Statistical Evaluation of MRS Line Shapes - a New Paradigm for Quantitative Analysis of Tissue Heterogeneity

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Target audience

Researchers and clinicians interested in new quantitative parameters of tissue heterogeneity. Spectroscopists interested in maximizing information obtainable from in-vivo MRS signals.

Purpose

It has long been known that the exact position of a resonance in an NMR spectrum depends not only on the intramolecular environment of the observed spin but also, to varying degrees, on its extramolecular physicochemical environment (e.g., 'solvent effects'). Therefore, chemical shifts of suitable NMR signals have been used to measure parameters such as sample pH, temperature, the concentration of particular ions etc. Since biological tissues are usually heterogeneous, the overall shape of an in-vivo MRS signal that is sensitive to such a parameter will reflect the entire range of parameter values occurring within the measured tissue volume. Up until now, this type of signal has only been used to extract one parameter value thought to be representative of the tissue volume (or voxel) in question. This number is usually determined based on the chemical shift value at the global peak maximum, and is commonly presented as 'the' tissue parameter value in question (e.g., 'the' intracellular pH value [1]). However, in this way all tissue *heterogeneity* information that is actually contained in the corresponding signal *shape* is lost, and the resulting parameter value may be far from representative. We present here a new, general paradigm: the shape of a suitable MRS resonance (whose chemical shift is a function of a physical or chemical tissue parameter of interest) reflects the statistical distribution of the parameter values within the measured volume. Therefore, adequate evaluation of such a resonance requires statistical analysis of the entire line shape. As a result, detailed statistical information on the tissue parameter of interest can be obtained, accurately reflecting a particular aspect of tissue heterogeneity in a quantitative manner. We have recently developed and validated algorithms that are required in this approach, with tissue pH serving as an example of a parameter of interest. [2] We now suggest to use these algorithms for an extended multiparametric analysis of tissue heterogeneity by MRS, in accordance with our paradigm.

Methods

Statistical methods can be used to calculate parameters that characterize frequency distributions based on histograms. Adopting this approach, we first transform a suitable localized-MRS resonance (Fig. 1 A) into a histogram essentially representing the statistical distribution of values for a tissue parameter of interest (Fig. 1 E). This is achieved by converting, for each digital point i constituting the spectral line (i = 1 to i = n, Fig. 1 B), chemical-shift value δ_i into the corresponding tissue parameter value p_i using the appropriate equation. In general, the relationship between the original chemical-shift scale and the targeted tissue parameter scale will not be linear. This results in non-equidistant data points (Fig. 1 C); in our example, intervals between points are larger at the wings of the distribution than they are at the center, although the original spectral data set is composed of equidistant points (Fig. 1 B). Then, the height of the data points is corrected for this nonlinearity (Fig. 1 D). The tissue parameter histogram (Fig. 1 E) and the tissue parameter distribution curve (Fig. 1 F) are equivalent representations of Fig. 1 D. While the envelopes of Figs. 1 D - F accurately reflect the distribution of tissue parameter values, the uneven density of columns in the histogram (Fig. 1 E) has to be taken into account in the calculation of quantitative statistical parameters. [2]

The diagrams in our example (Fig. 1) have been modeled on the conversion of a 3-aminopropylphosphonate (3-APP) ^{31}P MRS resonance into a pH profile [2] (numerical values in parentheses). However, the *general* conversion procedure is identical for any ppm-to-tissue parameter transformation that is based on an MRS resonance whose chemical shift is a function of the tissue parameter of interest. All calculations can performed using an EXCEL spreadsheet. [2]

Results and Discussion

Based on a histogram such as shown in Fig. 1 E the following quantitative statistical parameters can be obtained for any tissue parameter distribution investigated by our method: weighted mean, weighted median, skewness (asymmetry), kurtosis (pointedness), and entropy (smoothness). In addition, from a distribution curve such as shown in Fig. 1 F the global mode (curve maximum), and multiple modes (for a multimodal distribution) can be determined (our example: two modes). Moreover, the relative sizes of tissue volumes characterized by different tissue parameter ranges can be estimated by numerical integration of the areas under the curve in question (Fig. 1 F, vertical green bar separating area 1 and from area 2). Further statistical parameters describing distribution functions can be found in specialized statistics textbooks and publications (e.g., moment-generating functions and characteristic functions). However, the usefulness of these functions for analysis of tissue heterogeneity is very limited; therefore we did not attempt to include these functions in our concept.

The new paradigm presented here lends itself to a broad range of applications. Of course, the equation to be used for a particular chemical shift-to-tissue parameter conversion is specific to the resonance used *and* to the tissue parameter to be analyzed. Many of these equations can be found in the published literature; their integration into our approach is straight forward. Also, the algorithm needed to correct the height of the data points for the nonlinearity between the chemical-shift scale and the tissue parameter scale is application-specific: the uncorrected height is divided by the derivative of the equation used for the conversion (e.g., the Henderson-Hasselbalch equation for ppm-to-pH conversion [3]). Beyond the analysis of extracellular pH heterogeneity by the ^{31}P signal of exogenous 3-APP (mentioned above), parameters that can in principle be addressed under our paradigm are: (i) intracellular pH by the ^{31}P signal of endogenous inorganic phosphate [2]; (ii) extracellular pH by the ^{1}H signal of exogenous imidazol compounds [4]; (iii) tissue pH by the ^{13}C signal of exogenous ^{13}C-labeled bicarbonate [5]; (iv) Mg^{2+} concentration by the β-^{31}P signal of endogenous ATP [6]; (v) temperature by the water ^{1}H signal [7], and possibly others. In general, any tissue parameter that has a significant influence on the chemical shift of a detectable reporter molecule nucleus, and whose value varies significantly across the measured tissue volume (or voxel), has the potential to be amenable to quantitative multiparametric assessment of its statistical distribution throughout that volume.

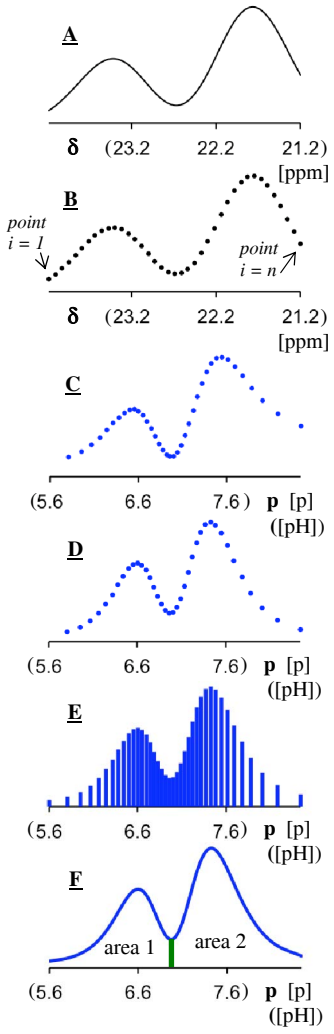

Fig. 1 Example for conversion of MRS resonance into tissue parameter profile. [p]: unit of tissue parameter analyzed (here: [p] = [pH], obtained from 3-APP ^{31}P MRS of mouse tumor [2]).

Conclusion

Tissue heterogeneity can be quantitatively described by tissue parameter distributions based on appropriate MRS resonances. The full range of tissue parameters that can be accessed under this paradigm remains to be explored. Further improvements should minimize undesired line shape contributions (e.g., due to magnetic-field inhomogeneity or spin-spin coupling). Integration of this analysis with imaging methods can also be envisaged (e.g., magnetic resonance spectroscopic imaging). [8]

References

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