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HOMOLOGY MODELLING AND SIMULATION STUDY OF PARKIN PROTEIN FROM HOMOSAPIENS

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ABSTRACT

Parkinson's disease (PD) is a slowly progressive disorder that affects movement, muscle control, and balance. It is characterized by the loss of dopaminergic neurons in the substantia nigra and accumulation of Lewy bodies. An early onset form of Parkinson's disease (AR-JP) has been associated with a loss of function mutation in the gene parkin, although in this form Lewy bodies do not accumulate. Mutations in Parkin are a major cause of autosomal recessive juvenile Parkinsonism. Parkin lacks exon 4 which encodes amino acid residues 179 - 206 of Parkin. Tertiary Structure of Parkin protein has not yet been solved. So in our present work we will model the structure of Parkin using Modeller9v1 and Validate the modeled structure by RMSD Calculation using Combinatorial Extension and by plotting the Ramachandran graph using Procheck. Then the modeled structure will be subjected to Molecular Dynamics Studies using GROMACS.

INTRODUCTION

Parkinson's disease (PD) is a slowly progressive disorder that affects movement, muscle control, and balance. Parkinson's disease is referred to as idiopathic, which means that the cause is unknown. This term distinguishes the primary disease from parkinsonism , which are the symptoms occurring from a known cause.[1-6] In addition to its effects on motor control, Parkinson's disease is now recognized as a broader condition that can include cognitive and behavioral disturbances, sleep disorders, speech difficulties, and other problems.
Parkinson's Disease and Dopamine Loss

Parkinson's disease occurs from the following process in the brain:

- PD develops as cells are destroyed in certain parts of the brain stem, particularly the crescent-shaped cell mass known as the substantia nigra .

Parkinson's disease is a slowly progressive disorder that affects movement, muscle control, and balance. Part of the disease process develops as cells are destroyed in certain parts of the brain stem, particularly the crescent-shaped cell mass known as the substantia nigra.[7-9] Nerve cells in the substantia nigra send out fibers to tissue located in both sides of the brain. There the cells release essential neurotransmitters that help control movement and coordination.

- Nerve cells in the substantia nigra send out fibers to the corpus stratia , gray and white bands of tissue located in both sides of the brain.
- There the cells release dopamine , an essential neurotransmitter (a chemical messenger in the brain). Loss of dopamine in the corpus stratia is the primary defect in Parkinson's disease. [10-12]

Dopamine. Dopamine deficiency is the hallmark feature in PD. It is one of three major neurotransmitters known as catecholamines , which help the body respond to stress and prepare it for the fight-or-flight response. Loss of dopamine negatively affects the nerves and muscles controlling movement and coordination, resulting in the major symptoms characteristic of Parkinson's disease.[13-15] Dopamine also appears to be important for

efficient information processing, and deficiencies may also be responsible for problems in memory and concentration that occur in many patients.

Although it is clear that dopamine deficiency is the primary defect in Parkinson's disease, it is not clear what causes dopamine loss.[16-19] The culprit is less likely to be a single cause than a combination of genetic and biologic factors, which are triggered by some environmental assault.

MATERIALS AND METHODS

4.1. MATERIALS:

This section describes the tools and databases used in due course of the project work.

4.2. DESCRIPTION OF DATABASES USED:

NCBI

Website: www.ncbi.nlm.nih.gov

Biology today is being transformed by an explosive growth of data emerging from laboratories worldwide. [20-23]The challenge is to transform data into knowledge, knowledge that will lead to a better understanding of the biological processes underlying both health and disease. The quest for this knowledge drives NCBI investigators to develop new methods for integrative, computer-based data analysis to mine massive and complex datasets.

4.3. DESCRIPTION OF TOOLS USED:

Basic Local Alignment Search Tool (BLAST)

Website: www.ncbi.nlm.nih.gov/blast

The discovery of sequence homology to a known protein or family of proteins often provides the first clues about the function of a newly sequenced gene. As the DNA and amino acid sequence databases continue to grow in size they [24-29]become increasingly useful in the analysis of newly sequenced genes and proteins because of the greater chance of finding such homologies.

