QUANTITATIVE DCE-MRI: ON DEVELOPMENT OF METHODOLOGY AND EVALUATING ITS APPLICATIONS IN GLIOMA GRADING

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by

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Dedicated to

Achan, Amma, Sunda, and "the unborn"!

CERTIFICATE

This is to certify that the thesis entitled, "**Quantitative DCE-MRI: On Development of Methodology and Evaluating its Applications in Glioma Grading**", submitted by **Mr. Dinil Sasi S (2016BMZ8111)** for the award of the degree of the **Doctor of Philosophy** to the Centre for Biomedical Engineering, Indian Institute of Technology Delhi, is a record of the bonafide research work carried out by him under my supervision and guidance. He has fulfilled the requirements for the submission of this thesis, which to the best of my knowledge, has reached the requisite standard.

The contents of this thesis have not been submitted in part or full to any other university or institute for the award of any other degree or diploma.

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ABSTRACT

This Ph.D. thesis is aimed at addressing some of the challenges towards reliable computation and standardization of quantitative dynamic-contrast-enhanced magnetic resonance imaging (DCE-MRI) parameters for glioma grading in a routine clinical setting. The scope of the research work presented in this thesis resulted in developing the protocol for the DCE-MRI data acquisition and methods for data analysis, which can help clinicians in better diagnosis, prognosis, and treatment planning of glioma.

The first chapter starts with a discussion of glioma, its molecular characteristics, epidemiology, and state of art prognostic measures. Next, a basic introduction about underlying physics and image formation in MRI is provided. Overview of different tissue relaxation and basic concepts behind image acquisition with different tissue contrasts and basic pulse sequences are discussed. Next, this chapter discusses about conventional MRI protocols used for brain tumor patients. A brief overview of advanced imaging techniques for the quantitative evaluation of glioma and its application to glioma grading, tissue segmentation, and follow-up studies are also included in this chapter. This chapter then highlights the advantages of DCE-MRI over other advanced MRI techniques for glioma characterization. A description of the pipeline of state-of-art methods for quantitative DCE-MRI analysis and the application of DCE-MRI for glioma characterization are also included in this section. Before identifying the research gap and forming the objectives, a literature review of currently available literature about different methods used for quantitation of DCE-MRI derived tracer-kinetic-parameters (TKPs), reliability and variability of TKPs estimation, and current challenges faced for the routine clinical application are included.

The purpose of the study mentioned in chapter-2 was to determine an optimum scan acceleration factor (R) to accelerate DCE-MRI data acquisition while achieving full brain coverage

with an improved spatial resolution for the analysis of patients with glioma in a clinical setting. The performance of SENSE and Compressed-SENSE (CSENSE) based scan acceleration techniques have been evaluated. The quality of structural images (T_1-W, T_2-W) and computed precontrast T_1 maps (T_{10}) (at different CSENSE factors) were compared with SENSE acquisitions. Analysis was carried out on data from healthy volunteers and an in-house developed phantom to obtain an optimum acceleration factor for acquiring T_1-W, T_2-W, and 3D T_1-W FFE images. Error propagation to T_{10} estimation was also evaluated. The efficacy of quantitative DCE-MRI parameters in differentiating LGG and HGG using the optimized protocol (protocol-2) was evaluated and compared with the conventional protocol (protocol-1) used at our Centre.

Among the previously reported works of literature on the applications of Generalized-tracer-kinetic-model (GTKM) parameters, the accuracy of differentiation and classification using TKPs exhibit large discrepancies and variations. Also, the magnitude scales of parameter values reported in these studies are not consistent due to multiple factors mentioned earlier. One of the major factors that affect the magnitude scale of these parameters is the variations in arterial input function (AIF), which is important for fitting GTKM to concentration-time curves. So, the study presented in the chapter-3 consisted of three sub-objectives; (i) to develop an optimized subject-specific AIF estimation method, (ii) to comprehensively evaluate the sensitivity to noise and inter/intra-subject variability of TKPs in different tissue regions (contrast-enhancing (CE) tumor, non-enhancing tumor (NET), normal-appearing gray matter (GM) and white matter (WM) regions) of glioma patients mainly due to variations in AIF, and (iii) to evaluate the impact of different normalization techniques in mitigating the inter-subject variability of TKPs to corresponding values computed from healthy tissue regions. A reliable estimation of volume transfer constant (K^{trans}) and blood plasma volume fraction (v_p) are possible in normal-appearing and tumor tissue regions. Normalization of K^{trans} and v_p in tumor regions to corresponding parameters in the normal-appearing tissue regions have mitigated the inter-subject and intra-subject variability and has improved the accuracy of differentiation of HGG and LGG.

