s}(t-a)\right)\mathrm{e}^{-\delta a} & a<t \\ 0 & a>t \end{cases},$$

The upper right block matrix of the Jacobian is:

$$f'_{\varepsilon_s,2\times 2} = \begin{pmatrix} 0 & 0 \\ (1-\varepsilon_s)\int_0^t \rho R(a,t) \times \frac{\partial I(a,t)}{\partial \frac{\partial T}{\partial \varepsilon_s}}\mathrm{d}a & (1-\varepsilon_s)\int_0^t \rho R(a,t) \times \frac{\partial I(a,t)}{\partial \frac{\partial V}{\partial \varepsilon_s}}\mathrm{d}a \end{pmatrix}$$

and the transposed last two rows of the Jacobian are:

$$\left(\left(f'_{\varepsilon_s,3}\right)^{\mathrm{tr}}, \left(f'_{\varepsilon_s,4}\right)^{\mathrm{tr}}\right) := \begin{pmatrix} -\beta\frac{\partial V}{\partial \varepsilon_s} & \begin{array}{l} -\int_0^t \rho R(a,t)\frac{\partial I(a,t)}{\partial T}\mathrm{d}a \\ +(1-\varepsilon_s)\int_0^t \rho\frac{\partial R(a,t)}{\partial \varepsilon_s}\frac{\partial I(a,t)}{\partial T}\mathrm{d}a \\ +(1-\varepsilon_s)\int_0^t \rho R(a,t)\frac{\partial\frac{\partial I(a,t)}{\partial \varepsilon_s}}{\partial T}\mathrm{d}a \end{array} \\ -\beta\frac{\partial T}{\partial \varepsilon_s} & \begin{array}{l} -\int_0^t \rho R(a,t)\frac{\partial I(a,t)}{\partial V}\mathrm{d}a \\ +(1-\varepsilon_s)\int_0^t \rho\frac{\partial R(a,t)}{\partial \varepsilon_s}\frac{\partial I(a,t)}{\partial V}\mathrm{d}a \\ +(1-\varepsilon_s)\int_0^t \rho R(a,t)\frac{\partial\frac{\partial I(a,t)}{\partial \varepsilon_s}}{\partial V}\mathrm{d}a \end{array} \\ -d-\beta V & \begin{array}{l} -\int_0^t \rho R(a,t)\frac{\partial I(a,t)}{\partial\frac{\partial T}{\partial \varepsilon_s}}\mathrm{d}a \\ +(1-\varepsilon_s)\int_0^t \rho\frac{\partial R(a,t)}{\partial \varepsilon_s}\frac{\partial I(a,t)}{\partial\frac{\partial T}{\partial \varepsilon_s}}\mathrm{d}a \\ +(1-\varepsilon_s)\int_0^t \rho R(a,t)\frac{\partial\frac{\partial I(a,t)}{\partial \varepsilon_s}}{\partial\frac{\partial T}{\partial \varepsilon_s}}\mathrm{d}a \end{array} \\ -\beta T & \begin{array}{l} -\int_0^t \rho R(a,t)\frac{\partial I(a,t)}{\partial\frac{\partial V}{\partial \varepsilon_s}}\mathrm{d}a \\ +(1-\varepsilon_s)\int_0^t \rho\frac{\partial R(a,t)}{\partial \varepsilon_s}\frac{\partial I(a,t)}{\partial\frac{\partial V}{\partial \varepsilon_s}}\mathrm{d}a \\ +(1-\varepsilon_s)\int_0^t \rho R(a,t)\frac{\partial\frac{\partial I(a,t)}{\partial \varepsilon_s}}{\partial\frac{\partial V}{\partial \varepsilon_s}}\mathrm{d}a \\ -c \end{array} \end{pmatrix},$$

