

**SYSTEMS PERSPECTIVES TO UNDERSTAND AGING AND  
NEURODEGENERATION**

Submitted in partial fulfillment of the requirements for the  
award of

Bachelor of Technology Degree in Bioinformatics

By

**EDA. ARTHI**

**(37220002)**



**DEPARTMENT OF BIOINFORMATICS  
SCHOOL OF BIO AND CHEMICAL ENGINEERING**

**SATHYABAMA  
INSTITUTE OF SCIENCE AND TECHNOLOGY  
(DEEMED TO BE UNIVERSITY)**

**Accredited with Grade "A" by NAAC**

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**MARCH – 2021**



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**DEPARTMENT OF BIOINFORMATICS**

**BONAFIDE CERTIFICATE**

This is to certify that this Project Report is the bonafide work of EDA ARTHI (37220002) who carried out the project entitled **"SYSTEMS PERSPECTIVE TO AGING AND NEURODEGENERATIONMETION"** under my supervision from September 2020 to April 2021.

**Internal Guide**

**Dr. D. ALEX ANAND**

**Head of the Department**

**Submitted for Viva voce Examination held on**

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**Internal Examiner**

**External Examiner**

## **DECLARATION**

I, **EDA. ARTHI** (37220002), hereby declare that the Project Report entitled **“SYSTEMS PERSPECTIVE TO AGING AND NEURODEGENERATION”** done by me under the guidance of **Dr. D.ALEX ANAND** (Internal guide) **Department of Bioinformatics at Sathyabama Institute of Science and Technology, Chennai, Tamil Nadu** is submitted in partial fulfillment of the requirements for the award of Bachelor of Technology degree in BIOINFORMATICS.

**DATE:**

**PLACE:**  
**CANDIDATE**

**SIGNATURE OF THE**

## **ACKNOWLEDGEMENT**

I am pleased to acknowledge my sincere thanks to Board of Management of **SATHYABAMA** for their kind encouragement in doing this project and for completing it successfully. I am grateful to them.

I convey my thanks to **Dr. SWETHA SUNKAR and Dr. JEMMY CHRISTY**, Heads of the Department, Dept. of Bioinformatics for providing me necessary support and details at the right time during the progressive review

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**EDA. ARTHI**

## ABSTRACT

Over the last few decades, neurodegeneration research has seen an immense increase in the genetic, transcriptomic, proteomic, biochemical, physiological and metabolic studies of the partial aspects of disease pathophysiology and its related cognitive impairment. In this picture, ageing emerges as one of the key risk factors identified for neurodegeneration, especially for those types of presentation called "Late-Onset Neurodegeneration." However, despite some ground-breaking attempts, the dominant approach in this area appears to be genomic or proteomic-centric. Over the last decades, this reductionist approach has successfully established the pathways responsible for the so-called "family" neuro degeneration. But this approach provides only little knowledge of how system properties arise and are disrupted under the most general circumstances of the disorder, as it cannot clarify the aetiology of the so-called "sporadic" neurodegeneration. In direct contrast to the prevailing reductionist model, Systems Biology promotes a systematic and inclusive approach to such a complex multi-factorial pathology. The broad variety of causes and effects of this complex biological system can be best discussed when static or dynamic measurements are accompanied by data integration in some kind of mathematically formalised or computerised models. In addition, the results drawn by these models can be retro-fed and include concrete guidelines on which experimental work should be geared. We are therefore planning to contribute to this research subject, Systems Biology Approaches, to map the transition from ageing to neurodegeneration. We assume that this research issue will discuss both theoretical and experimental advances.

## CONCEPTS

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1.2 Aging changes in cells, tissues, and organs

1.3 Age causes diseases

1.4 Neurodegeneration

Chapter 2

Materials and Methods

2.1 Databases

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## 1.INTRODUCTION

Aging is the process of growing old. It is a natural and irreversible process. It is the reason for the highest mortality risk. The study of aging is called gerontology. It takes place in different organisms, actually we can see wrinkles in the skin and greying of the hair. It affects our teeth, heart and sexuality. It brings about many diseases and disorders including diabetes, heart problems, digestive issues, and memory loss. The neurodegenerative disorders may also be due to aging to some extent. In skin the signs of aging that include wrinkles, pigmentation and sagging.