In chapter-4, a tissue-specific hybrid two compartmental model (HTCM) for the blood-brain barrier (BBB) permeability assessment in glioma patients is proposed. GTKM and Patlak model (PM) are the widely accepted models in clinics for glioma characterization. PM is generally preferred for shorter durations (data less than 1 minutes) and GTKM is optimum for longer duration data (~4-10 minutes) in tumor regions. However, in healthy tissue regions, for longer duration data, GTKM derived leakage volume fraction (v_e) is not relevant since the BBB is intact. It was observed that the reliability and magnitude of v_e don't change in healthy tissue regions with data length. Hence, GTKM may over-fit the healthy tissue curves. On the other hand, PM leads to under-fitting since it assumes a unidirectional flow, which doesn't hold for medium (1-3 min) or long-duration data. To address this problem, this chapter discusses an optimized tissue-specific model, which acts as both GTKM and PM depending on the contrast agent transients of the tissue representing voxel. The hybrid two compartmental model (HTCM) has shown significant improvement in computation time (~40%). The parameters computed from HTCM and GTKM in CE regions have exhibited a high correlation for DCE-MRI data less than 2 minutes. One of the major advantages while fitting the HTCM is that the maximum number of parameter estimation is always two. However, it is possible to differentiate between K^{trans} depending on the underlying physiology of the representing voxel.

Cerebral blood volume (CBV) and cerebral blood flow (CBF) computed from the first-pass analysis of DCE-MRI data have shown wide potential in clinical applications such as initial grading and tumor sub-class segmentation. However, the estimation of these parameters is erroneous due to the leakage of the contrast agent in the tumor tissues with BBB breakdown. In CE tissues, a significant amount of leakage contribution is incorporated to CBV and CBF due to BBB leakage. However, in non-enhancing and healthy tissue regions, the contribution of leakage profile is due to multiple factors like elevated steady-state contrast agent (CA) concentration in the vasculature (AIF) after FP, and diffusion effect (shutter speed effect). Recently, CTUM has been proposed for the simultaneous computation of leakage corrected CBV and CBF (it is coined as v_p and F_p in CTUM) from DCE-MRI. This model was proposed and evaluated for DCE-MRI data with data length less than 4 minutes. So, in chapter-5, a method for leakage correction was implemented for both CBV and CBF (from first-pass), and it was compared with CTUM and PM parameters. Also, the efficacy of leakage corrected CBV and CBF were evaluated on application to glioma grading. Comparing the hemodynamic maps computed using first-pass analysis and CTUM, both CBV and CBF (with and without leakage corrected) maps were smoother than v_p and F_p maps. Even though absolute quantification of blood flow and blood volume were possible using both methods, leakage correction didn't improve the glioma grading for the data presented in the current study.

The research work presented in this thesis has been converted into a post-processing tool for quantitative DCE-MRI analysis of glioma. The author believes that the methods and post-processing tool presented in this thesis can help clinicians to improve the diagnosis and treatment planning of glioma and will also benefit the patients who are suffering from glioma and humankind in general.

सार

यह पीएच.डी. थीसिस का उद्देश्य नियमित नैदानिक सेटिंग में ग्लियोमा ग्रेडिंग के लिए मात्रात्मक गतिशील-विपरीत-संवर्धित चुंबकीय अनुनाद इमेजिंग (डीसीई-एमआरआई) मापदंडों की विश्वसनीय गणना और मानकीकरण की दिशा में कुछ चुनौतियों का समाधान करना है। इस थीसिस में प्रस्तुत शोध कार्य का दायरा डीसीई-एमआरआई डेटा अधिग्रहण और डेटा विश्लेषण के तरीकों के लिए प्रोटोकॉल विकसित करने में परिणत हुआ, जो चिकित्सकों को ग्लियोमा के बेहतर निदान, निदान और उपचार योजना में मदद कर सकता है।

