PhD Thesis:
Computer Assisted Diagnosis of Brain Tumors based on Statistical Methods and Pattern Recognition Techniques

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“Αν είδα μακρύτερα, είναι επειδή στάθηκα στους ώμους γιγάντων”
(Ισαάκ Νεύτων, 1676)
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# TABLE OF CONTENTS

**CHAPTER 1 - Preface** ......................................................................................................................... 1
  1.1 Abstract .......................................................................................................................................... 1
  1.2 Aim, novelties and contributions of the thesis ............................................................................... 2
  1.3 Organization of the thesis ............................................................................................................. 4
  1.4 Research funding ............................................................................................................................ 5

**CHAPTER 2 - Brain tumors** ............................................................................................................. 7
  2.1 Brain tumors .................................................................................................................................. 8
    2.1.1 General ...................................................................................................................................... 8
    2.1.2 Causes ...................................................................................................................................... 8
    2.1.3 Symptoms ................................................................................................................................. 8
    2.1.4 Types ....................................................................................................................................... 9
  2.2 Gliomas .......................................................................................................................................... 10
    2.2.1 Classification ............................................................................................................................ 10
      2.2.1.1 By type of cell .................................................................................................................... 10
      2.2.1.2 By grade ............................................................................................................................ 11
      2.2.1.2 By location .......................................................................................................................... 11
    2.2.2 Causes ...................................................................................................................................... 11
    2.2.3 Symptoms ................................................................................................................................ 11
    2.2.4 Pathology .................................................................................................................................. 12
    2.2.5 Diagnosis ................................................................................................................................. 12
    2.2.6 Treatment ................................................................................................................................. 13
  2.3 Meningiomas .................................................................................................................................. 14
    2.3.1 Causes ...................................................................................................................................... 14
    2.3.2 Symptoms ................................................................................................................................ 14
    2.3.3 Pathology .................................................................................................................................. 14
    2.3.4 Diagnosis ................................................................................................................................. 15
    2.3.5 Treatment ................................................................................................................................. 15
  2.4 Brain metastasis ............................................................................................................................. 16
    2.4.1 Sources of brain metastases ...................................................................................................... 17
    2.4.2 Symptoms ................................................................................................................................ 17
    2.4.3 Diagnosis .................................................................................................................................. 17
    2.4.4 Treatment ................................................................................................................................ 17

**CHAPTER 3 - Nuclear magnetic resonance imaging and spectroscopy** ........................................... 19
  3.1 Basic physics and techniques ........................................................................................................... 20
  3.2 Data analysis ................................................................................................................................... 24
CHAPTER 7 - Combining MR textural and spectroscopic features to discriminate between meningioma and solitary metastasis

7.1 Introduction

7.2 Review of the literature

7.3 Brain tumor characterization employing 3D MR textural features and MR spectroscopic features

7.3.1 Clinical material

7.3.2 MRI and MRS feature extraction

7.3.3 Design of the classification scheme

7.3.4 Results

7.3.5 Discussion and contribution

7.3.6 Summary and conclusions

CHAPTER 8 - Summary, important conclusions and future perspectives

8.1 Summary and important conclusions

8.2 Future perspectives

REFERENCES

APPENDIX I - List of publications as result of the research work performed for the purposes of the present thesis

APPENDIX II – Abbreviations

APPENDIX III - List of figures

APPENDIX IV - List of tables
ΠΕΡΙΛΗΨΗ ΣΤΑ ΕΛΛΗΝΙΚΑ

ΕΙΣΑΓΩΓΗ

Η εισαγωγή της Μαγνητικής Τομογραφίας (ΜΤ) στην κλινική πρακτική και η συμπληρωματική πληροφορία που δίνει η Φασματοσκοπία Μαγνητικού Συντονισμού (ΦΜΣ) συνιστά μια από τις πιο σημαντικές εξελίξεις στη διάγνωση ασθενών με καρκίνο εγκεφάλου [1]. Παρ’ όλα αυτά, οι εικόνες ΜΤ είναι συχνά δύσκολο να ερμηνευθούν από τους ειδικούς λόγω α/ της υποκειμενικότητας και περιορισμένης εμπειρίας του παρατηρητή στην εκτίμηση εικόνων που παράγει η σχετικά νέα αυτή τεχνολογία, β/ των ποικίλων κλινικών χαρακτηριστικών των όγκων (π.χ. τύπος, διαβάθμιση κακοήθειας κλπ.) και γ/ της ιδιαιτερότητας των όγκων στην αντίθεση που παρουσιάζουν με τον περιβάλλοντα ιστό.

Μόνο λιγοστές μελέτες έχουν διεξαχθεί για να χαρακτηρίσουν ιστούς εγκεφάλου μέσω της ανάλυσης ποσοτικών χαρακτηριστικών από εικόνες εγκεφάλου ΜΤ [3, 4]. Ενώ έχει ήδη τουνιστεί η αναγκαιότητα συσχετισμού της διαγνωστικής και προγνωστικής πληροφορίας που προέρχεται από εικόνες ΜΤ και σήματα ΦΜΣ στη διεθνή βιβλιογραφία [5], υπάρχουν λιγοστές αναλύσεις αναφορές για τον σχεδιασμό και υλοποίηση συστήματος Η/Υ αυτόματης διάγνωσης όγκων εγκεφάλου κάνοντας συνδυασμό ποσοτικής πληροφορίας προερχόμενης από εικόνες ΜΤ και σήματα ΦΜΣ [6, 7].

ΣΤΟΧΟΙ ΤΗΣ ΠΑΡΟΥΣΑΣ ΔΙΑΤΡΙΒΗΣ

Οι στόχοι της παρούσας διατριβής εστιάζονται στα παρακάτω:

➢ στη μελέτη, ανάπτυξη και η υλοποίηση υπολογιστικού συστήματος αυτόματης ταξινόμησης όγκων του εγκεφάλου μέσω της ποσοτικής ανάλυσης εικόνων ΜΤ το οποίο θα βελτιώνει την ακρίβεια ταξινόμησης σε σχέση με ήδη υπάρχοντα συστήματα [4, 8, 9], όπως αυτά περιγράφονται στην διεθνή βιβλιογραφία μεταξύ πρωτογενών και δευτερογενών όγκων εγκεφάλου καθώς και μεταξύ γλουτών και μηνιγγιών με την χρήση δεντρου εραρχικής απόφασης δύο επιπέδων. Επιπλέον, στην ανάδειξη πως η χρήση ενός μη- γραμμικού πολυωνυμικού μετασχηματισμού ελάχιστων τετραγώνων των
χαρακτηριστικών υφής έχει ως αποτέλεσμα την βελτίωση της ακρίβειας ταξινόμησης του ταξινομητή πιθανοκρατικού νευρωνικού δικτύου.

- στην επέκταση και την βελτίωση του συστήματος αυτόματης ταξινόμησης όγκων του εγκεφάλου χρησιμοποιώντας α/ ογκομετρικές ποσοτικές παραμέτρους εικόνων ΜΤ, β/ ταξινομητή μηχανών διανυσμάτων στήριξης μαζί με τη μεθοδολογία συνάθροισης αποτελεσμάτων ταξινόμησης από τυχαιοποιημένα δείγματα κατηγοριών δημιουργημένων με επαναδειγματοληψία για κάθε κόμβο δεύτερου επίπεδου υποθεσίας από ρανθοποιημένη διαχείριση μεταξύ πρωτογενών και δευτερογενών όγκων εγκεφάλου και στο δεύτερο και μεταξύ γλοιωμάτων και μηνιγγιώμάτων και γ/ έναν τροποποιημένο πυρήνα ακτινικής συνάρτησης βάσης για τον ταξινομητή μηχανών διανυσμάτων στήριξης ο οποίος περιλαμβάνει την τεχνική μη-γραμμικού πολυωνυμικού μετασχηματισμού ελάχιστων τετραγώνων με στόχο την βελτίωση της ακρίβειας ταξινόμησης.

- στην περαιτέρω επέκταση και την βελτίωση του συστήματος αυτόματης ταξινόμησης μεταξύ μηνιγγιώματων και μονήρων μεταστάσεων.

ΠΕΙΡΑΜΑΤΙΚΟ ΜΕΡΟΣ

Μελέτη, ανάπτυξη και η υλοποίηση υπολογιστικού συστήματος αυτόματης ταξινόμησης όγκων του εγκεφάλου μέσω της ποσοτικής ανάλυσης εικόνων ΜΤ.

Για την εκπαίδευση και την αξιολόγηση του υπολογιστικού συστήματος αυτόματης ταξινόμησης όγκων του εγκεφάλου χρησιμοποιήθηκαν 67 εγκάρσιες εικόνες ΜΤ (21 μεταστάσεις, 19 μηνιγγιώματα και 27 γλοιώματα), οι οποίες λήφθηκαν με ακολούθια T1 – S.E. (TR = 400 – 500 ms, TE = 7 – 15 ms) μετά την χορήγηση σκιαγραφικού παράγοντα (γαδολίνιο). Σε συνεργασία με έμπειρο
ακτινολόγο, εξήχθηκαν από τις εικόνες περιοχές ενδιαφέροντος από τα κέντρα των όγκων. Έπειτα, από τις περιοχές ενδιαφέροντος υπολογίσθηκαν συνολικά 36 ποσοτικά χαρακτηριστικά υφής, τα οποία περιλάμβαναν 4 στατιστικά χαρακτηριστικά πρώτου βαθμού, 22 χαρακτηριστικά που παρήχθησαν από τους πίνακες χωρικής συν-εμφάνισης των τόνων του γκρι [10] και 10 χαρακτηριστικά που παρήχθησαν από τους πίνακες μήκους διαδρομής των τόνων του γκρι [11]. Το πλήθος των χαρακτηριστικών υφής μειώθηκε σε δέκα (10) με την χρήση της μη παραμετρικής στατιστικής δοκιμασίας Wilcoxon. Κατά συνέπεια, μόνο χαρακτηριστικά με υψηλή διακριτική ικανότητα (p<0.001) μεταξύ των προτύπων των κατηγοριών των όγκων εγκεφάλου επιλέχθησαν για να εισαχθούν στο σύστημα ταξινόμησης.

Ο ταξινομητής που χρησιμοποιήθηκε αποτελεί μια τροποποίηση του ταξινομητή πιθανοκρατικού νευρωνικού δικτύου [12]. Συγκεκριμένα, για τον καλύτερο διαχωρισμό των τύπων των όγκων εγκεφάλου, στα δεδομένα εισόδου εφαρμόστηκε ένας μη-γραμμικός πολυωνυμικός μετασχηματισμός ελάχιστων τετραγώνων από το χώρο των χαρακτηριστικών στο χώρο των κατηγοριών, με πλήθος διαστάσεων ίσο με τον αριθμό των προς ταξινόμηση κατηγοριών. Στο πρώτο επίπεδο του δένδρου απόφασης, στα διανύσματα χαρακτηριστικών εισόδου στον ταξινομητή εφαρμόστηκε μετασχηματισμός ελάχιστων τετραγώνων δευτέρου βαθμού, ενώ στο δεύτερο επίπεδο εφαρμόστηκε μετασχηματισμός ελάχιστων τετραγώνων τρίτου βαθμού.

Η αξιολόγηση της απόδοσης του συστήματος πραγματοποιήθηκε με εφαρμογή της μεθόδου διαδοχικής παράλειψης ενός προτύπου [13], ώστε να διεξαχθεί εκτίμηση από τα δεδομένα εκπαίδευσης και να θεωρούνται από το σύστημα ως άγνωστα. Για την επιλογή του καλύτερου συνδυασμού χαρακτηριστικών χρησιμοποιήθηκε η μέθοδος της εξαντλητικής αναζήτησης όλων των δυνατών συνδυασμών των στατιστικά σημαντικών χαρακτηριστικών [13].

Στο πρώτο επίπεδο του ειραχικού δένδρου, το ποσοστό ολικής ακρίβειας (το πηλίκο των ορθά ταξινομημένων προτύπων προς το σύνολο των προτύπων κατά τη διάρκεια της διαδικασίας αξιολόγησης) ταξινόμησης των μεταστατικών και των πρωτογενών όγκων εγκεφάλου ήταν 94.03%, χρησιμοποιώντας 3 χαρακτηριστικά υφής (μέση τιμή, εντροπία, διαφορική εντροπία).

Στο δεύτερο επίπεδο του ειραχικού δένδρου, το ποσοστό ολικής ακρίβειας ταξινόμησης των γλοιωμάτων και μηνιγγιωμάτων ήταν 100%, χρησιμοποιώντας 3
χαρακτηριστικά υψής (μέση τιμή, δεύτερη γωνιακή ροπή, αντίστροφη διαφορική ροπή).

Για λόγους σύγκρισης, για την ταξινόμηση των δεδομένων χρησιμοποιήθηκε και πιθανοκρατικό νευρωνικό δίκτυο χωρίς μετασχηματισμό των δεδομένων πριν την είσοδό τους σε αυτό. Στο πρώτο επίπεδο του ειραρχικού δένδρου, το ποσοστό ολικής ακρίβειας ήταν 89.55%, ενώ στο δεύτερο 97.83%.

Επέκταση και την βελτίωση του συστήματος αυτόματης ταξινόμησης όγκων του εγκεφάλου χρησιμοποιώντας ογκομετρικές ποσοτικές παραμέτρους εικόνων ΜΤ.

Από τα ίδια κλινικά δεδομένα, σε συνεργασία με έμπειρο ακτινολόγο, εξήχθηκαν από τις εικόνες χώροι ενδιαφέροντος με την χρήση του λογισμικού που αναπτύχθηκε για αυτόν τον σκοπό. Επειτα, από τους τρισδιάστατους χώρους ενδιαφέροντος υπολογίσθηκαν συνολικά 36 ογκομετρικά ποσοτικά χαρακτηριστικά υψής, τα οποία περιλάμβαναν 4 στατιστικά χαρακτηριστικά πρώτου βαθμού, 22 χαρακτηριστικά που παρήχθησαν από τους πίνακες χωρικής συν-εμφάνισης των τόνων του γκρι και 10 χαρακτηριστικά που παρήχθησαν από τους πίνακες μήκους διαδρομής των τόνων του γκρι [10, 11, 14, 15].

Στη συνέχεια αναπτύχθηκε και υλοποιήθηκε λογισμικό ταξινόμησης, που αποτελεί μια τροποποίηση του ταξινομητή μηχανών διανυσμάτων στήριξης [16]. Συγκεκριμένα, για τον καλύτερο διαχωρισμό των τύπων των όγκων εγκεφάλου, στα δεδομένα εισόδου εφαρμόστηκε ένας μη-γραμμικός πολυώνυμος μετασχηματισμός ελάχιστων τετραγώνων από το χώρο των χαρακτηριστικών στο χώρο των κατηγοριών, με πλήθος διαστάσεων 4 στον αριθμό των προς ταξινόμηση κατηγοριών [17].

Το σχήμα ταξινόμησης που χρησιμοποιήθηκε αποτελείται από μία ομάδα τριών ταξινομητών μηχανών διανυσμάτων στήριξης. Ο κάθε ταξινομητής της ομάδας εκπαιδεύτηκε με μικρές παραλλαγές των δεδομένων εκπαίδευσης, συμφωνά με την μεθοδολογία συνάθροισης αποτελεσμάτων ταξινόμησης από τυχαιοποιημένα δείγματα κατηγοριών δημιουργημένων με επαναδειγματοληψία [18] με σκοπό την αύξηση του ποσοστού της ολικής ακρίβειας ταξινόμησης των όγκων εγκεφάλου.

Η αξιολόγηση της απόδοσης του συστήματος πραγματοποιήθηκε με εφαρμογή της μεθόδου εξωτερικής διεξαγωγής, ώστε τα δεδομένα εκτίμησης να είναι άγνωστα στο σύστημα ταξινόμησης σε σχέση με τα δεδομένα εκπαίδευσης. Σύμφωνα
με την ανωτέρω τεχνική, το σύνολο των δεδομένων χωρίσθηκε σε δύο ομάδες. Τάς των δεδομένων χρησιμοποιήθηκαν για τον βέλτιστο σχεδιασμό του συστήματος ταξινόμησης, ενώ το υπόλοιπο ¼ για την αξιο λόγηση του συστήματος. Η διαδικασία του βέλτιστου σχεδιασμού του συστήματος περιλαμβάνει την εύρεση του καλύτερου συνδυασμού ογκομετρικών χαρακτηριστικών, η οποία αξιολογήθηκε με εφαρμογή της μεθόδου διαδοχικής παράλειψης ενός προτύπου. Για την επιλογή του καλύτερου συνδυασμού χαρακτηριστικών χρησιμοποιήθηκε η μέθοδος της εξαντλητικής αναζήτησης όλων των μέχρι ανά 5 δυνατών συνδυασμών των χαρακτηριστικών υφής. Ως βέλτιστος συνδυασμός χαρακτηριστικών θεωρήθηκε εκείνος ο οποίος έδωσε τη μέγιστη ολική ακρίβεια ταξινόμησης σύμφωνα με τη μέθοδο διαδοχικής παράλειψης ενός προτύπου και με το ελάχιστο πλήθος χαρακτηριστικών. Στη συνέχεια, από τα δεδομένα σχεδιασμού δημιουργήθηκαν τρεις ομάδες κατηγοριών με επαναδειγματοληψία, χρησιμοποιώντας μόνο το βέλτιστο συνδυασμό χαρακτηριστικών, τα οποία και εκπαίδευσαν τρεις ξεχωριστούς ταξινομητές. Αυτή η εκπαίδευμενή ομάδα απευθύνθηκε για να ταξινομήσει τα δεδομένα αξιολόγησης. Η έξοδος του κάθε ταξινομητή χρησιμοποιήθηκε για την εξαγωγή συλλογικής απόφασης πλειοψηφίας. Η παραπάνω διαδικασία εξωτερικής διεξαγωγής επαναλήφθηκε 10 φορές και υπολογίστηκε η μέση τιμή και η τυπική απόκλιση της ολικής ακρίβειας του συστήματος ταξινόμησης.

Στο πρώτο επίπεδο του ιεραρχικού δένδρου, το μέσο ποσοστό ολικής ακρίβειας (το πηλίκο των ορθά ταξινομημένων προτύπων προς το σύνολο των προτύπων κατά τη διάρκεια της διαδικασίας αξιολόγησης) ταξινόμησης των μεταστατικών και των πρωτογενών ογκών εγκεφάλου ήταν 88.18% χρησιμοποιώντας 5 ογκομετρικά χαρακτηριστικά υφής. Στο δεύτερο επίπεδο του ιεραρχικού δένδρου, το μέσο ποσοστό ολικής ακρίβειας ταξινόμησης των γλοιωμάτων και μηνιγγιωμάτων ήταν 97.33%, χρησιμοποιώντας επίσης 5 ογκομετρικά χαρακτηριστικά υφής.

Περαιτέρω επέκταση και την βελτίωση του συστήματος αυτόματης ταξινόμησης με την εισαγωγή χαρακτηριστικών προερχόμενων από σήματα ΦΜΣ.

Για την διερεύνηση της ικανότητας των χαρακτηριστικών ΦΜΣ στην περαιτέρω βελτίωση της ακρίβειας του συστήματος αυτόματης ταξινόμησης όγκων εγκεφάλου, προσεγγίσθηκε το ιατρικό πρόβλημα του διαχωρισμού μονήρων μεταστάσεων που προσφύγουν στην μήνιγγα από τα μηνιγγιώματα.
Οι μονήρεις μεταστάσεις είναι η δεύτερη συχνότερη αλλοίωση που συναντάται στις μήνιγγες των οποίων η ακτινολογική εικόνα είναι σχετικά δύσκολο να διαχωριστεί από τα μηνιγγιώματα [19]. Επιπλέον, ορισμένες μορφές αυτών των μεταστάσεων εποπτικών ακτινολογικά χαρακτηριστικά τα οποία παραπέμπουν σε πρωτογενή όγκο [20]. Στην βιβλιογραφία υπάρχουν αρκετές αναφορές οι οποίες υποδεικνύουν το πρόβλημα της διαφοροδιάγνωσης μεταξύ των δύο αυτών όγκων [19, 21-25].

