Modelling the Dementia Brain

Fourth Year Project

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Project Aim

To model and quantitatively measure the affect of the pericytes response on Alzheimer's dementia (AD).

Outline

Research

- Failure in trials targeting the amyloid cascade hypothesis.
- Push for innovative modelling methods.
- Blood flow modelling offers hope.
- Pericytes recently emerging as a vital component of microvasculature blood flow control.
- Further reinforcing of the pericytes having a potential role in Alzheimer's Dementia.

Model overview

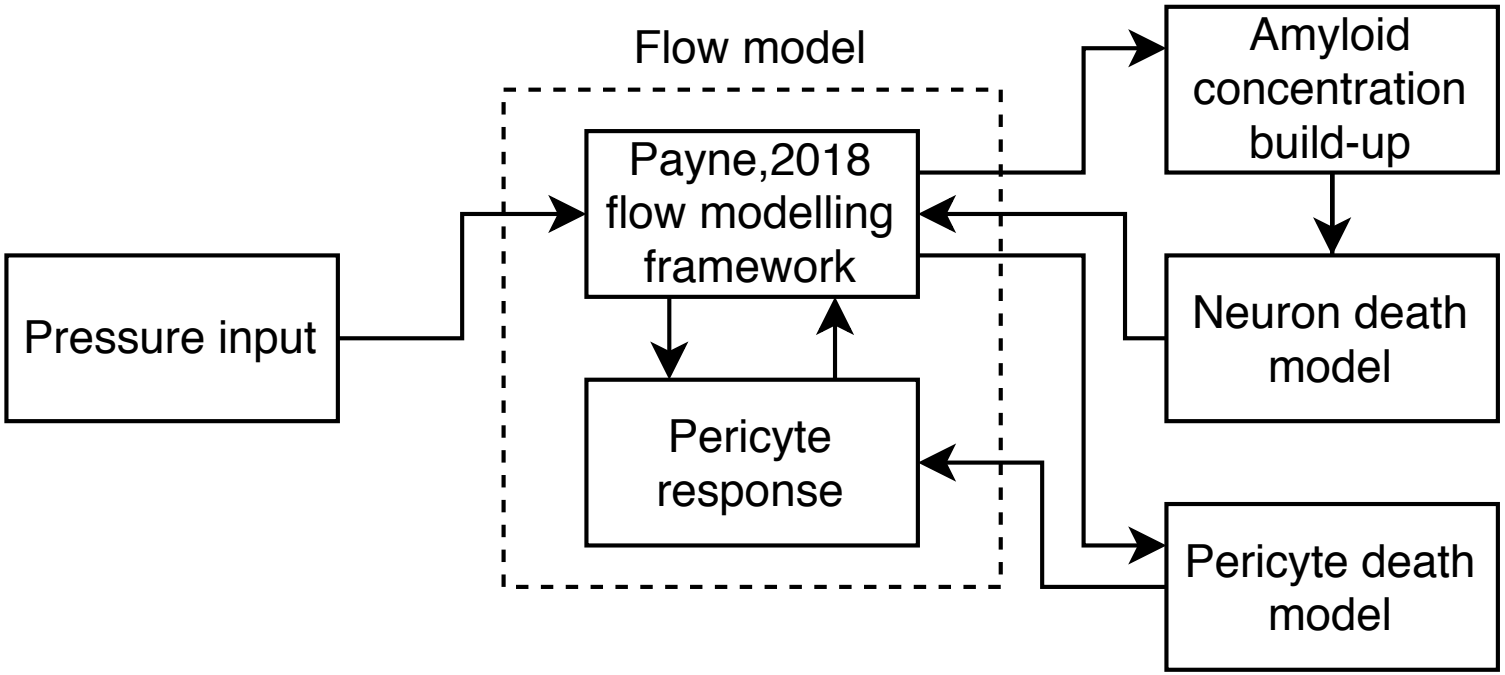


Figure: Block diagram illustrating structure of model.

VAN

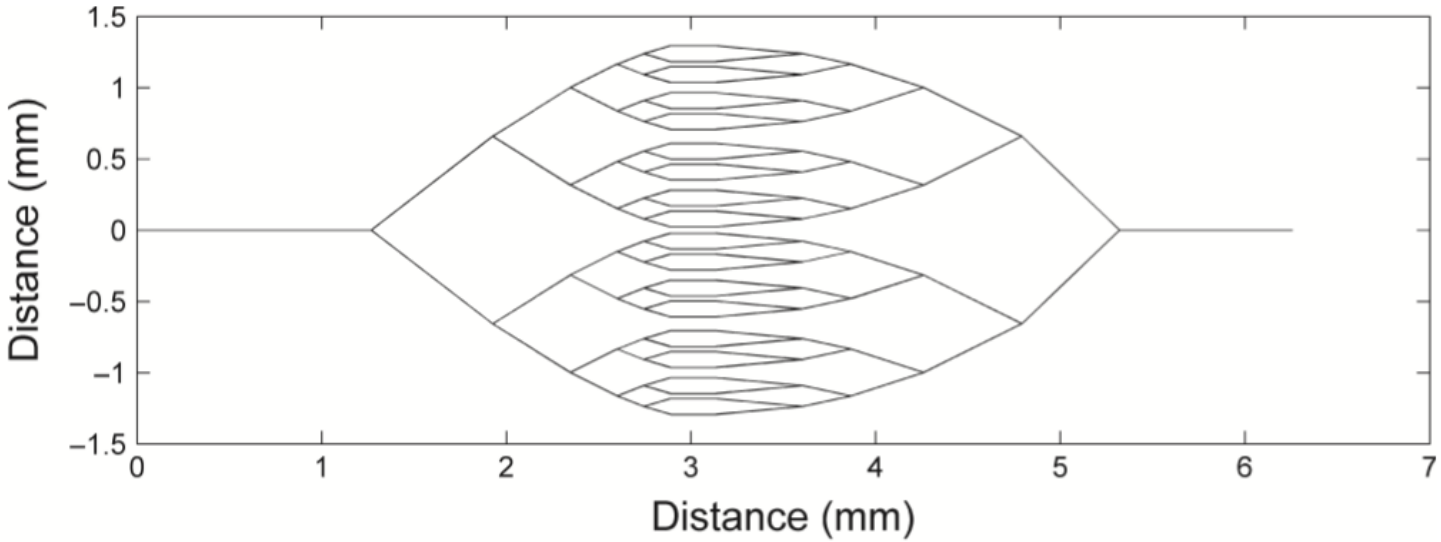


Figure: Diagram demonstrating the arrangement of the vessel network Payne and Lucas (2018).

Flow Model Equations

From Payne and Lucas (2018):

$$\alpha_t V_t \frac{\partial p_t}{\partial t} = \frac{2\pi KRL}{h}\left(\frac{1}{2}(p_{b,in} + p_{b,out}) - p_t\right) - MV_t \tag{1}$$

$$V_b \frac{1}{2}\left(\frac{\partial S_{in}}{\partial t} + \frac{\partial S_{out}}{\partial t}\right) + \frac{1}{2}\left(Q_{in} + Q_{out}\right)\left(S_{out} - S_{in}\right) = -\frac{2\pi KRL}{hc_{Hb}H}\left(\frac{1}{2}(p_{b,in} + p_{b,out}) - p_t\right) \tag{2}$$

Resistor analogy:

$$\Delta p_{network} = Q_{network} . R_{network} \tag{3}$$

Pericyte response

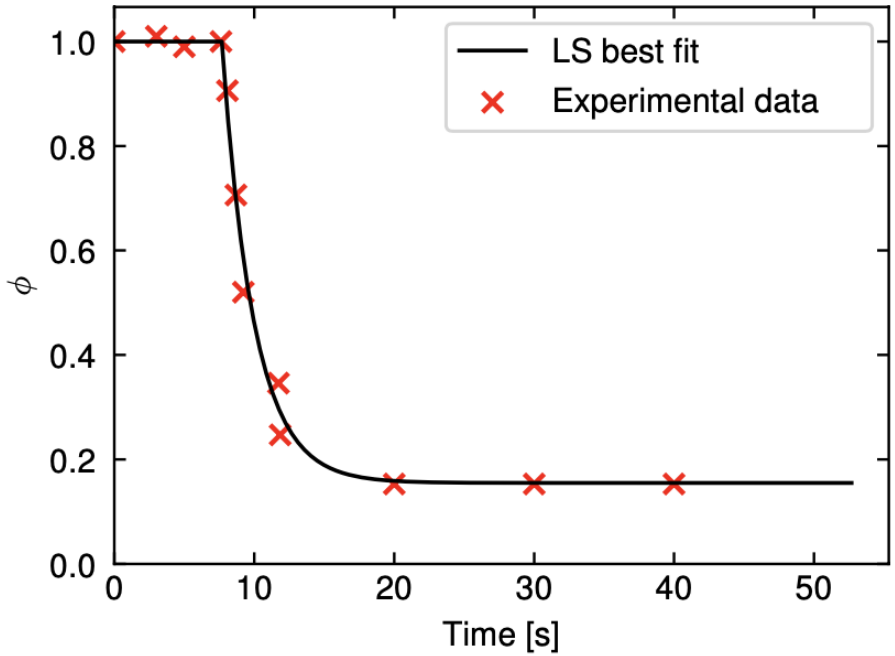


Figure 4.4: Fit to experimental data of the pericyte response in full ischaemia.

for:

$$\phi(t) = \begin{cases} 1 & \text{if } t <= \tau_d, \\ \phi_{FI} + \frac{1-\phi_{FI}}{\tau_p(t-\tau_d)+1} & \text{if } t > \tau_d. \end{cases} \tag{4}$$

Pericyte response cont.

