TARGETED METABOLOMICS ANALYSES FOR BRAIN TUMOR MARGIN ASSESSMENT DURING SURGERY

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INTRODUCTION

Gliomas are the most prevalent brain tumor type. They are histopatologically graded between I and IV. High-grade gliomas are malignant tumors with poor prognosis and low survival rate, and low-grade gliomas have the potential to progress. Hence, the surgical management of the tumor is important for the survival of the patient.

Maximum resection of the tumor attenuates recurrence risk drastically, but tumor tissue left on the excision cavity constitutes a risk for patient survival. Spectroscopy-based intraoperative feedback mechanisms have been useful in detecting the bounds of tumor infiltration.

High-Resolution Magic Angle Spinning Nuclear Magnetic Resonance (HRMAS NMR) spectroscopy is a good fit for use in tumor surgeries because of its ability to analyze small, intact, and unprocessed tissue samples in minutes. HRMAS NMR outputs a free induction decay (FID) signal whose frequency domain representation can be analyzed by a technician and a pathologist in ~20 min.

LIMITATIONS IN THE MANUAL FEEDBACK MECHANISM

- Overlapping metabolite peaks in the spectrum can prevent the expert to decide.
- Only peaks for a few metabolites can be checked.
- Strict time constraints of the surgery
- The availability and proficiency of human experts during surgery
- High dimensionality of the raw spectrum (over 16k)

PROPOSED FEEDBACK MECHANISM

- Automated metabolite quantification could handle overlapping metabolite peaks.
- Takes significantly less time
- Minimizes the dependency to technicians and human experts.
- Dimensionality reduced from 16k to 37

METHODS

1) Surgeon removes the tumor and prepares tissue samples.
2) Samples are sent to HRMAS NMR spectroscopy.
3) HRMAS NMR output spectrum are preprocessed.
4) 37 metabolites are quantified via metabolite specific models. (Performance comparison is shown in Figure 2.)
5.1) Random Forest detects the tumor samples from the metabolite concentrations. (Performance benchmark is shown in Figure 3.)
5.2) Random Forest classifies the tumors as benign or malignant. (Performance benchmark is shown in Figure 4.)
6) Feature importance analysis reveals a new biomarker. (Importance depiction can be seen in Figure 5.)

