AIF Induced Limits of Parameter Uncertainty in Pharmacokinetic Models of Pre-Clinical DCE-MRI

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Motivation – How fast an AIF do I need?

- The arterial input function (AIF) of contrast agent (CA) concentration in the blood plasma is crucial for the application of pharmakokinetic (PK) models in dynamic contrast-enhanced magnetic resonance imaging (DCE-MRI).
- The functional form of the AIF itself is an inherent limitation to parameter accuracy.
- **Slow injection → wide AIF → low accuracy**

Questions

1. How does the CA injection rate and subsequent AIF affect the precision of model parameters (K^{trans})?
2. How do the simplifications within PK models affect this precision?

Goal

- Derive an estimate for the variability of K^{trans} estimates as a function of injection rate and model imperfections:

$$\mathbf{Var\hat{i}ance}\left[\hat{\mathbf{K}}^{\mathbf{trans}}(\mathbf{Injection\ Rate}, \mathbf{Model})\right]$$

Tracer Distribution Model (TDM)

Connection: Injection Profile ⟶ AIF is established by a phenomenological TDM:

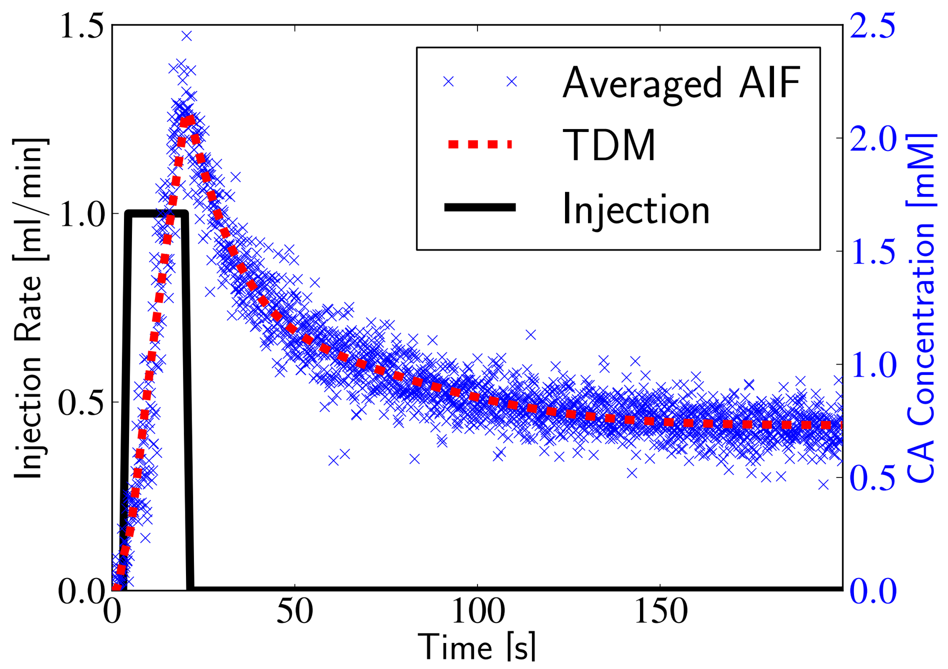
- Predicts AIFs by convolution of the injection input $I(t)$ with the transfer function:

$$AIF(t) = H_{TDM}(t) * I(t),$$

- Third-order linear transfer function in the frequency domain:

$$\tilde{H}_{TDM}(\omega) = \frac{B_3\omega^3 + B_2\omega^2 + B_1\omega + B_0}{\omega^3 + A_2\omega^2 + A_1\omega + A_0}$$

- Parameters (A_i, B_i) are determined by fitting simulated to measured population-averaged AIF. ($[C]_{CA}$ =60mM, Δt =100ms, 4 mice)

