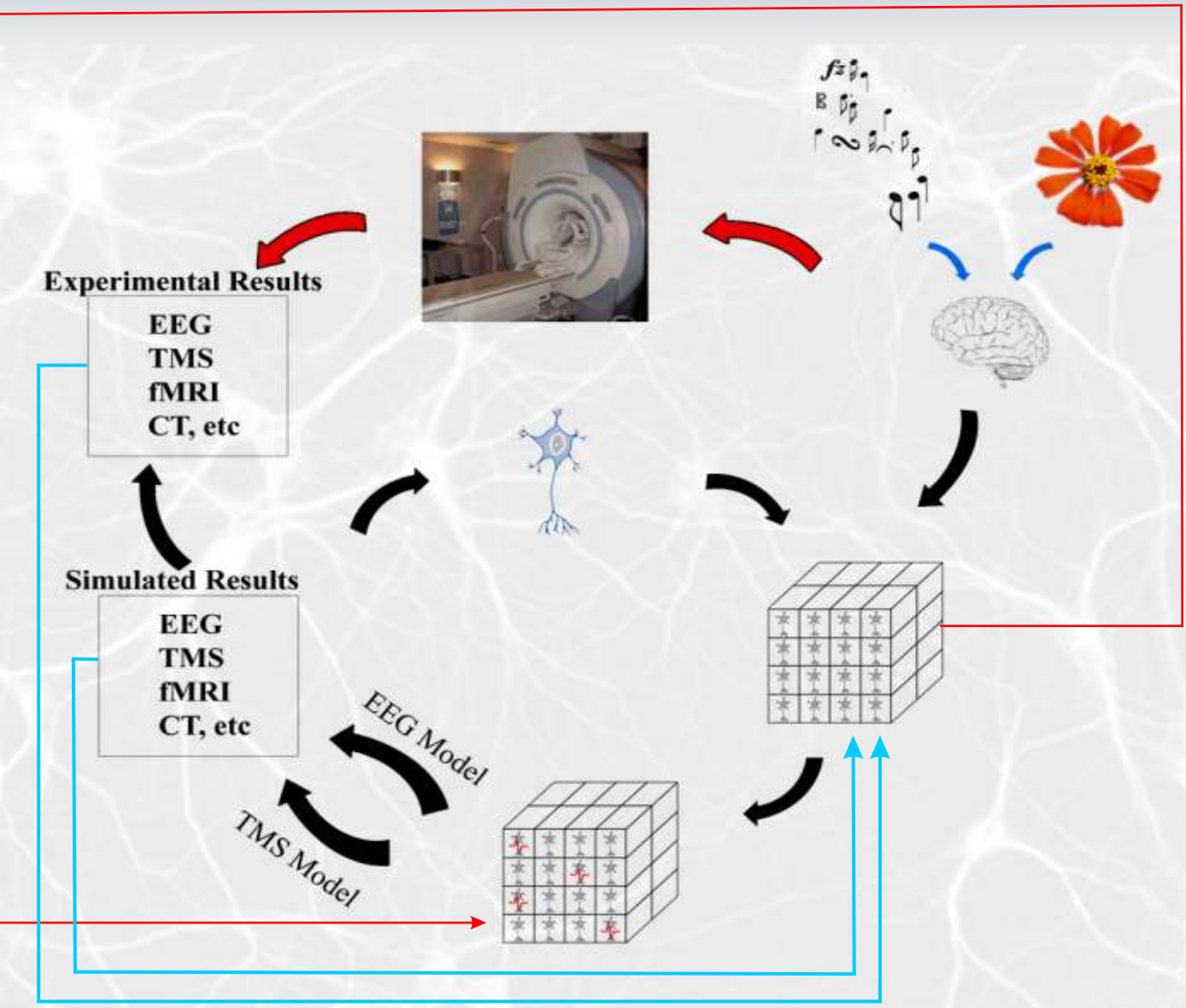
PRADHĪKALANĀ



WARFT

REGION-SPECIFIC NEURONAL INTERCONNECTIVITY PREDICTION FOR EFFECTIVE DRUG DESIGN : An Inter-disciplinary Research Initiative Towards Combating Human Brain Diseases

The research focus at Waran Research FoundaTion (WARFT) is to drive progress in the discovery of brain related drugs. This effort requires inter and multi-disciplinary research initiatives and enormous resources. Thus, WARFT conducts research through its seven research groups - Charaka, Vishwakarma, Marconi, Ramanujan, Hardy, Naren and Bhaskara. These research groups conduct unique research with active interaction between them.

