Stability of tissue model parameters: Using the full analytical solution or the asymptotic approximation?

Sebastian Domsch[1], Sebastian Weingärtner[1], Jascha Zapp[1], and Lothar R. Schad[1]
[1]*Computer Assisted Clinical Medicine, Heidelberg University, Mannheim, Baden-Württemberg, Germany*

Purpose: The oxygen extraction fraction (OEF) is of great clinical interest providing a biomarker for brain tissue viability [1] and a parameter for the evaluation of diseases such as tumor [2], stroke [3], and Alzheimer's disease [4-5]. The analytical tissue model in the static dephasing regime [6-7] has facilitated promising in-vivo results [8-17] by mapping hemodynamic parameters such as the OEF and the venous blood volume fraction (λ) separately using MRI. Most publications have used the asymptotic approximation (A-model) [10-17] of the full tissue model (F-model) without giving further justification. The question arises whether using the A- and not the F-model compromises fitting and therefore the estimation of hemodynamic parameters since the full potential of the data is not utilized. The present work shows a comparison between the fit results using the F-model and the A-model in terms of accuracy and precision based on Monte-Carlo simulations and robustness in-vivo.

Methods: The in-vivo measurements were carried out on a 3 T MR scanner (Magnetom Trio, Siemens Healthcare, Erlangen, Germany) equipped with a standard 12-channel head coil. The MRI protocol consisted of a gradient-echo sampled spin-echo (GESSE) sequence [7] and a high resolution T_1-weighted sequence. Background fields were removed from the GESSE signal before the fit-parameters were estimated based on the method proposed in [7]. The models used for simulations and OEF quantification are shown in Tab. 1. The OEF was computed using Eq. 3 after fitting the GESSE signal by separately using the F-model (Eq. 1) and the A-model (Eq. 2). The Monte-Carlo simulation consisted of the following steps:

1. As depicted in Fig. 1, the MR signal, S(t), was simulated in the range of 20 ms before and 40 ms after the SE with a sampling frequency of 1 ms using Eq. 1. The parameters held fixed to the values of S(SE) = 40 [a.u.], R2 = 10 [Hz], R2' = 3 [Hz], λ = 2 [%].
2. Zero mean Gaussian noise, σ, was added: $S_N(t) = S(t) + \sigma$. Both, the F-model and the A-model (Eq.2) were used for fitting. The A-model was fitted in the long term regime between [-20...-10] ms and [10…40] ms around the SE. For both models, S(SE) was estimated by the analytical approximation of the full model in the short-term regime (i.e. from [-10…10] ms around the SE) given by: $\ln(S(t))=\ln(S(SE))-(0.3\cdot R2'^2/\lambda)\cdot t^2-R2\cdot t$ [7].
3. All simulations were repeated multiple times for varying noise.

(1)	$\ln\left(\frac{S(t)}{S(SE)}\right)=-\frac{1}{3}\cdot\int_0^1(2+u)\sqrt{1-u}\cdot\lambda\cdot\frac{1-J_0\left(\frac{3\cdot R2'\cdot u\cdot t}{2\cdot\lambda}\right)}{u^2}du-R2\cdot t$	F-model
(2)	$\ln\left(\frac{S(t)}{S(SE)}\right)=\lambda-R2'\cdot\lvert t\rvert-R2\cdot t$	A-model: $\lvert R2'\cdot t/\lambda\rvert\geq 1.5$ (long-term regime)
(3)	$\mathrm{OEF}=\frac{3}{4\pi\cdot\gamma\cdot B_0}\cdot\frac{R_2'}{\lambda}\cdot\frac{1}{\Delta\chi_{do}\cdot Hct}$	

Table 1. Full model, asymptotic approximation and OEF quantification. *S(t): signal around a spin echo (SE); R2', R2: reversible and irreversible relaxation rates; J_0: 1st kind zero-order Bessel function; γ: gyromagnetic ratio; B_0: magnetic field strength; Hct = 0.34; $\Delta\chi_{do}$ = 0.27ppm.*

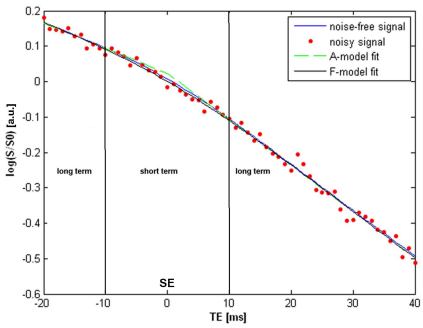

Figure 1. Simulated GESSE signal with and without noise and respective fits. *The SNR was set to 80 [a.u.].*

Results and Discussion: The Monte-Carlo simulation (Fig. 2) shows that both accuracy and precision of the fit-parameters R2' and λ were significantly improved for clinical SNR level (i.e. SNR < 100) using the A-model. For higher SNR requiring longer measurement times both models yield the similar precision whereas the A-model results in reduced accuracy. The in-vivo parameter maps (Fig. 3) demonstrate that using the A-model yields visually superior fit-quality compared to using the F-model. Severe fitting artifacts can be seen when the F-model was used. Thereby, the λ-map exhibits large areas where the fit converged against the upper bound. In similar region also R2' was clearly overestimated. The A-model parameter estimates for R2' and λ of 3-6 Hz and 2-6 %, respectively, were in close agreement with the physiological range reported in literature [8, 15, 17] compared to the overestimated F-model parameter estimates. It can further be seen that using both models, the R2' and λ parameter maps are spatially correlated leading to rather homogeneous OEF maps, well known from ^{15}O-PET studies [18]. The severely overestimated λ-values using the F-model led to the underestimation of the OEF in the range of 20-40 %. In contrast, more realistic OEF values between 40-60 % were obtained when the A-model was used. The inferior fit conditioning of the F-model particularly in the short-term regime might be a co-founder to the inferior fit results when the F-model was used.