Scaling function:

$$\phi_{min} = 1 - \alpha^{0.25}(1 - \phi_{FI})(1 - Q_{\text{norm}}) \tag{5}$$

Pericyte governing equation:

$$\tau_{\text{p}} \frac{d\phi}{dt} = -\phi(t - \tau_{\text{d}}) + Q_{\text{norm}}(1 - \phi_{\text{min}}) + \phi_{\text{min}} \tag{6}$$

Boundary conditions satisfied when all pericytes respond to flow stimulus ($\alpha = 1$):

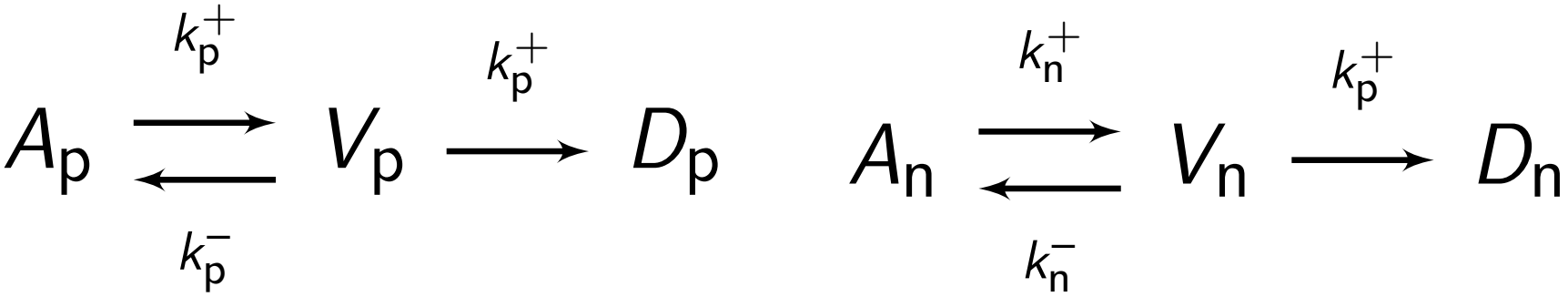
$$\phi_{\text{min}} = \phi_{\text{FI}} \quad \text{for} \quad Q_{\text{norm}} = 0 \tag{7}$$

$$\phi_{\text{min}} = 1 \quad \text{for} \quad Q_{\text{norm}} = 1 \tag{8}$$

AB accumulation

$$\tau_c \frac{dc}{dt} c = R - c(k + Q_{\text{norm}}) \tag{9}$$

Health models



(a) Pericyte health model.

(b) Neuron health model.

Figure: The health models set up.

$$\frac{dA}{dt} = -k^+.A + k^-.V \tag{10}$$

$$\frac{dV}{dt} = k^+.A - k^-.V - k^+.V \tag{11}$$

$$\frac{dD}{dt} = k^-.V \tag{12}$$

$$1 = A + V + D \tag{13}$$

AB accumulation cont.

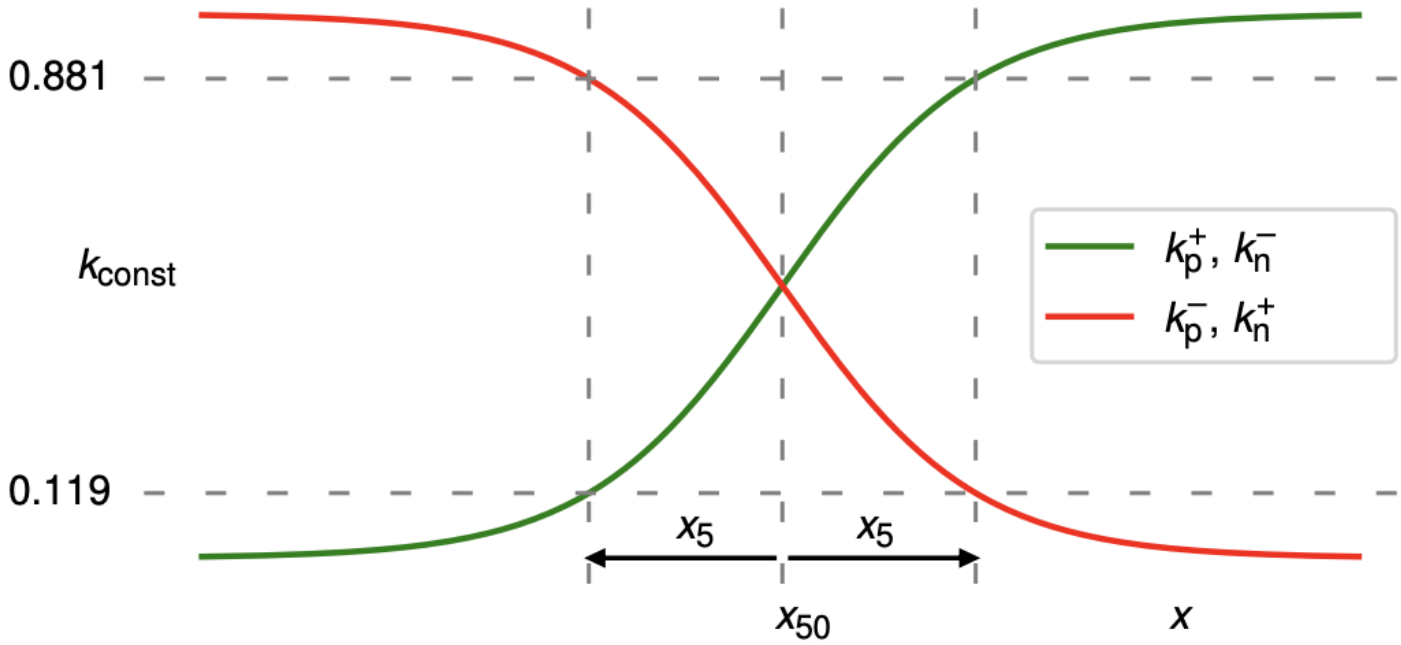


Figure 4.6: Illustration of the constant values set in the pericyte and neuron health models.

General case:

$$k(x) = \frac{k_{const}}{2}\left(1 \pm \tanh\left(\frac{x - x_{50}}{x_5}\right)\right) \tag{14}$$

Neuron health model

$$k_n^+(c) = \overline{k}_n \frac{1}{2}\left(1 + \tanh\left(\frac{c - c_{50}}{c_5}\right)\right) \tag{15}$$

$$k_n^-(c) = \overline{k}_n \frac{1}{2}\left(1 - \tanh\left(\frac{c - c_{50}}{c_5}\right)\right) \tag{16}$$

$$M = A_n M_{\text{hill}} \tag{17}$$

Pericyte health model

$$\hat{p}_{\mathrm{t}} = \frac{1}{\sum_{i=1}^{\mathrm{N}} V_{\mathrm{t,i}}} \sum_{i=1}^{\mathrm{N}} p_{\mathrm{t,i}} V_{\mathrm{t,i}} \tag{18}$$

$$k_{\mathrm{p}}^{+}(\hat{p}_{\mathrm{t}}) = \overline{k}_{\mathrm{p}} \frac{1}{2} \left(1 - \tanh \left(\frac{\hat{p}_{\mathrm{t}} - \hat{p}_{\mathrm{t,50}}}{\hat{p}_{\mathrm{t,5}}} \right) \right) \tag{19}$$

$$k_{\mathrm{p}}^{-}(\hat{p}_{\mathrm{t}}) = \overline{k}_{\mathrm{p}} \frac{1}{2} \left(1 + \tanh \left(\frac{\hat{p}_{\mathrm{t}} - \hat{p}_{\mathrm{t,50}}}{\hat{p}_{\mathrm{t,5}}} \right) \right) \tag{20}$$

$$\tau_{\mathrm{p}} \frac{d\phi}{dt} = -\phi(t - \tau_{\mathrm{d}}) + A_{\mathrm{p}} \left[f(1 - \phi_{\mathrm{min}}) + \phi_{\mathrm{min}} \right] \tag{21}$$

Model development conclusion

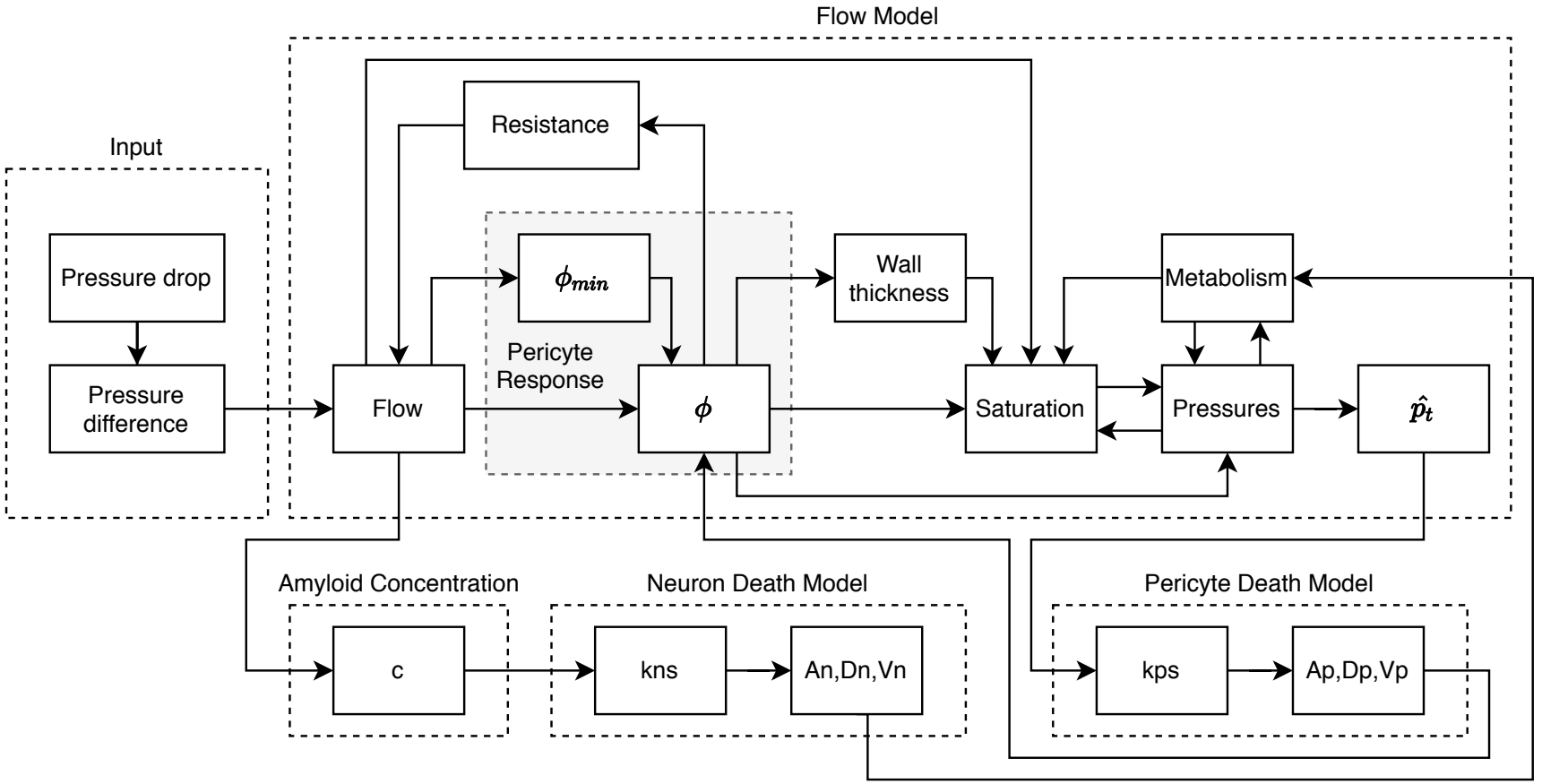


Figure: Full model block diagram of all parameters

Numerical solver

Modified Runge-Kutta 4th order method:

$$
\begin{aligned}
\frac{dy_i}{dt} &= f(t, \mathrm{y}), \\
\mathrm{y}(t_0) &= \mathrm{y}_0, \\
\mathrm{y}_{n+1} &= \mathrm{y}_n + \frac{1}{6} h \left(\mathrm{a} + 2\mathrm{b} + 2\mathrm{c} + \mathrm{d}\right), \\
t_{n+1} &= t_n + h, \\
a_i &= f(t_n, \mathrm{y}_n), \\
b_i &= f\left(t_n + \frac{h}{2}, \mathrm{y}_n + h\frac{\mathrm{a}}{2}\right), \\
c_i &= f\left(t_n + \frac{h}{2}, \mathrm{y}_n + h\frac{\mathrm{c}}{2}\right), \\
d_i &= f\left(t_n + h, \mathrm{y}_n + h\mathrm{d}\right).
\end{aligned}
$$

$$
\begin{aligned}
\mathrm{y} &= \begin{bmatrix} y_1 & y_2 & \dots & y_\mathrm{k} \end{bmatrix}, \\
\mathrm{a} &= \begin{bmatrix} a_1 & a_2 & \dots & a_\mathrm{k} \end{bmatrix}, \\
\mathrm{b} &= \begin{bmatrix} b_1 & b_2 & \dots & b_\mathrm{k} \end{bmatrix}, \\
\mathrm{c} &= \begin{bmatrix} c_1 & c_2 & \dots & c_\mathrm{k} \end{bmatrix}, \\
\mathrm{d} &= \begin{bmatrix} d_1 & d_2 & \dots & d_\mathrm{k} \end{bmatrix},
\end{aligned}
$$

Results

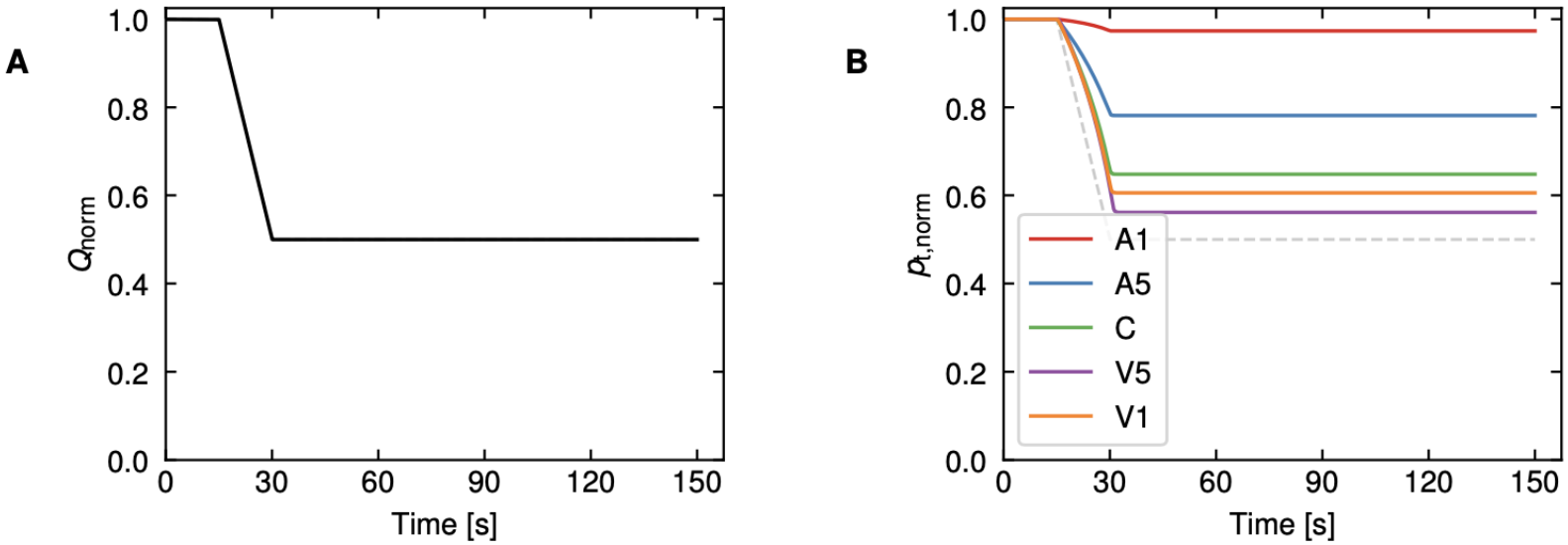


Figure 5.5: Base flow model results.
A: normalised flow rate response; **B**: the distribution of the normalised partial tissue pressure of oxygen surrounding a selection of vessels.

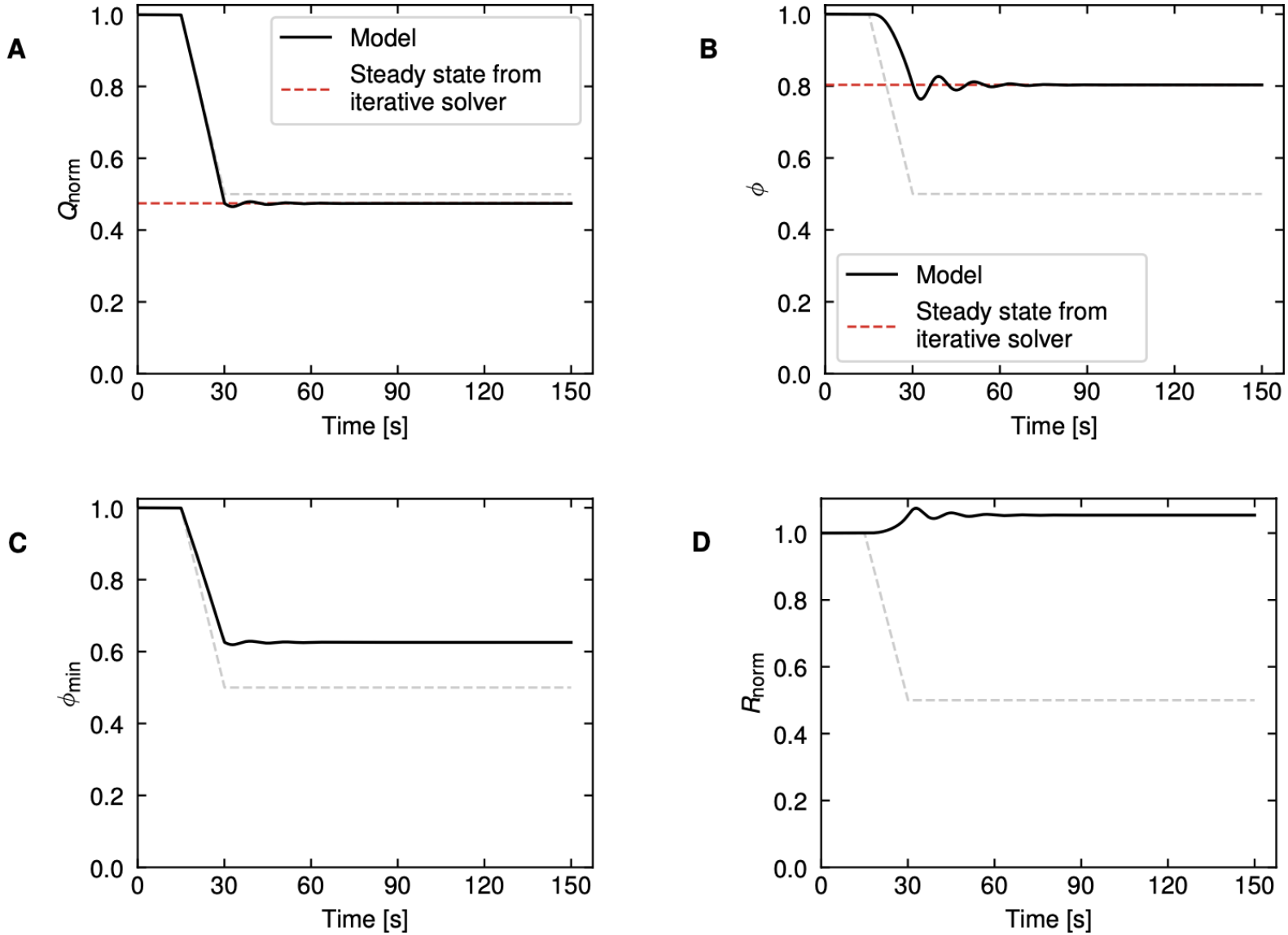


Figure 5.6: Pericyte response results.
A: normalised flow rate response; **B**: normalised capillary bed diameter response; **C**: ϕ_{min} scaling factor; **D**: normalised total resistance of the network.