$$
\frac{\partial \frac{\partial f}{\partial \varepsilon_s}}{\partial t} = \begin{aligned}
&\Big[0, \\
&-\int_0^\infty \rho \left(\tfrac{\partial R(a,t)}{\partial t} I(a,t) + R(a,t) \tfrac{\partial I(a,t)}{\partial t} \right) \mathrm{d}a \\
&+ (1-\varepsilon_s) \int_0^\infty \rho \left(\frac{\partial \frac{\partial R(a,t)}{\partial \varepsilon_s}}{\partial t} I(a,t) + \tfrac{\partial R(a,t)}{\partial \varepsilon_s} \tfrac{\partial I(a,t)}{\partial t} \right) \mathrm{d}a \\
&+ (1-\varepsilon_s) \int_0^t \rho \left(\tfrac{\partial R(a,t)}{\partial t} \tfrac{\partial I(a,t)}{\partial \varepsilon_s} + R(a,t) \frac{\partial \frac{\partial I(a,t)}{\partial \varepsilon_s}}{\partial t} \right) \mathrm{d}a \Big]
\end{aligned}
$$

where:

$$
\frac{\partial \frac{\partial R(a,t)}{\partial \varepsilon_s}}{\partial t} = \begin{cases}
-\gamma\rho \frac{(1-\varepsilon_\alpha)\alpha \mathrm{e}^{-\gamma t}}{\left((1-\varepsilon_s)\rho+\kappa\mu-\gamma\right)^2} \\
+\gamma\rho \frac{(1-\varepsilon_\alpha)\alpha \mathrm{e}^{-\gamma(t-a)}}{\left((1-\varepsilon_s)\rho+\kappa\mu-\gamma\right)^2} \mathrm{e}^{-((1-\varepsilon_s)\rho+\kappa\mu)a} & a < t \\
+\gamma\rho a \frac{(1-\varepsilon_\alpha)\alpha \mathrm{e}^{-\gamma(t-a)}}{(1-\varepsilon_s)\rho+\kappa\mu-\gamma} \mathrm{e}^{-((1-\varepsilon_s)\rho+\kappa\mu)a} \\
\\
-\gamma\rho \frac{(1-\varepsilon_\alpha)\alpha \mathrm{e}^{-\gamma t}}{\left((1-\varepsilon_s)\rho+\kappa\mu-\gamma\right)^2} \\
+((1-\varepsilon_s)\rho+\kappa\mu)\rho \frac{(1-\varepsilon_\alpha)\alpha}{\left((1-\varepsilon_s)\rho+\kappa\mu-\gamma\right)^2} \mathrm{e}^{-((1-\varepsilon_s)\rho+\kappa\mu)t} \\
+\rho\left(\frac{\alpha}{\rho+\mu} + \left(1-\frac{\alpha}{\rho+\mu}\right) \mathrm{e}^{-(\rho+\mu)(a-t)} - \frac{(1-\varepsilon_\alpha)\alpha}{(1-\varepsilon_s)\rho+\kappa\mu-\gamma} \right) \mathrm{e}^{-((1-\varepsilon_s)\rho+\kappa\mu)t} & a > t \\
+(\rho+\mu)\rho t \left(1-\frac{\alpha}{\rho+\mu}\right) \mathrm{e}^{-(\rho+\mu)(a-t)} \mathrm{e}^{-((1-\varepsilon_s)\rho+\kappa\mu)t} \\
-((1-\varepsilon_s)\rho+\kappa\mu)\rho t \left(\frac{\alpha}{\rho+\mu} + \left(1-\frac{\alpha}{\rho+\mu}\right) \mathrm{e}^{-(\rho+\mu)(a-t)} - \frac{(1-\varepsilon_\alpha)\alpha}{(1-\varepsilon_s)\rho+\kappa\mu-\gamma} \right) \\
\times \mathrm{e}^{-((1-\varepsilon_s)\rho+\kappa\mu)t}
\end{cases} .
$$

Parameter ε_α:

The derivative of the general function f (the vector $[T, V]$) with respect to ε_α is:

$$\frac{\partial f}{\partial \varepsilon_\alpha}(t, y^{\varepsilon_\alpha}) = \Big[- d\frac{\partial T}{\partial \varepsilon_\alpha} - \beta\left(\frac{\partial V}{\partial \varepsilon_\alpha} T + V\frac{\partial T}{\partial \varepsilon_\alpha}\right), \\ (1-\varepsilon_s)\int_0^\infty \rho \frac{\partial R(a,t)}{\partial \varepsilon_\alpha} I(a,t)\mathrm{d}a \\ +(1-\varepsilon_s)\int_0^t \rho R(a,t)\frac{\partial I}{\partial \varepsilon_\alpha}(a,t)\mathrm{d}a - c\frac{\partial V}{\partial \varepsilon_\alpha}\Big]$$

where $y^{\varepsilon_\alpha} = \begin{cases} T \\ V \\ \frac{\partial T}{\partial \varepsilon_\alpha} \\ \frac{\partial V}{\partial \varepsilon_\alpha} \end{cases}$.

