

The author has made a commendable effort to accurately calculate ^1H line widths in proteins, using GB1 and BPTI as test systems. As noted by the author, many theoretical issues are difficult to clearly resolve in doing the calculations. The author ultimately concludes about BPTI: "But how do we do with our calculations within the bulk of the distribution? Figure 6B shows that it is not good at all and not much worse than for GB1 (Figure 4B). There is hardly a correlation between experiment and calculation". Clearly, if this was the end of the story, then the paper hardly could be publishable.

I am less pessimistic than the author however. Given current technology, the goal of calculating ^1H line widths quantitatively probably is unattainable. Even if all the challenges presented by relaxation theory were solved, structural differences in solution compared to the crystal structure, even if minor, have a large effect on relaxation, owing to the $1/r^6$ dependence of the dipole coupling (as noted by the author). To obtain quantitative agreement, averaging over an MD simulation (or some other ensemble) would be needed. But if we had such a reliable simulation or ensemble, we would hardly need to look at the line widths to discern dynamics.

So what can be done? The distributions of the calculated and experimental line widths for BPTI shown in Figure 6B are similar (ignoring the clearly exchange broadened residues in Figure 6A). Thus, given the effect of structural noise, etc. I think it is reasonable to regard the different residues then as representing random samples of different magnetic environments (that is, the calculated linewidth for residue X is not the experimental linewidth for residue X, but the experimental linewidth for a residue Y that happens to have a ^1H density in solution similar to residue X in the crystal). The similar distributions then between the calculated and experimental measurements therefore would suggest that the author has gotten a lot of the physics right, but the correct physics is disguised by structural/dynamical noise. The standard deviation for the calculated linewidths is ~ 1.6 Hz (I estimated values from the figure). I have taken the liberty of rescaling Figure 6B and drawing the 1 sigma and 2 sigma contours (in practice, it might make sense to winsor the data a bit, but that is another topic). The similarity of the distributions is evident. In this scenario, the best that can be done is to identify outliers from the distribution, which the author has done. Thus, the author's work strikes me as a reasonable achievement.