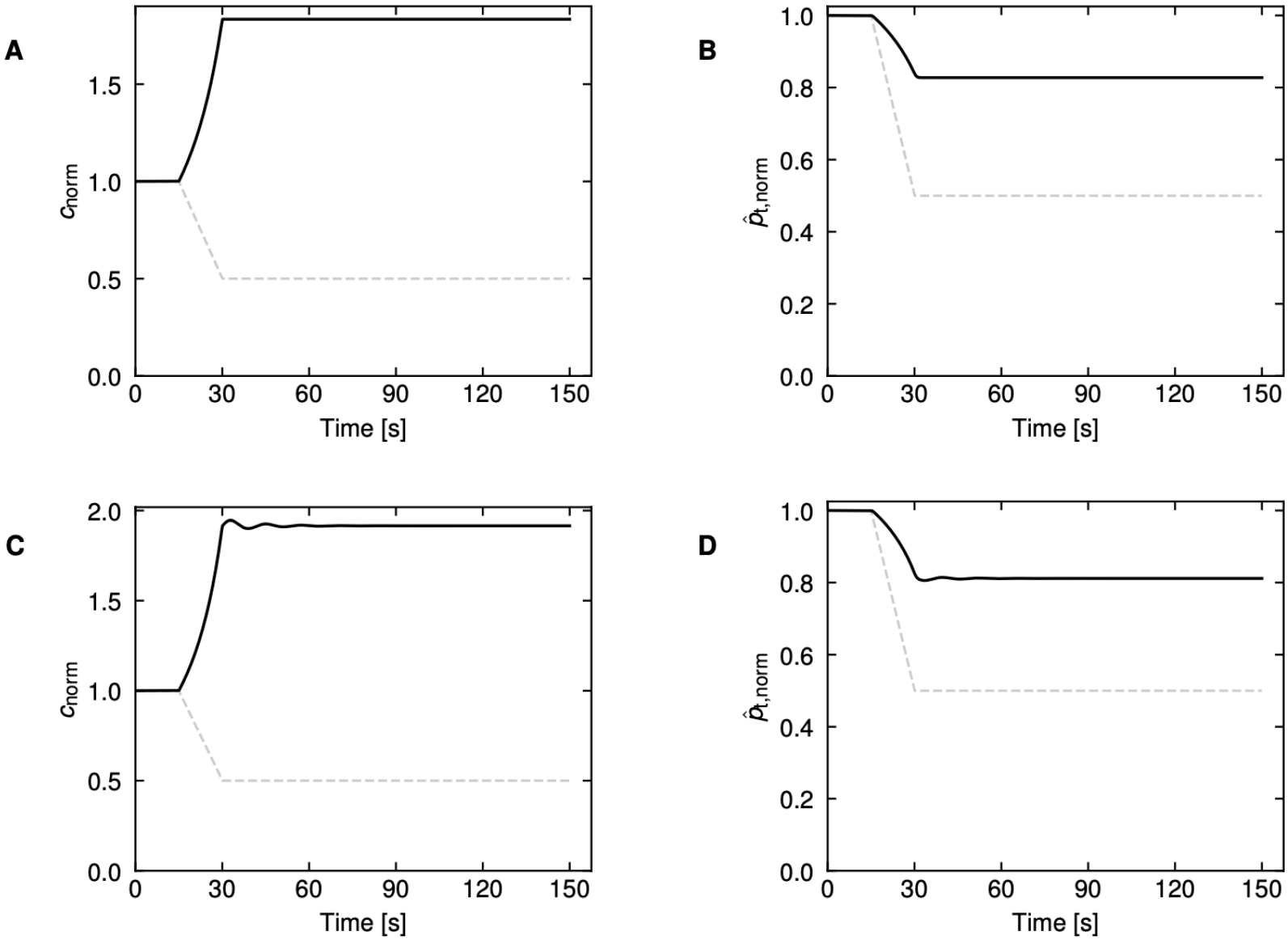


Figure 5.7: Health metrics.
A & **B**: AB concentration and $\hat{p}_{t,norm}$ plots for the flow model; **C** & **D**: AB concentration and $\hat{p}_{t,norm}$ plots for the pericyte response model.

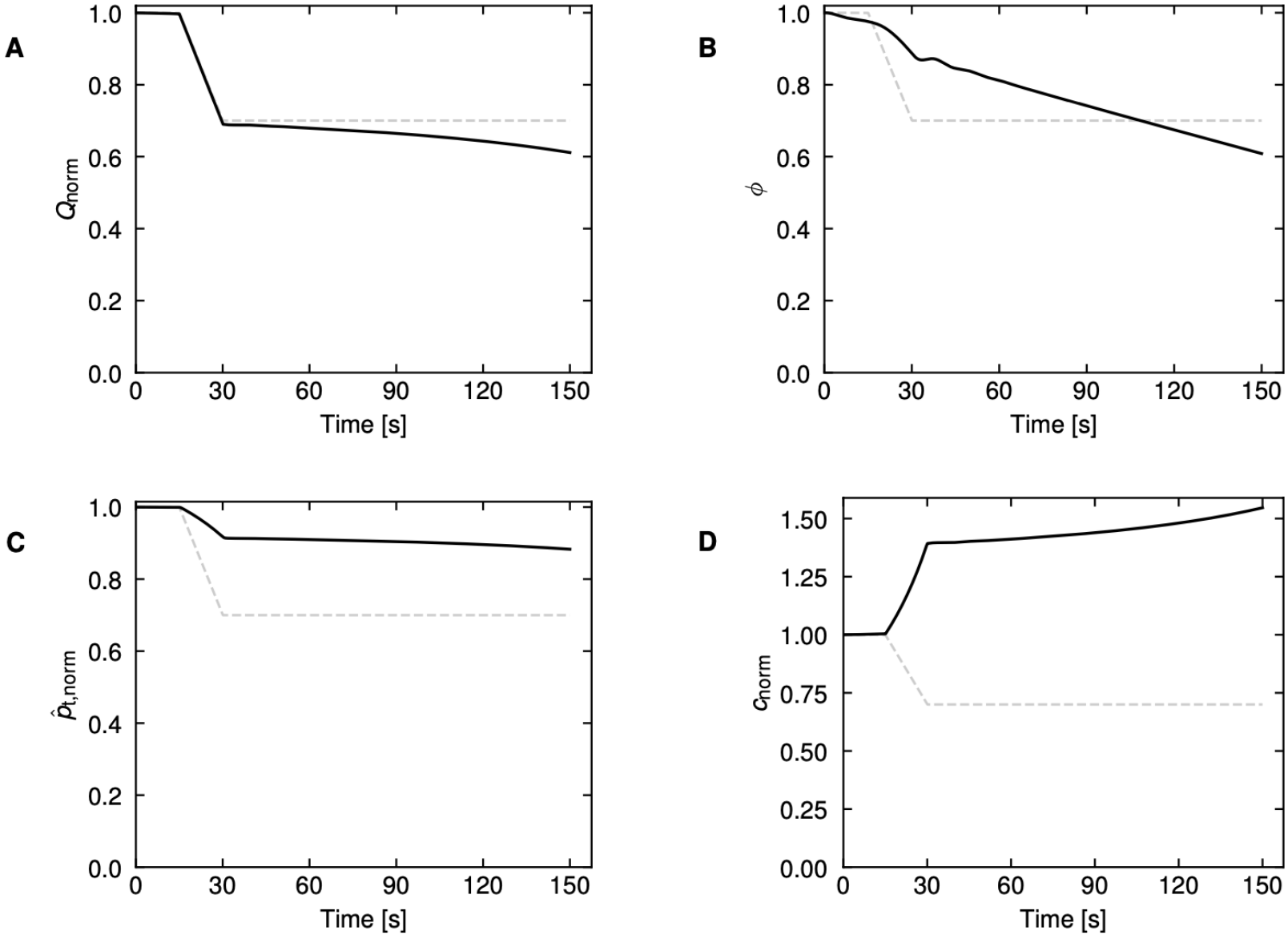


Figure 5.8: Pericyte health model results.
A: normalised flow rate response; **B**: ϕ response; **C**: $\hat{p}_t$ response; **D**: normalised AB concentration response; **E**: normalised vessel p_t response; **F**: pericyte health model states.

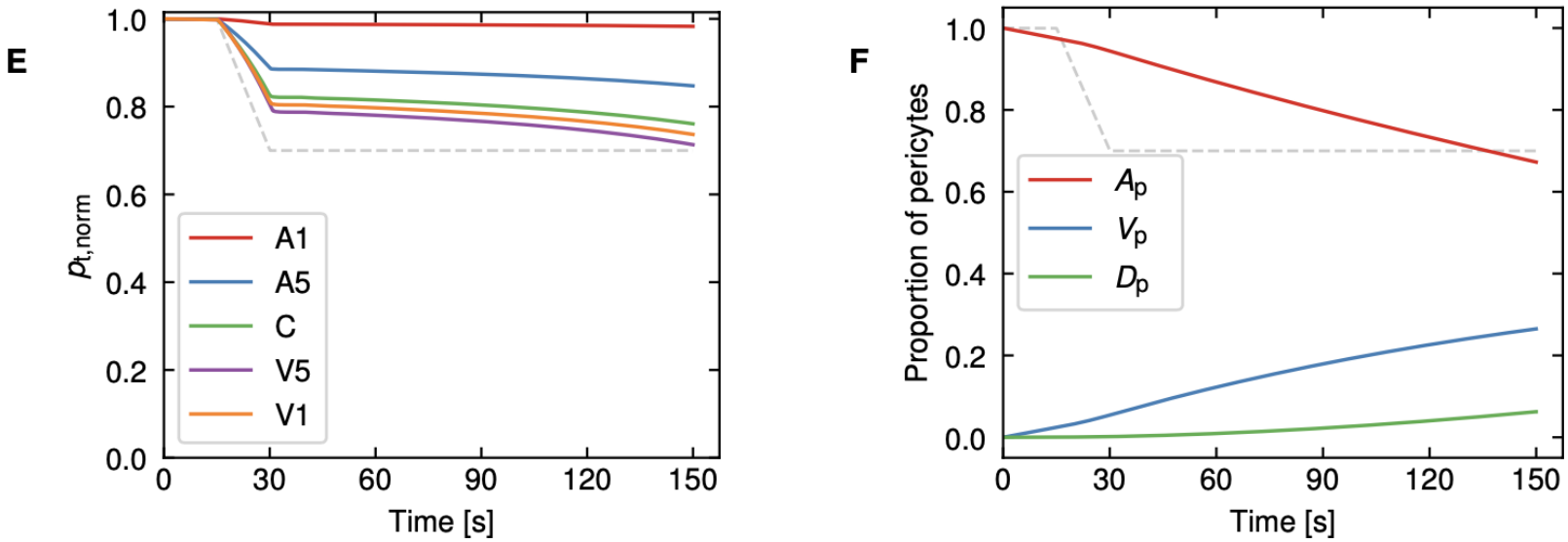


Figure 5.8: Pericyte health model results.
A: normalised flow rate response; **B**: ϕ response; **C**: $\hat{p}_t$ response; **D**: normalised AB concentration response; **E**: normalised vessel p_t response; **F**: pericyte health model states.

