National Technical University of Athens
School of Electrical & Computer Engineering
Division of Communication, Electronic & Information Engineering

Non-invasive glucose sensing methodologies for the measurement of human blood glucose levels

Ph.D. Thesis

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Abstract

This thesis explores the innovative field of non-invasive glucose monitoring (NGM), a promising avenue for improving diabetes management by providing painless and continuous monitoring of blood glucose levels. Diabetes, a chronic condition affecting millions globally, requires effective glucose monitoring to manage complications. Traditional invasive methods, such as finger-prick tests and continuous glucose monitors, although effective, often cause discomfort and compliance issues.

A key contribution of this work is the development of a Time-of-Flight (ToF)-based sensor designed for glucose detection in physiological conditions. This novel optical sensor utilizing the Time-of-Flight principle was developed and successfully demonstrated its capability to achieve adequate depth penetration and sensitivity for detecting glucose-induced optical changes in human skin. Computational simulations, including Finite Element Method (FEM) modeling and Monte Carlo simulations, were employed to optimize the sensor design and predict light-tissue interactions. Despite its promising performance, the sensor's accuracy was influenced by factors such as hydration levels, tissue scattering, and external environmental conditions.

Efforts to measure glucose using bioimpedance spectroscopy through RF scattering parameters (S_{11} and S_{21}) revealed repeatable but inconclusive correlations with glucose levels.

The findings underscore the potential of optical methods while highlighting the need for multi-modal systems to address the inherent limitations of individual techniques. Future research directions include integrating optical and bioimpedance sensing modalities into a unified framework, leveraging machine learning for data fusion, and reducing environmental and physiological noise. These advancements aim to achieve robust, accurate, and clinically viable non-invasive glucose monitoring systems.

Keywords

Non Invasive glucose sensing, diabetes, Time-of-Flight, bioimpedance.

Περίληψη

Αυτή η διδακτορική διατριβή εξερευνά τον καινοτόμο τομέα της μη επεμβατικής παρακολούθησης γλυκόζης (Non-Invasive Glucose Monitoring - NGM), μια πολλά υποσχόμενη προσέγγιση για τη βελτίωση της διαχείρισης του διαβήτη μέσω ανώδυνου και συνεχούς ελέγχου των επιπέδων γλυκόζης στο αίμα. Ο διαβήτης, μια χρόνια πάθηση που επηρεάζει εκατομμύρια ανθρώπους παγκοσμίως, απαιτεί αποτελεσματική παρακολούθηση γλυκόζης για τη διαχείριση σχετικών επιπλοκών. Οι παραδοσιακές επεμβατικές μέθοδοι, όπως οι μετρήσεις με τρύπημα δακτύλου και οι συνεχείς μετρητές γλυκόζης, αν και αποτελεσματικές, συχνά προκαλούν δυσφορία και προβλήματα συμμόρφωσης.

Μια βασική συνεισφορά αυτής της εργασίας είναι η ανάπτυξη ενός αισθητήρα βασισμένου στην αρχή του Χρόνου Πτήσης (Time-of-Flight - ToF) για την ανίχνευση γλυκόζης σε φυσιολογικές συνθήκες. Αυτός ο καινοτόμος οπτικός αισθητήρας που χρησιμοποιεί την αρχή του ToF αναπτύχθηκε και αποδείχθηκε επιτυχώς ότι μπορεί να επιτύχει επαρκή διείσδυση βάθους και ευαισθησία για την ανίχνευση αλλαγών που προκαλούνται από τη γλυκόζη στο ανθρώπινο δέρμα. Υπολογιστικές προσομοιώσεις, συμπεριλαμβανομένης της μεθόδου Πεπερασμένων Στοιχείων (Finite Element Method - FEM) και προσομοιώσεων Monte Carlo, χρησιμοποιήθηκαν για τη βελτιστοποίηση του σχεδιασμού του αισθητήρα και την πρόβλεψη αλληλεπιδράσεων φωτός-ιστού. Παρά την ελπιδοφόρα απόδοσή του, η ακρίβεια του αισθητήρα επηρεάστηκε από παράγοντες όπως τα επίπεδα ενυδάτωσης, η σκέδαση ιστών και οι εξωτερικές περιβαλλοντικές συνθήκες.

Προσπάθειες για τη μέτρηση της γλυκόζης μέσω μέτρησης βιοαντίστασης και παραμέτρων σκέδασης RF (S_{11} και S_{21}) ανέδειξαν επαναλαμβανόμενες αλλά μη πειστικές συσχετίσεις με τα επίπεδα γλυκόζης.

Τα ευρήματα της εργασίας, αναδεικνύουν τη δυναμική των οπτικών μεθόδων ενώ υπογραμμίζουν την ανάγκη για πολυπαραμετρικά συστήματα που αντιμετωπίζουν τους εγγενείς περιορισμούς των μεμονωμένων τεχνικών. Οι μελλοντικές ερευνητικές κατευθύνσεις περιλαμβάνουν την ενσωμάτωση οπτικών τεχνικών και τεχνικών βιοαντίστασης σε ένα ενιαίο πλαίσιο, την αξιοποίηση της μηχανικής μάθησης για συγχώνευση δεδομένων και τη μείωση του θορύβου που προκαλείται από περιβαλλοντικούς και φυσιολογικούς παράγοντες. Αυτές οι περαιτέρω ερευνητικές προτάσεις αποσκοπούν στην επίτευξη ανθεκτικών, ακριβών και κλινικά βιώσιμων

συστημάτων μη επεμβατικής παρακολούθησης γλυκόζης.

Λέξεις–Κλειδιά

Μη επεμβατική μέτρηση γλυκόζης, διαβήτης, Time-of-Flight, βιοεμπέδηση.

Εκτεταμένη Περίληψη

Ενότητα 1: Διαβήτης και Παρακολούθηση Γλυκόζης Αίματος

Ο σακχαρώδης διαβήτης αποτελεί μια παγκόσμια υγειονομική κρίση, αφού επηρεάζει εκατομμύρια άτομα και θέτει ένα σημαντικό βάρος στα συστήματα υγειονομικής περίθαλψης παγκοσμίως. Πρόκειται για μια χρόνια μεταβολική διαταραχή που χαρακτηρίζεται από επίμονη υπεργλυκαιμία, η οποία οφείλεται είτε σε μειωμένη παραγωγή ινσουλίνης (Διαβήτης Τύπου 1) είτε σε αντίσταση στην ινσουλίνη (Διαβήτης Τύπου 2). Αυτές οι καταστάσεις οδηγούν σε μακροχρόνιες επιπλοκές, όπως καρδιαγγειακά νοσήματα, νευροπάθεια, αμφιβληστροειδοπάθεια και νεφρική ανεπάρκεια, οι οποίες συμβάλλουν σημαντικά στη νοσηρότητα και τη θνησιμότητα παγκοσμίως. Ο Παγκόσμιος Οργανισμός Υγείας (ΠΟΥ) προβλέπει αύξηση του διαβήτη από 463 εκατομμύρια προσβεβλημενων ατόμων το έτος 2019 σε πάνω από 700 εκατομμύρια έως το έτος 2045, σηματοδοτώντας έτσι την επείγουσα ανάγκη για προηγμένα εργαλεία παρακολούθησης και διαχείρισής του.

Οι παραδοσιακές μέθοδοι παρακολούθησης της γλυκόζης, συμπεριλαμβανομένων των τεστ με τρύπημα του δακτύλου και των συστημάτων συνεχούς παρακολούθησης γλυκόζης (continuous glucose monitoring - CGM), χρησιμοποιούνται ευρέως αλλά χαρακτηρίζονται από δημιουργία δυσφορίας, ταλαιπωρία και υψηλό κόστος που επιβαρύνουν τον ασθενη, γεγονός που εμποδίζει τη συμμόρφωση και την προσβασιμότητα στους μηχανισμούς παρακολούθησης του διαβήτη για πολλούς ασθενείς. Παρόλο που τα τεστ με τρύπημα του δακτύλου παρέχουν ακριβείς μετρήσεις των επιπέδων γλυκόζης στο αίμα μέσω ενζυματικής ανάλυσης του εξαγόμενου αίματος, η επεμβατική τους φύση συχνά αποθαρρύνει τη συχνή παρακολούθηση. Από την άλλη πλευρά, τα συστήματα CGM προσφέρουν παρακολούθηση σε πραγματικό χρόνο και έγκαιρες ειδοποιήσεις για υπογλυκαιμικά ή υπεργλυκαιμικά επεισόδια. Ωστόσο, η εξάρτησή τους από την υποδόρια εμφύτευση προκαλεί δυσφορία στον ασθενή και μπορεί να οδηγήσει σε ερεθισμό του δέρματος με την πάροδο του χρόνου, μειώνοντας περαιτέρω τη συμμόρφωση των ασθενών.

Τα ανωτέρω αρνητικά στοιχεία που σχετίζονται με τις επεμβατικές μεθόδους αναδεικνύουν το αυξανόμενο ενδιαφέρον για τις τεχνολογίες μη επεμβατικής παρακολούθησης γλυκόζης (non-invasive glucose monitoring - NGM). Αυτές οι

προσεγγίσεις με επεμβατικής παρακολούθησης της γλυκόζης στοχεύουν στην εξάλειψη της ανάγκης για εξαγωγή αίματος, αξιοποιώντας οπτικές, ηλεκτρικές ή χημικές μεθόδους για την έμμεση μέτρηση των επιπέδων γλυκόζης. Τεχνικές όπως η Φασματοσκοπία Υπερύθρου (NIR), η Φασματοσκοπία Raman και η μέτρηση βιοεμπέδησης είναι πολλά υποσχόμενες εναλλακτικές λύσεις, αν και παρουσιάζουν σημαντικές προκλήσεις όσον αφορά την ακρίβεια, την αξιοπιστία και το κόστος τους.

Σε αυτήν την ενότητα εξετάζονται επίσης οι διάφοροι παράγοντες που επηρεάζουν την ακρίβεια των συσκευών παρακολούθησης γλυκόζης, όπως η φυσιολογική μεταβλητότητα στο πάχος του δέρματος, τα επίπεδα ενυδάτωσης του δέρματος και η πυκνότητα αγγείων στους ιστούς. Περιβαλλοντικές συνθήκες όπως η θερμοκρασία και η υγρασία του περιβάλλοντος διαδραματίζουν επίσης κρίσιμο ρόλο στην απόδοση των συστημάτων μέτρησης της γλυκόζης που βασίζονται σε οπτικές ιδιότητες ή/και στην βιοεμπέδηση. Επιπλέον, η παρουσία άλλων βιομορίων, όπως η αιμοσφαιρίνη, παρεμβαίνει στις μετρήσεις, δημιουργώντας σημαντική σχετική πρόκληση στους ερευνητές.

Οι μελλοντικές κατευθύνσεις έρευνας δίνουν έμφαση στην ανάγκη για πολυτροπικές προσεγγίσεις ανίχνευσης της γλυκόζης που ενσωματώνουν διαφορετικές τεχνικές μέτρησής της, με στόχο τη βελτίωση της ακρίβειας και της αξιοπιστίας. Η ενσωμάτωση αλγορίθμων μηχανικής μάθησης στις συσκευές NGM υπόσχεται να ενισχύσει τις δυνατότητες ανάλυσης δεδομένων, μειώνοντας τον θόρυβο και την περιβαλλοντική παρέμβαση. Επιπλέον, οι προσπάθειες για σμίκρυνση των συσκευών μέτρησης και μείωση του κόστους κατασκευής τους θα μπορούσαν να οδηγήσουν σε ευρύτερη προσβασιμότητα, μεταμορφώνοντας ενδεχομένως τη διαχείριση του διαβήτη σε παγκόσμια κλίμακα.

Ενότητα 2: Τεχνικές Μη Επεμβατικής Μέτρησης Γλυκόζης

Η μη επεμβατική παρακολούθηση γλυκόζης έχει αναδειχθεί ως μια νέα και ιδιαίτερα σημαντική προσέγγιση στη διαχείριση του διαβήτη, προσφέροντας τη δυνατότητα για ανώδυνη και πιο προσιτή παρακολούθηση των επιπέδων γλυκόζης στον ασθενή. Αυτή η ενότητα παρέχει μια ολοκληρωμένη ανασκόπηση του τεχνολογικού τοπίου των NGM, εστιάζοντας στις κύριες μεθοδολογίες, τις αρχές τους, τις προκλήσεις και τις εφαρμογές τους.

Η Φασματοσκοπία Κοντινού Υπερύθρου (NIR) είναι μία από τις πιο ευρέως ερευνηθείσες τεχνικές NGM, αξιοποιώντας τα χαρακτηριστικά απορρόφησης της γλυκόζης στο φάσμα του υπέρυθρου φωτός (μήκος κύματος 700–2500 nm). Με την μέτρηση της απορρόφησης και τη διάχυση του φωτός καθώς αυτό διέρχεται από βιολογικούς ιστούς, η NIR μπορεί να εκτιμήσει μη επεμβατικά τις συγκεντρώσεις γλυκόζης στους ιστούς. Πρόσφατες εξελίξεις στην τεχνολογία φωτοανιχνευτών και στους αλγορίθμους μηχανικής μάθησης έχουν βελτιώσει σημαντικά την ευαισθησία

και την εξειδίκευση των συστημάτων NIR. Ωστόσο, εξακολουθούν να υπάρχουν προκλήσεις, όπως η παρέμβαση στην μέτρηση από την απορρόφηση του νερού και άλλων βιολογικών μορίων, καθώς και η μεταβλητότητα λόγω μελάγχρωσης και ενυδάτωσης του δέρματος.

Η φασματοσκοπία Raman αποτελεί μια άλλη πολλά υποσχόμενη τεχνική, που προσφέρει υψηλή εξειδίκευση μέσω της ανίχνευσης μοναδικών δονητικών ενεργειακών επιπέδων των μορίων γλυκόζης. Σε αντίθεση με τη NIR, η Raman επηρεάζεται λιγότερο από την απορρόφηση του νερού, καθιστώντας την τεχνική Raman ιδιαίτερα κατάλληλη για την παρακολούθηση της γλυκόζης. Η τεχνική περιλαμβάνει την εκπομπή ενός μονοχρωματικού λέιζερ στο δέρμα και την ανάλυση του φάσματος του σκεδασμένου φωτός. Παρά την εξειδίκευσή της ωστόσο, η Raman αντιμετωπίζει προκλήσεις όπως η χαμηλή ένταση σήματος, το υψηλό κόστος εξοπλισμού και η ευαισθησία στην κίνηση του ασθενούς.

Η βιοεμπέδηση είναι μια εναλλακτική τεχνική. Μετρά την ηλεκτρική αντίσταση των βιολογικών ιστών, η οποία μεταβάλλεται ανάλογα με τα επίπεδα γλυκόζης λόγω αλλαγών στην ενυδάτωση και την ιοντική σύνθεση των ιστών. Αυτή η μέθοδος είναι οικονομικά αποδοτική και εύκολα κλιμακούμενη για φορητές συσκευές. Ωστόσο, η ακρίβειά της επηρεάζεται από εξωτερικούς παράγοντες όπως η θερμοκρασία και ο ιδρώτας του ασθενούς, απαιτώντας έτσι προηγμένες τεχνικές βαθμονόμησης και μετρήσεις πολλαπλών συχνοτήτων για αξιόπιστα αποτελέσματα.

Η τεχνολογία μικροκυμάτων αξιοποιεί τις διηλεκτρικές ιδιότητες της γλυκόζης στις συχνότητες GHz για να εκτιμήσει τις συγκεντρώσεις της. Με τη μετάδοση μικροκυμάτων μέσω του δέρματος και την ανάλυση των ανακλώμενων ή μεταδιδόμενων σημάτων, αυτή η τεχνική προσφέρει μεγαλύτερη διείσδυση ιστών σε σύγκριση με τις οπτικές μεθόδους. Πρόσφατες καινοτομίες, όπως η χρήση συστοιχιών κεραιών και μηχανικής μάθησης, έχουν ενισχύσει την ακρίβεια των συστημάτων μικροκυμάτων. Ωστόσο, οι προκλήσεις, όπως η ευαισθησία στις αλλαγές του σημείου μέτρησης και η ανάγκη για ακριβή βαθμονόμηση, παραμένουν σημαντικές.

Το φωτοακουστικό φαινόμενο μπορεί επίσης να χρησιμοποιηθεί για την μη επεμβατική μέτρηση γλυκόζης. Συνδυάζει την οπτική απορρόφηση με την παραγωγή ακουστικών κυμάτων για την ανίχνευση επιπέδων γλυκόζης. Αυτή η υβριδική τεχνική παρέχει υψηλή ευαισθησία και είναι κατάλληλη για ενσωμάτωση σε φορητές συσκευές. Ωστόσο, οι περιορισμοί όπως η εξασθένηση του σήματος και ο ακουστικός θόρυβος πρέπει να αντιμετωπιστούν μέσω προηγμένων υλικών και τεχνολογιών λέιζερ.

Στην ενότητα αυτή τέλος υπογραμμίζονται οι προκλήσεις που αντιμετωπίζουν οι τεχνολογίες NGM, όπως η ανάγκη για συνεχείς βαθμονομήσεις, οι παρεμβολές από άλλα βιομόρια και το υψηλό κόστος παραγωγής. Η ενσωμάτωσή τους σε φορητές συσκευές και η εφαρμογή τεχνολογιών IoT θεωρούνται πολλά υποσχόμενες για την

πραγματική παρακολούθηση και την εξατομικευμένη διαχείριση του διαβήτη.

Ενότητα 3: Σχεδιασμός στοιχείων για ανάλυση με βιοεμπέδηση

Η μέθοδος ανάλυσης της βιοεμπέδησης για την μη επεμβατική παρακολούθηση γλυκόζης αποτελεί μια πολλά υποσχόμενη εναλλακτική προσέγγιση στις παραδοσιακές επεμβατικές μεθόδους, αξιοποιώντας τις ηλεκτρικές ιδιότητες των βιολογικών ιστών που επηρεάζονται από τα επίπεδα γλυκόζης. Στην ενότητα αυτή αναλύονται οι αρχές της βιοεμπέδησης, οι πειραματικές μεθοδολογίες και η ανάπτυξη καινοτόμων αισθητήρων βασισμένων σε κεραίες.

Η μέτρηση βιοεμπέδησης βασίζεται στις διηλεκτρικές ιδιότητες των βιολογικών ιστών, όπως η επιτρεπτικότητα και η αγωγιμότητα, οι οποίες αλλάζουν με τα επίπεδα γλυκόζης στο διάμεσο υγρό και στις κυτταρικές μεμβράνες. Με την εφαρμογή ενός εναλλασσόμενου ηλεκτρικού ρεύματος στο σημείο μέτρησης και τη μέτρηση της προκύπτουσας αντίστασης, μπορούν να ανιχνευθούν μεταβολές στις ηλεκτρικές ιδιότητες των ιστών που προκαλούνται από τη γλυκόζη.

Ο σχεδιασμός και η δοκιμή καινοτόμων αισθητήρων βασισμένων σε κεραίες είναι κεντρικό στοιχείο αυτής της ενότητας. Αναπτύχθηκαν τρεις παραλλαγές αισθητήρων – «μικρός», «μεσαίος» και «μεγάλος» αισθητήρας λόγω των σχετικών μεγεθών τους - με μοναδικές διαμορφώσεις χάλκινων πίσω επιφανειών και ελλειπτικά σχήματα για τη βελτιστοποίηση της ευαισθησίας. Οι αισθητήρες σχεδιάστηκαν βάσει προηγούμενων μελετών, ενσωματώνοντας τροποποιήσεις για τη βελτίωση της απόδοσης σε μη επεμβατικές εφαρμογές. Για παράδειγμα, η ενσωμάτωση χάλκινων πίσω επιφανειών παρείχε μια γειωμένη επιφάνεια, μειώνοντας τον θόρυβο και βελτιώνοντας τη σταθερότητα των μετρήσεων.

Τα σχετικά πειράματα πραγματοποιήθηκαν με τη χρήση διαλυμάτων γλυκόζης σε φυσιολογικές συγκεντρώσεις, που μετρήθηκαν με προχωρημένους αναλυτές δικτύου. Οι δοκιμές διεξήχθησαν σε ένα ευρύ φάσμα συχνοτήτων για την αξιολόγηση της ανταπόκρισης των αισθητήρων στις μεταβολές συγκέντρωσης γλυκόζης.

Ενότητα 4: Τεχνική Μέτρησης μέσω Βιοεμπέδησης

Αυτή η ενότητα εστιάζει στο πειραματικό πλαίσιο, τις μεθοδολογίες και τα ευρήματα που σχετίζονται με την τεχνική μέτρησης μέσω βιοεμπέδησης για τη μη επεμβατική παρακολούθηση γλυκόζης. Η βιοεμπέδηση, που περιλαμβάνει τη μέτρηση της ηλεκτρικής αντίστασης των βιολογικών ιστών, προσφέρει μια πολλά υποσχόμενη προσέγγιση για την παρακολούθηση των επιπέδων γλυκόζης, αξιοποιώντας τις διηλεκτρικές και αγώγιμες ιδιότητες των ιστών που μεταβάλλονται με τις συγκεντρώσεις γλυκόζης. Αυτή η προσέγγιση παρουσιάζει μια οικονομικά αποδοτική εναλλακτική λύση σε σχέση με τα παραδοσιακά επεμβατικά συστήματα παρακολούθησης γλυκόζης.

Η μελέτη της τεχνικής ξεκίνησε με την προετοιμασία δειγμάτων γλυκόζης που μιμούνταν τις φυσιολογικές και υπεργλυκαιμικές συγκεντρώσεις γλυκόζης. Δημιουργήθηκαν διαλύματα χρησιμοποιώντας αποστειρωμένο αλατούχο διάλυμα και εργαστηριακής ποιότητας D-γλυκόζη, με συγκεντρώσεις που κυμαίνονταν από 24 mg/dl έως 500 mg/dl. Οι S παράμετροι των δειγμάτων μετρήθηκαν υπό ελεγχόμενες συνθήκες χρησιμοποιώντας αναλυτή δικτύου, ο οποίος βαθμονομήθηκε για να ελαχιστοποιηθεί ο περιβαλλοντικός και οργανολογικός θόρυβος. Η πειραματική διάταξη περιλάμβανε επίσης ειδικά σχεδιασμένα στηρίγματα για να εξασφαλιστεί η σταθερή τοποθέτηση των δειγμάτων και η απόσταση από τους αισθητήρες.

Τα αποτελέσματα των πρώτων δοκιμών έδωσαν βασικές πληροφορίες για την απόκριση των αισθητήρων υπό διάφορες συνθήκες. Χρησιμοποιώντας ένα εύρος συχνοτήτων από 1 MHz έως 200 MHz, τα πειράματα αποκάλυψαν ότι οι συγκεντρώσεις γλυκόζης επηρεάζουν μη γραμμικά την απόκριση βιοηλεκτρικής αντίστασης. Ανάμεσα στα τρία σχέδια αισθητήρων - ο μικρός αισθητήρας αποκλείστηκε από περαιτέρω δοκιμές λόγω της αδυναμίας του να παρέχει διακριτά αποτελέσματα.

Στη συνέχεια, οι δοκιμές επεκτάθηκαν με μεσαίους και μεγάλους αισθητήρες, διευρύνοντας το φάσμα συχνοτήτων έως τα 6 GHz. Αυτή η υψηλότερη συχνότητα μελετήθηκε για να αξιολογηθεί ο αντίκτυπός της στην ευαισθησία της τεχνικής, παρά το μικρό βάθος που «εισέρχεται» μια τέτοια συχνότητα στο δέρμα. Τα αποτελέσματα έδειξαν βελτιωμένη απόκριση από τους μεσαίους και μεγάλους αισθητήρες, ιδιαίτερα σε αποστάσεις 1 cm, 5 cm και 10 cm από το δείγμα. Αυτές οι αποστάσεις αντιστοιχούσαν σε βασικά σημεία διαφοροποίησης στην καμπύλη απόκρισης βιοεμπεδήσης.

Η επεξεργασία των δεδομένων περιλάμβανε την εφαρμογή φίλτρων χαμηλής διέλευσης και τεχνικών κινητού μέσου όρου για την αφαίρεση θορύβου υψηλής συχνότητας, διατηρώντας παράλληλα τα χρήσιμα σήματα. Αναλύθηκε η τυπική απόκλιση επαναλαμβανόμενων μετρήσεων για την αξιολόγηση της σταθερότητας, με τα αποτελέσματα να υποδεικνύουν συνεπή απόδοση των αισθητήρων σε πολλαπλές δοκιμές. Τα τελικά αποτελέσματα έδειξαν σημαντική διαφοροποίηση στις αποκρίσεις των αισθητήρων, με τον αισθητήρα μεσαίου μεγέθους να παρουσιάζει την πλέον ελπιδοφόρα απόδοση. Παρόλα αυτά, τα αποτελέσματα δεν κρίθηκαν ικανοποιητικά για περαιτέρω χρήση.

Ενότητα 5: Συμπεράσματα για τη Μέθοδο Μέτρησης Βιοεμπέδησης

Στην ενότητα αυτή συντίθενται τα ευρήματα από τα πειράματα μέτρησης βιοηλεκτρικής αντίστασης μέσω κεραιών, αξιολογώντας την αποτελεσματικότητα

των διαφόρων σχεδίων αισθητήρων και την ικανότητά τους να μετρούν τα επίπεδα γλυκόζης μη επεμβατικά. Μέσα από μια σειρά ελεγχόμενων πειραμάτων, σημειώθηκε σημαντική πρόοδος στον εντοπισμό των δυνατοτήτων και των περιορισμών αυτών των αισθητήρων. Τα βασικά ευρήματα περιλαμβάνουν τη διαφοροποίηση μεταξύ συγκεντρώσεων γλυκόζης σε ένα εύρος φυσιολογικών επιπέδων, ιδίως με τους αισθητήρες μεσαίου και μεγάλου μεγέθους που ήταν εξοπλισμένοι με χάλκινες πίσω επιφάνειες. Αυτά τα σχέδια παρουσίασαν βελτιωμένη ευαισθησία και αξιοπιστία σε σύγκριση με τους μικρότερους αισθητήρες, οι οποίοι δυσκολεύτηκαν να παράσχουν διακριτά σήματα.

Οι κεραίες με χάλκινη πλάτη, ειδικότερα, έδειξαν συνεπή απόδοση στη μείωση του θορύβου και στη βελτίωση της σαφήνειας των σημάτων. Ωστόσο, αναγνωρίστηκαν αρκετές προκλήσεις, όπως η περιβαλλοντική μεταβλητότητα και η επίδραση φυσιολογικών παραγόντων, όπως η ενυδάτωση και η δομή των ιστών, στην ακρίβεια των μετρήσεων. Επιπλέον, η εξάρτηση από ελεγχόμενες εργαστηριακές συνθήκες υπογράμμισε την ανάγκη για περαιτέρω ανάπτυξη, ώστε αυτοί οι αισθητήρες να μεταβούν σε πρακτικές κλινικές ή καταναλωτικές εφαρμογές.

Η ενότητα τονίζει τη σημασία της βαθμονόμησης, της επεξεργασίας σημάτων και της ενσωμάτωσης πολυτροπικών τεχνολογιών ανίχνευσης για την ενίσχυση της αξιοπιστίας των συστημάτων μέτρησης βιοηλεκτρικής αντίστασης. Οι μελλοντικές έρευνες πρέπει να επικεντρωθούν στη βελτίωση του σχεδιασμού των αισθητήρων, την επέκταση του εύρους συχνοτήτων για λεπτομερέστερη συλλογή δεδομένων και την ενσωμάτωση αλγορίθμων μηχανικής μάθησης για αναγνώριση προτύπων και διόρθωση σφαλμάτων. Το συμπέρασμα της ενότητας αυτής είναι ότι, παρόλο που οι μέθοδοι μέτρησης μέσω κεραιών φαίνεται να έχουν σημαντική προοπτική ανάπτυξης, παραμένουν τεχνικά και ρυθμιστικά εμπόδια πριν από την εμπορευματοποίησή τους.

