Properties of Compensatory Mutation in Artificial Gene Regulatory Networks

Yifei Wang[1], Joanna J. Bryson[1], and Nicholas K. Priest[2]

[1] Intelligent Systems Group, Department of Computer Science, University of Bath, Bath, BA2 7AY, United Kingdom
[2] Department of Biology and Biochemistry, University of Bath, Bath, BA2 7AY, United Kingdom
yifei.wang@computer.org; j.j.bryson,n.priest@bath.ac.uk

Here we shed light on the network property by examining a significant open problem in evolutionary biology: How do gene pathways evolve? Historically, mutations have been modelled as random noise and therefore expected to be far more likely to be harmful than neutral or beneficial, given the elaborate and complex interactions in evolved genetic systems [1–3]. However, more recent research on evolvability [4, 5] suggests that evolution itself may come to buffer against and even exploit likely variations in the genome [6]. Here we present simulation outcomes supporting the likelihood of this. We show that even in simple gene networks evolved artificially, compensatory mutation (CM) is a much more probable and systematic process than might be expected at first glance.

Compensatory mutations have long been considered of great potential significance in their hypothesised role of restoring a loss of fitness caused by some prior deleterious mutations [7–9]. Theses mutations could contribute to the neutral evolution for gene pathways [1, 10–12]. However, existing theory has assumed that compensatory mutations are very rare. They are therefore assumed to be inconsequential, occurring only in low-fitness lineages which are eventually eliminated by natural selection. However, if a deleterious mutation occurs at a locus not presently subject to strong selective pressure, then as long as the compensatory mutations occur before the lineage is driven to extinction, they may restore the lineage's fitness. Thus the frequency and nature of compensatory mutations are of substantial importance to understanding the impact of mutation on evolution.

In our work, we employ the evolutionary framework provided by gene regulatory network theory [4, 13, 14]. The key insight of our model is that whether a mutation is deleterious or not is entirely dependent on its context within a complex system – a network evolved for stability. In our simulations, the artificial gene networks are generated randomly, but we only focus on the networks that are stable. Then, unstable networks compromised by deleterious mutations were selected. The compensatory mutations can restore the stability of previously compromised networks. In our modelling approach, we are either assuming that time lags occur between bouts of selection or that selection only acts sporadically on the networks we observe. Therefore, the timescale for accumulating mutations is longer than the timescale between rounds of strong selection.

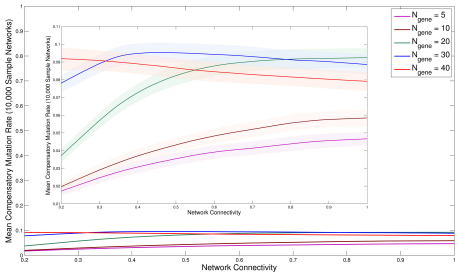

Fig. 1. Compensatory mutation frequency of randomly-generated stable gene networks. For each network size (N_{gene} = 5, 10, 20, 30 and 40) with each connectivity given from a range of values in continuous interval $[0.2, 1]$ (step size 0.02), we tested CM frequency of $10,000$ randomly-generated networks. Shaded areas represent 95% confidence intervals based on 100 independent runs.

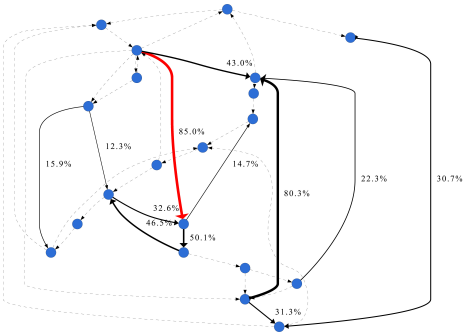

Fig. 2. An example of spatial probability of CM occurring on gene networks. In this example $N_{gene} = 20$, for a particular compromised network (deleterious mutation site marked by red) that was stable initially we executed one additional mutation round $1,000$ times on each link. Then, we measured the percentage of each broken link that could be fixed (Note: CM occurred on this link) after the mutation operation. Finally, we marked each broken link whose percentage was above 0%.

