

# The influence of assortativity on the robustness and evolvability of gene regulatory networks upon gene birth\*

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## Abstract

Gene regulatory networks (GRNs) represent the interactions between genes and gene products, which drive the gene expression patterns that produce cellular phenotypes. GRNs display a number of characteristics that are beneficial for the development and evolution of organisms. For example, they are often robust to genetic perturbation, such as mutations in regulatory regions or loss of gene function. Simultaneously, GRNs are often evolvable as these genetic perturbations are occasionally exploited to innovate novel regulatory programs. Several topological properties, such as degree distribution, are known to influence the robustness and evolvability of GRNs. Assortativity, which measures the propensity of nodes of similar connectivity to connect to one another, is a separate topological property that has recently been shown to influence the robustness of GRNs to point mutations in *cis*-regulatory regions. However, it remains to be seen how assortativity may influence the robustness and evolvability of GRNs to other forms of genetic perturbation, such as gene birth via duplication or *de novo* origination. This abstract outlines a recent publication, in which we employed a computational model of genetic regulation to investigate whether the assortativity of a GRN influences its robustness and evolvability upon gene birth. We considered GRNs to be robust if they conserved all their phenotypes (attractors) following the introduction of a new gene, and evolvable if they were able to innovate at least one novel phenotype. We found that the robustness of a GRN generally increases with increasing assortativity, while its evolvability generally decreases (Figure 1; above), and this results in an increased proportion of assortative GRNs that are simultaneously robust and evolvable (Figure 1; below). This is due to: (1) Assortative GRNs have shorter attractors, which are more likely to be conserved (Figure 2), and (2) assortative GRNs have smaller out-components, resulting in a reduced chance of innovation (Figure 3). This work extends our understanding of how the assortativity of a GRN influences its robustness and evolvability to genetic perturbation.

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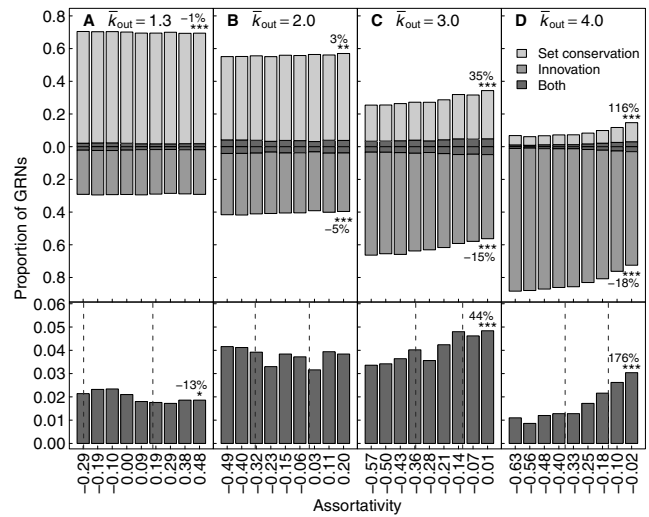


Figure 1: Proportion of GRNs with set conservation, innovation, or both as a function of assortativity. (Above) Light gray bars show the proportion of GRNs at a fixed assortativity value that exhibited set conservation after gene birth. Medium gray bars represent the proportion that exhibited innovation. Dark gray bars show the overlap, which is the proportion that both conserved and innovated. Each bar is a proportion of 5000 GRNs for each of:  $\bar{k}_{out} \in \{1.3, 2.0, 3.0, 4.0\}$  and 9 assortativity values. (Below) The proportion of the overlap is shown at a zoomed-in scale. Note that total proportions of conservation and innovation may not add up to 1, as some GRNs may exhibit neither. The percentage change from the smallest to the largest assortativity value is shown for conservation, innovation, and both. Statistical significance for Spearman's correlation is denoted by \* ( $p < 0.05$ ), \*\* ( $p < 0.01$ ), or \*\*\* ( $p < 0.001$ ). Vertical dashed lines show the minimum and maximum assortativity values for the middle 95% of the null distribution for each  $\bar{k}_{out}$ .