Apart from the genetic causes there are environmental factors that cause aging. Aging is a biological process that represents the functional changes in an organism over time. It is a genetically regulated process that responsive to environmental influences. That the human was staying in different environments and in the diet, exercise, past illnesses affect the aging process and more age related changes occur in all tissues of the body and effect the function of body system.

### 1.1 Aging changes in organs, tissues and cells:

All organs begin to lose some functions as you age. Aging changes occur in all body cells, tissues and organs and it changes and affect the functioning of all body systems. There are different type of cells but all have the same basic structures. Tissues are made up of cells, tissues are layers of similar cells that perform a specific function. Different types of tissues group to form organs. All cells experience changes with aging. They become larger less able to divide and multiply. There is increase in pigments and fatty substances inside the cell. Many cells lose their ability to function or begin to function abnormally. Because of cell and tissue changes, your organs also changes as you age. Aging organs slowly lose function. The biggest changes in organ reserve occur in the heart, lungs, kidneys.

In a cellular level, there is cell damage which causes shortening of DNA, triggering apoptosis or programmed cell death. In a normal healthy cell that shortening is prevented by telomeres. Even mitochondria contributes towards ageing. As well as knowing it is a power house of cell, it release oxygen free radical by products during its normal functions. These free radicals cause DNA damage, triggering apoptosis.

Telomeres, the specific DNA- protein structures found at both ends of each chromosome, protect genome from nucleolytic degradation, unnecessary recombination repair, and interchromosomal fusion. Telomeres play a important role in preserving the information in our genome. In cellular aging, ensuring that individual cells live for a certain amount of time before dying. We can see in telomeres are stretches of DNA and protein at the ends of our chromosomes. Each time a cell divides, these stretches naturally get shorter. Once telomere length reaches a particular cut-off point, the cell becomes senescent, meaning that it can no longer divide and will subsequently die.

### 1.2 Age related disease:

Sensory changes after aging in body: Hearing loss and increased cerumen production with aging contribute to difficulty hearing. Over the age of 85 have hearing loss. Visual acuity decreases normally with age. Vestibular function dizziness is common multifactorial geriatric syndrome contributing to falls, vestibular function declines with age. Immunosenescence it is a wide variety of age related changes in the immune system, some mediated by chronic proinflammatory state. There is a decline in B-cell function, a decline in T cell generation, the changes weaken the body's capacity to fight infection. Urologic changes the urinary bladder is often not sterile in older adults but rather is colonized with bacteria not causing infection.

Somatic disease and multiple chronic conditions: Cardiovascular diseases remains the most common cause of death of older adults, it has chronic ischemic heart disease, congestive heart failure, and arrhythmia. Normally aging includes vascular remodeling and vascular stiffness. Atherosclerosis causes inflammation and future vascular changes increasing risk for cardiac events, cerebrovascular events, peripheral vascular disease, cognitive impairment, and other organ damage. Hypertension is the most common chronic disease of older adults, isolated systolic hypertension is particularly common among older adults and associated with mortality even at advanced ages. Diabetes mellitus now a days in every family one or two members are having diabetes. Diabetes remains a strong risk factor for cardiovascular disease at age of old. If sugar level get increases in body means that may cause the damage of any organism in your body.

Psychological and cognitive aging: the cognitive aging is a mild short-term memory loss, word finding difficulty and slower processing speed and normal parts of aging that are often by age 85. Brain aging does not happen at a uniform rate may be protective. Normal cognitive aging does not lead to dementia. Empathy and altruism also may increase with age. Dementia increase with age. It cause the memory loss and judgement. It is a group conditions characterized by impairment of at least two brain functions.