Though clinical experimentation is a must in designing the drugs, neuronal network based simulations needs to be performed to speed up the clinical process of exactly fixing up of the composition of the drugs. For drug design, testing of such drugs including their side effects, knowledge of large scale biologically realistic neuronal interconnectivity specific to a brain region is essential. Further biological modeling of brain diseases essentially needs the interconnectivity pattern across the neuronal structure. Clinical research will be more efficient if predictive methods are evolved to use experimental data to arrive at possible faults characterizing a disease. This interconnectivity prediction is bound to help the clinical researchers while drawing in their data and expertise.

Multi MIllion Neuron interconnectivity - Dendrite Axon Soma and Synapse (MMINi-DASS) - the flagship project of WARFT, belonging to CHARAKA group, endeavors to facilitate discovery of brain drugs through a systematic and detailed models of single neurons and neuronal interconnectivity prediction of specific regions of the brain. The MMINi-DASS project upon completion will assist clinical research in order to expedite drug discovery.

Large scale neuronal network simulations of the proposed magnitude require massive computing resources that not just gives competent peak performances on benchmark tests, but also perform efficiently and cost-effectively for a real world application. WARFT is developing a novel node architecture design, the MIP SCOC (Memory In Processor SuperComputer On Chip) to achieve Exaop performance at the cluster level. The CHARAKA and VISHWARKARMA(high performance computing) groups work in tandem to achieve WARFT's research goal of facilitating drug discovery for the brain.

THE MMINi-DASS PROJECT : Neuronal Interconnectivity Prediction

The MMINi-DASS project is a large-scale brain simulation carried out to predict interconnectivity of a specific brain region and makes use of fMRI BOLD response of various brain regions. This results in understanding of brain dynamics from the most fundamental level to cognitive and behavioral aspects. Modeling individual brain entities is in itself a challenging task. Predicting their interconnectivity through simulation requires enormous computing power and thus, the project banks on the exponentially increasing computing power and its decreasing cost.
The aim is to generate biological neuronal networks (using biologically realistic models for the Dendrite, Axon, Soma and Synapse and other large number of entities) from which the state and dynamics are extracted. This is then linked with a model of blood flow dynamics to simulate Blood Oxygen Level Dependent (BOLD) response. The simulated BOLD map is correlated with a BOLD map generated by experiments. Based on the level of correlation between the maps, large number interdependent bio-physical, bio-chemical, electrical, geometrical parameters driving the network model are temperature scheduled within the simulated annealing loop towards convergence. fMRI recordings are only one of the experimental benchmarks and MMINi-DASS can tune single neurons and networks against other experimental data like electrophysiological and TMS recordings. Another major breakthrough research taken up at WARFT is towards developing energetics based models for the soma, synapse, dendrite and axon. This will highly simplify the modeling of the dynamics between the neuronal spatio-temporal activities and the BOLD.

APPLICATION OF THE MMINi-DASS PROJECT TOWARDS DRUG DISCOVERY

The brain is plagued by myriad of diseases. The difficulty in discovering drugs for such diseases is that drugs work at the molecular level while many brain diseases are cognitive in nature with their root causes not completely understood. For example, we do not know whether the neurofibrillary tangles in Alzheimer's are the cause or a secondary effect of the disease.

