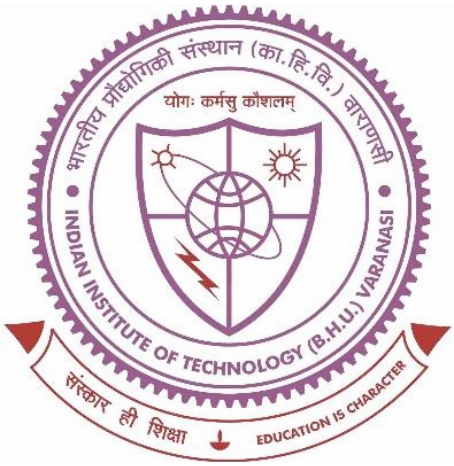
Computational, Machine Learning and Multi Target Directed Ligand (MTDL) Approaches to Identify Novel Leads for Alzheimer's Disease



Thesis submitted in partial fulfilment for the Award of Degree

Doctor of Philosophy

By

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CERTIFICATE

It is certified that the work contained in the thesis titled "**Computational, Machine Learning and Multi Target Directed Ligand (MTDL) Approaches to Identify Novel Leads for Alzheimer's Disease**" by **Ms. Powsali Ghosh** has been carried out under my supervision and that this work has not been submitted elsewhere for a degree.

It is further certified that the student has fulfilled all the requirements of Comprehensive Examination, Candidacy and SOTA for the award of Ph.D. Degree.

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I, **Powsali Ghosh**, certify that the work embodied in this Ph.D. thesis is my own bona fide work and carried out by me under the supervision of **Prof. Sushil K. Singh** from **December, 2021 to June, 2025** at the **Department of Pharmaceutical Engineering & Technology, Indian Institute of Technology (Banaras Hindu University), Varanasi**. The matter embodied in this Ph.D. thesis has not been submitted for the award of any other degree/diploma. I declare that I have faithfully acknowledged and given credit to the research workers wherever their works have been cited in my work in this thesis. I further declare that I have not wilfully copied any other's work, paragraphs, text, data, results, *etc*. reported in the journals, books, magazines, reports, dissertations, theses, *etc*., or available at websites and have not included them in this Ph.D. thesis and have not cited as my own work.

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Acknowledgements

At the very outset, I express my utmost respect and heartfelt reverence to ***Bharat Ratna Pandit Madan Mohan Malaviya Ji*** *and the esteemed* ***Late Prof. M.L. Schroff*** *for their visionary and humanitarian efforts in establishing this distinguished temple of learning, which has been instrumental in nurturing generations of scholars and fostering academic excellence.*

I wish to convey my deepest sense of gratitude to my supervisor, ***Prof. Sushil Kumar Singh****, for his constant support, insightful guidance, and unwavering belief in my capabilities throughout my doctoral journey. His mentorship, constructive criticism, and invaluable advice have been a source of inspiration and have played a pivotal role in shaping both my academic and personal growth.*

I sincerely thank ***Dr. Ashok Kumar*** *for his valuable guidance and constructive suggestions throughout my Ph.D.*

I am profoundly thankful to ***Prof. Sairam Krishnamurthy****, Head, Department of Pharmaceutical Engineering & Technology, IIT (BHU) Varanasi, for providing the essential resources, research facilities, and a stimulating environment conducive to the successful completion of my work. I am especially grateful to him and his research group for their generous support and cooperation in facilitating the in vivo studies that formed an integral part of my doctoral research. His encouragement and support at every stage of my research have been deeply appreciated.*

I also express my sincere gratitude to the former Heads of the Department, **Prof. S.K. Shrivastava** and **Prof. (Mrs.) S. Hemalatha***, for their constant support, motivation, and guidance, which greatly contributed to the smooth execution of my research activities.*

I am sincerely grateful to all the esteemed faculty members of the department, **Prof. B. Mishra, Prof. Senthil Raja A, Prof. M.S. Muthu, Dr. Alakh N. Sahu, Dr. Ashish K. Agrawal, Dr. G.P. Modi, Dr. Ruchi Chawla, Dr. S.K. Jain, Dr. Vinod Tiwari, Dr. P.K. Nayak, Dr. S.K. Mishra, Dr. Rajnish, Dr. Deepak Kumar, Dr. Dinesh Kumar, Dr. Jairam Meena***, and* **Dr. Arun Khatri***, for their constant encouragement, insightful discussions, and kind support, which have been invaluable throughout my academic journey.*

