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ABSTRACTS

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GA16- Development and Evaluation of D-Fluoroalanine and D-Fluoroalanine-d3 as PET Imaging Agents for Bacterial Infection

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Category: Infection
Abstract Body: Novel positron emission tomography (PET) imaging agents are needed to detect and diagnose deep-seated bacterial infections.[1] D-amino acids, which are selectively taken up by bacteria, are attractive targets for radiotracer development.[2] This has resulted in the synthesis and evaluation of several ^{11}C-labeled D-amino acids including D-Met,[3] D-Ala,[4] and D-Gln.[5] Given that D-alanine is an essential component of bacterial peptidoglycan, and in order to expand the studies to ^{18}F tracers which have a longer half-life than ^{11}C, D-FAla and D-FAla-d_3 were synthesized and evaluated in a soft-tissue infection model, laying the groundwork for the wider application of ^{18}F-labeled D-amino acids for bacterial imaging.
D-FAla and D-FAla-d_3 were synthesized using cyclic D-sulfamidate precursors involving a 2-step radiofluorination followed by acidic deprotection. Uptake experiments were performed with both Gram-negative (*Escherichia coli*) and Gram-positive (*Staphylococcus aureus*) bacteria, and a *S. aureus* Xen29 rat soft-tissue infection model was utilized for *in vivo* PET imaging. *In vivo* bioluminescent imaging was used to monitor the bacterial infection starting from the 2nd day post inoculation. Once a robust infection had developed, 90-min dynamic PET imaging was used to analyze the biodistribution of D-FAla (n=4) and D-FAla-d_3 (n=4), while the *ex vivo* biodistribution was evaluated at the conclusion of the PET imaging. Heat killed bacteria were used to generate an inflammatory response in the contralateral triceps to compare and contrast with radiotracer accumulation in the infected triceps. D-FAla and D-FAla-d_3 were prepared with radiochemical yields (decay corrected) of 19–21% and radiochemical purities of >98%. For D-FAla and D-FAla-d_3, the uptake in heat-killed *E. coli* was reduced to 2%−4% of the uptake in live *E. coli*, while the uptake in heat-killed *S. aureus* was decreased to 31–41% of that observed in live bacteria. The uptake of both tracers in bacteria was dose-dependently blocked by D-alanine. *In vivo* PET imaging was initiated when a strong bioluminescent signal was detected in the infected (right) triceps which *ex vivo* analysis of the tissue showed was due to ~10^7 colony-forming units (CFU)/ml of *S. aureus* Xen29. Based on the PET data, the uptake in the infected triceps at 15 min post injection of D-FAla and D-FAla-d_3 was 0.78 ± 0.07 %ID/cc and 0.64 ± 0.03 %ID/cc, respectively, which was ~2-fold higher than the uptake at the site of sterile inflammation.
The PET imaging data demonstrated that both D-FAla and D-FAla-d_3 can detect and localize bacterial infection. Subsequent studies will involve the evaluation of the radiotracers in models of prosthetic joint infection and endocarditis, and extending the studies to fungal infections. The future studies will support the clinical translation of D-FAla and D-FAla-d_3 for the management of infection.
Disclosures: The authors have no conflicts of interest to disclose.
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pulser-receiver's synchronization pulse. Acoustical signal response was transformed from time domain to frequency domain for characteristic A-line identification, then scaled to decibel range, smoothed through a linear moving-average filter, and averaged across all measurements taken for each scenario. Each mouse (eight-week-old male mice, n=3, Charles River Laboratories) was imaged at three different time points (repeated 5 times): 1. baseline (before tail vein injection); after tail vein injection of 2. uncoated or pure MBs (10,000 MBs/mL, FujiFilm, 1.5 μm) and 3. anti-antibody (5μg/mL) coated MBs (300,000:1 ratio) incubated with cancer cells (1000 cells/mL, Fig.1E). We investigated two CTCs lines: (i) RH30 (rhabdomyosarcoma or soft tissue childhood cancer), and (ii) Caki-1 (clear cell renal carcinoma). Three blood vessels were imaged: right coronary artery (RCA), left coronary artery (LCA), and tail vein. Each mouse received unique injections—M1 (mouse 1): EpCAM-targeted MBs with RH30; M2 (mouse 2): CD147-targeted MBs with Caki-1; M3 (mouse 3): CA9-targeted MBs with Caki-1 followed by CA9/CD147-targeted MBs with Caki-1 cells after 40 minutes. MSOT Acuity (iThera Medical) was used for hemoglobin (Hb) and oxyhemoglobin (HbO_2) visualization at all 3 locations. Mean ± standard deviation (SD) was calculated for the hydrophone data based on 5 trials at each vessel. Statistical analysis for the optoacoustic signals was based on regions-of-interest (ROI=5 mm^2). All experiments were conducted under full anesthesia (UTSW IACUC: 2023–103473). Image analysis and signal processing used iLabs, MATLAB, Aperio, and R.

Although time domain was indifferent (Fig.1F), distinctive characteristic A-lines were detected for the frequency domain among baseline, pure MBs, and coated MBs with CTCs (Figs.1G-H). Absence of MBs in the blood exhibited only noise. However, when pure MBs circulated in the blood, the A-line appeared to be bell-shaped. The coated MBs attached to CTCs showed many distinctive features: 1. EpCAM coated MBs with RH30 had a second peak at 15 MHz before falling at 18 MHz (Fig.1G); 2. CA-9 coated MBs with Caki-1 exhibited a plateau at 3–7.5 MHz and a second peak at 20 MHz (Fig.1H); 3. CD-147 coated MBs did not have any plateau but showed a secondary peak at 16 MHz; and 4. CA-9/CD-147 coated MBs did not show any distinctive peaks, resembling pure MBs. Mean±SD for all A-lines was 17.44±5.94. HbO_2 saturations were significantly higher than Hb for all animals (Figs.1I-O, $p<0.05$). Our study will open a new horizon in early detection of cancer recurrence that will positively impact both individuals and society.

