**Comparative Review of Algorithms and Methods for proton-density fat fraction (PDFF) quantification**

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**Introduction**: To obtain the proton-density fat fraction(PDFF)[1], quantitative biomarker of fatty depots, recent methods of fat-water signal separation have been developed. The purpose of this work was to assess the performances of state-of-the-art Fat-Water reconstruction methods for PDFF and T2* quantification since the 2012 ISMRM challenge[2].

**Methods:** An open-source toolbox available both in Python and Matlab enabled to numerically compare recent Fat-Water separation algorithms[3–10] (Table 1). Additionally, an extensible human fat spectra[11–13] library was implemented to be plugged with each algorithm. Synthetic CSE-MRI volumes were modeled with PDFF=0-100%, B0=-300:6:300Hz, 100 repetitions, gaussian noise (SNR=50:10:100) and T2*=20ms. Different numbers of echo times (NTE=3,5,7,9) and schemes (realistic minimal, IDEAL and in/out-of-phase) were considered. The Bias, precision and limits of agreement (LOA) were evaluated for PDFF, B0 and T2*. Algorithms' discrepancies were demonstrated practically on challenging in vivo datasets (cardiac & supraclavicular). Finally, synthetic signals were processed with either the same simulated spectrum or another (NTE=9) to probe sensitivity to fat spectra.

**Results:** For NTE=3: fat/water swaps were present in Fatty-Riot-GC, B0-NICE, IDEAL-CE and VLGCA. PDFF measured with Hernando-GC and VLGCA were influenced by B0 inhomogeneity (NTE=3 IN/OPP & MINIMAL). GOOSE led to a significant global bias (>15%). For NTE>=5, B0-NCE and GOOSE proved to be highly biased whereas other algorithms demonstrated robustness to B0 and fat/water swaps.

PDFF absolute bias error decreased significantly with more TE (p<0.0001) for all algorithms. However, VLGCA and Hernando-GC, were still influenced by echo spacing (Fig1). Considering the best echo spacing, algorithms provided similar PDFF bias (bias<0.2 LOA<4%). Extrema PDFF (<10% or >90%) remained challenging. Algorithms provided a low T2* mean bias (<1ms) but a large LOA depending on echo times. Among two comparable algorithms (IDEAL-CE and MSGCA-A) with PDFF LOA differences of only 2%, challenging datasets demonstrated significant PDFF discrepancies in water tissues. Finally, processing data with a different spectrum than the one employed for simulation revealed significant bias of 1% PDFF and 0.7ms T2* respectively.

*Table 1 Summary of evaluated state-of-the-art open-source Fat-Water reconstruction algorithms*

| Reference | Referred as | Method | Code | 2D/3D | Spectrum choice | Echo spacing | Code acceleration | Year |
|---|---|---|---|---|---|---|---|---|
| Boehm et al. [10] | VLGCA | Graph-cut | Matlab | 2D | Free | Uniform | Parallel computing | 2021 |
| Bydder *et al.* [9] | IDEAL-CE | IDEAL | Matlab | 3D | Model Constrained | Free | GPU computing | 2020 |
| Andersson et al. [8] | MSGCA-A | Graph-cut | Matlab | 3D | Free | Uniform | No | 2018 |
| Cui et al.[7] | GOOSE | Graph-cut | Matlab | 2D | Fixed[1] | Uniform / Free | No | 2015 |
| Berglund et al.[6] | MSGCA-B | Graph-cut | Python | 3D | Free | Uniform | No | 2017 |
| Liu et al. [5] | B0-NICE | Region-based | Matlab | 3D | Fixed[2] | Uniform | No | 2015 |
| Berglund et al.[4] | Fatty-Riot-GC | Graph-cut | Matlab | 3D | Free | Uniform | No | 2012 |
| Hernando et al. [3] | Hernando-GC | Graph-cut | Matlab | 2D | Free | Uniform / Free | No | 2012 |

[1]ISMRM challenge spectrum     [2]own spectrum



Echo times
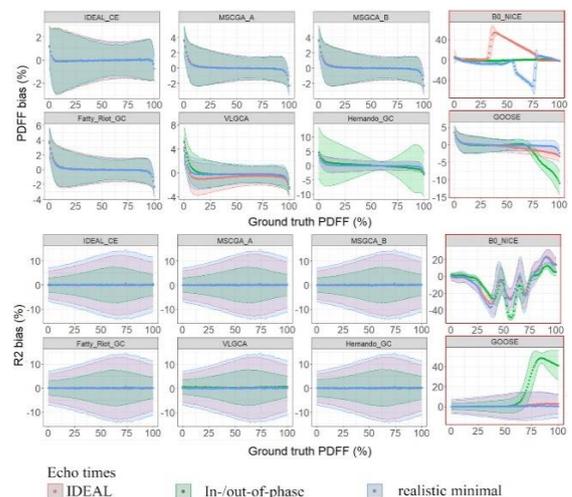▪ IDEAL    ▪ In-/out-of-phase    ▪ realistic minimal

*Figure 1. Comparison of PDFF and R2 bias of each algorithm over synthetic volume with NTE=7 and SNR=100.*

**Discussion**: An open-source toolbox has been implemented to compare state-of-the-art open-source fat-water separation algorithms over synthetic multi-echo data which varied in fat-fraction, B0, SNR, number of echoes and echo spacings. Most algorithms proved to be biased for 3 echoes data. For 5 echoes and more, six algorithms were comparable, but two algorithms proved to be inaccurate. Echo spacing scheme impacted quantitative limits of agreements. For PDFF quantification in the extreme ranges, graph-cut approaches provided similar results while IDEAL-CE provided more reliable results. Interestingly, the toolbox also revealed PDFF/T2* quantification to be sensitive to the choice of the fat spectrum.

**Conclusion**: This open-source multi-language toolbox offers the possibility to better assess novel algorithms compare to state-of-the-art open-source algorithms. Benchmarking synthetic multi-echo data enables acquisition parameter optimizations (number of echoes, echo spacing) to obtain more accurate quantitative maps. Bias and limits of agreement revealed disparities between algorithms. The toolbox repository will be available shortly.

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