This is a largely exploratory manuscript investigating the potential to obtain (semi-)quantitative results on protein dynamics based on backbone amide 1H linewidths in 1H-15N HSQC or TROSY spectra. As Zuiderweg states himself, the underlying idea to glean dynamic information from the HSQC spectrum is commonly used by NMR spectroscopists in a qualitative sense by identifying particularly sharp or broadened cross-peaks. Here, Zuiderweg provides a more comprehensive analysis by attempting to account for all contributions to the 1HN linewidth from various relaxation mechanisms and other effects, such as unresolved J-couplings and B0 inhomogeneity. Naturally, the dominant part of the relaxation is due to dipole-dipole relaxation, which is estimated for each backbone amide based on the high-resolution crystal structure of the protein in question.

The end result is that the calculated linewidths show only fair agreement with the experimental ones, but outliers appear to reliably identify backbone amides that are either undergoing large-amplitude fast internal dynamics (i.e., residues with low order parameters) or residues undergoing conformational exchange. Thus, we are left with the conclusion that 1HN linewidths cannot provide more detailed information than what is customarily obtained from a qualitative, first-glance interpretation of HSQC-type spectra. To this extent, the work clearly does not advance the field since it does not provide any substantial conclusions beyond current knowledge. Still, I appreciate the comprehensive, semi-quantitative analysis offered by Zuiderweg, which clearly shows the limitations of the proposed analysis. In essence, the work demonstrates that 1HN linewidths cannot be interpreted in terms of dynamics to any detailed extent. For these reasons, I believe that the study could be worth publishing.

Minor points:

p. 4, Eq [1]: I do not follow this equation fully: the last two factors are not defined and it is not clear why they appear in the equation. The first exponential assumes that each step in the reverse polarization transfer (after t1) contributes equally to the linewidth, but this is not true for all pulse sequences (it depends on the details of the PEP scheme, etc).

l. 94: aromatic ring flipping does not cause exchange linebroadening of amide protons (since the end states are identical).

Table 1: Please clarify what is listed in this table. By comparing with Fig. 4, I assume that
the Sum of 1HN linewidths is taken over all residue pairs in the protein(?). This should be stated in the Table header (or footnote).

Figure 6 legend: "open diamonds" should be 'open squares'.

The text should be checked for typos, incorrect order of words, missing words, etc.