

Gene Expression of *C. elegans* Neurons Carries Significant Information on Their Synaptic Connectivity

Alon Kaufman¹, Gideon Dror² and Eytan Ruppin³

¹Hebrew University, Israel. ²The Academic College of Tel-Aviv-Yaffo, Israel. ³Tel-Aviv University, Israel.

The claim that genetic properties of neurons significantly influence their synaptic network structure is a common notion in Neuroscience, and has been supported by many specifically targeted experimental studies. The nematode *C. elegans* provides an exciting opportunity to approach this question in a computational large scale manner. Its synaptic connectivity network has been identified and, combined with information from gene expression studies, we now have connectivity and gene expression “signatures” for most of its neurons [1, 2].

Based on this data, the current study presents the first large-scale quantitative investigation of the relation between neuronal *gene expression and connectivity signatures*, concomitantly addressing the majority of *C. elegans* neurons. We specifically address two attributes of this relation: First, is it possible to predict a neuron's connectivity signature (divided into incoming and outgoing connections) based solely on its expression signature? The results obtained manifest an area under the ROC curve (AUC) accuracy of 0.594 ($p=10^{-85}$) and 0.601 ($p=10^{-75}$) in predicting the incoming and outgoing connectivity signatures respectively. This accuracy level is moderate but manifests a markedly statistically significant signal. Second, we study to what extent do neurons with similar expression signatures have similar connectivity signatures, utilizing a co-variation correlation assay. We find low-magnitude but markedly significant Pearson correlations of 0.075 ($p<10^{-4}$) and 0.176 ($p<10^{-4}$) between the expression neighborhood relations and the incoming and outgoing synaptic neighborhood relations, respectively. Importantly, the relations between the expression and connectivity signatures and the ability to predict connectivity from expression both remain marked and significant also when controlling for neuron types (both for the incoming and outgoing signatures). This shows that the genetic expression information determining neural connectivity goes beyond that determining neural cell type.

Employing feature selection methods gives rise to a list of candidate genes which are likely to play a major role in determining the specificity of neuronal connectivity. The list of selected genes shows a statistically significant overlap with contemporary knowledge (obtained by a comprehensive literature search): Both for the incoming connectivity ($p=0.0005$ and $p=0.02$ in the prediction and correlation co-variation assays, respectively), and for the outgoing connectivity ($p=0.002$ and $p=0.01$, respectively). Focusing on genes which emerge in all assays we find some genes which were already identified in previous axonogenesis studies, such as *unc-5*, *tax-2*, *tax-4* and *lin-11*. For others on our selected genes list, whose direct role in axon guidance in *C. elegans* has not yet been reported in the literature, we find interesting clues for their actual involvement: One such example is the *che-23* gene that has a *Drosophila melanogaster* homolog, *dhb-9*, which is known to be involved in axonal pathfinding and target recognition in the fly.

Finally, in a small set of neurons responsible for chemotaxis, we study the relations between the expression and connectivity signatures to a third factor, the functional contribution of these neurons. The latter *neuron contribution signatures* denote the functional importance of each neuron to a variety of different chemo attractant tasks. They are obtained via multi-perturbation analysis [3] of neural laser ablation data [4]. Quantifying these relations, we address a classical question in Neuroscience; what dominates the functionality of a neural circuit – the local, genetic basis of the individual neurons, or the overall network structure. To this end we find borderline but significant correlations between a neuron's contribution signature to its expression signature (mainly) and to its outgoing connectivity signature (to a lesser extent), both after performing feature selection. This testifies that the neuron's functional contribution is not solely a global, emergent, property of the network in which it is embedded, but also depends on its local genetic and connectivity properties.

In summary, this study is the first to rigorously quantify the relation between genetic and connectivity properties of neurons in a large scale manner. Despite the crude and noisy data available, a marked signal is found which permits the identification of a putative list of genes which specify the neurons' connections.

1. White, J.G. et al. (1986) The structure of the nervous system of the nematode *Caenorhabditis elegans*. *Phil. Trans. R. Soc. Lond* 314, 1-340.

2. WormBase database (<http://wormbase.org> version WS140) and R. M. Durbin (<http://elegans.swmed.edu/parts/neurodata.txt>).

3. Kaufman, A. et al. (2005) Quantitative Analysis of Genetic and Neuronal Multi-Perturbation Experiments. *PLoS Comput. Biol.* 1:e64.

4. Bargmann, C.I. et al. (1991) Chemosensory neurons with overlapping functions direct chemotaxis to multiple chemicals in *C. elegans*. *Neuron* 7.