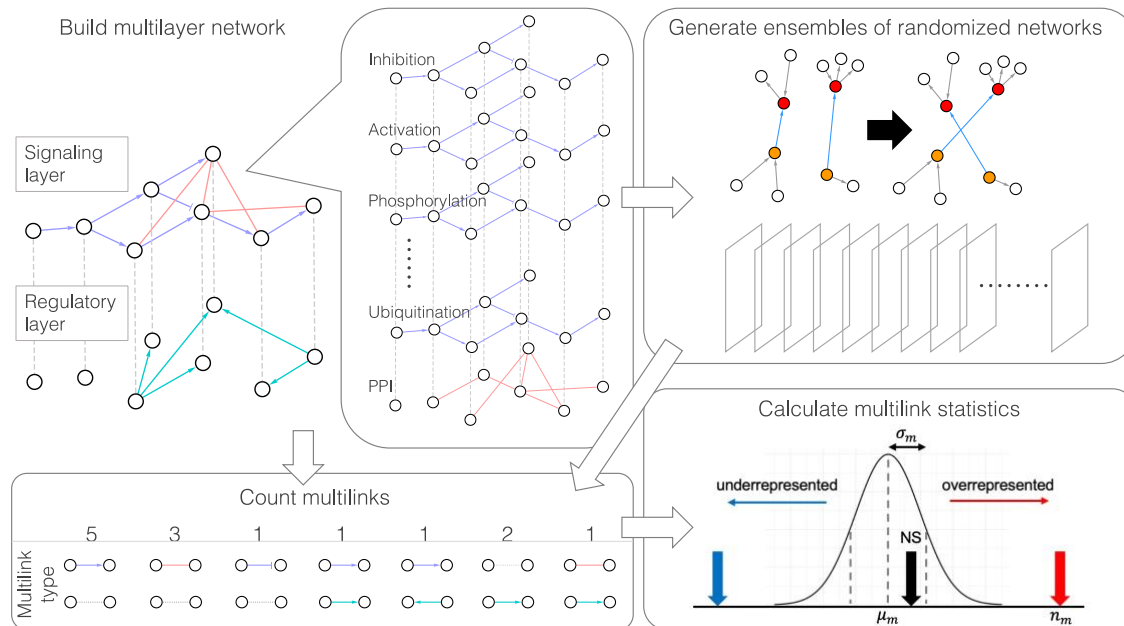


# MuXTalk: Detecting and dissecting signaling crosstalk via multilayer networks

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## Abstract

Signaling crosstalk occurs when the stimulation of a signaling pathway's receptors results in downstream effects on another signaling pathway. While numerous network-based methods identify the presence of signaling crosstalk, they do not distinguish between different signaling events and therefore offer limited mechanistic insights into crosstalk. Given the context-specific and often concurrent types of interactions in cellular signaling, multilayer networks offer the potential to better understand signaling pathways and predict their crosstalk. We built a multilayer network consisting of a gene regulatory layer and a signaling layer, and developed a statistical framework, MuXTalk, that uses high-dimensional edges, or *multilinks*, to model signaling crosstalk. Using statistically over-represented multilinks as proxies of crosstalk between signaling pathways, we identified potentially crosstalking pathway pairs among 61 KEGG pathways. In our benchmark, MuXTalk had a higher area under the ROC and precision-recall curves compared to all single layer-based methods tested, identifying additions to the current gold-standard. Crosstalk predictions in our “discovery” set of pathway pairs were highly supported in the literature with a precision >80% for the top 50 pairs. Overall, our findings suggest the utility of the multilayer modeling of signaling crosstalk, with possible future applications to extend our approach to tissue- and disease-specific crosstalk.