Computational Approach to the Gene Regulatory Network in the *Mus Musculus* Mouse Eye Development

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Extended Abstract

Gene regulatory networks set a second order approximation to genetics understanding, where the first order is the knowledge at the single gene activity level. With the increasing number of sequenced genomes, including human's, the time has come to investigate the interactions among myriads of genes that result into complex behaviours. The composition and unfolding of interactions among genes determine the activity of cells and, when is considered during development, the organogenesis. Hence the interest of building representative networks of gene expression and their temporal evolution, i.e. the structure as the network dynamics (Barabási (2005)), for certain development processes.

This paper shows research on the gene regulatory network that controls the early development of the mouse (*Mus musculus*) eye. The developmental stages chosen comprise the specification of the eye progenitor cells (E9: nine days post fertilization), the morphogenesis of the optic cup (E10.5) and the specification of the first neuronal precursors (E11.5). The reason for this choice of stages was two-fold: first, all subsequent stages are contingent upon these ones. And second, the complexity of cell types is reduced, so we can consider that the tissue we analyze is composed of basically one cell type. The gene network construction (see Figure 1) has been carried out from our gene transcription profiling experiments of murine eyes at the already mentioned embryonic stages and a wide bibliographic review for their interactions (see Rebay et al. (2005), Sansom et al. (2009) and Purcell et al. (2005)). The resulting network can be analysed through network theory, where genes are the network nodes and interactions are the network links (U. Alon (2006)).

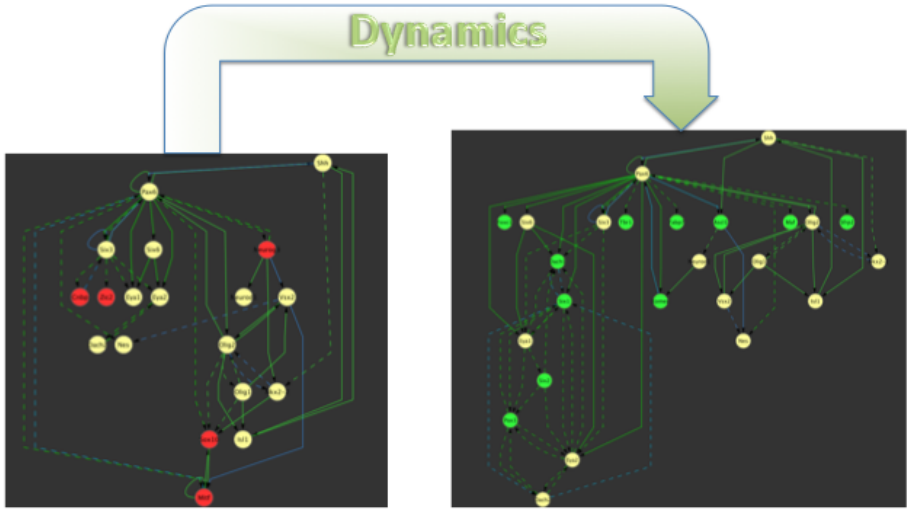

Figure 1: Visual transformation dynamics between E9 (left) to E10.5 (right) stages. Nodes: $Red = E9$, $Green = E10.5$, $Yellow = Common$; Links: $Green = Activator$, $Blue = Repressor$, $Solid = Functional\ interaction$, $Dashed = Protein - protein\ interaction$.

With the aim of determining a pathway through these links from E9 to E10.5, and then to E11.5, i.e. the process dynamics, a genetic algorithm (GA) has been developed (Mitchell (1999)). In this GA, each "chromosome" in the initial population consists of two parts. The first one involves the activity of the interactions among all nodes, i.e. activation, inhibition and non-interaction. The second part includes an activation/inhibition set of rules for the inputs into each gene. Each chromosome generates a dynamics to build a possible E10.5 stage starting from the well-known E9 stage (later E11.5 from found E10.5), where the input interactions for each node will determine its next state.

The GA fitness function is made of two suitably weighted addends: the first one, and the most important in the global computation, a distance between the experimental stage and the resulting from the GA; and the second one, a distance between the chromosome part formed by the genes interactions and the ones experimentally found.

It should be mentioned that certain experimental interactions may be lacking or be incorrect, so the interaction fitting must not be totally strict.

The results lead to a complete fitting for the gene activation states and to a good approximation for the links, and allow discovering some development dynamics. Further analysis, based on biological considerations, additional experiments and network pruning, will allow a final tuning to select the best network and dynamics for the early phases of eye development as a general model of organogenesis.

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