[SY08] Molecular Symposium

SY08-01

Deep learning in MRS

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The potential applicability of a recurrent neural network (RNN) in the reconstruction of spectra from truncated FIDs was explored. A RNN was trained on a set of simulated full FIDs with varying metabolite concentrations. Then, the performance of the trained RNN was tested on severely truncated FIDs (~95% truncation). our preliminary study suggests that RNNs may be used in the restoration of truncated FIDs and thus reconstruction of spectra including tiny multiplets. A well trained RNN may be applicable to the situations where data sampling is highly limited such as in cardiac MRS and spectroscopic magnetic resonance fingerprinting (sMRF).

^{1}H-MRS can quantify brain metabolites noninvasively. However, in a typical clinical setting, human brain spectra are indispensably degraded due to low SNR, line-broadening, and unknown spectral baseline, and consequently, quantification of brain metabolites is challenging even with the current state-of-the-art software. Given the recent accomplishment of deep-learning in a variety of different tasks, we developed a convolutional-neural-network (CNN) that maps the degraded brain spectra into noise-free, line-narrowed, baseline-removed, metabolite-only spectra. The robust performance of the proposed method as validated on both simulated and in vivo human brain spectra strongly supports the potential of deep learning in ^{1}H-MRS of human brain.

Noninvasive identification of isocitrate dehydrogenase (IDH)-mutational status in glioma patients using ^{1}H-MRS is diagnostically and prognostically valuable. However, the most widely used short TE method is reported to be more subject to false diagnosis due to the severe spectral overlap of 2-hydroxyglutarate (2HG). We explored the potential applicability of deep learning in addressing this issue. A deep neural network that was trained on a large number of simulated spectra substantially improved the overall diagnostic accuracy on the patient spectra, compared to the LCModel analysis. As no spectral fitting is involved, our results are not subject to ambiguity arising from the CRLB-based data interpretation**.**

Keywords : Magnetic resonance spectroscopy, Deep learning

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SY08-02

Fluorescence probe development by DOFLA and its application to bioimaging

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Diversity Oriented Fluorescence Library Approach (DOFLA): Fluorescent sensors and probes have attracted attention due to their high sensitivity and their exceptional ease of handling when compared to their radioactive counterparts. The conventional Analyte Oriented Approach is combining known analyte binding motifs to fluorescence molecules through a linker. Although many fluorescence-based sensors have been developed through this approach, each individual development requires a major effort in both design and synthesis of the sensors. Also, the sensor's scope of application is intrinsically limited only to the pre-selected specific analytes, and thus excluding a possibility of new binding motif discovery. To overcome this limitation and to accelerate novel sensor discovery, we proposed an alternative Diversity Oriented Approach. The basic hypothesis is DOFL (Diversity Oriented Fluorescence Library) of the same fluorescence scaffold, but with various diversity elements directly attached around the core, may selectively respond to a broader range of analytes with differing fluorescence responses. The specific binding of fluorescent small molecule is readily detectable and the target protein can be tracked visibly during all the target identification processes by adding an affinity tag to the molecule. Altogether, more than 10,000 fluorescent compounds were synthesized and tested in various cell types. We have used DOFLA to produce novel sensors and probes that detect a variety of biological and chemical molecules in vivo as well as in vitro. Live-cell imaging has become essential in modern biology for the study of molecular and cellular events along with recent technological advancements in fluorescence microscopy and cell culture in vitro. Although fluorescent proteins and fluorophore-conjugated antibodies have been widely used for the detection of cell-type specific markers, these methods require genetic manipulations and binding of xenogenic antibodies which may not be applicable to natural cells and detection of intracellular markers in live cells, respectively. These problems can be overcome by using fluorescent small molecules which can freely enter live cells and interact with cell-type specific molecules. The DOFLA has recently been applied to the development of novel imaging probes that detects various biological and chemical molecules in vitro, specific type of cells, organs and systems in living organisms. Here, we summarize intrinsically fluorescent small molecules that identify pluripotent stem cells, neural stem cells, myocytes, pancreatic islet cells, certain types of cancer cells, microglia and the cells containing high levels of histamine and glutathione developed by DOFLA

Keywords : DOFLA, Fluorescent probe, Bioimaging, Chemical compound, Small molecule

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SY08-03

Gadolinium-based MRI contrast agents: Targeted Imaging and Therapy

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Countless numbers of contrast-enhanced magnetic resonance imaging (MRI) exams are performed annually in the world. The gadolinium (III) based contrast agents which are almost exclusively small and hydrophilic, improve diagnostic accuracy.