पहला अध्याय ग्लियोमा, इसकी आणविक विशेषताओं, महामारी विज्ञान और कला रोगनिरोधी उपायों की चर्चा के साथ शुरू होता है। इसके बाद, एमआरआई में अंतर्निहित भौतिकी और छवि निर्माण के बारे में एक बुनियादी परिचय प्रदान किया गया है। विभिन्न ऊतक छूटों का अवलोकन और विभिन्न ऊतक विरोधाभासों और मूल पल्स अनुक्रमों के साथ छवि अधिग्रहण के पीछे की बुनियादी अवधारणाओं पर चर्चा की जाती है। इसके बाद, यह अध्याय ब्रेन ट्यूमर रोगियों के लिए उपयोग किए जाने वाले पारंपरिक एमआरआई प्रोटोकॉल के बारे में चर्चा करता है। ग्लियोमा के मात्रात्मक मूल्यांकन के लिए उन्नत इमेजिंग तकनीकों का संक्षिप्त अवलोकन और ग्लियोमा ग्रेडिंग, ऊतक विभाजन और अनुवर्ती अध्ययनों के लिए इसके अनुप्रयोग को भी इस अध्याय में शामिल किया गया है। यह अध्याय तब ग्लियोमा लक्षण वर्णन के लिए अन्य उन्नत एमआरआई तकनीकों पर डीसीई-एमआरआई के लाभों पर प्रकाश डालता है। मात्रात्मक डीसीई-एमआरआई विश्लेषण के लिए अत्याधुनिक विधियों की पाइपलाइन का विवरण और ग्लियोमा लक्षण वर्णन के लिए डीसीई-एमआरआई के आवेदन को भी इस खंड में शामिल किया गया है। अनुसंधान अंतराल की पहचान करने और उद्देश्यों को बनाने से पहले, डीसीई-एमआरआई व्युत्पन्न ट्रेसर-काइनेटिक-पैरामीटर (टीकेपी), विश्वसनीयता और टीकेपी अनुमान की परिवर्तनशीलता, और वर्तमान चुनौतियों का सामना करने के लिए उपयोग की जाने वाली विभिन्न विधियों के बारे में वर्तमान में उपलब्ध साहित्य की एक साहित्य समीक्षा। नियमित नैदानिक अनुप्रयोग शामिल हैं।

अध्याय -2 में उल्लिखित अध्ययन का उद्देश्य नैदानिक सेटिंग में ग्लियोमा के रोगियों के विश्लेषण के लिए एक बेहतर स्थानिक संकल्प के साथ पूर्ण मस्तिष्क कवरेज प्राप्त करते हुए डीसीई-एमआरआई डेटा अधिग्रहण में तेजी लाने के लिए एक इष्टतम स्कैन त्वरण कारक (आर) निर्धारित करना था। SENSE और कंप्रेस्ड-सेंस (CSENSE) आधारित स्कैन त्वरण तकनीकों के प्रदर्शन का मूल्यांकन किया गया है। संरचनात्मक छवियों की गुणवत्ता (T_1-W, T_2-W) और कंप्यूटेड प्रीकॉन्ट्रास्ट T1 मैप्स (T_{10}) (विभिन्न CSENSE कारकों पर) की तुलना SENSE अधिग्रहण से

की गई। T_1-W, T_2-W, और 3D T_1-W FFE छवियों को प्राप्त करने के लिए एक इष्टतम त्वरण कारक प्राप्त करने के लिए स्वस्थ स्वयंसेवकों और एक इन-हाउस विकसित प्रेत के डेटा पर विश्लेषण किया गया था। T_{10} अनुमान में त्रुटि प्रसार का भी मूल्यांकन किया गया था। अनुकूलित प्रोटोकॉल (प्रोटोकॉल -2) का उपयोग करके एलजीजी और एचजीजी में अंतर करने में मात्रात्मक डीसीई-एमआरआई मापदंडों की प्रभावकारिता का मूल्यांकन किया गया और हमारे केंद्र में उपयोग किए जाने वाले पारंपरिक प्रोटोकॉल (प्रोटोकॉल -1) के साथ तुलना की गई।

