Computational analysis of positive feedback loops and phenotypic plasticity in cancer metastasis

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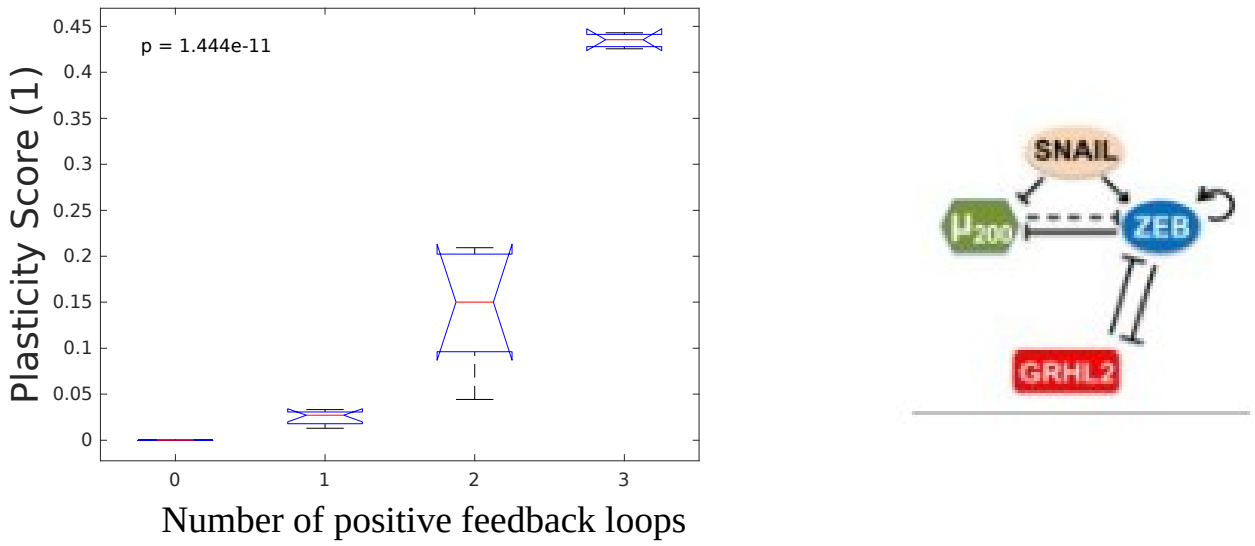
Phenotypic plasticity is the ability of cells to change their phenotypes. Epithelial-Mesenchymal plasticity (EMP) is the driving force of cancer metastasis, a phenomenon that is responsible for 90% of cancer deaths. EMP greatly enhances tumour progression by allowing it to spread to distant organs, evade therapies and evade the immune system. Most therapeutics fail when cancer metastasizes, therefore it is essential to have a detailed analysis of EMP if a long-term viable cure is to be found. EMP is governed by a network of interactions consisting of multiple transcription factors and microRNAs with complex dynamics and feedback mechanisms. In this study, a set of these networks are analysed using a computational tool named RACIPE (RAndom Circuit PErturbation). Using this tool, a thorough analysis of EMP is done and we determine the underlying network principles that give rise to phenotypic plasticity. For the analysis, we perturb the various EMP networks by randomising, adding, deleting and changing the nature of interactions to see how the system responds to these perturbations. We observed that the number of positive feedback loops in the regulatory network directly correlates with the overall phenotypic plasticity of the cancer cells. We then suggest a possible therapeutic solution to reduce plasticity by deleting certain interactions which would reduce the number of positive feedback loops. Reducing plasticity could possibly curb metastasis.



Plasticity vs Number of positive feedback loops (Left) for an EMP network (Right)