### 1.3 NEURODEGENERATION:

Although systemic diseases have the greatest impact on human health and well-being, a decaying brain is gradually becoming the arbiter of death, which is accompanied by a progressive loss of the essence of being. Nearly all disorders, including neurodegenerative diseases, become more common as people age. Age affects every organ in the body and appears to be partially encoded in a blood-based signature, which is central to neurodegeneration and dementia.

Circulatory factors have been shown to slow down the ageing process and rejuvenate a variety of organs, including the brain. The detection of such causes, as well as a better understanding of their roles, is ushering in a new period of ageing and dementia science. While the oldest old, those over 80 years old, are the fastest growing segment of the population in developed regions, the majority of this growth will come from emerging regions. Despite these gains in life expectancy, Alzheimer's disease (AD) and other neurodegenerative diseases have arguably become the most feared diseases of the elderly. The fact that almost all aged brains exhibit characteristic changes related to neurodegeneration raises the question of whether these hallmarks are minor aspects of brain ageing that have no impact on function or whether they are early warning signs of neurodegenerative diseases. Immune cells and secreted communication factors, which are involved in tissue homeostasis, are likely to play a role in brain ageing and neurodegeneration.

However, recognising and managing the immune response as people age has proved difficult. The brain appears to be vulnerable to both cell-intrinsic and local signals, as well as cues from the systemic environment, in the ageing organism. Animal models show that circulatory system cues can either speed up or slow down aspects of brain ageing and cognitive function. In most of the brains of elderly people who had not been diagnosed with a neurological disorder, population-based autopsy studies regularly confirm the presence of amyloid plaques, neurofibrillary tangles, Lewy bodies, inclusions of TAR DNA-binding protein 43, synaptic dystrophy, neuron death, and brain volume loss. Individuals differ considerably in terms of these characteristics, with certain lesions dominating specific areas of the brain or being limited to certain regions.

It's unclear what causes these lesions, or whether they're precursors to neurodegeneration and disease, or merely the product of brain ageing. Other subcellular structures containing cross-linked proteins, carbohydrates, or lipids accumulate in ageing brains, either in the extracellular space or within glial cells or neuronal cells, in addition to classic protein deposits.

Although most of these mechanisms are poorly understood and their role in neurodegeneration is unknown, it is likely that they have an impact on normal brain function.

#### DATABASES USED:

**GenAge:** GenAge is divided into genes related to longevity and ageing in model organisms and aging-related human genes. Human genes are thus considerably better annotated and include more information. It is a database of genes commonly altered during ageing, drawn from a microarray meta-analysis study and the longevity map, a database of human genetic variants associated with longevity. It is a curated database of genes related to human ageing.

**Panther db:** PANTHER (protein analysis through evolutionary relationships) classified system is a large curated biological database of gene/protein families and their functionally related subfamilies that can be used to classify and identify the function of gene products. Panther is part of the gene ontology reference genome project designed to classify proteins and their genes for high-throughput analysis. Proteins are classified according to family, molecular function, biological function, and pathway. The most important application of Panther db is to accurately infer the function of uncharacterized genes from any organism based on their evolutionary relationships to genes with known functions. It is used to analyze gene expression experiments, and will be able to: Obtain information about a particular gene of interest. Discover protein families and subfamilies, pathways, biological processes, molecular functions and cellular components. Create lists of genes related to a particular protein family/subfamily, molecular function, biological process or pathway. Analyse lists of genes, proteins or transcripts.

GENEONTOLOGY

Unifying Biology

PANTHER

Classification System

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Upload IDs:

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2. Select organism.