I gratefully acknowledge the constructive feedback and valuable suggestions provided by my Research Progress Evaluation Committee members, **Dr. Shreyans Kumar Jain and Prof. Abha Mishra**, *whose inputs have greatly helped in refining and strengthening my research work.*

It is my pleasure to express my heartfelt appreciation to my friends and colleagues, ***Sagorika Nag, Sanheeta, Pallavi, Pooja, Soki, Rasha,*** *and* ***Nilesh****, for their friendship, enriching discussions, and the constant moral support that made this journey less challenging and more fulfilling.*

I also extend my sincere gratitude to my seniors and lab members, ***Dr. Ravi Singh****,* ***Dr. Swetha Rayala****,* ***Dr. Ankit Ganeshpurkar****,* ***Dr. Gopichand Gutti****, and* ***Dr. Devendra Kumar****, for their invaluable guidance, technical support, and insightful suggestions, which contributed significantly to my research. Additionally, I wish to acknowledge the constant encouragement and support from my seniors,* ***Dr. Rangan Mitra****,* ***Mr. T.A. Gajendra****,* ***Dr. Anurag T.K. Baidya****,* **Dr. Shreyasi Majumdar,** ***Dr. Digambar Waikar, Dr. Aiswarya Chaudhuri****, and* ***Dr. Samarpita Das,*** *whose academic discussions, constructive feedback, and moral support have been instrumental in my academic journey.*

I gratefully acknowledge the PARAM Shivay Supercomputing Facility, the Centre for Computing and Information Services (CCIS), and the Central Instrument Facility (CIF) of IIT (BHU) for providing the necessary infrastructure, advanced instrumentation, and technical support, which were critical to the successful execution of my research.

I am grateful to **IIT (BHU)** *for providing me with a Teaching Assistantship, which not only supported me financially but also enriched my academic experience.*

I am thankful to all the non-teaching staff of the department for their administrative assistance and technical support. In particular, I extend my gratitude to ***Mr. Yashwant Singh*** *and* ***Mr. Anand****, whose constant help and willingness to assist in every possible way greatly contributed to my research activities.*

*I also wish to acknowledge the invaluable contribution of **laboratory animals** used during my research. Their role in advancing scientific knowledge cannot be overstated, and I express my deepest gratitude and respect for their sacrifice in the interest of pharmaceutical research.*

Above all, I am eternally indebted to my beloved parents and sister for their unconditional love, patience, and unwavering belief in me. Their constant encouragement, sacrifices, and support have been the foundation of my perseverance and success. I would also like to express my heartfelt gratitude to my husband, Lokesh, whose presence, understanding, and unwavering support have been a source of immense strength and motivation throughout this journey.

To all those who, in one way or another, contributed to the successful completion of my doctoral work, your support is deeply appreciated, and I remain ever grateful.

Date:

Place: IIT (BHU), Varanasi

(Powsali Ghosh)

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List of Abbreviations

Abbreviation	Full Form
3D	Three-dimensional
5-CV	5-fold cross-validation accuracy
10-CV	10-fold cross-validation accuracy
A	Balanced accuracy
Aβ	Amyloid beta
Ach	Acetylcholine
AChE	Acetylcholinesterase
AD	Alzheimer's disease
ADMET	Absorption, distribution, metabolism, excretion, and toxicity
AI	Artificial intelligence
ARIA	Amyloid-related imaging abnormalities
ASCII	American standard code for information interchange
AUC	Area under the curve
BOA	Bayesian optimization algorithm
CADD	Computer-aided drug design
CDSS	Clinical decision support systems
ChAT	Choline acetyltransferase
CNS	Central nervous system
COX-1	Cyclooxygenase-1
COX-2	Cyclooxygenase-2
CSF	Cerebrospinal fluid
DA	Dopamine
DAPK1	Death-associated protein kinase 1
DCM	Dichloromethane
DL	Deep learning
DT	Decision tree
EGF	Epidermal growth factor
EF	Enrichment factor
EEG	Electroencephalography

