

## **Exhaustive Petri net modeling to infer mechanisms of genetic interactions**

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Understanding the molecular mechanisms of genetic interactions and their relation to various biological processes is crucial to decipher pathway organization, cellular organization and disease progression. Several potential mechanisms have been suggested before. Many of these however lack systematic and exhaustive exploration of the complete modeling space. Here, an exhaustive petri net modeling approach is presented to systematically investigate and infer mechanisms of genetic interactions. Using twenty-six gene pairs between signaling proteins and gene-specific transcription factors all genetic interaction patterns are first grouped in different types. Inversion is a genetic interaction type primarily associated with gene-specific transcription factors and investigated further. Exhaustive petri net modeling is then employed to simulate over nine million four node models with two regulatory nodes, two downstream nodes and quantitative edges. This demonstrates that inversion can be explained using a minimum of three nodes and that a quantitatively regulatory difference is a mechanistic requirement when observing inversion. In combination with a fourth node, buffering is the most frequently observed genetic interaction pattern together with inversion. Taken together these results show that the petri net modeling approach can be successfully applied to systematically infer mechanisms of genetic interactions and that this approach is useful to infer common patterns underlying genetic interactions.