3. Select Analysis.

☐ Functional classification viewed in gene list
☒ Functional classification viewed in graphic charts
☐ Bar chart
☒ Pie chart
☐ Statistical overrepresentation test

## RESULTS:

Set of genes related to aging for humans collected from GenAge database

|        |        |        |        |        |        |        |          |       |       |
|--------|--------|--------|--------|--------|--------|--------|----------|-------|-------|
| GHR    | ERCC2  | STAT5B | NGF    | ERBB2  | PDGFRB | BRCA1  | VCP      | TOP2B | TGFB1 |
| GHRH   | ERCC8  | STAT3  | IRS1   | INSR   | EPOR   | PIN1   | POLG     | NFKB1 | ERCC6 |
| SHC1   | WRN    | STAT5A | PTPN1  | NCOR1  | SST    | PTEN   | IGFBP3   | TOP1  | STK11 |
| POU1F1 | LMNA   | NRG1   | IRS2   | NBN    | PRKCD  | CREBBP | HSP90AA1 | RAD51 | EP300 |
| PROP1  | IGF1R  | HDAC3  | AKT1   | JUND   | PPARA  | HIF1A  | NR3C1    | UBE2I | APTX  |
| TP53   | TXN    | GH1    | PIK3CB | IL2    | RET    | UBB    | EGR1     | TNF   | PML   |
| TERC   | KL     | IL7R   | NGFR   | PDGFB  | PLCG2  | RPA1   | VEGFA    | PDPK1 | GSK3B |
| TERT   | E2F1   | IGF1   | HRAS   | EGF    | PEX5   | BLM    | ABL1     | CEBPA | HTT   |
| ATM    | PTPN11 | IGF2   | MYC    | IL2RG  | TCF3   | BCL2   | BRCA2    | CEBPB | PRKCA |
| PLAU   | NFKB2  | INS    | EGFR   | FOS    | PARP1  | S100B  | TOP2A    | MXI1  | SSTR3 |
| HELLS  | SIRT1  | HMGB1  | CDK1   | CDKN2A | ARNTL  | NCOR2  | SERPINE1 |       |       |
| APOC3  | HDAC1  | CCNA2  | TFDP1  | PPP1CA | CLOCK  | SUN1   | SPRTN    |       |       |

|        |        |        |        |          |          |        |        |
|--------|--------|--------|--------|----------|----------|--------|--------|
| EEF2   | HSPA9  | HMGB2  | DDIT3  | DBN1     | HIC1     | BAK1   | RICTOR |
| ERCC3  | GPX1   | MAP3K5 | POLA1  | NOG      | PAPPA    | IGFBP2 | CTF1   |
| TERF1  | GSR    | TAF1   | MAPT   | ELN      | ADCY5    | PYCR1  | TRAP1  |
| PRKDC  | GSS    | LMNB1  | CTGF   | ATR      | PPARGC1A | TP73   | TRPV1  |
| CAT    | GSTA4  | SDHC   | HDAC2  | UCP3     | GPX4     | CNR1   | NFE2L1 |
| ERCC5  | GSTP1  | FOXO4  | MAX    | ZMPSTE24 | UCP1     | NFE2L2 | IFNB1  |
| AR     | MT-CO1 | HESX1  | MXD1   | TP63     | FGF23    | CDKN1A | GDF11  |
| GTF2H2 | HSPD1  | PIK3R1 | MDM2   | UCP2     | EFEMP1   | PDGFRA |        |
| XRCC5  | HSPA1A | BSCL2  | SUMO1  | POLB     | ERCC4    | PIK3CA |        |
| PCNA   | HSPA1B | AGPAT2 | H2AFX  | GCLC     | CETP     | C1QA   |        |
| FEN1   | PCMT1  | BMI1   | HOXB7  | GCLM     | PPARG    | CDKN2B |        |
| FAS    | MAPK8  | EEF1A1 | HOXC4  | SIRT6    | AGTR1    | EIF5A2 |        |
| TERF2  | YWHAZ  | TFAP2A | JAK2   | BUB3     | CISD2    | MIF    |        |
| XRCC6  | PTK2B  | BDNF   | ESR1   | RAE1     | EEF1E1   | DGAT1  |        |
| POLD1  | PTK2   | CREB1  | LEP    | PMCH     | EPS8     | MT1E   |        |
| BAX    | IL7    | ATF2   | LEPR   | MLH1     | KCNA3    | FGF21  |        |
| RB1    | MAPK14 | TBP    | NFKBIA | CSNK1E   | SIRT7    | HTRA2  |        |
| EMD    | FGFR1  | APEX1  | CLU    | STUB1    | SLC13A1  | GSK3A  |        |
| GRB2   | SP1    | HBP1   | MTOR   | PPM1D    | SOCS2    | NUDT1  |        |
| FOXO3  | FLT1   | BUB1B  | GHRHR  | CHEK2    | TPP2     | IKBKB  |        |
| FOXO1  | JUN    | PTGS2  | CTNNB1 | PCK1     | TP53BP1  | SQSTM1 |        |
| HSF1   | MED1   | HSPA8  | PSEN1  | ARHGAP1  | SIRT3    | CDK7   |        |
| MAPK3  | MAPK9  | SIN3A  | DLL3   | CDC42    |          | GRN    |        |
|        | MAPK3  |        |        |          |          |        |        |