Η ΦΜΣ καθορίζει την παρουσία συγκεκριμένων ενώσεων επιλεκτικά, χωρίς επέμβαση. Αυτές καλύνται μεταβολίτες. Στον υγιή ιστό τα προϊόντα του μεταβολισμού που ανυχρεούνται μέσω της φασματοσκοπίας υπάρχουν σε συγκεκριμένες ενώσεις που κατακτητρίζουν συγκεκριμένους ιστούς. Το άγχος, οι λειτουργικές διαταραχές ή οι ασθένειες μπορεί να προκαλέσουν μεταβολές στις συγκεκριμένες ενώσεις. Η φασματοσκοπία μαγνητικού συντονισμού δίνει την δυνατότητα να παρατηρηθούν αυτές οι αλλαγές [26]. Οι μεταβολίτες που χρησιμοποιήθηκαν στην παρούσα διατριβή είναι οι εξής: α/ N-Ακετυλασπαρτικό οξύ (NAA). Ένα χαρακτηριστικό αυτού του μεταβολίτη είναι πως σε όγκους παρατηρείται συχνά μείωση του σήματός του. β/ Κρεατίνη (CR). Της οποίας στον εγκεφαλικό ιστό η ένταση του σήματος παραμένει σταθερή ακόμη και κατά την διάρκεια παθολογικών αλλαγών. γ/ Χωλίνη (Cho) Χαρακτηριστικό αυτού του μεταβολίτη είναι πως αυξημένες συγκεκριμένες ενώσεις των νεοπλασιών νεοπλασματικού υποδεικνύουν παθολογικές αλλαγές [27, 28]. Φυσικά υπάρχουν και άλλοι μεταβολίτες που είναι εξίσου σημαντικοί αλλά αυτοί οι τρεις είναι οι πιο διαδεδομένοι και χρησιμοποιούνται στην καθημερινή κλινική πράξη. Οι σχέσεις που παρουσιάζουν μεταξύ τους είναι πολύ σημαντικές για την αξιολόγηση των χημικών ιδιοτήτων των νεοπλασιών του εγκεφάλου, για το αυτό και συνήθως συναντούνται στην διεθνή βιβλιογραφία να συμμετέχουν στα κλάσματα [27, 28]. Στην παρούσα διατριβή χρησιμοποιήθηκαν ως χαρακτηριστικά φασματοσκοπίας τα κλάσματα Cho/NAA, Cho/CR και NAA/CR.

Για την εκπαίδευση και την αξιολόγηση του υπολογιστικού συστήματος αυτόματης ταξινόμησης όγκων του εγκεφάλου χρησιμοποιήθηκαν 40 σειρές MT (21 μεταστάσεις, 19 μηνιγγιώματα). Από τα κλινικά δεδομένα, σε συνεργασία με έμπειρο ακτινολόγο, εξήχυθηκαν από τις εικόνες χώροι ενδιαφέροντος με την χρήση του λογισμικού που αναπτύχθηκε για αυτόν τον σκοπό. Έπειτα, από τους τρισδιάστατους χώρους ενδιαφέροντος υπολογίσθηκαν συνολικά 36 ογκομετρικά ποσοτικά χαρακτηριστικά υψής, τα οποία περιλάμβαναν 4 στατιστικά χαρακτηριστικά πρώτου
βαθμού, 22 χαρακτηριστικά που παρήχθησαν από τους πίνακες χωρικής συνεμφάνισης των τόνων του γκρι και 10 χαρακτηριστικά που παρήχθησαν από τους πίνακες μήκους διαδρομής των τόνων του γκρι [10, 11, 14, 15]. Σε αυτό το σετ χαρακτηριστικών προστέθηκαν και τα 3 χαρακτηριστικά που εξήχθησαν από τα δεδομένα της ΦΜΣ.

Στη συνέχεια αναπτύχθηκε και υλοποίηθηκε λογισμικό ταξινόμησης, με βάση τον ταξινομητή μηχανών διανυσμάτων στήριξης [16]. Η αξιολόγηση της απόδοσης του συστήματος πραγματοποιήθηκε με εφαρμογή της μεθόδου εξωτερικής διεξαγρίας, ώστε τα δεδομένα εκτίμησης να είναι άγνωστα στο σύστημα ταξινόμησης σε σχέση με τα δεδομένα εκπαίδευσης [29].

Το μέσο ποσοστό ολικής ακρίβειας ταξινόμησης των μεταστατικών όγκων εγκεφάλου και των μηνιγγιωμάτων ήταν 92.15% χρησιμοποιώντας 4 ογκομετρικά χαρακτηριστικά υφής και 1 χαρακτηριστικό φασματοσκοπίας.

ΣΥΜΠΕΡΑΣΜΑΤΑ

Τέλος κάνοντας μια περίληψη, η παρούσα διατριβή διαπραγματεύεται τον σχεδιασμό, ανάπτυξη και υλοποίηση μεθόδων και αλγορίθμων για την επεξεργασία και ανάλυση ιατρικών εικόνων, επικεντρώνοντας ειδικότερα στην εφαρμογή των μεθόδων αυτών για την διάγνωση του τύπου των όγκων εγκεφάλου. Τα πιο βασικά συμπεράσματα που απορρέουν από την παρούσα διατριβή είναι τα ακόλουθα: α/ Το σύστημα ταξινόμησης των τύπων των όγκων εγκεφάλου που σχεδιάστηκε και υλοποιήθηκε αυξάνει τα ποσοστά ορθής ταξινόμησης σε σχέση με τα υπάρχοντα. β/ Η κωδικοποίηση των ιδιοτήτων της υφής που προέρχεται από τον σύνολο του όγκου παρέχει επιπρόσθετη πληροφορία στο σύστημα ταξινόμησης αυξάνοντας τα ποσοστά επιτυχούς διαχωρισμού. γ/ Τα χαρακτηριστικά φασματοσκοπίας μαγνητικού συντονισμού αποτελούν επιπρόσθετη αξία στο χαρακτηρισμό του τύπου των όγκων εγκεφάλου μιας και οδήγησαν στην αύξηση του ποσοστού επιτυχούς διαχωρισμού του συστήματος ταξινόμησης.

ΜΕΛΛΟΝΤΙΚΗ ΔΟΥΛΕΙΑ

Θα ήταν εξαιρετικά ενδιαφέρον να γίνει περαιτέρω μελέτη του συνδυασμού των χαρακτηριστικών υφής και φασματοσκοπίας και σε άλλους τύπους όγκων μιας.
και από τα αποτελέσματά μας φάνηκε η σπουδαιότητα της επιπρόσθετης πληροφορίας που τα χαρακτηριστικά φασματοσκοπίας εισαγάγουν. Μια ακόμη ενδιαφέρουσα ιδέα θα ήταν η χρήση χαρακτηριστικών που μπορούν να εξαχθούν από άλλα ακεικονιστικά συστήματα, όπως η αξονική τομογραφία, καθώς και η εισαγωγή ποιμικών χαρακτηριστικών που απορρέουν από την κλινική εικόνα του ασθενούς και ο συνδυασμός τους με τα ποσοτικά που χρησιμοποιήθηκαν στην παρούσα διατριβή.

Τέλος, ο απώτερος σκοπός αυτής της έρευνας είναι η εφαρμογή του συστήματος σε πραγματικό κλινικό περιβάλλον. Για να επιτευχθεί αυτός ο σκοπός όλες οι τεχνικές που αναπτύχθηκαν και χρησιμοποιήθηκαν πρέπει να ενσωματωθούν σε ένα εύχρηστο περιβάλλον το οποίο θα πρέπει να υποστεί εκτεταμένες κλινικές δοκιμές έτσι ώστε να διασφαλιστεί η σωστή λειτουργία του.
CHAPTER 1 - Preface

1.1 Abstract

The process of brain tumor characterization requires a rather intricate assessment of the various Magnetic Resonance (MR) image and spectroscopic features and is typically performed by experienced radiologists. Despite the inherently subjective nature of many of the decisions associated with this process, an expert radiologist is able to perform this task with a significant degree of precision and accuracy. However, in the effort to deliver more effective treatment, clinicians are continuously seeking for greater accuracy in the pathological characterization of brain tissues.

The aim of the present thesis was to design, implement, and evaluate a software classification system for discriminating between different brain tumor types on Magnetic Resonance Imaging (MRI), employing textural and spectroscopic features. The clinical material consisted of sixty seven T1-weighted post-contrast MR brain images (21 metastases, 19 meningiomas, and 27 gliomas), obtained from patients with verified and untreated intracranial tumors. Thirty-six 2-dimensional textural features (2D), from the image histogram and the co-occurrence and run-length matrices, were extracted from each one of 67 MR-images. Similarly, an equal number of 3-dimensional textural features (3D) were also calculated in the attempt to maximize classification performances. Finally, MR-spectroscopy features were also incorporated for improving classification accuracies.

Classification methods employed included i/ a modified Probabilistic Neural Network (PNN) and Support Vector Machines (SVM) algorithms, incorporating a non-linear Least Squares Features Transformation (LSFT) into the classifiers and ii/ an ensemble classification scheme employing the LSFT-SVM classifier. The LSFT improved classifiers’ performances, increased class separability, and resulted in dimensionality reduction. For evaluating the performance of the designed classification schemes, evaluations were performed by means of the external cross validation process, which is considered indicative of the generalization performance of the designed classification system to ‘unseen’ cases.
It was found that the LSFT features transformation enhanced the performance of the PNN and SVM algorithms, achieving classification accuracies of 73.48% in distinguishing metastatic from primary tumors and 88.67% in discriminating gliomas from meningiomas. When volumetric 3-dimensional features were employed, these results improved to 88.18% for discriminating between metastatic and primary tumors and 97.33% for distinguishing gliomas from meningiomas. The textural features employed in the design of the optimum classification scheme were associated primarily with image texture homogeneity. Finally, when MR-spectroscopy features were also incorporated, classification accuracy was boosted up from 95% in discriminating meningiomas from metastasis to 100%.

The MR-image features that participated in the optimum feature vector were related to the degree of homogeneity, the amount of randomness and the dispersion of the gray-tone intensity values within the texture of the tumor. These textural characteristics are related to textural parameters that physicians employ in diagnosis and they were proportional to the textural imprint of brain tumors, i.e. gliomas have heterogeneous texture while meningiomas appear to be homogeneous in MR imaging.

The MR-spectroscopy feature that participated in the optimum feature vector was the Choline (Cho) / N-Acetyl Aspartate (NAA) metabolite integral ratio. It was found that both meningiomas and metastases are characterized from low concentrations of NAA while meningiomas exhibit higher concentrations of Cho than metastases, which could be attributed to increased synthesis of tumor cell membranes.

Finally, the proposed system might be of value as an assisting tool for brain tumor characterization on volumetric MRI series.

1.2 Aim, novelties and contributions of the thesis

This thesis has been carried out in search of new computerized methods to improve computer-assisted brain tumor type discrimination. The aims of the present thesis were:

- to design, implement, and evaluate a pattern recognition system, which, by analyzing routinely taken T1 post-contrast magnetic resonance images, would improve brain tumor classification accuracy between metastatic and primary brain tumors and between gliomas and meningiomas, employing a two-level
hierarchical decision tree. Additionally, to demonstrate that by employing
textural features from magnetic resonance images and by conditioning those
features by means of a non-linear least squares features transformation, the
performance of the probabilistic neural network classification accuracy was
boosted significantly.

- to improve the accuracy of the designed brain tumor classification system i/ by
designing, implementing, and evaluating a pattern recognition system
employing 3-dimensional textural features for improving brain tumor
classification accuracies when analyzing routinely taken T1 post-contrast
magnetic resonance image series, ii/ by utilizing a support vector machines-
based ensemble classification scheme along with bootstrap aggregation
(bagging) at each node of a two-level hierarchical decision tree, for
discriminating between metastatic and primary brain tumors at the 1st level
and between gliomas (malignant tumors) and meningiomas (benign tumors) at
the 2nd level and iii/ by introducing a modified radial basis function kernel for
the support vector machines classifier that incorporated the least squares
features transformation technique to improve classification accuracy.

- to further extend and improve the designed classification system on brain
tumor characterization by additionally incorporating spectroscopic features to
investigate whether the combination of post-contrast magnetic resonance
image and spectroscopic features might improve discrimination between
meningiomas and solitary metastases.

The first contribution of the current thesis is the development of a computer-
assisted brain tumor type classification system, for improving the accuracy, with
regards to existing similar systems, of discriminating between metastatic and primary
brain tumors and between gliomas and meningiomas [APPENDIX I: PUBLICATIONS 1, 2].

The second contribution of this research is i/ the introduction of a new radial
basis function kernel to the support vector machines classifier and ii/ the incorporation
of the least squares feature transformation technique for improving classification
accuracy. This transformation was also applied in the probabilistic neural network classifier also resulting in the classifier’s discrimination accuracy enhancement [APPENDIX I: PUBLICATIONS 1, 2, 3].

Finally, the third contribution resides in the fusion of features derived from magnetic resonance imaging and spectroscopy in a unified computer-assisted brain tumor type classification system that further improved the discrimination accuracy between meningiomas and solitary metastases [APPENDIX I: PUBLICATION 4].

1.3 Organization of the thesis

The thesis is divided into two main parts. Part I comprises chapters 2-4 and deals with the general principles of computer-assisted brain tumor type discrimination systems that employ data deriving from Nuclear Magnetic Resonance (NMR). Part II consists of chapters 5-7 and presents detailed analysis and results of the methods applied in automated type discrimination of brain tumors.

Chapter 2 includes a literature review concerning the etiology, formation, and confrontation of brain tumors, with emphasis given to gliomas, meningiomas and metastasis. The fundamental parts (instrumentation and pattern recognition system) in computer-assisted brain tumor type discrimination are examined in Chapters 3 and 4. More specifically, Chapter 3 presents a brief introduction in the basic principles of NMR focusing in the application of Magnetic Resonance Imaging (MRI) and Magnetic Resonance Spectroscopy (MRS). In Chapter 4 the essential parts of pattern recognition systems are explained, with more emphasis given to classification algorithms, since this thesis focuses on issues of pattern recognition.

Chapter 5 presents the design, implementation and evaluation of a pattern recognition system, which aims towards improving brain tumor classification accuracy by analyzing routinely taken T1 post-contrast MR images. Employing a two-level hierarchical decision tree, distinction between metastatic and primary brain tumors and between gliomas and meningiomas were performed at the first and second level of the decision tree, respectively. Additionally this chapter demonstrates that by conditioning the 2D features generated from the MR images by means of a non-linear least squares features transformation, the performance of the PNN classifier was boosted significantly. Chapter 6 presents the design, implementation and evaluation of a pattern recognition system employing 3D textural features for improving brain
tumor classification accuracies when analyzing routinely taken T1 post-contrast MR-image series. Employing an SVM-based ensemble classification scheme along with bootstrap aggregation at each node of a two-level hierarchical decision tree, discrimination between metastatic and primary brain tumors at the first level and between gliomas (malignant tumors) and meningiomas (benign tumors) at the second level was performed. Additionally this chapter demonstrates a modified RBF kernel for the SVM classifier that incorporated the LSFT technique to improve classification accuracy. Chapter 7 presents the design, implementation and evaluation of a pattern recognition system that combines MR 3D textural and spectroscopic features in order to improve brain tumor classification accuracies. Employing an SVM-based classification scheme, discrimination between solitary metastatic tumors and meningiomas was performed.

Finally, Chapter 8 summarizes important conclusions and discusses future perspectives of this thesis. In Appendix I the list of publications as result of the research work performed for the purposes of the present thesis can be found. In Appendixes II, III, IV and V the Abbreviations, List of Figures and List of Tables of this manuscript are listed respectively.

1.4 Research funding

The present research was founded by the University of Patras Research Committee under the basic research program ‘K. Karatheodori’, project title ‘Computer Assisted Diagnosis of Brain Tumors based on Statistical Methods and Pattern Recognition Techniques’.
PART I
BASIC THEORY
CHAPTER 2 - Brain tumors

This chapter includes a review of the literature concerning the etiology, creation, and confrontation of brain tumors, with emphasis given to meningiomas, gliomas and metastasis.
2.1 Brain tumors

2.1.1 General

As stated in a recent statistical report published by the United States’ Central Brain Tumor Registry (CBTRUS), approximately 39,550 patients were newly diagnosed with primary benign and primary malignant brain tumors in 2002 [30-32]. In addition, in the year 2000 in the United States alone, more than 81,000 people were living with a primary malignant brain tumor while 267,000 were living with a primary benign brain tumor. It should also be noted that according to the same report, the incidence rate of primary brain tumors, whether benign or malignant, is 14 per 100,000, while median age at diagnosis is 57 years [32].

In contrast to primary brain tumors, secondary or metastatic brain tumors [30], originate in tissues outside the central nervous system and they constitute a common complication of systemic cancer. Brain metastases not only outnumber primary brain tumors, but they are currently considered as the most frequent intracranial tumors. Other studies indicate that brain metastases occur in 20% to 40% of all cancer patients, and that more than 100,000 individuals per year will develop brain metastases [32].

2.1.2 Causes

Besides an identified association with exposure to vinyl chloride, there are no known chemical or environmental agents that lead to the development of brain tumors [33]. Although there has been some concern that electromagnetic fields might provoke some glial tumors, there is no evidence to support this notion [34]. A predisposition to developing a brain tumor could be induced by a number of inherited, genetic syndromes including von Hippel-Lindau syndrome, neurofibromatosis, and tuberous sclerosis [35].

2.1.3 Symptoms

The initial symptom of a brain tumor of any type can be a headache accompanied by vomiting. Headaches occur because malignant masses tend to
significantly increase pressure within the brain, causing additional symptoms such as blurred, double or even lost vision. Other symptoms include seizures, weakness or numbness of a side or part of the body, or changes in mood, thinking or general state of well being [33].

Both location and size of the brain tumor affect and define the symptoms caused [36]. Frontal lobe: Frontal lobe brain tumors usually cause seizures, impaired judgment and memory, changes in personality or mental capacity, and paralysis affecting one side of the body. Parietal lobe: When a tumor is located in the parietal lobe most common symptoms include loss of the ability to write, speech disturbances, in case the tumor is in the left hemisphere, and seizures. Occipital lobe: Due to the fact that the occipital lobe is involved with vision, blindness in one direction and seizures are common symptoms in case a tumor is located there. Temporal lobe: In most cases tumors that occur in the temporal lobe cause no symptoms at all and only in certain occasions they create speech disturbances or seizures. Ependyma: The earliest symptom is hydrocephaly (dilation, or enlargement, of the ventricles and accumulation of cerebrospinal fluid). Meninges: It refers to a case that a tumor grows in the meninges. The symptoms are usually caused by compression of the area of the brain being pressured. Secondary tumors: Metastatic brain tumors cause swelling (edema) that, in turn, causes headache, vomiting, and nausea [36].

2.1.4 Types

Brain tumors are categorized into two main groups: primary brain tumors that originate in the brain and secondary (metastatic) that stem from cancerous cells that have migrated from their original location and have entered into the central nervous system via the blood-brain barrier.

Primary brain tumors are made up of either neuronal (brain cells) or neuroepithelial cells (support cells) and are characterized as benign (non-cancerous) or malignant (cancerous) [37].

The main characteristic of benign tumors is that they comprise slow-growing cells in formations with well defined boundaries. Due to the fact that these kinds of cells resemble normal cells when observed under the microscope, diagnosis can be an intricate task. It must be noted that benign tumors constitute approximately 40% of all primary brain tumors. Therapy is effective when the tumor is not situated at a vital
area and thus surgical removal can be applied. An alternative curative way is radiation therapy, especially when life-threatening conditions are provoked due to the location of the benign growth [32].

Malignant tumors provoke life-threatening conditions because of their aggressive and invasive nature and also due to the uncontrolled mass growth that eventually causes serious complications like pressure to vital structures. Unlike other types of malignant tumors (lung, liver, breast etc.), brain cancers are mostly localized and rarely spread (metastasize) to other body regions. Additionally, surgical removal is considered extremely dangerous due to the sensitivity of surrounding brain tissue. The most common type of malignant primary brain tumor is glioblastoma multiforme (grade IV astrocytomas), which accounts for approximately 20% of all primary brain tumors [38].

The brain tumor categories employed in the present thesis were gliomas, meningiomas and metastasis. These brain tumor categories were selected on the fact that brain metastasis occurs in 20% to 40% of all cancer patients while meningiomas and gliomas are the two higher incidence rated types of benign and malignant primary brain tumors, respectively [32].

2.2 Gliomas

A glioma is a type of tumor that arises from glial cells and starts in the brain or spine. The most common site of gliomas is the brain [39].

2.2.1 Classification

Gliomas are classified by cell type, by grade, and by location.

2.2.1.1 By type of cell

Gliomas are named according to the specific type of cell they most closely resemble. Hence, the main types of gliomas are: ependymomas (ependymal cells), astrocytomas (astrocytes), oligodendrogliomas (oligodendrocytes) and mixed gliomas, such as oligoastrocytomas, contain cells from different types of glia [39].
2.2.1.2 By grade

According to their grade, which is determined by pathologic evaluation of the tumor, gliomas can be further categorized: i/ Low-grade gliomas are well-differentiated (not anaplastic); these are benign and portend a better prognosis for the patient. ii/ High-grade gliomas are undifferentiated or anaplastic; these are malignant and carry a worse prognosis. Currently, World Health Organization (WHO) grading system for astrocytomas constitutes the most common grading system in use [39].

2.2.1.2 By location

Gliomas can be classified according to whether they are located above or below a membrane in the brain called the tentorium. It must be noted that the tentorium separates the cerebrum, above, from the cerebellum, below. i/ Supratentorial: Above the tentorium, in the cerebrum, mostly in adults (70%). ii/ Infratentorial: Below the tentorium, in the cerebellum, mostly in children (70%) iii/ Pontine: Located in the pons of the brainstem [39].

2.2.2 Causes

Although hereditary genetic disorders such as neurofibromatoses (type I and type II) and tuberous sclerosis complex are commonly accepted to introduce a predisposition towards their development, the exact causes of gliomas are not yet known [40].