EOAD	Early-onset Alzheimer’s disease
FAD	Familial Alzheimer’s disease
FPR	False positive rate
FP	False positive
FRET	Fluorescence resonance energy transfer
GANs	Generative adversarial networks
GABA	Gamma-aminobutyric acid
GH	Goodness of hit
GMQE	Global model quality estimation
GNNs	Graph neural networks
HBAs	Hydrogen bond acceptors
HBDs	Hydrogen bond donors
HTVS	High-throughput virtual screening
ICV	Intracerebroventricular
InChI	IUPAC international chemical identifier
IRLS	Iteratively reweighted least squares
LBDD	Ligand-based drug design
LE	Ligand efficiency
LGA	Lamarckian genetic algorithm
LOAD	Late-onset Alzheimer’s disease
LR	Logistic regression
LRR	Leucine-rich repeat
MBD	Membrane-binding domain
MAE	Mean absolute error
MAP	Microtubule-associated protein
MCC	Matthews correlation coefficient
MD	Molecular dynamics
MDD	Major depressive disorder
MDL	Minimal description length
MM-GBSA	Molecular mechanics–Generalised Born surface area
MM-PBSA	Molecular mechanics-Poisson-Boltzmann surface area
MMSE	Mini-mental state examination

MTLDs	Multi-target-directed ligands
NA	Noradrenaline
NIA-AA	National institute on aging and Alzheimer's association
NFTs	Neurofibrillary tangles
NMR	Nuclear magnetic resonance
NO	Nitric oxide
NOD	The nucleotide-binding oligomerization domain
OA	Overall accuracy
PAINS	Pan-assay interference compounds
PBS	Phosphate buffer saline
PI	Propidium iodide
PK/PD	Pharmacokinetic and pharmacodynamic
PR	Precision
QMEAN	Qualitative model energy analysis
QSAR	Quantitative structure-activity relationships
QSPR	Quantitative structure--property relationship
Rg	Radius of gyration
REOS	Rapid Elimination of Swill
RF	Random Forest
RC	Recall
RDF	Radial distribution function
ROC	Receiver Operating Characteristic
RoF	Rule of Five
RNNs	Recurrent neural networks
RMSD	Root-mean-square deviation
RMSF	Root mean square fluctuation
SBDD	Structure-based drug design
SCO	Scopolamine hydrobromide
SCMC	Sodium carboxymethylcellulose
SL	Supervised learning
TBA	Thiobarbituric acid
TBARS	Thiobarbituric acid reactive substance

TDP	Transactive response DNA-binding protein
TEA	triethylamine
TMS	transcranial magnetic stimulation
TN	true negative
TP	true positive
tDCS	Transcranial direct current stimulation
TPSA	topological polar surface area
UFF	universal force field
UMAP	uniform manifold approximation and projection
VAEs	variational autoencoders
WHO	World Health Organization
XGB	Extreme Gradient Boosting

List of Symbols

Symbol	Meaning
α	Alpha
β	Beta
δ	Delta
Δ	Delta
ε	Epsilon
λ	Lambda
ºC	Degree Celsius
Å	Angstrom
©	Copyright
g	Gram
mg	Milligram
µg	Microgram
ng	Nanogram
mmol	Millimole
µM	Micromolar
nM	Nanomolar
mM	Millimolar
mL	Millilitre
µL	Microlitre
µm	Micrometer
mm	Millimetre
cm	Centimetre
mV	Millivolt
h	Hour
s	Second; Singlet
nm	Nanometre
ppm	Parts per million
rpm	Revolutions per minute
Kcal	Kilocalories
Hz	Hertz
MHz	Megahertz
J	Coupling constant
d	Doublet
t	Triplet

Symbol	Meaning
m	Multiplet
dd	Doublet of doublet
m/z	Mass-to-charge ratio
%	Percent
pH	Potential of hydrogen
≤	Less than or equal
<	Less than
>	More than
±	Plus or minus