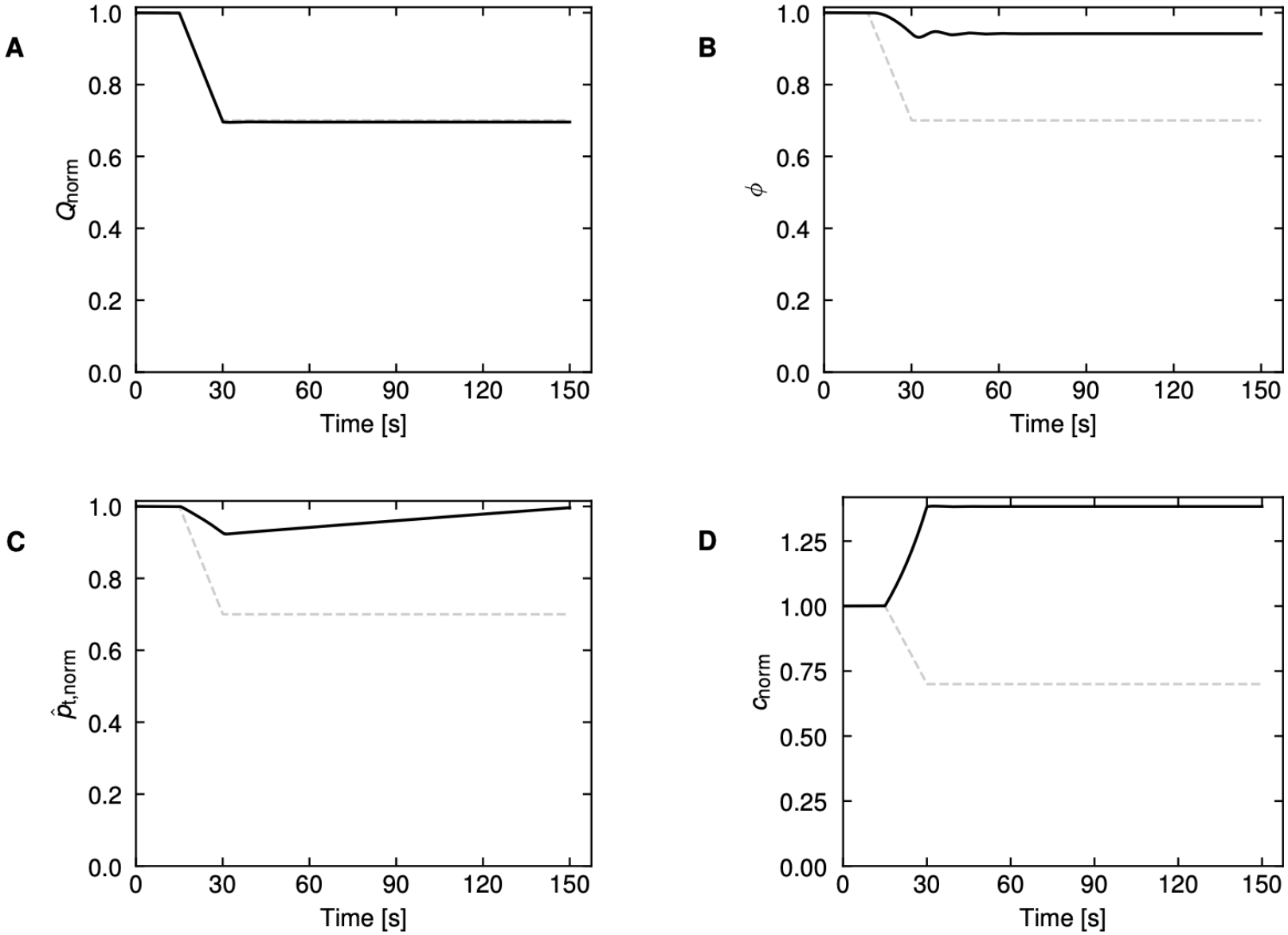


Figure 5.9: Neuron health model results.
A: normalised flow rate response; **B**: ϕ response; **C**: $\hat{p}_t$ response; **D**: normalised AB concentration response; **E**: normalised vessel p_t response; **F**: neuron health model states.

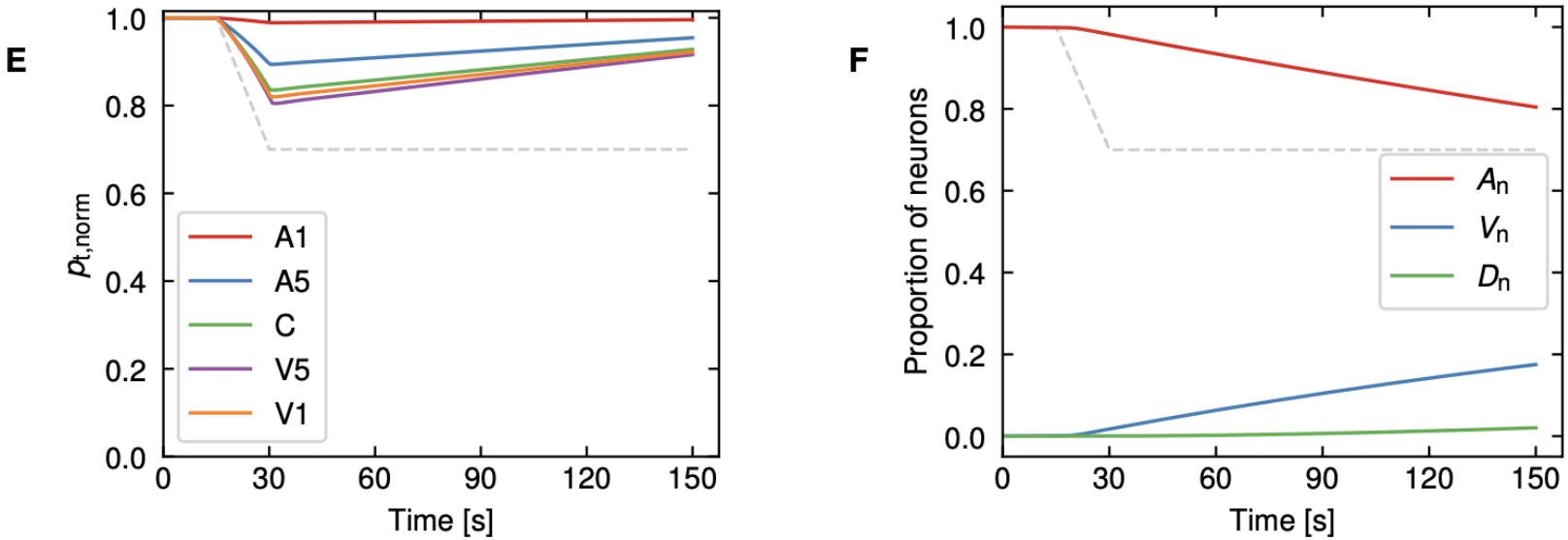


Figure 5.9: Neuron health model results.
A: normalised flow rate response; **B**: ϕ response; **C**: $\hat{p}_t$ response; **D**: normalised AB concentration response; **E**: normalised vessel p_t response; **F**: neuron health model states.

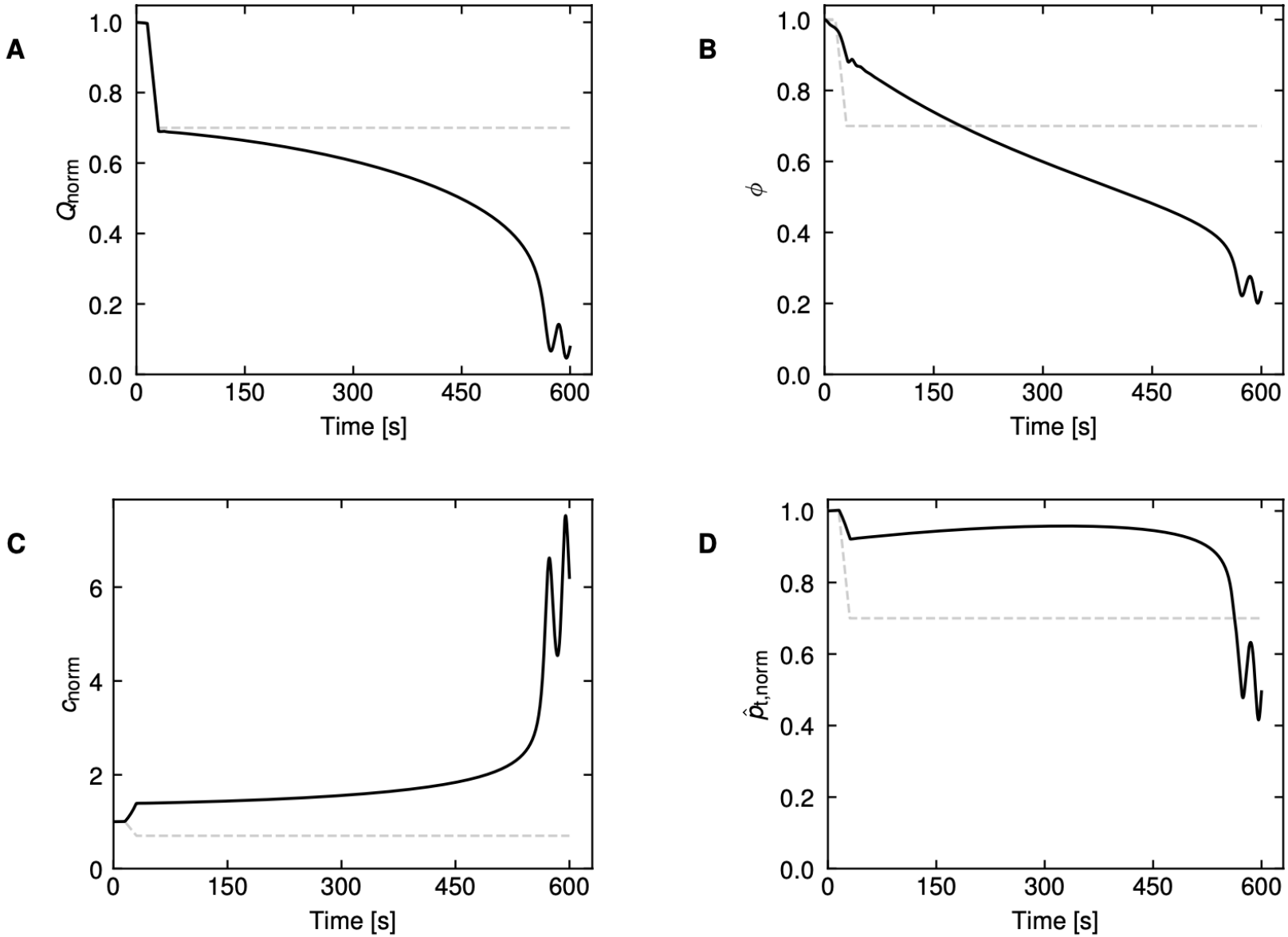


Figure 5.11: Default values results.
A: normalised flow rate response; **B**: ϕ response; **C**: normalised AB concentration response; **D**: $\hat{p}_t$ response; **E**: pericyte health model states; **F**: neuron health model states.

