I would like to dedicate my thesis to my beloved parents, my inspiration and my epitome of hard work, honesty and happiness. They have always nurtured me with their unconditional love, trust and belief. My Sister and brother who always encourages me to do greater things in life.

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……. Grateful and blessed

……For my beautiful family

….My forever guiding light (Papa) this is for you

तेजपुर विश्वविद्यालय/TEZPUR UNIVERSITY
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(A Central University established by an Act of
Parliament)
संकायाध्यक्ष का कार्यालय, शोध व विकास
Department of Molecular Biology and Biotechnology
तेजपुर-784028 :: असम / TEZPUR-784028 :: ASSAM

Dr. Venkata Satish Kumar Mattaparthi, M.Tech., Ph.D.,
Assistant Professor,
Department of Molecular Biology and Biotechnology

E-mail: venkata@tezu.ernet.in,
mvenkatasatishkumar@gmail.com
Phone no: 918811806866/03712-275443
Fax: 03712-267005/267006(O)

CERTIFICATE OF THE PRINCIPAL SUPERVISOR

This is to certify that the thesis entitled *"Computational investigation of membrane induced self-assembly and aggregation of α-Synuclein"* submittedto the School of Sciences, Tezpur University in partial fulfillment for the award of the degree of Doctor of Philosophy in Molecular Biology and Biotechnology is a record of original research work carried out by **Ms. Dorothy Das** under my personal supervision and guidance.

All helps received by her from various sources have been duly acknowledged. Nopart of this thesis has been reproduced elsewhere for award of any other degree.

Date: 24/10/2024

Place: Tezpur University, Tezpur

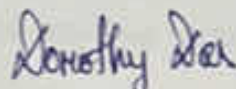**(Venkata Satish Kumar Mattaparthi)**
Supervisor

Declaration

I hereby declare that the thesis entitled *"Computational investigation of membrane induced self-assembly and aggregation of a-Synuclein"* has been submitted to Tezpur University in the Department of Molecular Biology and Biotechnology under the School of Sciences for partial fulfillment for the award of the degree of Doctor of Philosophy in Molecular Biology and Biotechnology.

I am the sole author of this thesis. This is a true copy of an original work carried out by me including any required final revisions, as accepted by my examiners.

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Dorothy Das

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Place: Tezpur University, Tezpur   **Registration No.:** TZ203952 of 2020

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Dr. Venkata Satish Kumar Mattaparthi, M.Tech., Ph.D.,
Assistant Professor,
Department of Molecular Biology and Biotechnology

E-mail: venkata@tezu.ernet.in,
mvenkatasatishkumar@gmail.com
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Date:

Place: Tezpur University, Tezpur

(Venkata Satish Kumar Mattaparthi)

Supervisor

CERTIFICATE OF THE EXTERNAL EXAMINER
AND ODEC

This is to certify that the thesis entitled **"*Computational investigation of membrane bound self-assembly and aggregation of α-Synuclein"*** submitted by **Ms. Dorothy Das** to Tezpur University in the Department of Molecular Biology and Biotechnology under the School of Sciences in partial fulfillment of the requirement for the award of the degree of Doctor of Philosophy in Molecular Biology and Biotechnology has been examined by us on ………………………………… and found to be satisfactory.

The committee recommends for the award of the degree of Doctor of Philosophy.

Signature of:

Principal Supervisor   **External examiner**

Date: **Date:**

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Regards,
Dorothy Das

List of Figures

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List of Abbreviations

Å	Angstrom
AD	Alzheimer's disease
α-Syn	Alpha Synuclein
AMBER	Assisted Model Building with Energy Refinement
BBB	Blood brain Barrier
BFE	Binding free energy
β-Syn	Beta Synuclein
CASTp	Computed Atlas of Surface Topography of proteins
CHARMM	Chemistry at HARvard Macromolecular Mechanics
CoM	Centre of Mass
COMT	catechol-O-methyl transferase
cryoEM	cryo-electron microscopy
1CSSI	one-character secondary structure information
CTD	C-Terminal domain
3-D	3-Dimensional
3DFFT	three-dimensional fast Fourier transform
CGenFF	CHARMM general force field
CPCM	conductor-like polarizable continuum model
CPPTRAJ	A rewrite of PTRAJ in C++
DBS	Deep Brain Stimulation
DFT	Density Functional theory
DLB	dementia with Lewy Bodies
DNA	Deoxyribonucleic Acid
DOPC	1,2-Dioleoyl-sn-glycero-3-phosphotidylcholine
DOPE	1,2-Dioleoyl-sn-glycero-3-phosphotidylethanolamine
DOPS	1,2-Dioleoyl-sn-glycero-3-phoshotidylserine
DSSP	Dictionary of Secondary Structure for Protein
ω	electrophilicity
EA	Electron affinity
EDP	Electron density profile
ELE	electrostatic energy
ESBRI	Evaluating the Salt BRIdges in Proteins
FEL	Free energy landscape
FFT	Fast Fourier Transform
FF99SB	Force-field 99 Stony Brook
γ-Syn	Gamma synuclein
GABA	gamma-aminobutyric acid
GAFF	General Amber force field

