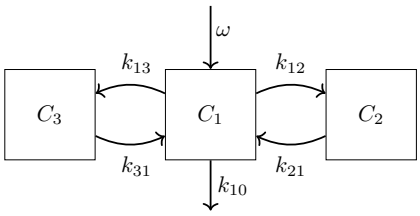

Figure 6: A three-compartment model for Propofol pharmacokinetics.

B SUPPLEMENTARY MATERIAL

B.1 Rate constants for PK models

The three-compartment pharmacokinetic models described in Section 2 model instantaneous drug doses across physiological compartments C_1, C_2, C_3 modelled by transport and elimination processes. The matrix A in equation (1) is constructed from rate constants k_{ij} which describe the rate of transfer from compartment C_i to C_j. An additional index 0 denotes elimination from the system. A can then be defined as:

$$A = \begin{bmatrix} -(k_{10}+k_{12}+k_{13}) & k_{21} & k_{31} \\ k_{12} & -k_{21} & 0 \\ k_{13} & 0 & -k_{31} \end{bmatrix} \tag{10}$$

with Figure 6 illustrating the structure of A for a TCI pump infusion $u(t)$. Various studies have proposed personalisation of these rate constants via Nonlinear Mixed Effects modelling (see e.g. Eleveld et al. 2018).

B.2 Derivation of discrete-time relationship for piecewise constant $\mathbf{u}(t)$

Equation (2) can be solved by integration using Laplace transformations. Let $U(s)$ be the Laplace transform of $u(t)$, and $X(s)$ the Laplace transform of $x(t)$. Define further a piecewise $u(t) = \sum_{i=0}^{T-1} R(t-i)u_i$ with a slight abuse of notation for u, and for $R(\cdot)$ the the unit rectangle function. Then we have:

$$sX(s) = k_{1e}U(s) - k_{e0}X(s) \tag{11}$$

$$\Rightarrow X(s) = \frac{k_{1e}U(s)}{s+k_{e0}}. \tag{12}$$

Recognising the RHS as the product of two known Laplace transformations gives:

$$\mathcal{L}(x(t)) = \mathcal{L}(k_{1e}u(t)) \cdot \mathcal{L}(e^{-k_{e0}t}H(t)) \tag{13}$$

for the Heaviside step function $H(t)$. Then using the convolution theorem:

$$\Rightarrow x(t) = k_{1e}\int_0^t e^{-k_{e0}\tau}u(t-\tau)\,\mathrm{d}\tau \tag{14}$$

$$= k_{1e}\left[\sum_{i=0}^{t-1} u_i \int_0^t e^{-k_{e0}\tau}R(t-\tau-i)\,\mathrm{d}\tau\right] \tag{15}$$

$$= k_{1e}\left[\sum_{i=0}^{t-1} u_i \int_{t-i-1}^{t-i} e^{-k_{e0}\tau}\,\mathrm{d}\tau\right] \tag{16}$$

$$= k_{1e}\sum_{i=0}^{t-1} u_i \frac{1}{k_{e0}}\left[e^{-k_{e0}(t-i-1)} - e^{-k_{e0}(t-i)}\right] \tag{17}$$

$$= \sum_{i=0}^{t-1} \frac{k_{1e}}{k_{e0}} u_i \left(1-e^{-k_{e0}}\right) e^{-k_{e0}(t-i-1)} \tag{18}$$

$$= \frac{k_{1e}}{k_{e0}}\left(1-e^{-k_{e0}}\right)\sum_{i=0}^{t-1} u_i (e^{-k_{e0}})^{t-i-1}. \tag{19}$$

Equation (3) can be written explicitly as $x_{tj} = \beta_{1j}\sum_{i=0}^{t-1}\beta_{2j}^{t-i-1}u_i$ by unrolling the recursion. The relationships given in Section 3.1 are then derived by comparison with eq. (19).

B.3 Example prediction plots

Some example plots are provided in Figure 7 to give the reader an intuition for the multi-task model. The examples were chosen to demonstrate the benefit of MTL over the Cohort model, and also the situations in which the model can perform worse. The first two examples (patient 12 and 19) demonstrate the model successfully adapting to patient dynamics for different channels. The example of patient 34 is one of a significant violation to modelling assumptions; no PD model is able to account for the uplift at 20 minutes. Patient 36 does not obviously follow the pattern of expected vital signs; the MTL model predicts an uplift at $T = 30$ as expected from a reduction in dose, but the vitals instead reduce. Patient 27 shows an example where MTL is a little over-confident after 30 minutes; the Cohort model out-performs MTL at this stage by predicting a flatter curve.