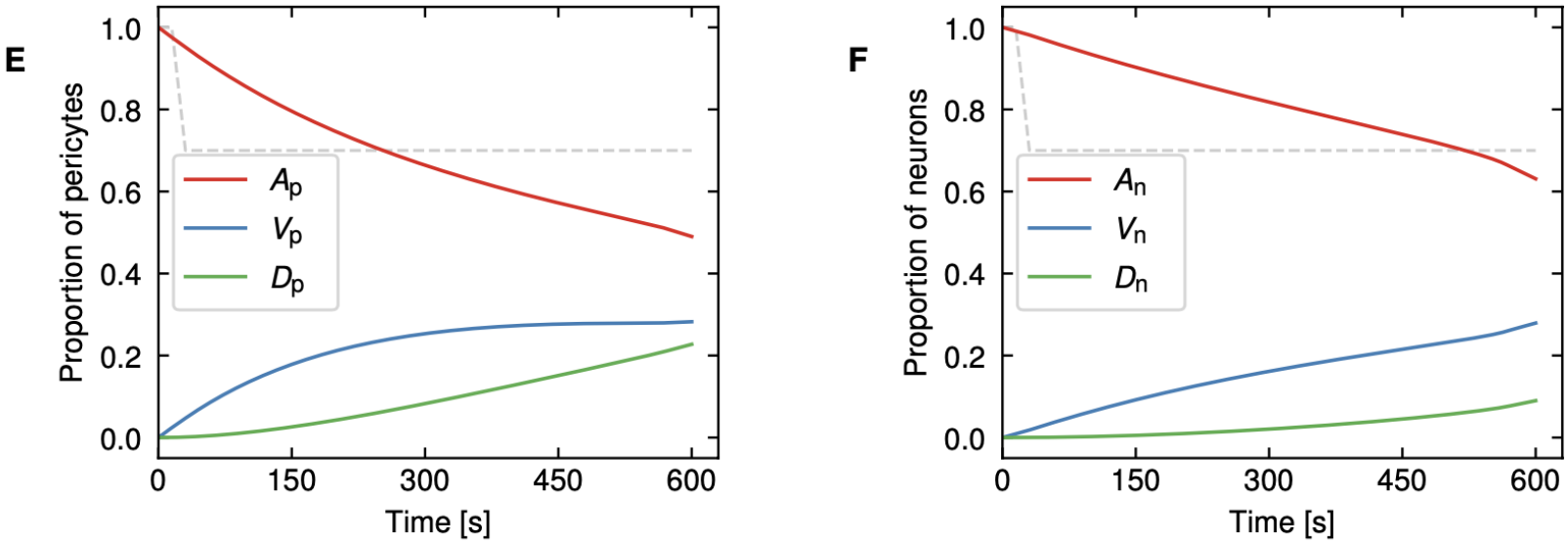


Figure 5.11: Default values results.
A: normalised flow rate response; **B**: ϕ response; **C**: normalised AB concentration response; **D**: $\hat{p}_t$ response; **E**: pericyte health model states; **F**: neuron health model states.

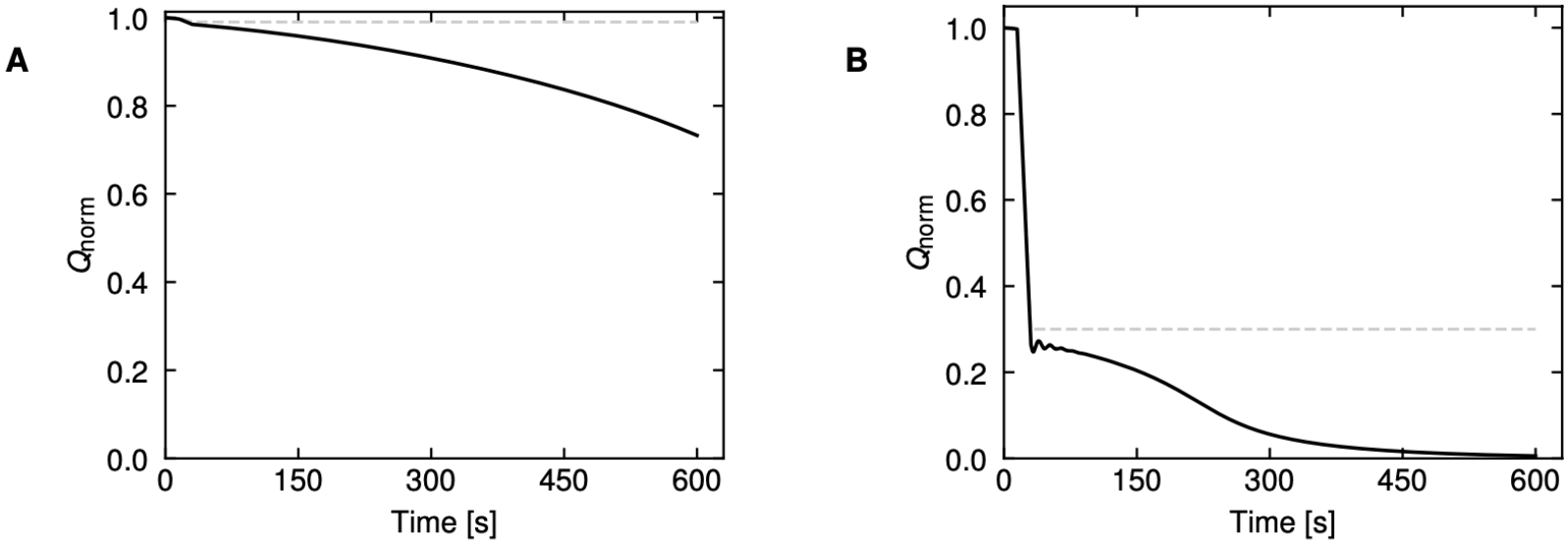


Figure 5.12: Comparing pressure drop values.
A: Flow rate plot for low pressure drop (0.01); **B**: Flow rate plot for high pressure drop (0.7).

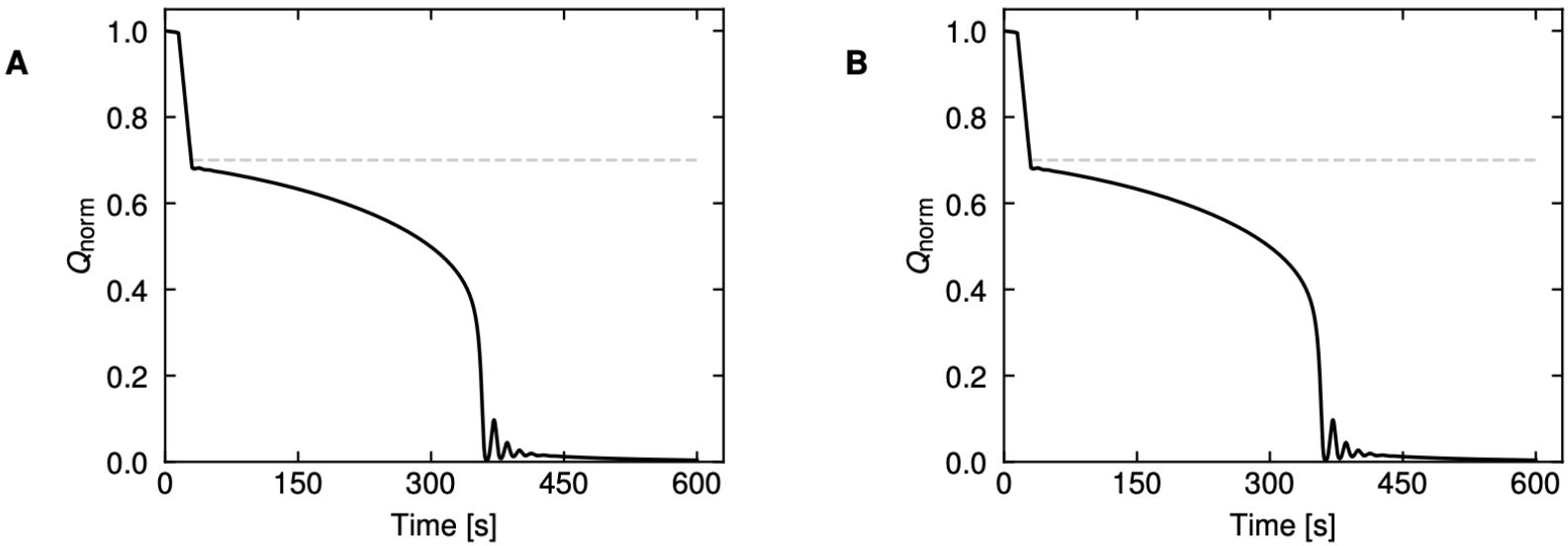


Figure 5.13: Comparing delay for α = 0.5.
A: Flow rate plot for low delay (0); **B**: Flow rate plot for high delay (7.62).

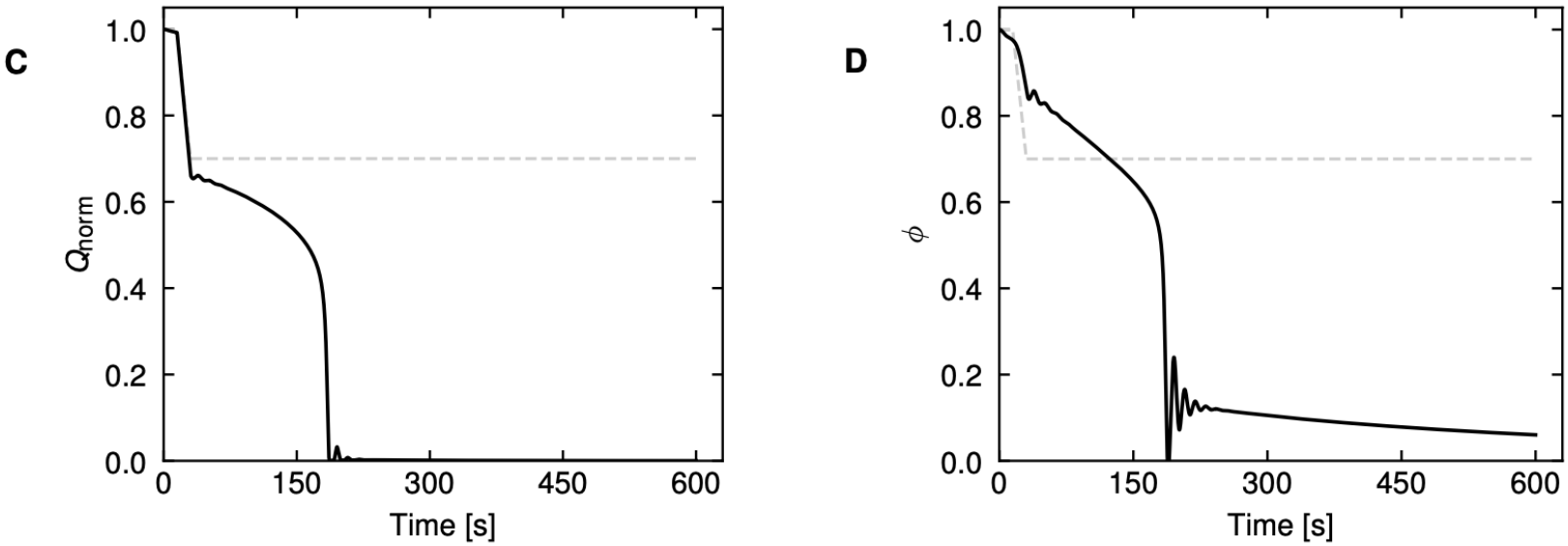


Figure 5.14: Showing high α results.
A: Flow rate plot for high alpha (0.9); **B**: ϕ plot for high alpha (0.9);

