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Editorial

Neurocomputational models of brain disorders

Recent decades have witnessed dramatic accumulation of knowledge about the genetic, molecular, pharmacological, neurophysiological, anatomical, imaging and psychological characteristics of brain disorders. Despite these advances, however, experimental brain science has offered very little insight into the theoretical framework for integrating neurobiological and psychological data. Surgical treatment of neurological disorders like Parkinson's disease, dystonia and epilepsy were until recently mainly based on applying lesions at specific parts of the brain. While these procedures nowadays have been replaced by more reversible neurostimulation methods, most therapies for brain disorders are still based on trial-and-error and effective mechanisms remain unknown.

The goal of the special issue is to provide insights into neuronal network processes and interactions underlying normal and abnormal behavior based on computational models. These models describe network behavior at a microscopic (cellular) or macroscopic (system) level. The usefulness of the models in understanding neural organization and behavior is emphasized. The neuroanatomical and neurophysiological principles that are included in the models are clearly stated including the simplifications that are adopted. Experimental data is presented that form the basis for the acceptance of the model and its reductions both in describing normal and abnormal behavior.

The special issue starts with a paper by **Traub, Cunningham and Whittington** introducing an in vitro model of low-amplitude very fast oscillations (>70–80 Hz) via gap junctions. They show that the gain of gap junction-mediated circuits under certain conditions can be larger than the gain in excitatory synaptic circuits. They conclude that if such observations are proven to be general then gap junction-mediated interactions may be the primary source of epileptogenesis.

Vincent, **Courville and Pineau** introduce a detailed computational model of epileptiform activity exhibiting transitions between inter-seizure and seizure states and back with state durations similar to the in vitro model. Changes in certain ion concentrations drive their simulated system towards epileptiform state, whereas decrease of a slow depression variable can cause the system to spontaneously leave the seizure-like state.

In an attempt to develop effective techniques to eliminate widespread pathological brain rhythms as occurring during epileptic seizures, **Ming Luo and Jian Xu** discuss the suppression of neural synchronization in interacting neural groups using washout filter aided feedback. By testing two control strategies it was found that synchronization in a system of neural networks can be completely suppressed by individual control of all subpopulation.

Quentin Huys, Michael Moutoussis and Jonathan Williams debate a more general question: Are computational models of any use to psychiatry? Four fundamental objections against modeling are raised, involving inability to describe subjective experiences, pain and suffering, maturity of understanding problems in psychiatry and sufficiency of theoretical techniques, and communication between clinicians and theoreticians. Although limitations of computational approaches in expressing concepts dear to psychiatrist are clear, computational models should help psychiatric research to integrate psychiatry and general neuroscience, and improve statistical testing of hypotheses. Closer collaboration is needed before computational models will really influence psychiatric practice.

Migliore, **de Blasi**, **Tegolo and Migliore** investigate the cellular mechanisms of the reported distorted perception of objects in schizophrenic behavior via single neuron modeling. Their model of the CA1 neuron show how and to what extent a pathological hypofunction of a context-dependent distal input on NMDA synapses can generate hallucinations by altering the normal recall of objects on which the neuron has been previously tuned.

Porr, **McCabe**, **di Prodi**, **Kolodziejski and Woergoetter** investigate how feedback inhibition in a cortical microcircuit affects spike timing-dependent plasticity by shortening the time window of LTD but not LTP. They then test the hypothesis about interneuron hypofunction and conclude that a reduction in GAD67 is the most likely cause for the observed hypofrontality in schizophrenia.

Jansen and Du developed a neuroanatomically inspired neural network model of normal and abnormal auditory information processing. It has been used to study sensory gating, that is the ability to attenuate irrelevant sensory stimulation. The key role in this case is played by the thalamic reticular nucleus (TRN). Several aspects of this model can be compared with experimental facts. The gating deficits observed in schizophrenia may result from decrease in the prefrontal cortex dopamine (DA) activity, which lower the excitatory and inhibitory feedback gains in the auditory and prefrontal cortical modules.

Moustafa and Gluck have built models of prefrontal–striatal and striatal–hippocampal interactions which simulate cognitive dysfunction in PD and schizophrenia. The functional role of the basal ganglia in stimulus–response learning is modeled using the actor–critic architecture. The hippocampus is argued to play a role in stimulus–stimulus representational learning, and the prefrontal cortex in stimulus selection during learning about multidimensional stimuli. Past models are reviewed and new simulation results for PD and schizophrenia are provided.