2.2.3 Symptoms

As in all tumors, symptoms of gliomas depend on which part of the central nervous system is affected. Due to the increased intracranial pressure induced, a brain glioma can cause headaches, nausea and vomiting, seizures, and cranial nerve disorders. A glioma of the optic nerve can cause visual loss, while spinal cord gliomas can induce pain, weakness, or numbness in the extremities. Although gliomas do not metastasize by the bloodstream, they can spread via the cerebrospinal fluid and cause ‘drop metastases’ to the spinal cord [39].
2.2.4 Pathology

High-grade gliomas are highly-vascular tumors and have a tendency to infiltrate. They have extensive areas of necrosis and hypoxia. In many cases tumor growth causes a breakdown of the blood-brain barrier in the vicinity of the tumor. As a rule, high-grade gliomas almost always grow back even after complete surgical excision. Low-grade gliomas, on the other hand, grow slowly, often over many years, and can be followed without treatment unless they grow and cause symptoms.

Several acquired (not inherited) genetic mutations have been found in gliomas. TP53 is an early mutation. TP53 is the ‘guardian of the genome,’ which, during DNA and cell duplication, makes sure that the DNA is copied correctly and destroys the cell (apoptosis) if the DNA is mutated and can't be fixed. When TP53 itself is mutated, other mutations can survive. PTEN, another protein that also helps destroy cells with dangerous mutations, is itself lost or mutated. EGFR, a growth factor that normally stimulates cells to divide, is amplified and stimulates cells to divide too much. Together, these mutations lead to cells dividing uncontrollably, a hallmark of cancer. Recently, mutations in IDH1 and IDH2 were found to be part of the mechanism and associated with a more favorable prognosis [41]. The IDH1 and IDH2 genes are significant because they are involved in the citrate cycle in mitochondria. Mitochondria are involved in apoptosis. Additionally, the altered glycolysis metabolism in some cancer cells leads to low oxygen (hypoxia). The normal response to hypoxia is to stimulate the growth of new blood vessels (angiogenesis). So these two genes may contribute to both the lack of apoptosis and vascularization of gliomas.

2.2.5 Diagnosis

The traditional neurological examination by the physician constitutes the initial step in the diagnosis on gliomas. During this examination abnormalities in certain neurological functions (like eye movement, reflexes etc.) can provide clues about the location of the tumor [37, 42]. The next step involves the application of specialized imaging techniques and laboratory tests that can detect the presence of a tumor and provide information about its location, type, and extent of spread. Computed Tomography (CT) and MRI provide information concerning the location the extent and composition of the malignant growth [43, 44]. CT is superior for detecting
calcification, skull lesions, and hyper acute hemorrhage (bleeding less than 24 hours old). On the other hand, isodense lesions, edemas, and infractions, can be better detected with MRI. Positron Emission Tomography (PET) and Single Photon Emission Tomography (SPECT) are mostly used for postoperative purposes, such as for differentiating radiation necrosis from tumor recurrence [43].

Biopsy constitutes the final step to complete the diagnostic procedure. Through surgical intervention, a minute tissue sample that belongs to the suspected tumor is removed in order to be examined under the microscope by a histopathologist. Therapy assessment is strongly interrelated with the histopathologist’s conclusion about the tissue sample cells [36, 42].

2.2.6 Treatment

Location, cell type and the grade of malignancy are the factors that mainly affect the treatment for brain gliomas. In many cases, treatment approach combines surgery, radiation therapy, and chemotherapy. The radiation therapy is in the form of external beam radiation or the stereotactic approach using radiosurgery. Spinal cord tumors can be treated by surgery and radiation. Temozolomide is a chemotherapeutic drug that is able to cross the blood-brain barrier effectively and is being used in therapy. In cases of recurrent high-grade glioblastoma, recent studies have taken advantage of angiogenic blockers such as bevacizumab in combination with conventional chemotherapy, with encouraging results [45]. The use of oncolytic viruses or gene therapy using prodrug converting retroviruses and adenoviruses is being studied for the treatment of gliomas [46, 47].

According to the results of a 2007 meta-analysis that compared surgical resection and biopsy as the initial surgical management option, there is insufficient evidence to make a reliable decision [48]. For high-grade gliomas, a 2003 meta-analysis compared radiotherapy with radiotherapy and chemotherapy. It showed a small but clear improvement from using chemotherapy with radiotherapy [49]. For glioblastoma multiforme, a 2008 meta-analysis showed that Temozolomide is an effective treatment for prolonging survival and delaying progression as part of primary therapy without impacting on quality of life and with a low incidence of early adverse events [50].
2.3 Meningiomas

Meningiomas, arising from the arachnoid ‘cap’ cells of the arachnoid villi in the meninges, constitute the second most common primary tumor of the central nervous system [51]. These tumors are usually benign in nature; however, they can be malignant [52].

2.3.1 Causes

Persons who have undergone radiation to the scalp are more at risk for developing meningiomas [53]. The most frequent genetic mutations involved in meningiomas are inactivation mutations in the neurofibromatosis 2 gene (merlin) on chromosome 22q. Other possible genes include: MN1 [54], PTEN [55] and an unknown gene at 1p13 [56].

2.3.2 Symptoms

Small tumors (e.g., < 2.0 cm) are usually incidental findings at autopsy without having caused symptoms. Larger tumors can cause symptoms depending on the size and location. Some of the symptoms include focal seizures and progressive spastic weakness in legs. Increased intracranial pressure eventually occurs, but is less frequent than in gliomas [57].

2.3.3 Pathology

Meningiomas arise from arachnoidal cells, most of which are near the vicinity of the venous sinuses, and this is the site of greatest prevalence for meningioma formation. They are most frequently attached to the dura over the superior parasagittal surface of frontal and parietal lobes, along the sphenoid ridge, in the olfactory grooves, the sylvian region, superior cerebellum along the falx cerebri, cerebellopontine angle, and the spinal cord. The tumor is usually gray, well-circumscribed, and takes on the form of space it occupies. They are usually dome-shaped, with the base lying on the dura. Histologically, the cells are relatively uniform, with a tendency to encircle one another, forming whorls and psammoma
bodies (laminated calcific concretions). They have a tendency to calcify and are highly vascularised [57].

### 2.3.4 Diagnosis

Meningiomas are readily visualized with contrast CT, MRI with gadolinium, and arteriography, all attributed to the fact that meningiomas are extra-axial and vascularized. CSF protein is usually elevated if lumbar puncture is attempted. Though the majority of meningiomas are benign, they can have malignant presentations. Classification of meningiomas are based upon the WHO classification system [58]. The classification includes: i/ the benign meningiomas (Grade I) which is the 90% of the cases, ii/ the atypical meningiomas (Grade II) which is the 7% of the cases and iii/ the anaplastic/malignant meningiomas (Grade III) which is the 2% of the cases.

The mean overall survival for atypical meningiomas according to a recent retrospective review of atypical and anaplastic meningioma cases was found 11.9 years vs. 3.3 years for anaplastic meningiomas. Additionally, mean relapse free survival for atypical meningiomas was 11.5 years vs. 2.7 years for anaplastic meningiomas [59].

### 2.3.5 Treatment

Only in cases a meningioma is small and asymptomatic, observation with close imaging follow-up can be employed. In a retrospective study on 43 patients, it was found that 63% of patients had no growth on follow-up, and the 37% found to have growth grew at an average of 4 mm / year. According to the same study, younger patients were found to have tumors that were more likely to grow on repeat imaging, therefore rendering them poorer candidates for observation. Observation is not recommended in tumors that are already causing symptoms. In addition, close follow-up with imaging is required with an observation strategy to rule out an enlarging tumor [60].

Meningiomas can usually be surgically resected with permanent cure if the tumor is superficial on the dural surface and easily accessible. Transarterial embolization has become a standard preoperative procedure in the preoperative management. In case invasion of the adjacent bone takes place, total removal is nearly
impossible. Malignant transformation is rare. The probability of tumor recurrence or growth after surgical resection can be estimated by the tumor's WHO Grade and by the extent of surgery by the Simpson Criteria [61, 62].

Radiation therapy comprises Gamma Knife, proton beam treatment, or fractionated external beam radiation. Gamma Knife radiosurgery is employed in lieu of surgery in small tumors located away from critical structures [63]. Fractionated external beam radiation can also be used as primary treatment for tumors that are surgically unresectable, or for patients who are inoperable for medical reasons. Radiation therapy is often considered for WHO Grade I meningiomas after subtotal (incomplete) tumor resections. The clinical decision to irradiate after a subtotal resection is somewhat controversial as no class I randomized controlled trials exists on the subject [64]. Nevertheless, both progression free survival (i.e. prevents tumor recurrence) and overall survival are improved by the addition of post-operative radiation to incomplete resections, according to numerous retrospective studies [65]. In the case of a Grade II or Grade III meningioma, the current standard of care involves post-operative radiation treatment regardless of the degree of surgical resection mainly due to the proportionally higher rate of local recurrence for these higher grade tumors [66].

Current chemotherapies are likely not effective. Antiprogestin agents have been used, but with variable results [67]. Recent evidence that hydroxyurea has the capacity to shrink unresectable or recurrent meningiomas is being further evaluated [68].

2.4 Brain metastasis

A cancer that has metastasized (spread) to the brain from another location in the body constitutes a brain metastasis [69]. Brain metastases are the most common cause of intracranial mass lesions, and up to 45% of cancer patients eventually develop brain metastases during the course of their illness, with 98,000 to 170,000 new cases diagnosed each year in the US alone. Patients with cancer are fortunately living longer and longer after initial treatment than ever before, as primary cancer treatments like surgery, radiation therapy and chemotherapy have become more effective over the past few decades. Nevertheless, brain metastases still occur in many patients months
or even years after their original cancer treatment. Brain metastases have a poor prognosis for cure, but modern treatments are allowing patients to live months and sometimes years after the diagnosis [69, 70].

2.4.1 Sources of brain metastases

Lung cancer, breast cancer, melanoma, genitourinary tract cancers, osteosarcoma, neuroblastoma, head and neck cancer, lymphoma and gastrointestinal cancers, especially colorectal and pancreatic carcinoma are the most common sources of brain metastases [69, 71].

2.4.2 Symptoms

In many cases, patients have no obvious symptoms indicating that their cancer has spread to the brain. Usually the cancer is found on a scan during a routine follow up visit to the doctor. Brain metastases can cause a wide variety of symptoms, many of which are also present in minor, more common conditions. These symptoms include: vertigo, new onset headaches, cognitive, personality, and behavioral changes, nausea and vomiting, memory loss, increased intracranial pressure, paraesthesia, visual changes, bells palsy, ataxia and seizure [30].

2.4.3 Diagnosis

The diagnosis for brain metastases is variable. It depends on the type of primary cancer, the age of the patient, the absence or presence of extracranial metastases, and the number of metastatic sites in the brain. For all patients combined, median survival is only 2.3 months. However, in some patients, such as those with no extracranial metastases, those who are younger than 65, and those with a single site of metastasis in the brain only, prognosis is much better, with median survival rates of up to 13.5 months [70].

2.4.4 Treatment
Treatment for brain metastases is primarily palliative, with the goals of therapy being reduction of symptoms and prolongation of life. Still, in some patients, particularly younger, healthier patients, aggressive therapy with open craniotomy and maximal excision, aggressive chemotherapy, and radiosurgical intervention (gamma knife radiosurgery).

As brain metastases often result in severe, debilitating symptoms, symptomatic care should be given to all patients with brain metastases. In patients with brain metastases, treatment consists mainly of: i/ Corticosteroids. Corticosteroid therapy is essential for all patients with brain metastases, as it prevents development of cerebral edema, as well as treating other neurological symptoms such as headache, cognitive dysfunction, and emesis. Dexamethasone is the corticosteroid of choice. ii/ Anticonvulsants. Anticonvulsants should be used in all of the 30–40% of patients with brain metastases who experience seizures, as there is a risk of status epilepticus and death. Phenytoin is the most commonly used drug in this setting, but valporic acid and other anticonvulsants could also be used [69].

Radiotherapy plays a critical role in the treatment of brain metastases, and includes whole-brain irradiation, fractionated radiotherapy, and radiosurgery. For decades, whole brain irradiation has been advocated for patients with multiple lesions, a life expectancy of less than three months, or a low Karnofsky performance score, and it does appear at least somewhat effective. However, it often causes severe side effects, including radiation necrosis, dementia, leukoencephalopathy, headache, partial to complete hair loss, nausea, headache, and otitis media while in children the treatment may cause mental retardation, psychiatric disturbances, and other neuropsychiatric effects. Patients are encouraged to talk to their radiation oncologists to weigh the risks and the benefits of some types of whole brain radiation [72].

Brain metastases are often managed surgically, with maximum surgical resection followed by whole-brain irradiation delivering superior survival compared to whole brain irradiation alone. Therefore, in patients with one metastatic brain lesion, limited, absent, or controlled systemic disease, a life expectancy of at least 3 months, and good performance status [73].
CHAPTER 3 - Nuclear magnetic resonance imaging and spectroscopy

Being developed since the middle of the 20th century, NMR is a technique to inspect molecules by observing their interaction with an external magnetic field. MRI is probably the most popular application of this method, since it produces anatomical images of tissues by means of a safe, non-invasive procedure. Other applications of NMR are related to the field of spectroscopy, where the chemically-distinctive nature of NMR is exploited to examine the chemical composition of a given sample. The field of in vivo NMR spectroscopy is referred as MRS. Specifically, MRS is used to study biochemical and metabolic changes in human tissue, typically a localized brain volume, with respect to disease processes. The fundamental principles of NMR focusing in the application of MRS are briefly discussed in this chapter.
3.1 Basic physics and techniques

Based on matter’s fundamental property of nuclear spin and its interaction with an external magnetic field to induce an electrical signal which is sampled and processed digitally, MRI and MRS can provide useful clinical information.

Nuclei able to be observed by NMR have non-zero spin. Spin can take on specific quantized integer and half-integer values, depending on the atomic weight and number of the nucleus under observation (for example, the hydrogen nucleus has a spin of \( \frac{1}{2} \)). Most importantly, a nucleus with spin can be visualized as a vector with an axis of rotation. Since it is not yet feasible to measure single-spins, instead an average of many spins, called a spin packet, is measured, and it has a specific magnetization vector. Once placed in an external magnetic field, the magnetization vector aligns itself either parallel or anti-parallel to the external field. Thus, the axis of rotation of the spins is either parallel or anti-parallel to the magnetic field. Boltzmann statistics can be used to describe the ratio of spins in the high-energy (parallel) and low-energy (anti-parallel) states:

\[
\frac{P}{AP} = e^{-\frac{\Delta E}{kT}},
\]

Eq. 1

where \( P \) is the number of protons in the parallel state, \( AP \) is the number of protons in the anti-parallel state, \( \Delta E \) is the energy difference between the high- and low-energy states, \( k \) is the Boltzmann constant and \( T \) is the temperature in Kelvin [74]. Moreover, the spins precess about the axis of rotation at a specific frequency – the Larmor frequency:

\[
v = \gamma B_0,
\]

Eq. 2

where \( \gamma \) is the gyromagnetic ratio of the nucleus, \( B_0 \) is the strength of the external magnetic field (in T), and \( v \) is the Larmor frequency. When absorbed by the spin, a photon at the Larmor frequency, causes it to flip states from the low- to the high-energy state. Consequently, the magnitude of the magnetization vector along the Z-axis decreases. Equation 3 (Eq. 3) describes the rate with which the equilibrium magnetization is restored to the system [74].
\[ M_z = M_0 \left(1 - e^{-\frac{t}{T_1}}\right), \quad \text{Eq. 3} \]

where \( M_z \) is the instantaneous magnetization along the Z-axis, \( M_0 \) is the equilibrium magnetization along the Z-axis, \( t \) is the time after the pulse, and \( T_1 \) is a constant that describes the restoration rate for different substances [74, 75].

When repeating pulse sequences for additional measurements or signal averaging to improve Signal-to-Noise Ratio (SNR), the Repetition Time (TR), or the time between successive applications of the pulse sequence, becomes of immense importance. It becomes apparent by Eq. 3, that waiting a longer time \( t \) between repetitions (a long TR) allows for restoration of the longitudinal magnetization. In case the TR time is not long enough to allow for \( T_1 \) relaxation, the magnetization does not have enough time to restore itself to its equilibrium state, and therefore successive acquisitions at the short TR will cause the signal amplitude to decrease as less and less spins are excited by the pulse sequence. The term for this undesirable effect that causes signal to be underestimated in quantitative analysis is saturation of spins. The application of a 90° RF pulse at the Larmor frequency will incline the magnetization vector onto the XY-plane, while still rotating about the Z-axis at the Larmor frequency. Hence, if a coil is placed near the system, perpendicular to one of the X- or Y-axes, it will experience a sinusoidally changing magnetic field and a signal induced in the coil. This is termed a Free Induction Decay (FID), and is a sum of exponentially decaying sinusoids which contains the information useful for MRI and MRS. The exponential decay of the FID is induced by a phenomenon called spin-spin relaxation, or \( T_2 \) relaxation. According to this, small vibrations and rotations of the molecules cause minute perturbations in the magnetic field, causing each spin to precess at a slightly different Larmor frequency; meaning that when the magnetization vector is tipped into the XY-plane by an RF pulse, the spin packet loses phase coherence. The net result is a loss in transverse magnetization governed by

\[ M_{XY} = M_{XY0} e^{-\frac{t}{T_2}}, \quad \text{Eq. 4} \]

where \( M_{XY} \) is the instantaneous transverse magnetization, \( M_{XY0} \) is the initial transverse magnetization right after the pulse, \( t \) is the time after the pulse and \( T_2 \) is a constant particular to the substance in question [75]. Other interactions such as magnetic field
inhomogeneity and sample magnetic susceptibility will effectively speed this dephasing, yielding a rate termed $T_2^*$ (also called $T_2$ Star). The phenomenon of $T_2$ relaxation naturally gives rise to a technique that is used frequently in MRI and MRS, known as spin-echo. The application of a 90° pulse causes the magnetization to dephase, causing a decay of the signal from $T_2^*$ effects. If an 180° pulse is subsequently applied, the magnetization vector is reversed with respect to the $z$-axis, causing precession to occur in the opposite direction. Then, the magnetization will rephase as it is 'dephasing' in the opposite direction, counteracting the phase advance that was imparted earlier. This reestablishment of phase coherence results in an ‘echo’, as the signal returns, and then dephases again. The time from the beginning of the pulse to the maximum amplitude of the echo is termed TE, or Echo Time. Due to the nature of the spinecho, many $T_2^*$ effects, such as magnetic field inhomogeneity and susceptibility, are reversed by this process, which makes the spin-echo effective for measuring $T_2$ relaxation in itself. The presence of other atoms close to a nucleus will slightly affect its Larmor frequency, depending on the chemical structure of particular substances. Namely, the negative charge of electron spins generates a small magnetic field that opposes the external field. This process is known as chemical shielding [74, 75]. As a result, Eq. 2, which described the Larmor frequency, has to be modified:

$$\nu_t = \gamma B_0 (1 - \sigma_t).$$  \hspace{1cm} \text{Eq. 5}$$

The introduction of $\sigma_t$ denotes a small perturbation in the external magnetic field. As a consequence, the Larmor frequency is slightly different than the center frequency. RF pulses generally have a carrier frequency, which is equal to the center frequency, as well as a range of frequencies close to the carrier, to excite all spins in the volume of interest. Thus, the slightly-varying rotation speeds are detected by the coil as signals with slightly different frequencies. Since water is in very high abundance in the brain, the signal due to other chemicals is several orders of magnitude smaller than the signal due to water, and this effect, termed chemical shift, is thus negligible in imaging applications. However, since chemical shift is unique for each distinct chemical species, it follows that the chemical composition of a specimen can be measured by observing the distribution of spins that precess at these frequencies. A further property of chemical shift that is useful for MRS is that it is
independent of field strength. The frequency information of a metabolite can be expressed in terms of Hz, like the Larmor frequency, but that same trait makes the frequency information dependent on the magnetic field strength, hindering interoperability between different scanners. Chemical shift is conventionally measured in parts per million (ppm), defined as the chemical shift of a metabolite with respect to a reference:

$$\delta_i = \frac{v_i - v_{\text{ref}}}{v_{\text{ref}}} \cdot 10^6,$$

Eq. 6

In proton MRS, $v_{\text{ref}}$ is typically taken as the resonance frequency of tetramethylsilane [74, 75].