सामान्यीकृत-ट्रेसर-काइनेटिक-मॉडल (जीटीकेएम) मापदंडों के अनुप्रयोगों पर साहित्य के पहले रिपोर्ट किए गए कार्यों में, टीकेपी का उपयोग करके भेदभाव और वर्गीकरण की सटीकता बड़ी विसंगतियों और विविधताओं को प्रदर्शित करती है। इसके अलावा, इन अध्ययनों में बताए गए पैरामीटर मानों के परिमाण पैमाने पहले बताए गए कई कारकों के कारण संगत नहीं हैं। इन मापदंडों के परिमाण पैमाने को प्रभावित करने वाले प्रमुख कारकों में से एक धमनी इनपुट फ़ंक्शन (एआईएफ) में भिन्नता है, जो जीटीकेएम को एकाग्रता-समय घटता में फिट करने के लिए महत्वपूर्ण है। तो, अध्याय -3 में प्रस्तुत अध्ययन में तीन उप-उद्देश्य शामिल थे; (i) एक अनुकूलित विषय-विशिष्ट एआईएफ आकलन पद्धति विकसित करने के लिए, (ii) शोर के प्रति संवेदनशीलता और विभिन्न ऊतक क्षेत्रों (विपरीत-बढ़ाने (सीई) ट्यूमर, गैर-बढ़ाने वाले ट्यूमर में टीकेपी की अंतर / अंतर-विषय परिवर्तनशीलता का व्यापक मूल्यांकन करने के लिए) (एनईटी), सामान्य दिखने वाला ग्रे मैटर (जीएम) और सफेद पदार्थ (डब्ल्यूएम) क्षेत्र) ग्लियोमा रोगियों के मुख्य रूप से एआईएफ में भिन्नता के कारण, और (iii) अंतर-विषय परिवर्तनशीलता को कम करने में विभिन्न सामान्यीकरण तकनीकों के प्रभाव का मूल्यांकन करने के लिए। स्वस्थ ऊतक क्षेत्रों से गणना किए गए संबंधित मूल्यों के लिए टीकेपी। सामान्य दिखने वाले और ट्यूमर ऊतक क्षेत्रों में वॉल्यूम ट्रांसफर कॉन्स्टेंट (K^{trans}) और रक्त प्लाज्मा वॉल्यूम अंश (v_p) का एक विश्वसनीय अनुमान संभव है। ट्यूमर क्षेत्रों में Ktrans और v_p के सामान्य दिखने वाले ऊतक क्षेत्रों में संबंधित मापदंडों के सामान्यीकरण ने अंतर-विषय और अंतर-विषय परिवर्तनशीलता को कम कर दिया है और HGG और LGG के भेदभाव की सटीकता में सुधार किया है।

अध्याय -4 में, ग्लियोमा रोगियों में रक्त-मस्तिष्क बाधा (बीबीबी) पारगम्यता मूल्यांकन के लिए एक ऊतक-विशिष्ट हाइब्रिड दो कंपार्टमेंटल मॉडल (एचटीसीएम) प्रस्तावित है। जीटीकेएम और Patlak मॉडल (PM) ग्लियोमा लक्षण वर्णन के लिए क्लीनिकों में व्यापक रूप से स्वीकृत मॉडल हैं। पीएम को आम तौर पर छोटी अवधि (1 मिनट से कम डेटा) के लिए पसंद किया जाता है और जीटीकेएम ट्यूमर क्षेत्रों में लंबी अवधि के डेटा (~ 4-10 मिनट) के लिए इष्टतम है। हालांकि, स्वस्थ ऊतक क्षेत्रों में, लंबी अवधि के डेटा के लिए, जीटीकेएम व्युत्पन्न रिसाव मात्रा अंश (v_e) प्रासंगिक नहीं है क्योंकि बीबीबी बरकरार है। यह देखा गया कि डेटा लंबाई के साथ स्वस्थ ऊतक क्षेत्रों में ve की विश्वसनीयता और परिमाण नहीं बदलता है।

