Title. Neuroswarm: a methodology to explore the constraints that function imposes on simulation parameters in large-scale networks of biological neurons.

Authors. David Gomez-Cabrero (1,2), Salva Ardid (3,4), Maria Cano-Colino (5), Jesper Tegner (1), Albert Compte (5)

Institutions.

(1) Department of Medicine, Karolinska Institutet,
(2) Bioinformatics Infrastructure for Life Sciences,BILS, Sweden
(3) Dept. of Biology, York University, Canada;
(4) Centre for Vision Research, York University, Canada
(5) Institut d'Investigacions Biomediques August Pi i Sunyer (IDIBAPS), Barcelona, Spain

Introduction. Mechanistic aspects of brain function can be studied with the use of biologically detailed computational models. A critical question that arises from theoretical models is to what extend conclusions depend on particular simulation parameters. Thus, to demonstrate whether a network model is unique in reproducing some relevant phenomenology can be a tall order. This issue has recently been approached for single neurons and small neural networks (Achard & Schutter (2006)). However, an account for large-scale biological networks is still missing.

Here, we design a computational strategy (workflow) to explicitly explore this issue on large-scale neural models. We applied the workflow to study: (a) a specific cognitive function, the visuo-spatial working memory, for which we consider a biological neural network that mimics the properties and dynamics of neurons in the prefrontal cortex (PFC, Compte et al. (2000)); and (b) the role of the serotonergic modulation on affecting working memory (Sero-PFC, Cano-Colino et al. (2011)).

The models.

PFC-Working Memory Model. 1,024 excitatory neurons and 256 inhibitory (integrate-and-fire model) neurons were disposed on a ring and interconnected via conductance-based synapses (AMPA, NMDA and $GABA_A$ dynamics). Neurons disposed closely on the ring were more strongly connected. As described before (Compte et al 2000), this network has regimes of operation compatible with working memory physiology: tuned persistent memory-period activity and unstructured, bistable with a low-rate spontaneous activity. The simulation has over 100 parameters, many of which are at most weakly constrained directly by experimental measures.

Serotonergic modulation of PFC-WM model. In an extension of the above model, we included serotonergic receptors (Cano-Colino et al. 2011). When activated, these receptors affect a number of membrane and synaptic currents in model neurons. The description of these dynamics adds some 19 loosely constrained parameters to the model above. The resulting network simulations are again expected to produce bistable function between a tuned persistent activity state and an unstructured spontaneous activity state.

Workflow.

We provide a workflow approach to identify and characterize feasible parameter sets for large-scale neural network models. For illustration purposes we focus on a specific cognitive function (working memory). The workflow proposed is similar to the one proposed in Gomez-Cabrero et al. (2011), which was used to analyze a computational model of atherosclerosis. Next we describe key workflow steps.

Exploring parameter space: parameter space is sampled in order to find sets of parameters which yield simulations that match experimental measurements; we denote this set as *feasible parameter set* (*FPS*). Compliance with experiments is assessed using several evaluation functions: spontaneous activity in the network, stimulus-dependent mnemonic persistent activity after stimulation, in terms of maximum and minimum firing rates in the population, and others. Because of non-linearities both in the model and in the parameter set evaluation, no exact algorithm can be used to find the parameters that minimize the evaluation function. We used instead a heuristic algorithm to search for FPS: the Particle Swarm Optimization Algorithm. As a black-box optimization algorithm, the Particle Swarm Optimization Algorithm can operate with any fitness function and it is originally designed to optimally search in a hyperspace of real numbers (Kennedy & Eberhart (1995)).

Computational requirements to explore the parameter space: Due to the high computational demands (each network simulation ran for approximately one hour and each iteration of the PSO algorithm required about 500 simulations, for near 50 iterations in total), we executed all simulations in parallel in a computational facility with ca. 200 available CPUs and with a modified parallelized code (we used the Grid-SuperScalar technology at BSC-CNS for which we adapted the code).

Characterization of the set of FPS's: once we have identified a sufficient number of FPS's, we analyze this sample by:

1) Characterizing the ranges and values of the observed parameters values.
2) Clustering solutions in the parameter space.
3) Studying compensatory mechanisms.
4) Grouping solutions by qualitative differences, as for instance the activity of the inhibitory population in the model.
5) Studying the relation between those groups and the parameters.

Our approach is successful in identifying the main mechanistic players in these networks and can guide the design of specific tests to further isolate the critical parameters in the simulations.

Conclusion.

We show here that large-scale biological simulations of neural networks for specific cognitive functions can be evaluated for generality and robustness using an optimization procedure in their high-dimensional parameter space. Typically, these simulations are very unconstrained and generality has been tested using mathematical simplifications in mean field formulations. While this approach is indeed very general, the initial assumptions on the simplifications to use may be partly arbitrary. Our computational workflow approach can classify what parameters are more critical for the identified behavior, and what compensatory or synergistic associations between parameters are imposed by the required behaviors. These relationships can guide simplifications for further mathematical analysis. In Ardid et al. (2010) a similar workflow to the one proposed here was used to confirm that a specific property observed in one model was general to the class of possible models constrained by experimental and behavioral results.

There are recent serious efforts devoted to explore families of solutions; those studies (Marder et al (2007,2011)) are extending those focused on the development of optimization resources for neuroscience models (Van Geit et al. (2007,8)). Our study provides two major conclusions arguing for the exploration, which support and extend those shown in Marder et al (2007,2011). First, to consider a single solution (such as a single set of parameters fitting the expected data) provides limited insights of a given model: *are we sure that the conclusions observed in a single solution (parameter set) is true for all feasible parameter set*s?. Secondly, and a major adding to the first conclusion, the characterization of the set of feasible parameter sets provides a deeper understanding of a model and a more profound

impact on biological experiments because it can (a) characterize and enumerate the set of hypotheses that cannot be rejected based on the present experimental and theoretical understanding of the phenomenon; (b) identify specific experiments that can be most informative in distinguishing between these pending alternative scenarios; and (c) provide insights about what parameters of the models are critical, and could be used as targets for specific experimental manipulations.

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