In order for an MRS scan to be useful, it must be localized to a specific region of tissue. This is accomplished by a variety of different pulse schemes, such as Stimulated Echo Acquisition Mode (STEAM), Image-Selected In Vivo Spectroscopy (ISIS), and Point-Resolved Spectroscopy (PRESS). All of the aforementioned schemes use magnetic field gradients to spatially localize the MRS signal. Gradients are magnetic fields that vary in intensity linearly with respect to a spatial direction. Thus, the application of a gradient in a given direction will cause spins to precess at different Larmor frequencies depending on their location with respect to that axis:

$$v_x = \gamma(B_0 + xG_s) \quad v_y = \gamma(B_0 + yG_s) \quad v_z = \gamma(B_0 + zG_s),$$

Eq. 7

where $v_i$ denotes the modified Larmor frequency at distances $x$, $y$, and $z$ in those respective directions, $\gamma$ is the gyromagnetic ratio, $B_0$ the external magnetic field, and $G_s$ is the amplitude of the gradient. If an RF pulse is applied while the gradient is on, only spins in the slice that corresponds to $v_x$ (or $v_y$ or $v_z$) = $v_0$, where $v_0$ is the center frequency of the pulse, are excited. This gradient is therefore termed a slice select gradient. An example of its use is in PRESS. A slice select gradient with a 90° pulse is applied in one direction, which causes spins in one slice to be excited, and begin to dephase due to $T_2^*$ effects; the resulting FID is not sampled. Another slice select gradient is applied, this time with a 180° pulse, to rephase the spins in the intersecting column of the two orthogonal slices. A final gradient is applied with another 180° pulse, to rephase the spins in the intersection of all three slices, which is termed the
volume of interest. This final echo is sampled; owing to the PRESS sequence, the resulting data is known to come only from the volume of interest [76].

3.2 Data analysis

Acquisition of the time-domain signal yields an exponentially decaying sum of sinusoids – the FID. This data is digitized during the acquisition process, so the signal is a sequence of points at regular time intervals. The signal must then be Fourier transformed to yield a spectrum in the frequency domain, which is easier to interpret. Before that is done, the signal may be windowed or zero-filled to improve spectral quality. Windowing is the multiplication of the signal with a filter function, usually a decaying exponential. This filtering results in the signal attenuating to zero, which prevents step-function discontinuities in the signal from introducing truncation artifacts into the spectrum. Zero-filling has the same effect as interpolation of the frequency-domain spectrum and can therefore improve the resolution of the spectrum, causing fine details to be better shown. It is imperative that the signal be attenuated to background noise before it is zero-filled, though, otherwise the spontaneous addition of zeros to the end of the spectrum will cause a discontinuity, introducing artifacts into the spectrum [76].

A Fourier transform is then applied to the time domain signal. This process yields two spectra, termed real and imaginary, corresponding to the real and imaginary components of the signal that were sampled in quadrature from the 3 system. Ideally, these two spectra should correspond perfectly to the absorption and dispersion modes of the signal. However, RF pulse inhomogeneities and time delays can result in a phase shift of the signal, causing the real spectrum to be a mixture of absorptive and dispersive modes. Since the area of only the purely absorptive spectrum is proportional to the number of spins from a given frequency range, the complex spectrum must be phase-corrected before quantitative analysis can be performed. An alternative to phase correction is combining the real and imaginary parts to produce a magnitude, or absolute-value, spectrum. While this spectrum is free of phase effects, the linewidth is not optimal and the low signal-to-noise and overlapping peaks of in vivo spectroscopy make the magnitude spectrum unreliable for quantitative analysis. Phase correction is typically performed by computer analysis [76]. Finally, once the spectrum has been adequately phased, the spectrum is
quantified by identifying metabolite peaks and determining concentrations (either relative or absolute) by relative peak amplitudes [76].

3.3 Metabolites in proton brain MRS

N-acetyl-aspartate (NAA) is the most prominent metabolite in MRS of healthy brains and therefore commonly thought to be a marker of neuro-axonal integrity. The NAA peak appears at 2.02 ppm and its concentrations are decreased in conditions leading to axonal injury or neuronal loss. Decreased concentrations are also observed in tumors, infarction, and inflammatory conditions such as multiple sclerosis. Creatine (Cr) is located at 3.02 ppm and its stability, even in pathology, has led to its use as a standard internal reference. Choline (Cho), which is located at 3.22 ppm, represents various choline-containing compounds, such as acetylcholine, phosphocholine (lecithin), glycerophosphocholine, and various other intermediates of phospholipid metabolism. Cho is an indicator of cell density and cell wall turnover. In addition, elevated Cho levels are found in tumors, especially malignant ones, and in certain demyelinating diseases. Lactate (Lac) is present at 1.33 ppm only at TE times of 135 or 270. Due to its low concentration, lactate is not normally seen in healthy brain. Nevertheless, lactate is detectable in some cases of stroke or brain tumors, among other diseases. At shorter TE times, myo-inositol is visible. It is located past the Cho peak, at 3.56 ppm, and is visible in infants, decreasing as NAA increases with the onset of axonal development. Under certain circumstances, a broad signal from free lipids can be seen in the vicinity of 0.9-1.3 ppm, and can therefore interfere with the lactate signal [77-79].
CHAPTER 4 - Computer assisted diagnosis of brain tumors: pattern recognition system

This chapter explains the essential parts of pattern recognition systems with more emphasis given to feature generation and classification algorithms, since the core of the brain tumor discrimination systems developed for the purposes of this thesis rely on pattern classification techniques.
4.1 Pattern recognition in computer-assisted diagnosis of brain tumors

The process of brain tumor characterization requires a rather intricate assessment of the various MR image and spectra features and is typically performed by experienced radiologists. Despite the inherently subjective nature of many of the decisions associated with this process, an expert radiologist is able to perform this task with a significant degree of precision and accuracy. However, in the effort to deliver more effective treatment, clinicians are continuously seeking for greater accuracy in the pathological characterization of brain tissues [9]. To this need, image analysis techniques have been employed in previous studies for the extraction of diagnostic information from MR images and spectra [4, 8, 9]. These studies have employed pattern recognition techniques to discriminate between several types of human brain tumors. The accurate characterization of brain tumors is essential in order to provide patients the proper clinical management that may prolong survival and quality of life [24, 80]. Every pattern classification system consists of 3 important stages: i/ region and/or volume of interest extraction, ii/ feature generation, and iii/ feature selection and classification. In the following paragraphs theoretical and implementation aspects of methods for constructing the pattern classification systems, which were developed for the needs of the present thesis, will be presented.

4.2 Segmentation

In order to extract features only from the Regions Of Interest ROI or Volumes of Interest (VOI) (i.e. tumor), it is most important to initially divide the MR image into ‘meaningful’ (brain tumor) and ‘meaningless’ (surrounding tissue and remaining background) parts. The process mentioned afore refers to as segmentation. For the purposes of the present thesis two custom developed applications were developed and employed to semiautomatically segment the MR images in ROIs and VOIs respectively. Employing the first application, the radiologist specified square regions of ROIs within the tumor area. Each ROI was semiautomatically drawn around a pixel by a simple click on the mouse (see chapter 5.3.2). The second application by utilizing the marching cubes algorithm [81] and the Visualization Tool Kit (VTK) [82] was able to build 3-dimensional models from DICOM MRI-series and, thus, to
provide the radiologist with a visual aid for segmenting VOIs within brain tumors (see chapter 6.3.2).

4.3 Feature generation

From the segmented regions of interest, features are computed to encode clinically valuable information. In order to accurately discriminate between the types of human brain tumors, two categories of features have been proven powerful and used in the present thesis to provide the correct information to classification algorithms: i/ textural and ii/ spectroscopic features [7, 10, 11, 20, 78, 83-86].

4.3.1 Textural features

4.3.1.1 First order statistical features

The 1st order statistical features encode information related to the frequency of appearance of each gray level (histogram) in the region of interest (ROI). The 1st order statistical features are:

1. Mean Value

\[ m = \frac{\sum_{i} \sum_{j} g(i,j)}{N} \]  

where \( g(i,j) \) is the pixel intensity in position \((i,j)\) and \(N\) the total number of pixels of the ROI.

2. Standard Deviation

\[ std = \sqrt{\frac{\sum_{i} \sum_{j} (g(i,j) - m)^2}{N}} \]  

Standard deviation describes the variation of the ROI’s gray levels from the mean value.

3. Skewness

\[ sk = \frac{\sum_{i} \sum_{j} (g(i,j) - m)^3}{std^3} \]  

Skewness is related to the distribution asymmetry around the mean gray-tone value.
4. Kurtosis

\[ k = \frac{1}{N} \sum_{i} \sum_{j} \frac{(g(i, j) - m)^4}{\text{std}^4} \]

Kurtosis describes the gray-tone distribution sharpness as compared to the normal distribution.

4.3.1.2 Second order statistical features

Although the 1st order statistical features describe the gray level distribution of ROI, these features do not give any information regarding the spatial distribution of the various gray levels inside the ROI. This type of information can be extracted from the co-occurrence and run-length matrixes [10, 11].

4.3.1.2.1 Features extracted from the co-occurrence matrix

The co-occurrence matrix encodes the frequency of appearance of the same pairs of pixel gray tones at a distance \( d \) (inter-pixel distance) inside each ROI [81]. In order to extract information concerning spatial distribution and its orientation, four co-occurrence sub-matrices can be calculated across four scanning directions \( \theta \) (0°, 45°, 90°, 135°). The following example is illustrative of how the co-occurrence matrixes can be calculated (Figure 1i). Consider for instance, an image (Figure 1ii) with four gray levels \( f = 0, 1, 2, 3 \) and, more specifically, the pixel pair (2,3). The co-occurrence matrix element (2,3), in a given forward and backward scanning direction \( \theta \) with \( d=1 \), will be given a value equal to the frequency of appearance of two adjacent gray tones of value 2 and 3. Across the horizontal direction (0°) the pair (2,3) appears 1 time, across the diagonal (45°) 1 time, across the vertical (90°) 2 times and across the anti-diagonal (135°) 2 times. The results for the particular example can be found in Figure 1iii.

\[
\begin{array}{cccc}
0 & 0 & 1 & 1 \\
0 & 0 & 1 & 1 \\
0 & 2 & 2 & 2 \\
2 & 2 & 3 & 3 \\
\end{array}
\]

(i)
The classic definition of 2-dimensional co-occurrence matrix of distance $d$ and angle $\theta$ is given by [10]:

$$S(d, \theta)_{XY} = \frac{1}{2} [\Phi(d, \theta)_{XY} + \Phi^T(d, \theta)_{XY}],$$  \hspace{1cm} \textbf{Eq. 8}

where $S(d, \theta)_{XY}$ is a squared matrix of dimension $N_G \times N_G$ (number of gray levels), symmetrical around its diagonal axis. $\Phi^T(d, \theta)_{XY}$ is the transpose matrix of $\Phi(d, \theta)_{XY}$ which gives the sub-matrix in the reverse direction.

In the present thesis for the purpose of quantifying textural volume properties of brain tumors, the 3-dimensional (volumetric) equivalent of the co-occurrence matrix were also employed [14]. The features that can be extracted from the co-occurrence matrix, either 2-dimensional or 3-dimensional are [10]:

1. Angular Second Moment (ASM)

$$\text{ASM} = \sum_{i=0}^{N_g-1} \sum_{j=0}^{N_g-1} (p(i,j))^2$$  \hspace{1cm} \textbf{Eq. 9}
where $N_g$ is the number of gray levels in the image, $i,j=1,...,N_g$, and $p(i,j)$ is the co-occurrence matrix. ASM describes image smoothness and takes minimum values for smooth textures.

2. Contrast (CON)

$$CON = \sum_{n=0}^{N_g-1} n^2 \left( \sum_{i=0}^{N_g-1} \sum_{j=0}^{N_g-1} (p(i,j))^2 \right), |i-j| = n$$  \hspace{1cm} \text{Eq. 10}

CON increases for high contrast ROIs. The factor $n^2$ enhances big differences.

3. Inverse Different Moment (IDM)

$$IDM = \sum_{i=0}^{N_g-1} \sum_{j=0}^{N_g-1} \frac{p(i,j)}{1 + (i - j)^2}$$  \hspace{1cm} \text{Eq. 11}

IDM increases for low contrast ROIs due to the dependence on $(i - j)^2$.

4. Entropy (ENT)

$$ENT = \sum_{i=0}^{N_g-1} \sum_{j=0}^{N_g-1} p(i,j) \log(p(i,j))$$  \hspace{1cm} \text{Eq. 12}

ENT is a measure of randomness and takes low values for smooth ROIs.

5. Correlation (COR)

$$COR = \frac{\sum_{i=0}^{N_g-1} \sum_{j=0}^{N_g-1} (i-j)p(i,j) - m_x m_y}{\sigma_x \sigma_y}$$  \hspace{1cm} \text{Eq. 13}

where $m_x$, $m_y$, $\sigma_x$, and $\sigma_y$ are the respective mean values and standard deviations of $p_x$ and $p_y$, which are described in Equations 4.9-4.10. COR encodes the gray tones dependencies in ROIs.

$$p_x(i) = \sum_{j=1}^{N_{\text{rows}}} p(i,j)$$  \hspace{1cm} \text{Eq. 14}

$$p_y(i) = \sum_{j=1}^{N_{\text{columns}}} p(i,j)$$  \hspace{1cm} \text{Eq. 15}

6. Sum of Squares (SSQ)

$$SSQ = \sum_{i=0}^{N_g-1} \sum_{j=0}^{N_g-1} (1 - m)^2 p(i,j)$$  \hspace{1cm} \text{Eq. 16}
7. Sum Average (SAVE)  
\[ \text{SAVE} = \sum_{i=2}^{2N_g} ip_{x+y}(i) \]  
Eq. 17

where \( p_{x+y} \) is

\[ p_{x+y}(k) = \sum_{i=1}^{N_g} \sum_{j=1}^{N_g} p(i,j), i + j = k, k = 2,3, ..., 2N_g \]  
Eq. 18

8. Sum Entropy (SENT)  
\[ \text{SENT} = -\sum_{i=2}^{2N_g} p_{x+y}(i) \log(p_{x+y}(i)) \]  
Eq. 19

9. Sum Variance (SVAR)  
\[ \text{SVAR} = -\sum_{i=2}^{2N_g} (i - \text{SENT})^2 p_{x+y}(i) \]  
Eq. 20

10. Difference Variance (DVAR)  
\[ \text{DVAR} = \sum_{i=2}^{2N_g} (i - \text{SAVE})^2 p_{x-y}(i) \]  
Eq. 21

11. Difference Entropy (DENT)  
\[ \text{DENT} = -\sum_{i=0}^{N_g-1} p_{x-y}(i) \log(p_{x-y}(i)) \]  
Eq. 22

where \( p_{x-y} \) is

\[ p_{x-y}(k) = \sum_{i=1}^{N_g} \sum_{j=1}^{N_g} p(i,j), |i - j| = k, k = 2,3, ..., N_g - 1 \]  
Eq. 23

4.3.1.2.2 Features extracted from the run-length matrix

The run length matrix is used to describe the frequency of appearance of a set of consecutive pixels having the same gray value [11]. For understanding the calculation of the run length matrix, let us consider a 4 x 4 image with gray levels \( f=0, 1, 2, 3 \). Run length matrices are defined in 4 possible directions: horizontal (\( \theta=0^0 \)), diagonal
(θ=45°), vertical (θ=90°) and antidiagonal (θ=135°). By scanning the image only in the forward direction, the set of two consecutive pixels having the value 2 for example appears 1 time in the horizontal direction, 2 times in the diagonal direction, 1 time across the vertical direction and 0 times across the anti-diagonal direction (Figure 2).

\[
\begin{array}{ccc}
0 & 0 & 1 \\
0 & 0 & 1 \\
0 & 2 & 2 \\
2 & 2 & 3
\end{array}
\]

(i)

\[
\begin{array}{|c|c|c|c|}
\hline
\text{Run length} & \text{Run length} & \text{Run length} & \text{Run length} \\
0^0 & 45^0 & 90^0 & 135^0 \\
\hline
1 & 2 & 0 & 0 & 1 & 2 & 0 & 0 & 0 & 1 & 1 & 0 & 3 & 1 & 0 & 0 \\
0 & 2 & 0 & 0 & 2 & 1 & 0 & 0 & 0 & 2 & 0 & 0 & 2 & 1 & 0 & 0 \\
0 & 1 & 1 & 1 & 1 & 2 & 0 & 0 & 3 & 1 & 0 & 0 & 5 & 0 & 0 & 0 \\
0 & 1 & 0 & 0 & 2 & 0 & 0 & 0 & 2 & 0 & 0 & 0 & 2 & 0 & 0 & 0 \\
\hline
\end{array}
\]

(ii)

Figure 2 - Example of calculating the run-length matrix

In the present thesis for the purpose of encoding textural volume properties of brain tumors, the 3-dimensional (volumetric) equivalent of the run-length matrix were also utilized [15]. The features that can be extracted from the run-length matrix, either 2-dimensional or 3-dimensional are [11]:

1. Short Run Emphasis (SRE)

\[
SRE = \frac{\sum_{i=1}^{N_g} \sum_{j=1}^{N_r} \frac{r(i,j)}{j^2}}{\sum_{i=1}^{N_g} \sum_{j=1}^{N_r} r(i,j)}
\]

Eq. 24

where \( r(i,j) \) is the run length matrix, \( N_g \) is the number of gray values in the image, \( N_r \) is the largest possible run, \( i=1,\ldots,N_g, j=1,\ldots,N_r \). SRE tends to emphasize short runs due to the division with \( j^2 \) and takes high values for coarser ROIs.
2. Long Run Emphasis (LRE)

\[ LRE = \frac{\sum_{i=1}^{N_g} \sum_{j=1}^{N_r} j^2 r(i,j)}{\sum_{i=1}^{N_g} \sum_{j=1}^{N_r} r(i,j)} \quad \text{Eq. 25} \]

LRE tends to emphasize long runs and is large for smoother ROIs.

3. Gray Level Non-Uniformity (GLNU)

\[ GLNU = \frac{\sum_{i=1}^{N_g} \left( \sum_{j=1}^{N_r} r(i,j) \right)^2}{\sum_{i=1}^{N_g} \sum_{j=1}^{N_r} r(i,j)} \quad \text{Eq. 26} \]

GLNU increases for ROIs having many runs of the same gray level value.

4. Run Length Non-Uniformity (GLNU)

\[ RLNU = \frac{\sum_{j=1}^{N_r} \left( \sum_{i=1}^{N_g} r(i,j) \right)^2}{\sum_{i=1}^{N_g} \sum_{j=1}^{N_r} r(i,j)} \quad \text{Eq. 27} \]

RLNU takes low values for ROIs with homogeneous distribution of runs.

5. Run Percentage (RP)

\[ RP = \frac{\sum_{i=1}^{N_g} \sum_{j=1}^{N_r} r(i,j)}{P} \quad \text{Eq. 28} \]

where \( P \) is the total possible number of runs in the ROI. This feature takes its lowest value for ROIs with linear structures.

The dynamic range of the values of each of these features can be significantly different. This might provoke an imbalanced influence of features with larger and lower values when designing distance metric based classifiers [13]. To compensate this effect, features should be normalized to similar dynamic range, like for example to zero mean and unit deviation [13] according to:

\[ \tilde{x}_i = \frac{x_i - \text{mean}}{\text{std}} \quad \text{Eq. 29} \]

where \( x_i \) and \( \tilde{x}_i \) are the feature vectors prior and after the normalization, \( \text{mean} \) and \( \text{std} \) are the mean value and standard deviation of each feature respectively.

4.3.2 Spectroscopic features

MR spectroscopy has proven useful in the evaluation of many Central Nervous System (CNS) neoplasms. The clinical impact of spectroscopy on the assessment of contrast-enhancing lesions that have indeterminate imaging characteristics, distinguishing neoplasm from non-neoplastic CNS tissue, has been reported [5, 87].
Spectral changes often shown in brain tumors are an increase in Cho, a decrease or absence of NAA. It is not only the individual peaks and spectral changes that are important, but their relation toward each other as well. Such relationships can be evaluated by calculating ratios. Cho/NAA, Cho/Cr and NAA/Cr ratios have commonly been used by many investigators to distinguish neoplasm from non-neoplastic tissue in the central nervous system [88]. It has been shown that the results of MR spectroscopy of intracranial neoplasms correlate with histopathology from biopsy specimens, when measuring Cho, Cr and NAA metabolites [89]. Thus, in the present thesis these metabolite ratios were used as features to feed the pattern recognition systems designed in order to discriminate between different types of brain tumors. In Table 1 major metabolite changes are depicted for different types of brain tumors [28].

<table>
<thead>
<tr>
<th>Tumor Type</th>
<th>Major Metabolite Change</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>NAA</td>
</tr>
<tr>
<td>WHO II glioma</td>
<td>↓↓</td>
</tr>
<tr>
<td>WHO III glioma</td>
<td>↓↓</td>
</tr>
<tr>
<td>Glioblastoma</td>
<td>↓↓↓</td>
</tr>
<tr>
<td>Lymphoma</td>
<td>↓↓↓</td>
</tr>
<tr>
<td>Metastasis</td>
<td>↓↓↓</td>
</tr>
<tr>
<td>Gliomatosis</td>
<td>↓</td>
</tr>
<tr>
<td>Meningioma</td>
<td>↓↓↓</td>
</tr>
</tbody>
</table>

4.4 Feature selection and classification

The classifier which is the process of transforming the quantitative input (i.e. features) to qualitative output (i.e. diagnosis, prognosis etc) is considered the most important part of a pattern classification system. The output of the classifier can be either a distinct value, indicating one of the predefined classes, or a real value vector,
reflecting a likelihood that a pattern has originated from a specific class [90]. In order to maximize the performance of the classifier it is most important to optimally tune all the preceding stages (segmentation, feature extraction and selection). Setting up a classifier requires three stages: the learning stage, the performance evaluation stage, and the testing stage. These stages, in many cases, overlap, as will be discussed.