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Poster Presentation

GA261- Physics-informed Machine Learning for Segmentation of Low Resolution Diffusion Magnetic Resonance Images

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Category: Computational & Data Science

Abstract Body: Clinically-derived brain tissue classification on MRI is highly challenging due to the existence of apparent artefacts such as non-homogeneity, noise, aberrant tissue with a range of signal intensities, and the intricate anatomical structure of interest . This problem becomes worse in low-resource settings (such as in the global south) because of the low-field scanners. Physics-machine learning (ML) seamlessly combines data and mathematical physics models, even in partially understood, uncertain and high-dimensional contexts. In recent research efforts, the need for developing new frameworks and standardized benchmarks as well as new mathematics for scalable, robust and rigorous next-generation physics-informed learning machines has taken center stage. This study explores Physics-based models and traditional machine learning methods for automated image segmentation using a low-resolution diffusion magnetic resonance images.

Traditional physics-informed ML is constructed such that learning biases can be introduced by appropriate choice of loss functions, constraints and inference algorithms that can modulate the training phase of an ML model. However, in this study, we have extracted image data using the physics of diffusion MRI and then used the data to train traditional ML algorithms because these algorithms run easily with low computational resources. The MRI dataset was obtained from W-ResearchWorks Archive which is a digital library of Washington education platform (https://digital.lib.washington.edu/researchworks/handle/1773/33311?show=full). In this dataset, diffusion MRI at multiple b-values (200, 400, 1000, 2000, and 3000) was collected on a 3T Siemens Prisma MRI instrument in a single healthy individual. For this study, the scan at b = $200 s/mm^2$ was used and image processing was then carried out with FSL software (created by the Analysis Group, FMRIB, Oxford, UK). Brain Extraction Tool was used to extract brain tissues while the FMRIB's Automated Segmentation Tool was used for segmentation of the brain scan into white matter, gray matter and cerebrospinal fluid. Image data from the segmentation

was then extracted as numpy arrays. Equation (1) is the generalized partial differential equation for describing the dynamics of fluid spins under the influence of B_0 and B_1 field. After making a reasonable assumption, equation (3) can be derived from equation (1). A solution to equation (3) is given as equation (4), which was then used to filter the extracted image data (achieved by using this solution as an image filter). With this, the image data has been assigned to appropriate MR diffusion physics parameters. Traditional ML algorithms implemented in Python programming were then used to train the extracted image fitted data so as to learn the three tissue clusters.

The performances of the ML models have been presented in table 1 showing how the diffusion images predicted with the models compare with the ground truth. Figures 1–3 show the predicted images using 12 models. The parameters of some of the models were tuned to check their influence on image prediction.

Obviously, figure 1 and 2 show that most of the models performed poorly. However, figure 3b, 3c and 3d had perfect performance on the training set but performance on the testing set was not good enough. Overall, random forest classifier with max_depth of 2000, was the best performing model.

This study has addressed an imaging challenge often encountered in low-resource settings and methods consistent with this inadequacy has been presented. The results were not very impressive because the resolutions of the MRI scan used was low but we were able to demonstrate how ML and AI could help improve MRI analyses. Using larger dataset could prove to be very important to optimizing these models. Future studies making use of hyperparameter tuning and/or U-Net could lead to improvements in the performance of the models.

Disclosures: The authors have no conflicts of interest to disclose.

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Poster Presentation

GA262- Physics-informed Machine Learning Approach for Denoising Low Resolution Diffusion Magnetic Resonance Images

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Category: Computational & Data Science

Abstract Body: Image denoising is to remove noise from a noisy image for the purpose of restoration to the true image. Meanwhile, since noise, edge and texture are high frequency components, it is difficult to distinguish them in during denoising and the denoised images could inevitably lose some details. However, recovering meaningful information from noisy images in the process of noise removal to obtain high quality images is an important research problem in recent time. Although, image denoising is a classic problem which has been subject to studies for a long time, it remains a challenging and open task. This is because from a mathematical perspective, image denoising is an inverse problem with a non-unique solution. In recent time, various deep learning methods have been adopted to address denoising problem. Therefore, there have been efforts to develop machine learning methods with Physics contraints. This study attempts developing a Physics-informed machine learning model in which a modified Bloch-Torrey formulation of diffusion signal is used as a constraint.

The MRI dataset was obtained from W-ResearchWorks Archive which is a digital library of Washington education platform (https://digital.lib.washington.edu/researchworks/handle/1773/33311?show=full). In this dataset, diffusion MRI at multiple b-values (200, 400, 1000, 2000, and 3000) was collected on a 3T Siemens Prisma MRI instrument in a single healthy individual. For this study, the scan at b = 200s/mm^2 was used and image processing was then carried out with FSL software (created by the Analysis Group, FMRIB, Oxford, UK). BET was used to extract brain tissues and then the slices of the resulting image volume was then extracted as 72 2D images. The central slice was then selected as the reference image. Using python programming, gaussian and impulse noises were then added to this image so that we check how our model performs in removing them. Equation (1) is the generalized partial differential equation for describing the dynamics of fluid spins under the influence of B0 and B1 fields. After making a reasonable assumption, equation (3) can be derived from equation (1). A solution to equation (3) is given as equation (4),