

The T_1 -Dispersion Curve as a Biomarker of Colorectal Cancer

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Synopsis

A graph of T_1 versus applied magnetic field, obtained via Fast Field-Cycling (FFC) NMR relaxometry, can be used as a diagnostic tool thanks to the information it provides about molecular dynamics. In this work, FFC NMR relaxometry, extended to magnetic fields below 17 μT , was used to investigate new biomarkers of colorectal cancer. The acquired results indicated that there were significant differences in the molecular motions with correlation times 0.1-10 ms and 0.5–1.4 μs between the healthy and cancer tissues examined, showing great potential for diagnosis, staging and monitoring response to treatment.

Purpose

T_1 -dispersion curves, acquired with Fast Field-Cycling (FFC) NMR relaxometry, plot T_1 relaxation time versus the applied magnetic field strength. They are used for the investigation of the molecular dynamics of complex systems, with applications in biomedicine¹. The purpose of the study was to acquire T_1 -dispersion curves that extend to magnetic fields below 17 μT for the study of the slowest molecular dynamics, and then to investigate their use as new biomarkers of colorectal cancer.

Materials and Methods

Colorectal tissue samples were provided by the Grampian Biorepository with the informed consent of the patients. 19 fresh, non-frozen samples were used in total. These were obtained between October 2015 and September 2016 from four male and seven female patients, aged between 35-87 years, who had colorectal cancer (seven Dukes B cases and four Dukes C cases respectively). The samples comprised: matched pairs of healthy and diseased tissue samples from eight patients; one healthy and two diseased tissue samples from a further three patients.

The samples were measured using a commercial FFC NMR relaxometer (Stelar S.l.r., Italy), using samples of volume ca 1 mL at a controlled temperature of 37 °C. A Field-Cycling Inversion-Recovery Carr-Purcell-Meiboom-Gill (IRCPMG) pulse sequence was used, with the evolution field varying between 10 MHz to 700 Hz proton Larmor frequency (PLF). To extend the FFC NMR techniques, and thus the acquired T_1 -dispersion curves, below 10 kHz PLF, a novel calibration method previously presented² was applied.

The models applied to fit the acquired curves, presented as R_1 ($R_1=1/T_1$) versus field, were a sum of power law functions applied to fit the background curves, and a sum of Lorentzian functions previously published³, applied to fit the quadrupole peaks consistently observed in biological samples between 0.4-0.9 MHz and 1.5-3.5 MHz PLF. The

parameters presented in this study as biomarkers are the vertical shifts and slopes of the segments appearing in the ultra-low and low ranges of the applied magnetic fields, defined as 700 Hz-10 kHz and 0.7-1.8 MHz PLF respectively.

Results and Discussion

As seen in Figure 1, the R_1 -dispersion curves, acquired with the relaxometer calibrated, extended to magnetic fields as low as 700 Hz PLF (16.4 μ T), significantly less than the earth's field (ca 2 kHz). They showed three segments of power law distributions with different vertical shift, slope and length, as well as three quadrupole peaks of Lorentzian distribution. The segments below 10 kHz PLF, revealed after the calibration of the relaxometer, showed a different vertical shift and slope from the rest of the curves, indicating a slower motion (correlation times > 0.1 ms) in the examined tissues. Additionally, the diversion of T_1 values, measured between the healthy and cancer tissue, is increased with the decrease of the applied field from 10 MHz to 10 kHz PLF, indicating an enhanced T_1 -contrast at low fields.

Figure 2 summarises the values of the vertical shifts and slopes of the ultra-low- and low-field-segments which were shown on the R_1 -dispersion curves of healthy and diseased tissues. In the case of the ultra-low-field segments (Figure 2a,b), the values of the healthy and cancer tissue did not overlap, apart from an outlier at approximately 12 sec^{-1} observed in healthy tissue in Figure 2a. In the case of the low-field segments (Figure 2c,d), the box plots indicated that about 50% and 85% of the measured vertical shifts and slopes of the healthy tissues were smaller than the ones arising from the cancer tissues.

