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# Uncertainties on the Cramér-Rao bound : What are the consequences in quantitative NMR?

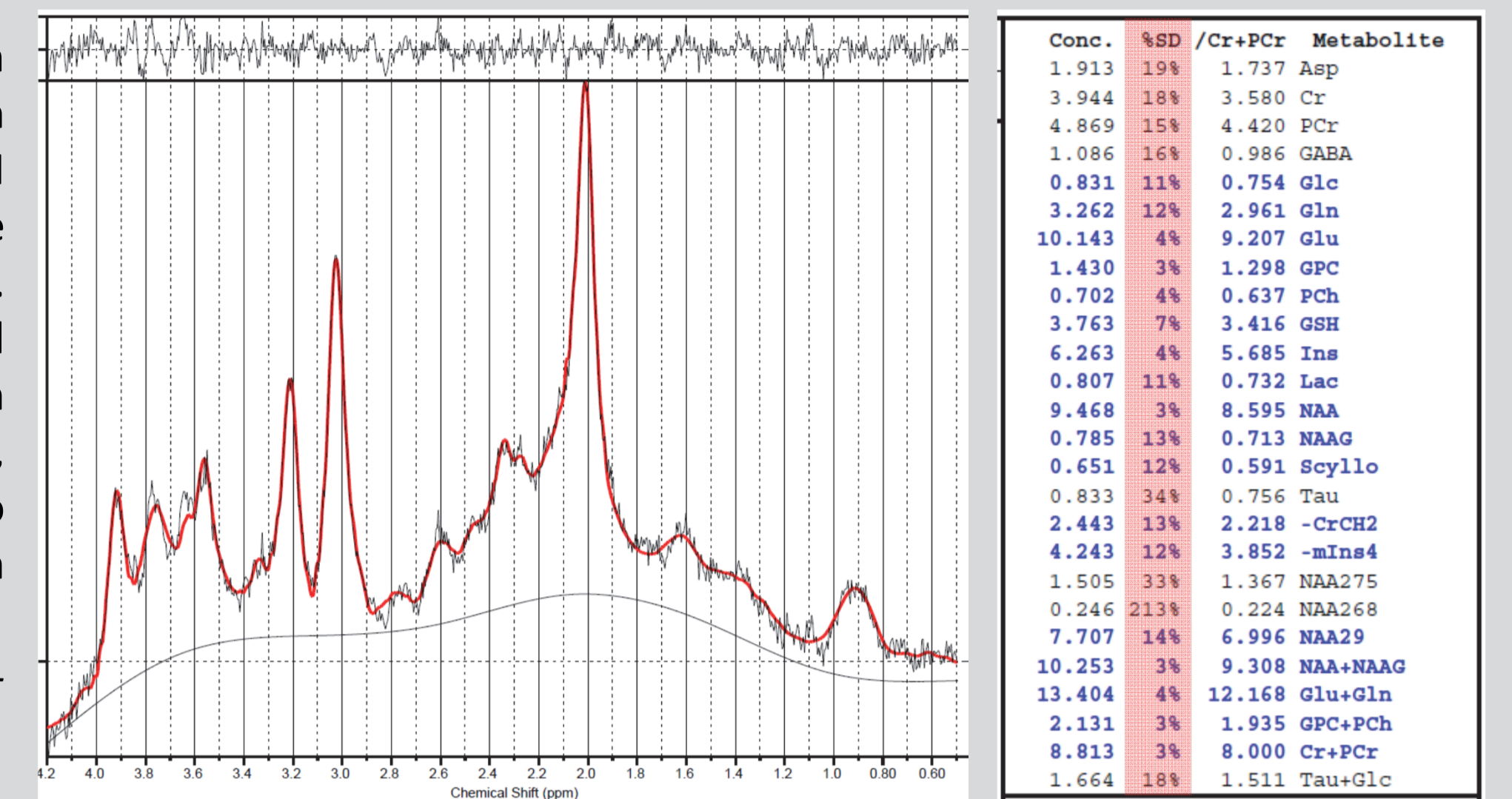
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NMR quantification of complex mixtures is generally based on the fit of a model to the experimental noisy data. In addition to the residual signal which allows viewing the *goodness-of-fit*, a popular indicator of pollution by noise is the Cramér-Rao bound (CRB). It provides an estimation of uncertainties calculated for each parameter and metabolite. For comparing this uncertainty to a percent threshold, CRB is normalized for obtaining the relative CRB (rCRB). Usually, the experimentalist prescribes an upper limit for quantification acceptance at  $\eta = 20\text{-}30\%$ . Recently, few papers warned on the use of this indicator (1,2). Here, we investigate why rCRB must be carefully used and we provide a rigorous framework for fixing  $\eta$ .

**Figure 1\***: Fit (red line) of a MR spectrum (black line) obtained *in vivo* in the human brain (putamen) at 3T (PRESS, VOI 10x30x15 mm<sup>3</sup>, TE/TR 29/1500 ms). The light black line represents the baseline. The top square highlights the residual signal after fitting the data. The table on the right summarizes fitting parameters, and especially the rCRB (red column) to estimate the percent uncertainty on concentration for each peak.