4.4. METHODS

4.4.1. STEPS IN HOMOLOGY MODELING

1. Identify a template protein for the target sequence (Sequence of the protein for which the structure is not present in Protein Data Bank.
1. Domain search was done using Pfam.
2. Alignment between the target and template sequence was done by using the malign.py program of Modeller9v1 package.
3. Tertiary structure of the target sequence is modeled using the model-default.py program of Modeller9v1 package.
4. Modelled Structure was validated by

   4.1 Calculating the Root Mean Square Deviation (RMSD) value between the target and the template. RMSD calculation between the target and template will help us identify the deviation between the target structure and the template structure.

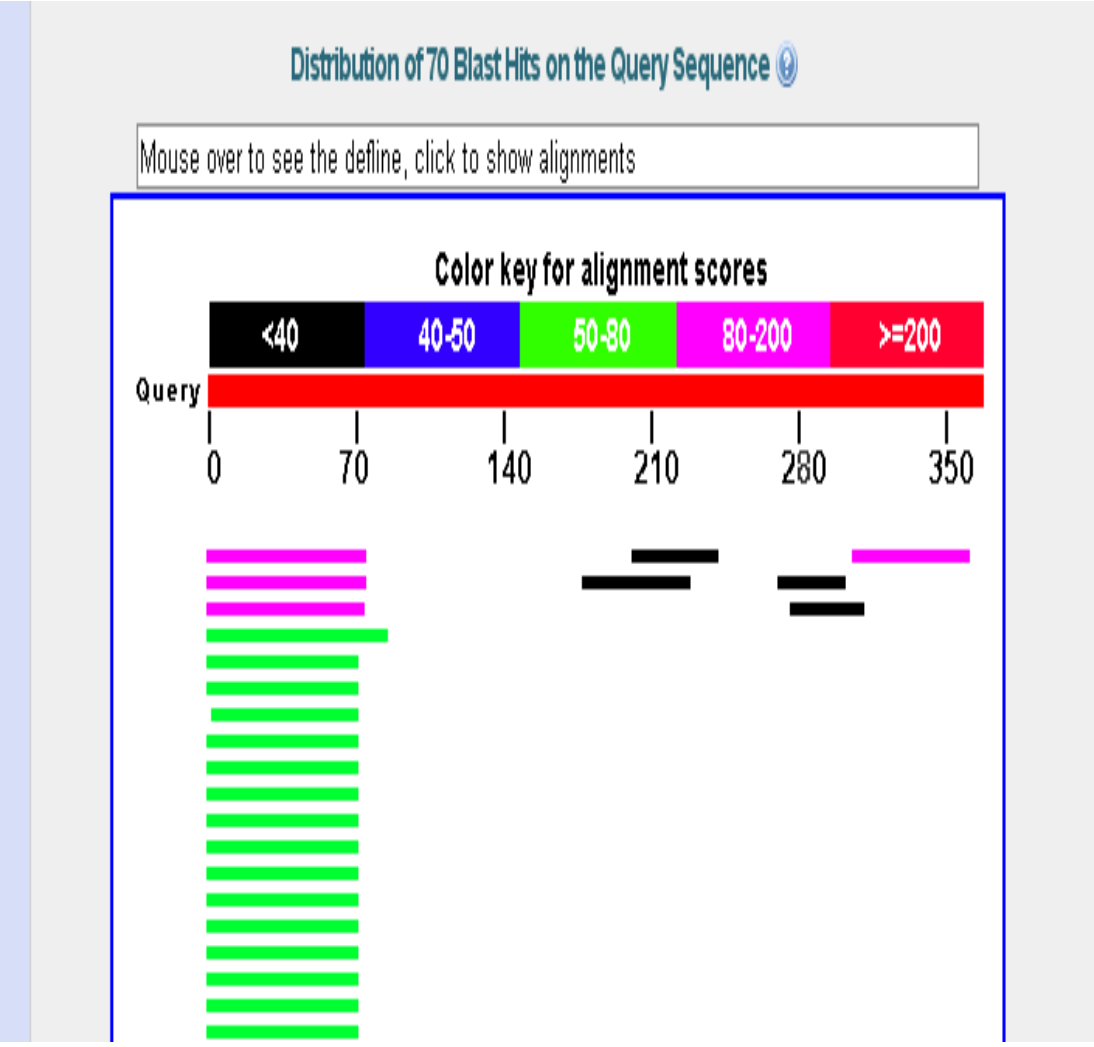
   4.2 Plotting the Ramachandran Plot. [30-34]

