

Early Detection of Pancreatic Cancer and Glioblastoma Multiforme by Active Feedback Magnetic Resonance

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Introduction: Early detection of high-grade malignancy, such as pancreatic cancers (PC) and glioblastoma multiforme (GBM), using enhanced MRI techniques significantly increases not only the treatment options available, but also the patients' survival rate. For this purpose, a conceptually new approach, termed "Active-Feedback MR", was developed. An active feedback electronic device was homebuilt to implement active-feedback pulse sequences to generate avalanching spin amplification (Fig. 1), which enhances the weak magnetic-field perturbations from magnetic nanoparticles in targeted PC (Fig. 2) or malignant physiological conditions in GBM (Fig. 3).

Theory and Methods: The general principle of the "Active-Feedback MR" is based on the feedback-induced nonlinear spin dynamics that we discovered, for examples [1-4]. Here, its specific applications to early tumor detection were developed and demonstrated [5,6]. (i) First, an active-feedback electronic device was home-built to generate feedback fields from the received FID current (Fig. 1). The device is to filter, phase shift, and amplify the signal from the receiver coils and then retransmit the modified signal into the RF transmission coil, with adjustable and programmable feedback phases and gains. The MR console computer can execute the active-feedback pulse sequences (Fig. 3A) to control the trigger signal, feedback phase/gain, and the duration of the feedback fields, allowing us to utilize the active feedback fields in novel ways. (ii) Next, an active-feedback pulse sequence was developed for early tumor detection (Fig. 3A) and was statistically tested on *in vivo* mice tumor models (Figs. 2 and 3). In essence, the enhanced tumor contrast arises from "selective self-excitation" and "fixed-point dynamics" generated by the bulk water ¹H under active feedback fields. Use the sensitive detection of magnetic nanoparticles as an example (Fig. 2). A small flip-angle ($\theta=5-10^\circ$) RF pulse tilts the sample equilibrium magnetization. Since the averaged transverse magnetization is mainly contributed from the bulk water ¹H spins, the resulting active feedback field possesses a frequency closer to that of the bulk water ¹H spins which are distant from the dipole center. By "selective self-excitation", the feedback field tilts the bulk water ¹H spins more effectively towards the stable fixed-point, $-z$ -axis (assume feedback phase 180°), while the ¹H spins near the dipole center are less affected due to resonance mismatch. This "selective self-excitation" process continues and enlarges the contrast between the longitudinal magnetization of the ¹H spins in bulk water and those near the dipole center. Maximum contrast in the longitudinal magnetization can be achieved and locked when all spin magnetizations evolve to the fixed point: all align along $-z$ in this case.

Results (1): Early Detection of Pancreatic Cancers: Anti-CA 19-9 antibodies were conjugated to NH₂-PEG-coated magnetic nanoparticles. The antigen binding capacity to CA 19-9 over-expressing cell lines (BxPC3) was confirmed by *in vitro* MR cellular images. *In vivo* images of human pancreatic tumors from nude mouse xenografts (Fig. 2A) show that, while T2-weighted image cannot clearly locate the magnetic nanoparticles (Fig. 2B), the active-feedback images (Fig. 2C) successfully highlight the magnetic nanoparticles distribution with a close correlation with iron-stained histopathology (Fig. 2D).

Results (2): Early Detection of Glioblastoma Multiforme: Stage-1 orthotopic GBM mouse models infected with human U87 cell line were imaged (Fig. 3). While both T2 parameter images (Fig. 3B) and T2-weighted images by spin echo (Fig. 3C) successfully locate the GBM tumor, our active-feedback images (Fig. 3C) and decay constant mapping (Fig. 3B) provide 4-5 times of improvements in GBM tumor contrast through sensitively imaging the susceptibility variations due to irregular water contents and deoxyhemoglobin.

Discussion and Conclusion: *In vivo* PC and GBM mouse models validated the superior contrast/sensitivity and experimental robustness of the "Active-Feedback MR" for early tumor detection. Statistical results (N>10) for PC and GBM mouse models at various cancer stages [6], alternative active feedback pulse sequences with further improved performance and positive contrast [6], and active feedback pulse sequences for enhanced R1/R2-weighted images will also be presented.