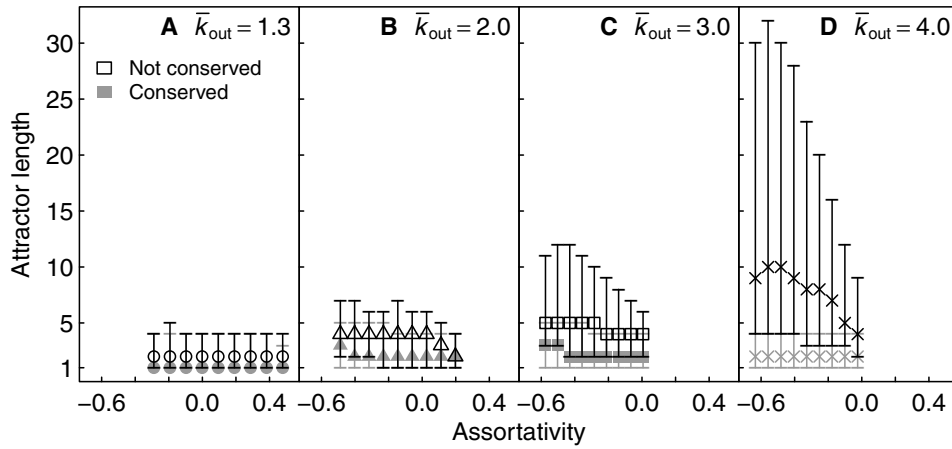


Figure 2: Lengths of attractors that were or were not conserved as a function of assortativity. Each point represents the median length of unique attractors before gene birth in 5000 GRNs at a fixed assortativity value. Error bars represent the 25<sup>th</sup> and 75<sup>th</sup> percentiles. Medians and percentiles for attractors that were not conserved are shown in black, whereas those for attractors that were conserved are shown in gray. GRNs are grouped according to their  $\bar{k}_{out}$  and assortativity value, as in Figure 1. Conserved attractors are significantly shorter for every assortativity value and every  $\bar{k}_{out}$  (Wilcoxon Rank Sum test,  $p \ll 0.001$ ).

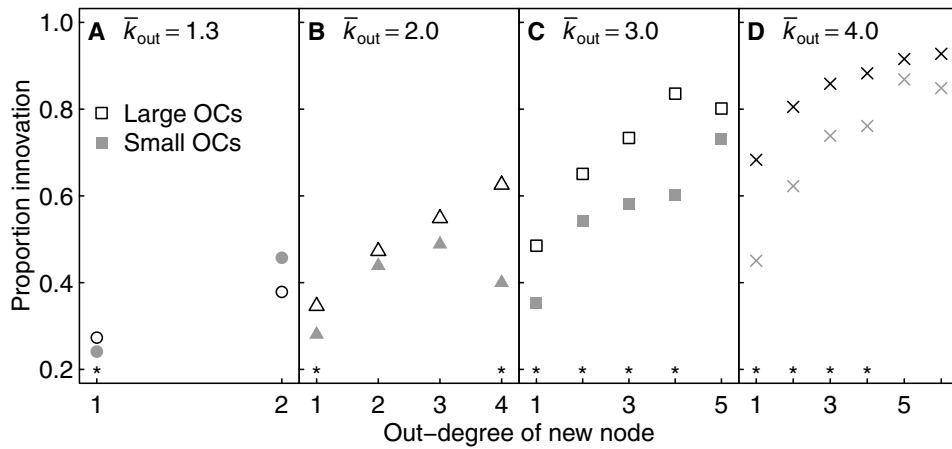


Figure 3: Proportion of innovation as a function of the out-degree of the newly introduced node, and whether the new node possesses a large or small out-component (OC). The OC of a node  $i$  in the GRN is the set of nodes in the GRN that is reachable via directed paths starting from  $i$ . The 5000 GRNs at the highest assortativity value for each  $\bar{k}_{out}$  were first binned by the out-degree of the new node, since this property positively influences the ability of the new node to cause innovation. Each out-degree bin was then split into two groups according to whether the new node possesses a large OC (larger or equal to the median OC size) or small OC (smaller than the median OC size). Black markers represent the proportion of GRNs that innovated at least one attractor where new nodes possess large OCs, and gray markers represent innovation for GRNs where new nodes possess small OCs. Asterisks mark significant differences in proportions between large and small OC categories ( $p < 0.05$ , Pearson’s chi-squared test). Only out-degrees for which at least 30 GRNs were present in large and small OC bins are plotted.