During the learning stage, the classifier is trained to learn the differences between the known classes on the basis of input feature vectors of known labels. Based on the input feature vectors, the classifier creates a ‘unique’ description of each predefined classification category. The input feature vectors from each class are referred to as ‘training sets’. When learning is completed, the classifier is ready to conclude classification-labels on new data that haven’t been used for its training.

Although it might seem logical that a larger number of features would be more informative that a smaller number of features, this is not the case in real world applications, due to the following three main reasons [13, 90]: Firstly, the complexity and computational cost of the classifier increases radically. Secondly, although the number of misclassified data might decrease, when more features are added for training the classifier, it has been shown that the generalization error will eventually increase [91]. Thirdly, in the case of limited number of available data and large number of available features, it is more likely that features with little or no discrimination power will induce noise, degrading the generalization of the classifier to unknown data [29, 91]. Therefore, feature selection is an important step for bringing out the most informative features and for optimal tuning the classifier’s capacity to reliably classify unknown data.

There are two kinds of feature selection processes, depending on if the feature selection criterion is based on the classifier used to construct the prediction rule. If it is independent of the criterion, the feature selection process follows a ‘filtering’ approach. If it depends on the criterion, then the feature selection process follows a ‘wrapper’ approach [29, 91].

Among most common filter approaches are the t-test, sequential forward and backward selection methods, principal component analysis, and independent component analysis, which use statistical criteria to find the most important features [13, 91].

An optimal wrapper based feature selection process is the exhaustive search algorithm. According to this method, features are combined in all possible ways
(combinations of 2, 3 up to the total number of features). The classifier is then designed using each distinct combination. As best feature vector is considered the subset of features that leads to the minimum misclassification error. Methods, like the self-consistency, the holdout, the cross-validation and the leave-some-out are typical choices for validating the classification error and assessing the performance of the classifier [13, 91]. The self-consistency method estimates the reliability of the classifier using all available training data, first for training and then for testing. The result of self-consistency is an optimistically biased estimate of the classifier performance, since the same dataset is used for both training and testing. However, it is an important step for assessing the reliability of the classifier in correctly classifying the data that are used for its design. According to the holdout method, a part of data is selected for training the classifier while the remaining data are used for testing its performance. If only one data sample is held out for classification, then the Leave-One-Out (LOO) method is formed. Another popular method is the k-fold cross-validation [29]; data are randomly split into k-training sets (usually $k=10$) of approximately same size and a test set. The training sets are used for constructing the classifier, whereas the test set is used to assess the performance on each possible feature subset. As best feature combination is considered the subset of features that leads to the minimum classification error. This procedure is repeated multiple times. By averaging the test error of each repetition more reliable results can be obtained. Classifier’s performance evaluation using any of the methods described before is more likely to give an optimistically biased estimate of the error rate, if it is calculated ‘internally’ to the feature selection process. By ‘internally’ is meant that all available data are used for feature selection. This practically means that the ‘internal’ error would be indicative of the classifier’s performance on the training data only, and cannot be used to predict reliable error rates to new unclassified data [29, 91]. Ideally, splitting the data into independent training sets for feature selection and a test set, which will not be used during the feature selection process, can give more reliable estimates of the prediction error to unknown data. Nevertheless, for small data sample sizes with large number of features, and especially when we don’t have the luxury of withholding a part of data external to the feature selection process for testing, an ‘external’ k-fold CV (ECV) should be employed for predicting reliable error rates to unclassified data [29, 91]. With the ECV process, at each stage of the CV process, the
same feature selection method is implemented only to the training data, external to the test subset, correcting in this way for the feature selection bias [29, 91].

In the following paragraphs the theory behind classification algorithms developed for the purposes of the present thesis will be presented.

4.4.1 Probabilistic neural network (PNN)

The PNN classifier [12], encompasses both the Bayes’ classification approach and the Parzen’s estimators of probability density functions. The decision function of the PNN classifier is described by:

\[
d_k(x) = \frac{1}{(2\pi)^{n/2}\sigma^n N_k} \sum_{i=1}^{N_k} e^{-\frac{||x-x_i||^2}{2\sigma^2}}
\]

Eq. 30

where \(x_i\) is the \(i_{th}\) training input pattern, \(x\) is the unknown pattern to be classified, \(N_k\) is the number of patterns forming the class \(x_k\), \(n\) is the number of textural features forming the input pattern while sigma \(\sigma\) is an adjusting parameter, taking values ranging between 0 and 1. According to Eq. 30, as the distance between \(x\) and \(x_i\) (||\(x-x_i||||) increases, the exponential term approaches 0, indicating a small similarity between the two pattern vectors. On the other hand, as the distance between \(x\) and \(x_i\) (||\(x-x_i||||) decreases, the exponential term approaches 1, indicating a significant similarity between the two pattern vectors. As \(\sigma\) approaches 0, even small differences between \(x_i\) and \(x\) will provide a zero value for the exponential term, while larger values of sigma provide more smooth results. As it can be concluded, the selection of sigma affects the estimation error of the PNN and is determined experimentally by comparing the accuracies obtained for different values of the parameter. The unknown pattern \(x\) is classified to the class with the highest value of decision function \(d_k(x)\).
As presented in Figure 3, the basic PNN architecture consists of an input layer, a pattern layer, a summation layer, and an output layer. The input layer stores temporarily each pattern vector, which is fed to the network. The number of neurons (nodes) that structure the input layer is equal to the dimensionality of the input pattern. Each input pattern is mapped to each one of the neurons of the pattern layer. Each neuron in the pattern layer represents a training pattern. In the pattern layer, the Euclidean distance between the input and each training pattern is computed. The decision function (Eq. 30) is then applied to provide the output of the pattern neuron. The summation layer has one neuron for each class, and implements the summation term of Eq. 30 for the outputs of the patterns corresponding to the class. As it can be observed, each summation neuron is connected to the neurons of the corresponding pattern layer. The output layer contains one neuron and assigns the input vector to a class by implementing a classification rule. In particular, the unknown pattern is classified to the class with the highest value of decision function $d_k(x)$ [12].

4.4.2 Support vector machines (SVM)

In the case of linear separable data, the linear Support Vector Machine classifier (SVM) tries to find among all hyperplanes that minimize the training error, the one...
that separates the training data with maximum distance from their closest points (maximal margin hyperplane). This hyperplane for binary pattern classification problems is given by

$$y_i[w^T x_i + b] \geq 1, \ldots, n$$  \hspace{1cm} \text{Eq. 31}

where $x_i$ are the training data belonging to either class $y_i = [-1, +1]$, $w$ are weight parameters and $b$ a bias parameter [16]. The maximal margin hyperplane is the one that satisfies the constrains of Eq. 31, while at the same time minimizes $||w||^2$. The latter is a quadratic optimization problem with inequality constrains that can be solved using the Lagrangian method by maximizing

$$L_d(a) = \sum_{i=1}^{n} a_i - \frac{1}{2} \sum_{i,j=1}^{n} y_i y_j a_i a_j x_i^T x_j$$  \hspace{1cm} \text{Eq. 32}

subject to

$$a_i \geq 0$$

$$\sum_{i=1}^{n} a_i y_i = 0$$  \hspace{1cm} \text{Eq. 33}

In a matrix notation the problem can be expressed as

Maximize $L_d(a) = -0.5a^T Ha + f^T a$

Under the constrain that $y^T a = 0, \quad a \geq 0$

where $(a)_i=a_i$, $H$ is the Hessian matrix that is calculated as $H_{ij} = y_i y_j (x_i^T x_j)$ $f$ is a unit vector of the form $f = 1 = [1 \ 1 \ \ldots \ 1]^T$

After the calculation of the Lagrange multipliers the maximal margin hyperplane can be constructed by computing the set of parameters $w_0$ and $b_0$ as follows:

$$w_0 = \sum_{i=1}^{n} a_0 y_i x_i, \quad i = 1, \ldots, n$$  \hspace{1cm} \text{Eq. 35}
where \( N_{sv} \) is the number of support vectors, that is, the fraction of training data that are needed for the construction of the maximal margin hyperplane. The Lagrange multipliers of support vectors are positive \( a_i > 0 \) whereas the Lagrange multipliers of the remaining training data are zero \( a_i = 0 \). After having calculated \( a_i, w_0 \) and \( b_0 \) the discriminant function of the linear SVM classifier can be deduced:

\[
d(x) = \sum_{i=1}^{N} w_0 x_i + b_0 = \sum_{i=1}^{N} a_i y_j x^T x_j + b_0
\]

Eq. 36

The non-linear SVM classifier [16] is designed for non-linear separable data. The basic idea comprises two consecutive steps: i/ Map the input feature space into a higher dimensional feature space, using a non-linear transformation function (kernel). The mapping is performed in order to find a feature space, in which data can be linearly separable. ii/ In that feature space, the machine constructs the maximal margin hyperplane as described before. The discriminant function of the non-linear SVM classifier for two-class classification problems is:

\[
d(x) = \sum_{i=1}^{N} a_i y_j K(x, x_i) + b_0
\]

Eq. 37

subject to \( 0 < a_i < C \), where \( x_i \) are the training data belonging to either class \( y_i \in [+1, -1] \), \( N \) is the number of training samples, \( a_i \) are the Lagrange multiplies, \( b_0 \) the bias weight coefficient, \( K(x, x_i) \) the kernel function and \( C \) a cost parameter that influences the tolerance of misclassifications. Most popular kernel functions are considered the Radial Basis Function (RBF) and polynomial kernels. The parameter \( \sigma \) of the RBF kernel is usually experimentally determined. Note that in some cases the bias parameter \( b_0 \) can be incorporated into the kernel function (i.e. in the case of Gaussian kernel) and thus can be dropped from Eq. 38 [16].

\[
K_{RBF}(x, x_i) = \exp \left( -\frac{\|x - x_i\|^2}{2\sigma^2} \right)
\]

Eq. 38
4.4.3 Least squares features transformation (LSFT)

To enhance the discrimination accuracy of the classification algorithms employed in this thesis, training patterns \( x_{ij} \), prior to entering the classifier, were transformed by means of a non-linear least squares feature transformation (LSFT) technique, to render classes more separable by clustering the patterns of each class around arbitrary pre-selected points. The proposed LSFT method is an extension of the linear least squares mapping technique, introduced by [17]. Initially, pattern vectors were extended with \( n \)-degree elements. Let \( x = [x_1 \ x_2 \ \ldots \ x_d] \) be a pattern vector, where \( d \) is the feature space dimensionality, and \( x_i, \ i=1,2,\ldots,d \) are the feature values of pattern \( i \). The pattern vector \( x \) was augmented with the up to \( n \)-th degree elements so that, finally, the augmented pattern vector \( \hat{x} \) consisted of all polynomial \( k \)-degree terms \( (k=1,2,\ldots,n) \) of the form:

\[
\hat{x} = \begin{bmatrix}
  x_i^p & i=1,2,\ldots,d, \ p=1,2,\ldots,n, \\
  x_i x_j^p & i,j=1,2,\ldots,d, \ i \neq j, \ p,q=1,2,\ldots,n-1, p<q, \\
  x_i x_j x_k^p & i,j,k=1,2,\ldots,d, \ i \neq j \neq k, \ p,q,r=1,2,\ldots,n-2, p<q<r, \\
  \vdots \\
  x_i x_j \ldots x_{i(n-1)}^p & i,i_2,\ldots,i_{(n-1)}=1,2,\ldots,d, \ i_i \neq i_2 \neq \ldots \neq i_{(n-1)}, \\
  [x_i x_j \ldots x_i] & i,i_2,\ldots,i_n=1,2,\ldots,d, \ i_i \neq i_2 \neq \ldots \neq i_n
\end{bmatrix}
\]

The dimensionality of the extended pattern vector \( \hat{x} \) is equal to [13]:

\[
\hat{d} = \frac{(d+n)!}{d!n!} - 1.
\]

For the formulation of a LSFT 2-class problem, let space \( S \), with dimensionality equal to the number of classes \( (K = 2) \), and let \( P_i = [p_{i1} \ p_{i2}], \ i = 1, 2 \) be arbitrary defined points in space \( S \), corresponding to each class \( i \). A transformation \( T \) is sought such that the total mean square error between the transformed extended vectors \( T\hat{x}_i \) and \( P_i \) is minimized as follows (assuming equal a-priori probabilities for each class \( i \)):
\[ \nabla_T \left[ \sum_{i=1}^{K} \left( \frac{1}{N_i} \sum_{j=1}^{N_i} (T\hat{x}_{ij} - P_i)'(T\hat{x}_{ij} - P_i) \right) \right] = 0 \quad \text{Eq. 41} \]

or

\[ \sum_{i=1}^{K} \left( \frac{1}{N_i} \sum_{j=1}^{N_i} \left[ \nabla_T (\hat{x}_{ij}'T'\hat{x}_{ij}) - 2\nabla_T (\hat{x}_{ij}'P_i) + \nabla_T (P_i'P_i) \right] \right) = 0 \quad \text{Eq. 42} \]

where \( K \) is the number of classes, \( N_i \) is the number of patterns of class \( i \), and \( \hat{x}_{ij} \) are the \( n \)-degree extended training patterns of class \( i \). Applying basic matrix algebra to the terms of Equation 4.37:

\[ \nabla_T (\hat{x}_{ij}'T'\hat{x}_{ij}) = 2T(\hat{x}_{ij}\hat{x}_{ij}') \quad \text{Eq. 43} \]

\[ \nabla_T (\hat{x}_{ij}'P_i) = P_i\hat{x}_{ij}' \quad \text{Eq. 44} \]

\[ \nabla_T (P_i'P_i) = 0 \quad \text{Eq. 45} \]

Equations (6-9) give:

\[ \sum_{i=1}^{K} \left( \frac{1}{N_i} \sum_{j=1}^{N_i} \left[ 2T(\hat{x}_{ij}\hat{x}_{ij}') - 2P_i\hat{x}_{ij}' \right] \right) = 0 \quad \text{Eq. 46} \]

or

\[ T \sum_{i=1}^{K} \left( \frac{1}{N_i} \sum_{j=1}^{N_i} \hat{x}_{ij}\hat{x}_{ij}' \right) - \sum_{i=1}^{K} \left( \frac{1}{N_i} \sum_{j=1}^{N_i} P_i\hat{x}_{ij}' \right) = 0 \quad \text{Eq. 47} \]

which results in:

\[ T = \left[ \sum_{i=1}^{K} \left( \frac{1}{N_i} \sum_{j=1}^{N_i} P_i\hat{x}_{ij}' \right) \right]^{-1} \left[ \sum_{i=1}^{K} \left( \frac{1}{N_i} \sum_{j=1}^{N_i} \hat{x}_{ij}\hat{x}_{ij}' \right) \right]^{-1} \quad \text{Eq. 48} \]
Transformation matrix $T$ is a $K \times d$ matrix, so the decision space dimensionality is equal to the number of brain tumor classes.

The LSFT procedure was applied in the discriminant functions of the classifiers employed in the present thesis resulting in the LSFT-PNN and the LSFT-SVM classification algorithms. By applying the LSFT procedure to the discriminant function of the PNN (Eq. 30) the resulting discriminant function of the LSFT-PNN is:

$$d_k(x) = \frac{1}{{\hat n}} \sum_{i=1}^{N_k} e^{-\frac{(\tau^T - \tau^T \hat y_j)^T (\tau^T - \tau^T \hat y_j)}{2\sigma^2}}$$  \hspace{1cm} \text{Eq. 49}$$

Likewise the discriminant function of the SVM-RBF classifier (Eq. 38) was transformed to:

$$f(x) = \text{sign} \left[ \sum_{i=1}^{N_x} a_i y_i \exp \left( \frac{-\|T \hat x_i - T \hat x \|^2}{2\sigma^2} \right) + b \right]$$  \hspace{1cm} \text{Eq. 50}$$

4.4.4 Bootstrap aggregation (Bagging)

Bagging, which stands for bootstrap aggregation, is another way of manipulating training data for ensemble classification schemes. In each iteration, the training subset is bootstrapped (resampled with replacement), to generate a different training subset. The logic behind bagging is that unstable classifiers, such as neural networks and decision trees, whose behavior could be significantly changed by small fluctuations in the training subset, are more likely to be stabilized after being trained with different input data [18]. Although the SVM classifier has been shown to provide a good generalization performance, the classification result of the SVM is often far from the theoretically expected level because SVM implementations usually employ approximation techniques [92]. In the present thesis, a bagging ensemble of three LSFT-SVMs (Eq. 50) was used to increase the discrimination accuracy of the proposed classification scheme.
PART II
EXPERIMENTAL RESEARCH
CHAPTER 5 - Improving brain tumor characterization on MRI by probabilistic neural networks and non-linear transformation of textural features

This chapter presents the design, implementation and evaluation of a pattern recognition system, which aims towards improving brain tumor classification accuracy by analyzing routinely taken T1 post-contrast MR images. Employing a two-level hierarchical decision tree, distinction between metastatic and primary brain tumors and between gliomas and meningiomas were performed at the first and second level of the decision tree, respectively. Additionally this chapter demonstrates that by conditioning the 2D features generated from the MR images by means of a non-linear least squares features transformation, the performance of the PNN classifier was boosted significantly. The proposed classification system has been presented in publication [93] (Appendix I).
5.1 Introduction

Brain tumor characterization is a process that requires a complicated assessment of the various MR image features and is typically performed by experienced radiologists. An expert radiologist performs this task with a significant degree of precision and accuracy, despite the inherently subjective nature of many of the decisions associated with this process. Nevertheless, in the effort to deliver more effective treatment, clinicians are continuously seeking for greater accuracy in the pathological characterization of brain tissues mainly from imaging investigations [9].

5.2 Review of the literature

To this need, image analysis techniques have been employed in previous studies for the extraction of diagnostic information from MR images [4, 8, 9]. These studies have employed pattern recognition and texture analysis techniques to characterize human brain tumors. In a recent study [6], an SVM-based classification system has achieved 95% overall accuracy in discriminating between gliomas and meningiomas. In another study [8], the hierarchical ascending classification with correspondence factorial analysis has been used for discriminating between different tumor types, with accuracies ranging between 49% (tumors versus oedemas) and 63% (benign versus malignant tumors). In a previous study [9], discriminant analysis and the k-nearest neighbor classifier have been adopted for distinguishing between human brain tumors and oedematous tissues, achieving maximum overall accuracy of 95%. In another study [94], several non-pictorial diagnostic factors, such as age, oedema, blood supply, calcification and haemorrhage, that were employed in an SVM classification scheme, have been found to be important in assessing brain gliomas. Finally, more recent studies have employed MR spectroscopic features [20, 83, 84, 95, 96] or combination of textural and spectroscopic features to discriminate between various types of brain tumors achieving accuracies up to 99% [86].

5.3 Brain tumor characterization employing 2D MR textural features

The aim was to design, implement and evaluate a pattern recognition system, which, by analyzing routinely taken T1 post-contrast MR images, would improve
brain tumor classification accuracy. Employing a two-level hierarchical decision tree (Figure 4), distinction between metastatic and primary brain tumors and between gliomas and meningiomas were performed at the first and second level of the decision tree, respectively. Additionally, it was demonstrated that by employing textural features from MR images and by conditioning those features by means of a non-linear least squares features transformation (see chapter 4.4.3), the performance of the PNN classifier was boosted significantly.

![Hierarchical tree classification scheme](image)

**Figure 4 - Hierarchical tree classification scheme**

### 5.3.1 Clinical material

A total number of 67 T1-weighted gadolinium-enhanced MR images were obtained from the Hellenic Airforce Hospital with verified intracranial tumors, using a SIEMENS-Sonata 1.5 Tesla MR Unit. The image dataset comprised 21 metastases, 19 meningiomas and 27 gliomas. From each case, only T1-weighted post-contrast (Gadolinium) images, with spin echo sequence, echo time 15 ms and repetition time 500 ms, were used for further analysis. The reason for employing T1 post-contrast images is the increased diagnostic information that they encapsulate in comparison to pre-contrast T1 or T2 weighted images. More specifically, contrast administration assists in the separation of tumor from oedema improving visualization, localization and tumor margin delineation. Contrast enhancement is intense because of the hi-
degree of blood brain barrier disruption [97]. Transverse images were selected through the tumor’s center by an expert radiologist.

5.3.2 Feature extraction and reduction

Utilizing these images, the radiologist specified square ROIs within the tumor area. Each ROI was semi-automatically drawn around a pixel by a simple click on the mouse. From each ROI, a series of 36 2D features were extracted; 4 features from the ROI’s histogram, 22 from the co-occurrence matrices [10], and 10 from the run-length matrices [11]. All features were normalized to zero mean and unit standard deviation [13].

