Séminaire de l'axe Pharmacométrie et pharmacothérapie,

en collaboration avec le Centre de recherches mathématiques (CRM)

The use of Pharmaco-dynamical and Neurocomputational Modeling for the Assessment of Parkinson Disease and other Neurological Disorders

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Malfunctions in the neural circuitry of the basal ganglia, induced by alterations in the dopaminergic system, are responsible for an array of motor disorders and milder cognitive issues in Parkinson's disease (PD). A neurocomputational model is presented, aimed at exploring the role of basal ganglia in action selection. The model is biologically inspired and reproduces the main basal ganglia structures and pathways (direct, indirect and hyperdirect), modeling explicitly both the dopaminergic and the cholinergic system. The model also includes synaptic plasticity aspects by means of an original two-term Hebb rule that trains synapses in response to rewards and punishments. Moreover, the neurocomputational model is interfaced with a compartmental model of Levodopa pharmacodynamics, to propose a general model of medicated Parkinson's disease. The effects of Levodopa treatment are assessed by simulating an alternate finger tapping task. The frequency of tapping is then used as the outcome of the whole model, to simulate effective clinical scores. The model has been applied to the simulation of real patients (13 stable and 13 fluctuating) via an automatic fitting procedure for the estimation pharmacodynamics on an individual basis. Simulation results show that the model can reproduce the temporal patterns of Levodopa in plasma after medication and the subsequent finger tapping score, differentiating between mild and severe PD patients. Specifically, the drug removal rate from the effect compartment, and the Hill coefficient of the concentration-effect relationship were significantly higher in the fluctuating than in the stable group. Furthermore, the model is used to investigate synapse aberrant learning as a concurrent cause of bradykinesia and dyskinesia. Through simulations of different learning procedures, performed both in the presence or absence or high dopamine levels, the model shows that training, performed under drug medication (levodopa), provides not only immediate but also delayed benefit lasting in time. Conversely, if performed in conditions of vanishing levodopa efficacy, training may result in dysfunctional corticostriatal synaptic plasticity, further worsening motor performances in PD subjects. Dyskinesia can also be simulated, as a consequence of insufficient differentiations between Go and NoGo pathways, due to aberrant learning.
The model can be of value to gain a deeper understanding on the pharmacokinetics and pharmacodynamics of the medication, and on the way dopamine is exploited in the neural circuitry of the basal ganglia, in patients with different PD severity scores and on patients with other neurological dysfunctions.