Furthermore:

$$\frac{\partial R(a,t)}{\partial \varepsilon_\alpha} = \begin{cases} -\frac{\alpha \mathrm{e}^{-\gamma t}}{(1-\varepsilon_s)\rho+\kappa\mu-\gamma} + \frac{\alpha \mathrm{e}^{-\gamma(t-a)}}{(1-\varepsilon_s)\rho+\kappa\mu-\gamma}\mathrm{e}^{-((1-\varepsilon_s)\rho+\kappa\mu)a} & a < t \\ -\frac{\alpha \mathrm{e}^{-\gamma t}}{(1-\varepsilon_s)\rho+\kappa\mu-\gamma} + \frac{\alpha}{(1-\varepsilon_s)\rho+\kappa\mu-\gamma}\mathrm{e}^{-((1-\varepsilon_s)\rho+\kappa\mu)t} & a > t \end{cases},$$

$$\frac{\partial \bar{T}}{\partial \varepsilon_\alpha} = 0, \\ \frac{\partial \bar{V}}{\partial \varepsilon_\alpha} = 0,$$

$$\frac{\partial I(a,t)}{\partial \varepsilon_\alpha} = \begin{cases} \beta\left(\frac{\partial V}{\partial \varepsilon_\alpha}(t-a)T(t-a) + V(t-a)\frac{\partial T}{\partial \varepsilon_\alpha}(t-a)\right)\mathrm{e}^{-\delta a} & a < t \\ 0 & a > t \end{cases},$$

The upper right block matrix of the Jacobian is:

$$f'_{\varepsilon_\alpha, 2\times 2} = \begin{pmatrix} 0 & 0 \\ (1-\varepsilon_s)\int_0^t \rho R(a,t) \times \frac{\partial I(a,t)}{\partial \frac{\partial T}{\partial \varepsilon_\alpha}}\mathrm{d}a & (1-\varepsilon_s)\int_0^t \rho R(a,t) \times \frac{\partial I(a,t)}{\partial \frac{\partial V}{\partial \varepsilon_\alpha}}\mathrm{d}a \end{pmatrix}$$

and the transposed last two rows of the Jacobian are:

$$\left(\left(f'_{\varepsilon_\alpha,3}\right)^{\mathrm{tr}}, \left(f'_{\varepsilon_\alpha,4}\right)^{\mathrm{tr}}\right) := \begin{pmatrix} -\beta\frac{\partial V}{\partial \varepsilon_\alpha} & \begin{array}{l}(1-\varepsilon_s)\int_0^t \rho\frac{\partial R(a,t)}{\partial \varepsilon_\alpha}\frac{\partial I(a,t)}{\partial T}\mathrm{d}a \\ \quad +(1-\varepsilon_s)\int_0^t \rho R(a,t)\frac{\partial \frac{\partial I(a,t)}{\partial \varepsilon_\alpha}}{\partial T}\mathrm{d}a\end{array} \\ -\beta\frac{\partial T}{\partial \varepsilon_\alpha} & \begin{array}{l}(1-\varepsilon_s)\int_0^t \rho\frac{\partial R(a,t)}{\partial \varepsilon_s}\frac{\partial I(a,t)}{\partial V}\mathrm{d}a \\ \quad +(1-\varepsilon_s)\int_0^t \rho R(a,t)\frac{\partial \frac{\partial I(a,t)}{\partial \varepsilon_\alpha}}{\partial V}\mathrm{d}a\end{array} \\ -d-\beta V & \begin{array}{l}(1-\varepsilon_s)\int_0^t \rho\frac{\partial R(a,t)}{\partial \varepsilon_s}\frac{\partial I(a,t)}{\partial \frac{\partial T}{\partial \varepsilon_\alpha}}\mathrm{d}a \\ \quad +(1-\varepsilon_s)\int_0^t \rho R(a,t)\frac{\partial \frac{\partial I(a,t)}{\partial \varepsilon_\alpha}}{\partial \frac{\partial T}{\partial \varepsilon_\alpha}}\mathrm{d}a\end{array} \\ -\beta T & \begin{array}{l}(1-\varepsilon_s)\int_0^t \rho\frac{\partial R(a,t)}{\partial \varepsilon_s}\frac{\partial I(a,t)}{\partial \frac{\partial V}{\partial \varepsilon_\alpha}}\mathrm{d}a \\ \quad +(1-\varepsilon_s)\int_0^t \rho R(a,t)\frac{\partial \frac{\partial I(a,t)}{\partial \varepsilon_\alpha}}{\partial \frac{\partial V}{\partial \varepsilon_\alpha}}\mathrm{d}a - c\end{array} \end{pmatrix},$$