5.RESULTS & DISCUSSION

TARGET PROTEIN ID

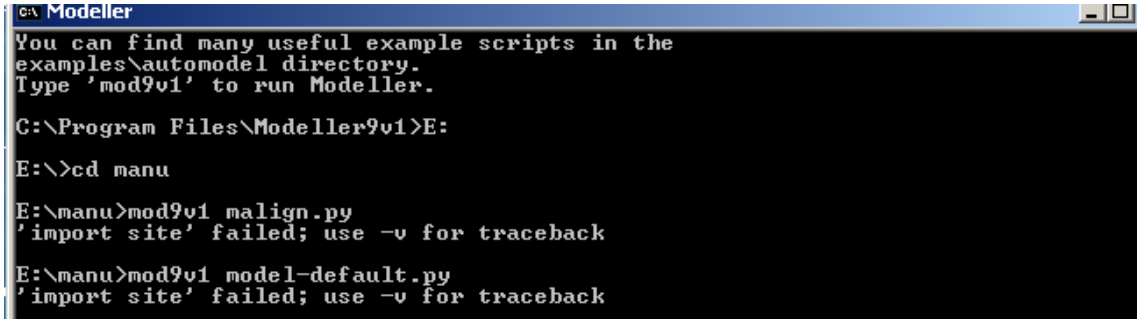
```
FEATURES             Location/Qualifiers
     source          1..368
                     /organism="Homo sapiens"
                     /db_xref="taxon:9606"
                     /chromosome="6"
                     /map="q25.3-27"
                     /clone="RP1-45F6"
                     /clone_lib="RPCI-1"
     Protein         1..368
                     /product="Parkinson disease (autosomal recessive,
                     juvenile) 2, parkin"
     Region          3..72
                     /region_name="parkin_N"
                     /note="parkin_N  parkin protein is a RING-type E3
                     ubiquitin ligase with an amino-terminal ubiquitin-like
                     (Ubl) domain and an RBR signature consisting of two RING
                     finger domains separated by an IBR/DRIL domain.  Naturally
                     occurring mutations in parkin are...; cd01798"
                     /db_xref="CDD:29200"
     Site            42
                     /site_type="other"
                     /note="Arg42Pro mutation site"
                     /db_xref="CDD:29200"
     CDS             1..368
                     /gene="PARK2"
                     /locus_tag="KB-152G3.1-002"
                     /standard_name="OTTHUMP00000017563"

ORIGIN
        1 mivfvrfnss hgfpvevdsd tsifqlkevv akrqgvpadq lrvifagkel rndwtvqncd
       61 ldqqsivhiv qrpwrkgqem natggddprn aaggcerepq sltrvdlsss vlpgdsvgla
      121 vilhtdsrkd sppagspagr siynsfyvyc kgpcqrvqpg klrvqcstcr qatltltqgp
      181 scwddvlipn rmsgecqsph cpgtsaefff kcgahptsdk etsvalhlia tnsrnitcit
      241 ctdvrspvlv fqcnsrhvic ldcfhlycvt rlndrqfvhd pqlgyslpcv agcpnslike
```