List of Abbreviations

GB	Generalized Born
GBSA	Generalized Born Surface Area
GUI	Graphical user interface
HOMO	highest occupied molecular orbitals
IDP	Intrinsically Disordered Protein
IDR	Intrinsically Disordered Regions
IP	ionization potential
kDa	kilo Dalton
LB	Lewy Bodies
LBD	Lewy Bodies disease
L-DOPA	L-3,4-dihydroxyphenylalanine
LHOP	local helix origin points
LN	Lewy neurites
LUMO	lowest unoccupied molecular orbitals
MAO	monoamine oxidase
MC	Monte Carlo
MD	Molecular Dynamics
MESP	molecular electrostatic potential map contour
MM	Molecular mechanics
MO	Molecular orbitals
MSA	multiple system atrophy
N	nucleophilicity
NAC	non-amyloid component
NBO	Natural bond orbital
NIH	National Institutes of Health
NMR	Nuclear Magnetic Resonance
NPT	constant-temperature, constant-pressure ensemble
ns	Nanosecond
NVT	constant volume
PBC	Periodic boundary conditions
PCA	Principal Component Analysis
PD	Parkinson's Disease
PDB	Protein Data Bank
PDD	PD Dimentia
PDI	protein disulfide isomerase
PME	Particle Mesh Ewald
PPI	protein-protein interactions
ps	Picosecond
pS87	Phosphorylated at Serine 87

pS129	Phosphorylated at Serine 129
PTM	Post Translational Modification
PTRAJ	Short for Process TRAJectory
pY39	Phosphorylated at Tyrosine 39
RBVI	Resource for Biocomputing, Visualisation, and Informatics
RCSB	Research Collaboratory for Structural Bioinformatics
Rg	Radius of Gyration
RMSD	Root Mean Square Deviation
RMSF	Root Mean Square Fluctuation
SA	Surface Area
SASA	Solvent-accessible surface area
SCF	Self-consistent field
SCOP	Structural Classification of Proteins
SDM	Site directed mutator
SOPMA	self-optimized prediction multiple alignment method
SVs	Synaptic vesicles
TCNE	tetracyanoethylene
TFE	trifluoroethanol
TIP3P	Transferable Intermolecular Potential Three-point
TIP4Pew	Transferable Intermolecular Potential four-point ewald
UCL	University College, London
UCSF	University of California, San Francisco
VDW	van der Waals contribution
VMD	Visual Molecular Dynamics
WHO	World Health Organization
WT	Wild Type

List of Publications

This thesis is partly based on the following original communications:

1. **Das, D.** and Mattaparthi, V.S.K. Computational investigation on the conformational dynamics of C-terminal truncated α-Synuclein bound to membrane. *Journal of Biomolecular Structure and Dynamics*, 2024. DOI: https://doi.org/10.1080/07391102.2024.2310788

2. **Das, D.**, Bharadwaz, P. and Mattaparthi, V.S.K. Computational investigations on the effect of the pepditomimetic inhibitors (NPT100-18A and NPT200-11) on the α-Synuclein and lipid membrane interactions. *Journal of Biomolecular Structure and Dynamics*, 2023. DOI: https://doi.org/10.1080/07391102.2023.2262599

3. **Das, D.** and Mattaparthi, V.S.K. Conformational dynamics of A30G α-Synuclein that causes familial parkinson disease. *Journal of Biomolecular Structure and Dynamics*, 2023. DOI: https://doi.org/10.1080/07391102.2023.2193997

