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Phenotypic spandrel: absolute discrimination and ligand antagonism

Recent works in quantitative evolution have shown that biological structures are constrained by selected phenotypes in unexpected ways . This is also observed in simulations of gene network evolution, where complex realistic traits naturally appear even if they have not been explicitly selected . An important biological example is the absolute discrimination between different ligand "qualities", such as immune decisions based on binding times to T cell receptors (TCRs) or FcϵRIs. In evolutionary simulations, the phenomenon of absolute discrimination is not achieved without detrimental ligand antagonism: a "dog in the manger" effect in which ligands unable to trigger response prevent agonists to do so. A priori it seems paradoxical to improve ligand discrimination in a context of increased ligand antagonism, and how such contradictory phenotypes can be disentangled is unclear. Here we establish for the first time a direct mathematical causal link between absolute discrimination and ligand antagonism. Inspired by the famous discussion by Gould and Lewontin, we thus qualify antagonism as a "phenotypic spandrel": a phenotype existing as a necessary by-product of another phenotype. We exhibit a general model for absolute discrimination, and further show how addition of proofreading steps inverts the expected hierarchy of antagonism without fully cancelling it. Phenotypic spandrels reveal the internal feedbacks and constraints structuring response in signalling pathways, in very similar way to symmetries structuring physical laws.