$$\frac{\partial \frac{\partial f}{\partial \varepsilon_s}}{\partial t} = \Big[0, \quad (1-\varepsilon_s)\int_0^\infty \rho\left(\frac{\partial \frac{\partial R(a,t)}{\partial \varepsilon_\alpha}}{\partial t} I(a,t) + \frac{\partial R(a,t)}{\partial \varepsilon_\alpha}\frac{\partial I(a,t)}{\partial t}\right)\mathrm{d}a + (1-\varepsilon_s)\int_0^t \rho\left(\frac{\partial R(a,t)}{\partial t}\frac{\partial I}{\partial \varepsilon_\alpha}(a,t) + R(a,t)\frac{\partial \frac{\partial I(a,t)}{\partial \varepsilon_\alpha}}{\partial t}\right)\mathrm{d}a\Big]$$

where:

$$\frac{\partial \frac{\partial R(a,t)}{\partial \varepsilon_\alpha}}{\partial t} = \begin{cases} \gamma\frac{\alpha \mathrm{e}^{-\gamma t}}{(1-\varepsilon_s)\rho+\kappa\mu-\gamma} - \gamma\frac{\alpha \mathrm{e}^{-\gamma(t-a)}}{(1-\varepsilon_s)\rho+\kappa\mu-\gamma}\mathrm{e}^{-((1-\varepsilon_s)\rho+\kappa\mu)a} & a<t \\ \gamma\frac{\alpha \mathrm{e}^{-\gamma t}}{(1-\varepsilon_s)\rho+\kappa\mu-\gamma} - ((1-\varepsilon_s)\rho+\kappa\mu)\frac{\alpha}{(1-\varepsilon_s)\rho+\kappa\mu-\gamma}\mathrm{e}^{-((1-\varepsilon_s)\rho+\kappa\mu)t} & a>t \end{cases}.$$

Parameter κ:

The derivative of the general function f (the vector $[T, V]$) with respect to κ is:

$$\begin{aligned}\tfrac{\partial f}{\partial \kappa}(t, y^{\kappa}) = \Big[& -d\tfrac{\partial T}{\partial \kappa} - \beta\left(\tfrac{\partial V}{\partial \kappa}T + V\tfrac{\partial T}{\partial \kappa}\right), \\ & (1-\varepsilon_s)\textstyle\int_0^{\infty} \rho \tfrac{\partial R(a,t)}{\partial \kappa} I(a,t)\mathrm{d}a \\ & +(1-\varepsilon_s)\textstyle\int_0^{t} \rho R(a,t)\tfrac{\partial I}{\partial \kappa}(a,t)\mathrm{d}a - c\tfrac{\partial V}{\partial \kappa}\Big]\end{aligned}$$

where $y^{\kappa} = \begin{cases} T \\ V \\ \frac{\partial T}{\partial \kappa} \\ \frac{\partial V}{\partial \kappa} \end{cases}$.

