A. Appendix

A.1. Sampling Rate Selection Continuous to Discrete Conversion

The accuracy of digital signal processing is affected by two main factors. First, is the noise floor, which is the measured signal created from the sum of all noise sources within the measurement system. In case of the purely simulated system where we generate AIF, the noise floor is from the precision of floating point arithmetic. Secondly, the sampling rates used to approximate the continuous system.

As an illustration of error due to sampling in system approximation, the continuous system impulse response $H_1(j\omega)$ can be approximated by a discrete system with finite-impulse response (FIR) using window approach to filter design or infinite impulse response (IIR) using bi-linear transformation (also known as Tustin’s method). The system $H_e(j\omega)$ has the highest amplitude high frequency components when $K_{trans} = 5ml/g/min$ and $K_{ep} = 10ml/g/min$. Figure 6 shows impulse amplitude response of the continuous system $H_1(j\omega)$ with those parameter values as well as the discrete approximations. Attempting to fit $K_{ep}$ as high as 10 ml/g/min using the 1 Hz FIR approximation would produce a signal that overshoots the measured signal. It would be expected that the numerical optimization algorithm would incorrectly adjust the parameters to compensate for lack of accuracy in the continuous to discrete conversion. Therefore, the discrete approximation must match the continuous-time system until the cutoff frequency.

Figure 6: Continuous To Discrete Mapping at Sampling Rate 1 Hz

The AIF and tissue curves have sampling requirements described by Nyquist as 2x the cutoff frequency. The experimentally derived AIF does not have an ideal cutoff frequency - although the frequency components get progressively smaller as infinity is approached. Under-sampling causes error where the high frequency components are folded into the lower band - i.e. aliasing error. The extent of this error can be minimized by an analog low pass filter (LPF) before sampling and quantization that attenuates the frequencies past the cutoff to values below the noise floor - i.e. below either acceptable noise or background noise that is technically infeasible to get rid of in the system. For example in analog systems the attenuation in the stop band of the
low-pass filter is typically chosen to be equal to the SNR of the quantizer (19) which represents
the noise floor in that particular stage. In ideal simulation the noise floor is dictated by round-off
error of floating point arithmetic when the expression for the experimentally derived AIF is
computed. Although uniform quantization error is fairly well understood (20), floating point
quantization depends on magnitude of the values. Pseudo-Quantization Noise (PQN) model from
the area of research into statistical theory of quantization (21) could be used to try and derive the
error distribution. However analytical derivation is difficult because the order of operations
matters, there are many operations involved and exact underlying implementation of the
exponential function are not always available. A rough estimate can be derived for single
precision floating point error by performing the calculation using double precision and
estimating the $\sigma^2_{\text{noise}} = \text{VAR}(\text{AIF}_{\text{double}} - \text{AIF}_{\text{single}})$ then computing the $\text{SNR} = 10 \times \log_{10}(\frac{\sigma^2_{\text{signal}}}{\sigma^2_{\text{noise}}})$. The SNR of calculating experimentally derived AIF was found to be 137 dB.
Figure 7 shows the relative magnitude of the frequency components of the experimentally
derived AIF sampled at 700Hz which shows the highest frequency falling just below 137 dB -
the noise floor level. Note that double precision arithmetic offers much more resolution and
higher SNR, however cutoff frequency would be in the megahertz range making some of the
computation such as calibration analysis infeasible on current hardware.

![Figure 7: Experimentally Derived AIF Spectrum at 700 Hz Sampling](image)

Choosing the single precision noise floor of 137 dB, the cutoff frequency is 350Hz. Given this
cutoff frequency the FIR and IIR filters were implemented to approximate the continuous time
system at 10x the cutoff frequency - of 3500 Hz - to ensure the filters match the continuous
system extremely closely up to the cutoff frequency for all range of parameter values. This
choice also satisfies the Nyquist sampling rate. It should also be noted that with the SNR level
chosen to be 137 dB and the resulting sampling rate of 3500Hz, the run-time during calibration
summarized in Table 4 ranged from 14.5 seconds to over 3 hours per voxel. To achieve double
precision accuracy where SNR is over 300 dB, sampling rates would need to be in the megahertz
range and it would not be feasible to run the calibration on given hardware.
A.2. Discrete System: FIR Approximation