Ενότητα 6: Προσομοίωση του Ανθρώπινου Δέρματος

Στην ενότητα αυτή εξετάζεται ο κρίσιμος ρόλος της προσομοίωσης του ανθρώπινου δέρματος στην ανάπτυξη συστημάτων μη επεμβατικής παρακολούθησης γλυκόζης. Η ακριβής μοντελοποίηση των αλληλεπιδράσεων του φωτός και των ηλεκτρομαγνητικών κυμάτων με το δέρμα είναι απαραίτητη για τον σχεδιασμό και τη βελτιστοποίηση τεχνολογιών ανίχνευσης. Αρχικά στην ενότητα αυτή αναλύεται η πολυπλοκότητα του ανθρώπινου δέρματος ως πολυεπίπεδης βιολογικής δομής, που αποτελείται από την επιδερμίδα, το χόριο και τα υποδόρια στρώματα, καθένα με διαφορετικές οπτικές και ηλεκτρικές ιδιότητες. Αυτά τα στρώματα επηρεάζουν τη διείσδυση, τη σκέδαση και την απορρόφηση του φωτός και των ηλεκτρομαγνητικών κυμάτων, στοιχεία κρίσιμα για τις μεθόδους ανίχνευσης γλυκόζης.

Χρησιμοποιήθηκαν προηγμένες υπολογιστικές μέθοδοι για τη μοντελοποίηση αυτών των αλληλεπιδράσεων, όπως προσομοιώσεις Monte Carlo, ανάλυση

πεπερασμένων στοιχείων (FEA) και τεχνικές μεταφοράς ακτινοβολίας. Οι προσομοιώσεις Monte Carlo παρείχαν πληροφορίες για τη μετανάστευση φωτονίων μέσα στο δέρμα, επιτρέποντας την αξιολόγηση των σχεδίων αισθητήρων υπό διαφορετικές φυσιολογικές συνθήκες. Η FEA χρησιμοποιήθηκε για τη μοντελοποίηση της κατανομής ηλεκτρομαγνητικών πεδίων και των διηλεκτρικών ιδιοτήτων.

Μία από τις κύριες προκλήσεις που αναδείχθηκαν είναι η μεταβλητότητα στις ιδιότητες του δέρματος μεταξύ των ασθενών/ατόμων, η οποία επηρεάζεται από παράγοντες όπως η ηλικία, η ενυδάτωση και η περιεκτικότητα σε μελανίνη. Αυτές οι διαφορές απαιτούν την ανάπτυξη προσαρμοστικών αλγορίθμων για τη διόρθωση των ατομικών διαφορών. Επιπλέον, στην ενότητα αυτή παρουσιάζονται οι περιορισμοί των τρεχουσών μεθόδων προσομοίωσης, συμπεριλαμβανομένης της υψηλής υπολογιστικής έντασης και της αδυναμίας πλήρους αναπαραγωγής δυναμικών φυσιολογικών συνθηκών, όπως η ροή αίματος και οι διακυμάνσεις γλυκόζης.

Τα ευρήματα υπογραμμίζουν την ανάγκη για πολυκλιμακωτές προσεγγίσεις μοντελοποίησης που ενσωματώνουν τις αλληλεπιδράσεις σε μοριακό επίπεδο με μακροσκοπικές προσομοιώσεις. Ο συνδυασμός αυτών των τεχνικών με αλγορίθμους μηχανικής μάθησης μπορεί να ενισχύσει την ακρίβεια και την αξιοπιστία των συστημάτων παρακολούθησης γλυκόζης. Στο κλείσιμο της ενότητας τονίζεται η σημασία της επικύρωσης μέσω πειραματικών δεδομένων, επισημαίνοντας την αλληλεπίδραση μεταξύ προσομοιώσεων και φυσικών δοκιμών για την πρόοδο των μη επεμβατικών τεχνολογιών ανίχνευσης γλυκόζης.

Ενότητα 7: Σχεδιασμός Αισθητήρα

Στην ενότητα αυτη παρουσιάζεται ο λεπτομερής σχεδιασμός και η ανάπτυξη του αισθητήρα βασισμένου στην τεχνική Time-of-Flight (ToF) για τη μη επεμβατική παρακολούθηση γλυκόζης. Η αρχή λειτουργίας του ToF βασίζεται στη μέτρηση του χρόνου που χρειάζεται το φως να διανύσει μια απόσταση, ανιχνεύοντας αλλαγές στις οπτικές ιδιότητες του δέρματος που προκαλούνται από τη γλυκόζη. Ο καινοτόμος σχεδιασμός του αισθητήρα είχε στόχο τη μεγιστοποίηση της διείσδυσης σε βάθος και της ευαισθησίας, ταυτόχρονα με τη μείωση του θορύβου και των περιβαλλοντικών παρεμβολών.

Ο αισθητήρας ToF αναπτύχθηκε με μια συμπαγή, αρθρωτή αρχιτεκτονική κατάλληλη για ενσωμάτωση σε φορητές συσκευές. Κύρια συστατικά του περιλαμβάνουν έναν προχωρημένο φωτοανιχνευτή, LED υψηλής απόδοσης και μια προσαρμοσμένη πλακέτα τυπωμένου κυκλώματος (PCB) για επεξεργασία σήματος. Ο σχεδιασμός περιλάμβανε λειτουργίες όπως η προσαρμοστική μετατόπιση φάσης και η δειγματοληψία υψηλής συχνότητας για τη βελτίωση της ακρίβειας και τη μείωση των τεχνητών παραμορφώσεων στη μέτρηση.

Διεξήχθησαν εκτεταμένες δοκιμές για την επικύρωση της απόδοσης του αισθητήρα υπό ελεγχόμενες συνθήκες. Οι δοκιμές περιλάμβαναν τη χρήση δειγμάτων με διαφορετικές συγκεντρώσεις γλυκόζης, μεταβαλλόμενα επίπεδα φωτισμού περιβάλλοντος και επίπεδα ενυδάτωσης του δέρματος, με στόχο την αξιολόγηση της ανθεκτικότητας του αισθητήρα. Τα αποτελέσματα απέδειξαν την ικανότητα του αισθητήρα να ανιχνεύει λεπτές αλλαγές στις οπτικές ιδιότητες που συσχετίζονται με τα επίπεδα γλυκόζης. Παρόλα αυτά, παρατηρήθηκαν περιορισμοί, όπως η ευαισθησία στον περιβαλλοντικό θόρυβο.

Για την αντιμετώπιση αυτών των ζητημάτων, εφαρμόστηκαν τεχνικές φιλτραρίσματος των σημάτων. Στην ενότητα αυτή εξετάζεται επίσης η δυνατότητα ενσωμάτωσης του αισθητήρα ToF σε φορητές πλατφόρμες, όπως έξυπνα ρολόγια και επιθέματα, για συνεχή παρακολούθηση της γλυκόζης. Η δυνατότητα κλιμάκωσης και η οικονομική αποδοτικότητα του σχεδιασμού υπογραμμίζονται ως κρίσιμοι παράγοντες για την εμπορική βιωσιμότητα του αισθητήρα.

Στο τέλος της ενότητας αναφέρονται συστάσεις για περαιτέρω βελτιστοποίηση του αισθητήρα, συμπεριλαμβανομένης της σμίκρυνσης του αισθητήρα, της βελτίωσης της ενεργειακής απόδοσης και της κλινικής επικύρωσης για την εξασφάλιση της καταλληλότητας του για χρήση σε πραγματικό περιβάλλον.

Ενότητα 8: Μετρήσεις - Αποτελέσματα Χρησιμοποιώντας τη Μέθοδο ToF

Στην ενότητα αυτή αναλύεται η πειραματική αξιολόγηση του αισθητήρα Time-of-Flight (ToF), εστιάζοντας στην ικανότητά του να μετρά με ακρίβεια τις συγκεντρώσεις γλυκόζης σε συνθήκες που προσομοιώνουν φυσιολογικές καταστάσεις. Το πειραματικό πλαίσιο περιλάμβανε δείγματα γλυκόζης με διαφορετικές συγκεντρώσεις και ελεγχόμενες περιβαλλοντικές συνθήκες για να εξασφαλιστεί η επαναληψιμότητα και η αξιοπιστία. Η συλλογή δεδομένων περιλάμβανε προηγμένες τεχνικές επεξεργασίας, όπως μείωση θορύβου και ενίσχυση σήματος, για να βελτιωθεί η ακρίβεια των μετρήσεων.

Τα αποτελέσματα επιβεβαίωσαν την ικανότητα του αισθητήρα να ανιχνεύει αλλαγές που προκαλούνται από τη γλυκόζη στις οπτικές ιδιότητες. Οι μέσες αποκρίσεις φάσης και πλάτους του αισθητήρα έδειξαν σαφή διαφοροποίηση ανάμεσα σε επίπεδα συγκέντρωσης γλυκόζης, αποδεικνύοντας την ευαισθησία και την ακρίβεια του. Συγκριτική ανάλυση με άλλες μεθόδους ανίχνευσης ανέδειξε την ανωτερότητα του αισθητήρα ToF όσον αφορά τη διείσδυση σε βάθος και την ανθεκτικότητα στις παρεμβολές από μόρια εκτός της γλυκόζης.

Παρατηρήθηκαν προκλήσεις κατά τη διάρκεια των πειραμάτων, όπως η μεταβλητότητα της έντασης του σήματος και η παρουσία εξωτερικού περιβαλλοντικού θορύβου. Για την αντιμετώπιση αυτών των ζητημάτων,

χρησιμοποιήθηκαν προηγμένοι αλγόριθμοι για φιλτράρισμα δεδομένων.

Στην ενότητα αυτή εξετάζεται επίσης η δυνατότητα κλιμάκωσης της μεθόδου ToF για ενσωμάτωση σε πραγματικές εφαρμογές. Παρουσιάστηκαν πρωτότυπα φορητών συσκευών που ενσωματώνουν τον αισθητήρα ToF, αποδεικνύοντας τη σκοπιμότητα της συνεχούς, μη επεμβατικής παρακολούθησης γλυκόζης. Ωστόσο, επισημάνθηκε η ανάγκη για εκτεταμένες κλινικές δοκιμές για να επικυρωθεί η απόδοση του αισθητήρα σε διαφορετικούς πληθυσμούς.

Ενότητα 9: Συμπεράσματα για τη Μέθοδο ToF

Στην ενότητα αυτή συνοψίζονται τα κύρια ευρήματα και οι επιπτώσεις της χρήσης της μεθόδου Time-of-Flight (ToF) για μη επεμβατική παρακολούθηση γλυκόζης. Ο αισθητήρας ToF επέδειξε υψηλό βαθμό ευαισθησίας στις αλλαγές των επιπέδων γλυκόζης, αξιοποιώντας την ικανότητά του να μετρά λεπτές μεταβολές στις οπτικές ιδιότητες των ιστών του δέρματος. Ο σχεδιασμός του αισθητήρα, με την αρθρωτή αρχιτεκτονική και τις προσαρμοστικές δυνατότητες, αποτελεί σημαντικό βήμα προς την ανάπτυξη πρακτικών συστημάτων παρακολούθησης γλυκόζης σε πραγματικό χρόνο.

Τα ευρήματα ανέδειξαν τα πλεονεκτήματα της μεθόδου ToF, όπως τη διείσδυση σε βάθος σε σχέση με παραδοσιακές οπτικές μεθόδους και τη σχετική ανθεκτικότητα στις παρεμβολές από μόρια εκτός της γλυκόζης. Παρόλα αυτά, παραμένουν προκλήσεις. Η απόδοση του αισθητήρα παρουσίασε ευαισθησία στη φυσιολογική μεταβλητότητα, όπως διαφορές στον τόνο του δέρματος, τα επίπεδα ενυδάτωσης και τη σκέδαση των ιστών. Επιπλέον, η ευαισθησία του αισθητήρα στον περιβαλλοντικό θόρυβο, όπως το φως και οι θερμοκρασιακές διακυμάνσεις, υπογραμμίζει την ανάγκη για περαιτέρω βελτιώσεις στον σχεδιασμό του υλικού και τους αλγόριθμους επεξεργασίας σήματος.

Η ενσωμάτωση της μηχανικής μάθησης για την ανάλυση δεδομένων και τη μείωση του θορύβου αναδείχθηκε ως κρίσιμος τομέας για περαιτέρω ανάπτυξη. Χρησιμοποιώντας προχωρημένα μοντέλα πρόβλεψης, ο αισθητήρας ToF θα μπορούσε να διαχειριστεί καλύτερα τη φυσιολογική και περιβαλλοντική μεταβλητότητα, βελτιώνοντας την ακρίβεια και την αξιοπιστία του.

Συμπερασματικά στην ενότητα τονίζονται οι δυνατότητες της μεθόδου ToF για ενσωμάτωση σε φορητές πλατφόρμες, όπως έξυπνα ρολόγια ή επιθέματα, επιτρέποντας τη συνεχή παρακολούθηση γλυκόζης. Οι συστάσεις για μελλοντική έρευνα περιλαμβάνουν εκτεταμένη κλινική επικύρωση σε διαφορετικούς πληθυσμούς, τη σμίκρυνση του αισθητήρα για βελτιωμένη φορητότητα και τη μείωση του κόστους για ενίσχυση της προσβασιμότητας από ασθενείς.

Συμπεράσματα και Περαιτέρω Έρευνα

Η παρούσα διατριβή καταλήγει συνθέτοντας τις συνεισφορές των διαφόρων μεθόδων μη επεμβατικής παρακολούθησης γλυκόζης και εντοπίζοντας διαδρομές για μελλοντικές βελτιώσεις. Η έρευνα υπογράμμισε τις δυνατότητες των οπτικών μεθόδων, ιδίως των καινοτόμων σχεδιασμών Time-of-Flight (ToF) ενώ έδειξε επίσης τα προβλήματα τις τεχνικής μέτρησης μεσω βιοεμπέδησης. Αυτές οι μέθοδοι προσφέρουν σημαντικά πλεονεκτήματα σε σχέση με τις παραδοσιακές επεμβατικές τεχνικές, περιλαμβάνοντας μεγαλύτερη άνεση για τον ασθενή, τη δυνατότητα συνεχούς παρακολούθησης και την εξάλειψη της ανάγκης για αιμοληψία.

Παρά τις υποσχέσεις τους, τα συστήματα μη επεμβατικής παρακολούθησης γλυκόζης αντιμετωπίζουν ωστόσο σημαντικές προκλήσεις. Η φυσιολογική μεταβλητότητα, οι περιβαλλοντικές παρεμβολές και οι εγγενείς περιορισμοί των μονοτροπικών προσεγγίσεων ανίχνευσης αποτελούν σημαντικά εμπόδια για την κλινική αποδοχή τους. Στη διατριβή επισημαίνεται η σημασία των πολυτροπικών συστημάτων ανίχνευσης που συνδυάζουν οπτικές, βιοηλεκτρικές και άλλες τεχνικές για τη βελτίωση της ακρίβειας και της αξιοπιστίας.

Οι κατευθύνσεις για μελλοντική έρευνα περιλαμβάνουν την ενσωμάτωση μη επεμβατικών αισθητήρων σε φορητές πλατφόρμες και πλατφόρμες IoT για παρακολούθηση σε πραγματικό χρόνο και κοινή χρήση δεδομένων. Η σμίκρυνση των αισθητήρων και η ανάπτυξη οικονομικά αποδοτικών διαδικασιών κατασκευής είναι κρίσιμες για τη βελτίωση της προσβασιμότητας και τη διείσδυση στην αγορά. Οι κλινικές δοκιμές σε ποικίλους πληθυσμούς είναι απαραίτητες για την επικύρωση της απόδοσης αυτών των συστημάτων σε πραγματικές συνθήκες.

Η παρούσα έρευνα αντιπροσωπεύει ένα σημαντικό βήμα προς την κατεύθυνση της επίτευξης κλινικά βιώσιμων συστημάτων μη επεμβατικής παρακολούθησης γλυκόζης. Αντιμετωπίζοντας τις προκλήσεις που περιγράφηκαν και αξιοποιώντας τις εξελίξεις στην τεχνολογία αισθητήρων, την ανάλυση δεδομένων και τη διεπιστημονική συνεργασία, ο τομέας μπορεί να κινηθεί περαιτέρω στην παροχή σημαντικών και καινοτόμων λύσεων για τη φροντίδα του διαβήτη.

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List of Author's Publications

International Peer–Reviewed Journals

1. **Asimakopoulos, K.**; Hristoforou, E. Non-Invasive Glucose Measurement Technique Based on Time-of-Flight. Appl. Sci. 2024, 14, 11602. DOI: 10.3390/app142411602

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International Peer–Reviewed Conferences

1. C. Dimas, **K. Asimakopoulos** and P. P. Sotiriadis, "A highly tunable dynamic thoracic model for Electrical Impedance Tomography," *IEEE 20th International Conference on Bioinformatics and Bioengineering (BIBE)*, Cincinnati, OH, USA, 2020, pp. 961-968, DOI: 10.1109/BIBE50027.2020.00163.

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Abbreviations

2D	2–Dimensional
AC	Alternating Current
DC	Direct Current
FEM	Finite Element Modeling
NGM	Non-invasive glucose monitoring
NIR	Near Infrared
ToF	Time-of-Flight

Μετάφραση Όρων

2D	Δισδιάστατο
AC	Εναλλασσόμενο Ρεύμα
DC	Συνεχές Ρεύμα
FEM	Μοντελοποίηση Πεπερασμένων Στοιχείων
NGM	Μη Επεμβατική μέτρηση γλυκόζης
NIR	Εγγύς Υπέρυθρο
ToF	Χρόνος Πτήσης

Thesis Outline

The thesis begins with an introduction that provides a comprehensive overview of diabetes as a critical global health issue and highlights the necessity of effective glucose monitoring for managing the condition. Traditional invasive methods, such as finger-prick tests and continuous glucose monitoring (CGM), are discussed in the context of their limitations, particularly in terms of patient comfort, accessibility, and adherence. This sets the stage for the exploration of non-invasive glucose sensing technologies as a revolutionary alternative.

The subsequent sections delve into the landscape of current blood glucose monitoring methodologies, contrasting invasive techniques with emerging non-invasive approaches. A detailed exploration of non-invasive methodologies follows, encompassing optical spectroscopy (including Near-Infrared and Raman spectroscopy), bioimpedance spectroscopy, microwave sensing, and photoacoustic techniques. Each methodology is critically analyzed, with attention to its principles, applications, and the factors influencing its accuracy.

The experimental framework and methodology section introduces the design and validation of innovative sensing elements. This includes calibration protocols, the setup of measurement systems, and data acquisition strategies, laying the foundation for the experimental results and discussion. The results highlight the performance of these sensing technologies, with a focus on their advantages and limitations compared to existing methods.

Further into the thesis, the challenges of simulating human skin for glucose sensing are addressed. A simplified model of the skin is developed, and advanced computational methods such as Monte Carlo simulations and radiative transfer techniques are applied. The limitations and complexities encountered during these simulations are discussed, emphasizing the need for more sophisticated models.

The centerpiece of the thesis is the presentation of a novel Time-of-Flight (ToF)-based sensor. This innovative device is described in terms of its operational principles, experimental implementation, and validation. Its potential for integration into wearable technologies and IoT platforms for real-time glucose monitoring is explored, positioning it as a transformative development in diabetes management.

Challenges and limitations inherent to non-invasive glucose monitoring are then examined in detail. These include issues related to accuracy, environmental and phys-

iological variability, and economic scalability. The thesis concludes with a synthesis of the findings, offering a vision for future research and development to overcome these barriers and advance the field. Recommendations emphasize the integration of machine learning, multi-modal sensing approaches, and interdisciplinary collaboration.

Part I

Current Trends in Invasive and Non-Invasive Glucose Sensing

1 Diabetes and Blood Glucose Monitoring

1.1 Introduction to Diabetes

Diabetes mellitus is a global health crisis affecting millions worldwide. It is characterized by persistent hyperglycemia caused by impaired insulin production (Type 1 diabetes) or insulin resistance (Type 2 diabetes) [1]. Beyond its acute symptoms, diabetes has long-term complications, including cardiovascular diseases, neuropathy, retinopathy, and renal failure, contributing significantly to morbidity and mortality globally [2]. In 2021, diabetes accounted for approximately 11% of global healthcare expenditures [3].

The World Health Organization (WHO) estimates that the prevalence of diabetes will rise from 463 million in 2019 to over 700 million by 2045 [2]. This increase highlights an urgent need for improved management tools. Frequent glucose monitoring plays a critical role in disease management, enabling patients to control glycemic levels effectively and reduce complications.

Despite the availability of effective monitoring systems like finger-prick tests and continuous glucose monitors (CGMs), these methods are often invasive, leading to discomfort, inconvenience, and poor patient adherence. These limitations underscore the growing interest in non-invasive glucose monitoring technologies, which promise to revolutionize diabetes care [4].

1.2 Traditional Monitoring Methods

Conventional glucose monitoring relies on enzymatic methods involving blood extraction and subsequent chemical analysis. Finger-prick tests, which measure glucose concentration using electrochemical strips, are the most widely used technique [5]. These methods are highly accurate and provide immediate results but are limited to discrete measurements.

Continuous glucose monitoring (CGM) systems represent an improvement, offering real-time data and alerts for hypo- or hyperglycemic episodes. However, CGMs require subcutaneous implantation, which can lead to skin irritation and discomfort. The high cost of CGM devices further restricts their accessibility [3].

1.3 Non-Invasive Monitoring Techniques

Non-invasive glucose monitoring eliminates the need for blood extraction, relying instead on physical or chemical properties of glucose. Below, key methodologies and their applications are presented:

1.3.1 Optical Spectroscopy

Optical spectroscopy utilizes the interaction between light and glucose molecules to estimate glucose levels:

- **Near-Infrared (NIR) Spectroscopy**: Measures light absorption in the 700–2500 nm range. NIR is non-destructive and less sensitive to interference from water but has limited sensitivity due to scattering in tissue [1].
- **Mid-Infrared (MIR) Spectroscopy**: Targets glucose-specific absorption bands, providing higher specificity. However, MIR measurements face challenges due to strong water absorption and limited tissue penetration [4].
- **Raman Spectroscopy**: Detects molecular vibrations unique to glucose. Raman spectroscopy offers high specificity and resistance to interference but requires complex equipment, making it less accessible [2].

1.3.2 Bioimpedance Spectroscopy

Bioimpedance spectroscopy measures tissue impedance, which varies with glucose concentration. It is low-cost and portable but influenced by hydration, temperature, and physiological noise, requiring advanced calibration [5].

1.3.3 Photoacoustic Spectroscopy

Photoacoustic methods involve light absorption by glucose, resulting in heat generation and acoustic wave production. This technique shows promise for in-vitro applications but requires further refinement for in-vivo use [4].

1.3.4 Polarimetry

Polarimetry exploits glucose's ability to rotate polarized light. While theoretically promising, practical implementation is hindered by interference from other optically active molecules, such as proteins [3].

1.4 Factors Influencing Accuracy

The accuracy of non-invasive glucose monitoring is affected by several factors:

- **Physiological Variability**: Differences in skin thickness, hydration, and vascularization can introduce noise into measurements [5].
- **Environmental Conditions**: External factors such as ambient temperature and humidity affect the performance of optical and bioimpedance systems [4].
- **Interference from Other Molecules**: Many glucose measurement methods are susceptible to interference from substances such as hemoglobin and water [2].

1.5 Challenges in Development

Non-invasive glucose monitoring technologies face significant barriers to adoption:

1. **Regulatory Hurdles**: Devices must meet stringent accuracy and reliability standards set by organizations such as the FDA and ISO [3].
2. **Technological Limitations**: Current methods lack the precision required for clinical use, especially for detecting rapid glucose fluctuations [4].
3. **Cost Constraints**: High development and production costs limit the accessibility of advanced technologies like Raman spectroscopy [1].

1.6 Future Directions

Emerging research focuses on overcoming these challenges through:

- **Multi-Modal Approaches**: Combining techniques like NIR and bioimpedance to improve accuracy and reliability.
- **Machine Learning Integration**: Advanced algorithms can analyze complex datasets, enabling more precise glucose predictions [2].

- **Miniaturization**: Reducing device size and power consumption to enhance portability and user comfort.
- **Cost Reduction**: Developing scalable manufacturing processes to lower costs and increase accessibility [5].

1.7 Conclusion

Non-invasive glucose monitoring represents a paradigm shift in diabetes care. While current technologies remain limited in their accuracy and practicality, ongoing research is driving significant improvements. The integration of advanced sensing techniques with machine learning holds the potential to transform these devices into reliable, cost-effective solutions. Achieving this goal will require interdisciplinary collaboration and robust clinical validation.

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2 Non Invasive glucose measurement techniques

Abstract

Non-invasive glucose monitoring (NGM) is a cornerstone in advancing diabetes management technologies. Unlike traditional invasive methods, NGM offers a painless and more user-friendly approach to monitoring blood glucose levels. This review delves into the evolution of NGM, focusing on key technological advancements such as near-infrared spectroscopy, Raman spectroscopy, bioimpedance analysis, and microwave sensing. The challenges associated with accuracy, physiological interference, and scalability are discussed in depth, along with insights into recent integrations with wearable and IoT devices.

2.1 Introduction

NGM technologies aim to address these limitations by offering methods that do not require blood extraction, thereby improving patient compliance and enabling frequent monitoring. Over the past few decades, significant progress has been made in developing and commercializing non-invasive glucose monitors using techniques such as spectroscopy, bioimpedance, and microwave sensing. This paper provides a detailed exploration of these technologies, their underlying principles, and the challenges they face.

2.2 Techniques in Non-Invasive Glucose Monitoring

2.2.1 Near-Infrared Spectroscopy (NIRS)

Near-Infrared Spectroscopy (NIRS) utilizes the specific absorption characteristics of glucose in the near-infrared region of the electromagnetic spectrum (700–2500 nm)

[1]. By measuring the absorption and scattering of light, NIRS can estimate glucose concentrations non-invasively. This method benefits from its potential for miniaturization and integration into wearable devices, such as wristbands and smartwatches [2].

Despite these advantages, the high absorption of water and interference from other biological molecules in the tissue pose significant challenges. Sophisticated algorithms and calibration models are required to extract meaningful data from the noisy signals. Additionally, factors such as skin pigmentation, hydration, and environmental light can impact the accuracy of NIRS-based devices [3].

Recent advancements have focused on enhancing the sensitivity and specificity of NIRS through the use of advanced photodetectors and machine learning algorithms, which can analyze patterns in spectral data and correct for noise and interferences [1, 4].

2.2.2 Raman Spectroscopy

Raman spectroscopy is a highly specific technique that measures glucose concentrations by detecting the unique vibrational energy levels of glucose molecules. Unlike NIRS, Raman spectroscopy is less affected by water interference, making it a promising candidate for NGM [5].

The technique involves shining monochromatic light onto the skin and measuring the inelastically scattered light, which carries molecular-specific information. While its specificity is a significant advantage, Raman spectroscopy faces challenges such as weak signal intensity and high equipment costs. Additionally, patient motion and varying skin conditions can complicate measurements [6].

Efforts to commercialize Raman spectroscopy-based devices have included the development of portable Raman spectrometers and integration with machine learning models to enhance signal processing and prediction accuracy [7].

2.2.3 Bioimpedance Spectroscopy

Bioimpedance spectroscopy measures the electrical impedance of biological tissues, which varies with glucose levels due to changes in tissue hydration and ionic content [8]. This technique is cost-effective, fast, and highly scalable, making it an attractive option for wearable applications.

Devices utilizing bioimpedance have shown promise in clinical trials, though their accuracy can be affected by factors such as temperature, hydration status, and the presence of sweat. Advanced device designs now incorporate multi-frequency measurements and adaptive algorithms to improve the reliability of bioimpedance-based glucose monitoring systems [9].

2.2.4 Microwave Sensing

Microwave sensing is a novel approach that leverages the dielectric properties of glucose at GHz frequencies. By transmitting microwaves through the skin and measuring the reflected or transmitted signals, glucose concentrations can be inferred [10].

Microwave sensing offers the advantage of deeper tissue penetration and minimal interference from external factors such as ambient light. However, it requires precise calibration and is sensitive to anatomical variations between individuals. Recent developments in this area include the use of antenna arrays and machine learning algorithms for data interpretation and real-time monitoring [4].

2.2.5 Photoacoustic Spectroscopy

Photoacoustic spectroscopy combines optical absorption and acoustic wave generation to detect glucose levels. This hybrid technique provides high sensitivity and has been explored for integration into compact, portable devices [11].

However, challenges such as signal attenuation, acoustic noise, and limited penetration depth remain significant barriers. Ongoing research is exploring advanced materials and laser technologies to enhance the performance of photoacoustic glucose monitors [2].