Furthermore:

$$\tfrac{\partial R(a,t)}{\partial \kappa} = \begin{cases} -\mu\frac{(1-\varepsilon_\alpha)\alpha \mathrm{e}^{-\gamma t}}{\left((1-\varepsilon_s)\rho+\kappa\mu-\gamma\right)^2} \\ +\mu\frac{(1-\varepsilon_\alpha)\alpha \mathrm{e}^{-\gamma(t-a)}}{\left((1-\varepsilon_s)\rho+\kappa\mu-\gamma\right)^2}\mathrm{e}^{-((1-\varepsilon_s)\rho+\kappa\mu)a} & a < t \\ -\mu a\left(1 - \frac{(1-\varepsilon_\alpha)\alpha \mathrm{e}^{-\gamma(t-a)}}{(1-\varepsilon_s)\rho+\kappa\mu-\gamma}\right)\mathrm{e}^{-((1-\varepsilon_s)\rho+\kappa\mu)a} \\ \\ -\mu\frac{(1-\varepsilon_\alpha)\alpha \mathrm{e}^{-\gamma t}}{\left((1-\varepsilon_s)\rho+\kappa\mu-\gamma\right)^2} \\ +\mu\frac{(1-\varepsilon_\alpha)\alpha}{\left((1-\varepsilon_s)\rho+\kappa\mu-\gamma\right)^2}\mathrm{e}^{-((1-\varepsilon_s)\rho+\kappa\mu)t} & a > t \\ -\mu t\left(\frac{\alpha}{\rho+\mu} + \left(1 - \frac{\alpha}{\rho+\mu}\right)\mathrm{e}^{-(\rho+\mu)(a-t)} - \frac{(1-\varepsilon_\alpha)\alpha}{(1-\varepsilon_s)\rho+\kappa\mu-\gamma}\right)\mathrm{e}^{-((1-\varepsilon_s)\rho+\kappa\mu)t} \end{cases},$$

$$\begin{aligned}\tfrac{\partial \bar{T}}{\partial \kappa} &= 0, \\ \tfrac{\partial \bar{V}}{\partial \kappa} &= 0,\end{aligned}$$

$$\tfrac{\partial I(a,t)}{\partial \kappa} = \begin{cases} \beta\left(\frac{\partial V}{\partial \kappa}(t-a)T(t-a) + V(t-a)\frac{\partial T}{\partial \kappa}\right)\mathrm{e}^{-\delta a} & a < t \\ 0 & a > t \end{cases},$$

The upper right block matrix of the Jacobian is:

$$f'_{\kappa,2\times 2} = \begin{pmatrix} 0 & 0 \\ (1-\varepsilon_s)\int_0^t \rho R(a,t) \times \frac{\partial I(a,t)}{\partial \frac{\partial T}{\partial \kappa}}\mathrm{d}a & (1-\varepsilon_s)\int_0^t \rho R(a,t) \times \frac{\partial I(a,t)}{\partial \frac{\partial V}{\partial \kappa}}\mathrm{d}a \end{pmatrix}$$

and the transposed last two rows of the Jacobian are:

$$\left(\left(f'_{\kappa,3}\right)^{\mathrm{tr}}, \left(f'_{\kappa,4}\right)^{\mathrm{tr}}\right) := \begin{pmatrix} -\beta\frac{\partial V}{\partial \kappa} & \begin{array}{l}(1-\varepsilon_s)\int_0^t \rho\frac{\partial R(a,t)}{\partial \kappa}\frac{\partial I(a,t)}{\partial T}\mathrm{d}a \\ +(1-\varepsilon_s)\int_0^t \rho R(a,t)\frac{\partial \frac{\partial I(a,t)}{\partial \kappa}}{\partial T}\mathrm{d}a\end{array} \\ -\beta\frac{\partial T}{\partial \kappa} & \begin{array}{l}(1-\varepsilon_s)\int_0^t \rho\frac{\partial R(a,t)}{\partial \kappa}\frac{\partial I(a,t)}{\partial V}\mathrm{d}a \\ +(1-\varepsilon_s)\int_0^t \rho R(a,t)\frac{\partial \frac{\partial I(a,t)}{\partial \kappa}}{\partial V}\mathrm{d}a\end{array} \\ -d-\beta V & \begin{array}{l}(1-\varepsilon_s)\int_0^t \rho\frac{\partial R(a,t)}{\partial \kappa}\frac{\partial I(a,t)}{\partial \frac{\partial T}{\partial \kappa}}\mathrm{d}a \\ +(1-\varepsilon_s)\int_0^t \rho R(a,t)\frac{\partial \frac{\partial I(a,t)}{\partial \kappa}}{\partial \frac{\partial T}{\partial \kappa}}\mathrm{d}a\end{array} \\ -\beta T & \begin{array}{l}(1-\varepsilon_s)\int_0^t \rho\frac{\partial R(a,t)}{\partial \kappa}\frac{\partial I(a,t)}{\partial \frac{\partial V}{\partial \kappa}}\mathrm{d}a \\ +(1-\varepsilon_s)\int_0^t \rho R(a,t)\frac{\partial \frac{\partial I(a,t)}{\partial \kappa}}{\partial \frac{\partial V}{\partial \kappa}}\mathrm{d}a - c\end{array} \end{pmatrix},$$