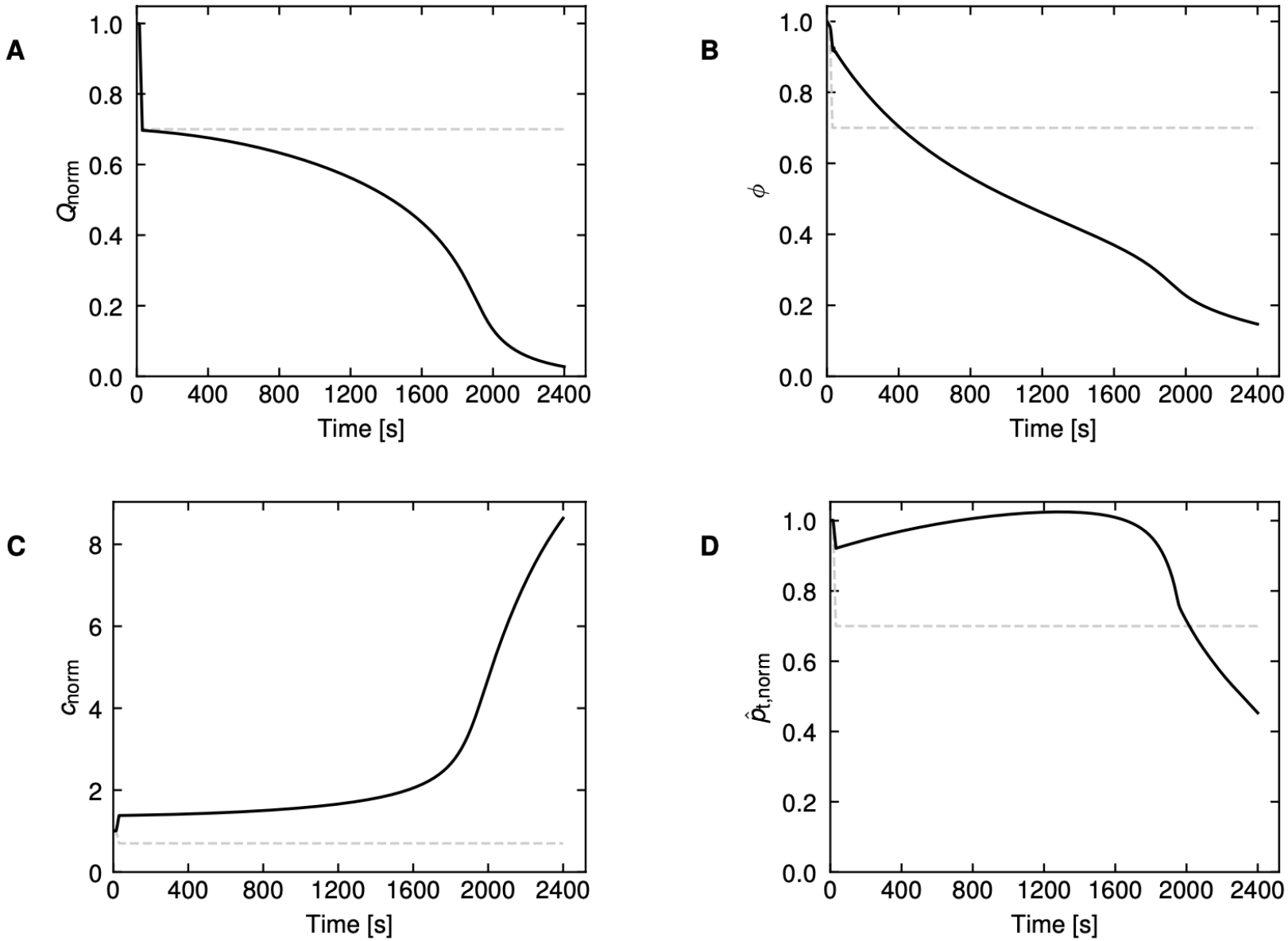


Figure 5.15: Slow response results..
A: normalised flow rate response; **B**: ϕ response; **C**: normalised AB concentration response; **D**: $\hat{p}_t$ response; **E**: pericyte health model states; **F**: neuron health model states.

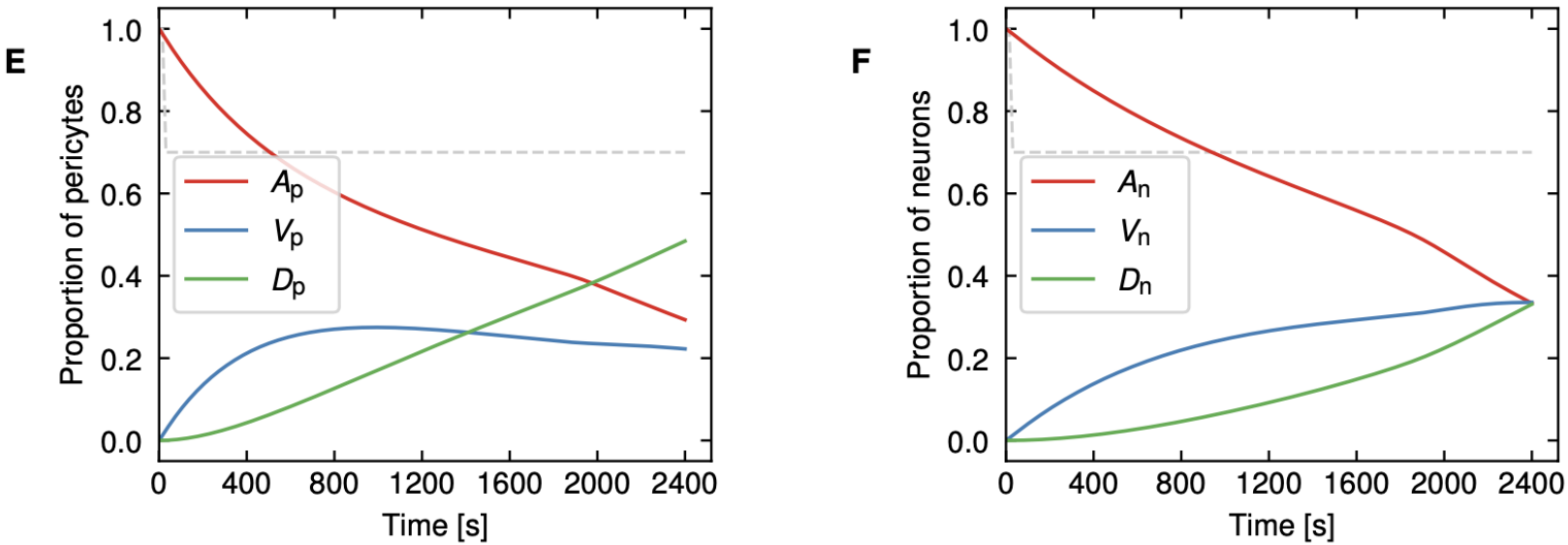


Figure 5.15: Slow response results..
A: normalised flow rate response; **B**: ϕ response; **C**: normalised AB concentration response; **D**: $\hat{p}_t$ response; **E**: pericyte health model states; **F**: neuron health model states.

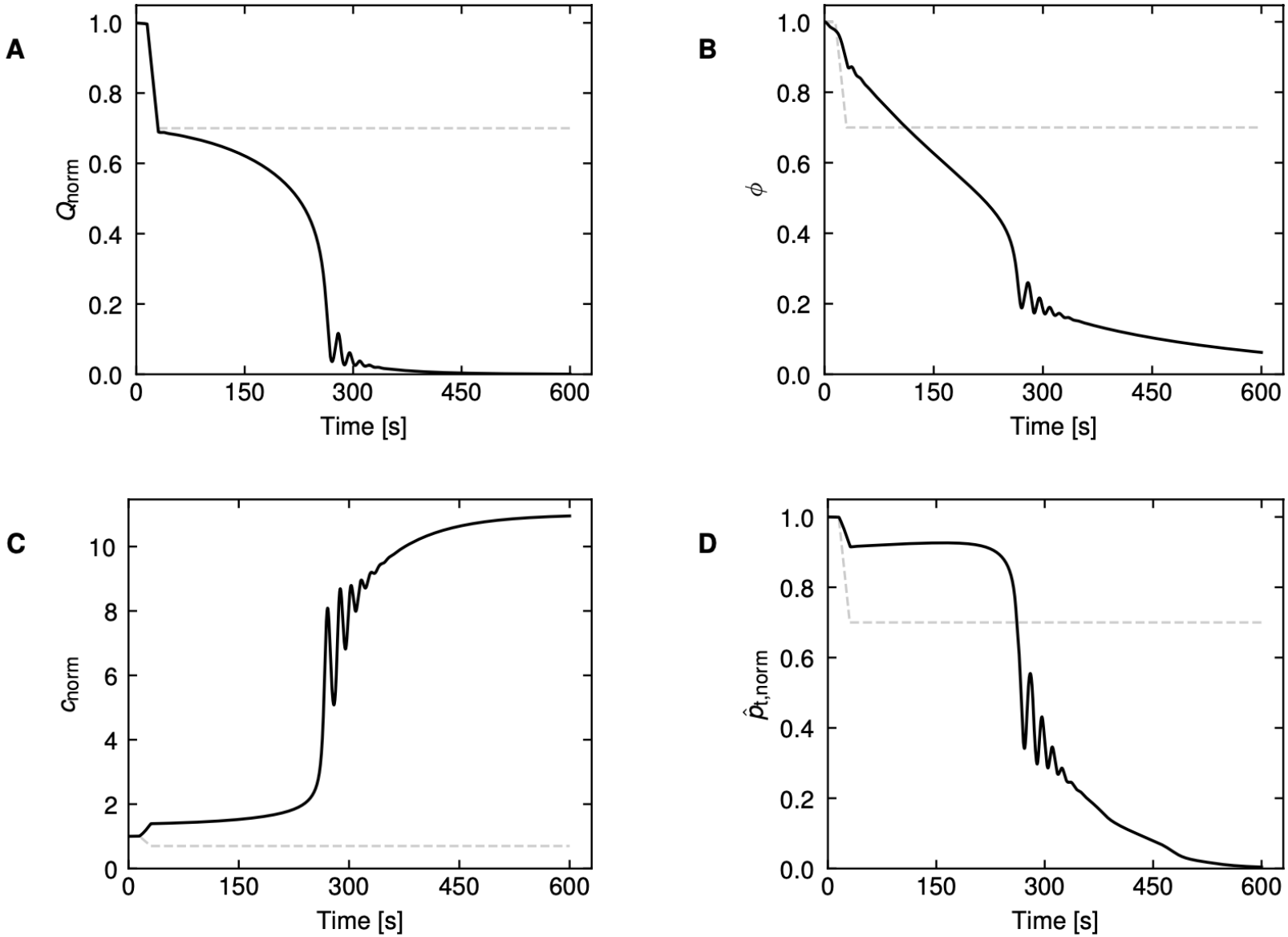


Figure 5.16: Accelerated response results..
A: normalised flow rate response; **B**: ϕ response; **C**: normalised AB concentration response; **D**: $\hat{p}_t$ response; **E**: pericyte health model states; **F**: neuron health model states.