TARGET PROTEIN INFORMATION



5.1. SIMILARITY ANALYSIS- BLAST RESULT

5.2. C-MODELLER FILES:



Modeller9v1

Fig.1. MODELED STRUCTURE OF PARKIN

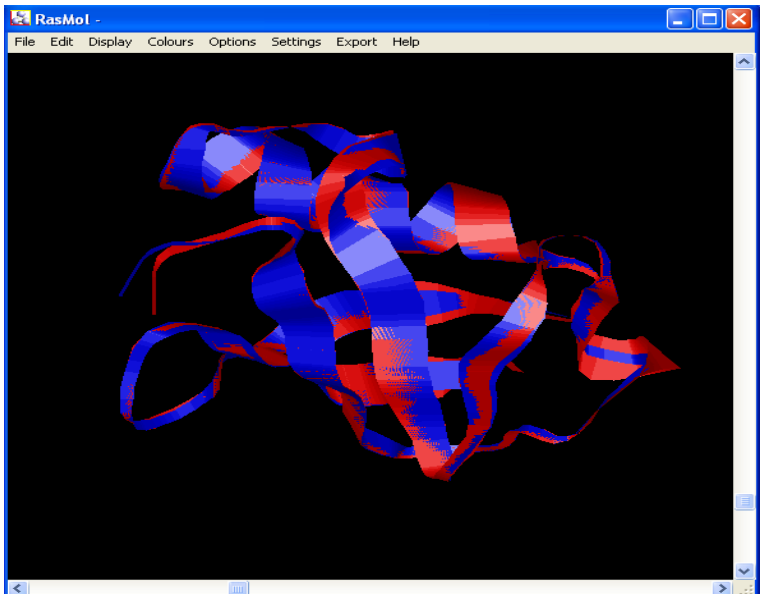
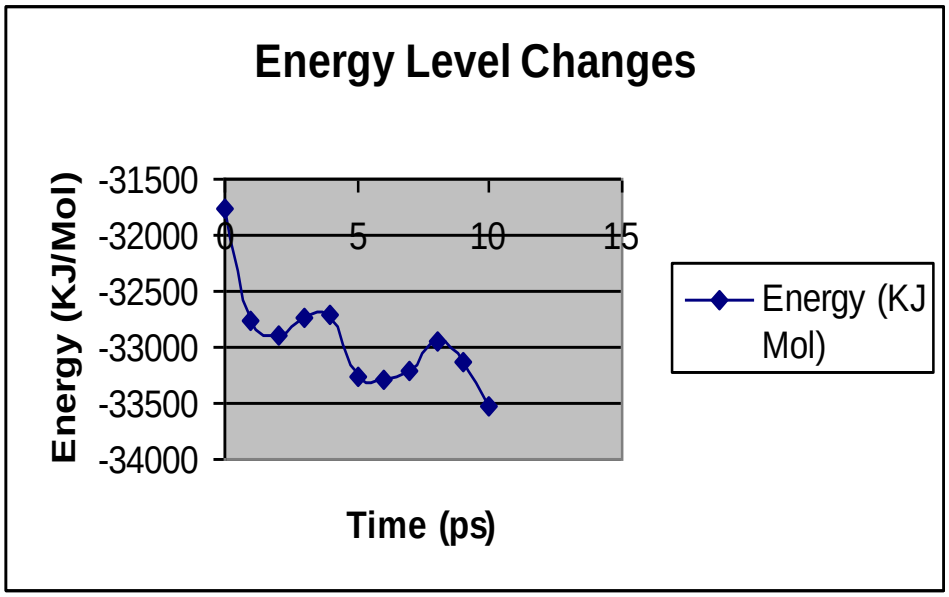


Fig.2. SUPERIMPOSED STRUCTURE

G ENERGY – ENERGY CALCULATION

Time (.ps)	Energy (KJ Mol)
0	-31760.74564
1	-32756.64619
2	-32894.6459
3	-32749.19219
4	-32712.68521
5	-33263.14878
6	-33285.78755
7	-33198.75356
8	-32957.94619
9	-33133.02631
10	-33526.49231