Fig

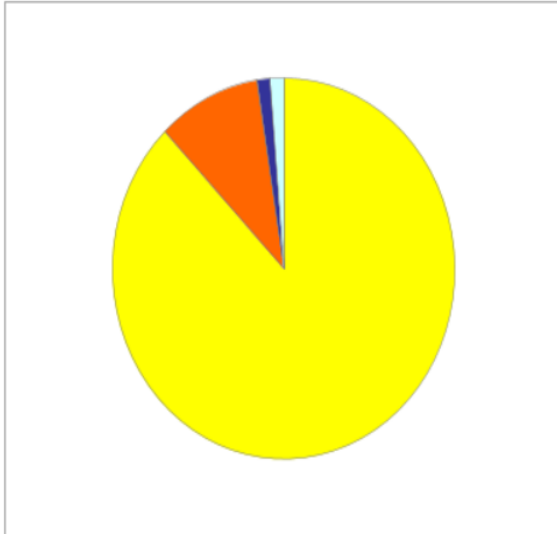
Select Ontology: **Molecular Function** View: **100%**

### PANTHER GO-Slim Molecular Function

Level 1: binding (GO:0005488)

Level 2: organic cyclic compound binding (GO:0097159)

Total # Genes: 82 Total # function hits: 82



\*\*Chart tooltips are read as: Category name (Accession): # genes; Percent of gene hit against total # genes; Percent of gene hit against total # Function hits

Click to get gene list for a category:

- [nucleic acid binding \(GO:0003676\)](#)
- [nucleoside phosphate binding \(GO:1901265\)](#)
- [steroid binding \(GO:0005496\)](#)
- [tetrapyrrole binding \(GO:0046906\)](#)

Color picker powered by Web Colors by VisiBone

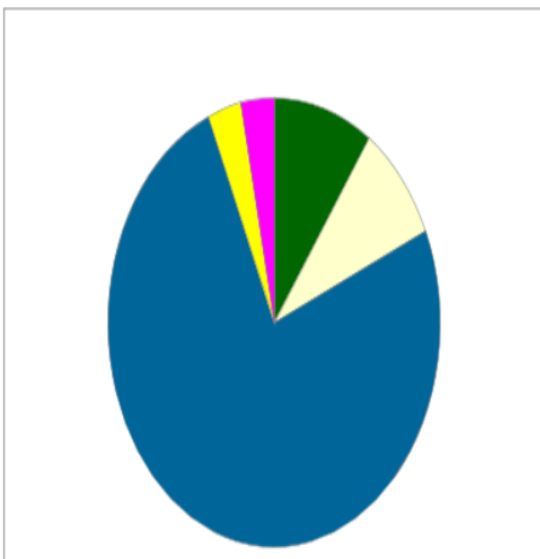
Select Ontology: **Biological Process** View: **100%**

### PANTHER GO-Slim Biological Process

Level 1: cellular process (GO:0009987)

Level 2: cellular metabolic process (GO:0044237)

Total # Genes: 82 Total # process hits: 93



Click to get gene list for a category:

- [DNA biosynthetic process \(GO:0071897\)](#)
- [DNA replication \(GO:0006260\)](#)
- [transcription, DNA-templated \(GO:0006351\)](#)
- [translation \(GO:0006412\)](#)
- [translational elongation \(GO:0006414\)](#)

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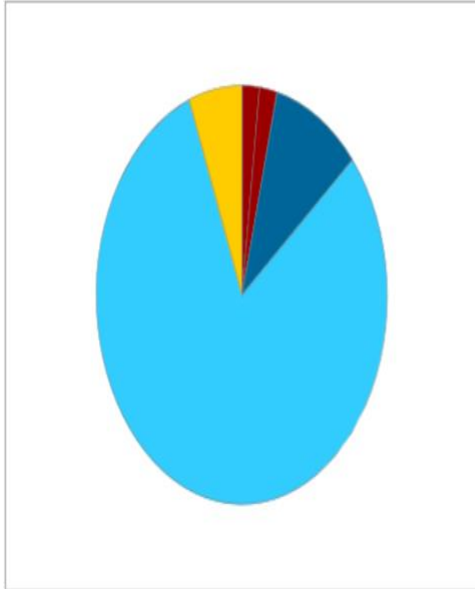
Select Ontology:  View:

### PANTHER GO-Slim Cellular Component

Level 1: cellular anatomical entity (GO:0110165)

Level 2: organelle (GO:0043226)

Total # Genes: 141 Total # component hits: 152



Click to get gene list for a category:

- [endoplasmic reticulum \(GO:0005783\)](#)
- [microbody \(GO:0042579\)](#)
- [mitochondrion \(GO:0005739\)](#)
- [nucleus \(GO:0005634\)](#)
- [vacuole \(GO:0005773\)](#)

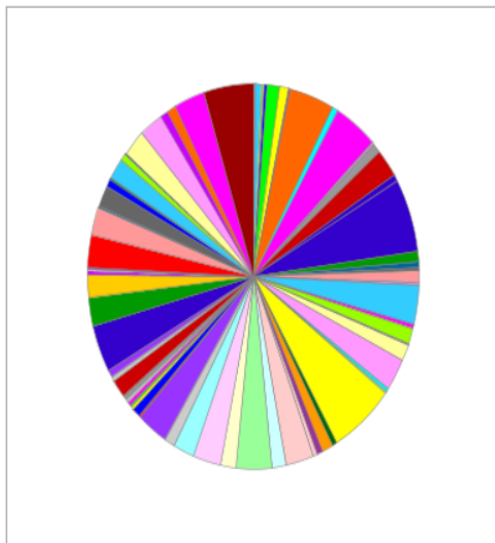
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Select Ontology:  View:

### PANTHER Pathway

Total # Genes: 323 Total # pathway hits: 668



Click to get gene list for a category:

- [5HT1 type receptor mediated signaling pathway \(P04373\)](#)
- [5HT2 type receptor mediated signaling pathway \(P04374\)](#)
- [5HT3 type receptor mediated signaling pathway \(P04375\)](#)
- [5HT4 type receptor mediated signaling pathway \(P04376\)](#)
- [Alpha adrenergic receptor signaling pathway \(P00002\)](#)
- [Alzheimer disease-amyloid secretase pathway \(P00003\)](#)
- [Alzheimer disease-presenilin pathway \(P00004\)](#)
- [Androgen/estrogene/progesterone biosynthesis \(P02727\)](#)
- [Angiogenesis \(P00005\)](#)
- [Angiotensin II-stimulated signaling through G proteins and beta-arrestin \(P05911\)](#)
- [Apoptosis signaling pathway \(P00006\)](#)
- [Axon guidance mediated by Slit/Robo \(P00008\)](#)
- [Axon guidance mediated by netrin \(P00009\)](#)
- [B cell activation \(P00010\)](#)
- [Blood coagulation \(P00011\)](#)
- [CCKR signaling map \(P06959\)](#)
- [Cadherin signaling pathway \(P00012\)](#)
- [Circadian clock system \(P00015\)](#)
- [Cytoskeletal regulation by Rho GTPase \(P00016\)](#)