$$\frac{\partial \frac{\partial f}{\partial \kappa}}{\partial t} = \begin{array}{l}\Big[0, \\ (1-\varepsilon_s)\int_0^\infty \rho\left(\frac{\partial \frac{\partial R(a,t)}{\partial \kappa}}{\partial t} I(a,t) + \frac{\partial R(a,t)}{\partial \kappa}\frac{\partial I(a,t)}{\partial t}\right)\mathrm{d}a \\ \quad + (1-\varepsilon_s)\int_0^t \rho\left(\frac{\partial R(a,t)}{\partial t}\frac{\partial I(a,t)}{\partial \kappa} + R(a,t)\frac{\partial \frac{\partial I(a,t)}{\partial \kappa}}{\partial t}\right)\mathrm{d}a\Big]\end{array}$$

where:

$$
\frac{\partial \frac{\partial R(a,t)}{\partial \kappa}}{\partial t} = \begin{cases} +\gamma\mu \frac{(1-\varepsilon_\alpha)\alpha \mathrm{e}^{-\gamma t}}{\left((1-\varepsilon_s)\rho+\kappa\mu-\gamma\right)^2} \\ -\gamma\mu \frac{(1-\varepsilon_\alpha)\alpha \mathrm{e}^{-\gamma(t-a)}}{\left((1-\varepsilon_s)\rho+\kappa\mu-\gamma\right)^2} \mathrm{e}^{-((1-\varepsilon_s)\rho+\kappa\mu)a} & a < t \\ -\gamma\mu a \frac{(1-\varepsilon_\alpha)\alpha \mathrm{e}^{-\gamma(t-a)}}{(1-\varepsilon_s)\rho+\kappa\mu-\gamma} \mathrm{e}^{-((1-\varepsilon_s)\rho+\kappa\mu)a} \\ \\ +\gamma\mu \frac{(1-\varepsilon_\alpha)\alpha \mathrm{e}^{-\gamma t}}{\left((1-\varepsilon_s)\rho+\kappa\mu-\gamma\right)^2} \\ -((1-\varepsilon_s)\rho+\kappa\mu)\mu \frac{(1-\varepsilon_\alpha)\alpha}{\left((1-\varepsilon_s)\rho+\kappa\mu-\gamma\right)^2} \mathrm{e}^{-((1-\varepsilon_s)\rho+\kappa\mu)t} \\ -\mu\left(\frac{\alpha}{\rho+\mu} + \left(1-\frac{\alpha}{\rho+\mu}\right)\mathrm{e}^{-(\rho+\mu)(a-t)} - \frac{(1-\varepsilon_\alpha)\alpha}{(1-\varepsilon_s)\rho+\kappa\mu-\gamma}\right)\mathrm{e}^{-((1-\varepsilon_s)\rho+\kappa\mu)t} & a > t \\ -(\rho+\mu)\mu t\left(1-\frac{\alpha}{\rho+\mu}\right)\mathrm{e}^{-(\rho+\mu)(a-t)}\mathrm{e}^{-((1-\varepsilon_s)\rho+\kappa\mu)t} \\ +((1-\varepsilon_s)\rho+\kappa\mu)\mu t\left(\frac{\alpha}{\rho+\mu} + \left(1-\frac{\alpha}{\rho+\mu}\right)\mathrm{e}^{-(\rho+\mu)(a-t)} - \frac{(1-\varepsilon_\alpha)\alpha}{(1-\varepsilon_s)\rho+\kappa\mu-\gamma}\right) \\ \times \mathrm{e}^{-((1-\varepsilon_s)\rho+\kappa\mu)t} \end{cases} .
$$