ENERGY VALUES



5.5. ENERGY GRAPH

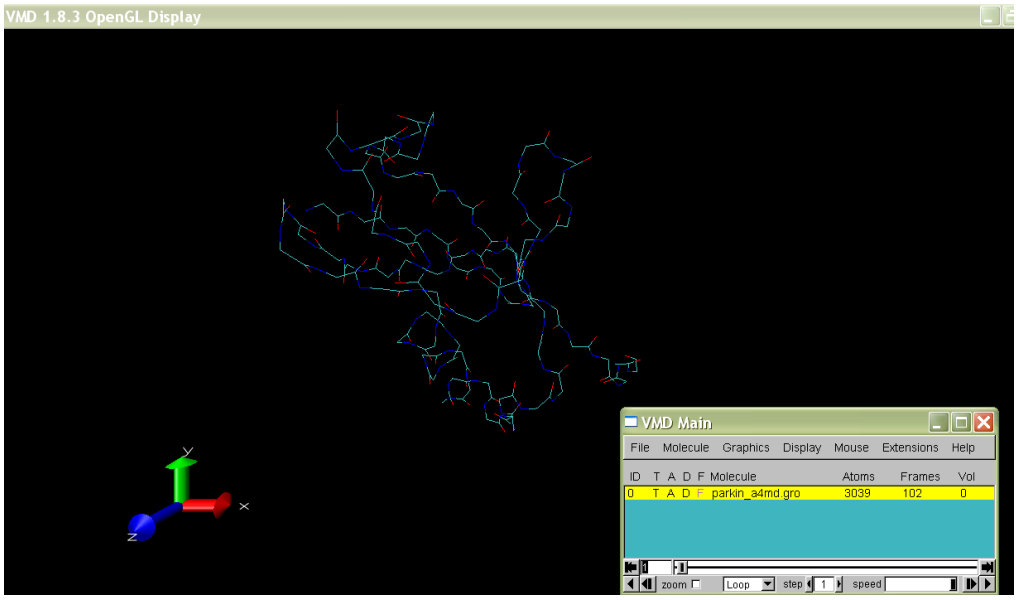


Fig.5. MOLECULE VISUALIZED AT 1 PICO SEC

DISCUSSION

The protein sequence of *parkin* sequence was obtained from GenBank. Domain analysis against Pfam database suggests the presence of a ubiquitin family sequence from 8 to 76. Modeling template was searched by using PBLAST. BLAST suggests 2ZEQ (PDB ID) as a template with a identity of 89%. Molecular structure of Parkin from *Homo sapiens* was modeled by using MODELLER 9v1. Molecular Dynamics Simulation was performed with GROMACS to obtain the structural information of parkin at 310.15 K (37°C) in aqueous environment. Parkin was simulated with the OPLS all-atom force field with the GROMACS molecular dynamics package. Energy minimization was performed to remove the overlapping atoms. Simulated structure was used to study the energy level changes. The values were recorded and graph was plotted. [36-45]

CONCLUSION

Parkin is the protein which may be the cause of Parkinson's disease (PD) in humans.The protein is involved in ubiquitin-proteasome system for the clearance of misfolded proteins and other target molecules. It also serves as the E3 enzyme in the system.Parkin codes for parkin 2 gene and the mutations caused in this gene causes the parkinsons disease .the structutre is modeled for parkin and validation of the modeled structure suggests that the modeled structure is a good model. Molecular Dynamics Simulation study of parkin suggest that the energy is getting minimized from initial structure to the simulated structure. The simulated structure is visualized and the changes in the protein structure at different picoseconds are noted .Further molecular dynamics study of the parkin protein at different temperature will help us in understanding its influence in parkinsons disease.

REFERENCES:

1. Nimal, R.J.G.R., Hussain, J.H., Effect of deep cryogenic treatment on EN24 steel, International Journal of Pure and Applied Mathematics, V-116, I-17 Special Issue, PP-113-116, 2017
2. Parameswari, D., Khanaa, V., Deploying lamport clocks and linked lists, International Journal of Pharmacy and Technology, V-8, I-3, PP-17039-17044, 2016
3. Parameswari, D., Khanaa, V., Case for massive multiplayer online role-playing games, International Journal of Pharmacy and Technology, V-8, I-3, PP-17404-17409, 2016
4. Parameswari, D., Khanaa, V., Deconstructing model checking with hueddot, International Journal of Pharmacy and Technology, V-8, I-3, PP-17370-17375, 2016
5. Parameswari, D., Khanaa, V., The effect of self-learning epistemologies on theory, International Journal of Pharmacy and Technology, V-8, I-3, PP-17314-17320, 2016
6. Pavithra, J., Peter, M., GowthamAashirwad, K., A study on business process in IT and systems through extranet, International Journal of Pure and Applied Mathematics, V-116, I-19 Special Issue, PP-571-576, 2017
7. Pavithra, J., Ramamoorthy, R., Satyapira Das, S., A report on evaluating the effectiveness of working capital management in googolsoft technologies, Chennai, International Journal of Pure and Applied Mathematics, V-116, I-14 Special Issue, PP-129-132, 2017
8. Pavithra, J., Thooyamani, K.P., A cram on consumer behaviour on Mahindra two wheelers in Chennai, International Journal of Pure and Applied Mathematics, V-116, I-18 Special Issue, PP-55-57, 2017
9. Pavithra, J., Thooyamani, K.P., Dkhar, K., A study on the air freight customer satisfaction, International Journal of Pure and Applied Mathematics, V-116, I-14 Special Issue, PP-179-184, 2017
10. Pavithra, J., Thooyamani, K.P., Dkhar, K., A study on the working capital management of TVS credit services limited, International Journal of Pure and Applied Mathematics, V-116, I-14 Special Issue, PP-185-187, 2017
11. Pavithra, J., Thooyamani, K.P., Dkhar, K., A study on the analysis of financial performance with reference to Jeppiaar Cements Pvt Ltd, International Journal of Pure and Applied Mathematics, V-116, I-14 Special Issue, PP-189-194, 2017
12. Peter, M., Dayakar, P., Gupta, C., A study on employee motivation at Banalari World Cars Pvt Ltd Shillong, International Journal of Pure and Applied Mathematics, V-116, I-18 Special Issue, PP-291-294, 2017
13. Peter, M., Kausalya, R., A study on capital budgeting with reference to signware technologies, International Journal of Pure and Applied Mathematics, V-116, I-18 Special Issue, PP-71-74, 2017
14. Peter, M., Kausalya, R., Akash, R., A study on career development with reference to premheerasurgicals, International Journal of Pure and Applied Mathematics, V-116, I-14 Special Issue, PP-415-420, 2017

15. Peter, M., Kausalya, R., Mohanta, S., A study on awareness about the cost reduction and elimination of waste among employees in life line multispeciality hospital, International Journal of Pure and Applied Mathematics, V-116, I-14 Special Issue, PP-287-293, 2017
16. Peter, M., Srinivasan, V., Vignesh, A., A study on working capital management at deccan Finance Pvt Limited Chennai, International Journal of Pure and Applied Mathematics, V-116, I-14 Special Issue, PP-255-260, 2017
17. Peter, M., Thooyamani, K.P., Srinivasan, V., A study on performance of the commodity market based on technicalanalysis, International Journal of Pure and Applied Mathematics, V-116, I-18 Special Issue, PP-99-103, 2017
18. Philomina, S., Karthik, B., Wi-Fi energy meter implementation using embedded linux in ARM 9, Middle - East Journal of Scientific Research, V-20, I-12, PP-2434-2438, 2014
19. Philomina, S., Subbulakshmi, K., Efficient wireless message transfer system, International Journal of Pure and Applied Mathematics, V-116, I-20 Special Issue, PP-289-293, 2017
20. Philomina, S., Subbulakshmi, K., Ignition system for vechiles on the basis of GSM, International Journal of Pure and Applied Mathematics, V-116, I-20 Special Issue, PP-283-286, 2017
21. Philomina, S., Subbulakshmi, K., Avoidance of fire accident by wireless sensor network, International Journal of Pure and Applied Mathematics, V-116, I-20 Special Issue, PP-295-299, 2017
22. Pothumani, S., Anuradha, C., Monitoring android mobiles in an industry, International Journal of Pure and Applied Mathematics, V-116, I-20 Special Issue, PP-537-540, 2017
23. Pothumani, S., Anuradha, C., Decoy method on various environments - A survey, International Journal of Pure and Applied Mathematics, V-116, I-10 Special Issue, PP-197-199, 2017
24. Pothumani, S., Anuradha, C., Priya, N., Study on apple iCloud, International Journal of Pure and Applied Mathematics, V-116, I-8 Special Issue, PP-389-391, 2017
25. Pothumani, S., Hameed Hussain, J., A novel economic framework for cloud and grid computing, International Journal of Pure and Applied Mathematics, V-116, I-13 Special Issue, PP-5-8, 2017
26. Pothumani, S., Hameed Hussain, J., A novel method to manage network requirements, International Journal of Pure and Applied Mathematics, V-116, I-13 Special Issue, PP-9-15, 2017
27. Pradeep, R., Vikram, C.J., Naveenchandra, P., Experimental evaluation and finite element analysis of composite leaf spring for automotive vehicle, Middle - East Journal of Scientific Research, V-12, I-12, PP-1750-1753, 2012
28. Pradeep, R., Vikram, C.J., Naveenchandran, P., Experimental evaluation and finite element analysis of composite leaf spring for automotive vehicle, Middle - East Journal of Scientific Research, V-17, I-12, PP-1760-1763, 2013