Cutsuridis extended his model of bradykinesia and rigidity in Parkinson's disease to explain the mechanisms of the repetitive and co-contractive activation of antagonist muscles observed in Parkinson's disease (PD) patients and MPTP treated animals. He showed that an oscillatory disrupted globus pallidus internal segment (GPi) response signal comprising of at least two excitation–inhibition sequences as an input to a normally functioning

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cortico-spinal model of movement generation results in a repetitive, but *not* co-contractive agonist–antagonist pattern of muscle activation. A repetitive *and* co-contractive pattern of muscle activation results when dopamine is also depleted in the cortex. Additional dopamine (DA) depletion in the spinal cord results in a reduction of the size, duration and rate of change of the repetitive and co-contractive EMG bursts. These results have important consequences in the development of PD therapies such as DA replacement in cortex and spinal cord, which can alleviate some impairments of PD such as slowness of movement (bradykinesia) and rigidity.

Deep brain stimulation (DBS) is becoming a common therapy for severe Parkinson's disease (PD), but the exact mechanism of the amelioration of the symptoms and the optimal site and parameters of stimulation are still open issues. **Guo and Rubin** performed a computational study of how multi-site stimulation of the subthalamic nucleus (STN), which is a common target for DBS in Parkinson's disease, can improve the fidelity of thalamocortical (TC) relay in a parkinsonian network model including part of the basal ganglia network. Two stimulation paradigms were tested and both showed promising results for possible clinical application.

Although STN stimulation has proven to be successful for the improvement of the cardinal symptoms of PD, it has only limited effect on gait disturbances and postural instability. The pedunculopontine nucleus (PPN) has been suggested as an alternative or additional target for DBS to improve these axial symptoms. **Lourens, van Gils and Heida** explore the effects of PPN DBS. A single compartment model of a PPN cell, showing dynamic behavior comparable to experimentally recorded firing patterns, in combination with part of the basal ganglia network was simulated under normal and parkinsonian conditions, and the effects of low and high frequency stimulation in PPN (and STN) were analyzed.

Alzheimer's disease (AD) was investigated by **Bhattacharya, Coyle, and Maguire** using a lumped computational model of the thalamo-cortico-thalamic circuitry. A modified synaptic structure in the thalamic part of the model was introduced and the synaptic connectivity parameters in this module were varied to simulate the effects of AD on brain synaptic circuitry. It is shown that the overall shift of the EEG power content towards the lower end of the frequency spectrum, i.e. alpha rhythm slowing as observed in AD patients, is dependent on the total number of active synapses in the thalamic cell populations.

Since AD involves breakdown in the brainstem nuclei, hippocampus and auditory cortex in the temporal lobe of the brain, it may be expected that auditory skills differ across individuals with and without AD. The aim of the study of **Krishnamurti, Drake, and King** is therefore to discover the hidden and non-linear associations among higher-order auditory and cognitive processes in individuals with and without AD. With the use of artificial neural network analysis auditory test data from a group of AD patients and an age-matched control group were analyzed. From the results it is concluded that central auditory function declines with age, regardless of changes in cognitive function.

Congenital prosopagnosia (CP) is an enigmatic disease in which recognition of faces are specifically impaired while recognition of other visual objects is normal. **Stollhoff, Kennerknecht, Elze and Jost** captures the critical feature of CP as the lack of holistic feature detection at the computational level and the sparseness of synaptic connections at the neural implementation level. They took two kinds of independent component analysis (ICA) algorithms, spatial ICA and temporal ICA, to bridge together the two levels and confirmed their predictions in psychophysical experiments using the face images produced by the two algorithms.

Finally, **Foulsham**, **Barton**, **Kingstone**, **Dewhurst and Underwood** investigate whether bottom-up saliency driven cues or top-down active strategies can explain the profound object recognition impairments observed in visual agnostic subjects. They show that saliency is not a good predictor of fixation in agnosia as the saliency–fixation relationship varies as function of task changes by same amount as in normal observers. They conclude that top-down strategies play a pivotal role in eye movement control.

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