2.3 Challenges in NGM Technologies

The development and commercialization of NGM technologies are hindered by several challenges:

- **Accuracy and Specificity**: NGM devices often struggle with interference from other biomolecules and variability in physiological conditions, leading to reduced accuracy [12].
- **Calibration**: Continuous calibration against invasive glucose measurements is often required to maintain device reliability, particularly in varying environmental conditions[8].
- **Cost and Scalability**: High costs of production and the need for advanced materials and sensors limit the accessibility of NGM technologies to broader populations[10].

2.4 Integration with Wearable and IoT Devices

NGM technologies are increasingly being integrated into wearable platforms, enabling real-time glucose monitoring and data analysis. Devices such as smartwatches and

patches leverage multi-modal sensing techniques to improve accuracy and reduce errors [2]. Additionally, the integration of IoT and cloud computing facilitates the aggregation and analysis of glucose data, providing personalized insights for diabetes management [6, 4].

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Part II

Non-Invasive Glucose Sensing using RF

3 Previous Work – Antenna Design and Creation

Abstract

Bioimpedance-based non-invasive glucose monitoring (NGM) has emerged as a promising alternative to traditional invasive methods. This review explores the principles, experimental techniques, and clinical applications of bioimpedance methods in glucose monitoring. Advances in electrode designs, frequency range optimizations, and signal processing are discussed, supported by findings from clinical trials.

3.1 Introduction

Bioimpedance involves measuring the electrical impedance of biological tissues, which varies with glucose concentration due to changes in tissue dielectric properties. This review delves into the principles of bioimpedance, experimental techniques, and clinical applications in glucose monitoring.

3.2 Principles of Bioimpedance in Glucose Monitoring

Bioimpedance leverages the electrical properties of biological tissues, such as permittivity and conductivity, which are influenced by glucose levels in the interstitial fluid and cellular membranes. Dielectric spectroscopy, a key tool in bioimpedance, measures impedance across a range of frequencies to capture glucose-induced changes [1].

Studies reveal that glucose affects the dielectric properties of erythrocyte membranes and interstitial fluids. Variations in these properties alter the impedance, enabling indirect glucose measurement. Electrochemical impedance spectroscopy (EIS) has been extensively used for this purpose, with significant advancements in sensor designs and frequency analysis [2].

3.3 Experimental Techniques and Approaches

3.3.1 Electrode Configurations

The design and placement of electrodes are critical for accurate bioimpedance measurements. Studies have explored concentric and coplanar electrode geometries, with gold and silver coatings to enhance conductivity and minimize noise [3, 4]. Electrode placement on less variable regions, such as the forearm, has been shown to improve measurement reliability.

3.4 Methodology and Creation of Sensing Elements

There is a substantial body of work to draw upon for the measurement of glucose based on electromagnetic properties(eg [5],[6],[7]). Caduff et al especially, have in their work, used sensing elements of different sizes placed on top of the skin of diabetic patients, to try and determine the glucose levels in the human body [8].

The basic principle behind their attempts to noninvasively measure blood glucose levels is the capacitive coupling of the sensing elements to the body. By monitoring the changes of this coupling a correlation to blood glucose levels was established. Based on their work, three sensing elements were recreated to test. These elements were created to follow the suggestions of Caduff et al [8] but were modified to be single sided thus allowing for easier construction. Additionally, as they would not be used for capacitive sensing in contact with the sample but rather remote measurement, elements with a back made of copper were created as well to be compare with ones that did not have such a backplane. This backplane was designed to act as a ground reference for the sensing element (which essentially becomes an antenna). All three elements were formed as an two half elliptical shapes, connected by a rectangle. The first one (”large”) had a width of 4 mm, the second one (”medium”) a width of 1.5 mm and the third one (”small”) a width of 0.3 mm. They were each placed in separate copper pours that were connected to ground and separated from the pour with a gap of 4.2 mm, 1.7 mm and 0.5 mm respectively. They were all 25 mm in length. The main element was connected to the center pin of an SMA jack and the copper pour around it was connected to the outside of the SMA jack to act as ground. Each sampling element was manufactured twice; the second one had a copper backing connected to ground. The created elements are shown in fig. 3.1.

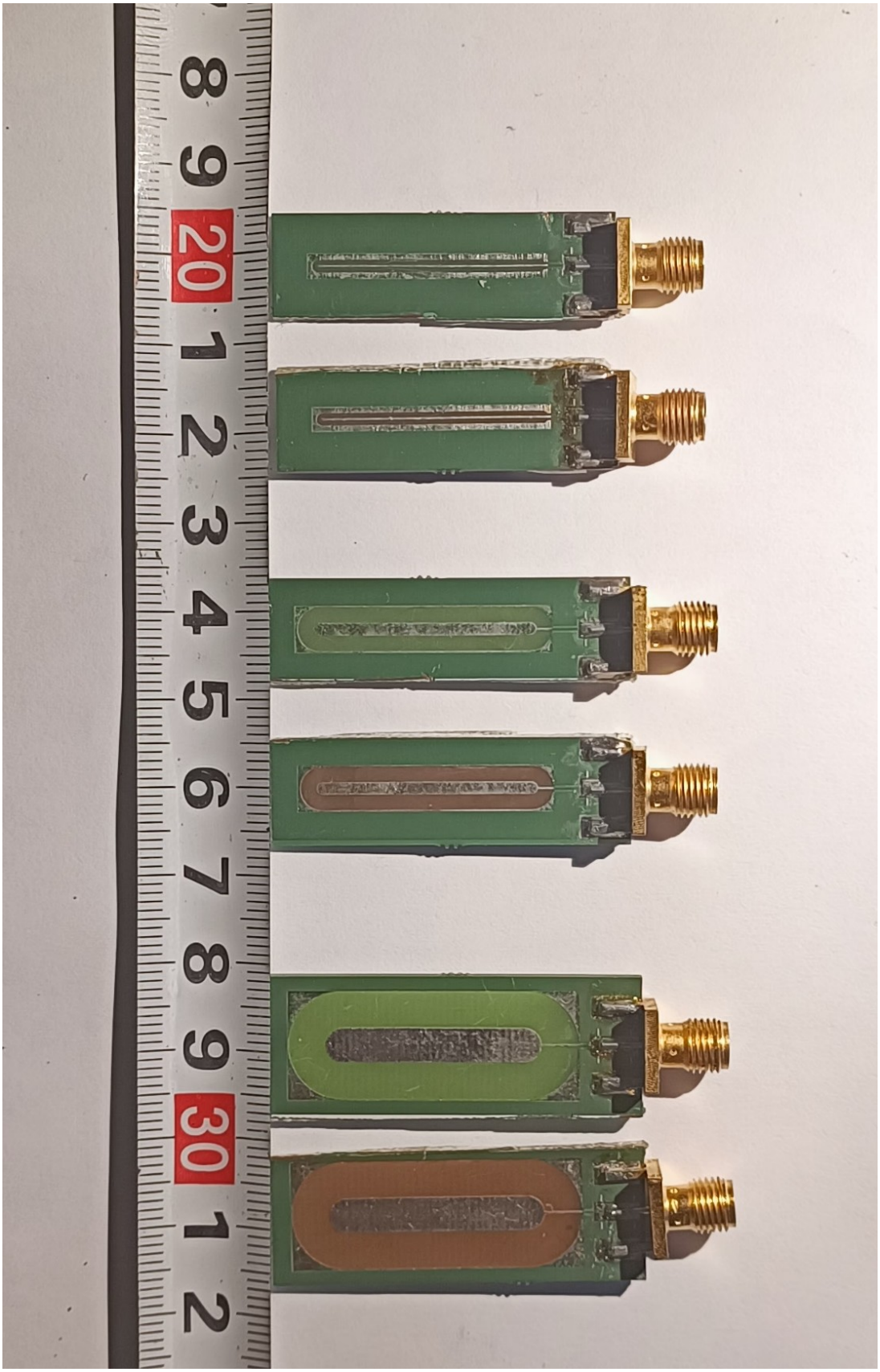

Figure 3.1: Antennas (sensing elements) created and used. From left to right: small, medium, large element pairs. For each pair the one on the left is the one without copper backplane and the one on the right includes it.

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4 Bioimpedance Measurement technique

4.1 Introduction

One of the most actively researched measurement methodology is through the electromagnetic properties of tissues and the varying effects of changing glucose levels on them. Work from multiple authors has shown this as a viable method to provide information on the current glucose levels[1],[2],[3]. Based on these observations, this section attempts to determine if the sensing elements manufactured, could be used in different configurations to increase measurement flexibility and ease.

4.2 Experimental Setup and results post-processing

The first step was the creation of samples. To this end samples were created using sterile physiological saline and laboratory grade D-Glucose. Each sample was placed initially in a cylindrical sample bottle for measurement. Samples were created with the following concentrations for the first round (mg/dl): 24, 40, 60, 80, 100, 120, 140, 160, 180, 200, 250, 300, 350, 400, 450, 500. A sample consisting of saline only was also created as a reference. For the second round the samples used (recreated) were (mg/dl): 50, 100, 150, 200, 250, 300, 350, 400, 450 and the reference. This range and stepping was selected to closely match human physiological glucose concentrations as well hyperglycemia [4].

All measurements presented in this section were performed using the HP 8753D network analyzer. Before each measurement session, the analyzer was allowed to idle for at least 30 minutes to allow it to reach operating temperatures and a steady state. Afterwards, a full 2 port calibration was performed using the HP 85033D calibration kit with all cables of the measurement setup installed. A MATLAB script was to created that allowed each measurement to be repeated 10 times with a time delay of 60 seconds between each measurement without needing to modify the measurement setup in any way.

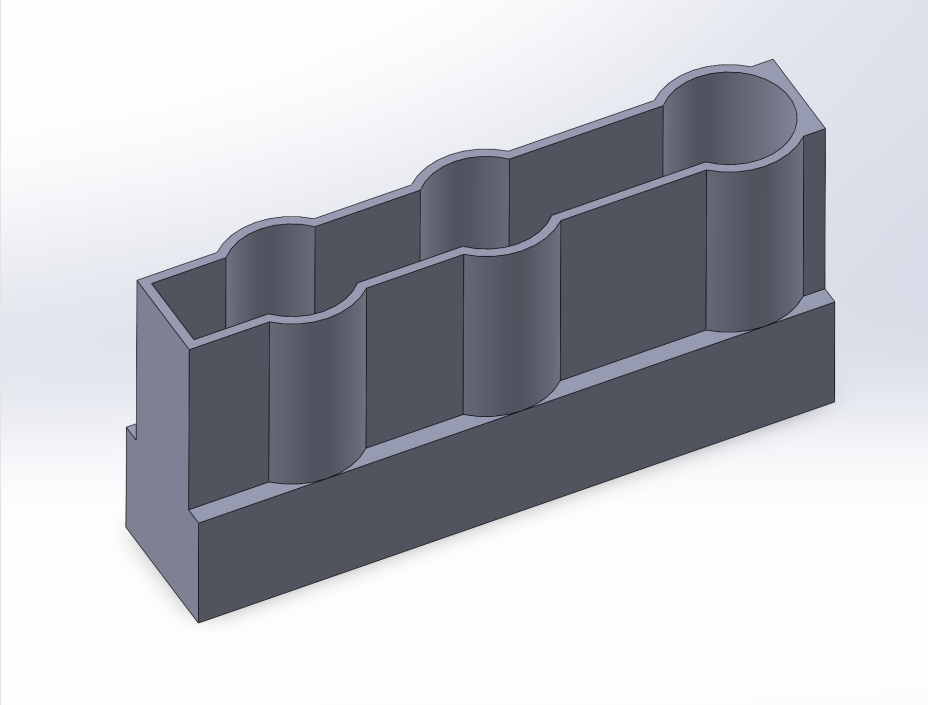

Figure 4.1: Sample holder for the S11 vs distance sample measurements.

To ensure repeatability due to the placement of the samples, special fixtures were created that ensured both distance and the relative placement of sample holder and sensing elements, remained the same across all experiments. The material of the fixtures did not affect the measurements - indeed measurements were repeated with and without the fixture to verify that the effect was minimal.

The resulting data were initially averaged and used for the sensing element comparison. To test the sensor response to different glucose concentrations the data were additionally low pass filtered using a moving average filter to remove high frequency noise. A window size of 50 sampling points was selected as this provided the best results. Higher sample window sizes tended to overly smooth the measured data, while lower sizes would not adequately filter it.

Finally, the standard deviation of all repeated measurements for each concentration/sensor combination was calculated and was used to verify that measurements remained relatively stable across multiple runs.

4.3 Results

4.3.1 First round of testing

The first round of tests consisted of measuring the S_{11} response of the sensing element when placed at different distances from a glucose containing sample. For the initial

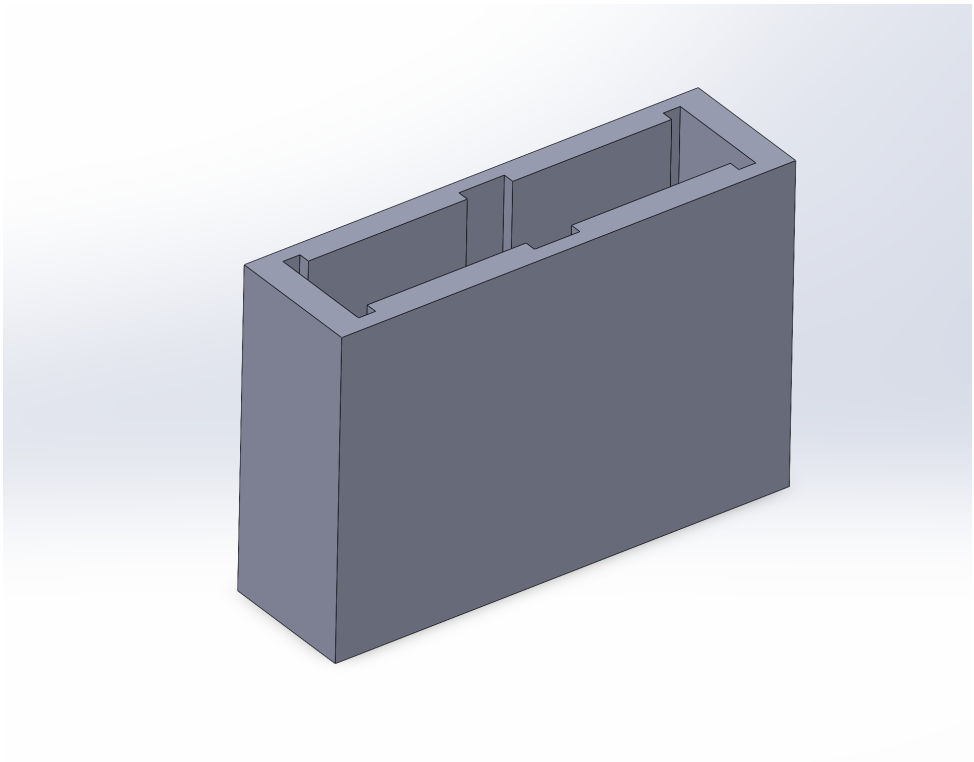

Figure 4.2: Sample holder for the S21 sample measurements.

experiments, the frequency range of $1-200MHz$ was selected. This range was selected as at the high limit of $200MHz$ the depth of RF penetration in the human body has dropped to about 7 cm [5], which was considered adequate for future expansion of the experiment to diabetic patients. Electrode polarization effects that could disturb any possible measurements were considered to be minimal due to the non-contact of the probe with the sample. However, measurements were performed to a lower limit of $1MHz$ to prevent any effects from occurring, as it should only affect the measurements at the low end of the range to be measured and specifically under 1kHz (as shown by Gabriel et al [6]). As the sample did not contact the sensing element, stray inductance effects were considered to be minimal.

Three groups of measurements were performed. For each of the electrodes, full measurements were performed initially in the range 0-10 cm from the sensor with a step of $1cm$, for the reference sample and the $500mg/dl$ sample. After analyzing these measurements, the distance points that provided the best response were selected ($1cm$, $5cm$, $10cm$). The response of each sample was measured and recorded at these distance points. Additionally, the "small" sensing element was removed from further tests due to the very small differentiation between the reference sample and the $500mg/dl$ sample(see also fig.4.3).

After the first round of experiments was completed, the most promising sensing elements were selected (medium and large element) and measurements were repeated

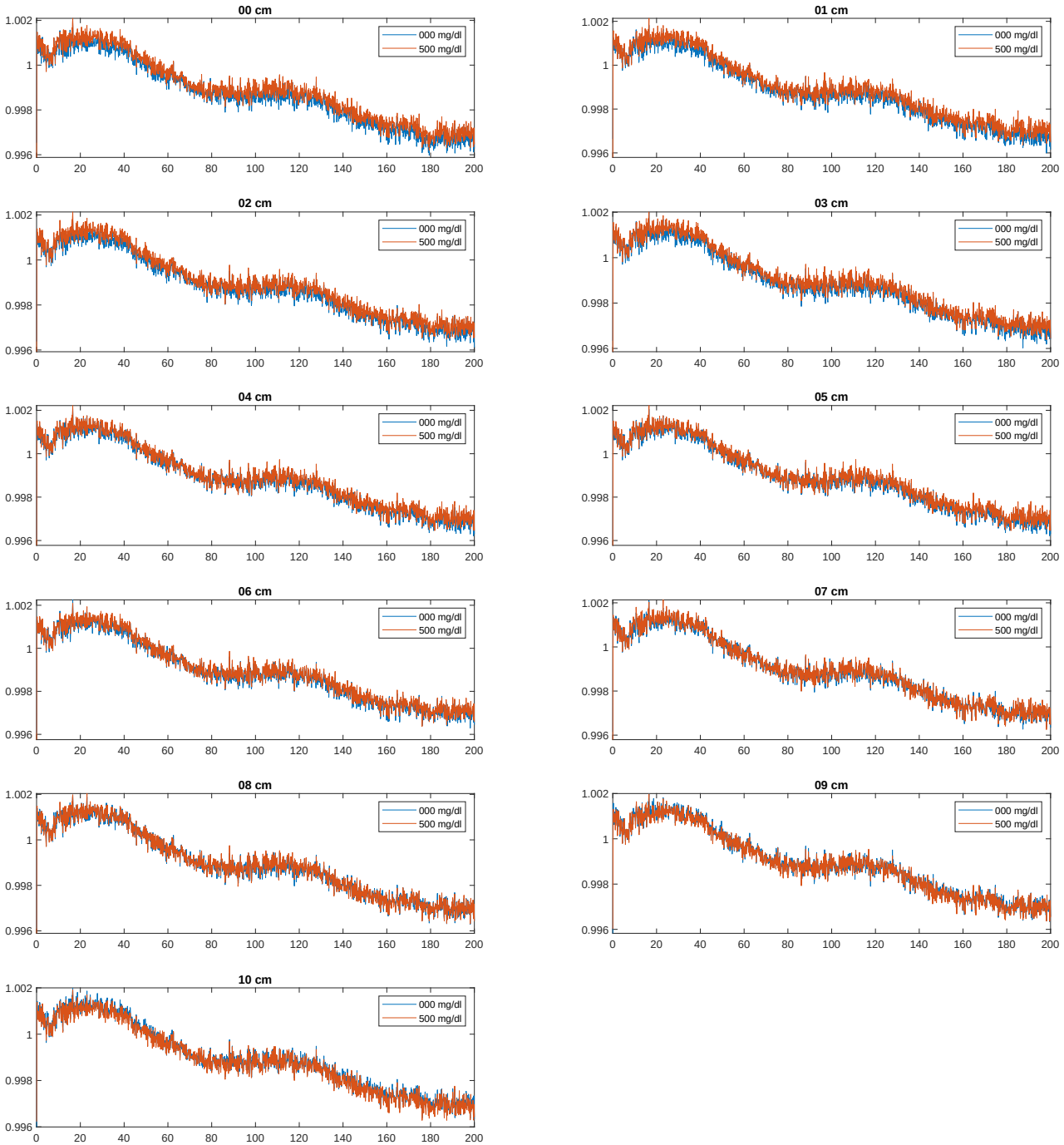

Figure 4.3: Comparison of Reference versus 500mg concentration with the small sensing element.

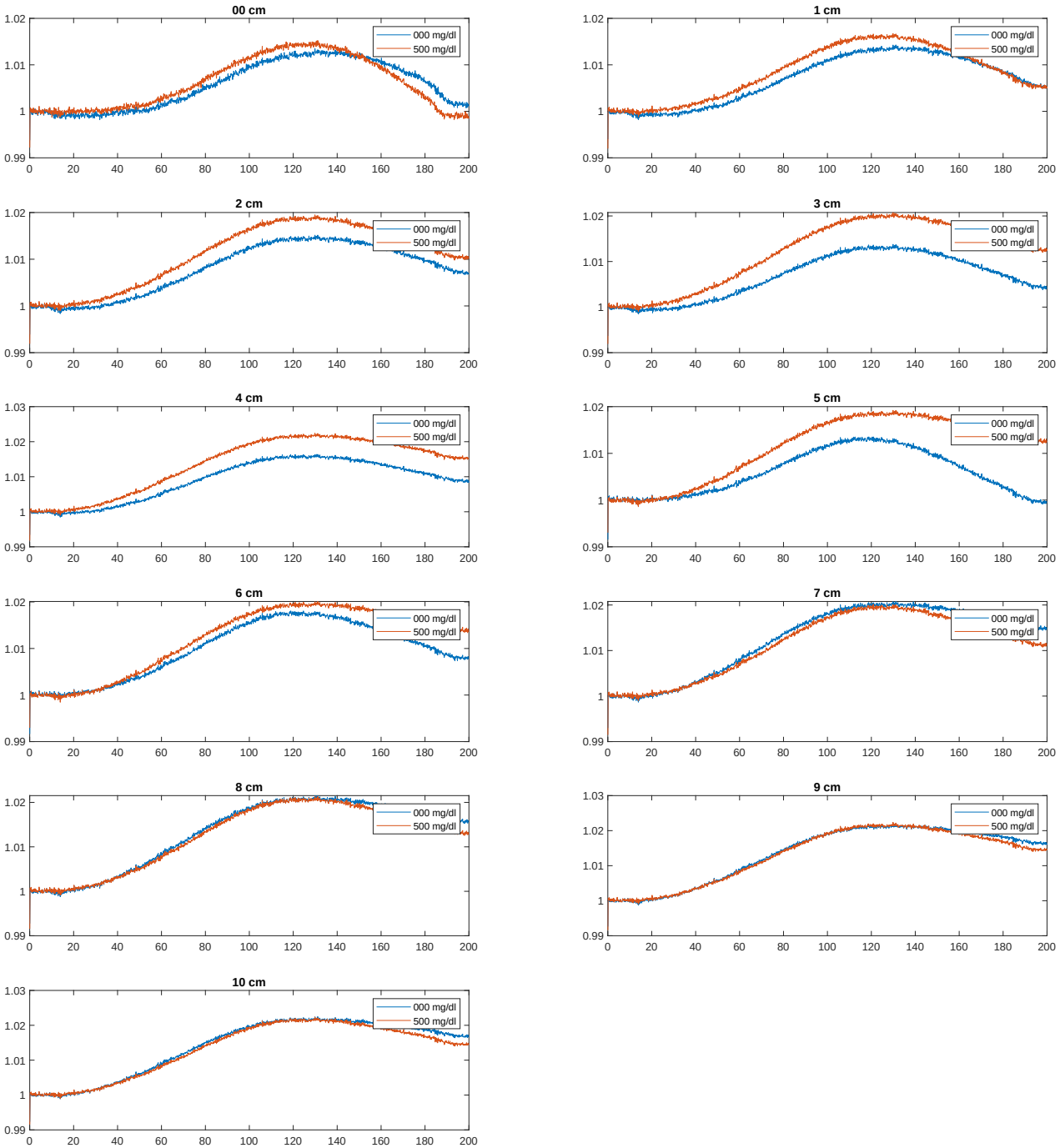

Figure 4.4: Comparison of Reference versus 500mg concentration with the large sensing element.

at higher frequencies, up to $6GHz$, to determine if higher frequencies would yield different results, even though there would be minimal penetration of the skin. Glucose levels in interstitial fluid are generally correlated to systematic glucose especially during rest and some time after food consumption. Consequently, skin properties change up to nearly the surface depending on glucose concentration - albeit with a slight time delay[7].

4.3.2 Second Round of Testing - Large Sensing Element Results

The measurement results of the first sensing element are shown in fig. 4.7, 4.8, 4.9. These figures present the results of measuring the samples at different distances from the sensor (01, 05 and 10 cm). Plotting the response versus concentration for a number of frequencies (equidistant points regularly spaced between the two extremes of the frequency axis) shows that the concentration affects non linearly the measured signal - figures 4.10, 4.11 and 4.12. The standard deviation of all measurements for a specific concentration and distance can be found in fig. 4.13, 4.13 and 4.15. These show that standard deviation of all measurements is sufficiently low even though not completely stable (which can be attributed to experimental variations).

4.3.3 Second Round of Testing - Medium size Sensing Element Results

The measurement results of the second sensing element are shown in fig. 4.16, 4.17, 4.18. These figures present the results of measuring the samples at different distances from the sensor (01, 05 and 10 cm). These show a greater differentiation of the resulting curve, dependent on the sample glucose concentration when compared to the previous sensor design. Plotting the response versus concentration for a number of frequencies (equidistant points regularly spaced between the two extremes of the frequency axis) shows that the concentration affects non linearly the measured signal - figures 4.19, 4.20 and 4.21. Finally, the standard deviation of all measurements for a specific concentration and distance can be found in fig. 4.22, 4.23 and 4.24. These show that the standard deviation of all measurements is sufficiently low but exhibit the same phenomenon as the previous sensing element.

4.3.4 Third round of testing

Finally, the effect of glucose concentration on the S_{21} parameter was measured by utilizing multiple sensing elements with the glucose containing sample placed between them. The results of these measurements did not show any ability to discern glucose concentration. The results are shown in figs. 4.5,4.6.

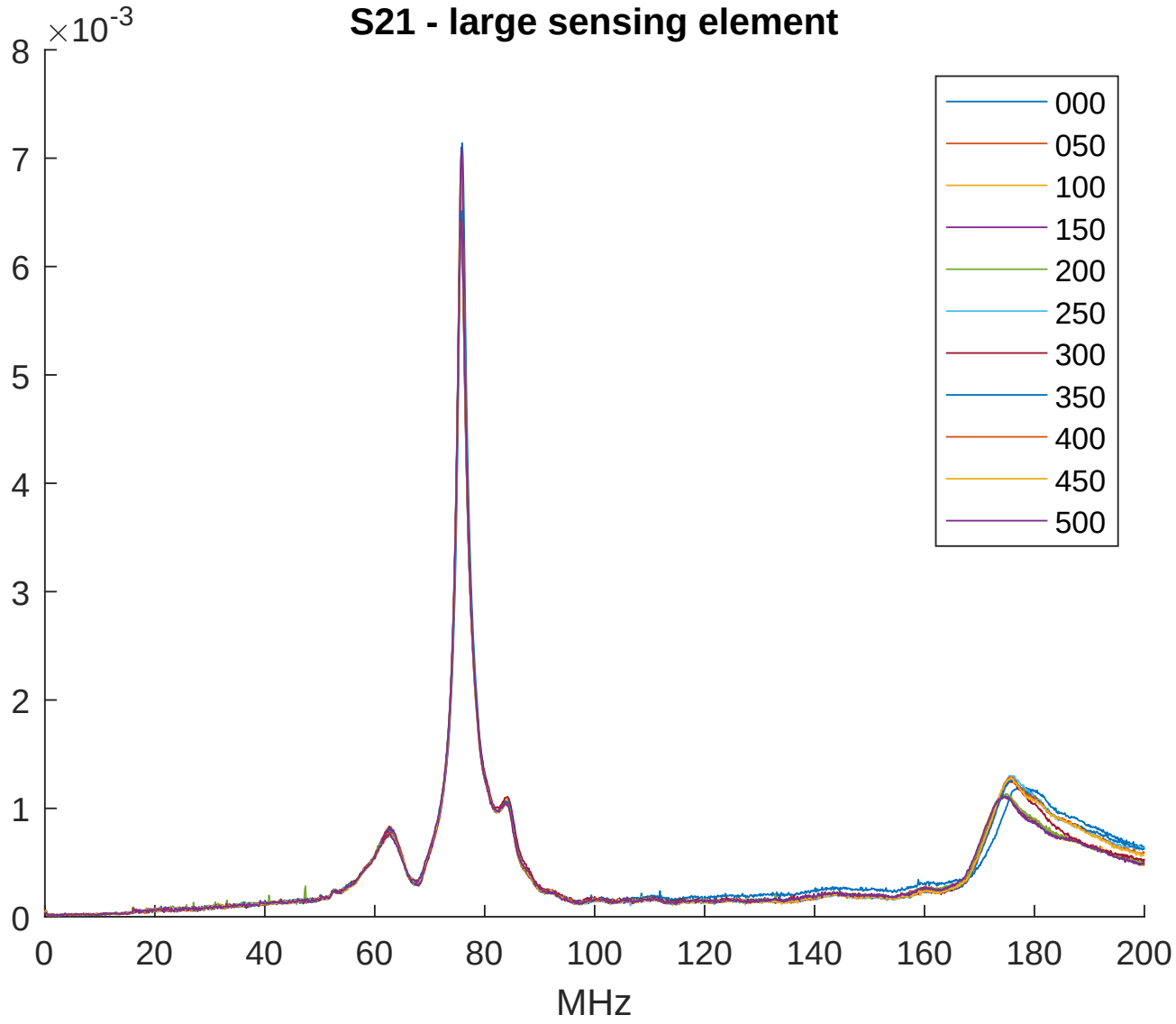

Figure 4.5: Comparison of the effect of different glucose concentrations on the S21 parameter - Large sensing elements.