Reference: [1] Science 290, 118 (2001) [2] Magn. Reson. Med. 56, 776 (2006) [3] Magn. Reson. Med. 61, 925 (2009) [4] J. Phys. Chem. B 110, 22071 (2006) [5] "Early Tumor Detection by Active Feedback MR Molecular Imaging" (submitted to Magn. Reson. Med.) [6] "Early Detection of Pancreatic Cancer and Glioblastoma Multiforme by Active Feedback MR" (submitted)

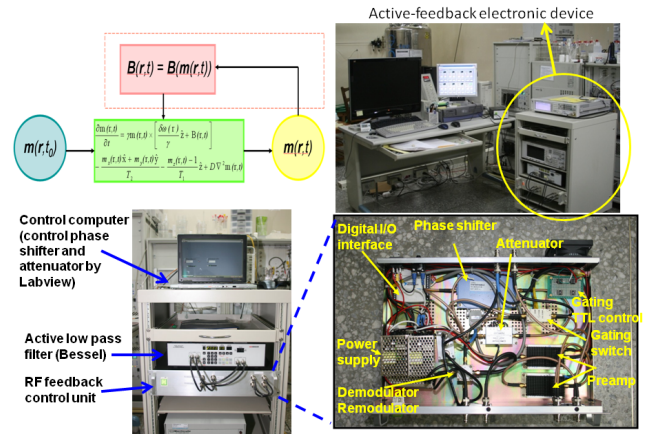


Fig. 1: Active feedback electronic device to implement a spin avalanching amplification scheme for early tumor detection.

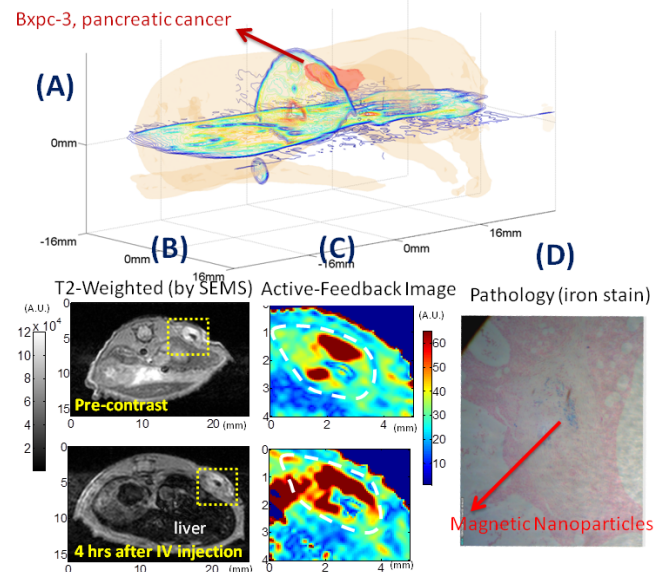


Fig. 2: Early detection of pancreatic cancers (A) by sensitive imaging of the dipolar fields induced by magnetic nanoparticles (D). The active feedback images show much improved post-injection contrast (C), compared with spin echo T2W images (B).

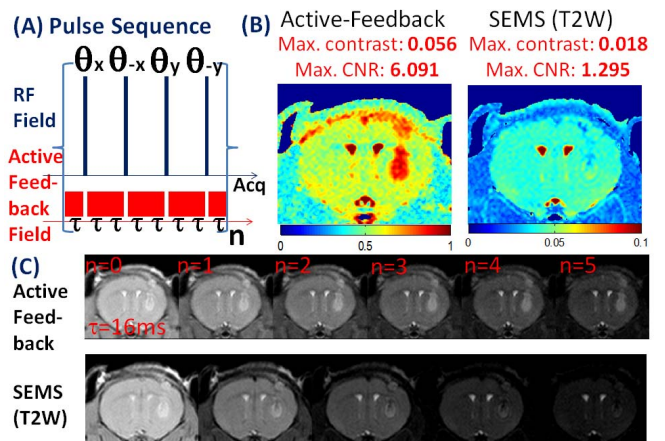


Fig. 3: Early detection of orthotopic human GBM (glioblastoma multiforme) by sensitive imaging the susceptibility variations due to irregular water contents and deoxyhemoglobin. The active feedback method (A) can significantly differentiate the decay constants between the healthy and tumor tissues to improve the contrast by 4-5 times, as compared with T2W images (B+C).