

Biological network rewiring at the second order

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In biological systems, genetic and epigenetic reprogramming can rewire molecular networks and introduce phenotypical divergence. Although many network rewiring methods have been developed, no model-free statistical methods can differentiate gene-gene pattern changes not attributed to marginal changes. Here we introduce a model-free method called Sharma-Song test to determine if two or more patterns differ in the second order (rewired interactions), relative to differential first-order (marginal differences) patterns across two or more biological systems. With simulation study, we have demonstrated the advantage of our methods over alternative methods. We explored and uncovered interesting biological rewired networks across different biological systems. While contrasting the mammalian systems, we report a lower frequency of co-expression network rewiring in nervous system tissues between human and mouse than the frequency of rewiring between different tissue types within the same species. We compared gene co-expression networks of planktonic microbial communities in cold California coastal water against the warm water of North Pacific Subtropical Gyre, revealing molecular circuitry that respond to environmental changes or stress. The method is generally applicable to many different types of biological systems to uncover changed relationships which may help reveal evidence for rewired biochemical circuitry due to evolution, environment, or disease.