Different stability of gene networks formed following induction of long-term potentiation

Gonzalo S. Nido[1], Joanna M. Williams[2,3], Lubica Benuskova[1,3]

[1] Dept of Computer Science, [2] Dept of Anatomy, [3] Brain Health Research Centre, University of Otago, New Zealand

Long-term potentiation (LTP) is a well-accepted model of long-term memory formation in the mammalian brain, shown to last for periods of weeks. This persistence is thought to be underpinned by altered gene expression. Indeed, the late phase of LTP is dependent of activation of distinct gene regulatory networks (GRN) at different time intervals after induction. Shortly after LTP induction, these networks have been shown to contribute to expansion of the gene response and regulation of key cell signalling mechanisms. Later GRNs are likely to contribute to synaptic reorganisation and a homeostatic gene response important in the consolidation and maintentance of LTP.

We hypothesised that the temporally specific LTP-related GRNs would show different dynamic properties over time, which reflect the compromise between stability to background noise and sensitivity to the meaningful perturbations. We carried out simulations of random Boolean networks (RBN) for GRNs identified at 20 min, 5 h, 24 h after LTP induction and as a benchmark, RBNs derived from a published yeast transcriptional network. First, we found that the LTP-related GRNs possess similar dynamic properties to the yeast network. Then we studied the dynamic differences between the 3 LTP networks and found that the rapidly induced GRNs are more sensitive to changes in the initial conditions, while the late network possesses a more stable architecture.

These data suggest that the LTP-related gene netwoks are vulnerable to change at early times but that the networks become more stable over time, a property consistent with stabilisation of LTP.

Introduction

Long-term potentiation (LTP) is a long-lasting enhancement in synaptic transmission, widely accepted as the cellular mechanism underlying learning and memory. The consolidation of LTP progresses through mechanistically distinct phases, with the late phases reliant on de novo gene expression. This LTP-related gene expression appears to be of fundamental importance for the persistence of LTP in vivo [1].

A number of studies suggest that network architecture plays an important role in the stability of cellular states and hence be under evolutionary pressures [4]. It can be expected that topological properties of networks differing in their functions or acting at different time scales will show different properties, tuned according to a particular compromise between robustness and plasticity. In this aspect, networks involved in early stages of a persistent mechanism are likely to be endowed with plastic properties, while networks regulated later on and responsible for the maintenance of the new homeostasis, will show a higher dynamic stability.

In the present study we use a random Boolean networks to model and characterise the dynamic differences between temporally distant LTP-related networks published by Ryan *et al.*[6]. These networks are regulated by LTP induction but act at different times (20 minutes, 5 hours and 24 hours post-LTP, see Figure 1). We compare these regulated networks with random models and we use the yeast transcriptional network as a benchmark. We show that the dynamics exhibited by the latest (24 h) network are less sensitive to perturbations than the earlier networks an effect consistent with a role in the consolidation of synaptic plasticity.

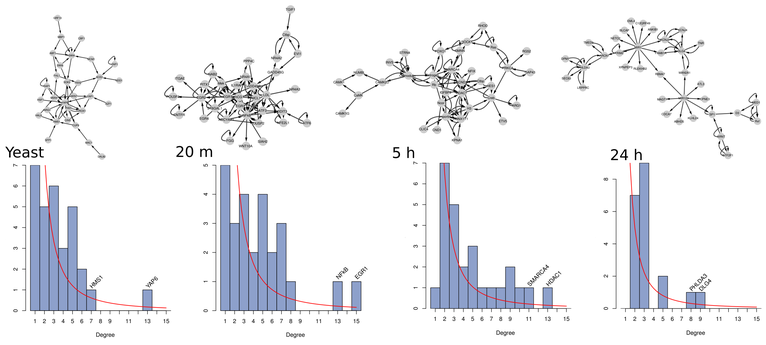

Figure 1: Network topologies used in the study: yeast, 20 m, 5 h, and 24 h post-LTP induction. The histograms represent the degree distributions for the corresponding network.

Methods

Random Boolean Networks

In Boolean networks, a bit vector $V(t) = (x_i, .., x_N)$ defines the state of the network at a particular time step. The states of the genes are updated according to a set of N Boolean functions, each with k_i number of inputs, where k_i corresponds to the in-degree of the node i. The input values correspond to the values $xi, ..., x_{k_i}$ of the genes connected to that node.

Both the set of Boolean rules B and the values of the state vector $V(t = 0)$ are initialised randomly. $V(t)$ is then updated synchronously, and the dynamics are deterministic. The state vector $V(t)$ will evolve until reaching an attractor. For a given network topology, a large number of simulations has to be run to properly sample random initial conditions $V(t = 0)$ and B.

Derrida Plots

The dynamics of RBNs can fall in the ordered or chaotic regime, depending on their dynamic stability Two initial states that differ in a number of positions, $H(0)$ (Hamming distance), are evolved in parallel for T time steps. The new Hamming distance, $H(T)$ is calculated. Plotting $H(T)$ against the original $H(0)$ for a large number of initial conditions $V(0)$ and Boolean rules B gives a Derrida plot [3].