Summary and Conclusion: In summary, our simulations have shown that both accuracy and precision of the model parameter estimates improve using the A- compared to the F-model in the presence of limited SNR or measurement time. In agreement with our simulations, the in-vivo results were clearly less robust when the F-model was used, which strongly suggests the use of the A-model for clinical OEF mapping. However, further multi-subject measurements are necessary in order to asses whether the A-model consistently yields superior results over the F-model.

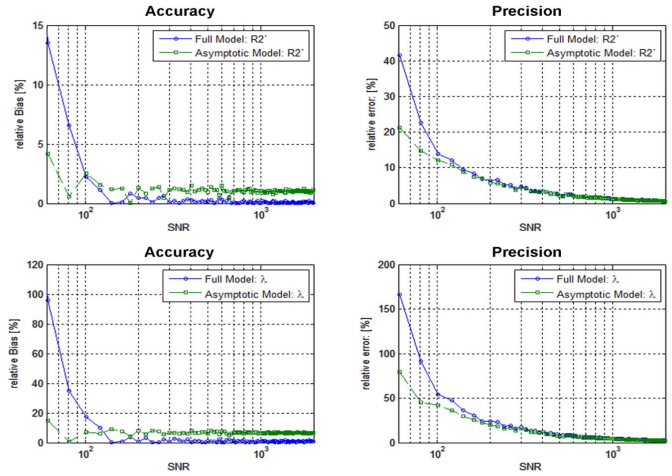

Figure 2. Estimated accuracy and precision of the fit-parameters R2' and λ in dependence of the SNR level based on a Monte-Carlo simulation. *The SNR was increased in the range of SNR = {60...2000} in steps of ΔSNR = 20 with n = 100 simulations per SNR level. The accuracy was defined as the relative bias of the respective parameter estimate from the simulated ground truth (i.e. $|\Delta p|/p$). The precision was defined as the relative error (i.e. the standard deviation) of the respective parameter (i.e. $var(p)^{1/2}/p$).*

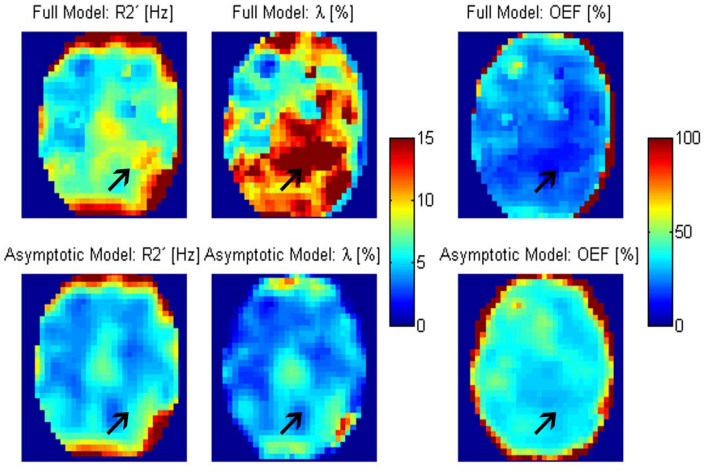

Figure 3. Parameter maps of a single subject using the full model (Eq. 1) and the asymptotic approximation (Eq. 2). *The black arrow points out an area with severe fit failure using the full model. The GESSE measurement time was 21 minutes yielding an SNR of approx. SNR ≈ 40 [a.u.].*

References: **[1]** Schmidt RF et al. *Springer* (1995) **[2]** Brown JM et al. *Cancer Res* 58(7): 1408-1416 (1998) **[3]** Derdeyn CP et al. *Brain* 125(Pt 3): 595-607 (2002) **[4]** Iadecola C. *Nat Rev Neurosci* 5(5): 347-60 (2004) **[5]** Yamauchi H et al. *Rinsho Shinkeigaku* 39(5): 513-9 (1999) **[6]** Yablonskiy DA et al. *Magn Reson Med* 32(6): 749-63 (1994) **[7]** Yablonskiy DA. *Magn Reson Med* 39(3): 417-28 (1998) **[8]** He X et al. *Magn Reson Med* 57(1): 115-26 (2007) **[9]** He X et al. *Magn Reson Med* 60(4): 882-8 (2008) **[10]** An H et al. *J Cereb Blood Flow Metab* 20(8): 1225-36 (2000) **[11]** An H et al. *Magn Reson Med* 47(5): 958-66 (2002) **[12]** An H et al. *Magn Reson Med* 48(4): 583-8 (2002) **[13]** Sedlacik J et al. *Magn Reson Med* 58(5): 1035-44 (2007) **[14]** Sedlacik J et al. Z Med Phys 19(1): 48-57 (2009) **[15]** Sedlacik J et al. *Magn Reson Med* 63(4): 910-21 (2010) **[16]** Christen T et al. *Magn Reson Med* 68(3): 905-11 (2012) **[17]** Fujita N et al. *Neuroimage* 20(4): 2071-83 (2003) **[18]** Yamaguchi T et al. *Stroke* 17(6): 1220-8 (1986)