Parameter c:

The derivative of the general function f (the vector $[T, V]$) with respect to c is:

$$\frac{\partial f}{\partial c}(t, y^c) = \Big[-d\frac{\partial T}{\partial c} - \beta\left(\frac{\partial V}{\partial c}T + V\frac{\partial T}{\partial c}\right), \\ (1-\varepsilon_s)\int_0^\infty \rho R(a,t)\frac{\partial I}{\partial c}(a,t)\mathrm{d}a - \left(V + c\frac{\partial V}{\partial c}\right)\Big]$$

where $y^c = \begin{cases} T \\ V \\ \frac{\partial T}{\partial c} \\ \frac{\partial V}{\partial c} \end{cases}$.

Furthermore:

$$\frac{\partial R(a,t)}{\partial c} = 0,$$

$$\frac{\partial \bar{T}}{\partial c} = 1/(\beta N), \\ \frac{\partial \bar{V}}{\partial c} = -Ns/c^2,$$

$$\frac{\partial I(a,t)}{\partial c} = \begin{cases} \beta\left(\frac{\partial V}{\partial c}(t-a)T(t-a) + V(t-a)\frac{\partial T}{\partial c}(t-a)\right)\mathrm{e}^{-\delta a} & a < t \\ -d/(\beta N)\mathrm{e}^{-\delta a} & a > t \end{cases},$$

The upper right block matrix of the Jacobian is:

$$f'_{c,2\times 2} = \begin{pmatrix} 0 & 0 \\ (1-\varepsilon_s)\int_0^t \rho R(a,t) \times \frac{\partial I(a,t)}{\partial \frac{\partial T}{\partial c}}\mathrm{d}a & (1-\varepsilon_s)\int_0^t \rho R(a,t) \times \frac{\partial I(a,t)}{\partial \frac{\partial V}{\partial c}}\mathrm{d}a \end{pmatrix}$$

and the transposed last two rows of the Jacobian are:

$$\left(\left(f'_{c,3}\right)^{\mathrm{tr}}, \left(f'_{c,4}\right)^{\mathrm{tr}}\right) := \begin{pmatrix} -\beta\frac{\partial V}{\partial c} & (1-\varepsilon_s)\int_0^t \rho R(a,t)\frac{\partial \frac{\partial I(a,t)}{\partial c}}{\partial \frac{\partial T}{\partial c}}\mathrm{d}a \\ -\beta\frac{\partial T}{\partial c} & (1-\varepsilon_s)\int_0^t \rho R(a,t)\frac{\partial \frac{\partial I(a,t)}{\partial c}}{\partial \frac{\partial V}{\partial c}}\mathrm{d}a - 1 \\ -d - \beta V & (1-\varepsilon_s)\int_0^t \rho R(a,t)\frac{\partial \frac{\partial I(a,t)}{\partial c}}{\partial \frac{\partial T}{\partial c}}\mathrm{d}a \\ -\beta T & (1-\varepsilon_s)\int_0^t \rho R(a,t)\frac{\partial \frac{\partial I(a,t)}{\partial c}}{\partial \frac{\partial V}{\partial c}}\mathrm{d}a - c \end{pmatrix},$$

$$\frac{\partial \frac{\partial f}{\partial c}}{\partial t} = \begin{matrix} \Big[0, \\ (1-\varepsilon_s)\int_0^\infty \rho\left(\frac{\partial R(a,t)}{\partial t}\frac{\partial I}{\partial c}(a,t) + R(a,t)\frac{\partial \frac{\partial I(a,t)}{\partial c}}{\partial t}\right)\mathrm{d}a\Big] \end{matrix}$$

Parameter δ:

The derivative of the general function f (the vector $[T, V]$) with respect to δ is:

$$\frac{\partial f}{\partial \delta}(t, y^\delta) = \Big[-d\frac{\partial T}{\partial \delta} - \beta\left(\frac{\partial V}{\partial \delta}T + V\frac{\partial T}{\partial \delta}\right), \\ (1-\varepsilon_s)\int_0^\infty \rho R(a,t)\frac{\partial I}{\partial \delta}(a,t)\mathrm{d}a - c\frac{\partial V}{\partial \delta}\Big]$$

where $y^\delta = \begin{cases} T \\ V \\ \frac{\partial T}{\partial \delta} \\ \frac{\partial V}{\partial \delta} \end{cases}$.