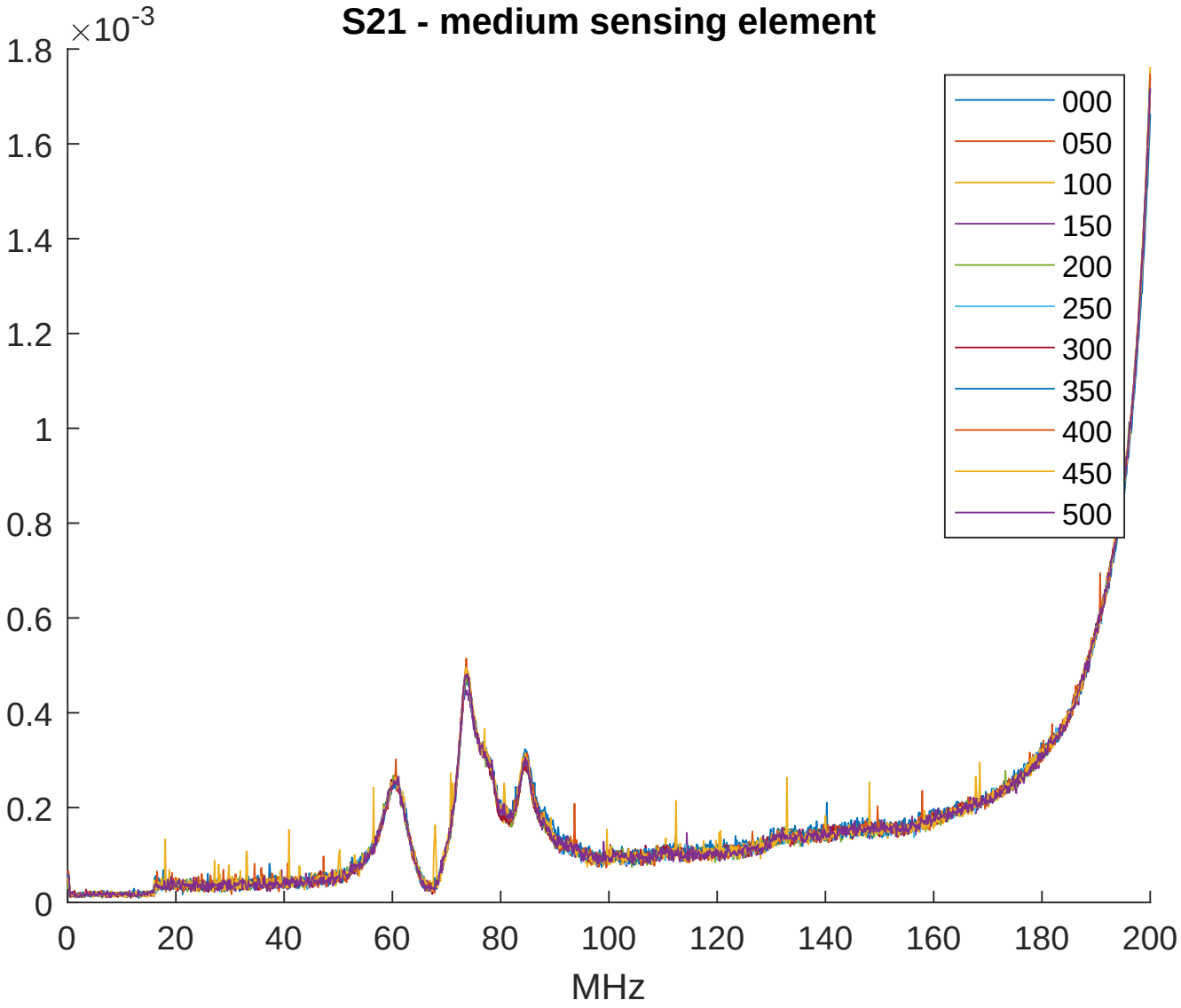

Figure 4.6: Comparison of the effect of different glucose concentrations on the S21 parameter - Medium sensing elements.

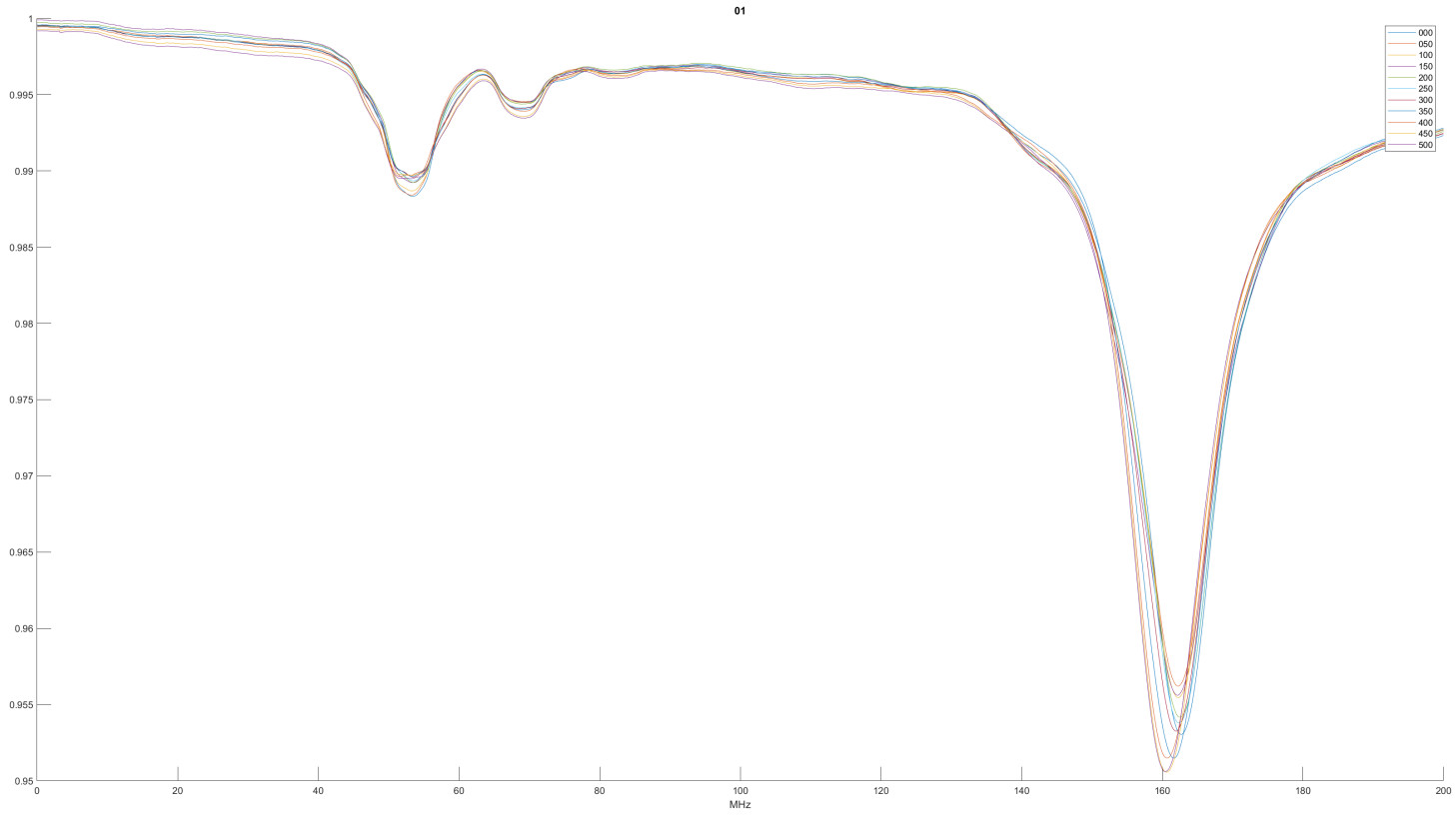

Figure 4.7: Sample response at different frequencies and concentrations - Large sensing element at 01 cm.

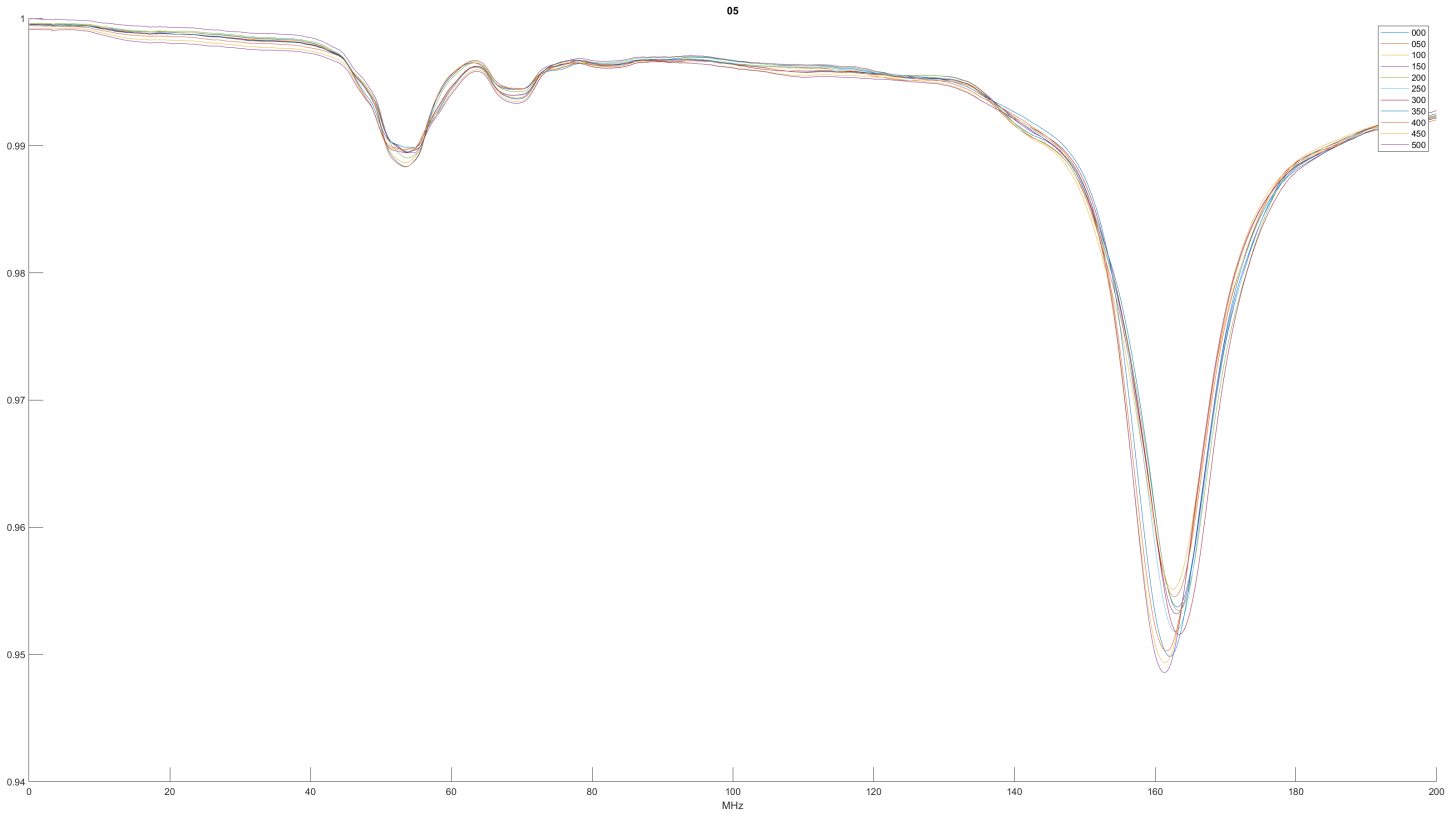

Figure 4.8: Sample response at different frequencies and concentrations - Large sensing element at 05 cm.

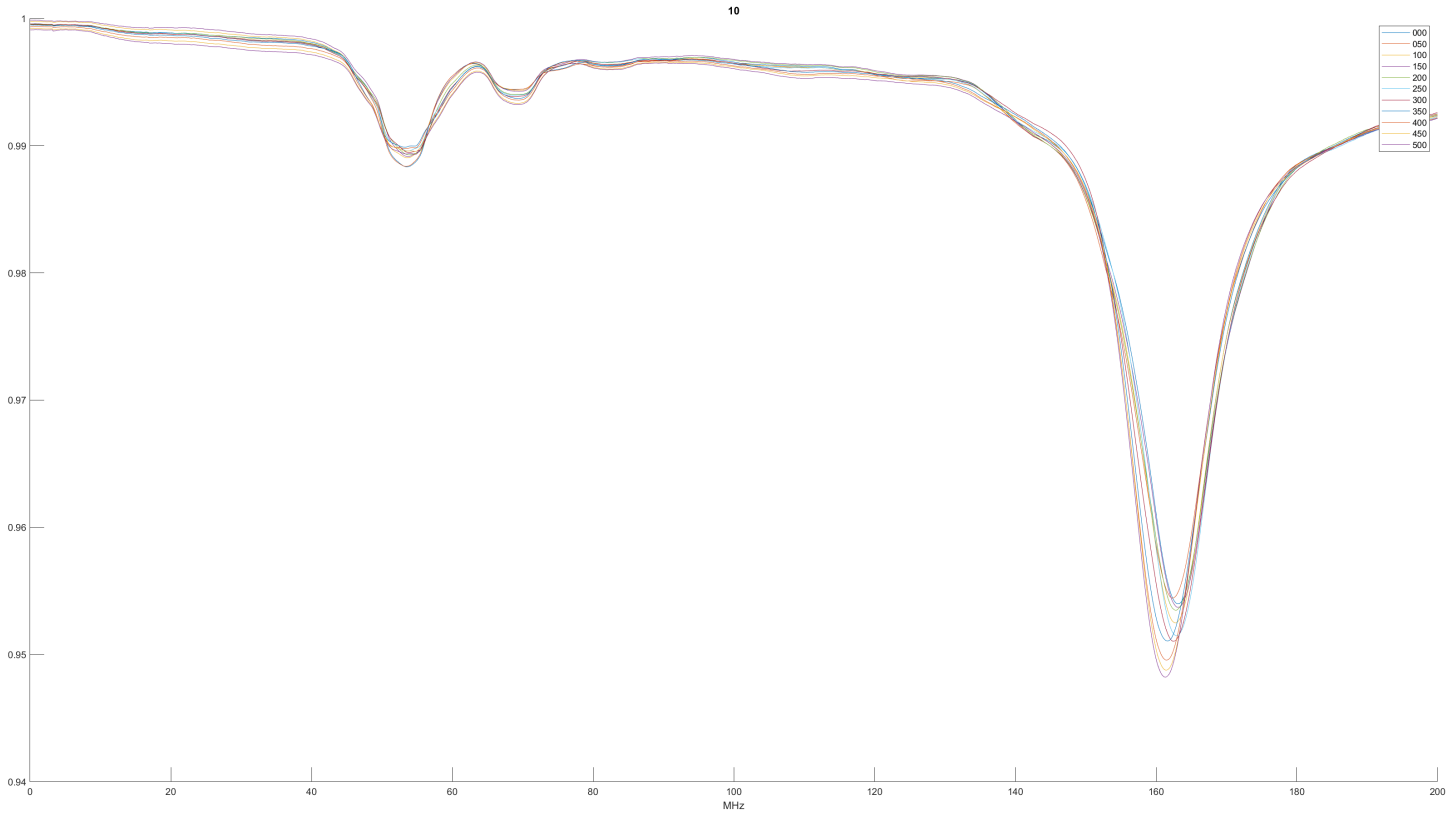

Figure 4.9: Sample response at different frequencies and concentrations - Large sensing element at 10 cm.

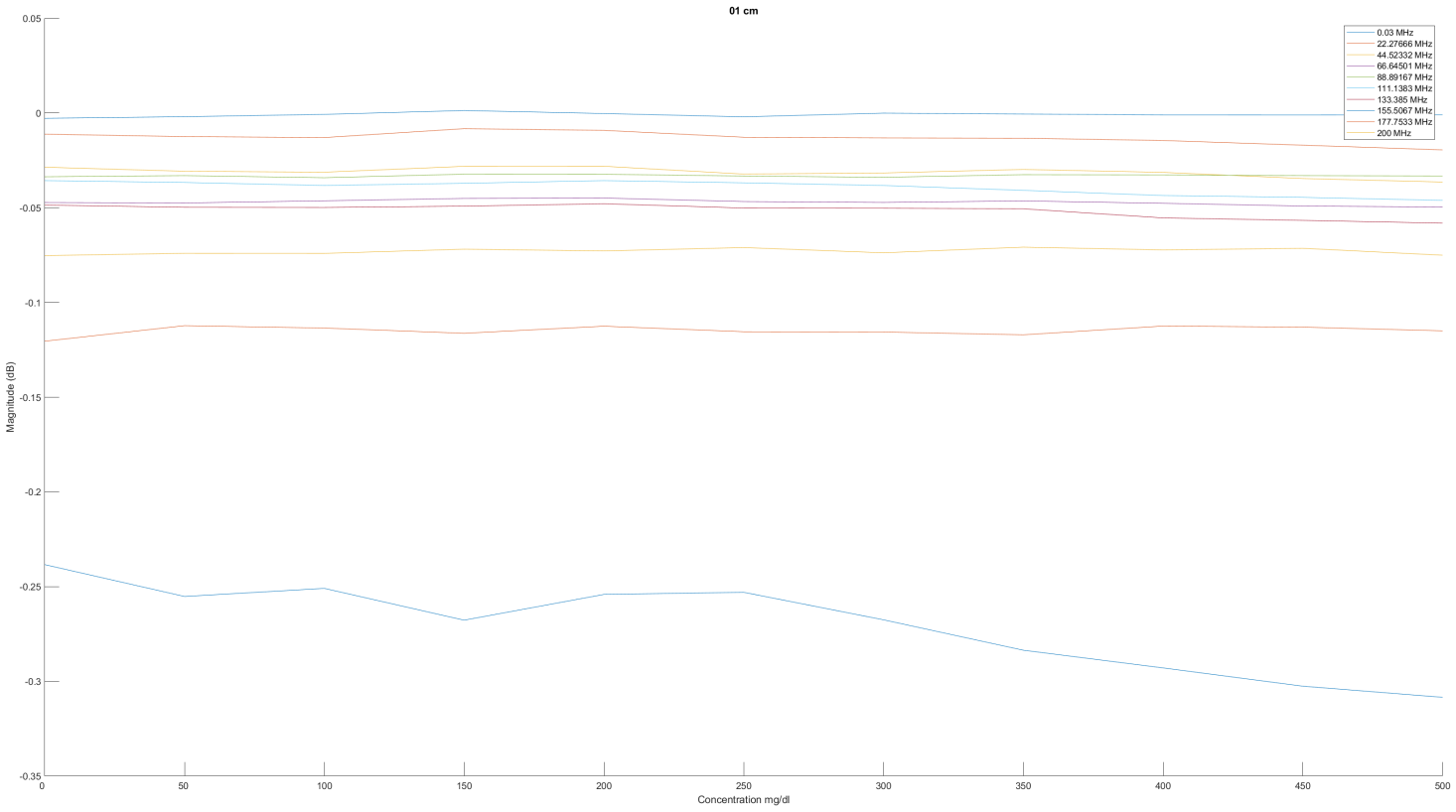

Figure 4.10: Sample response versus concentration at different frequencies - Large sensing element at 01 cm.

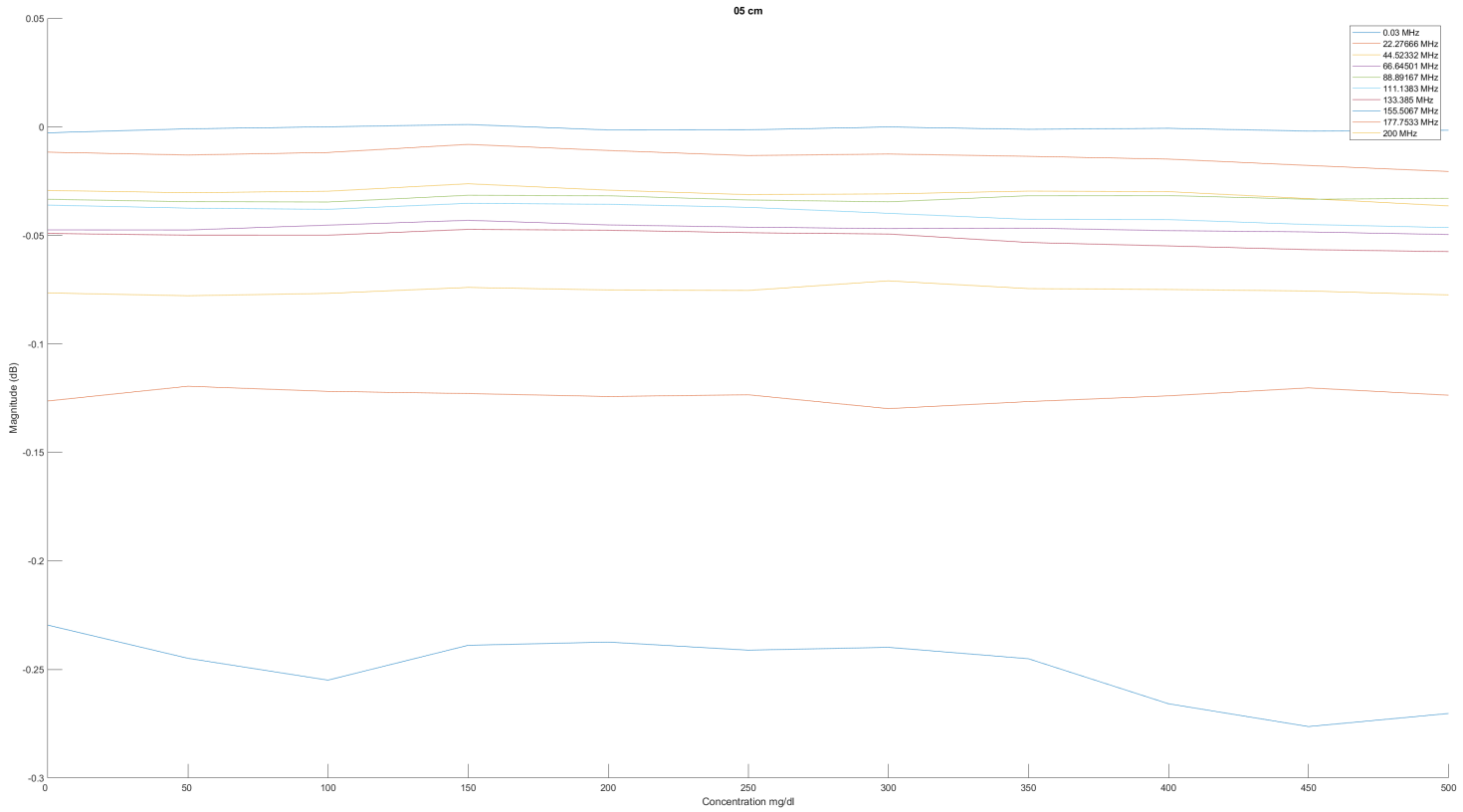

Figure 4.11: Sample response versus concentration at different frequencies - Large sensing element at 05 cm.

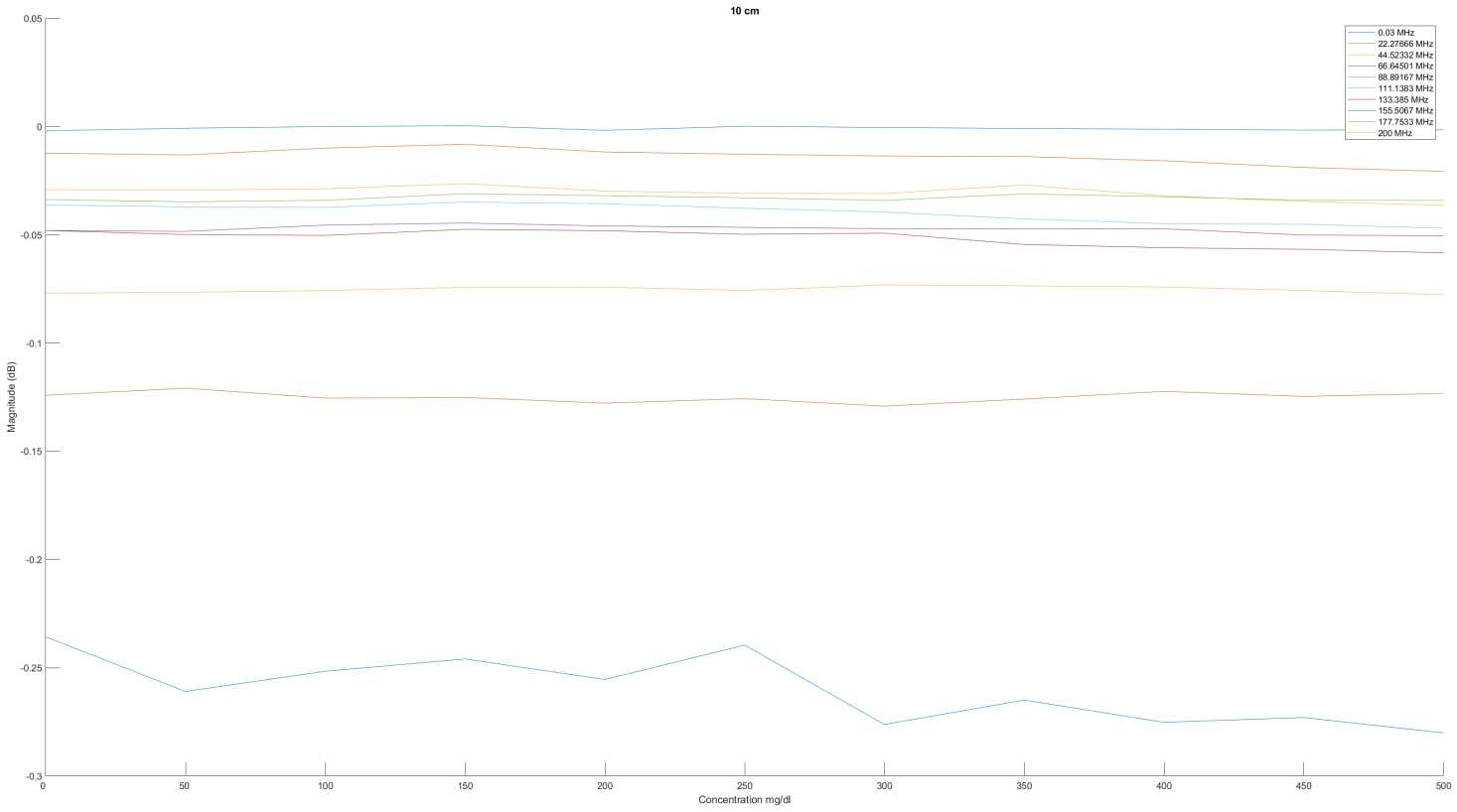

Figure 4.12: Sample response versus concentration at different frequencies - Large sensing element at 10 cm.