Regarding the latter, only 2-class classification problems (primary Vs secondary and gliomas Vs meningiomas) were considered, embedded in a two-level hierarchical decision-tree structure. In order to reduce feature dimensionality, the non-parametric Wilcoxon rank-sum test was employed. Accordingly, only features of high discriminatory ability (p<0.001), between the patterns of two classes, were selected to feed the classification scheme.

Images were obtained from the hospital’s database in DICOM format, and using custom software developed in C++, images were read, displayed, and ROIs were extracted for further processing (Figure 5).
5.3.3 Design of the classification scheme

A two level hierarchical decision tree was designed to discriminate the metastatic brain tumor cases from the gliomas and meningiomas (primary brain tumors) cases (Figure 4). At the 1\textsuperscript{st} level, the gliomas and the meningiomas cases were grouped into the primary brain tumor class and were classified against the metastatic brain tumor cases. At the 2\textsuperscript{nd} level, the primary tumor cases were further classified into cases with gliomas and meningiomas.

At each level, classification was performed using two different LSFT-PNN classifiers. At the 1\textsuperscript{st} level of the decision tree, a third degree (cubic) LSFT-PNN ($k = 3$ in Eq. 39) was employed to discriminate between primary and metastatic tumors while, at the 2\textsuperscript{nd} level, a second degree (quadratic) LSFT-PNN ($k = 2$ in Eq. 39) was used to classify gliomas and meningiomas. The choice of the classifier’s degree was made on the basis of optimal classification, following a multiple experimentation procedure.

Prior to entering the classification system, each classifier was optimized employing the available dataset. Optimization was performed, separately at both
levels of the decision tree, by exhaustively combining (in all possible combinations of 2, 3, etc. features) the statistically reduced feature vectors (10 features of high discriminatory power (p<0.001) were retained) and by using the LOO method [13], for assessing the performance of each feature combination.

The LSFT-PNN and the PNN classification schemes were optimized with respect to parameter settings and available feature data. The spread of Gaussian function for the LSFT-PNN and the PNN classifiers was experimentally set equal to $\sigma = 0.3$.

To avoid overfitting conditions, which may occur by using the same dataset in the feature selection and system evaluation stages, ECV method [29] was also used. Accordingly, the dataset was split in two sets, one was used for optimum classifier design (⅔ of the dataset) and the other for evaluation (⅓ of the dataset). Optimum classifier design was achieved by employing i/ the Wilcoxon non-parametric test for feature reduction and ii/ the LOO and exhaustive search methods for determining the highest classification accuracy with the least number of features. That optimum classifier design was next used to classify the evaluation subset. This cycle (design-classification) was repeated ten times, each time picking the training subset randomly and forming the evaluation subset by the remaining data. Finally, classification accuracy results were averaged for assessing the generalization performance of the proposed method.

This type of classifier training required several hours of processing time, while classification time, once the system has been trained, was infinitesimal. The overall accuracy of the classification system, in discriminating metastatic brain tumors from gliomas and meningiomas cases, was determined by multiplying the system’s performance at each level [13].

5.3.4 Results

The complexity of the problem has led us to adopt a hierarchical decision tree structure (see Figure 4). The overall classification accuracy at the 1st level of the decision tree was 94.03% employing the cubic LSFT-PNN classifier. Individual accuracies in discriminating between primary and secondary brain tumors were 93.48% and 95.24% respectively (Table 2).
Best feature vector, used for the optimal design of the cubic LSFT-PNN classifier, comprised the mean value, entropy, and difference entropy. Employing the ECV method, the mean overall accuracy of the cubic LSFT-PNN classifier was 78.26%, while the mean accuracies for primary and secondary brain tumors discrimination were 81.25% and 71.43% respectively.

The performance of the cubic LSFT-PNN algorithm, used at the 1st level of the decision tree, was tested against the PNN, the linear LSFT-PNN, the SVM-RBF, and the Artificial Neural Network (ANN) classifiers, which were trained in a similar manner to the cubic LSFT-PNN classifier. Comparative classification results employing the LOO and the ECV methods are presented in Table 3 and Table 4 respectively as well as in Figure 6.
Table 4 - Classification results for discriminating primary and secondary brain tumors utilizing the ECV method (averaged results after ten repetitions)

<table>
<thead>
<tr>
<th>Method</th>
<th>Primary Brain Tumors Accuracy (%)</th>
<th>Secondary Brain Tumors Accuracy (%)</th>
<th>Overall Accuracy (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PNN</td>
<td>84.38</td>
<td>52.86</td>
<td>74.78</td>
</tr>
<tr>
<td>Linear LSFT-PNN</td>
<td>89.38</td>
<td>37.14</td>
<td>73.48</td>
</tr>
<tr>
<td>SVM-RBF</td>
<td>93.75</td>
<td>30.00</td>
<td>74.35</td>
</tr>
<tr>
<td>ANN</td>
<td>88.13</td>
<td>61.43</td>
<td>80.00</td>
</tr>
<tr>
<td>Cubic LSFT-PNN</td>
<td>81.25</td>
<td>71.43</td>
<td>78.26</td>
</tr>
</tbody>
</table>

Figure 6 - Overall classification accuracy of the algorithms used for discriminating primary and secondary tumors

Figure 7 show scatter diagrams displaying primary and secondary tumor class separation for the cubic LSFT-PNN, the PNN, the SVM-RBF, and the ANN classifiers.
Figure 7 - Scatter diagrams of the optimum feature combination of the i/ cubic LSFT-PNN, ii/ PNN, iii/ SVM-RBF and iv/ ANN classifiers and the corresponding decision boundaries for discriminating primary and secondary tumors.

At the 2\textsuperscript{nd} level of the decision tree, employing the quadratic LSFT-PNN classifier, discrimination accuracy between the two types of primary brain tumors (gliomas and meningiomas) was 100\% (Table 5).

<table>
<thead>
<tr>
<th></th>
<th>Gliomas</th>
<th>Meningiomas</th>
<th>Accuracy (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gliomas</td>
<td>27</td>
<td>0</td>
<td>100</td>
</tr>
<tr>
<td>Meningiomas</td>
<td>0</td>
<td>19</td>
<td>100</td>
</tr>
</tbody>
</table>

The best feature vector, employed for the optimal design of the quadratic LSFT-PNN classifier, comprised the mean value, angular second moment, and the inverse
difference moment. Utilizing the ECV technique, the mean overall accuracy of the quadratic LSFT-PNN classifier was 99.33%, while the mean accuracies for gliomas and meningiomas discrimination were 88.89% and 100% respectively.

The classification accuracy of the quadratic LSFT-PNN classification scheme, used at the 2nd level of the decision tree, was tested against that of the PNN, the linear LSFT-PNN, the SVM-RBF, and the ANN classifiers. Both PNN and linear LSFT-PNN misclassified one glioma case resulting in 97.83% overall accuracy while SVM-RBF and ANN classifiers achieved overall discrimination accuracy of 100% and 93.43% respectively (Table 6, Table 7) (Figure 8).

Table 6 - Classification results for discriminating gliomas and meningiomas employing the LOO method

<table>
<thead>
<tr>
<th></th>
<th>Gliomas Accuracy (%)</th>
<th>Meningiomas Accuracy (%)</th>
<th>Overall Accuracy (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PNN</td>
<td>96.30</td>
<td>100</td>
<td>97.83</td>
</tr>
<tr>
<td>Linear LSFT-PNN</td>
<td>96.30</td>
<td>100</td>
<td>97.83</td>
</tr>
<tr>
<td>SVM-RBF</td>
<td>100</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>ANN</td>
<td>92.59</td>
<td>94.74</td>
<td>93.43</td>
</tr>
<tr>
<td>Quadratic LSFT-PNN</td>
<td>100</td>
<td>100</td>
<td>100</td>
</tr>
</tbody>
</table>

Table 7 - Classification results for discriminating gliomas and meningiomas utilizing the ECV method (averaged results after ten repetitions)

<table>
<thead>
<tr>
<th></th>
<th>Gliomas Accuracy (%)</th>
<th>Meningiomas Accuracy (%)</th>
<th>Overall Accuracy (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PNN</td>
<td>94.44</td>
<td>85.00</td>
<td>90.67</td>
</tr>
<tr>
<td>Linear LSFT-PNN</td>
<td>90.00</td>
<td>86.67</td>
<td>88.67</td>
</tr>
<tr>
<td>SVM-RBF</td>
<td>100</td>
<td>43.33</td>
<td>77.33</td>
</tr>
<tr>
<td>ANN</td>
<td>94.44</td>
<td>83.33</td>
<td>90</td>
</tr>
<tr>
<td>Quadratic LSFT-PNN</td>
<td>88.89</td>
<td>100</td>
<td>99.33</td>
</tr>
</tbody>
</table>
Figure 8 - Overall classification accuracy of the algorithms used for discriminating gliomas and meningiomas

Figure 9 show scatter diagrams displaying gliomas and meningiomas class separation employing the quadratic LSFT-PNN, PNN, SVM-RBF, and ANN classifiers.
Figure 9 - Scatter diagrams of the optimum feature combination of the i/ cubic LSFT-PNN, ii/ PNN, iii/ SVM-RBF and iv/ ANN classifiers and the corresponding decision boundaries for discriminating gliomas and meningiomas

The overall accuracies of the classification system in discriminating metastatic tumors from gliomas and meningiomas can be obtained by multiplying the corresponding accuracies achieved at each level of the decision tree [13]. Consequently, classification accuracies were 95.24% for the metastatic and 93.48% for both gliomas and meningiomas brain tumor cases, while employing the ECV method the classification accuracies were 71.43% for the metastatic, 72.22% for gliomas and 81.25% for meningiomas.

5.3.5 Discussion and contribution

The LSFT-PNN outperformed the PNN at both levels of the decision tree. At the 1st level, the LSFT-PNN achieved a sensitivity of 93.48% against PNN’s 86.96% in correctly characterizing primary tumors, assigning three more primary brain tumors to the appropriate class. This is important, since the precision of such a decision may be crucial in patient management.

On the other hand, the specificity achieved by both classifiers in assigning the metastatic brain tumors to the correct classes was the same (95.24%), both missing out only one secondary brain tumor. Again, this is of value since metastatic tumors require specific treatment protocols, such as radiation therapy and chemotherapy, while primary tumors may also require surgical intervention [98, 99]. The best features combination of the cubic LSFT-PNN classifier, at the 1st level of the decision tree, expresses the signal strength (mean value) and the degree of the in-homogeneity
(entropy and difference entropy) in the gray-tones of the ROIs. In a previous study [83] employing only MR spectroscopic data and the LS-SVM classification algorithm, precisions in distinguishing between metastatic brain tumors and meningiomas or glioblastomas or astrocytomas were 97%, 59%, and 96% respectively. Our findings are comparable, however employing solely textural features from the T1-contrast enhanced MR images.

At the 2nd level of the decision tree, the quadratic LSFT-PNN discriminated correctly all gliomas and meningiomas cases while the PNN classifier failed to classify correctly one glioma case. The best features combination of the quadratic LSFT-PNN expresses the signal strength (mean value) and a measure of the homogeneity (angular second moment and inverse difference moment) in the gray-tones of the ROIs [10]. These textural characteristics are related to textural parameters that physicians employ in diagnosis and they are proportional to the textural imprint of these two types of brain tumors, i.e. gliomas have heterogeneous texture while meningiomas appear to be homogeneous in MR imaging. In a recent study [6], an SVM-based classification system achieved 95% overall accuracy in discriminating between gliomas and meningiomas, employing as features image intensities from four sequences (T1, T2, PD, GD). When MR spectra from the lesions were also included as features, classification accuracy reached 99.8%. These results are comparable with our findings regarding discrimination between gliomas and meningiomas, where we have employed solely textural features from T1 post-contrast MR images.

Considering the results, it can be claimed that the non-linear LSFT-PNN outperforms the PNN and the linear LSFT-PNN. This may be attributed to the increased class separability that the LSFT procedure provides, especially when non-linear terms are introduced in the classifier’s discriminant function. Another advantage of the LSFT-PNN is the dimensionality reduction, equal to the number of classes, independently of the number of features, which leads to more robust classification. The computational requirements of the LSFT-PNN classifier are comparable to those of the PNN, as the additional time required to perform the LSFT procedure is gained in the classification step, due to the reduced dimensionality of the problem.

Additionally, the proposed non-linear LSFT-PNN algorithm was compared against the SVM-RBF and the ANN classifiers at both levels of the hierarchical decision tree. Judging from the results, the proposed algorithm achieved higher
discrimination accuracies than the SVM-RBF, at both levels of the decision tree, while its precision was close to the ANN classifier in discriminating primary from secondary tumors. However, it must be noted that both SVM-RBF and ANN classifiers required a significant amount of processing time in their training stage. The computational times required for the training and evaluation procedures (10 repetitions of ECV employing LOO and exhaustive search) were, approximately, 40 minutes for the proposed LSFT-PNN algorithm, 16 hours for the SVM-RBF classifier, and 11 hours for the ANN classifier (employing the sequential forward selection technique [13], since the exhaustive search was unrealistically time demanding for the ANN). This may be attributed to their internal optimization procedures, i.e. the sequential optimization procedure for the SVM-RBF and the back-propagation procedure for the ANN. On the other hand, the proposed algorithm does not require optimization, rendering the classification system fast and efficient in its training.

Employing the ECV method, the overall and individual discrimination accuracies were decreased. However, the adoption of this method rendered the system more general in its behavior regarding the classification of new datasets. The overall discrimination accuracy decrement using the ECV method was in accordance with [29]. The determination of a unique best feature vector was not possible employing the ECV technique as, at each repetition, different feature vectors were produced. However, most of those features were related to texture homogeneity of the ROIs.

The contribution of this approach constitutes the development of a pattern recognition system that improves discrimination accuracies between metastatic and primary brain tumors and between gliomas and meningiomas employing a two level hierarchical decision tree, a modified non-linear PNN classification algorithm and 2-dimensional MR textural features. An evolution of this system that exploits the volumetric information derived from an MRI examination is presented in the following section.

5.3.6 Summary and conclusions

The aim was to design, implement, and evaluate a software pattern recognition system in discriminating between metastatic and primary brain tumors and between gliomas and meningiomas employing a two level hierarchical decision tree using the
LSFT-PNN classification algorithm. Least squares features transformation was proved to improve the performance of the PNN classifier, mainly due to the increased class separability and to dimensionality reduction that the LSFT procedure provides.
CHAPTER 6 - Enhancing the discrimination accuracy between metastases, gliomas, and meningiomas on brain MRI by volumetric textural features and ensemble pattern recognition methods

This chapter presents the design, implementation and evaluation of a pattern recognition system employing 3D textural features for improving brain tumor classification accuracies when analyzing routinely taken T1 post-contrast MR-image series. Employing an SVM-based ensemble classification scheme along with bootstrap aggregation at each node of a two-level hierarchical decision tree, discrimination between metastatic and primary brain tumors at the first level and between gliomas (malignant tumors) and meningiomas (benign tumors) at the second level was performed. Additionally this chapter demonstrates a modified RBF kernel for the SVM classifier that incorporated the LSFT technique to improve classification accuracy. The proposed classification system has been presented in publication [100] (Appendix I).
6.1 Introduction

The subjective nature of many of the decisions related with the process of brain tumor characterization has led clinicians to continuously seek for greater accuracy in the characterization of brain tumor tissues, mainly from MR imaging findings [9]. The introduction of pattern recognition techniques has enabled experts to extract diagnostic information from the displayed texture on MR images. However, most of the proposed pattern recognition systems are limited to the analysis of textural features derived from a 2-dimensional image slice through the center of the tumor, despite the fact that often tumors extend to more than one slice. Thus, the exploitation of multi-slice volumetric features may offer additional information that will improve the accuracy of these systems.

6.2 Review of the literature

Until now, a few studies have employed 3D textural features in pattern recognition systems for improving the discrimination accuracies attained by 2D features. In particular, a recent study [101] has shown that the calculation of 3D texture measures from low resolution CT images might be useful in predicting micro-architectural properties of bone. In another study [102], intensity, gradient, and anisotropy 3D textural features have been used for separating between brain MR images of controls and patients suffering from white-matter encephalopathy and/or Alzheimer’s disease. Furthermore, another study [103] has found that 3D volumetric features were more sensitive and more specific than corresponding 2D features in assessing patterns of emphysema ranging from mild to severe and in distinguishing normal non-smokers from normal smokers, while in an other study [104] it has been shown that 3D features achieved higher classification accuracies when applied to lung pathology.

6.3 Brain tumor characterization employing 3D MR textural features

The aim was to extend and improve the accuracy on characterizing brain tumors by designing, implementing, and evaluating a pattern recognition system employing 3D textural features for improving brain tumor classification accuracies when
analyzing routinely taken T1 post-contrast MR-image series, ii/ by utilizing a SVM-based ensemble classification scheme along with bootstrap aggregation (bagging) at each node of a two-level hierarchical decision tree, for discriminating between metastatic and primary brain tumors at the first level and between gliomas (malignant tumors) and meningiomas (benign tumors) at the second level. These brain tumor categories were selected on the fact that brain metastasis occurs in 20% to 40% of all cancer patients while meningiomas and gliomas are the two higher incidence rated types of benign and malignant primary brain tumors [32] and iii/ by introducing a modified RBF kernel for the SVM classifier that incorporated the LSFT technique to improve classification accuracy.

6.3.1 Clinical material

The dataset consisted of the brain MR-image series of sixty seven patients with verified and untreated intracranial tumors. Patients were examined on a Siemens Sonata 1.5 Tesla MRI Unit (Siemens, Erlangen, Germany) at the Hellenic Airforce Hospital, Greece. The dataset comprised 21 metastases, 19 meningiomas, and 27 gliomas. From each case, only the T1-weighted post-contrast (Gadolinium) series, with spin echo sequence, echo time 15 ms, repetition time 500 ms and slice thickness 1.5 mm was used for further processing. T1 post-contrast series was chosen because it encapsulates increased diagnostic information in comparison to pre-contrast T1 or T2 weighted series [97]. Contrast enhancement in gadolinium-administered MRI series is intense because of the high degree of blood brain barrier disruption. Moreover, contrast administration assists in the separation of tumor from oedema improving visualization, localization, and tumor margin delineation resulting in information-rich MR images [97].

6.3.2 Volume of interest extraction and feature calculation

Utilizing these MRI series, expert radiologists specified cubic VOIs within each tumor using a software program, developed for the purposes of the present thesis. The program was designed using the C++ programming language and the VTK [82]. The developed software utilized the marching cubes algorithm [81] to build 3-dimensional models from DICOM MRI-series and, thus, to provide the radiologist with a visual
aid for segmenting VOIs within brain tumors (Figure 10). Each segmented MRI-VOI was then used to calculate a set of parameters (features) that quantified properties of volume-texture within the brain tumor.

![Figure 10 - Custom made application for VOI acquisition and volumetric features extraction](image)

Haralick et. al. [10] and Galloway [11] have described a set of textural features, based on the gray-level co-occurrence and run-length matrices, that quantified textural properties of 2D images. Their 3D (volumetric) equivalents [14, 15] were employed in the present thesis for the purpose of quantifying textural volume properties of brain tumors. In a MRI-VOI, adjacency and consecutiveness occur in each of 13 directions (compared to 4 directions in a 2D image) and, thus, 13 gray-level co-occurrence and run-length matrices were generated [14, 15]. Additionally, this set was enriched with features derived from the VOI’s histogram (mean value, standard deviation, skewness and kurtosis). Thus, a set of 36 volumetric textural features was extracted for each brain tumor; 4 from the VOI’s histogram, 22 from the co-occurrence and 10 from the run-length matrices. All features were normalized to zero mean and unit standard deviation [13].
6.3.3 Design of the classification scheme

An LSFT-SVM based ensemble classification scheme (Figure 11) was designed to discriminate between secondary (metastatic), primary benign (meningiomas), and primary malignant (gliomas) brain tumors using a two level hierarchical decision tree. At the 1st level, gliomas and meningiomas were grouped into the primary brain tumor class and were classified against the metastatic brain tumor cases while at the 2nd level, the primary tumor cases were further classified into cases with gliomas and meningiomas.

![Flowchart of the classification scheme utilized](image-url)

Figure 11 - Flowchart of the classification scheme utilized

The ECV technique was used to avoid bias conditions [29], which may occur by using the same dataset in the feature selection and evaluation stages. Therefore, the dataset was randomly split in two subsets, one was used for optimal classifier design (⅔ of the dataset) and the other for evaluation (⅓ of the dataset). The optimum feature combination in the design stage was determined by employing the exhaustive search.
Accordingly, the LSFT-SVM classifier was designed by all possible feature combinations (up to 5 features), and at each combination the classifier’s performance was evaluated by means of the LOO [13] method. Thus, the optimal feature vector retained was the one that gave the highest classification accuracy with the least number of features (Figure 12).