\* Data courtesy of C. Chassain, Clermont-Ferrand hospital.



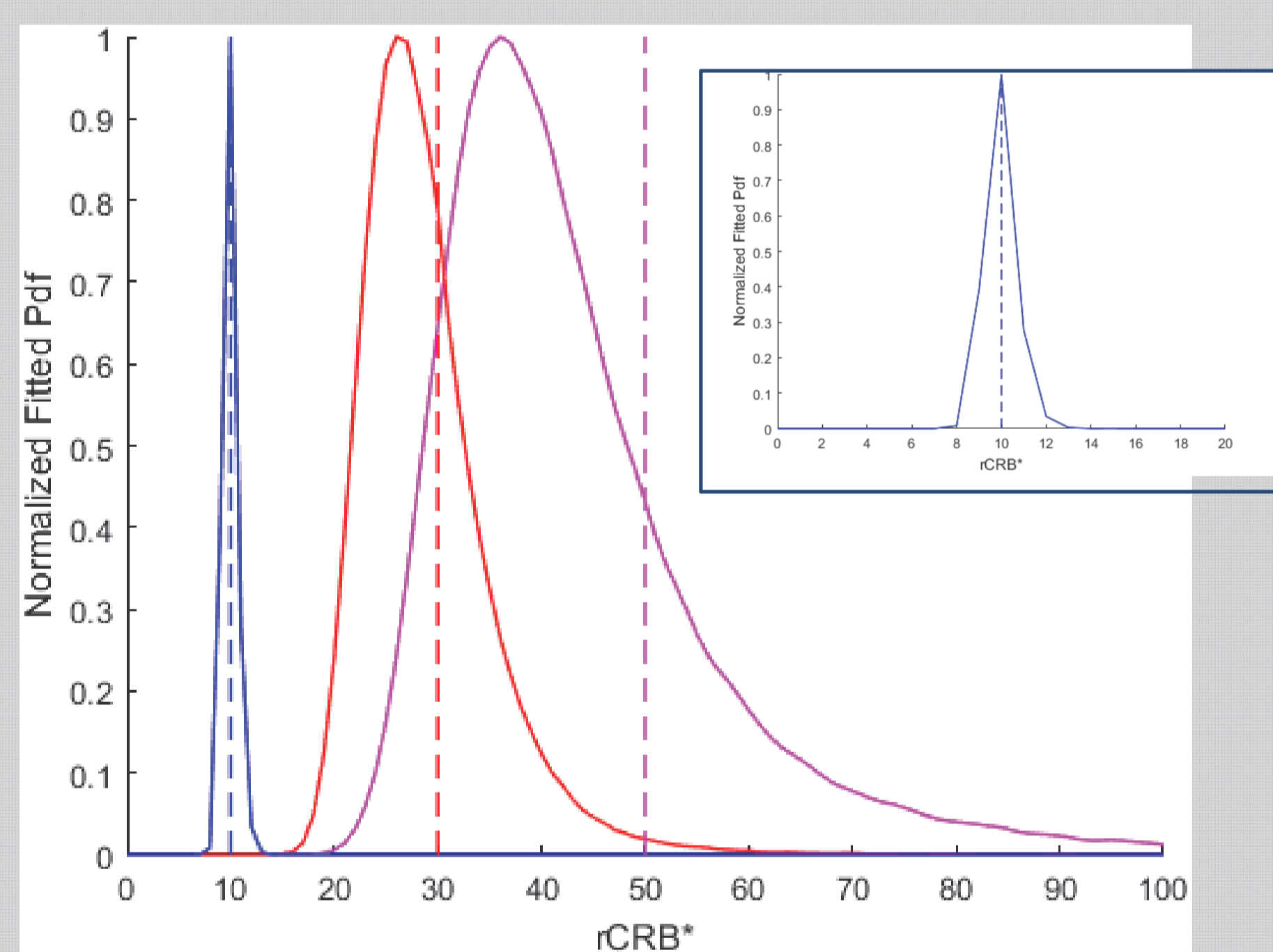
## From CRB to rCRB\*

- 1 CRB is a **minimal bound**. Standard deviation of estimates may converge to CRB (i.e. for high SNR and unbiased model).
- 2 CRB computation requires knowing **true** parameters (frequency, phase, amplitude and width at half maximum). In practice, true values need to be replaced by the noisy estimations. CRB becomes CRB\* (which means "approximation of CRB").
- 3 CRB is compared to a **percent threshold**, conventionally  $\eta = 30\%$ . For having a dimensionless index, CRB\* is divided by the noisy estimations instead of the true values, spoiling once more the CRB by noise. CRB\* becomes rCRB\*.