$$\hat{p}_{t,50} = \hat{p}_{t,baseline} \tag{22}$$

$$\hat{p}_{t,5} = 0.1.\hat{p}_{t,baseline} \tag{23}$$

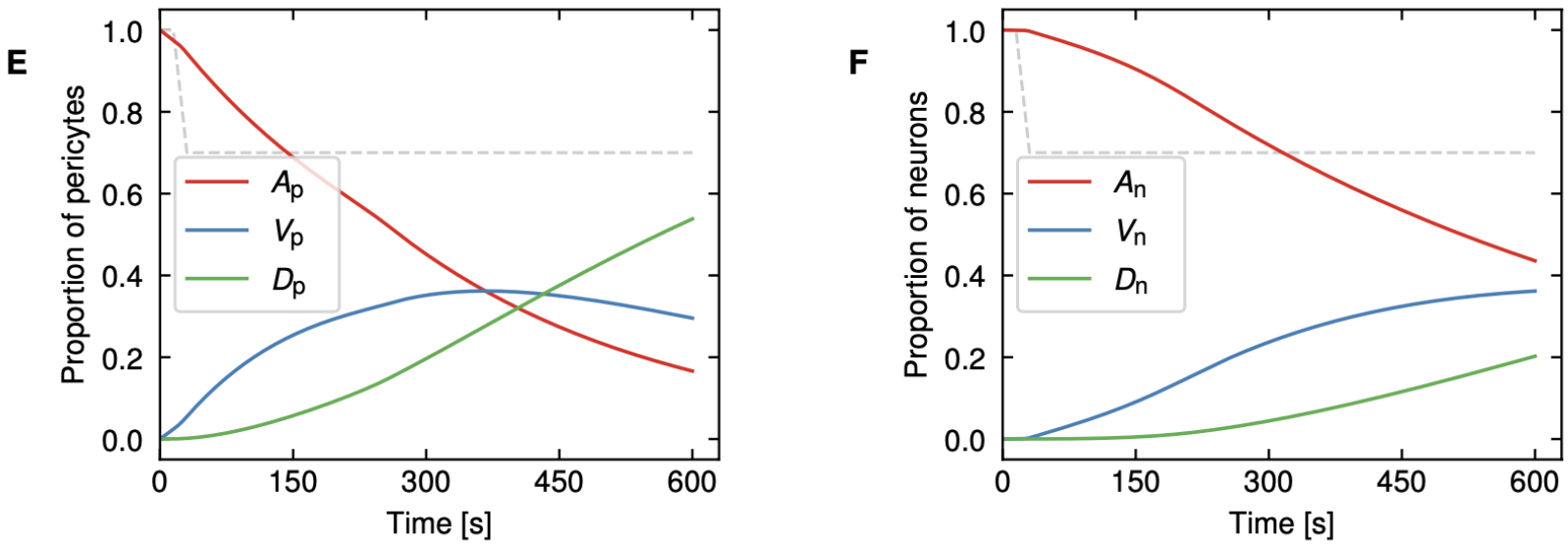


Figure 5.16: Accelerated response results..
A: normalised flow rate response; **B**: ϕ response; **C**: normalised AB concentration response; **D**: $\hat{p}_t$ response; **E**: pericyte health model states; **F**: neuron health model states.

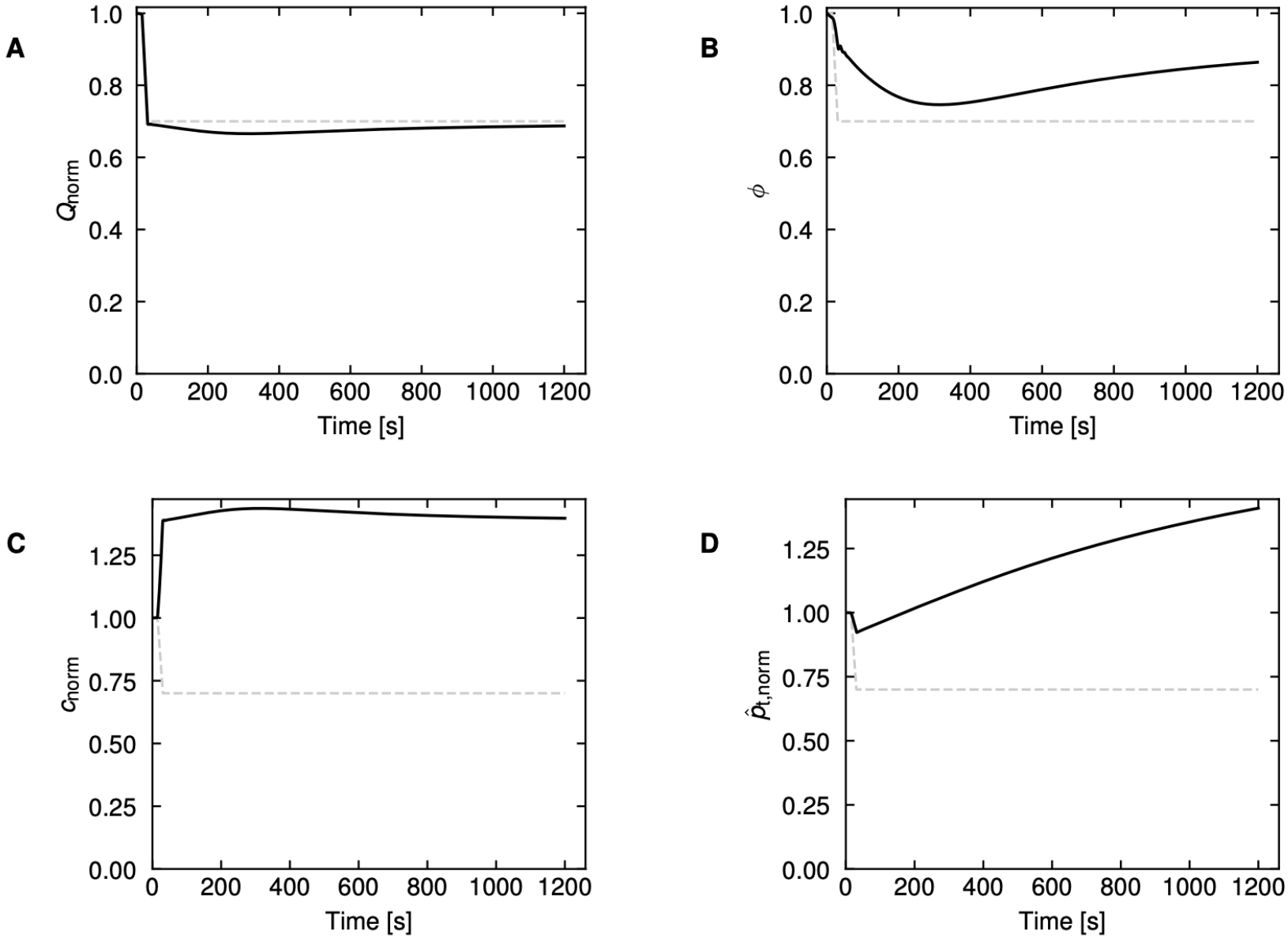


Figure 5.17: Second equilibrium results.
A: normalised flow rate response; **B**: ϕ response; **C**: normalised AB concentration response; **D**: $\hat{p}_t$ response; **E**: pericyte health model states; **F**: neuron health model states.

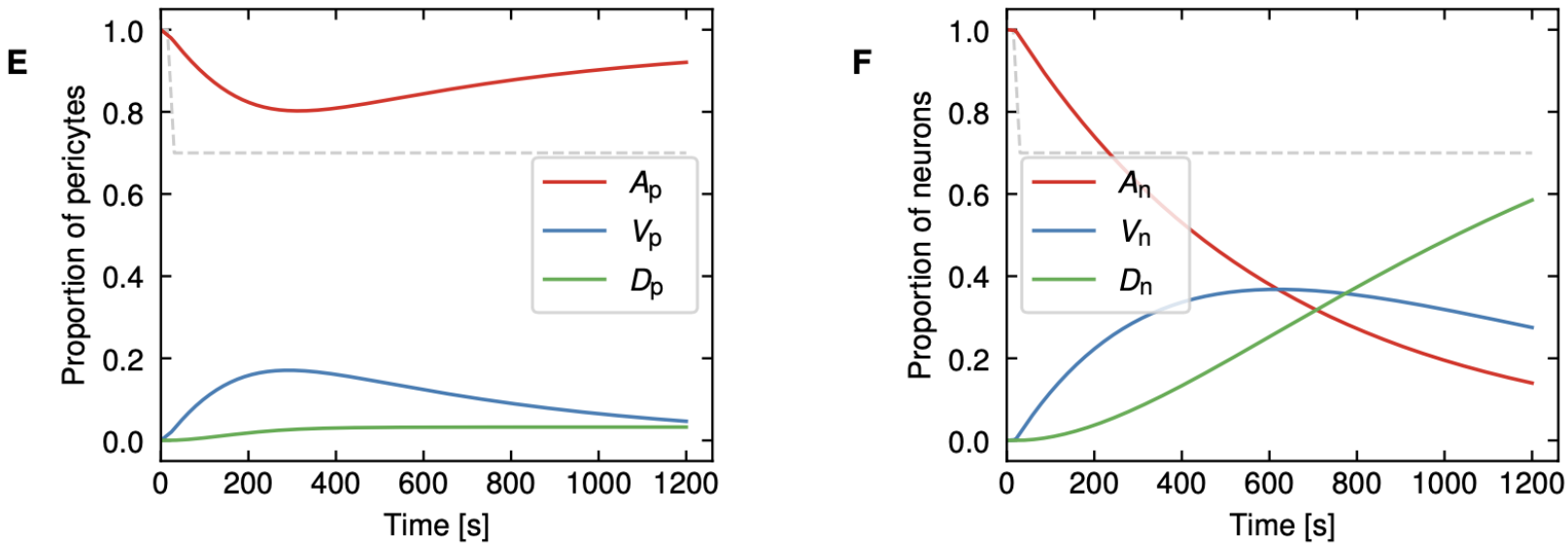


Figure 5.17: Second equilibrium results.
A: normalised flow rate response; **B**: ϕ response; **C**: normalised AB concentration response; **D**: $\hat{p}_t$ response; **E**: pericyte health model states; **F**: neuron health model states.

Conclusion

Results takeaways:

- Importance of pericyte health.
- Sacrificing neuron health to protect pericyte health

Areas for development:

- Confirming the site of contraction (capillary versus arterioles) from improved imaging methods and more studies
- Inclusion of likely upstream propogation of contracile signal
- Inclusion of hemodynamic or autoregulatory responses
- Experiment with different inputs to the model
- Longer duration simulations
- Improved numerical solver for the stiff nature of the system