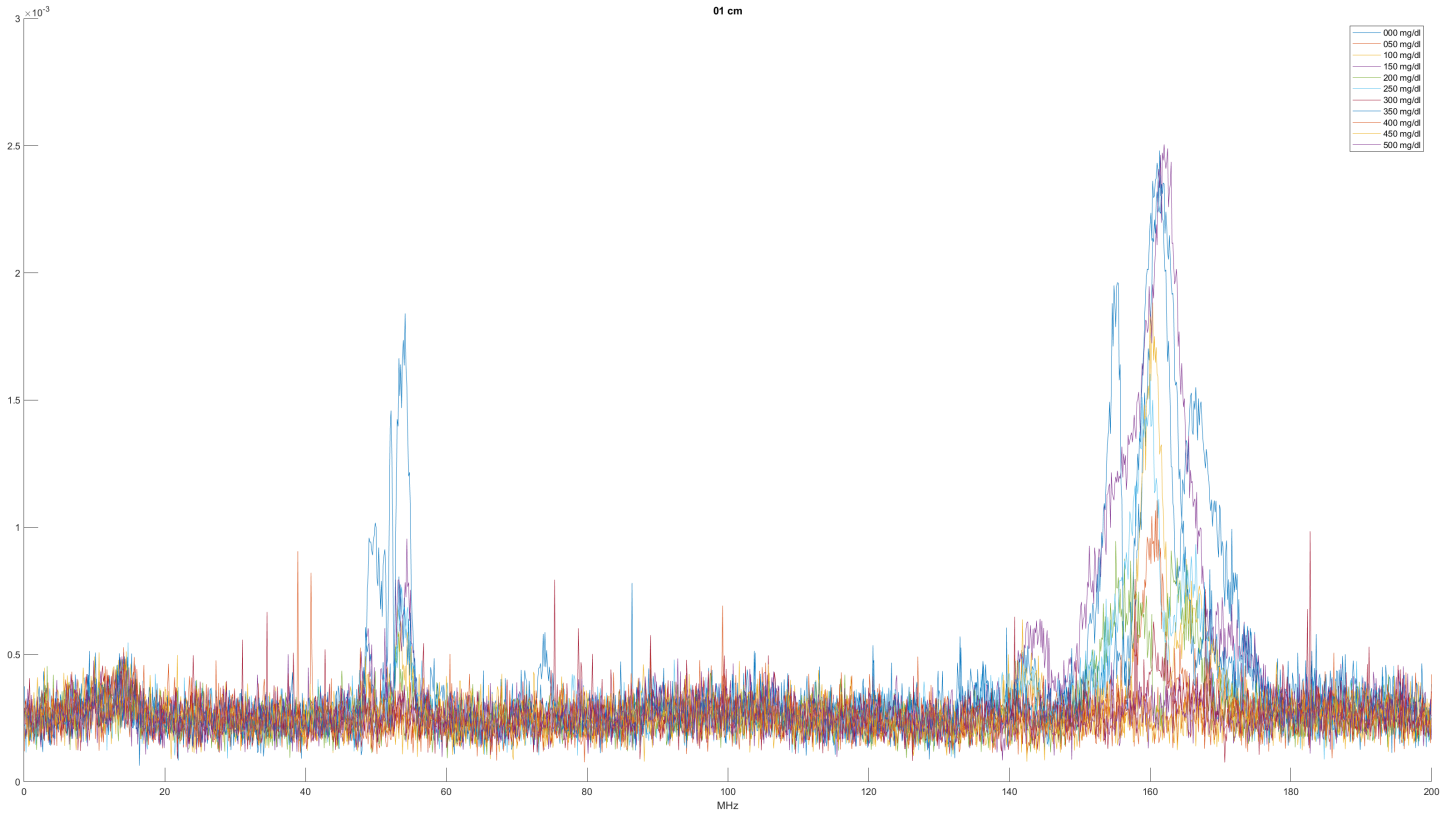

Figure 4.13: Standard deviation of all measurements for each concentration versus frequency - Large sensing element at 01 cm.

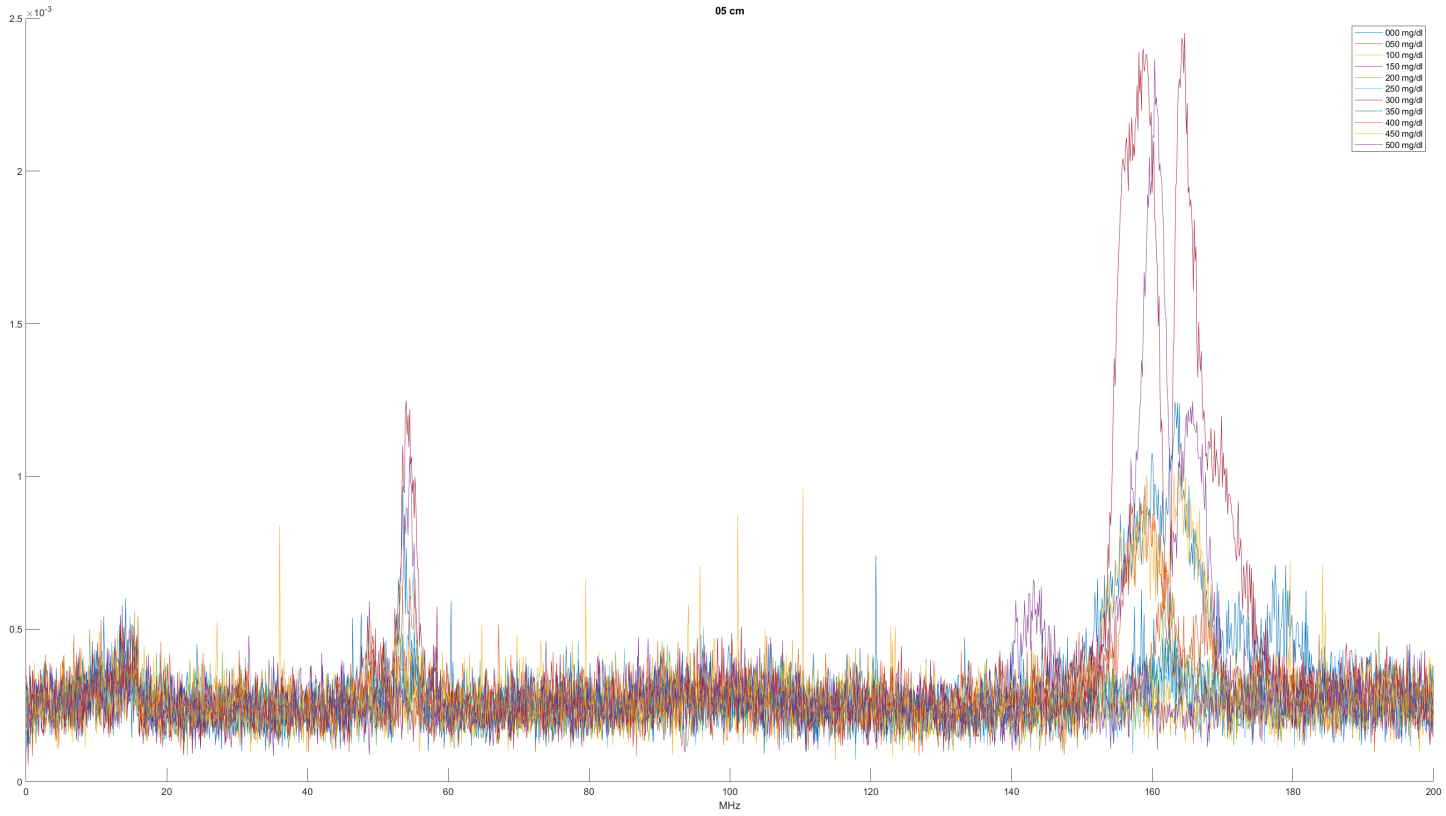

Figure 4.14: Standard deviation of all measurements for each concentration versus frequency - Large sensing element at 05 cm.

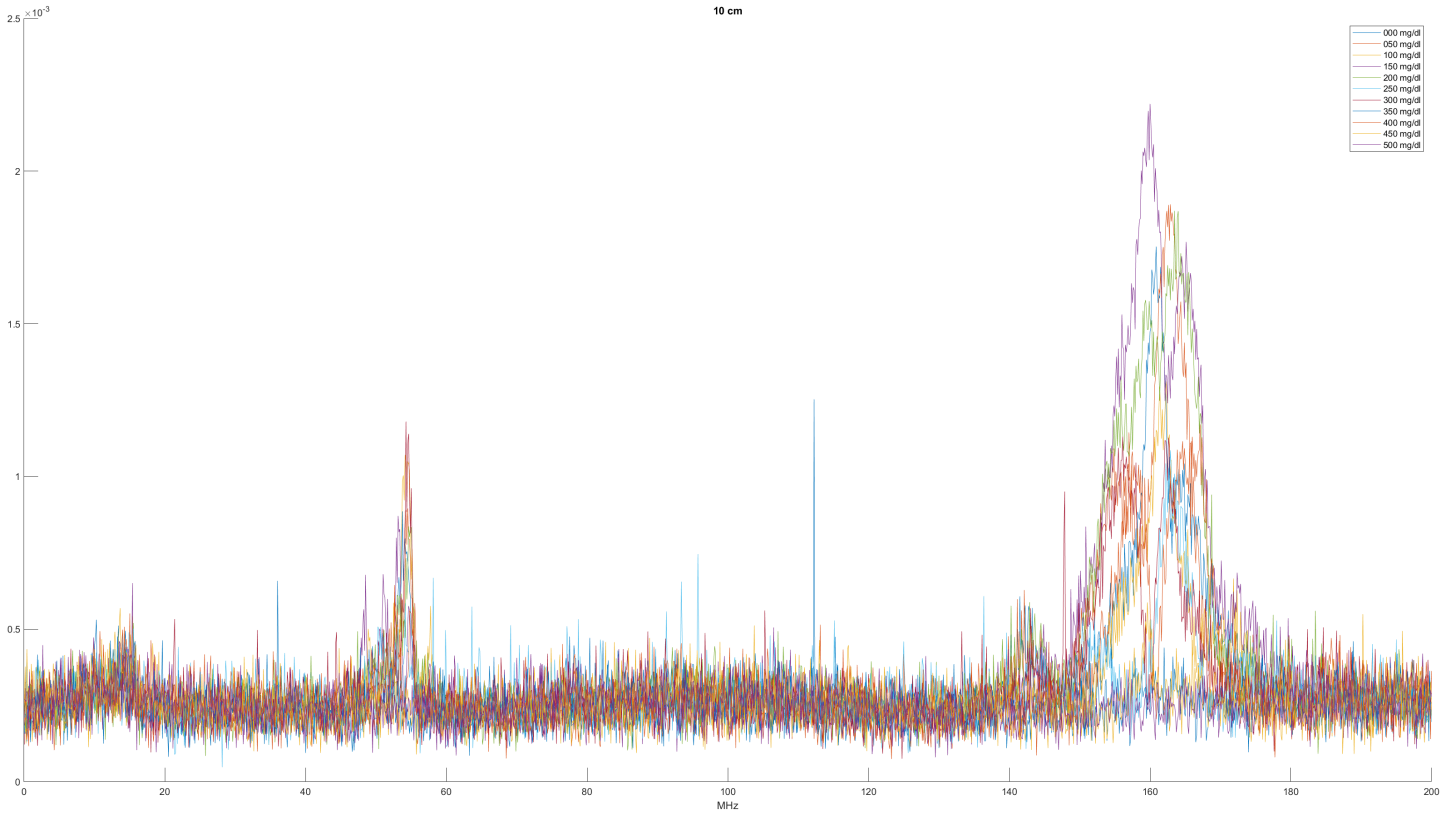

Figure 4.15: Standard deviation of all measurements for each concentration versus frequency - Large sensing element at 10 cm.

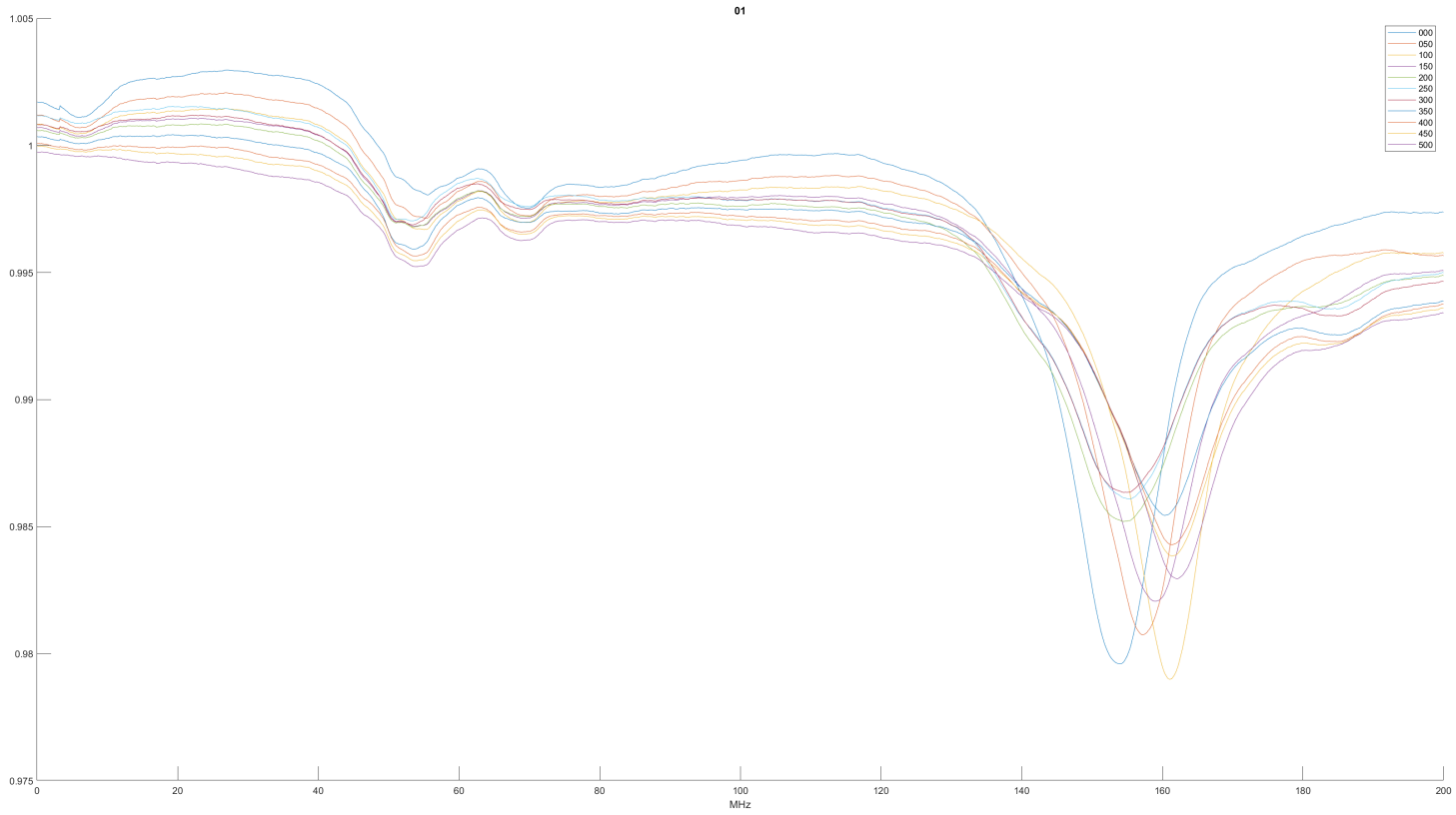

Figure 4.16: Sample response at different frequencies and concentrations - Medium sensing element at 01 cm.

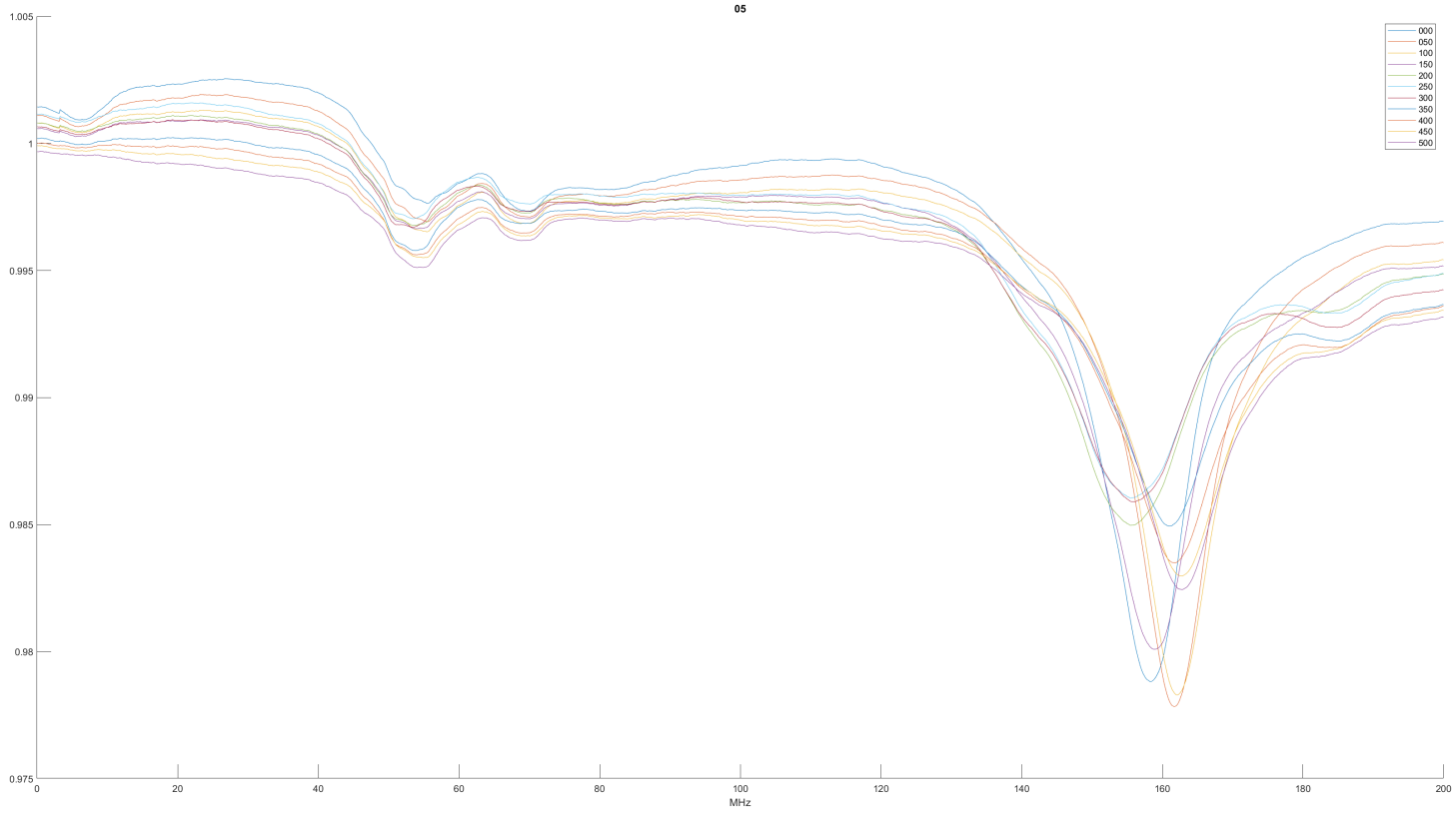

Figure 4.17: Sample response at different frequencies and concentrations - Medium sensing element at 05 cm.

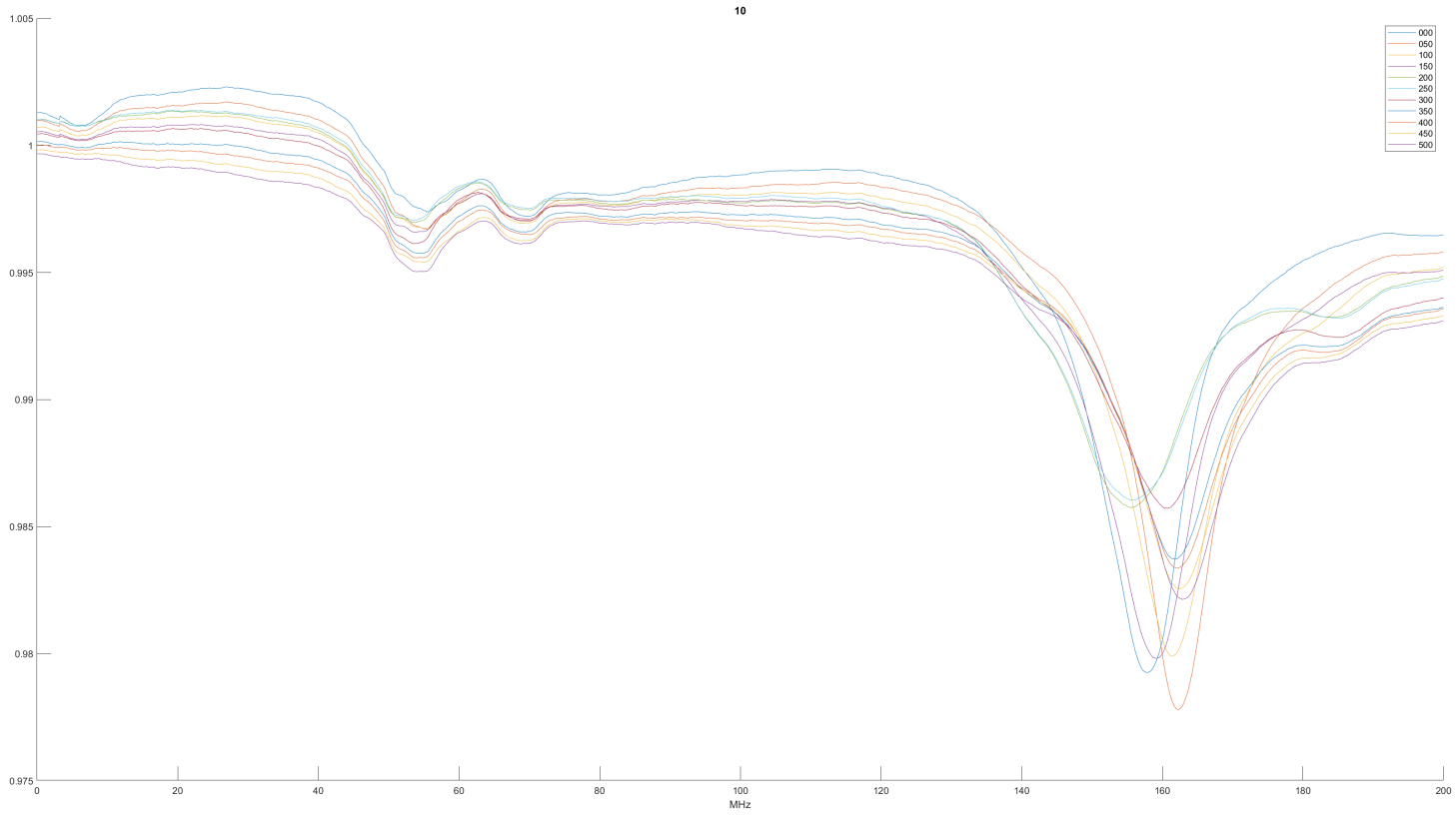

Figure 4.18: Sample response at different frequencies and concentrations - Medium sensing element at 10cm.

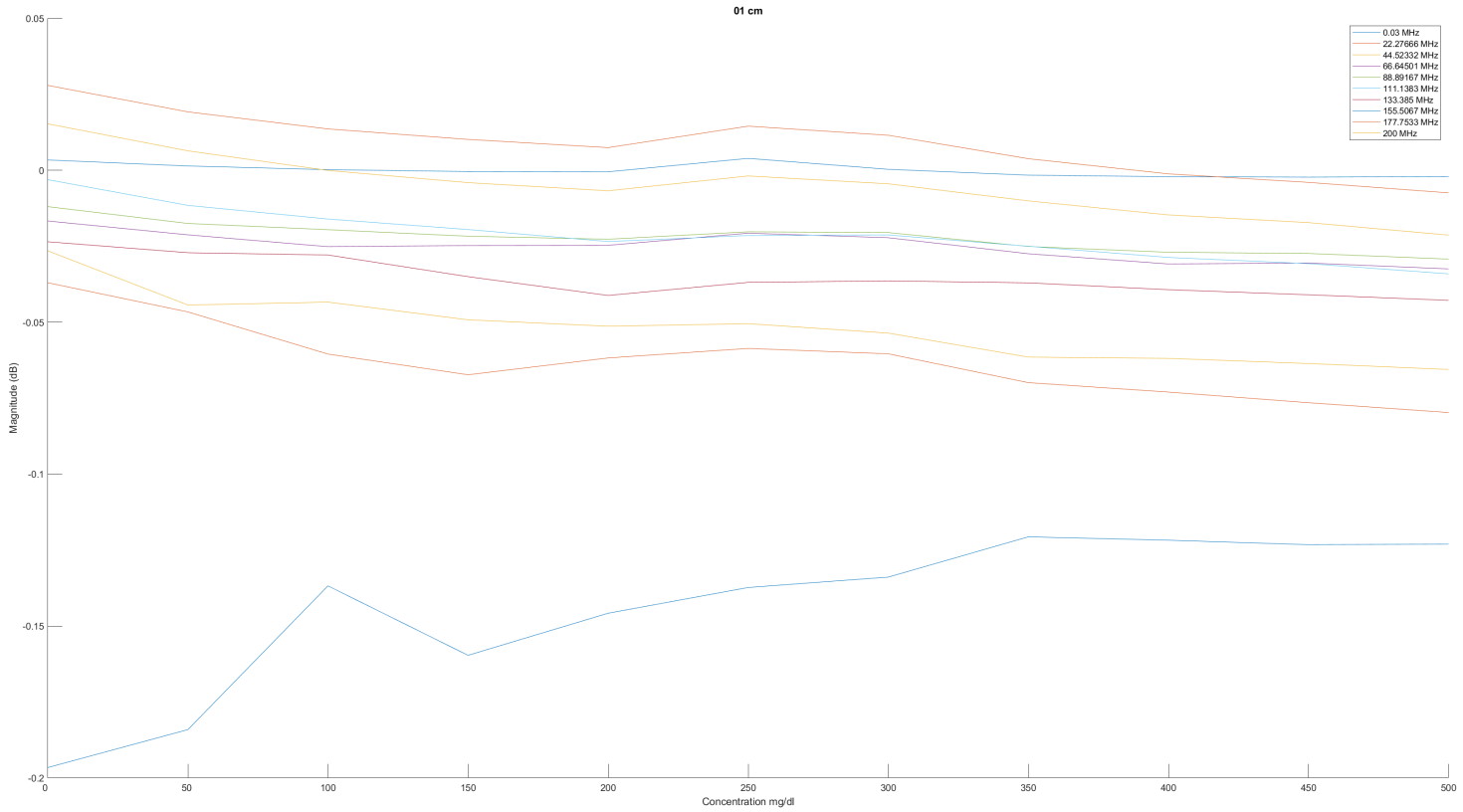

Figure 4.19: Sample response versus concentration at different frequencies - Medium sensing element at 01 cm.

