

Identification of driver nodes in genetic networks regulating macrophage activation

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Macrophage cells play an important role in the Multiple Sclerosis disease. They are known to participate both to the degenerative process, myelin destruction, and to the regenerative one, coordinating remyelination. The correct genetic activation of macrophage phenotypes permits a correct remyelinating response [1], thus the possibility to steer it towards a healthy state while acting on a limited number of genes (drivers) would be greatly advantageous.

We modeled macrophage activation as a network (Figure 1.a), where N nodes correspond to genes involved in phosphorylation and directed links corresponded to significant influences (inhibition or activation) as retrieved from the STRING Database [2]. We adopted the structural controllability framework [3], mapping the Kalman controllability criterion into the maximum cardinality matching on a graph, to identify the driver nodes.

Because different configuration of driver nodes are in general possible, we repeated the analysis $R = 60000$ times and we shuffled at each time the order of the nodes in the adjacency matrix in order to explore different configurations. Then, we defined the node *driverness* as:

$$Driverness_i = \frac{1}{R} \sum_{j=1}^R \delta_i^j \in [0, 1]$$

where $\delta_i^j = 1$ if node i was classified as driver in the repetition j and 0 otherwise.

Results showed that, in accordance with [3], driver nodes tend to avoid hubs (Figure 1.b), in fact nodes with low degree tend to have high driverness. Figure 1.c shows that signaling proteins (RELA, RELB, NFKB, MAPK, but not REL) have a low driverness (less than 0.3), which can be explained by their position in the ‘core’ of the network and their medium-high node degree; proteins which are end-products for the macrophages and which directly affect other cells (CXCL, CCL, CXCR, CCR, CD) have driverness less than 0.9 and in general tend not to be drivers. Transcription factors (STAT, IRF, OAS) have extreme values of driverness, both low and high. The high values are explained by the branching of the network, in fact OAS1, OAS3, OAS2, OASL and IRF6 have only one link, ingoing from STAT2, thus they will be drivers unless their own link is in the matching.

Our work is a preliminary step towards the identification of the genes influencing the inflammatory process of macrophages, which is a crucial mechanism in multiple sclerosis’ disease.

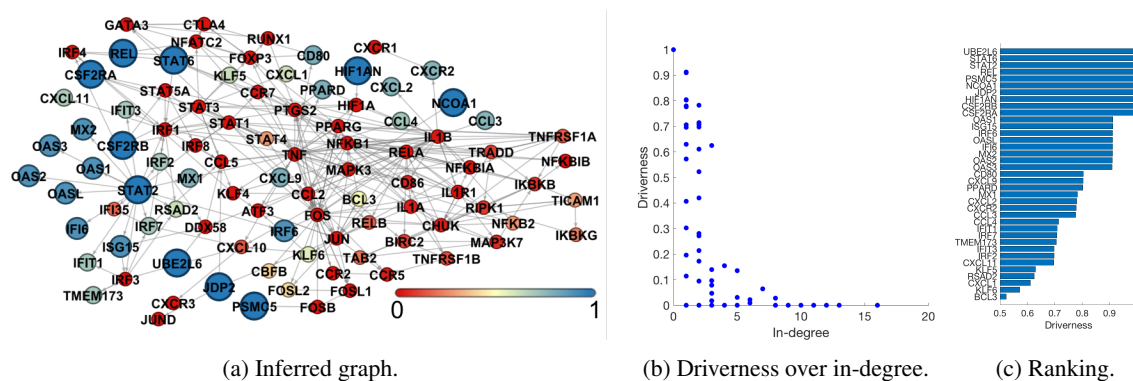


Figure 1: (a) Inferred network of genes involved in phosphorylation, with 95 nodes and 303 directed edges. Both intensity of color and size of the nodes increase as the driverness, computed as the frequency of times a node has been a driver over 60000 iterations of the maximum cardinality matching algorithm. (b) Driverness of the nodes over their in-degree. (c) Genes ranked by driverness.

[1] Miron VE et al. 2013. M2 Microglia/Macrophages Drive Oligodendrocyte Differentiation during CNS Remyelination. Nature Neuroscience 16(9): 1211-1218

[2] Szklarczyk D et al. 2016. The STRING Database in 2017: Quality-Controlled Protein-Protein Association Networks, Made Broadly Accessible. Nucleic Acids Res. 43(Database issue):D447-52

[3] Liu YY, Slotine JJ, Barabasi AL. 2011. Controllability of complex networks. Nature. 12;473(7346):167-73