इसलिए, जीटीकेएम स्वस्थ ऊतक वक्रों को अधिक फिट कर सकता है। दूसरी ओर, पीएम अंडर-फिटिंग की ओर जाता है क्योंकि यह एक यूनिडायरेक्शनल प्रवाह मानता है, जो मध्यम (1-3 मिनट) या लंबी अवधि के डेटा के लिए नहीं है। इस समस्या को हल करने के लिए, यह अध्याय एक अनुकूलित ऊतक-विशिष्ट मॉडल पर चर्चा करता है, जो जीटीकेएम और पीएम दोनों के रूप में कार्य करता है, जो कि स्वर का प्रतिनिधित्व करने वाले ऊतक के कंट्रास्ट एजेंट ट्रांज़िएंट पर निर्भर करता है। हाइब्रिड टू कंपार्टमेंटल मॉडल (एचटीसीएम) ने गणना समय (~ 40%) में महत्वपूर्ण सुधार दिखाया है। सीई क्षेत्रों में एचटीसीएम और जीटीकेएम से गणना किए गए मापदंडों ने डीसीई-एमआरआई डेटा के लिए 2 मिनट से कम समय के लिए उच्च सहसंबंध प्रदर्शित किया है। एचटीसीएम को फिट करते समय एक प्रमुख लाभ यह है कि पैरामीटर अनुमान की अधिकतम संख्या हमेशा दो होती है। हालांकि, प्रतिनिधित्व करने वाले स्वर के अंतर्निहित शरीर क्रिया विज्ञान के आधार पर K^{trans} के बीच अंतर करना संभव है।

डीसीई-एमआरआई डेटा के पहले-पास विश्लेषण से गणना की गई सेरेब्रल रक्त मात्रा (सीबीवी) और मस्तिष्क रक्त प्रवाह (सीबीएफ) ने प्रारंभिक ग्रेडिंग और ट्यूमर उप-वर्ग विभाजन जैसे नैदानिक अनुप्रयोगों में व्यापक क्षमता दिखाई है। हालांकि, बीबीबी टूटने के साथ ट्यूमर के ऊतकों में कंट्रास्ट एजेंट के रिसाव के कारण इन मापदंडों का अनुमान गलत है। सीई ऊतकों में, बीबीबी रिसाव के कारण सीबीवी और सीबीएफ में रिसाव योगदान की एक महत्वपूर्ण मात्रा शामिल है। हालांकि, गैर-बढ़ाने वाले और स्वस्थ ऊतक क्षेत्रों में, रिसाव प्रोफ़ाइल का योगदान एफपी के बाद वास्कुलचर (एआईएफ) में ऊंचा स्थिर-राज्य विपरीत एजेंट (सीए) एकाग्रता और प्रसार प्रभाव (शटर गति प्रभाव) जैसे कई कारकों के कारण होता है। हाल ही में, डीसीई-एमआरआई से लीकेज सुधारे गए सीबीवी और सीबीएफ (इसे सीटीयूएम में वीपी और एफपी के रूप में गढ़ा गया है) की एक साथ गणना के लिए सीटीयूएम का प्रस्ताव किया गया है। इस मॉडल को 4 मिनट से कम डेटा लंबाई वाले डीसीई-एमआरआई डेटा के लिए प्रस्तावित और मूल्यांकन किया गया था। इसलिए, अध्याय -5 में, सीबीवी और सीबीएफ (प्रथम-पास से) दोनों के लिए रिसाव सुधार के लिए एक विधि लागू की गई थी, और इसकी तुलना सीटीयूएम और पीएम मापदंडों के साथ की गई थी। इसके अलावा, ग्लियोमा ग्रेडिंग के लिए आवेदन पर लीकेज सुधारे गए सीबीवी और सीबीएफ की प्रभावकारिता का मूल्यांकन किया गया था। प्रथम-पास विश्लेषण और सीटीयूएम का उपयोग करके गणना किए गए हेमोडायनामिक मानचित्रों की तुलना में, सीबीवी और सीबीएफ (लीक सुधार के साथ और बिना) दोनों नक्शे वीपी और एफपी मानचित्रों की तुलना में चिकने थे। भले ही दोनों विधियों का उपयोग करके रक्त प्रवाह और रक्त की मात्रा की पूर्ण मात्रा का ठहराव संभव हो, लेकिन रिसाव सुधार ने वर्तमान अध्ययन में प्रस्तुत आंकड़ों के लिए ग्लियोमा ग्रेडिंग में सुधार नहीं किया।