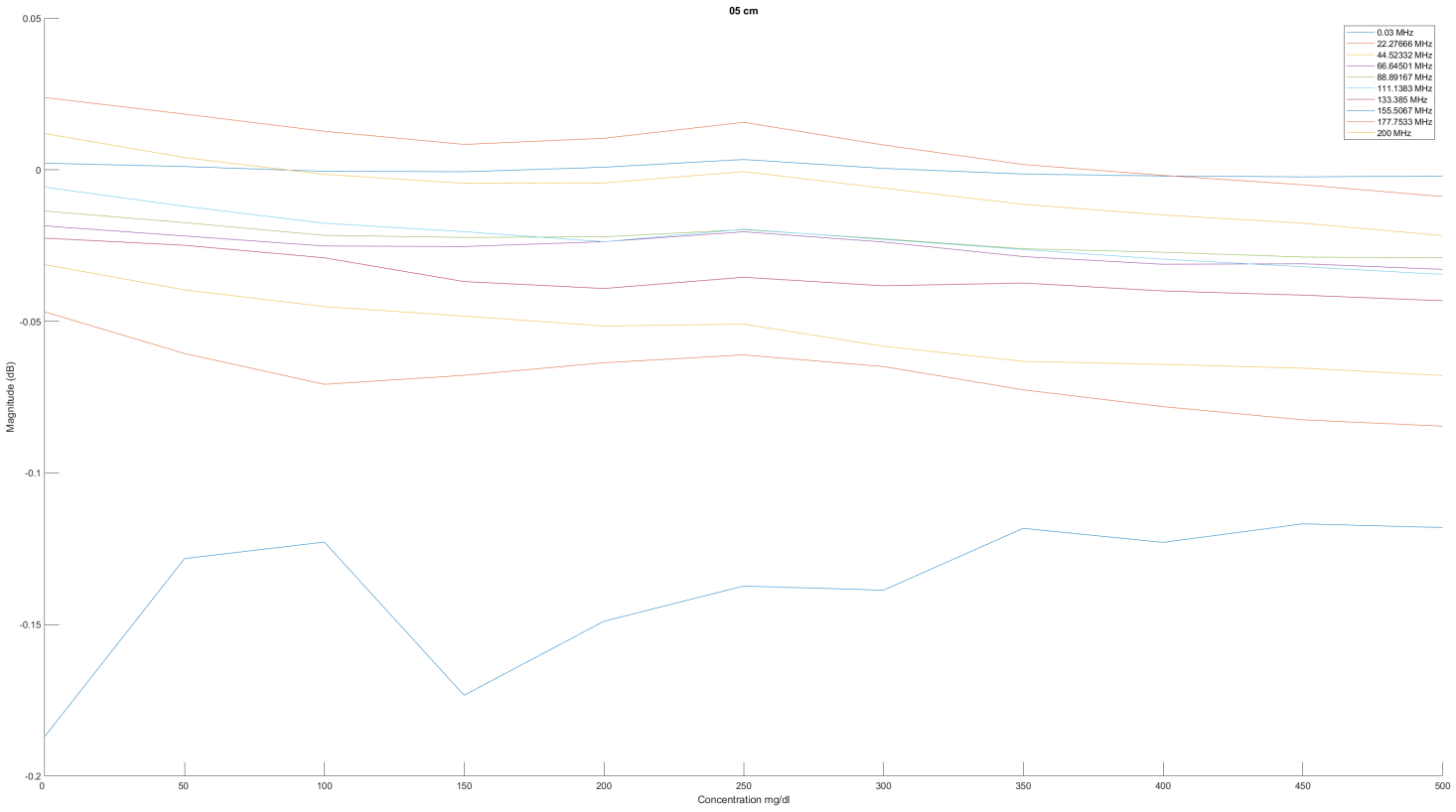

Figure 4.20: Sample response versus concentration at different frequencies - Medium sensing element at 05 cm.

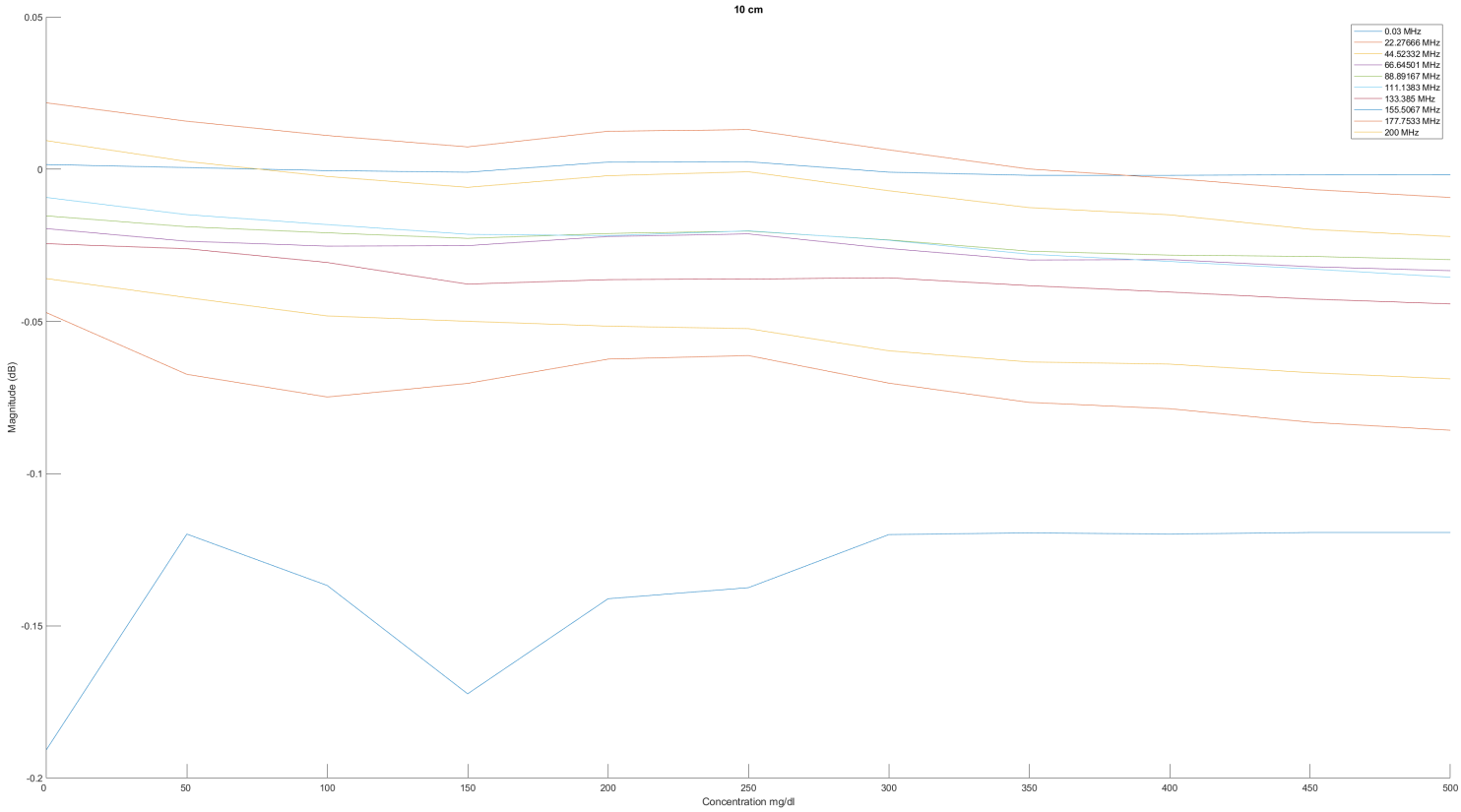

Figure 4.21: Sample response versus concentration at different frequencies - Medium sensing element at 10 cm.

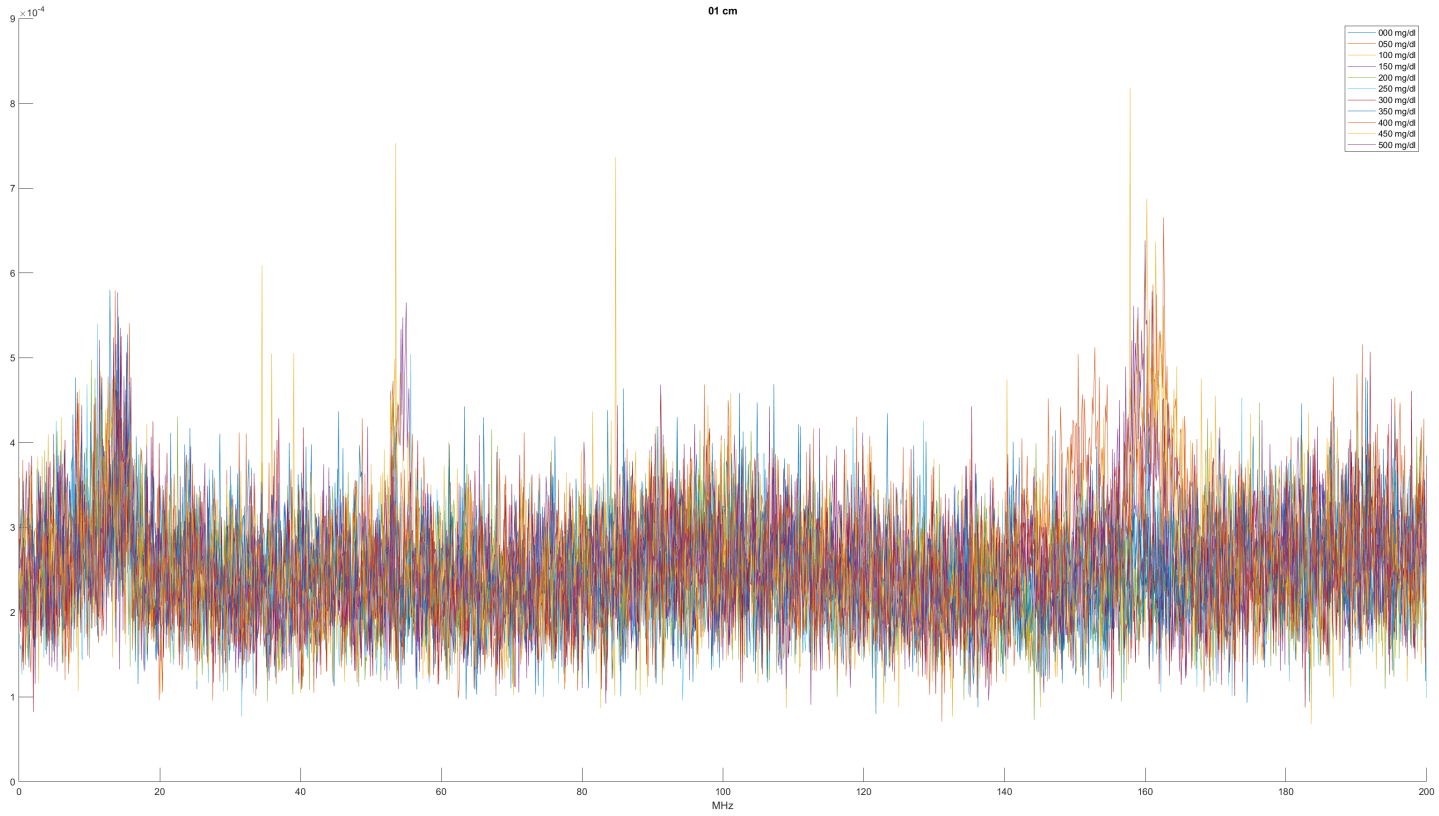

Figure 4.22: Standard deviation of all measurements for each concentration versus frequency - Medium sensing element at 01 cm.

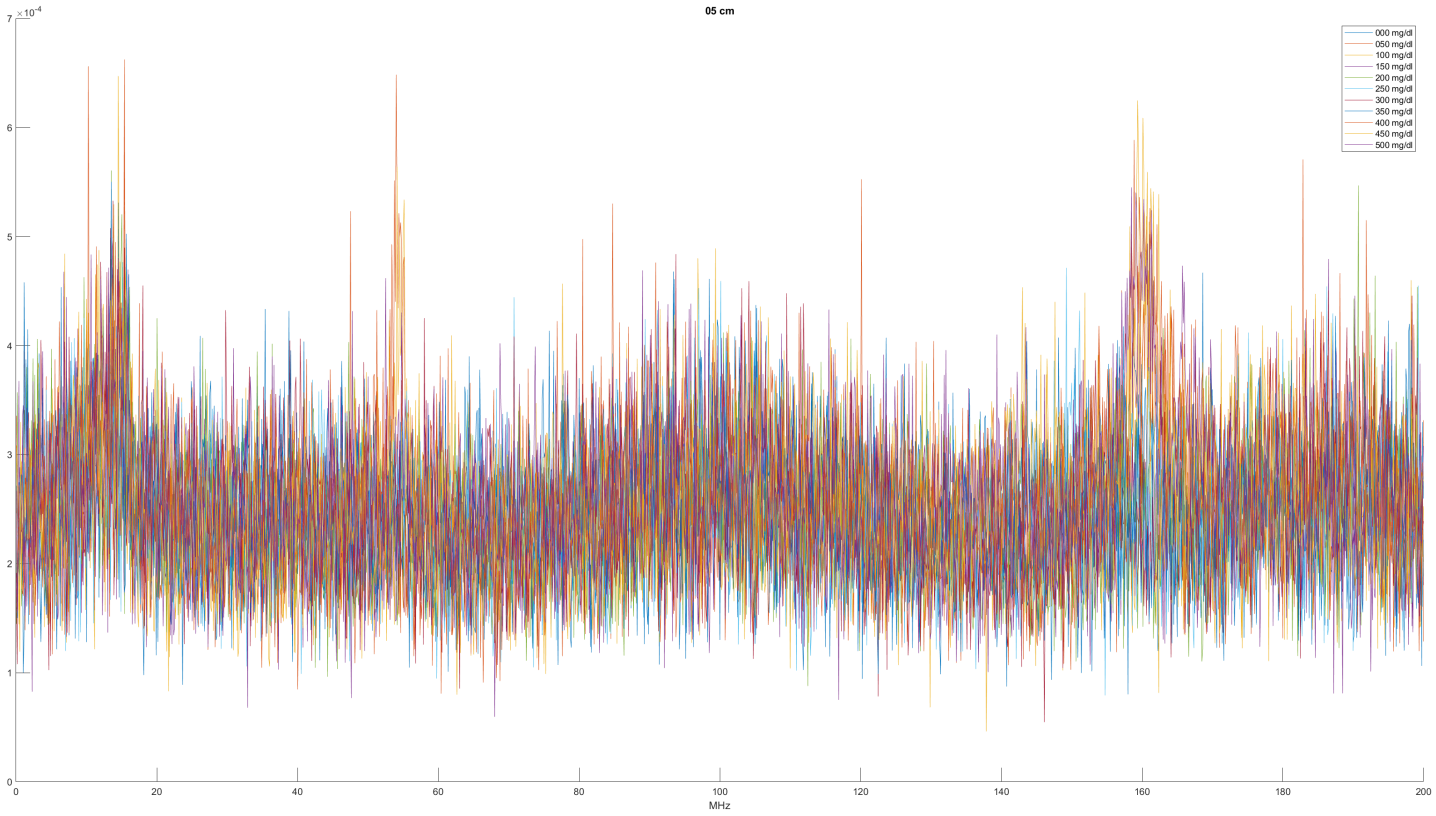

Figure 4.23: Standard deviation of all measurements for each concentration versus frequency - Medium sensing element at 05 cm.

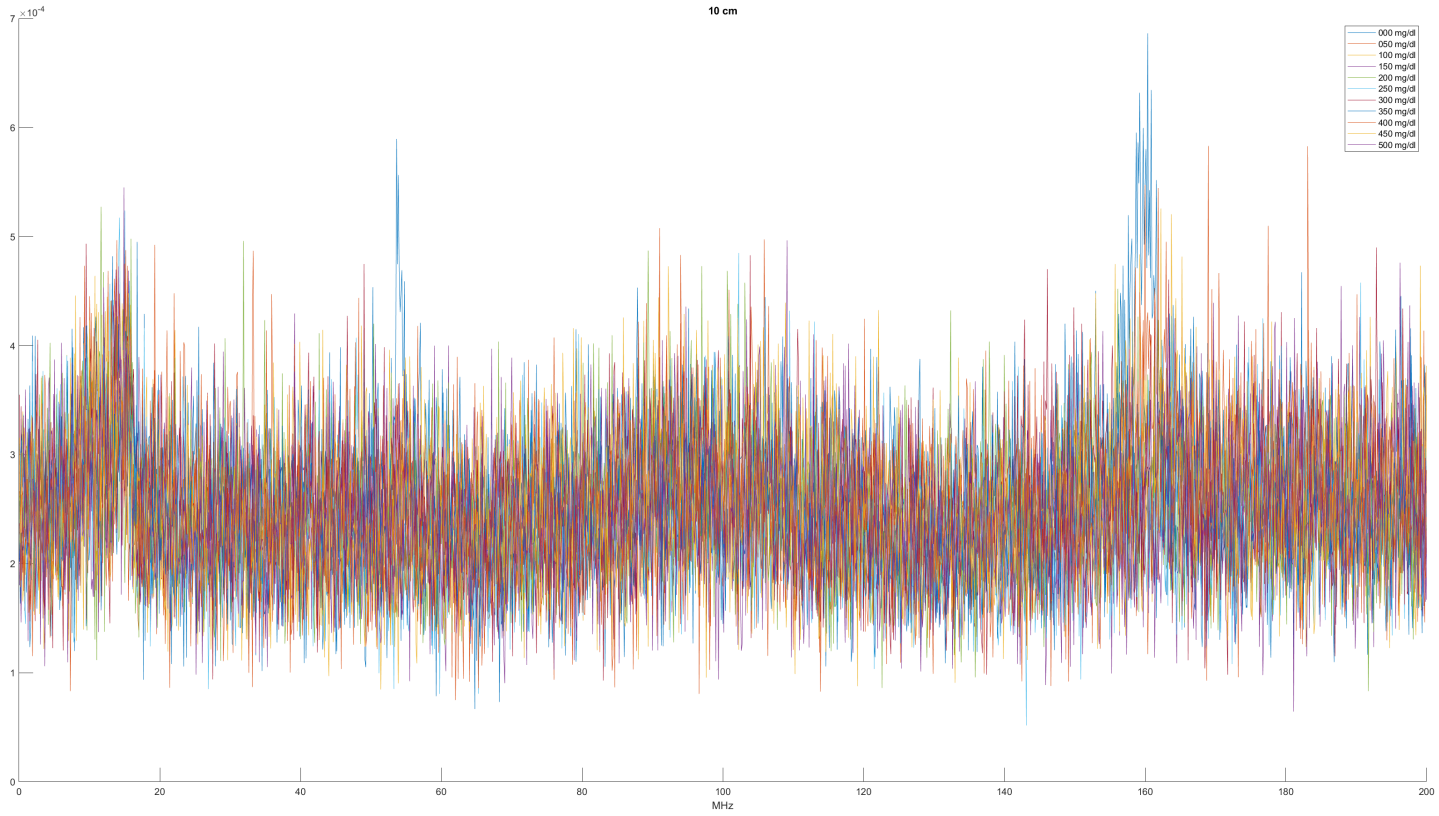

Figure 4.24: Standard deviation of all measurements for each concentration versus frequency - Medium sensing element at 10 cm.

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5 Conclusions for the antenna based measurement method

Conclusion

The experimental methodology focused on studying the S_{11} response across varying glucose concentrations and measurement distances. Despite consistent experimental execution and repeatable results, a definitive, linear dependence of sensor response on glucose concentration could not be established. The observed non-linearity suggests complexities in the interaction between the sensing elements and the medium, possibly influenced by environmental factors or sensor design limitations. Additionally, initial explorations into the S_{21} parameter and the integration of multiple sensing elements did not yield promising results, leading to the abandonment of this method in the current context. However, these findings underscore the need for further investigation to elucidate the nuanced behavior of the system.

Future Work

To address the limitations observed in this study and explore potential enhancements, the following avenues are proposed:

1. **Advanced Computational Modeling**: Utilizing a highly tunable dynamic model for impedance-based sensing, similar to the model described in Dimas et al [1] for Electrical Impedance Tomography (EIT), may provide deeper insights into the behavior of sensing elements in varying glucose concentrations. Such models can simulate environmental and structural variables, offering a platform for pre-experimental testing and calibration.

2. **Parameter Optimization**: Incorporating advanced machine learning techniques for optimizing sensor design parameters (e.g., geometry, material properties, and measurement protocols) can improve response sensitivity and reduce noise.

3. **Exploration of Non-Linearity**: Investigate the physical and chemical interactions causing non-linear behavior in the S_{11} response. Techniques such as

spectroscopic analysis or molecular simulations may identify underlying phenomena.

4. **Development of Multi-Element Systems**: Revisiting multi-sensor designs with improved data fusion algorithms could enable robust measurements. Emphasis should be on overcoming signal interference and enhancing the interpretability of combined S_{11} and S_{21} parameters.

5. **Integration with Dynamic Models**: Drawing inspiration from the referenced thoracic model, a parameterized framework tailored to glucose sensing could simulate varying concentration gradients and test response consistency across simulated and experimental datasets.

6. **Hardware Enhancements**: Addressing limitations in current measurement hardware, such as electrode design and signal processing circuits, to ensure higher fidelity and stability under varying measurement conditions.

7. **Data-Driven Insights**: Leveraging advanced data analytics and AI-driven approaches to interpret the experimental results, identify patterns in non-linear responses, and propose targeted improvements in sensor design.

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Part II

Non-Invasive Glucose Sensing using optical properties

6 Simulation of the Human Skin

6.1 Introduction

Modeling light propagation in human skin is critical for applications such as optical diagnostics, phototherapy, and glucose monitoring and specifically the development of a light-based sensor (as will be seen in the following chapters). Human skin's multilayered structure, comprising the epidermis, dermis, and subcutaneous tissue, presents challenges due to its heterogeneity and the complex interplay of scattering and absorption phenomena. This section presents the results of an exploration into several computational approaches, including the Finite Element Method (FEM), Monte Carlo methods using the Monte Carlo Simulation of Multi-layered Turbid Media (MCML), and the Discrete Ordinate Radiative Transfer (DISORT) method. Although all three methods were investigated, FEM was ultimately chosen for its ease of use and the quality of results.

6.2 Simulation Methods

6.2.1 Helmholtz Equation for Light Propagation

The Helmholtz equation, derived from Maxwell's equations, describes the behavior of electromagnetic waves in a medium:

$$\nabla^2 E + k^2 n^2 E = 0,$$

where E is the electric field amplitude, $k = 2\pi/\lambda$ is the wavenumber, λ is the wavelength of light, and n is the refractive index. This equation is particularly suitable for modeling biological tissues due to its ability to account for wave-like behavior, scattering, and absorption.

The equation was solved using FEM, which discretizes the computational domain

into smaller elements, allowing accurate simulation of complex geometries. The weak form of the Helmholtz equation used in FEM is:

$$\int_{\Omega} (\nabla\phi \cdot \nabla E - k^2 n^2 \phi E)\, d\Omega = 0,$$

where ϕ represents test functions, and Ω is the domain.

6.2.2 Monte Carlo Simulations Using MCML

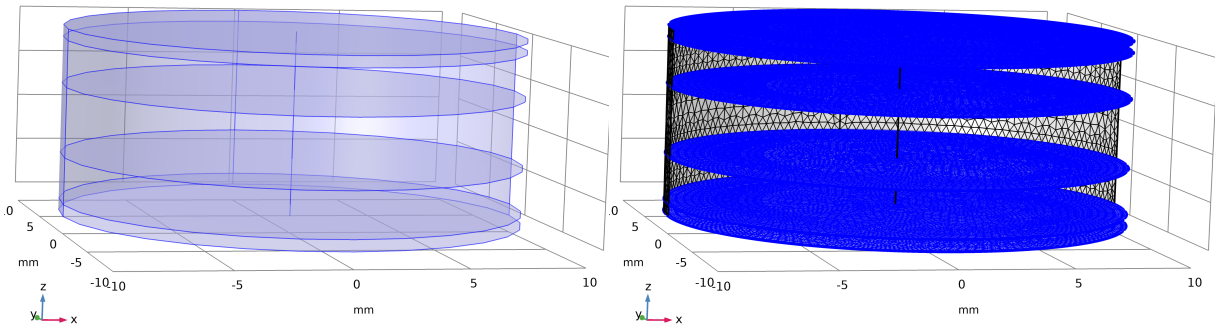
The Monte Carlo method, implemented via the Monte Carlo Simulation of Multilayered Turbid Media (MCML) algorithm, was initially explored to model light scattering and absorption. MCML is well-suited for simulating photon transport in multilayered tissues, incorporating Mie and Rayleigh scattering effects [1]. While Monte Carlo methods are widely considered the gold standard for accuracy, their computational expense proved a significant limitation. Additionally, the stochastic nature of the simulations required extensive averaging to reduce noise, further increasing computational time. These challenges made MCML less practical for iterative simulations.

6.2.3 DISORT for Radiative Transfer Simulations

The Discrete Ordinate Radiative Transfer (DISORT) method was also evaluated for its potential to model light-tissue interactions. DISORT solves the radiative transfer equation (RTE) for vertically inhomogeneous media using Legendre polynomial expansions for scattering phase functions [2]. It excels in handling layered structures and anisotropic scattering. However, setting up DISORT for realistic biological systems proved complex, particularly for incorporating the inhomogeneous and highly scattering nature of human skin. The computational setup and sensitivity to parameter tuning limited its usability for this application. A final barrier to adoption was the increased challenge of implementing the algorithms.

6.3 Finite Element Method for Modeling Light Propagation

Given the challenges with MCML and DISORT, FEM emerged as the most practical and effective method for modeling light propagation in human skin. FEM was used to solve the Helmholtz equation for a three-layered skin model, representing the epidermis, dermis, and subcutaneous tissue. The method provided flexibility in handling complex geometries and heterogeneous properties while maintaining computational efficiency.



(a) Model of the human earlobe developed in COMSOL.

(b) Mesh to be used for analysis on the previous model.

Figure 6.1: COMSOL model and the meshed output.

The earlobe was chosen as the simulation site due to its thin structure and relatively homogeneous layers. Boundary conditions were applied to simulate incident light and handle reflections at tissue interfaces. FEM simulations yielded high-quality results, including intensity distributions and absorption profiles, which aligned well with prior studies on light-tissue interaction [3].

Advantages of FEM:

- **Ease of Use**: Simplified setup compared to DISORT and MCML.
- **Result Quality**: Accurate representation of light propagation with minimal computational overhead.
- **Flexibility**: Effective handling of heterogeneous and layered structures.

Challenges and Limitations Despite its advantages, FEM faced challenges related to:

- **Complex Geometries**: High-resolution meshes are required to capture intricate structures like capillaries. As this work did not require such extreme accuracy and instead relied more on the average values of the tissues, this did not affect the results.
- **Boundary Conditions**: Accurate representation of light-tissue interfaces is critical for reliable results.

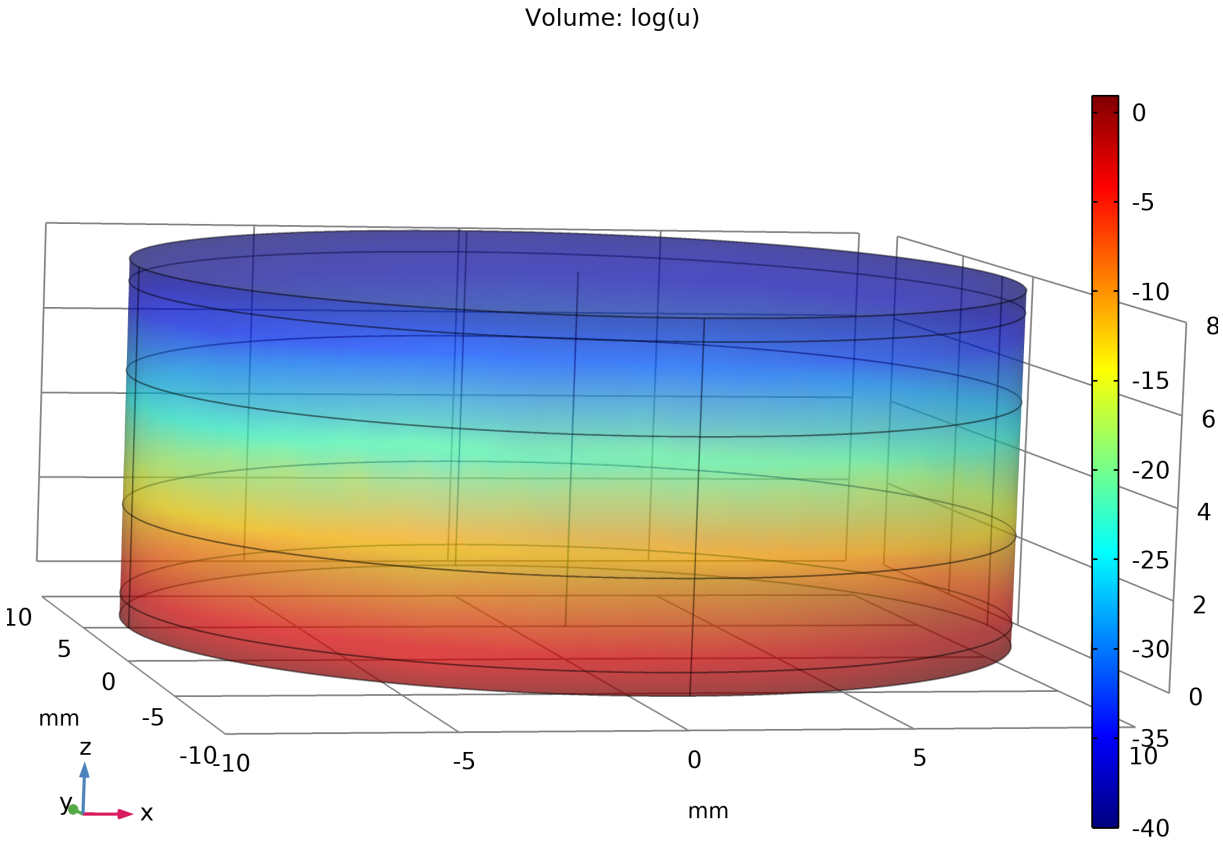


Figure 6.2: Simulated light absorption and propagation on human earlobe.