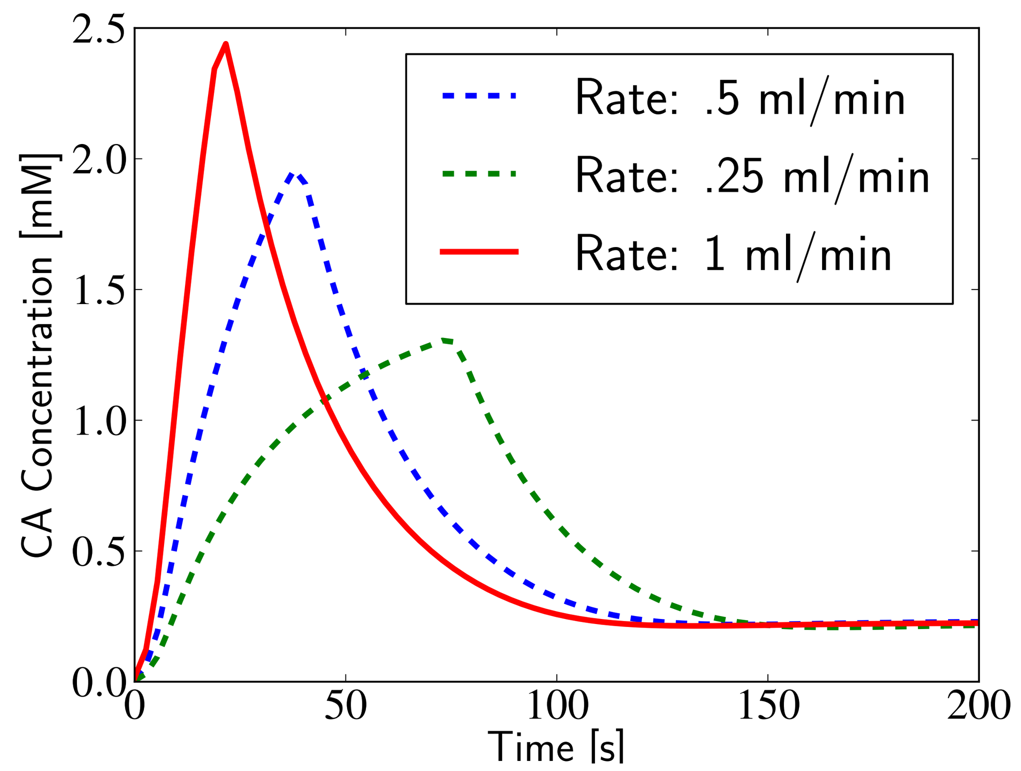


Procedure – Resampling Bootstrap

1. Generate AIFs for different injection rates (TDM).
2. Generate tissue uptake curves $C(t)$ for each AIF using MMID4 and ideal PK model predictions with fixed K^{trans}, v_e.
3. Add Gaussian noise to $C(t)$.
4. Fit Tofts Model to the AIF and the noisy $C(t)$.
5. Iterate steps 3 and 4 for different realizations of Gaussian noise (10^5 iterations) to derive a K^{trans} distribution.

Simulating the Arterial Input

- AIFs are derived for a variety of experimentally relevant injection rates (TDM).
- Trapezoidal injection profiles are assumed.

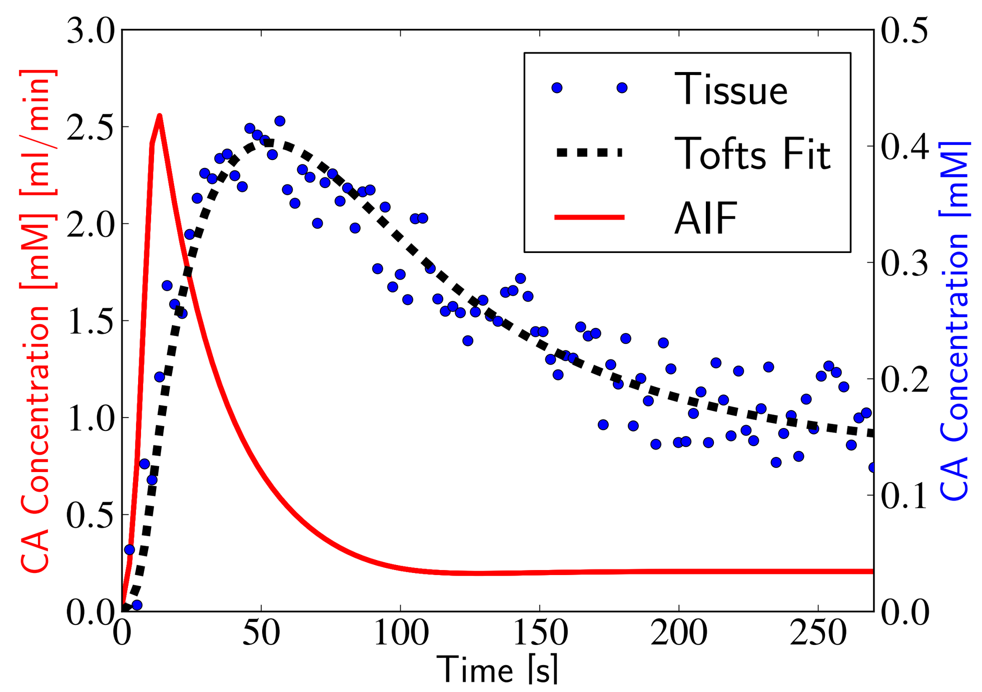


Tracer Uptake Models

MMID4

- Tissue exchange model with 20 flow paths
- Accounts for heterogeneity and flow dispersion

