Supplementary Material

#### Simulating CTP Data

Tissue TDCs were simulated by convolving a patient arterial TDC with various simulated flow-scaled IRFs as in Equation (4.1). The IRF was modeled by a gamma-variate function:

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|  | $$R\_{F}^{GV}\left(t\right)=F\left(\frac{t-T\_{0}}{T\_{max}}\right)^{α}e^{-α\left(\frac{t-T\_{0}}{T\_{max}}-1\right)}U\left(t-T\_{0}\right) $$ |  |

where $T\_{max}$ is the time-to-maximum of the IRF and in this study was fixed to $T\_{max}=T\_{0}+0.5MTT$ to reduce the number of free parameters, and $α$ is an exponential shape parameter that affects the MTT. A gamma-variate function was chosen to be different to the IRF shape of the model-dependent deconvolution methods and avoid providing an advantage to these methods. A total of 392 sets of perfusion parameters were tested: seven values of $T\_{0}$ (0.0, 0.5, 1.0, 2.0, 3.0, 4.0, 8.0 s), seven of MTT (16.0, 12.0, 10.0, 8.0, 6.0, 4.0, 3.4 s), and eight of CBV (0.5, 1.0, 1.5, 2.0, 2.5, 3.0, 4.0, 5.0 ml/100 g). CBF was then calculated by the Central Volume Principle as in Equation (3.7) and ranged from 1.9 to 88.2 ml/min/100 g. To minimize discretization errors, convolution was computed at 0.001 s sampling interval by linearly interpolating the arterial TDC and natively simulating the flow-scaled IRF at this fine interval.

Zero-mean Gaussian noise was added to the synthetic tissue TDCs to simulate noisy conditions expected in CTP. Two noise levels were investigated: $σ=2.5$ and $5.0$ HU. The former is the noise level expected after standard Gaussian smoothing of dynamic CTP images acquired at a standard brain protocol (80 kV, 100 mAs),93 whereas the latter simulated a low-dose CTP protocol (≈4$×$ dose reduction) to examine the effect of noise (as a surrogate to dose) on the accuracy of deconvolution-estimated perfusion parameters. Each deconvolution algorithm was used to deconvolve the arterial TDC from the tissue TDC to estimate CBF, CBV, and MTT. The model-dependent methods also estimated T0. To compute the mean, standard deviation, and the distribution of estimated parameters across different noise realizations, this experiment was repeated over 4,096 trials. The 4,096 estimated perfusion parameters were then arranged in a 64$×$64 square pattern such that post-deconvolution map filtering could be applied as is performed in many software packages. Only the central 32$×$32 (1024) values were used to compute statistics to avoid edge values where filtering is less effective. The 1024 estimated perfusion parameter values were compared against the known ground truth values. For brevity, only the results of CBF are reported.