इस थीसिस में प्रस्तुत शोध कार्य को ग्लियोमा के मात्रात्मक डीसीई-एमआरआई विश्लेषण के लिए पोस्ट-प्रोसेसिंग टूल में बदल दिया गया है। लेखक का मानना है कि इस थीसिस में प्रस्तुत तरीके और पोस्ट-प्रोसेसिंग टूल चिकित्सकों को ग्लियोमा के निदान और उपचार योजना में सुधार करने में मदद कर सकते हैं और सामान्य रूप से ग्लियोमा और मानव जाति से पीड़ित रोगियों को भी लाभान्वित करेंगे।

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List of abbreviations

ADC = Apparent diffusion coefficient

AIF = Arterial input function

ASL = Arterial spin labelling

AUC = Area under the curve

BAT = Bolus arrival time

BBB = Blood-brain barrier

BMS = Bulk magnetic susceptibility

C(t) = Concentration time curve

CA = contrast agent

CBF = Cerebral blood flow

CBF_Corr = Leakage corrected CBF

CBV = Cerebral blood volume

CBV_Corr = Leakage corrected CBV

CC = Correlation coefficient

CE = Contrast enhanced

CEST = Chemical exchange saturation transfer

CoV = Coefficient of variation

CS = Compressed sensing

CSENSE = Compressed SENSE

CT = Computed tomography

CTUM = Compartmental tissue uptake model

DCE-MRI = Dynamic contrast-enhanced magnetic resonance imaging

DKI = Diffusion kurtosis imaging

DSC = Dynamic susceptibility contrast

DTI = Diffusion tensor imaging

DWI = Diffusion weighted imaging

E = Extraction factor

EES = Extra-vascular extra-cellular space

FFE = Fast field echo

FID = Free induction decay

FL = Full length

FLAIR = fluid attenuated inversion recovery

FOV = Field of view

FP = First pass

FSE = Fast spin echo

FT = Fourier transform

FWHM = Full width half maximum

GBM = Glioblastoma

Gd = Gadolinium

GM = Gray matter

GM-C(t) = Concentration time curve of GM

GM-Type-1 = Type-1 normalization with respect to GM

GM-Type-2 = Type-2 normalization with respect to GM

GRE = Gradient echo

GTKM = Generalized tracer kinetic model

G_x = frequency encode gradient

G_y = phase encode gradient

G_z = Slice select gradient

Hct = Hematocrit

HGG = High grade glioma

HTCM = Hybrid two compartmental model

IFT = Inverse Fourier transform

IPS = Intra-vascular plasma space

IR = Inversion recovery

ITSS = Intratumoral susceptibility signal

K^{trans} / λ^{trans} = rate transfer constant

LGG = Low grade glioma

LM = Levenberg-Marquardt

LS = Leakage space

LTKM = Leaky tracer kinetic model

MRI = Magnetic resonance imaging

MTT/T_p = Mean plasma transit time

MVA = microvascular density/area

NAGM = Normal appearing gray matter

NAWM = Normal appearing WM

NET = Non enhancing tumor

NMR = Nuclear magnetic resonance

NMSE = Normalized mean squared error

PD = Proton density

PET = Positron emission tomography

PI = Parallel imaging

PL = Piece wise linear model

PM = Patlak model

QSM = Quantitative susceptibility mapping

R = acceleration factor

R(t) = Residue function

R^2 = Sum of squared residues

RF = Radio frequency

ROC = Receiver operating characteristic

ROI = Region of interest

RPE = Relative percentage error

S(t) = Signal intensity time curve

SD = standard deviation

SE = Spin echo

SENSE = Sensitivity encoding

SNR = Signal to noise ratio

SPGRE = Spoiled gradient echo

SWI = Susceptibility weighted imaging

T_{10} = Pre-contrast T_1 relaxation time

TE = Echo time

TI = inversion time

TK = Toft's-Kety

TKP = Tracer kinetic parameter

TR = Repetition time

TS = Tissue specific

TSE = Turbo spin echo

TTP = Time to peak

v_e = EES volume fraction

VEGF = Vascular endothelial growth factor

v_p = IPS volume fraction

W = Weighted.

WHO = World health organization

WM = White matter

WM-C(t) = Concentration time curve of WM

WM-Type-1 = Type-1 normalization with respect to WM

WM-Type-2 = Type-2 normalization with respect to WM

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