![Figure 12 - Optimum feature vector combination determination procedure](image)

Next, employing the optimal feature vector, the design dataset was bootstrapped (resampled with replacement) according to the bagging technique (see chapter 4.4.4) three times and an equal number (3) of LSFT-SVM classifiers was designed. To ensure that patterns in each bootstrapped sample were selected randomly, an implementation of the mersenne twister random number generation engine was used [105]. That ensemble classifier design was next utilized to classify the evaluation subset. The output of each LSFT-SVM classifier was used in the formulation of a collective decision using the majority vote rule [106]. Thus, the output of the system was expressed as in Eq. 51.
where \( r \) is the number of classifiers and \( D_j \) is a binary decision value for the \( j^{th} \) class.

The whole design and evaluation (ECV) procedure was repeated ten times and the classification results were averaged. Apart from the linear (1\(^{st}\) degree), the quadratic (2\(^{nd}\) degree) LSFT procedure was also employed to investigate the classification accuracy behavior of the proposed LSFT-SVM classifier as higher-degree non-linear elements were introduced in its discriminant function.

Prior to classifying volumetric textural features with the proposed classification scheme, comparison was performed between the discrimination efficiency of 2D and 3D textural features at both levels of the decision tree. To extract the 2D textural features, the central slice of the each VOI was used to calculate the 2D co-occurrence and run-length matrices. Thus, the following 2D features were extracted: 4 features from the slice’s histogram, 22 from the co-occurrence matrices and 10 from the run-length matrices. The classification accuracies of both 2D and 3D features were evaluated employing the LOO method for all, up to 5, possible feature combinations.

### 6.3.4 Results

To assess the discrimination efficiency of volumetric features as compared to 2D features, a comparative evaluation was performed at both levels of the decision tree using the SVM classifier.

At the 1\(^{st}\) level, the overall classification accuracy employing 2D textural features was 89.55\%, employing skewness, correlation, difference entropy, gray level non uniformity and run length non uniformity features combination. Individual accuracies in discriminating between primary and secondary brain tumors were 97.83\% and 71.43\% respectively (Table 8). Figure 13 show scatter diagrams displaying primary and secondary tumor class separation for the SVM classifier employing 2D and 3D textural features.
Table 8 - SVM classifier truth table for discriminating primary from secondary tumors at the 1st tree level using 2D and 3D textural features

<table>
<thead>
<tr>
<th></th>
<th>Primary Brain Tumors 2D (3D)</th>
<th>Secondary Brain Tumors 2D (3D)</th>
<th>Accuracy (%) 2D (3D)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary Brain Tumors</td>
<td>45 (45)</td>
<td>1 (1)</td>
<td>97.83 (97.83)</td>
</tr>
<tr>
<td>Secondary Brain Tumors</td>
<td>6 (3)</td>
<td>15 (18)</td>
<td>71.43 (85.71)</td>
</tr>
<tr>
<td>Overall Accuracy</td>
<td></td>
<td></td>
<td>89.55 (94.03)</td>
</tr>
</tbody>
</table>

Best 2D feature vector, used for the optimal design of the SVM classifier, comprised skewness, correlation, difference entropy, gray-level non-uniformity, and run-length non-uniformity. Three dimensional features increased overall classification accuracy to 94.03% using the same classifier. The individual accuracies were 97.83% and 85.71% respectively (Table 8). The best volumetric feature vector comprised standard deviation, kurtosis, angular second moment, contrast and long run emphasis.

At the 2nd level of the decision tree, both 2D and 3D features achieved 100% discrimination accuracy between primary benign and malignant tumors. Comparative classification results for various numbers of features and for both tree-levels, employing 2D and 3D features, are presented in Table 9. Figure 14 show scatter
diagrams displaying meningiomas and gliomas class separation for the SVM classifier employing 2D and 3D textural features.

Table 9 - Comparative classification results between 2D and 3D textural features employing the SVM classifier at both levels of the decision tree

<table>
<thead>
<tr>
<th>Number of features</th>
<th>1st level: Primary vs Metastatic Overall Accuracy (%)</th>
<th>2nd level: Malignant vs Benign Overall Accuracy (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>2D Textural Features</td>
<td>3D Textural Features</td>
</tr>
<tr>
<td>1</td>
<td>73.13</td>
<td>76.12</td>
</tr>
<tr>
<td>2</td>
<td>82.09</td>
<td>83.58</td>
</tr>
<tr>
<td>3</td>
<td>86.57</td>
<td>89.55</td>
</tr>
<tr>
<td>4</td>
<td>88.06</td>
<td>91.04</td>
</tr>
<tr>
<td>5</td>
<td>89.55</td>
<td>94.03</td>
</tr>
</tbody>
</table>

Figure 14 - Scatter diagram of the 3 optimum features of the SVM classifier and the corresponding decision boundary for discriminating meningiomas from gliomas employing i/ 2D and ii/ 3D textural features

To further enhance volumetric feature classification accuracies, the linear and the quadratic LSFT-SVM classifiers were employed at both levels of the decision tree. The overall classification accuracies at the 1st level of the decision tree
employing the linear and the quadratic LSFT-SVM classifier were 88.06% and 97.01%, respectively. At the 2\textsuperscript{nd} level, the classification accuracy for both 1\textsuperscript{st} and 2\textsuperscript{nd} degree LSFT-SVM was 100% (Table 10).

Table 10 - Comparative classification results employing the linear and the quadratic LSFT-SVM classifiers for both levels of the decision tree

<table>
<thead>
<tr>
<th>Number of features</th>
<th>1\textsuperscript{st} level: Primary vs Metastatic Overall Accuracy (%)</th>
<th>2\textsuperscript{nd} level: Malignant vs Benign Overall Accuracy (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Linear LSFT</td>
<td>Quadratic LSFT</td>
</tr>
<tr>
<td>1</td>
<td>73.13</td>
<td>77.61</td>
</tr>
<tr>
<td>2</td>
<td>80.60</td>
<td>82.09</td>
</tr>
<tr>
<td>3</td>
<td>83.58</td>
<td>91.04</td>
</tr>
<tr>
<td>4</td>
<td>88.06</td>
<td>95.52</td>
</tr>
<tr>
<td>5</td>
<td>88.06</td>
<td>97.01</td>
</tr>
</tbody>
</table>

Figure 15 show the scatter diagrams of the decision space along with the corresponding decision boundaries for primary and secondary tumors and for benign and malignant tumors respectively, using the quadratic LSFT-SVM classifier. The decision boundary of the LSFT-SVM is a line that partitions the decision space into regions, one for each class, satisfying the equality \( f(x) = 0 \) (see Eq. 50). The classifier then assigns all the points on one region of the decision boundary as belonging to one class and all those on the other region as belonging to the other class.
Figure 15 - Decision space scatter diagram of the optimum 5 feature combination of the quadratic LSFT-SVM classifier and the corresponding decision boundary for discriminating i/ primary from metastatic tumors and ii/ gliomas from meningiomas employing 3D textural features

The overall classification accuracy at the 1st level of the decision tree using 3 bootstrap aggregated quadratic LSFT-SVM classifiers was 98.51% (Table 11). Best feature vector, used for the optimal design of the classification system, comprised the skewness, kurtosis, inverse difference moment, difference variance and run percentage. Regarding the 2nd level of the decision tree, all gliomas and meningiomas cases were correctly classified resulting in 100% overall classification accuracy. The optimal feature vector comprised the mean value, kurtosis, correlation, difference variance and run-length non-uniformity.
Table 11 - Classification results employing the LSFT-SVM ensemble classifier scheme (bagging)

<table>
<thead>
<tr>
<th>Number of features</th>
<th>Primary vs Metastatic Overall Accuracy (%)</th>
<th>Malignant vs Benign Overall Accuracy (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>82.09</td>
<td>93.48</td>
</tr>
<tr>
<td>2</td>
<td>91.04</td>
<td>95.65</td>
</tr>
<tr>
<td>3</td>
<td>94.03</td>
<td>97.83</td>
</tr>
<tr>
<td>4</td>
<td>97.01</td>
<td>100</td>
</tr>
<tr>
<td>5</td>
<td>98.51</td>
<td>100</td>
</tr>
</tbody>
</table>

Employing the ECV method for assessing the generalized performance of the system, the mean overall classification accuracy at the 1st level of the decision tree was 88.18%. At the 2nd level of the decision tree the mean overall accuracy for discriminating between gliomas and meningiomas was 97.33% (Table 12).

Table 12 - Classification results utilizing the ECV method and the LSFT-SVM ensemble classifier scheme (average and standard deviation after ten ECV repetitions)

<table>
<thead>
<tr>
<th>Number of features</th>
<th>Primary vs Metastatic Overall Accuracy (%)</th>
<th>Malignant vs Benign Overall Accuracy (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>67.27 ± 2.03</td>
<td>90.67 ± 3.65</td>
</tr>
<tr>
<td>2</td>
<td>71.82 ± 2.03</td>
<td>92 ± 5.58</td>
</tr>
<tr>
<td>3</td>
<td>79.09 ± 2.49</td>
<td>93.33 ± 4.71</td>
</tr>
<tr>
<td>4</td>
<td>84.55 ± 2.49</td>
<td>96 ± 3.65</td>
</tr>
<tr>
<td>5</td>
<td>88.18 ± 2.49</td>
<td>97.33 ± 2.65</td>
</tr>
</tbody>
</table>

The overall accuracies of the classification system in discriminating metastatic tumors from gliomas and meningiomas can be obtained by multiplying the corresponding accuracies achieved at each level of the decision tree [13].
Consequently, employing the ECV method the classification accuracies were 77.14% for the metastatic, 89.19% for gliomas and 93.33% for meningiomas.

6.3.5 Discussion and contribution

An essential outcome is that 3D features have significantly improved classification accuracy in discriminating primary from metastatic tumors as compared to 2D features (improvement from 89.55% to 94.03%). Such a significant improvement was not observed for the discrimination of benign from malignant tumors, since both 2D and 3D features have resulted in 100% accuracy.

The reason for selecting only the central slice of the VOI in order to extract 2D textural features was to comply with the methodology followed by most previous studies [8, 9]. In this way, we could emphasize the benefits of using 3D textural features, which code information from the whole VOI, compared to selecting just one slice and extracting 2D features from this slice. However, it has to be pointed out that high classification accuracies achieved by 3D texture metrics might be due to the fact that 3D features exploit additional information derived from all available slices (and not just the central slice).

Another important conclusion is that the utilization of LSFT-SVM ensemble classifier scheme further improved classification accuracy as compared to using individual SVM classifiers (the SVM or the linear LSFT-SVM) for both levels of the decision tree. More specifically, at the 1st level of the decision tree improvement was from 97.01% to 98.51%, with only one metastatic tumor misclassified. At the 2nd level all gliomas and meningiomas were correctly assigned to the proper class (100% accuracy). The enhanced performance of the LSFT-SVM ensemble classifier scheme might be attributed to the increased class separability that the LSFT procedure provides when non-linear terms were introduced in the classifier’s discriminant function. A worth-mentioning characteristic of the LSFT method is that the classification problem is reduced to 2 dimensions regardless of the dimensionality of the input feature space.

Features that optimized classification results of the ensemble scheme at the 1st level of the decision tree, encoded information related to the distribution asymmetry around the mean gray-tone value (skewness), the gray-tone distribution sharpness as compared to the normal distribution (kurtosis), the degree of homogeneity (inverse
difference moment), the amount of randomness (difference variance) and measures of the linear structures appeared in the VOI (run percentage). At the 2\textsuperscript{nd} level of the decision tree, the optimum features described the gray-tone linear dependencies (correlation), the dispersion of the gray-tone intensity values (sum average), the variance of the normalized grey-tones in the spatial domain (sum variance), and the degree of homogeneity of the VOI (inverse difference moment, run length non uniformity). Some of these textural characteristics are related to textural parameters that physicians employ in diagnosis [8] and they are proportional to the textural imprint of brain tumors, i.e. gliomas have heterogeneous texture while meningiomas appear to be homogeneous in MR imaging.

The ECV method enabled us to assess the generalization of the system to new ‘unseen’ data. Under the ECV, the LSFT-SVM ensemble classifier scheme achieved accuracy of 88.18\% and 97.33\% at the 1\textsuperscript{st} and 2\textsuperscript{nd} level of the decision tree respectively. Moreover, for comparative purposes, the system was constructed using the SVM classifier without the LSFT technique and without feature reduction. Results have shown an inferior performance of the system with 80.64\% and 90.32\% at the 1\textsuperscript{st} and 2\textsuperscript{nd} level of the decision tree respectively. Feature reduction enabled the elimination of features with poor discrimination accuracy, whereas LSFT improved class separability, enhancing in this way the overall classification performance of the system. Thus, results using the LSFT-SVM ensemble system indicate that the proposed method might be used for accurate discrimination of benign, malignant and metastatic brain tumors. The latter is of crucial importance. Primary and metastatic tumors follow different treatment protocols (radiation therapy and chemotherapy for metastatic tumors while primary tumors may also require surgical intervention [98, 99]). Moreover, malignant tumors, according to their grade, may require specific post-surgery treatment such as external beam radiotherapy or chemotherapy [107] while benign tumors may require stereotactic radiosurgery [108].

Considering the results, the proposed classification system constructed with 3D textural features achieved higher accuracies than those obtained by using solely 2D features. In particular, using the same brain tumor categories and an LSFT modified probabilistic neural network and the ECV technique, discrimination accuracies of 71.43\% for the metastatic, 72.22\% for gliomas and 81.25\% for meningiomas has been achieved. The classification system designed improved these accuracies to 77.14\% for the metastatic, 89.19\% for gliomas and 93.33\% for meningiomas.
Moreover, in a recent study [6], an SVM-based classification system discriminated gliomas and meningo\mami with 95% overall accuracy, employing as features image intensities from four MR sequences (T1, T2, PD and GD). When features derived from MR spectroscopy were also included, classification accuracy reached 99.8%. In another study [83], employing the LS-SVM classification algorithm and MR spectroscopic data, overall accuracies in distinguishing between secondary brain tumors and meningo\mami or glioblastomas or astrocytomas were 97%, 59%, and 96% respectively. Our findings are comparable, however employing solely volumetric textural features from the T1-contrast enhanced MRI series.

The computational time required for the training and evaluation procedures were, approximately, 11 hours for the proposed classification system. This time demanding computational load is attributed to the iterative methods used for best feature selection (exhaustive search), and for system’s evaluation (ECV, LOO, optimal classifier’s design and parameter estimation). However, once the system has been designed, no iterative processes are required in order to classify a new case. Thus, classification of new cases is instantaneous.

The contribution of this approach constitutes the development of a pattern recognition system that improves discrimination accuracies between metastatic and primary brain tumors and between gliomas and meningo\mami employing a two level hierarchical decision tree, a modified non-linear RBF kernel utilized in an ensemble of SVM classifiers and 3D MR textural features. An evolution of this system that exploits both the volumetric textural information derived from MRI and the information derived from MR spectroscopy is presented in the following section.

6.3.6 Summary and conclusions

The utilization of 3D textural features improved accuracy in the characterization of brain tumors on volumetric MR images as compared to using 2D textural features. LSFT-SVM ensemble classifier scheme further enhanced classification results.
CHAPTER 7 - Combining MR textural and spectroscopic features to discriminate between meningioma and solitary metastasis

This chapter presents the design, implementation and evaluation of a pattern recognition system employing MR textural and spectroscopic features for improving brain tumor classification accuracies. Employing an SVM-based classification scheme, discrimination between solitary metastatic tumors and meningiomas was performed.
7.1 Introduction

Cerebral metastases are the most frequent brain tumors in adults. They grow mainly in the brain or cerebellum and less frequently in the meninges [19]. However, solitary dural metastases are the second most frequent meningeal lesions, which from an imaging point of view are difficult to differentiate from meningiomas [20]. Both these tumoral forms can uptake MRI contrast agent in a similar manner. Occasionally, isolated forms of these metastatic tumors have radiological features that strongly suggest a primary tumor, and furthermore, their macroscopic appearance during surgery may even be taken for a meningioma [19].

Until now, several studies have proposed and developed pattern recognition systems to provide clinicians’ second opinion tools that will assist them in the characterization of brain tumors. However, some of them have utilized features derived only from the tumor’s texture [8, 9, 14, 93, 109] and a few only from the tumor’s MR spectroscopy data [83, 84, 86]. The combination of textural and spectroscopic features may offer additional information that will improve the accuracy of such pattern recognition systems. However, to the best of our knowledge, there are only two studies in literature that have attempted to combine in pattern recognition systems textural and spectroscopic features [6, 7].

7.2 Review of the literature

There are several case studies reported in the literature pointing out the problem of differential diagnosis between these two types of brain tumors [19, 21-25]. Most of these studies have indicated that there is a radiographic similarity between these types of tumors while many of them have reported that the radiological images of metastases even display a ‘dural tail’, a sign usually associated with meningiomas. In particular, Tagle et. al [19] have reported four cases of isolated meningeal metastases, where in all of them a meningioma had been considered as the main preoperative diagnosis. Lath et. al. [23] have documented a case of extra-axial metastatic adenocarcinoma of the prostate that closely simulated a frontal, parasagittal meningioma, which, however, was revealed at histopathology to be a metastasis from adenocarcinoma of the prostate. In an other study [21], Laidlaw et. al. reported a case of dural metastases which, on both pre-operative CT and MRI and at surgery, had the
typical appearance of a falcine meningioma. Histopathology and immunohistochemistry revealed adenocarcinoma of renal cell origin, and the renal primary was identified on subsequent abdominal investigation.

Regarding the combination of MR textural and spectroscopic analysis, there are only two studies in literature that have attempted to combine in pattern recognition systems textural and spectroscopic features [6, 7]. More specifically, Luts et. al. [6, 7] have attained discrimination accuracies of 97% for astrocytomas, 94% for oligoastrocytomas, 92% for oligodendrogliomas, 96% for meningiomas, and 98% for gliomas by employing a combination of 4 textural features (the averaged values of pixel intensities within the tumor boundaries from 4 sequences - T1, T2, PD and GD) and 10 spectroscopic features (one from each quantified metabolite from the MR-spectra) and the LS-SVM classification algorithm. In another study, Devos et. al. [6] by combining the same textural and spectroscopic features, have achieved mean classification accuracy of 99% for discriminating between low from high grade tumors, low from high grade gliomas, meningiomas from gliomas and grade II from grade III gliomas. However, both these studies, which have relied on the same dataset, have utilized the same methodology; they have i/ employed only one textural feature (average value), thus depriving their system from higher-order, information rich, textural features, and ii/ have used features from MRS-data, concerning 10 metabolites that are cumbersome to quantify on MRI in everyday clinical routine.

7.3 Brain tumor characterization employing 3D MR textural features and MR spectroscopic features

The aim was to further extend and improve the designed classification system on brain tumor characterization by additionally incorporating spectroscopic features to investigate whether the combination of post-contrast magnetic resonance image and spectroscopic features might improve discrimination between meningiomas and solitary dural metastases.

7.3.1 Clinical material

The clinical material utilized consisted of brain MR-image series and MR-spectra of forty patients with verified and untreated intracranial tumors. Patients were
examined on a Siemens Sonata 1.5 Tesla MRI Unit (Siemens, Erlangen, Germany) at the Hellenic Airforce Hospital, Greece. The dataset comprised 21 patients with solitary metastases and 19 patients with meningiomas. The mean age of the patients was 67 years old (standard deviation: 11, range: 40-86, 25 male, 15 female). From each case, only the T1-weighted post-contrast (Gadolinium) series, with spin echo sequence, echo time 15 ms, repetition time 500 ms and slice thickness 1.5 mm were used for further processing. Regarding the acquisition of MR-spectra, a single volume spectroscopy, short time echo (TE = 35ms), STEAM 1H-MRSI sequence was used. Spectroscopic VOIs were determined from the T1-weighted post-contrast axial images, positioned entirely within the boundaries of the tumor.

### 7.3.2 MRI and MRS feature extraction

Based on the previous findings of this thesis, volumetric textural features may significantly improve classification accuracy in discriminating primary from metastatic tumors as compared to 2D features. Thus, in the designed classification system volumetric textural features were utilized, extracted from the MR series employing custom developed software that was designed using the C++ programming language and the VTK [82]. Both textural and spectroscopic features were derived from the same tumor volume.

From each VOI, a series of 36 textural features were extracted; 4 features from the VOI’s histogram, 22 from the volumetric co-occurrence matrices [10, 14], and 10 from the volumetric run-length matrices [11, 15]. The histograms’ features describe the occurrence frequency of all the gray tones in the VOI. The co-occurrence matrix measures describe the overall spatial relationships that the gray tones have to one another in the VOI while the run-length features describe the heterogeneity and tonal distribution of the gray tones in the VOI [10, 11]. From the spectroscopic data of each tumor, three metabolites were evaluated (Cho, NAA, Cr) and the following metabolite integral ratios were formed: Cho/NAA, Cho/Cr, and NAA/Cr, to be used as features in the proposed pattern recognition system. These ratios are used in everyday clinical practice by radiologists for assessing various chemical properties of brain neoplasms, thus providing an added value in tumor characterization and management [27, 28]. All features were normalized to zero mean and unit standard deviation [13].
7.3.3 Design of the classification scheme

An SVM-RBF based classification scheme (Figure 16) was designed to discriminate between meningiomas and metastatic brain tumors employing both textural and spectroscopic features.