Furthermore:

$$\frac{\partial R(a,t)}{\partial \delta} = 0,$$

$$\begin{aligned}
\frac{\partial \bar{T}}{\partial \delta} &= \frac{\partial \frac{1}{N}}{\partial \delta} c/\beta, \\
\frac{\partial \bar{V}}{\partial \delta} &= \frac{\partial N}{\partial \delta} s/c, \\
\frac{\partial N}{\partial \delta} &= \frac{\rho\left(\delta(\rho+\mu+\delta) - (\alpha+\delta)(\rho+\mu+\delta) - \delta(\alpha+\delta)\right)}{\delta^2(\rho+\mu+\delta)^2}, \\
\frac{\partial \frac{1}{N}}{\partial \delta} &= \frac{(\rho+\mu+\delta)(\alpha+\delta) + \delta(\alpha+\delta) - \delta(\rho+\mu+\delta)}{\rho(\alpha+\delta)^2},
\end{aligned}$$

$$\frac{\partial I(a,t)}{\partial \delta} = \begin{cases} \beta\left(\frac{\partial V}{\partial \delta}(t-a)T(t-a) + V(t-a)\frac{\partial T}{\partial \delta}(t-a) - aV(t-a)T(t-a)\right)\mathrm{e}^{-\delta a} & a < t \\ \left(-\frac{\partial \frac{1}{N}}{\partial \delta} dc/\beta - a(\beta N s - dc)/(\beta N)\right)\mathrm{e}^{-\delta a} & a > t \end{cases},$$

The upper right block matrix of the Jacobian is:

$$f'_{\delta,2\times 2} = \begin{pmatrix} 0 & 0 \\ (1-\varepsilon_s)\int_0^t \rho R(a,t) \times \frac{\partial I(a,t)}{\partial \frac{\partial T}{\partial \delta}}\mathrm{d}a & (1-\varepsilon_s)\int_0^t \rho R(a,t) \times \frac{\partial I(a,t)}{\partial \frac{\partial V}{\partial \delta}}\mathrm{d}a \end{pmatrix}$$

and the transposed last two rows of the Jacobian are:

$$\left(\left(f'_{\delta,3}\right)^{\mathrm{tr}}, \left(f'_{\delta,4}\right)^{\mathrm{tr}}\right) := \begin{pmatrix} -\beta\frac{\partial V}{\partial \delta} & (1-\varepsilon_s)\int_0^t \rho R(a,t)\frac{\partial \frac{\partial I(a,t)}{\partial \delta}}{\partial \frac{\partial T}{\partial \delta}}\mathrm{d}a \\ -\beta\frac{\partial T}{\partial \delta} & (1-\varepsilon_s)\int_0^t \rho R(a,t)\frac{\partial \frac{\partial I(a,t)}{\partial \delta}}{\partial \frac{\partial V}{\partial \delta}}\mathrm{d}a \\ -d-\beta V & (1-\varepsilon_s)\int_0^t \rho R(a,t)\frac{\partial \frac{\partial I(a,t)}{\partial \delta}}{\partial \frac{\partial T}{\partial \delta}}\mathrm{d}a \\ -\beta T & (1-\varepsilon_s)\int_0^t \rho R(a,t)\frac{\partial \frac{\partial I(a,t)}{\partial \delta}}{\partial \frac{\partial V}{\partial \delta}}\mathrm{d}a - c \end{pmatrix},$$

$$\frac{\partial \frac{\partial f}{\partial \delta}}{\partial t} = \begin{matrix} \Big[0, \\ (1-\varepsilon_s)\int_0^\infty \rho\left(\frac{\partial R(a,t)}{\partial t}\frac{\partial I}{\partial \delta}(a,t) + R(a,t)\frac{\partial \frac{\partial I(a,t)}{\partial \delta}}{\partial t}\right)\mathrm{d}a\Big] \end{matrix}$$