Research in Basal Ganglia and Parkinson's disease

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The CNS Lab is involved in developing systems-level models of various crucial brain systems. Their approach to brain modeling is based on a unique vision articulated here: (https://biotech.iitm.ac.in/Faculty/CNS_LAB/vision.html)

Research on the Basal Ganglia and Parkinson's Disease:

For the last 15 years, the CNS Lab has been developing a comprehensive, computational model of a brain region called **Basal Ganglia** (BG). Loss of cells in a part of BG leads to **Parkinson's disease**. The BG system has contributions to all major domains of brain function – sensory-motor, cognitive, affective and autonomous. In each of these domains, the BG has diverse roles.

Researchers have proposed different computational models for different functions but there is no consensus among the models. Taking **an important departure from the classical, textbook description of the functional anatomy of BG**, the CNS Lab was able to **model a wide range of motor functions of BG**. These results were worked out over **30 journal papers and 3 book chapters**, one of them being **an invited contribution to Encyclopedia of Computational Neuroscience from Springer. Their research in consolidated in a book form:**

Book:
Chakravarthy, V. S., & Moustafa, A. A. (2018). *Computational Neuroscience Models of the Basal Ganglia*. Springer Singapore. https://www.springer.com/gp/book/9789811084935

Model-based Clinical Applications for PD:

Based on the modeling work done so far it is possible to develop a range of clinical applications for PD.

1. **Simulators for the action of PD Drug L Dopa:**
   Currently there is an effort world over to develop large scale simulators of drug action to understand the link between the drug action and the relief symptoms. The emerging field of Computational Neuropharmacology deals with large multi-scale models that link drug action and symptoms. Big pharma companies are investing in creation of such simulators since they can save expense and time and minimize the role of expensive animal and clinical trials for validation of a drug molecule.
   The CNS Lab had developed one such simulator for relating L Dopa dosage and the ON/OFF periods of a PD patient.

   Nair, S. S., Muddapu, V. R., & Chakravarthy, V. S. (2022). A Multiscale, Systems-Level, Neuropharmacological Model of Cortico-Basal Ganglia System for Arm Reaching Under Normal, Parkinsonian, and Levodopa Medication Conditions. *Frontiers in computational neuroscience*, 122.

   Patenting:
   A national patent was filed for this model with plans pending for international filing.

2. **Deep Brain Stimulation for PD:**
   Deep Brain stimulation is one of the preferred therapies for late stage PD when the patient shows poor response to medication. However, the parameters of stimulation protocol – site of location, current amplitude, pulse frequency etc - are empirically determined by trial and error. The CNS Lab developed a computational model that simulates the effect of DBS on decision making.

   Mandali, A., Chakravarthy, V. S., Rajan, R., Sarma, S., & Kishore, A. (2016). Electrode position and current amplitude modulate impulsivity after subthalamic stimulation in parkinsons disease—a computational study. *Frontiers in physiology*, *7*, 585.

3. **A quantitative Diagnostic System for PD:**

   For PD diagnostics, the current Unified Parkinson's Disease Rating Scale (UPDRS) system, though numerical, suffers from subjectivity since the scores used in this system are mostly based on direct observation (Ramaker et al., 2002). On the other contrary, a direct measurement of physiological parameters using the necessary equipment will be more reliable.
   Although there have been efforts to extract such quantitative biomarkers for PD, most efforts of that kind have been piecemeal where focus is only on one aspect in a given

research study. However, such partial approach is inadequate in a clinical setting since a given PD patient may not have all the symptoms. A comprehensive system of symptom measurement and characterization is essential to understand the level of severity of various symptoms.

We propose to develop QUADiS-PD, a smart-phone based diagnostic system for PD that acquires clinical data from the following tasks and extracts biomarkers. The developed system is tested on existing PD databases.

1. Reaching movements of the hand
2. Handwriting
3. Speech
4. Eye movements
5. Gait
6. Decision making using gambling task (IGT)