6.4 Methods for Extracting Parameters of Human Skin

The accurate simulation of light propagation through human skin in finite element modeling (FEM) necessitates precise characterization of its optical and physical parameters. This section discusses methods for extracting key parameters, such as scattering coefficients, absorption coefficients, refractive indices, and anisotropy factors, based on contemporary research and techniques.

6.4.1 Light Scattering and Absorption Analysis

Light scattering and absorption are fundamental interactions governing light transport in skin. The Rayleigh and Mie scattering theories provide mathematical frameworks for describing scattering phenomena. Rayleigh scattering applies to small dielectric particles where the particle size is much smaller than the wavelength of light, while Mie scattering addresses larger particles with size parameters comparable to the wavelength. These models facilitate the estimation of scattering coefficients and anisotropy factors in multilayered skin structures [4].

Absorption properties are influenced by chromophores like melanin and hemoglobin. These are quantified by the absorption coefficient, derived experimentally using techniques such as diffuse reflectance spectroscopy [5].

6.4.2 Mueller Matrix Polarimetry

The Mueller matrix method, coupled with Stokes polarimetry, is an advanced technique for extracting parameters like birefringence, dichroism, and depolarization from turbid media such as human skin. By decomposing the Mueller matrix, effective parameters including linear birefringence, circular dichroism, and depolarization indices can be determined. These parameters are critical for simulating light behavior in complex tissue geometries [6].

6.4.3 Near-Infrared Spectroscopy

Near-infrared (NIR) spectroscopy provides non-invasive measurement capabilities for biological tissues. This technique captures glucose concentration, refractive index variations, and scattering properties by analyzing light interaction across the NIR spectrum (900–2500 nm). For instance, the interaction of polarized light with glucose solutions under varying conditions offers insights into the refractive index mismatch and aggregation properties of skin tissues [7, 8].

6.4.4 Multiscale Modeling

Multiscale modeling addresses the heterogeneous nature of skin by incorporating micro- and macroscopic interactions. It enables the integration of parameter variations, such as vascular structures and chromophore distributions, into FEM simulations. This approach highlights the limitations of classical homogenization techniques when applied to highly heterogeneous tissues [5].

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7 Sensor design

In this section, a novel sensor for the measurement of glucose in aqueous solution is presented. The sensor created uses off-the-shelf parts and achieves detection of changes of glucose concentration, in a physiological saline sample.

The proposed sensor is based on the measurement of the change of ToF when light travels through a sample containing glucose.

ToF sensors are widely utilized in distance measurement due to their precision and versatility. The fundamental principle involves emitting a signal, which travels to a target and reflects back to the sensor. The elapsed time, known as the time of flight, is directly related to the distance. While direct ToF measurement uses the travel time of the signal, phase-based ToF sensors utilize the phase difference between transmitted and received signals to infer distance, offering enhanced accuracy, particularly in short-range and high-precision applications.

In phase-based ToF sensors as the one used here, the transmitted signal is typically a continuous sinusoidal wave:

$$S(t) = A\sin(2\pi ft) \tag{7.1}$$

When this wave reflects off a target and is received back, it exhibits a phase shift:

$$R(t) = A\sin(2\pi ft + \phi) \tag{7.2}$$

The phase shift ϕ is directly proportional to the propagation delay (Δt) of the signal:

$$\Delta t = \frac{\phi}{2\pi f} \tag{7.3}$$

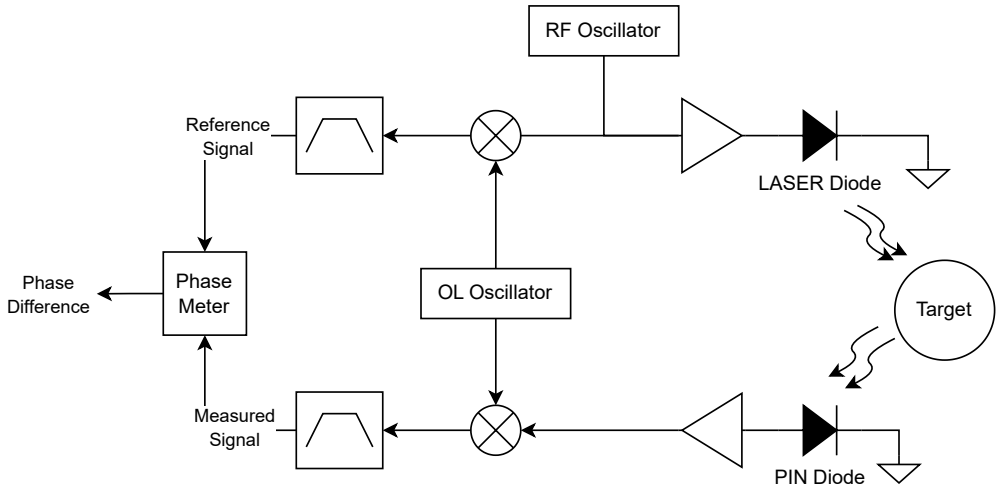


Figure 7.1: Simplified schematic of a heterodyne ToF sensor.

Using this time delay, the distance d can be computed as:

$$d = \frac{c \cdot \Delta t}{2} = \frac{c \cdot \phi}{4\pi f} \tag{7.4}$$

Here, c represents the speed of the wave (e.g., speed of light for optical signals). This method is advantageous for achieving high precision since small changes in phase can be detected with sub-wavelength accuracy.

Phase-based ToF sensors offer high accuracy due to their sensitivity to small phase shifts, making them ideal for applications requiring fine resolution. Additionally, such sensors allow for high sampling rates, as they do not require measurement of a full signal round-trip time, enabling real-time applications. However, phase difference measurement also presents challenges. If the round-trip distance exceeds the signal wavelength, the phase shift may repeat, leading to ambiguity. This issue can be addressed using multiple modulation frequencies to distinguish between different phase cycles. A second challenge is their environmental sensitivity - optical ToF sensors can be affected by the presence of ambient light. This can be countered either with selective filters or with precise setups that decrease ambient light effects. A relatively simple technique for this would be a heterodyne receiver as the one shown in fig. 7.1. (Additional information on ToF can be found in the work of Markus-Christian Amann et al. [1]).

For the sensor presented here, modulated, non polarized light of a narrow wavelength centered at 850nm enters the sample where it is absorbed and scattered by the presence of glucose(fig. 7.2). The optical properties of the tissue, including its scattering and absorption coefficients, are sensitive to changes in glucose concentration, making this a promising approach for non-invasive glucose monitoring. Kohl

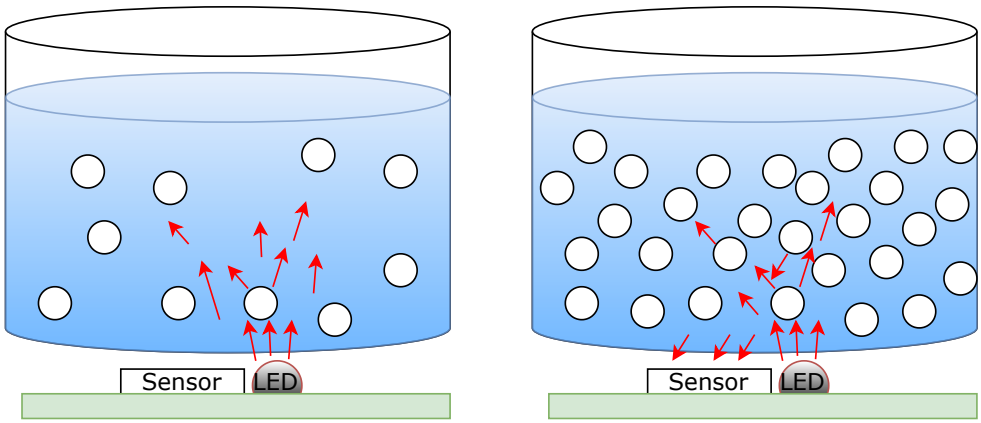


Figure 7.2: Representation of scattering of light from glucose molecules. Changing concentration affects sample scattering.

et al. have demonstrated that glucose concentration significantly affects the velocity of light and the scattering coefficient in tissue-simulating phantoms, providing a critical understanding of how glucose alters light transport properties in biological tissues [2]. This behavior directly impacts the intensity of light reaching the sensor due to the increased frequency of scattering events. Consequently, these scattering events influence the accuracy and sensitivity of the measurements made by the developed sensor. Changes in blood glucose levels also affect the extracellular fluid (ECF), leading to modifications in the optical properties of the tissue. Maier et al. observed that the reduced scattering coefficient can be utilized to detect glucose level changes both in the ECF and the bloodstream, supporting the use of scattering-based optical techniques for glucose monitoring [3]. This insight aligns with findings by Bruulsema et al., who established a correlation between blood glucose concentration and the tissue's reduced scattering coefficient [4]. Furthermore, studies by Larin et al. demonstrated the capability of optical coherence tomography (OCT - a technique dependent on scattering) to assess glucose-induced changes in tissue scattering properties with high specificity, suggesting its utility for glucose sensing applications [5]. These observations are further supported by the work of Amerov et al., who investigated glucose-induced alterations in light transport through blood, illustrating the significance of scattering dynamics in non-invasive glucose sensors [6]. This body of work collectively underscores the critical role of light scattering in non-invasive glucose sensing technologies. However, works available up to now were created using high complexity and cost equipment, usually only available in a laboratory setting. By leveraging these optical phenomena, as well as low cost of the shelf sensing element the presented sensor represents a promising step toward accurate, non-invasive glucose monitoring in clinical and daily use.

7.1 Experimental Setup

The experimental setup comprises a custom-designed sensor, a sample holder, and a 3D-printed adapter. The sensor is built around the Texas Instruments OPT8320 IC, which utilizes a phase-based ToF approach to measure distance. This IC drives an external infrared LED (Wurth Elektronik, Model 15411085A4570) emitting at 850nm. This wavelength was chosen due to the sensor's peak transmissivity at 850nm (see also [7]) and its position within the optical window of tissue, allowing optimal light penetration(see also Fig.1 in [8]). Additionally, glucose concentration significantly affects scattering at this wavelength range[2].

The OPT8320 features an 80x60 pixel sensing array accessible by its sensing engine, enabling individual measurement of each element. By exploiting the sensor's high sensitivity and configurability, it is possible to indirectly measure the degree of light scattering by a sample placed on the sensing element. The experimental setup developed is shown in Fig.7.8b.

Sensor data is output in a custom binary format over a 24MHz parallel bus, matching the IC's clock frequency. To capture this data, an interconnect circuit based on the Cypress FX3 USB 3.0 platform was developed, which supports direct acquisition of up to 32 bits of parallel data at high clock rates and streams it to a host computer via USB 3.0. The FX3 platform also configures the OPT8320 over an I^2C interface. This circuit connects the OPT8320 to the FX3 and supplies all necessary power rails, derived from the USB power supply. Adequate power supply filtering was added to mitigate noise from the USB port, following guidelines from relevant application notes (FTDI and Micrel/Microchip [9],[10]). The required voltages are generated using low-noise linear voltage regulators, and the negative bias voltage for the sensor is produced using a switched-capacitor inverter followed by a low-noise regulator. The OTP8320 schematic can be seen in figure 7.3. The schematic of the various power supplies used have been split in three parts. The first is the PMIC used that generates all the main rails. This can be seen at fig. 7.4. This supplies the OTP8320, the inverter that generates the necessary negative voltages (fig. 7.5) and finally the linear power supplies that step down the voltage with very low noise (fig. 7.6)

Software was developed to allow the FX-USB3 to initialize and control both the OPT8320 sensor. Custom software was also created to facilitate data capture from the FX-USB3 to a file on the PC. An example of the data provided, visualized as a grayscale image, is provided in fig. 7.7. A high level diagram of the circuit created is shown in fig. 7.8a and the PCB manufactured and mounted on the FX-USB3 platform is shown in fig. 7.9.

The sample was contained within a cylindrical cuvette, carefully chosen for its high transparency in the targeted wavelength range (Hellma Analytics $692-091-12$). To

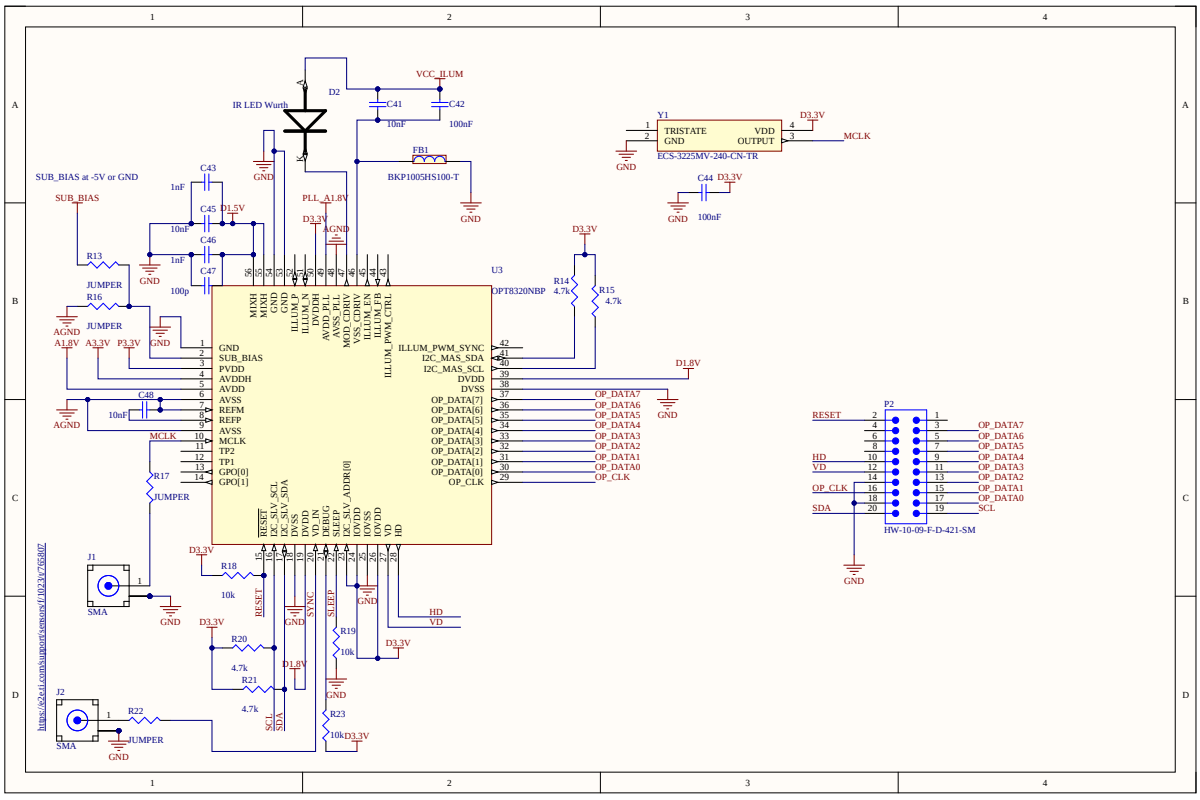


Figure 7.3: OTP8320 schematic.

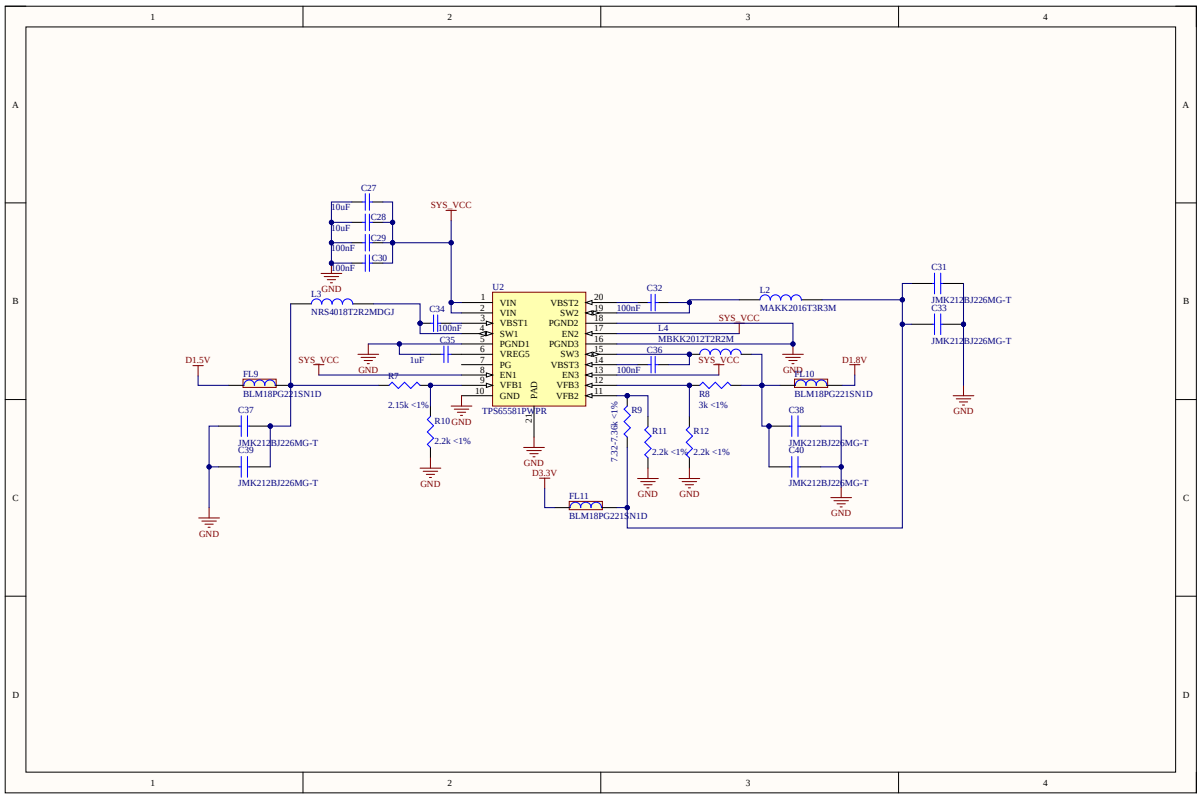


Figure 7.4: PMIC schematic.

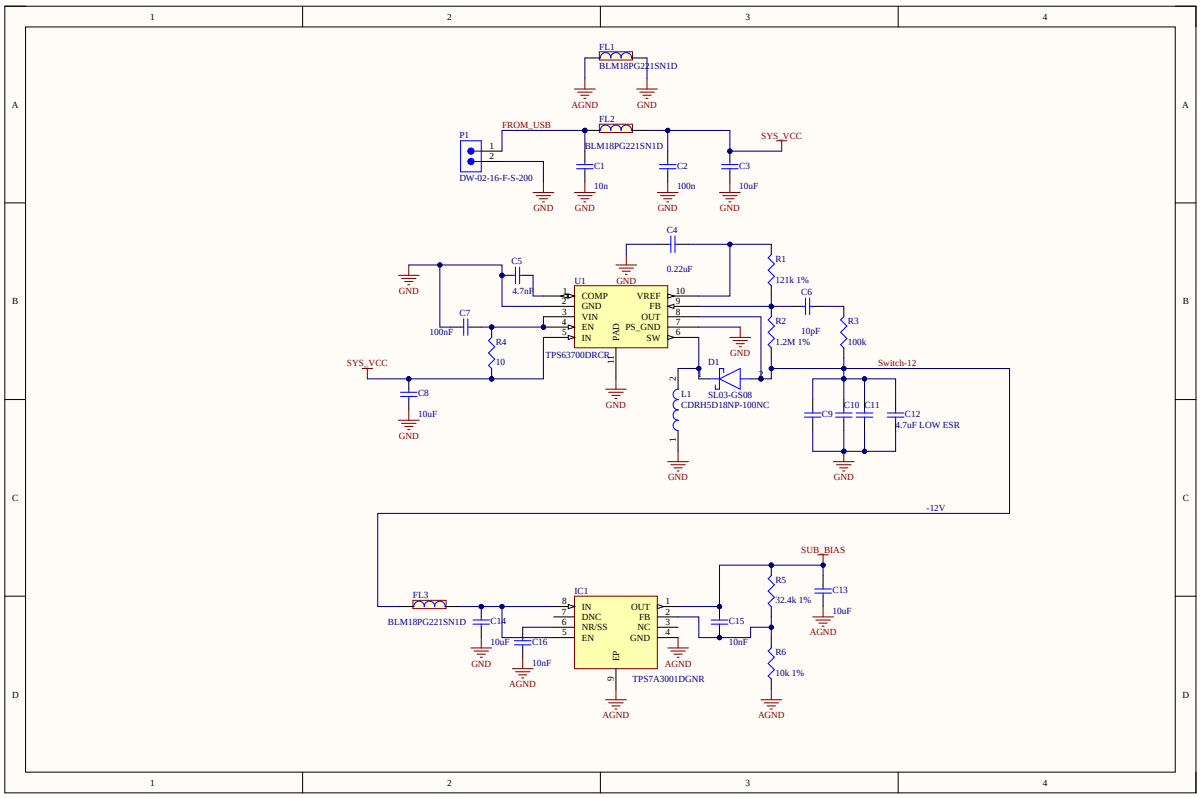


Figure 7.5: Inverter schematic.

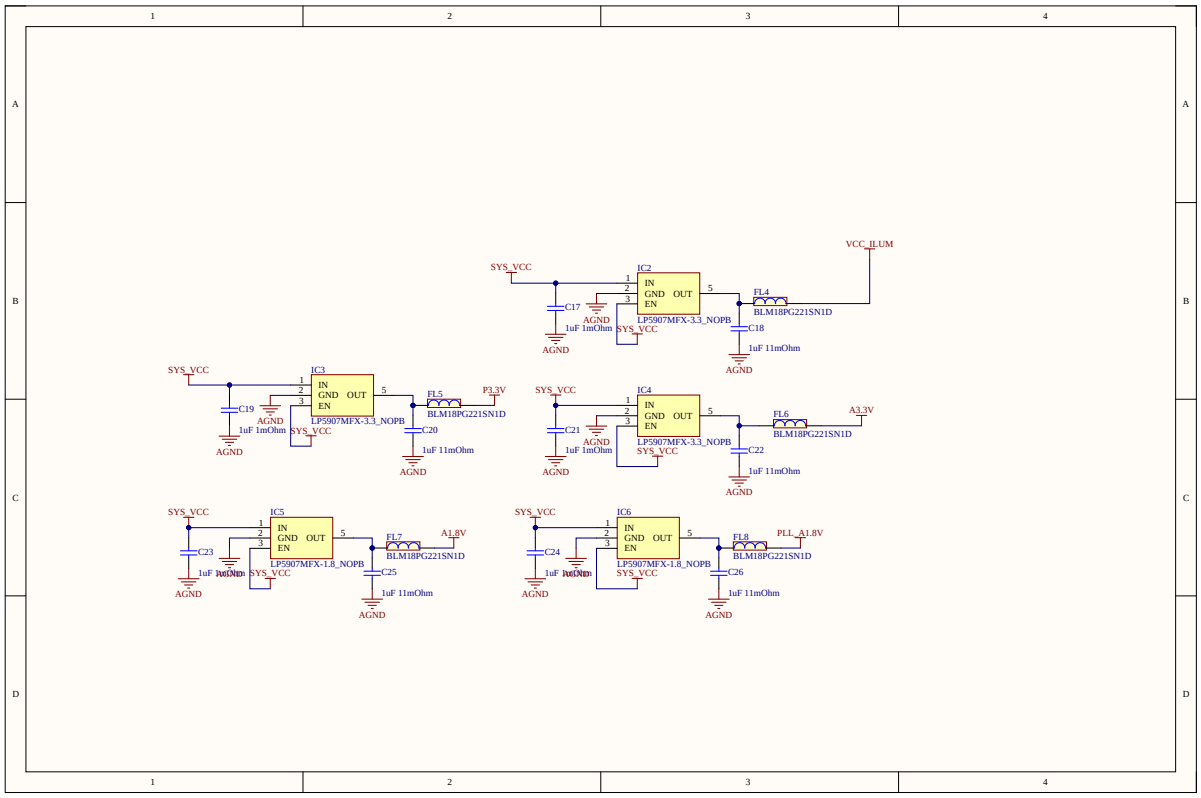


Figure 7.6: Linear Power Supplies schematic.

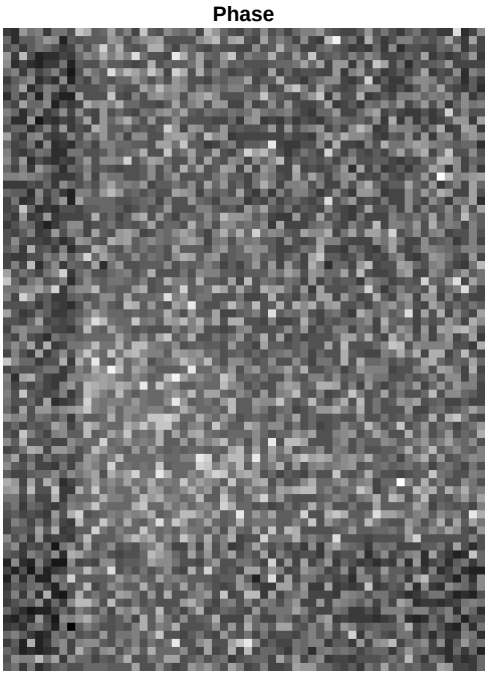
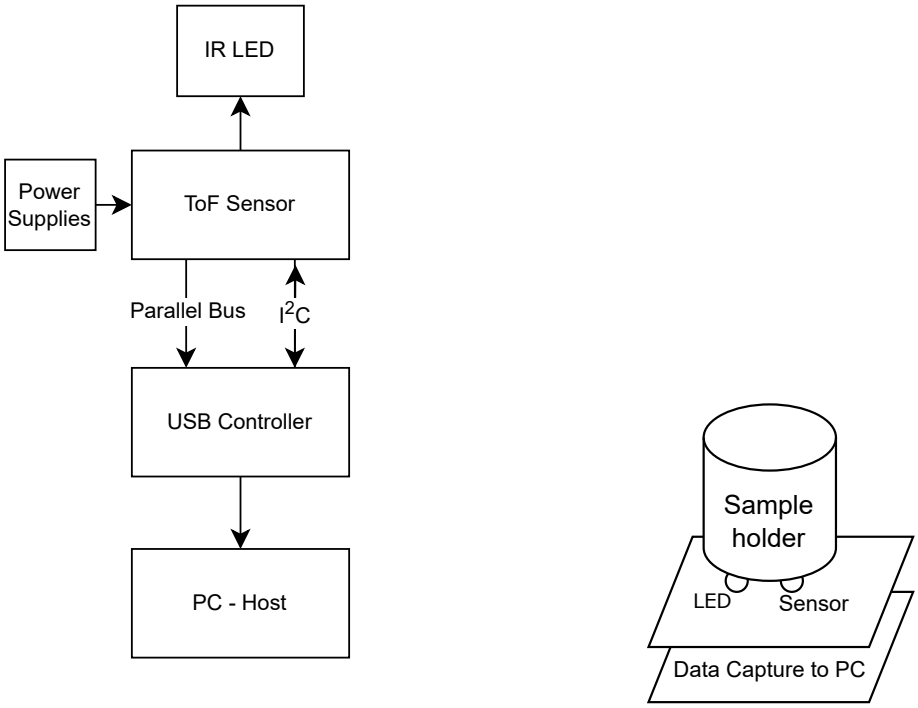


Figure 7.7: Phase data from sensor, rendered as grayscale image.



(a) High level diagram of the developed circuit around to operate the sensor.

(b) Setup schematic.

Figure 7.8: High level diagrams for the developed circuit.