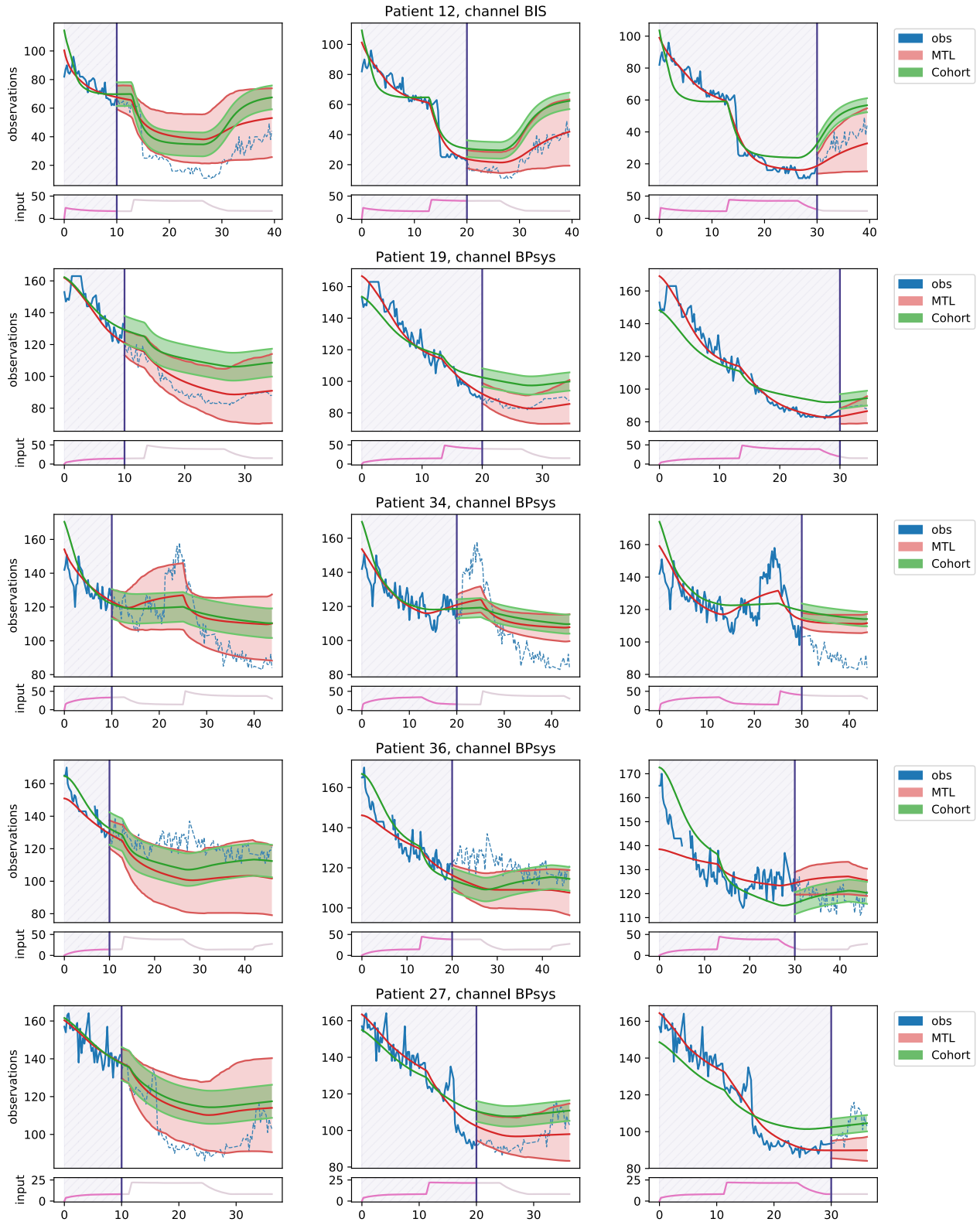

Figure 7: Example predictions for various patients and channels. Each row is a given (patient, channel) combination; columns show 90% predictive intervals at increasing points in time ($T = 10, 20, 30$ minutes).