4. **Das, D.**, Kakati, M., Gracy, A., Sanjeev, A., Patra, S.M., and Mattaparthi, V.S.K. Screening of druggable conformers of α-Synuclein using molecular dynamics simulation. *Biointerface Research in Applied Chemistry*, *10*, 5338-5347,2020.DOI: https://doi.org/10.33263/BRIAC103.338347

5. Kakati, M., **Das, D.**, Das, P., Sanjeev, A., and Mattaparthi, V.S.K. Effect of ethanol as molecular crowding agent on the conformational dynamics of α-Synuclein. *Letters in Applied NanoBioscience*, *9*,779-783, 2020. DOI: https://doi.org/10.33263/LIANBS91.779783

List of Publications

Other Publications:

1. Srivastava,V., Naik, B., Godara, P., **Das, D.**, Mattaparthi, V.S.K., and Prusty, D. Identification of FDA-approved drugs with triple targeting mode of action for the treatment of monkeypox: a high throughput virtual screening study. *Molecular Diversity*, *20*, 1-15, 2023. DOI: http://doi.org/10.1007/s11030-023-10636-4

2. Yata, V.K., Dutta, N., **Das, D.**, and Mattaparthi, V.S.K. An In Silico Study for the Identification of Novel Putative compounds Against the Wild and Mutant Type Penicillin Binding Protein 2 of Neisseria Gonorrhoeae. *Biointerface Research in Applied Chemistry*, *11(2)*, 2020. DOI: https://doi.org/10.33263/BRIAC112.89969006

3. Yata, V.K., **Das, D.**, Deb, A., Das, N., Mahanta, G., Arora, B., and Mattaparthi, V.S.K. An In-Silico Study of Stable and Environment-Friendly Oryza sativa Urease. *Biointerface Research in Applied Chemistry*, *11(3)*, 2020. https://doi.org/10.33263/BRIAC113.1023810247

4. Das, C., **Das, D.,** and Mattaparthi, V.S.K. Computational Investigation on the Efficiency of Small Molecule Inhibitors Identified from Indian Spices against SARS-CoV-2 Mpro. *Biointerface Research in Applied Chemistry*, 13(3), 2023. https://doi.org/10.33263/BRIAC133.235

5. Das, C., Hazarika, P.J., Deb, A., Joshi,P., **Das, D.**, and Mattaparthi, V.S.K. Effect of Double Mutation (L452R and E484Q) in RBD of Spike Protein on its Interaction with ACE2 Receptor Protein. *Biointerface Research in Applied Chemistry*, *13(1)*, 2023. DOI: http://doi.org/10.3390/vaccines11010023

6. Dutta, M., Deb, A., **Das, D.**, and Mattaparthi, V.S.K. A Computational Approach to Understand the Interactions Stabilizing the Aβ1-42 Oligomers. *Biointerface Research in Applied Chemistry*, *11(1),* 2021. DOI: https://doi.org/10.33263/BRIAC112.88048817

7. Das, C., **Das, D.**, and Mattaparthi, V.S.K. Effect of Mutations in the SARS-CoV-2 Spike RBD Region of Delta and Delta-Plus Variants on its Interaction with ACE2 Receptor Protein. *Letters in Applied NanoBioscience*, *12(4),* 2023. DOI: https://doi.org/10.33263/LIABNS124.118

In addition, this thesis also contain unpublished data.

1. **Das, D.**, and Mattaparthi, V.S.K. "Computational investigation on conformational ensembles of A30G α-Synuclein in its membrane bound state and in free solution that causes familial PD" National Seminar on "Excitements in Biological Research" held at Department of MBBT, Tezpur University on 6 th March, 2023. (Oral Presentation, 1st Prize).

2. **Das, D.**, and Mattaparthi, V.S.K. "Impact of phosphorylation at Ser87 on the α-Synuclein aggregation and synuclein-membrane interactions: an in silico study" in the National seminar "Research at the Interface of Chemical, Biological and Material Sciences" held at Department of Chemical Sciences, Tezpur University on 10th March, 2023. (Oral Presentation, 3rd prize)

3. **Das, D.**, and Mattaparthi, V.S.K. "Effect of pY39 Post-translational modification on the interactions between α-Synuclein and Lipid Membrane" the India-12th India-Japan Science and Technology Conclave: International Conference on Frontier Areas of Science and Technology (ICFAST-2022) held at the University of Hyderabad on September 09-10, 2022. (Poster Presentation)

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