Finding out what is precisely wrong in specific brain regions is a monumental task. MMINi-DASS aims to bridge this gap between cognitive / experimental data and molecular-level understanding. It helps drug discovery by deducing detailed faults (both in single neuron and network parameters) in the brain where experimental methods are cumbersome and inefficient. Information about such faults is crucial for drug design. For the project to effectively aid drug discovery, a close interaction with clinical research is required.

MMINi-DASS speeds up drug discovery in the following ways:

- For diseases localized in a brain region, MMINi-DASS can provide specific structural causes of the disease.
- For diseases whose causes are spread throughout the brain, MMINi-DASS can provide clues for further experiment and tuning of existing drugs.

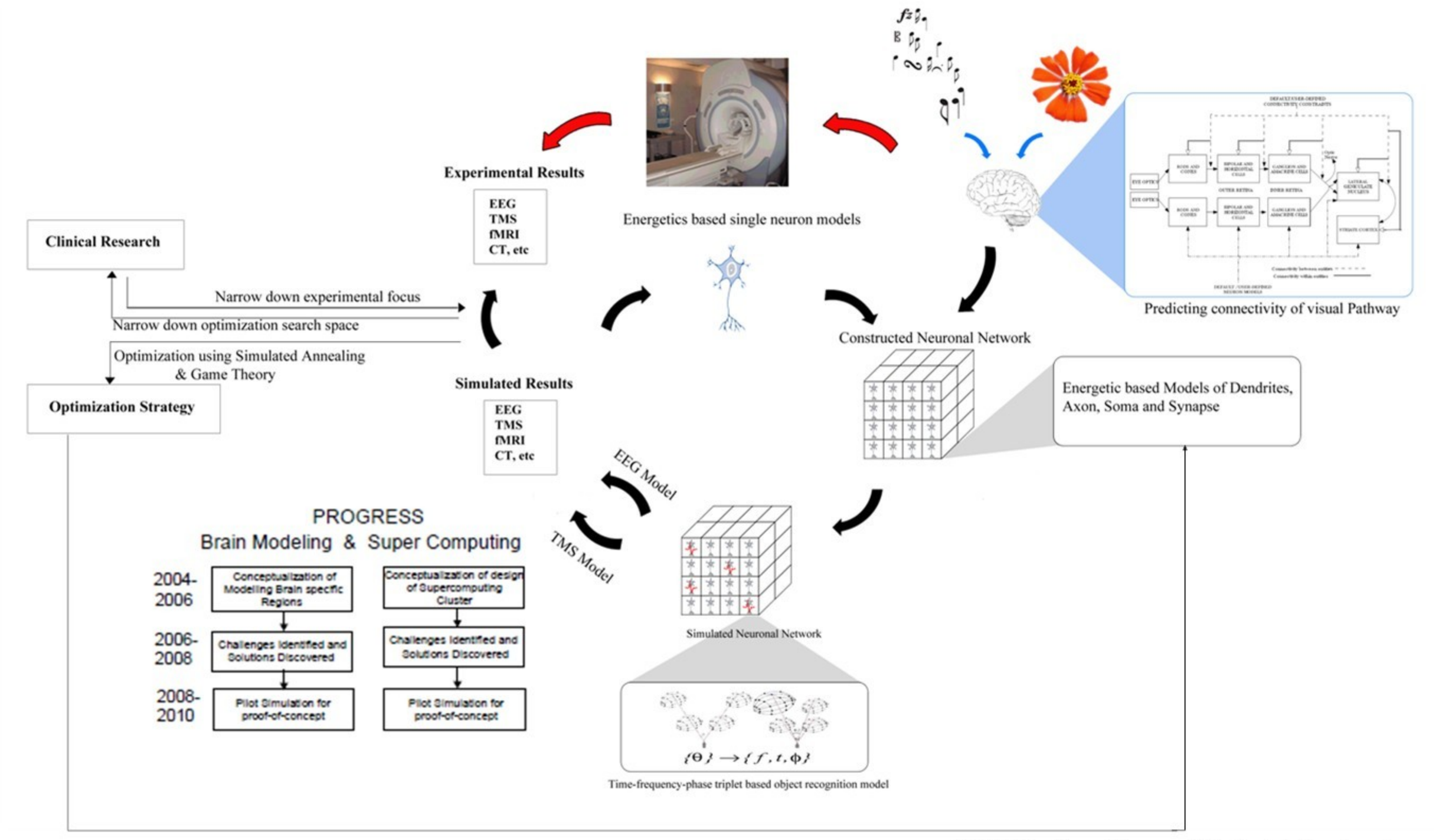
The MMINi-DASS will help model diseases and to predict the impact of a particular drug at the cortical level due to structural changes and molecular level reactions.