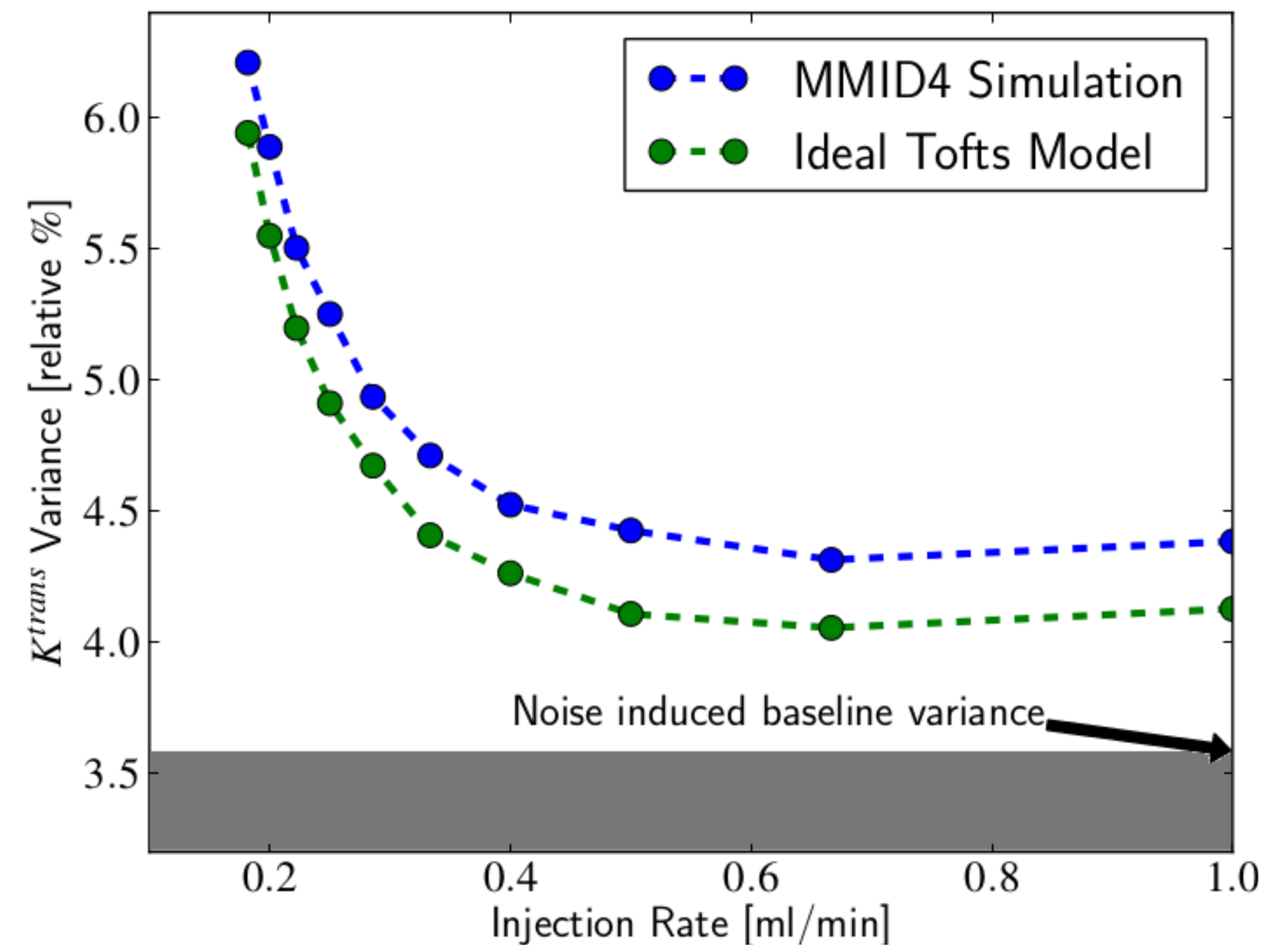
Tofts Model



- Based on a rate equation for tracer diffusion

$$C_t(t) = K^{trans}\int_0^t dt' C_p(t')e^{\left[-K^{trans}\cdot(t-t')/v_e\right]}$$

Results – Variance of Bootstrap K^{trans} distributions



1. Effect CA Injection Rate
   - Increase in K^{trans} variance induced by finite AIF widths for a typical noise level:
     15% (0.6 ml/min rate) up to 70% (0.2 ml/min rate)
   - Injection faster than 0.6 ml/min do not imporove precision.
   - Slower injections do not bias observed K^{trans} distributions (data not shown).
2. Effect of Model Simplificiations
   - Imperfections of the Tofts Model induce a K^{trans} variance of less than 10%.

Conclusion – Speed matters! - But within Limits

- Slow injections (wide AIFs) induce K^{trans} variances up to the same order of magnitude as typical measurement noise.
- The optimal K^{trans} precision is achieved for rates from 0.6 ml/min onwards.

References

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