The system design comprised two stages: i/ features reduction and ii/ information rich features selection for optimum classification system design.

In the features reduction stage, all possible combinations of features (employing the exhaustive search method [13]) were tested for designing the SVM-RBF classifier and the precision of each design was tested by the LOO method [13]. Finally, the features’ combination that provided the highest classification with the least number of features comprised the best features set that was used in the next stage of the system design. In this stage, an additional step was taken in order to investigate the
discriminatory ability of each particular type of features as well as their combination. In particular, the proposed SVM-RBF classification system was designed and evaluated by using solely i/ textural features or ii/ spectroscopic features, and iii/ the combination of textural and spectroscopic features.

Regarding the second stage, optimum system design was accomplished by means of the ECV method [29] and employing the best feature combination attained at the first stage of the design. The ECV is essential because the system’s performance may be assessed on ‘unseen data’. Accordingly, all possible combinations of features, chosen from within the best feature combination, were formed (e.g. combinations of 2, 3, 4 etc.). For each feature combination, the dataset was randomly split in two subsets, one was used to design the SVM-RBF classifier (⅔ of the dataset, containing both classes in equal percentages) and the other to evaluate its performance (⅓ of the dataset) [29]. This procedure (design-evaluation) was repeated ten times, each time splitting the dataset into two subsets (design set: ⅔ and test set: ⅓), however, choosing randomly subsets’ members from the original dataset and recording the precision accuracies achieved. Finally, mean classification accuracies and variances were evaluated at each number of combined features.

7.3.4 Results

Highest classification accuracy in discriminating meningiomas from metastases was 95%, employing only textural features (kurtosis, entropy, difference entropy, run length non uniformity and long run emphasis). Individual accuracies in classifying correctly meningiomas was 94.74% and metastatic brain tumors 95.24%. Comparative classification results for various numbers of features are presented in (Table 13).
Table 13 - Comparative classification results for discriminating meningiomas from metastatic tumors employing solely textural features

<table>
<thead>
<tr>
<th>Number Of Features</th>
<th>Meningiomas Correctly Classified (%)</th>
<th>Metastasis Correctly Classified (%)</th>
<th>Overall Accuracy (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>63.16</td>
<td>85.71</td>
<td>75</td>
</tr>
<tr>
<td>2</td>
<td>78.95</td>
<td>95.24</td>
<td>87.5</td>
</tr>
<tr>
<td>3</td>
<td>84.21</td>
<td>95.24</td>
<td>90</td>
</tr>
<tr>
<td>4</td>
<td>89.47</td>
<td>95.24</td>
<td>92.5</td>
</tr>
<tr>
<td>5</td>
<td>94.74</td>
<td>95.24</td>
<td>95</td>
</tr>
</tbody>
</table>

Figure 17 shows the scatter diagram of the three best features combination along with the corresponding decision boundary. Figure 18 depicts the boxplots of the best textural features for both meningiomas and metastases, normalized according to Eq. 29. The distribution of the normalized feature values was overlaid on the boxplots, employing a gradient bar were darker parts indicate higher value occurrences. Values marked with the plus sign are outliers and the horizontal lines within the boxes indicate median values.
Figure 17 - Scatter diagram of the optimum three features combination and the corresponding decision boundary for discriminating meningiomas from metastatic tumors employing only textural features

Figure 18 - Boxplot of the best textural features for i/ meningiomas and ii/ metastatic cases

Employing solely spectroscopic features, the overall classification accuracy was 90%. The feature combination that gave the highest discrimination accuracy between meningiomas and metastases comprised all three metabolite ratios utilized in the present thesis (Cho/NAA, Cho/Cr and NAA/Cr). The individual accuracies obtained were 89.47% for meningiomas and 90.48% for metastatic tumors (Table 14).
Table 14 - Comparative classification results for discriminating meningiomas from metastatic tumors, employing solely spectroscopic features

<table>
<thead>
<tr>
<th>Number Of Features</th>
<th>Meningiomas Correctly Classified (%)</th>
<th>Metastasis Correctly Classified (%)</th>
<th>Overall Accuracy (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>84.21</td>
<td>85.71</td>
<td>85</td>
</tr>
<tr>
<td>2</td>
<td>89.47</td>
<td>85.71</td>
<td>87.5</td>
</tr>
<tr>
<td>3</td>
<td>89.47</td>
<td>90.48</td>
<td>90</td>
</tr>
</tbody>
</table>

Figure 19 illustrates the scatter diagram of the spectroscopic metabolite ratios along with the corresponding decision boundary while Figure 20 depicts the boxplots for meningiomas and metastases.

Figure 19 - Scatter diagram of the optimum spectroscopic features combination and the corresponding decision boundary for discriminating meningiomas from metastatic tumors
When the textural features were combined with the spectroscopic, the overall classification accuracy was 100%. Best feature vector, used for the optimal design of the SVM-RBF classifier, comprised correlation, sum average, difference entropy, long run emphasis and the Cho/NAA ratio. Comparative classification results for various numbers of features are presented in (Table 15).

Table 15 - Comparative classification results for discriminating meningiomas from metastatic tumors employing both textural and spectroscopic features

<table>
<thead>
<tr>
<th>Number Of Features</th>
<th>Meningiomas Correctly Classified (%)</th>
<th>Metastasis Correctly Classified (%)</th>
<th>Overall Accuracy (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>84.21</td>
<td>85.71</td>
<td>85</td>
</tr>
<tr>
<td>2</td>
<td>89.47</td>
<td>85.71</td>
<td>87.5</td>
</tr>
<tr>
<td>3</td>
<td>94.74</td>
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</tr>
<tr>
<td>4</td>
<td>94.74</td>
<td>100</td>
<td>97.5</td>
</tr>
<tr>
<td>5</td>
<td>100</td>
<td>100</td>
<td>100</td>
</tr>
</tbody>
</table>

Figure 20 - Boxplot of the spectroscopic features for i/ meningiomas and ii/ metastatic cases

Figure 21 shows the scatter diagram of the three best features combination along with the corresponding decision boundary while Figure 22 depicts the boxplot of the best features for meningiomas and metastases.
Figure 21 - Scatter diagram of the optimum three features combination and the corresponding decision boundary for discriminating meningiomas from metastatic tumors employing both textural and spectroscopic features

Figure 22 - Boxplot of the best combination of textural and spectroscopic for i/ meningiomas and ii/ metastatic cases

Employing the ECV method, for assessing the generalized performance of the system to ‘unseen data’, the mean overall classification accuracy was 92.15% employing 5 features. The mean individual accuracies were 96.66% for meningiomas and 88.57% for metastatic tumors. Classification results for the 10-fold ECV process for various numbers of features are graphically presented in Figure 23. The graph
illustrates the mean value and the standard deviation of the classification accuracy for each number of feature combinations tested.

Figure 23 - Means and standard deviations of classification accuracies achieved by the 10-fold ECV process for various numbers of features combinations

7.3.5 Discussion and contribution

One significant finding is that the combination of textural and spectroscopic features improved discrimination accuracy between meningiomas and metastases as compared to the classification results obtained by employing solely textural or spectroscopic features. Discrimination accuracies attained using textural, spectroscopic, or a combination of both were 95%, 90%, and 100%, respectively. These results, however, are biased, obtained using the exhaustive search and the LOO evaluation method to design the SVM classifier. To assess the precision of the proposed classification system to ‘unseen data’, the ECV method was implemented that resulted in overall mean discrimination accuracy of 92.15% for distinguishing between meningiomas and metastases, with 96.66% for predicting correctly meningiomas and 88.57% metastatic tumors. The results obtained employing the ECV technique indicate that the proposed method might be used for accurate discrimination of meningiomas and dural metastases, which is of crucial importance since there are studies in literature pointing out the need for accurate tumor characterization in order to provide patients the proper clinical management, prolonging survival and quality of
life [24, 80]. More specifically, in a recent study, Chao et. al. [80] provided the evidence for the long-term survival of patients with single metastasis when early and acute tumor characterization along with good prognostic factors (young age, good recursive partitioning analysis) was followed by surgery or stereotactic radiosurgery. In another study, Marosi et. al [24] illustrated that patients with asymptomatic small benign meningiomas can be followed without therapy while in symptomatic patients, complete surgical resection should be attempted which is often curative. For incompletely resected benign tumors, radiotherapy is recommended while for recurrent previously completely resected tumors re-resection is recommended followed by radiotherapy.

The textural features that optimized classification results describe the gray-tone linear dependencies (correlation), the dispersion of the gray-tone intensity values (sum average) and the degree of the in-homogeneity of the gray-tones (difference entropy and long run emphasis) within the VOI [10, 11]. These features reflect radiological properties, such as texture homogeneity and signal intensity, that the expert physicians use in order to characterize the type of the tumor [110]. The spectroscopic feature that participated in the optimum feature vector was the Cho/NAA metabolite integral ratio. Cho represents various choline-containing compounds, such as acetylcholine, phosphocholine (lecithin), glycerophosphocholine, and various other intermediates of phospholipid metabolism. It is an indicator of cell density and cell wall turnover. Elevated Cho levels are found in tumors, especially malignant ones, and in certain demyelinating diseases. NAA is an amino acid found exclusively in neurons and is a marker of neuronal viability. NAA concentrations are decreased in conditions leading to axonal injury or neuronal loss. Decreased concentrations are also seen in tumors, infarction, and inflammatory conditions such as multiple sclerosis. When Cho/NAA ratio in a suspicious for lesion area is greater than one, the lesion is considered to be positive for neoplasm [27, 28]. Both meningiomas and metastases are characterized from low concentrations of NAA while meningiomas exhibit higher concentrations of Cho than metastases [110], which could be attributed to increased synthesis or increased degradation of tumor cell membranes [111]. Thus the Cho/NAA ratio provided a distinguishable pattern for our system in order to discriminate meningiomas from metastasis.

The enhanced boxplots (enriched with the information derived from the distribution of the normalized feature values) can furthermore provide an evidence of
the discrimination capability of the best feature set attained at the first stage of the system’s design. Evaluating the median values of the best normalized feature values of meningiomas and metastases, as presented in the boxplots, it can be observed that meningiomas had positive values while metastatic cases had negative values providing a clear discriminating margin for the classification system designed.

Judging from the results, the SVM-RBF classification system, constructed with 3D textural and spectroscopic features, achieved higher accuracies than those obtained using solely 2D or 3D textural features [93, 100, 109]. In particular, by employing an LSFT modified probabilistic neural network, 2D textural features and the ECV technique, discrimination accuracies of 71.43% for metastases and 81.25% for meningiomas has been achieved. By employing 3D textural features, the ECV method, bootstrap aggregation, and an LSFT modified SVM classifier, classification accuracies of 77.14% for metastases and 93.33% for meningiomas has been obtained. The classification system designed enhanced these accuracies to 88.57% for metastases and 96.66% for meningiomas employing the ECV method. Regarding studies from other groups, Devos et. al [83] attained classification accuracies of 97%, between metastatic brain tumors and meningiomas, employing only short time echo MR spectroscopic data and the LS-SVM classifier. In another study, Luts et. al. [112] attained individual discrimination accuracy of 96% for meningiomas by employing a combination of 4 textural, 10 spectroscopic features and the LS-SVM classification algorithm. The findings of the present thesis are comparable. However, since the aim was to provide evidence that the fusion of routinely taken MR images and spectra can provide better discrimination results from solely textural or spectroscopic features, no modification was applied in the classification scheme (e.g. Least Squares Features Transformation, Bagging, Classifier Ensemble) in order to enhance discrimination results.

The contribution of this approach constitutes the development of a pattern recognition system that improves discrimination accuracies between metastatic brain tumors and meningiomas employing a combination of MR textural and spectroscopic features.
7.3.6 Summary and conclusions

Concluding, the combination of the information derived from textural and spectroscopic analysis of meningiomas and metastasis on MRI can increase the discrimination accuracy of pattern recognition systems.
CHAPTER 8 - Summary, important conclusions and future perspectives

This chapter summarizes important conclusions and discusses possible future perspectives of this thesis.
8.1 Summary and important conclusions

Brain tumor type characterization is strongly related to the disease severity and serves as a guide to clinical practice for treatment planning and patient management. Incorrect diagnosis may result in inadequate therapy. There are several studies in literature pointing out the need for accurate tumor characterization in order to provide patients the proper clinical management, prolonging survival and quality of life [24, 80]. Primary and metastatic tumors follow different treatment protocols (radiation therapy and chemotherapy for metastatic tumors while primary tumors may also require surgical intervention [98, 99]). Moreover, malignant tumors, according to their grade, may require specific post-surgery treatment such as external beam radiotherapy or chemotherapy [107] while benign tumors may require stereotactic radiosurgery [108].

Important conclusions that were derived in the context of the present thesis are:

- **Brain tumor type characterization accuracy improved in regards to existing systems.** In particular, the overall accuracy for correctly discriminating metastatic brain tumors was 77.14%, for gliomas was 89.19% and for meningiomas was 93.33%, employing volumetric textural features. The overall accuracy for discriminating between metastatic tumors and meningiomas was 92.15% employing a combination of volumetric textural and spectroscopic features.

- **The encoding of textural properties derived from the tumor’s volume provided additional information to the classification system enhancing discrimination results.** The textural features that optimized classification performance were related to the degree of homogeneity of the texture. Homogeneity is one of the textural parameters that physicians employ in diagnosis and is proportional to the textural imprint of brain tumors, i.e. gliomas have heterogeneous texture while meningiomas appear to be homogeneous in MR imaging.

- **MR spectroscopic features provided an added value in tumor characterization and management.** The MR-spectroscopy feature that participated in the optimum feature vector, for discriminating between meningiomas and
metastasis, was the Cho/NAA metabolite integral ratio. Both meningiomas and metastases are characterized from low concentrations of NAA while meningiomas exhibit higher concentrations of Cho than metastases, which could be attributed to increased synthesis of tumor cell membranes.

8.2 Future perspectives

An interesting extension of this thesis would be to investigate and quantify the patterns extracted from other modalities (such as CT) and fuse them with the patterns employed in the present thesis. The construction of multimodal classification systems may improve the accuracy of brain tumor classification. Another interesting idea is to incorporate qualitative features along with the quantitative features derived from the MR image and spectra. There are already several studies in the literature regarding brain tumor classification systems that employ qualitative only features [94]. The adoption of qualitative and quantitative features in the tumor classification system may provide increased discrimination results.

From the technical point of view, further evolvement should be made concerning the performance evaluation and classification algorithms by adopting new, state-of-the-art techniques. In this way, a more accurate evaluation of the success of the tumor discrimination procedure may be feasible. Additionally, multi-classifier systems that have been shown to improve the performance of single classifier systems should be a further development of this research, i.e. to investigate whether further improvement in classification success rates is possible.

Reduction of computer processing time is another important issue, since for clinical routine applications calculations should not exceed the order of minutes. The algorithms developed in this thesis require extensive computations and, thus, they should be optimised with respect to faster implementation in a network of computers that will run in parallel mode. In this way, rapid calculations would be available.

However, the ultimate future goal of this ongoing research is to provide an everyday clinical tool that will assist clinicians in the diagnosis and discrimination of brain tumor types. To achieve this, all methods and techniques utilized in the present thesis must be integrated in a simple, easy to use environment. Finally, the system must undergo exhaustive clinical trials to ensure its proper functionality.
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[100] Georgiadis P, Cavouras D, Kalatzis I, Glotsos D, Athanasiadis E, Kostopoulos S, Sifaki K, Malamas M, Nikiforidis G, Solomou E. Enhancing the discrimination...


APPENDIX I - List of publications as result of the research work performed for the purposes of the present thesis

**Journal published papers**


**Journal submitted articles**


**Proceedings in conferences**


# APPENDIX II – Abbreviations

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Full Form</th>
</tr>
</thead>
<tbody>
<tr>
<td>ANN</td>
<td>Artificial Neural Network</td>
</tr>
<tr>
<td>CBTRUS</td>
<td>United States’ Central Brain Tumor Registry</td>
</tr>
<tr>
<td>Cho</td>
<td>Choline</td>
</tr>
<tr>
<td>CNS</td>
<td>Central Nervous System</td>
</tr>
<tr>
<td>Cr</td>
<td>Creatine</td>
</tr>
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<td>VTK</td>
<td>Visualization Tool Kit</td>
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<tr>
<td>WHO</td>
<td>World Health Organization</td>
</tr>
</tbody>
</table>
APPENDIX III - List of figures

Figure 1 - Example of calculating the co-occurrence matrix ........................................... 30
Figure 2 - Example of calculating the run-length matrix ................................................ 33
Figure 3 - The basic PNN architecture ........................................................................... 39
Figure 4 - Hierarchical tree classification scheme ......................................................... 48
Figure 5 - Custom made application for image visualization and ROI acquisition ....... 50
Figure 6 - Overall classification accuracy of the algorithms used for discriminating primary and secondary tumors .......................................................... 53
Figure 7 - Scatter diagrams of the optimum feature combination of the i/ cubic LSFT-PNN, ii/ PNN, iii/ SVM-RBF and iv/ ANN classifiers and the corresponding decision boundaries for discriminating primary and secondary tumors ........................................... 54
Figure 8 - Overall classification accuracy of the algorithms used for discriminating gliomas and meningiomas ................................................................. 56
Figure 9 - Scatter diagrams of the optimum feature combination of the i/ cubic LSFT-PNN, ii/ PNN, iii/ SVM-RBF and iv/ ANN classifiers and the corresponding decision boundaries for discriminating gliomas and meningiomas ........................................... 57
Figure 10 - Custom made application for VOI acquisition and volumetric features extraction ........................................................................................................... 64
Figure 11 - Flowchart of the classification scheme utilized .............................................. 65
Figure 12 - Optimum feature vector combination determination procedure .............. 66
Figure 13 - Scatter diagram of the 3 optimum features of the SVM classifier and the corresponding decision boundary for discriminating primary from secondary tumors employing i/ 2D and ii/ 3D textural features ................................................................. 68
Figure 14 - Scatter diagram of the 3 optimum features of the SVM classifier and the corresponding decision boundary for discriminating meningiomas from gliomas employing i/ 2D and ii/ 3D textural features ................................................................. 69
Figure 15 - Decision space scatter diagram of the optimum 5 feature combination of the quadratic LSFT-SVM classifier and the corresponding decision boundary for discriminating i/ primary from metastatic tumors and ii/ gliomas from meningiomas employing 3D textural features ................................................................. 71
Figure 16 - Classification scheme design ....................................................................... 80
Figure 17 - Scatter diagram of the optimum three features combination and the corresponding decision boundary for discriminating meningiomas from metastatic tumors employing only textural features ................................................................. 83
Figure 18 - Boxplot of the best textural features for i/ meningiomas and ii/ metastatic cases.

Figure 19 - Scatter diagram of the optimum spectroscopic features combination and the corresponding decision boundary for discriminating meningiomas from metastatic tumors.

Figure 20 - Boxplot of the spectroscopic features for i/ meningiomas and ii/ metastatic cases.

Figure 21 - Scatter diagram of the optimum three features combination and the corresponding decision boundary for discriminating meningiomas from metastatic tumors employing both textural and spectroscopic features.

Figure 22 - Boxplot of the best combination of textural and spectroscopic for i/ meningiomas and ii/ metastatic cases.

Figure 23 - Means and standard deviations of classification accuracies achieved by the 10-fold ECV process for various numbers of features combinations.
APPENDIX IV - List of tables

Table 1 - Metabolite changes for different types of brain tumors .................................35

Table 2 - Cubic LSFT-PNN classifier truth table for discriminating primary and secondary tumors ..............................................................................................................52

Table 3 - Classification results for discriminating primary and secondary brain tumors employing the LOO method ....................................................................................................52

Table 4 - Classification results for discriminating primary and secondary brain tumors utilizing the ECV method (averaged results after ten repetitions) ..........................53

Table 5 - Quadratic LSFT-PNN truth table for discriminating gliomas and meningiomas .............................................................................................................................54

Table 6 - Classification results for discriminating gliomas and meningiomas employing the LOO method .............................................................................................................55

Table 7 - Classification results for discriminating gliomas and meningiomas utilizing the ECV method (averaged results after ten repetitions) ........................................55

Table 8 - SVM classifier truth table for discriminating primary from secondary tumors at the 1st tree level using 2D and 3D textural features .....................................................68

Table 9 - Comparative classification results between 2D and 3D textural features employing the SVM classifier at both levels of the decision tree ........................................69

Table 10 - Comparative classification results employing the linear and the quadratic LSFT-SVM classifiers for both levels of the decision tree ................................................70

Table 11 - Classification results employing the LSFT-SVM ensemble classifier scheme (bagging) ......................................................................................................................72

Table 12 - Classification results utilizing the ECV method and the LSFT-SVM ensemble classifier scheme (average and standard deviation after ten ECV repetitions) ......................................................................................72

Table 13 - Comparative classification results for discriminating meningiomas from metastatic tumors employing solely textural features .................................................82

Table 14 - Comparative classification results for discriminating meningiomas from metastatic tumors, employing solely spectroscopic features .................................84

Table 15 - Comparative classification results for discriminating meningiomas from metastatic tumors employing both textural and spectroscopic features ......................85