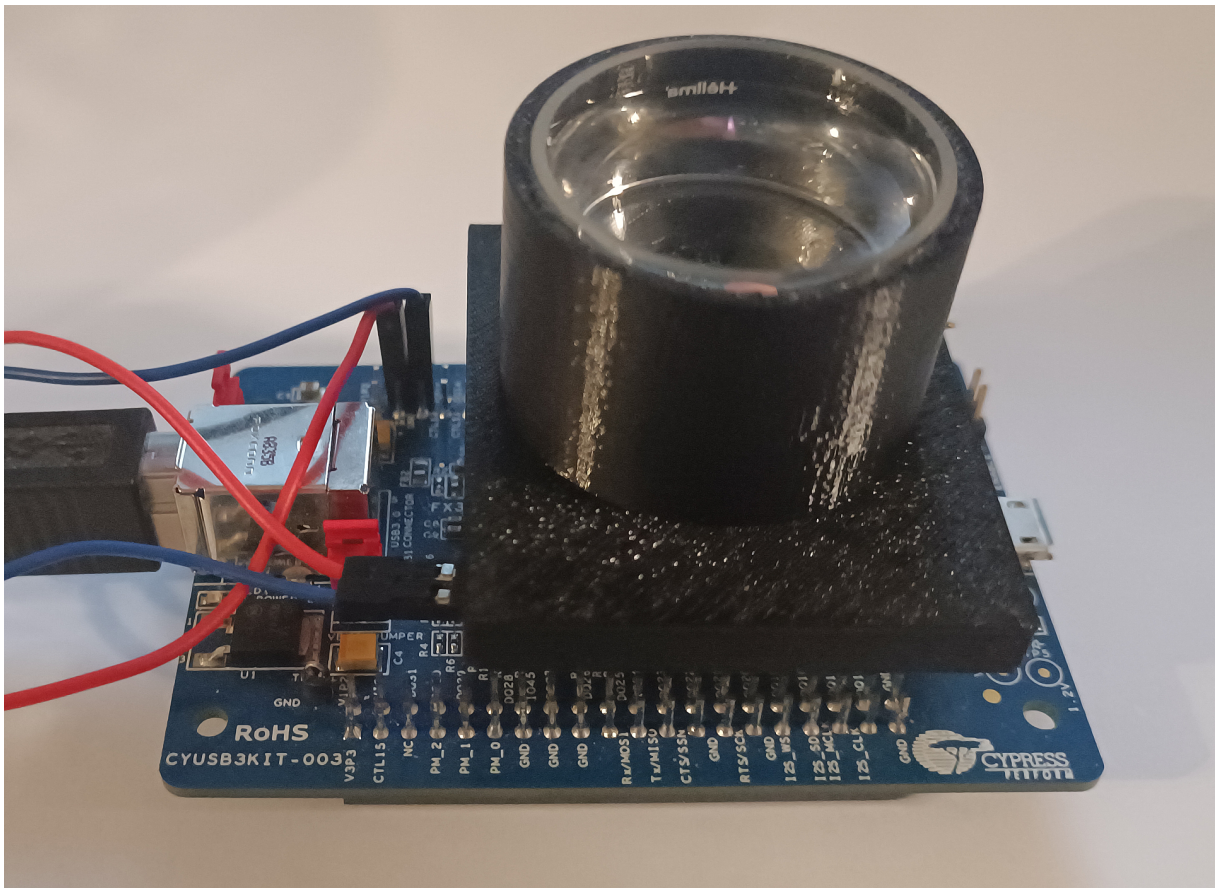


Figure 7.9: Picture of the PCB developed during measurement.

ensure it did not influence the measurements, the cuvette's transparency was further validated by conducting tests on both an empty cell and one filled with saline.

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8 Measurements – Results using the ToF method

8.0.1 Measurement Post Processing

As has already been mentioned, the sensor used provides data in the form of a binary stream. This data is captured and transferred to a PC as a single file to simplify firmware development on the hardware side. On the host PC, the binary file is converted to four separate binary arrays that include sensor phase and amplitude data. These were initially converted to simple grayscale images by mapping all possible sensor values to the 8bit grayscale image space (with the expected loss of information) in order to verify correct sensor operation and communication. This was achieved by commanding the sensor to switch to the integrated testing mode which switches the incoming data with a predictable array of increasing numbers (a simple binary counter). After successful verification of operation the test mode functionality was disabled.

To decrease possible noise from the sensor, multiple samples were acquired for each sample. Each measurement from the sensing element consists of 4 arrays of 4800 cells. The cells of each array correspond to a pixel of the sensor array while the arrays represent the four different data types that the senor provides. These are the amplitude of the signal received, flags that provide data for the operation of the relevant pixel (eg if it has been saturated), ambient light data (in case of operation in an area with near infrared sources) and the phase data of the received signal. The last one is the data used in this work. This is the phase difference of the captured signal to the reference signal (as created by modulating the LED driving current) with higher values representing higher difference and thus greater distance traveled.

The multiple recorded samples were averaged to produce a single array for each measurement. The data produced thus was in turn further filtered using a moving window averaging function with a sample size of 1000 to remove noise. This value was selected so as to prevent excessive smoothing but also remove spikes of noise in the produced data. The moving average filtering algorithm was selected over other possible algorithms (for example weighted averaging) due to several reasons - mainly

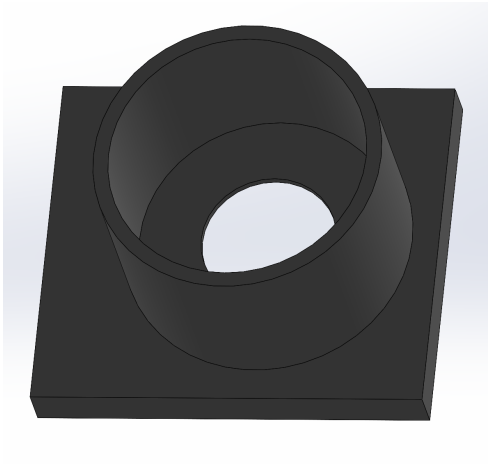

Figure 8.1: 3D rendering of the designed sample holder.

the following:

- The application allowed for a trade-off, between preserving fine details and simplicity. As a mean value was required fine detail was not necessary.
- Since the data was a one-dimensional array from a two-dimensional image, there was a number of spikes and anomalies (eg due to local two dimensional irregularities that were converted to periodic irregularities in the array). The moving average filter handled effectively their removal.
- At this stage of sensor development and to simplify testing, the moving average filter's straightforward implementation was considered an ideal choice.

Finally, the sensor provided amplitude data was also compared between different measurements and found to differ within the detection limits of the sensor ($\pm 2LSB$).

8.0.2 Measurements Performed

The performance of the sensor was determined by multiple measurements of the produced samples. A buffer solution of physiological saline was used, to which different amounts of D-glucose (Sigma Aldrich G8270-1KG) was added. The quantity added was adjusted so as to create multiple solutions with glucose concentrations that initially cover the range of human normal blood glucose levels ($70mg/dl - 140mg/dl$) [1]. Additional samples were created to cover values up to an upper limit of $500mg/dl$.

A cuvette holder was designed and 3D printed to prevent position changes during measurement and to attempt and preserve the cuvette placement while different samples were placed on the sensor (fig.8.1).

To verify that the sensor's measurements are not affected by the sample container used, full measurements were acquired using just an empty container. The results

showed that the sensor did not register significant signal change with or without the sample holder, that could not be attributed to ambient and system noise.

After initial verification of sensor operation, the full samples were measured using the sensor developed. The initial results were not as expected and indicated that the samples did not have the expected glucose concentration. This led to their recreation and verification using laboratory instruments. The samples were then relabeled based on the measured glucose concentration. The final measurements are shown in figures 8.2 and 8.3.

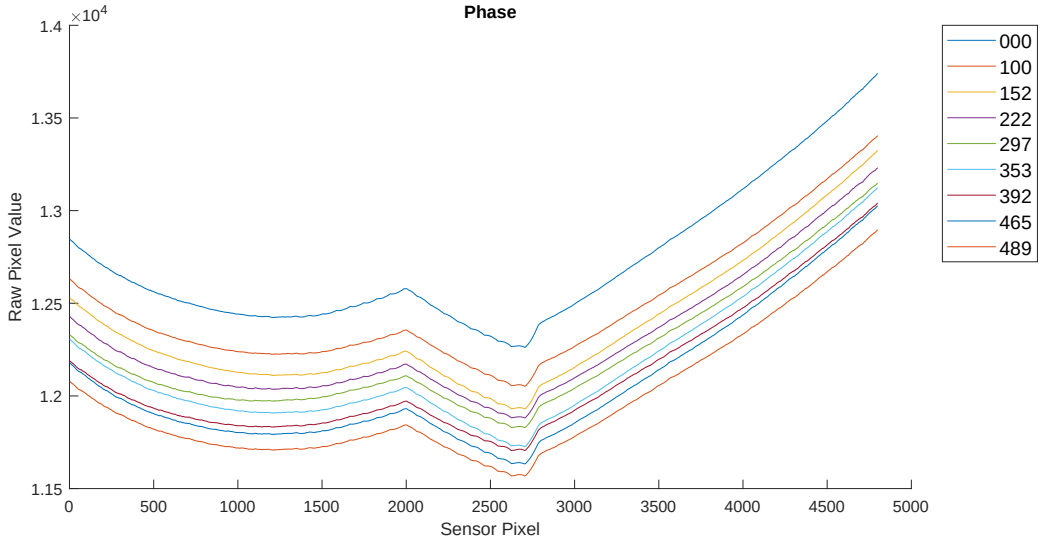

Figure 8.2: Averaged sensor output (phase of received signal) versus sensor pixel for different glucose concentrations in sample.

The results shown in the previous figures are the raw sensor values for each pixel of the sensor (an array of 80 x 60 pixels). This sensor value is proportional to the phase difference of the received signal vs the emitted(reference) signal. An increased value for a sensor pixel represents increased distance traveled by the light pulses emitted by the LED.

To correlate the measured values with real glucose values, the moving average window was increased to 4000 samples. The result of plotting the mean value of data received versus the concentration, is shown in figures 8.4,8.5 and 8.6. . Error bars were added using the values from multiple measurements performed on each sample (with the exception of figure 8.6). Error bars were added only on sensor measurements - glucose concentration of samples was verified with existing certified sensors. An initial linear fit was attempted - the polynomial degree was chosen so as to arrive to an $R^2 > 0.95$. Thus, a 1st degree polynomial was chosen for both the amplitude data and the phase data. The factors of those as well as the R^2 values are shown on the relevant figures.

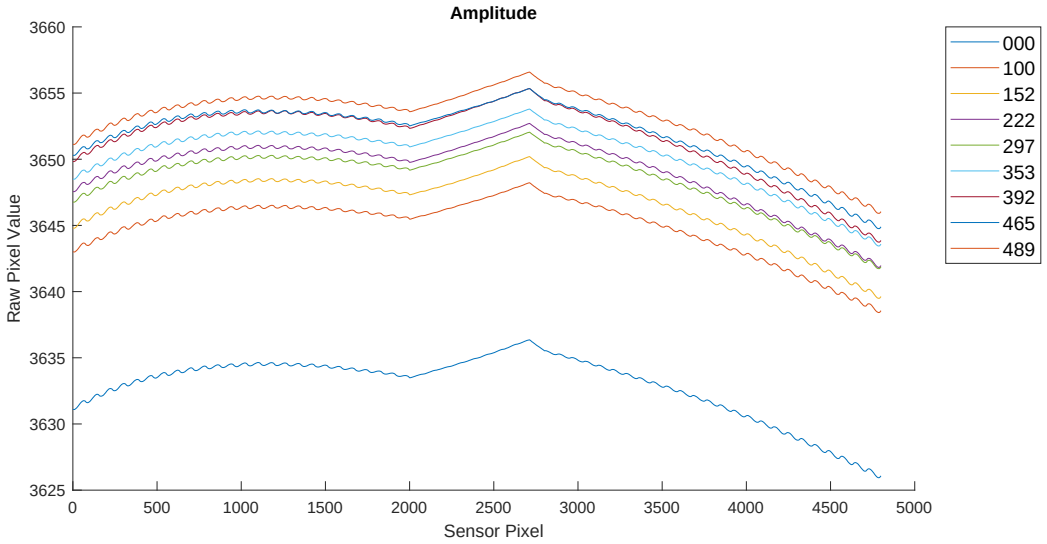

Figure 8.3: Averaged sensor output (amplitude of received signal) versus sensor pixel for different glucose concentrations in sample.

Additionally, the measured amplitude signal of the pure saline sample was used along with the amplitude signals of the rest of the samples, to create scaling factors. These were applied to the phase measurements and the results are shown in fig. 8.6.

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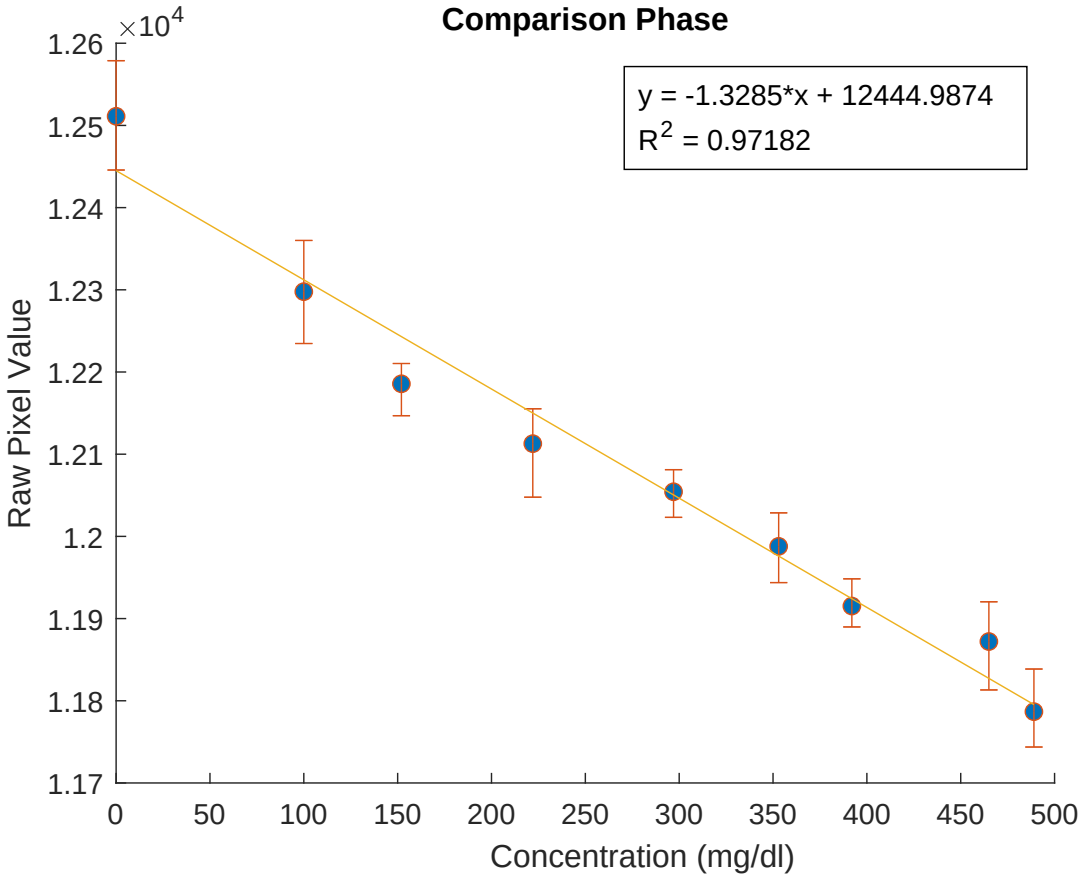

Figure 8.4: Averaged sensor output (phase channel) for different glucose concentrations.

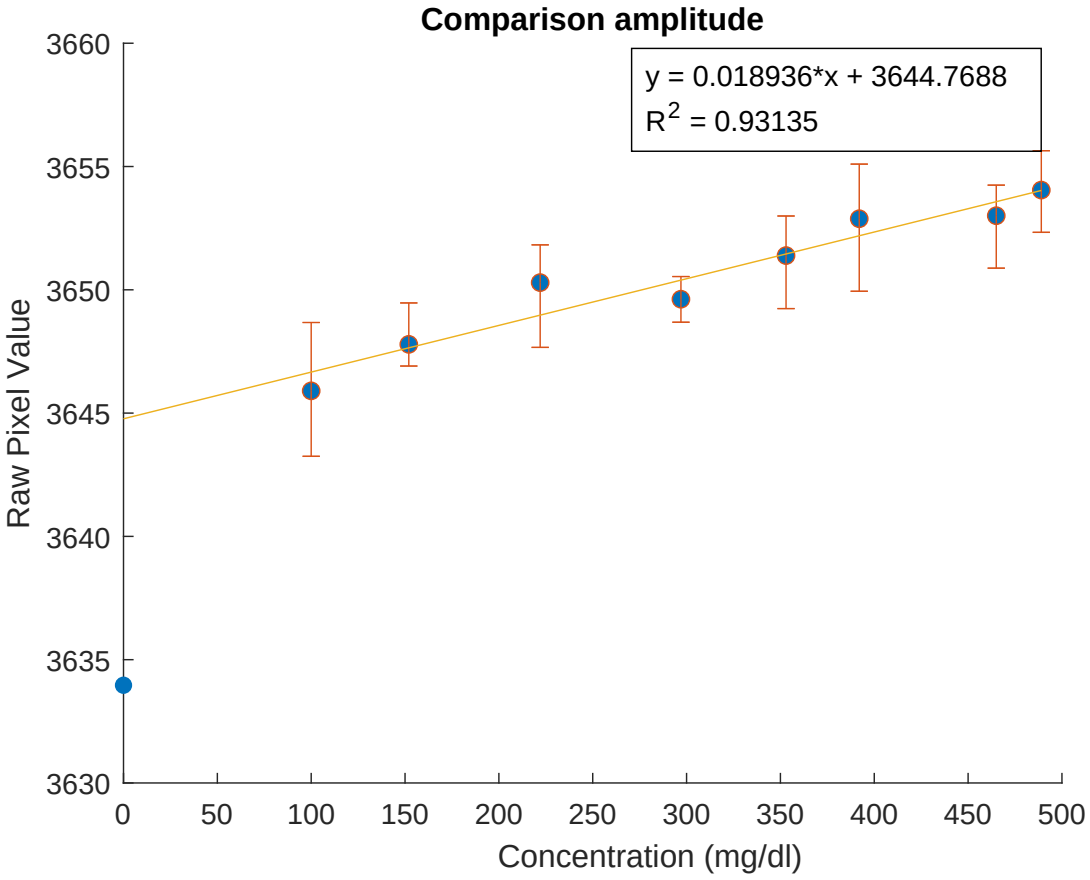

Figure 8.5: Averaged sensor output (amplitude channel) for different glucose concentrations.

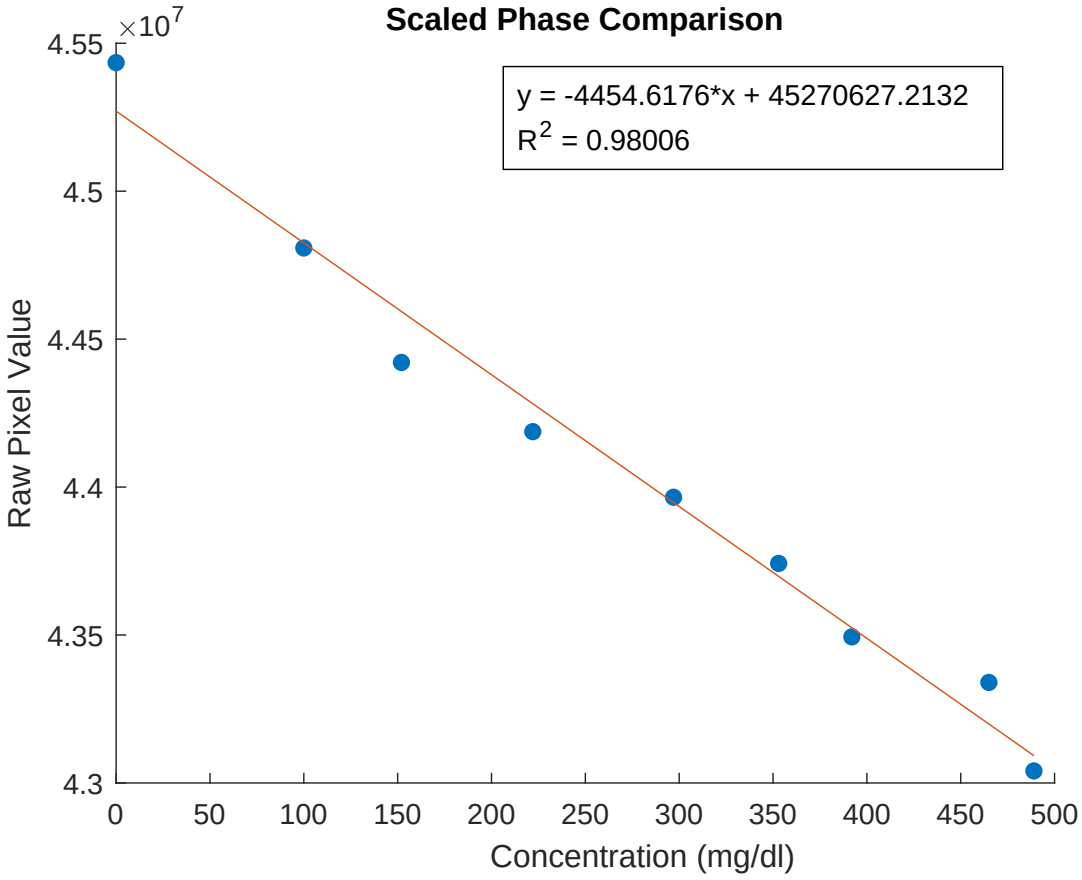

Figure 8.6: Averaged sensor output (phase channel scaled by amplitude channel) for different glucose concentrations.

9 Conclusions on using the ToF method

Based on the above results, the developed sensing method shows promise in the measurement of glucose in aqueous solutions, based on the change of the optical properties. The sensor developed allows for the detection of glucose changes based on the change of the time of flight of light through a sample using relatively inexpensive, off-the-shelf components. The results of the sensor show a correlation between the measured value and the sample glucose concentration. The error margins are relatively high but it should be possible to improve these with further fine tuning of the different sensor variables and circuit design. The developed sensor is considered to be at TRL3 - the sensor demonstrates basic functionality under in a research environment however further work is needed.

Future work on this TRL3 sensor should begin with experimental design, integrating both in vitro and in vivo testing stages alongside direct comparisons to benchmark equipment. To this end, experiments will be structured to include baseline readings, dynamic environmental exposures, and testing in the presence of potential interferents. The sensor could be tested on a lipid emulsion to simulate skin optical properties (as has been tried by Kirillin et al with good results [1]). The sensing element used has multiple parameters that should be further adjusted to improve the sensor response - initial values based on datasheet recommendations were used in this work. These parameters could also affect sensor response in different environments.

After reaching a well defined state for the sensor parameters, experimentation should be expanded to include live biological specimens or human subjects (where applicable) to finally observe the sensor's behavior in a biological matrix and revealing any potential effects by other biological materials, response time variations, and other sensor-material interactions. Initial work has already been done to verify that the LED wavelength and light emitted are sufficient to achieve an acceptable penetration depth (using data and skin models from Anderson et al and Bashkatov et al [2][3])

An additional experimental modification is the wavelenght used. Further work should increase the spectrum of wavelengths used - there have been promising results from using wavelengths in the NIR region between $1200nm$ up to $2500nm$ [4]. To ad-

dress this, revised versions of the sensor presented here are currently being designed that will operate in this region. Such sensors will probably have decreased area of measurement but will be based on the same principle. Work is ongoing to evaluate these updated sensing elements and optimizing the accompanying circuit design to enhance the sensor's stability and sensitivity. However, LEDs of sufficiently high speed and photodiodes of likewise high sensitivity able to operate in these wavelengths are prohibitively expensive when compared to devices tuned for wavelengths less than $1000nm$. Thus while such a research direction could prove beneficial as regards the sensor operation, it should be heavily weighted with the current implementation which is very low cost - a complete sensor package costing at the time of writing about 100 EUR.

On the processing side, future work shall focus on refining the quality of image-based data by employing advanced noise reduction algorithms. Adding to that, it is also important that the data processing workflow is further expanded and optimized or even improved upon. The moving average algorithm currently used, while effective in certain scenarios, has limitations and may not fully optimize noise reduction while preserving essential information. Techniques such as weighted averaging and bilateral filtering will be explored for their ability to preserve fine details while effectively mitigating noise, particularly in environments with high variability. Comparative studies will be conducted to identify the most suitable algorithm, balancing computational efficiency and performance. Prior research has demonstrated the utility of bilateral filtering in maintaining edge integrity in noisy medical images (as is done in general for images by Tomasi & Manduchi [5]) and the applicability of weighted averaging for reducing noise in imaging data. Additionally, the nonlocal-means algorithm has been used with promising results (as has been shown in the work of Buades et al. [6]). These insights will guide the optimization of the sensor's data processing pipeline, aiming to enhance the reliability and accuracy of glucose concentration measurements.

Finally, the results of the sensor should be compared with a robust theoretical model to complement the experimental findings. This model will be based on finite element analysis (FEA). A method is currently being developed to simulate light scattering in a multilayered tissue model (based of the work of Vasudevan et al[7], Liemert et al[8] and Saidi et al[9]). The objective is to establish a predictive framework that accurately reflects the sensor's performance and which will in turn should allow for optimization of sensor design for diverse applications. Furthermore, integrating this model with experimental validation will enhance the reliability of the sensor, providing deeper insights into its operating principles and enabling its use in more complex scenarios.

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10 Conclusion and Further Research

The pursuit of non-invasive glucose sensing technologies has been a focal point in advancing diabetes management, offering the potential for painless, real-time monitoring of blood glucose levels. This thesis explored various methodologies and techniques, including a more in depth analysis of bioimpedance spectroscopy, and optical spectroscopy providing a comprehensive understanding of their principles, applications, and limitations.

The experimental studies conducted as part of this research have demonstrated the promise of innovative sensor designs and advanced signal processing techniques, particularly those utilizing Time-of-Flight (ToF) principles. A novel optical sensor based on the Time-of-Flight (ToF) method was successfully developed, demonstrating sufficient depth penetration and sensitivity to detect glucose-induced changes in human skin. These promising results highlight the potential of optical methods as a cornerstone for reliable non-invasive glucose monitoring. Despite challenges such as interference from physiological variability and environmental factors, the findings underscore the feasibility of integrating non-invasive glucose monitoring technologies into wearable and IoT-enabled platforms.

Attempts to use bioimpedance spectroscopy and RF techniques, particularly through S_{11} and S_{21} parameter measurements, did not produce meaningful results. While repeatable measurements were achieved, no reliable correlation to glucose concentrations was found. These failures are attributed to the non-linear scattering behavior of electromagnetic waves in tissues, significant interference from water content, and variability in dielectric properties. Despite these challenges, the insights gained informed sensor refinement and highlighted the limitations of single-parameter approaches.

This work emphasizes the potential of optical methodologies for non-invasive glucose sensing while recognizing the need for complementary approaches to address unresolved challenges in signal accuracy and specificity.

Future Work

To address the limitations identified and advance non-invasive glucose sensing, the following directions are proposed:

1. **Integration of Multi-Modal Sensing Techniques**: Develop a multi-parameter sensor system that combines optical, bioimpedance, and RF techniques. Multi-modal approaches can leverage the strengths of individual methods while mitigating their limitations. For example, integrating near-infrared spectroscopy (NIRS) with bioimpedance and RF measurements could enable cross-validation of glucose-specific signals while compensating for water-related interference [1, 2].

2. **Eliminating Measurement Errors**: Emphasize methods to reduce physiological and environmental variability. Techniques that isolate glucose-specific effects from confounding factors, such as water content, tissue hydration, and motion artifacts, are critical. Spectroscopic methods targeting glucose-specific absorption bands could significantly reduce ambiguity [3].

3. **Data Fusion and Machine Learning**: Develop advanced data fusion techniques using machine learning to analyze and combine data from multiple sensing modalities. Such models can enhance signal-to-noise ratios, identify glucose-specific patterns, and improve predictive accuracy [4].

4. **Validation Across Populations**: Conduct extensive validation studies across diverse populations to ensure robustness against variability in skin tone, tissue composition, and physiological differences.

5. **Advanced Simulation and Modeling**: Expand computational modeling efforts, such as Finite Element Method (FEM) and Monte Carlo simulations, to simulate light-tissue interactions and dielectric properties under varying glucose concentrations. These simulations will guide sensor design and calibration [1].

6. **Miniaturization and Wearable Devices**: Focus on miniaturizing the multi-modal system into wearable platforms for continuous glucose monitoring. Integration with IoT platforms can enable real-time analytics and personalized diabetes management.

By addressing these challenges, future research aims to develop next-generation non-invasive glucose monitoring systems with improved reliability, accuracy, and user-friendliness.

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