29. Prakash, S., Jayalakshmi, V., Power quality improvement using matrix converter, International Journal of Pure and Applied Mathematics, V-116, I-19 Special Issue, PP-95-98, 2017
30. Prakash, S., Jayalakshmi, V., Power quality analysis & power system study in high voltage systems, International Journal of Pure and Applied Mathematics, V-116, I-19 Special Issue, PP-47-52, 2017
31. Prakash, S., Sherine, S., Control of BLDC motor powered electric vehicle using indirect vector control and sliding mode observer, International Journal of Pure and Applied Mathematics, V-116, I-19 Special Issue, PP-295-299, 2017
32. Prakesh, S., Sherine, S., Forecasting methodologies of solar resource and PV power for smart grid energy management, International Journal of Pure and Applied Mathematics, V-116, I-18 Special Issue, PP-313-317, 2017
33. Prasanna, D., Arulselvi, S., Decoupling smalltalk from rpcs in access points, International Journal of Pure and Applied Mathematics, V-116, I-16 Special Issue, PP-1-4, 2017
34. Prasanna, D., Arulselvi, S., Exploring gigabit switches and journaling file systems, International Journal of Pure and Applied Mathematics, V-116, I-16 Special Issue, PP-13-17, 2017
35. Prasanna, D., Arulselvi, S., Collaborative configurations for wireless sensor networks systems, International Journal of Pure and Applied Mathematics, V-116, I-15 Special Issue, PP-577-581, 2017
36. Priya, N., Anuradha, C., Kavitha, R., Li-Fi science transmission of knowledge by way of light, International Journal of Pure and Applied Mathematics, V-116, I-9 Special Issue, PP-285-290, 2017
37. Priya, N., Pothumani, S., Kavitha, R., Merging of e-commerce and e-market-a novel approach, International Journal of Pure and Applied Mathematics, V-116, I-9 Special Issue, PP-313-316, 2017
38. Raj, R.M., Karthik, B., Effective demining based on statistical modeling for detecting thermal infrared, International Journal of Pure and Applied Mathematics, V-116, I-20 Special Issue, PP-273-276, 2017
39. Raj, R.M., Karthik, B., Energy sag mitigation for chopper, International Journal of Pure and Applied Mathematics, V-116, I-20 Special Issue, PP-267-270, 2017
40. Raj, R.M., Karthik, B., Efficient survey in CDMA system on the basis of error revealing, International Journal of Pure and Applied Mathematics, V-116, I-20 Special Issue, PP-279-281, 2017
41. Rajasulochana, P., Krishnamoorthy, P., Ramesh Babu, P., Datta, R., Innovative business modeling towards sustainable E-Health applications, International Journal of Pharmacy and Technology, V-4, I-4, PP-4898-4904, 2012
42. Rama, A., Nalini, C., Shanthi, E., An iris based authentication system by eye localization, International Journal of Pharmacy and Technology, V-8, I-4, PP-23973-23980, 2016

43. Rama, A., Nalini, C., Shanthi, E., Effective collaborative target tracking in wireless sensor networks, International Journal of Pharmacy and Technology, V-8, I-4, PP-23981-23986, 2016
44. Ramamoorthy, R., Kanagasabai, V., Irshad Khan, S., Budget and budgetary control, International Journal of Pure and Applied Mathematics, V-116, I-20 Special Issue, PP-189-191, 2017
45. Ramamoorthy, R., Kanagasabai, V., Jivandan, S., A study on training and development process at Vantec Logistics India Pvt Ltd, International Journal of Pure and Applied Mathematics, V-116, I-14 Special Issue, PP-201-207, 2017