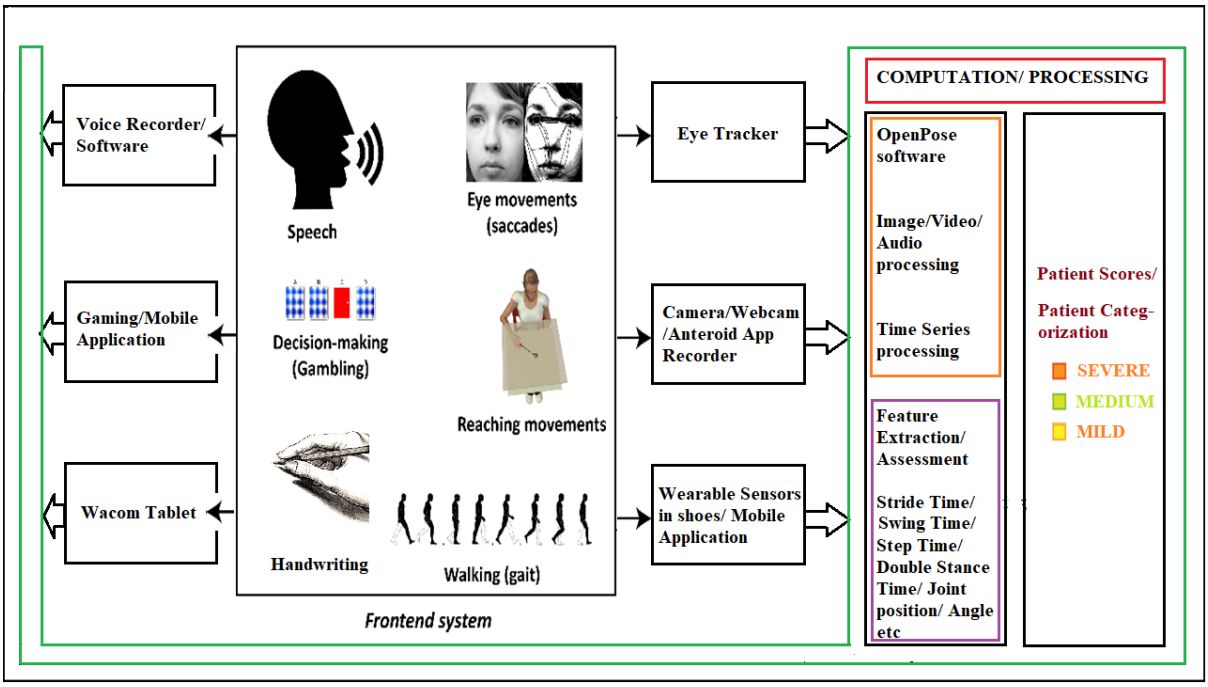

Figure 1: A schematic of the proposed comprehensive diagnostic system for Parkinson's disease

Nair, S. S., Muddapu, V. R. J., Sriram, M., Aditya, R., Gupta, R., & Chakravarthy, VS. (2022). Is There a Better Way to Assess Parkinsonian Motor Symptoms?—Experimental and Modelling Approach. In *Techniques for Assessment of Parkinsonism for Diagnosis and Rehabilitation* (pp. 151-167). Springer, Singapore.

4. **Model based therapeutics for PD:**
The ultimate goal of the CNSLab is to develop model-based therapeutics for PD (figure 2).

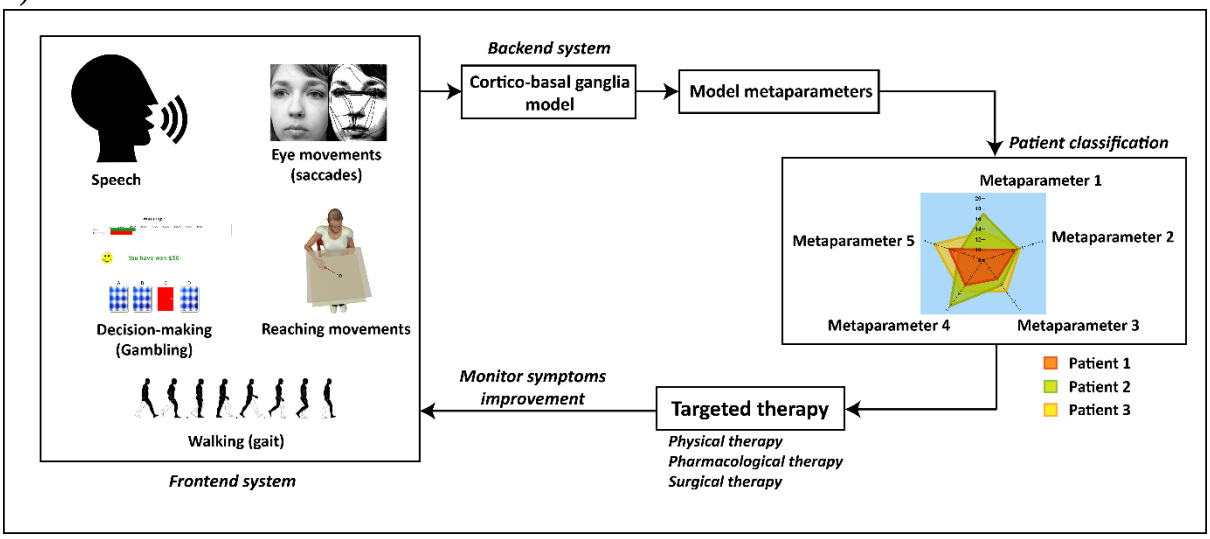

Figure 2: A schematic flowchart of the model-based therapeutic management of PD. The subjects are tested on different tasks to evaluate the disease condition, and the model is optimized so as to capture the performance of the subjects. The model meta parameters when instantiated in a model of BG, then provide a quantitative profile of the individual patient. The intended treatment procedures for that patient are first simulated on the model. Only the best combinations of treatment as demonstrated with the model are delivered to the real patient.

Budget:

The CNS Lab is seeking support from the IITM Alumni to take the above line of work to full fruition. A Ph D stipend of Rs 5 L / year is needed per student for a few Ph D scholars

This can also be in the form of an endowment of 1.05 Cr where 5 L is for the first year and endowment interest will support the stipend payments in future years.