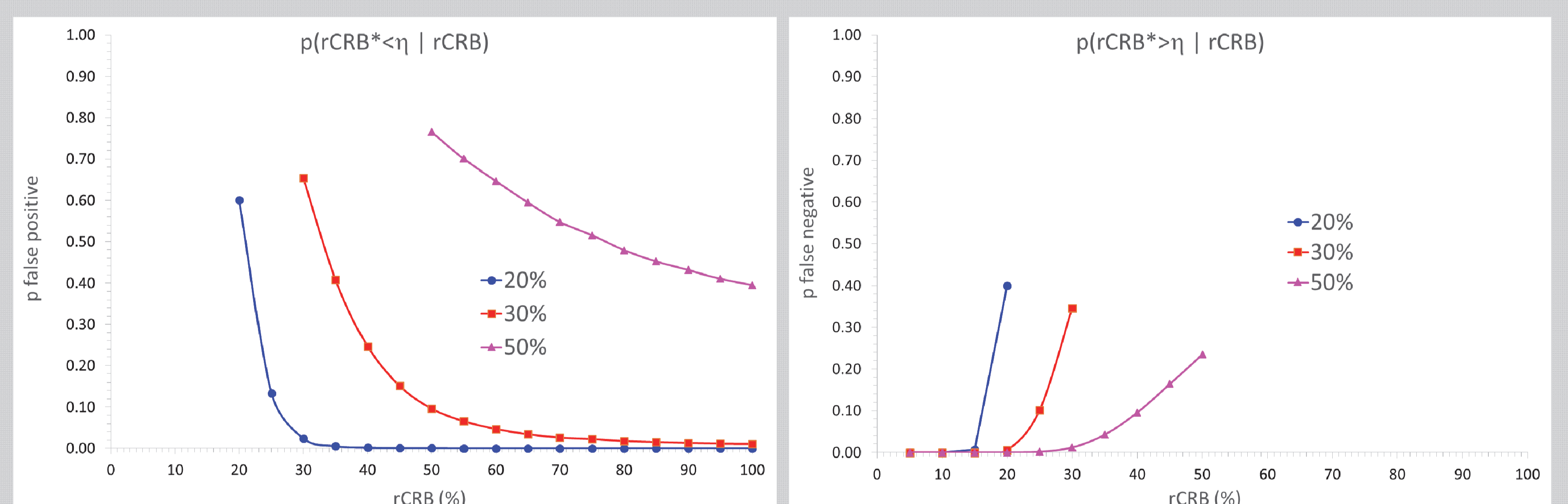
## Simulations

- 1 Exponentially damped sinusoidal signals were simulated. Noise level was adjusted for fixing the rCRB for the concentration of the peak of interest.
- 2 A large number ( $10^5$ ) of noisy NMR signals was simulated for computing probability density function (pdf) of rCRB\* for different true rCRB.
- 3 Two risks were computed. First, the probability to wrongly accept a spectrum because rCRB\* is below the threshold  $\eta$  while the true rCRB is unacceptable (i.e.  $rCRB > \eta$ ). It corresponds to the **false positive probability** (we are obtaining a low uncertainty when in truth it is larger than the chosen threshold). The second risk concerns the rejection of an acceptable estimation because rCRB\* is above the threshold  $\eta$  while the true rCRB is acceptable (i.e.  $rCRB \leq \eta$ ). It corresponds to the **false negative probability** (we are obtaining a large uncertainty when in truth it is smaller than the chosen threshold).

## Results



**Figure 2**: Pdfs of simulated rCRB\* when the signal contains only a single exponential ( $T_2^* = 40$  ms, freq. = 500 Hz, phase =  $-\pi/4$ ). The true rCRB was set (dashed lines) to 10 (blue), 30 (red) and 50% (magenta). Both the width and the left asymmetry of the rCRB\* pdf increase with rCRB. Hence, we concluded that the probability to have false positive significantly increases with the rCRB value.



**Figure 3**: Probability to obtain a false positive (left) or a false negative (right) for a true rCRB of 20 (blue), 30 (red) and 50% (magenta). The calculations were performed with the pdfs shown in figure 2. The figure on the left indicates that for  $\eta$  set at 50%, a rCRB of 100% - which should be strongly rejected - is in fact accepted almost one time out of two. For limiting such a false positive rate,  $\eta$  should be carefully set to a much lower value (below 20%). The case of false negative is less problematic. For  $\eta$  set at 50%, a rCRB of 45% - which is close to the threshold - leads to a relatively low probability of acceptance (below 20%). Furthermore, the false negative probability is rapidly decreasing with  $\eta$ . Similar results were obtained with a spectrum containing 5 peaks (data not shown).

## Conclusions

- rCRB is the lowest attainable level of uncertainty, but it does not mean that this level is reached under the experimental conditions.
- The rCRB\* used as index of uncertainty level is mostly prone to false positive errors.
- A conservative threshold of 20% seems to be more relevant.
- While false rejections corresponds to an underexploitation of the available NMR information, false acceptances will validate too many uncertain estimates of peak amplitudes. This latter case is undoubtedly the most problematic.

(1) A. Tisell, O. D. Leinhard, J. B. M. Warntjes, P. Lundberg (2013), *Magnetic Resonance in Medicine* (70) 905-915

(2) R. Kreis (2016) *Magnetic Resonance in Medicine* (75) 15-18