Statistical tests performed on the results acquired from the paired tissues showed that there were significant differences between the healthy and diseased tissues for all four parameters studied (p-values of 0.012, 0.012, 0.025, and 0.012, for the parameters presented in Figure 2 (a), (b), (c), and (d) respectively).

These results indicate that there are significant differences in the motions with correlation times 0.1-10 ms and 0.5–1.4 μ s, between the healthy and cancer tissues examined.

Conclusion

This work shows that T_1 -dispersion curves, extended to ultra-low magnetic fields, have potential as new biomarkers of colorectal cancer. The vertical shifts and slopes of their segments can also form the basis of new types of contrast in FFC MRI¹, highlighting the different dynamic processes which take place between healthy and cancer tissues. Next steps will include the application of localised FFC NMR relaxometry to acquire T_1 -dispersion curves from selected regions of the human body in vivo, and the acquisition of T_1 -weighted images at various field strengths using our newly-constructed whole-body 0.2 tesla FFC MRI scanner.

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References

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Figures

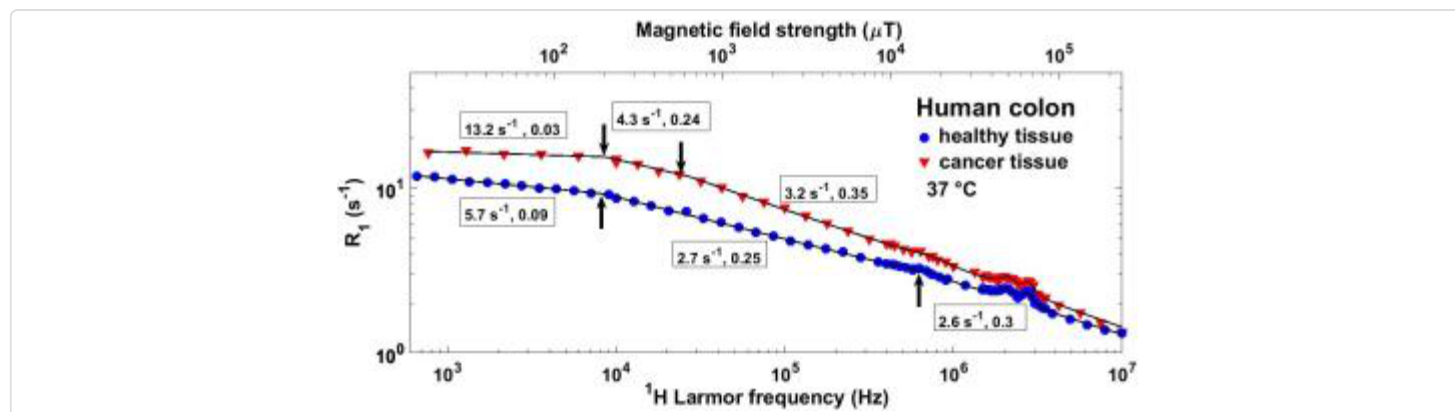


Figure 1. Example of two R_1 -dispersion curves which were acquired from samples of healthy and cancer tissue, extracted from the colon of a patient. The R_1 is plotted versus the applied field, expressed in units of μT and proton Larmor frequency, on logarithmic scales. The arrows illustrate the inflection points of the curves, and the boxes report the vertical shift (sec^{-1}) and slope (unitless) of each segment which were measured via the curve fit parameters ($R^2 > 0.99$).