Recently, long-term safety problem of gadolinium (III) based agents have come up and this has given impetus to research of alternatives. There has also been a driving force to develop new molecularly targeted contrast agents that can detect specific pathological changes in the topical environment. One way to improve the specificity of a contrast agent is to a receptor which internalizes the agent into a cell, or by direct protein binding. Here, we describe efforts to investigate gadolinium (III) based agents more specific for pathology by direct biochemical targeting.

Modern medicine is also currently going through a paradigm change from conventional treatments based on the generalized diagnosis to a more personalized treatment based on the molecular-level diagnosis. Hence, theranostics has emerged as a new class of next-generation medicine which combines specific targeted therapy based on targeted diagnosis. Theranostics are often related with nanomedicine which simultaneously provide imaging and therapeutic capabilities within a single agent as straightforward approach. On the other hand, low molecular theranostic agents have potential for better control of the physico-chemical properties and easier characterization. Theranostics based on gadolinium (III) complexes have been widely investigated so far, both in the class of nanoparticles and molecular probes. From there, we introduce approaches to development gadolinium (III) based agents as theranostics more promising for customized medicine.

Keywords : Gadolinium (III), MRI contrast agent, Targeting imaging, Theranostics, Low molecules

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Recent advances in the study of non-invasive MR pH imaging using chemical exchange saturation transfer

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Alteration in tissue pH is an indicator of many pathological processes. Noninvasive MR pH imaging will be much helpful for disorder characterization and therapy, even monitoring cell viability. Noninvasive brain pH measurements have routinely relied on ^{31}P magnetic resonance spectroscopy techniques which require additional hardware, take too long to be clinically useful, and provide very limited spatial resolution. Chemical exchange saturation transfer (CEST) is a versatile technique for MR molecular imaging, which has widely be used for non-invasive pH imaging and low-concentration biomolecule detection. For example, the potential of amide proton transfer (APT) had been proved for imaging pH effects in ischemic rat brain noninvasively [1].

A lot of important studies of non-invasive MR pH imaging using CEST have been published by different labs in recent years. With combination of amide and guanidyl CEST, the sensitivity of pH-weighted MR imaging can be enhanced for ischemic rat brain in a recent study [2]. Iopamidol, as a chemical exchange-dependent saturation transfer contrast medium, has been used to measure extracellular pH (pHe) [3]. A single dose of cariporide can induce a rapid change of intracellular pH (pHi) in animal glioblastoma multiforme, which is observed by using amine/amide concentration-independent detection (AACID) CEST MR imaging [4]. It was also found that the major contributors to in vivo T_1 -normalized MTR_{asym}(3.5 ppm) contrast between white and gray matter in normal brain are pH-insensitive macromolecular magnetization transfer (MT) and nuclear Overhauser enhancement. The pH-sensitive amine and amide effects account for nearly 60% and 80% of the MTR_{asym} changes seen in white and gray matter, respectively, after global ischemia, indicating that MTR_{asym} is predominantly pH-sensitive [5]. Clinical translation of pH-weighted MR imaging has been conducted for diagnosing human brain tumors [6].

In our most recent studies, *in vivo* gas challenge in an experimental glioma model in rats showed that enhanced pH-weighted MR imaging can more effectively localize tumor periphery. In addition, ioversol (a clinical CT contrast medium) CEST MR imaging can be exploited to achieve pHe mapping of human liver cancer microenvironment.

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Keywords : CEST, PH, Magnetic resonance imaging