The continuous system impulse response, \( H_1(j\omega) \), can be sampled to get the discrete approximation \( H_{ideal}(e^{j\omega}) \). The first issue is the impulse response extends to infinity in time domain making the system impossible to implement in finite memory. Typical window design approach to FIR filter approximation chooses finite number of samples \( M \) from the impulse response such that the mean square error between the ideal digital filter and the FIR approximation is minimized:

\[
\frac{1}{2\pi} \int_{-\pi}^{\pi} |H_{ideal}(e^{j\omega}) - H_{FIR}(e^{j\omega})|^2 \, d\omega \\
\sum_{k=-\infty}^{\infty} |h_{ideal}[k] - h_{FIR}[k]|^2 \\
\sum_{k=0}^{M} |h_{ideal}[k] - h_{FIR}[k]|^2 + \sum_{k=-\infty}^{0} |h_{ideal}[k]|^2 + \sum_{k=M}^{\infty} |h_{ideal}[k]|^2
\]

In the minimization equation (5), Parseval’s identity is used to convert mean square error function from Discrete-Time Fourier Transform (DTFT) domain, to time domain. From equation (5) it is clear that such error is minimized when \( h_{FIR}[k] = h_{ideal}[k] \) on the interval \([0..M] \).

Furthermore, because acquisition is restricted to \( c \) samples of the input, we only need \( M = \frac{c}{T} \) samples of the impulse response.

\[
h_1[n] = \frac{h_1(nT)}{(K_{trans} e^{-K_{ep}(nT)} u(nT))} \\
h_2[n] = V_b \delta[n] \\
\hat{C}_t[n] = T \sum_{k=-\infty}^{\infty} C_a[n]W_c[n]h_1[n-k] + \sum_{k=-\infty}^{0} C_a[n]W_c[n]h_2[n-k] \\
= (T \sum_{k=0}^{c} C_a[n]h_1[n-k]) + C_a[n]W_c[n]V_b
\]

In the above discussion on FIR approximation there was an implicit assumption that the digital \( H_{ideal}(e^{j\omega}) \) sampled version does not have severe aliasing due to sampling rate chosen. Equation (6) produces valid approximation of \( \hat{C}_t[n] \) for \( n \leq c \). The delay, not taken into account by (6), can be approximated by simply shifting the output by \( \text{round}(\tau) \) elements or using fractional delay approximation filter.

Direct convolution calculation speed is \( O(M^2) \) where \( M \) is the length of \( C_a[n]W_c[n] \) and sampled impulse response. Depending on signal and filter lengths calculation can be carried out faster using FFT, multiplication of frequency bin values, and IFFT in which case the complexity is \( O(N\log(N)) \). In our investigation, on average, the signal lengths must be over 600 samples for FFT to outperform straight time-domain convolution, however this is very much hardware dependent.

A.3. Discrete System: IIR Approximation

The transfer function in equation (2) can be discretized by applying bi-linear transform to the continuous time transfer function, with sampling period \( T \). The following is a transformation of the system \([H_1(s) + H_2(s)] \), which doesn’t include the delay element.
\[ s = \frac{2 - z^{-1}}{T(1 + z^{-1})} \]
\[ H(z) = \frac{b_0 + b_1 z^{-1}}{1 + a_1 z^{-1}} \]

Let \( K_1 = \frac{K_{\text{trans}}}{1 - HCT} \)

\[ b_0 = \frac{K_1 T + V_b K_{\text{ep}} T + 2V_b}{K_{\text{ep}} T + 2} \]
\[ b_1 = \frac{K_1 T + V_b K_{\text{ep}} T - 2V_b}{K_{\text{ep}} T + 2} \]
\[ a_1 = \frac{K_{\text{ep}} T - 2}{K_{\text{ep}} T + 2} \]

As with FIR approximation the delay can be approximated simply shifting the output by \( \text{round}(\tau) \) elements or using fractional delay approximation filter. This system can be implemented using recursive filter implementation running in \( O(M) \) time. The mapped discrete system is stable since the pole is within the unit circle for range of \( K_{\text{ep}} \) values of interest.