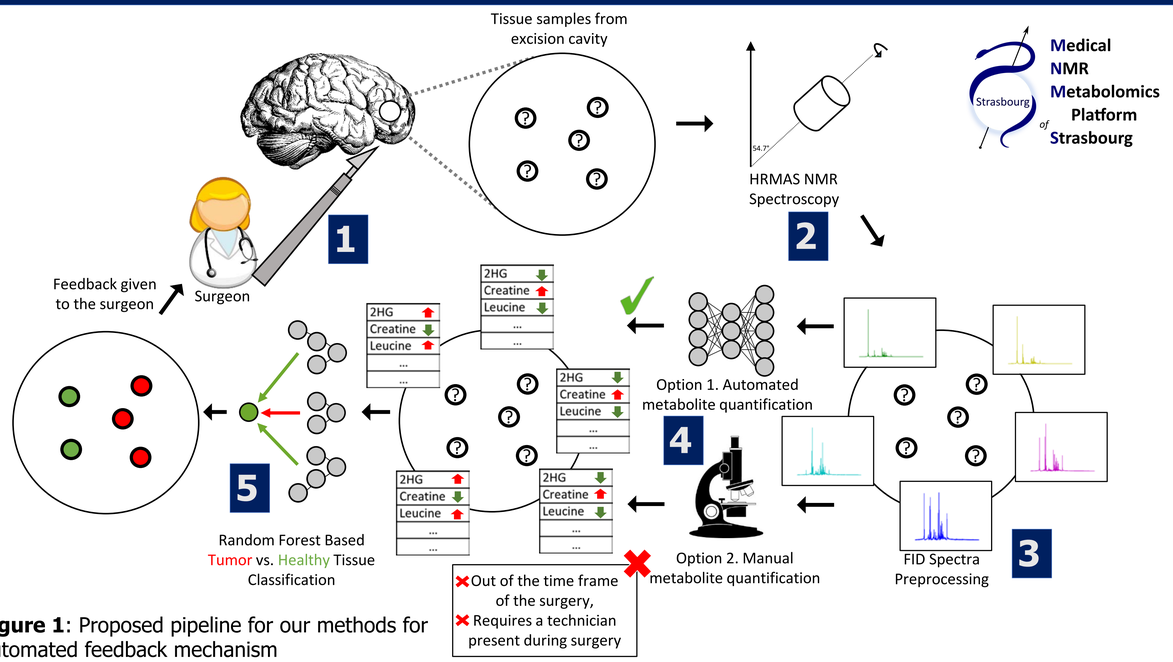

Figure 1: Proposed pipeline for our methods for automated feedback mechanism

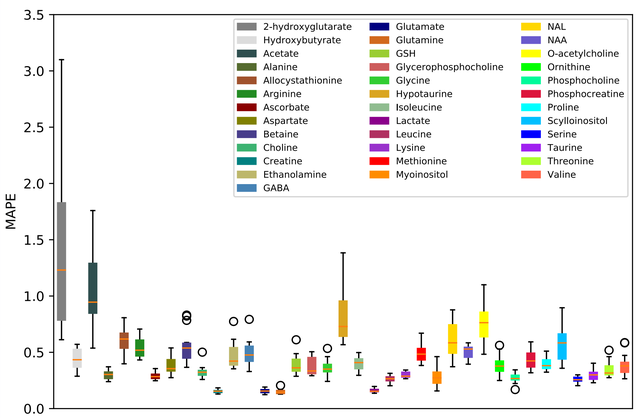

Figure 2: Performance of metabolite quantification models in terms of MAPE

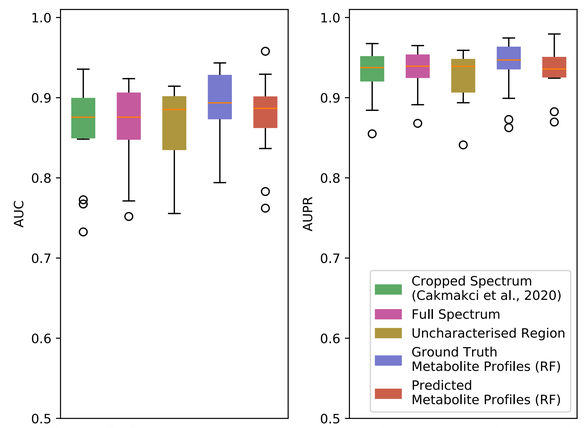

Figure 3: Performance comparison of models on tumor detection in terms of AUC-ROC (on left) and AUC-PR (on right)

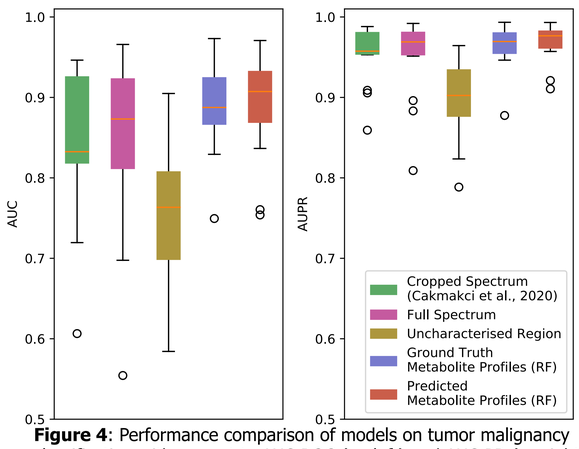

Figure 4: Performance comparison of models on tumor malignancy classification with respect to AUC-ROC (on left) and AUC-PR (on right)

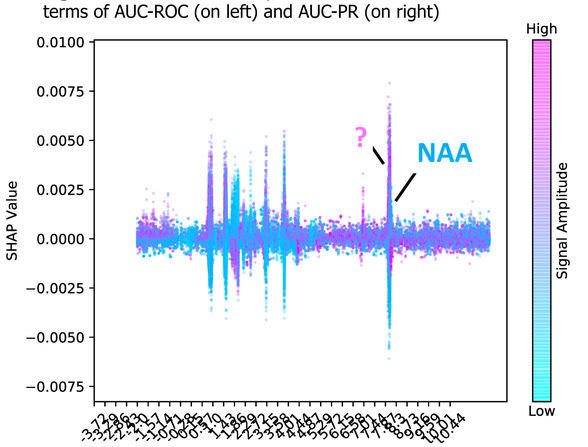

Figure 5: Calculated SHAP values of raw spectrum features on the prediction of models

RESULTS

- The most successfully quantified metabolites have been creatine, glutamate, glutamine and lactate.
- On the other hand, metabolite-specific quantification models could not quantify 2-hydroxyglutarate and acetate as well as other metabolites.
- Feature importance analysis reveals a very short region between 7.97 ppm and 8.09 ppm which very effectively distinguishes tumor and healthy tissues. (can be observed in Figure 5.)
- TOCSY experiment for the peak at the 8.07 ppm on the uncharacterized region reveals correlation with NAA.
- Visualization of control, benign and aggressive tumor, samples provided by t-SNE. (shown in Figure 6.)

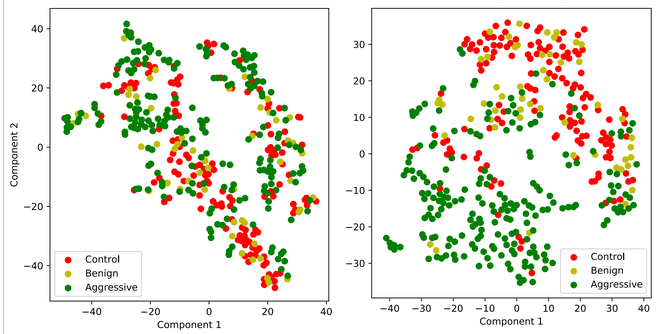

Figure 6: Control, benign and aggressive tumor visualization via t-SNE using raw spectrum (on left) and metabolite profiles (on right)

CONCLUSION

- 2-hydroxyglutarate and NAA are important metabolites for tumor and healthy sample distinction.
- Our methods detect tumor samples with a median AUC-ROC of 91.2% and AUC-PR of 96.7% and classifies them as benign and malignant with a median AUC-ROC of 90.6% and AUC-PR of 97.7%, finally informs the surgeon, in seconds.
- Random Forest models that use metabolite profiles detect and classify tumor samples 10 times faster than the ones using raw spectrum.
- Predicted metabolite levels provided by the automated metabolite quantification models can be used to detect tumor samples and pathologically classify them.

ACKNOWLEDGMENTS

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