PREDICTING INTERCONNECTIVITY OF VISUAL PATHWAY

Encoding and decoding along the visual pathway is a thriving area of research in neuroscience. But there are not many good models to comprehensively explain them in terms of neuronal interconnectivity. The emphasis of this work is on establishing neuronal connectivity of the visual pathway (for encoding) and the striate cortex(for decoding) while drawing important results from relevant existing work. This methodology is a reinforcement of the computational anatomy concept. An adaptation of the MMINi-DASS framework is proposed. The essential idea of the framework is to model the pathway and cortex using computationally attractive single-neuron models and keep the connectivity parameters open to fine-tuning and optimization. The framework allows for elegant analysis of receptive fields that are crucial for vision.

TEMPORAL SYNAPSE MODELS

This research aims to evolve the hypothesis to understand and explain the link between the neuronal dynamics and fMRI-BOLD signal. It makes use of the MMINi-DASS simulator. Various synaptic models are studied and a temporal synaptic model has been developed which is frequency dependent. Astrocytic activity which is crucial in understanding BOLD is also studied at the phenomenological level currently. Local Field Potential which is important in mapping a BOLD map to neuronal interconnectivity is modeled at a phenomenological level. Energetics based synapse model is under development using Petri-nets.



Multi MIllion Neuron interconnectivity - Dendrite Axon Soma Synapse (MMINi-DASS) Prediction Framework

TEMPLATE BASED COMPUTATIONALLY EFFICIENT DENDRITE MODELING : A Simplified Approach

Dendrite trees are built from pre-built template sub-trees. The sub-trees are modeled as RC circuits for which outputs to Green's function are obtained through SPICE circuit simulation. Finally, modulation of input current by a complete dendritic tree is obtained by curve-fitting techniques applied over each sub-tree's response to Green's function. While also providing for quicker simulations, the model also speeds up construction of dendritic trees. Ion channel based dendritic models are under development.

TIME-FREQUENCY-PHASE BASED OBJECT PERCEPTION MODELING

Our perception of space and our ability to use information about the environment to navigate in it constitutes one of the remarkable abilities of the brain. Existing theories of spatial perception indicate that spatial information is represented in two different brain regions - the Hippocampus and the Parietal Lobe. However, a lesser-studied aspect of Spatial Perception is its intricate relation to Object Recognition, how the different representations help in interplay of object information and spatial co-ordinate representation, and whether spatial representation is subjective to or is independent of the object geometry is an area of active research. This work attempts to demystify this process by computational modeling. MMINi-DASS is utilized to model the regions involved in spatial perception and object recognition. This model investigates encoding of objects by the spatio temporal neuronal spike activities in time-frequency-phase domain by studying the characteristics of “dominant harmonics” present in it.

SINGLE-NEURON BOLD

Since a very crude picture has emerged with regard to the correlation between fMRI BOLD and the electrical activity of neurons, this work aims at distilling out the uncertainties through the use of computational modeling. The ultimate purpose behind this is to extract the electrical response from the BOLD response. Numerous attempts to probe into the neuronal basis of fMRI have been made.

This work is unconventional due to two reasons.

-One, here we wish to tackle the problem at the synaptic level instead of relying on an averaged out response from a population of neurons.

-Two, here energetics based neuron model is used.

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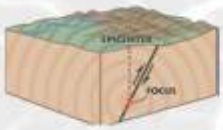
Primary Host Plane



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Secondary Host Plane

MIP Node Plane

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