The Hamming distances in ordered networks tend to decrease after evolving the network in time, while the chaotic or disordered networks show the opposite behaviour, $H(T) > H(0)$. Hence, the diagonal $H(0) = H(T)$ in the plot represents the transition from order to chaos.

Network topologies

Ryan *et al.* [5, 6] carried out a series of microarray experiments at different times after LTP induction. Specifically, their analyses identifed genes regulated 20 minutes, 5 hours, and 24 hours after LTP induction. For each of these groups, they provided the three highest scoring networks according to the analysis provided by the IPA software (Ingenuity Systems, www.ingenuity.com), making a total of 9 networks. In the present study we will analyse the highest scoring network for each time point (Figure 1).

In addition, we have used the yeast transcriptional network as a benchmark for RBN modelling.

We have used two different random models to generate the controls. For each of the 4 biological networks studied, we have generated

1. Ensembles of 100 random networks preserving the same number of nodes and edges
2. Ensembles of 100 random networks where each node has the same number of in- and out-roing edges as the original

The second random model serves to discriminate the effects of the networks local structure from the effects

Results

LTP-related networks are dynamically similar to the yeast network

We compared the LTP-related networks to their randomly rewired counterparts and we found a noticeable tendency towards the ordered regime. This tendency is even more marked than the one exhibited by the yeast network (see Figure 2).

These results reinforce the view by which the architecture of the networks is under a selective pressure. Yet, it remains unclear the contribution of the structural properties to the overall robustness of biological circuits. This tendency towards the stable regime represents only one mechanism yielding robust behaviour and does not rule out other genetic mechanisms.

The 24 h network shows a higher stability than earlier networks

The comparison of the dynamic stability between the networks obtained at different times after LTP-induction show that the regime becomes less chaotic with time after LTP induction (see Figure 2). In particular, the LTP-24h network appears to be considerably more ordered than the yeast, and ordered dynamics prevail under perturbations higher than a fraction of 0.38 genes. In contrast, both the LTP-20m and LTP-5h dynamic stability is comparable to the yeasts. This observation is readily accounted for in Figure 3, where two states differing in only one position are independently evolved over 5 time steps. The updated distances between the two state vectors are represented in the vertical axis. The amplification of the perturbation is clearly less pronounced than the one observed for the other networks, and the yeast network lies between the earlier networks (LTP-20m and LTP-5h) and the more stable 24 h network.

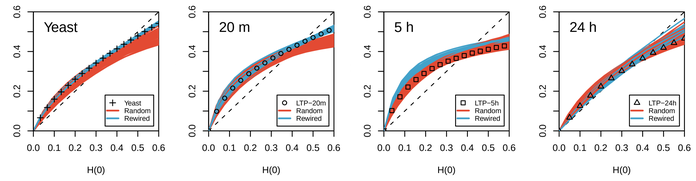

Figure 2: Derrida plots for the Yeast and LTP networks. Random networks for each of them are represented in red lines, Rewired networks in blue. The plots show the $H(0)$ distance plotted against $H(5)$. Despite showing slightly different behaviours, the curves corresponding to the real networks are above the diagonal for the same small perturbations. Contrarily to these dynamics, random Poissonian and scale-free networks dynamics have been shown to be ordered, and lie below the diagonal [2]. Each point in the plots is the average over 1,000 random rule assignments for 100 random initial conditions. The dashed diagonal, $H(0) = H(5)$, represents the edge between order and chaos.

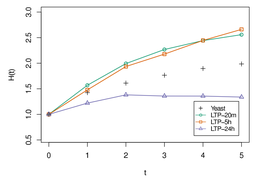

Figure 3: Effect of a small perturbation, $H(0) = 1$, over 5 time steps for the LTP and yeast networks. Initial states differing only on one position are sampled during 5 subsequent time steps for each LTP network. The latest network appearing after LTP induction, LTP 24 h (blue), shows a less pronounced tendency to amplify the perturbation. This result is consistent throughout all the initial perturbations in the chaotic regime.

Conclusions

- Using RBN modelling, we found that the networks derived in the early time points (20 min, 5 h), were more labile, while the most significant network derived at 24 h was more markedly more stable. This temporal effect on the vulnerability of the networks is mirrored by what is known about the vulnerability of LTP and memory itself.
- Results are in line with a model in which the rapidly induced networks following LTP induction exhibit a higher sensitivity to perturbations so that a switch-like response can be triggered in response to the signals that induce LTP in the neurons.
- Networks associated with the late phase of LTP have to posses a more stable architecture, contributing to the homeostatic response underpinned by gene expression.
- Our new data support the conclusion that the LTP-related gene networks contribute to the stabilisation of LTP.
- Our results support the idea that networks regulated at different levels possess different dynamic characteristics adjusted to their respective time frames.

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