Specifically, in our simulations, we find that the viability and initial robustness are quite different among varying sizes and levels of connectivity of gene regulatory networks. However, compensatory mutation frequency is not only insensitive to network size but also to network connectivity as can be seen in Figure 1. In addition, we find that generally compensatory mutation occurs in genes which closely interact with the deleterious genes (see an illustration in Figure 2). Moreover, both small networks and larger networks tend to have the same property. These theoretical results predict that the compensatory mutations may probably be observed in or adjacent to the original site of deleterious mutation in nature. Finally, we find that larger weight changes, both positive and negative, are associated with an increased compensatory mutation frequency. In our simulations, these negative and positive effects are equally likely to be useful in inter-gene regulation. However, if the compensatory mutations occur on on-self-regulating links, then they are far more likely to be caused by positive rather than negative regulation.

In summary, with a fairly simple extension of an existing model of gene networks, we have shown that in the context of evolved gene regulatory networks, deleterious mutations are able to be compensated at a frequency largely independent of the network size and network connectivity. Particularly, the very mutations that may be compensatory in a gene regulatory network that has already been compromised would have been deleterious in the context of the original network. We further observe a relatively high probability in compensatory mutations being found in genes at or adjacent to the site of the original

deleterious mutation, which is consistent with recent studies [15, 16]. Our simulation results also show that compensatory mutations that occur in self-regulating gene networks are more likely to be driven by positive weight changes (upregulation) than negative ones. These findings suggest that compensatory mutations may play a more important role in evolution than we had previously imagined.

References

1. Kimura, M.: The role of compensatory neutral mutations in molecular evolution. Journal of Genetics **64**(1) (1985) 7–19
2. Stephan, W.: The rate of compensatory evolution. Genetics **144**(1) (1996) 419–426
3. Wright, S.: Evolution in mendelian populations. Genetics **16**(2) (1931) 97–159
4. Wagner, A.: Does evolutionary plasticity evolve? Evolution **50**(3) (1996) 1008–1023
5. Wang, Y., Matthews, S.G., Bryson, J.J.: Evolving evolvability in the context of environmental change: A gene regulatory network (GRN) approach. In: Artificial Life 14: International Conference on the Synthesis and Simulation of Living Systems, The MIT Press (July 2014) 47–53
6. Campàs, O., Mallarino, R., Herrel, A., Abzhanov, A., Brenner, M.P.: Scaling and shear transformations capture beak shape variation in darwins finches. PNAS **107**(8) (2010) 3356–3360
7. Parsch, J., Tanda, S., Stephan, W.: Site-directed mutations reveal long-range compensatory interactions in the adh gene of drosophila melanogaster. PNAS **94**(3) (1997) 928–933
8. Whitlock, M.C., Otto, S.P.: The panda and the phage: compensatory mutations and the persistence of small populations. Trends in Ecology & Evolution **14**(8) (1999) 295–296
9. Wagner, A.: Robustness against mutations in genetic networks of yeast. Nature Genetics **24**(4) (2000) 355–361
10. Moore, F.B., Rozen, D.E., Lenski, R.E.: Pervasive compensatory adaptation in escherichia coli. Proceedings of the Royal Society B: Biological Sciences **267**(1442) (2000) 515–522
11. Levin, B.R., Perrot, V., Walker, N.: Compensatory mutations, antibiotic resistance and the population genetics of adaptive evolution in bacteria. Genetics **154**(3) (2000) 985–997
12. Meer, M.V., Kondrashov, A.S., Artzy-Randrup, Y., Kondrashov, F.A.: Compensatory evolution in mitochondrial trnas navigates valleys of low fitness. Nature **464**(7286) (2010) 279–U159
13. Siegal, M.L., Bergman, A.: Waddington's canalization revisited: Developmental stability and evolution. PNAS **99**(16) (2002) 10528–10532
14. Azevedo, R.B.R., Lohaus, R., Srinivasan, S., Dang, K.K., Burch, C.L.: Sexual reproduction selects for robustness and negative epistasis in artificial gene networks. Nature **440**(7080) (2006) 87–90
15. Poon, A., Chao, L.: The rate of compensatory mutation in the dna bacteriophage phi x174. Genetics **170**(3) (2005) 989–999
16. Davis, B.H., Poon, A.F.Y., Whitlock, M.C.: Compensatory mutations are repeatable and clustered within proteins. Proceedings of the Royal Society B: Biological Sciences **276**(1663) (2009) 1823–1827