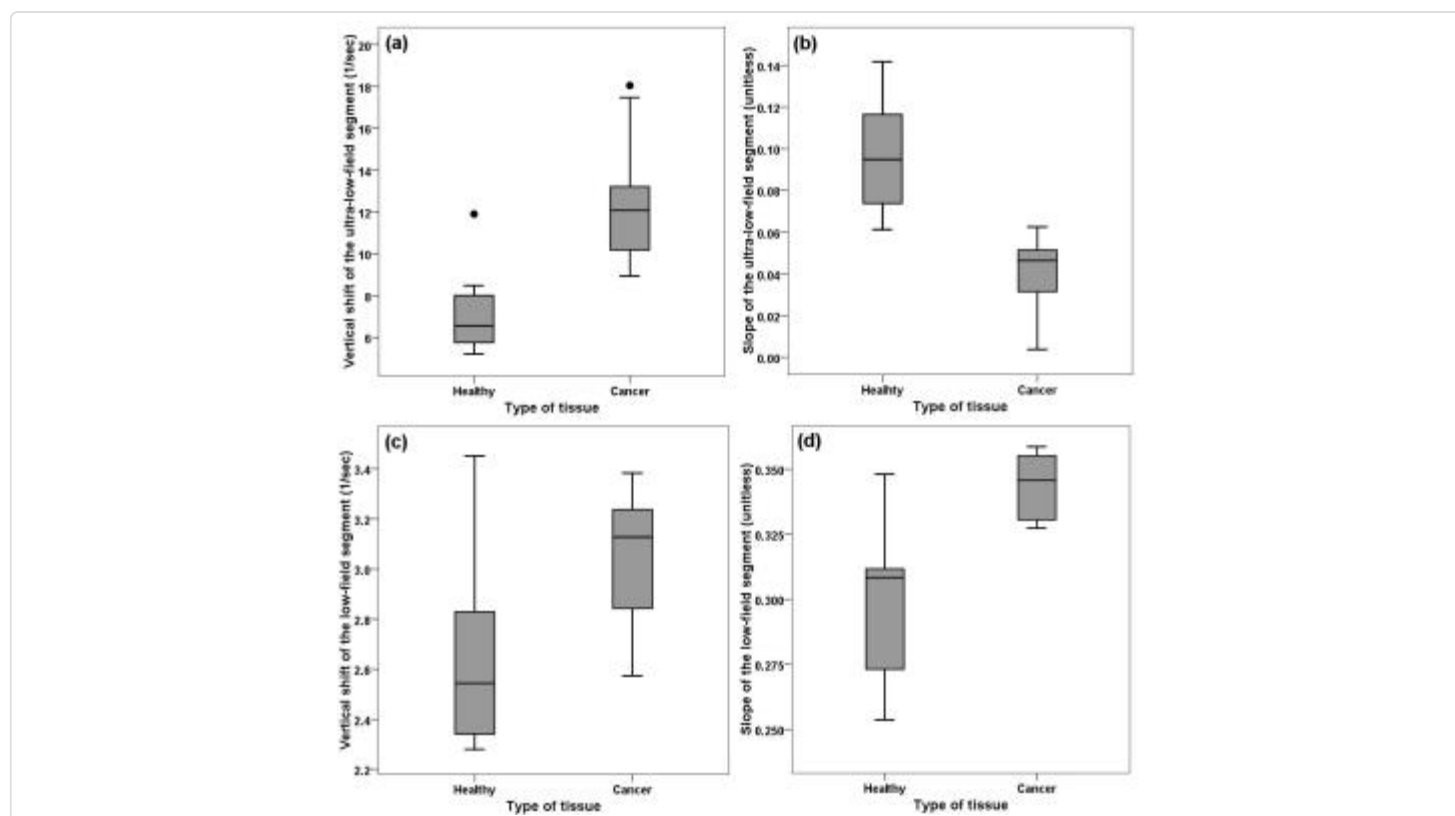


Figure 2. Box plots summarising the measurements of the vertical shifts and slopes of the ultra-low- and low-field segments shown on the acquired dispersion curves. The horizontal lines in the box plots indicate the median values. The data points shown outside the box plots in (a) indicate outliers which are larger than the maximum value of their respective box by 1.5 to 3 times its interquartile range (range between the maximum and minimum value of the box).