Claudin-low triple negative breast cancer is an aggressive subtype of the diseases with high rates of metastasis and low survival rates. It has a poor prognosis because it does not respond to targeted therapies or cytotoxic drugs.

We are exploring tumor reversion as a potential therapeutic strategy in treating this disease. Tumor reversion is the biological process by which a tumor loses a significant fraction of its malignant phenotype, and it has actually been observed in vitro and ex vivio with a CL TNBC cell line.

At a cellular level, the development of cancer can be viewed as a systems-level dynamical process driven by a tumorigenic intracellular signaling network. This can be visualized with the aid of Waddington’s epigenetic landscape. A stem-cell starts at the top of the epigenetic landscape and travels down the landscape as it differentiates until it lands in a valley, reaching a stable state. This stable state represents the fully differentiated cell and its corresponding cell phenotype.

Kauffman showed that the epigenetic landscape is more than just a metaphor. It is derived from the dynamics of the intracellular signaling network. Consider a network with n nodes. Then the epigenetic landscape is a projection of the n-dimensional state space of the network. Peaks represent unstable states with high potential, while valleys represent stable states, or attractors of the network. Thus, the attractors of the network correspond to cell phenotypes. A shift between cell phenotypes is analogous to moving the cell from one valley to another.

Kauffman also introduced the idea of cancer attractors, which are preexisting attractors of the network, however they are not accessible to healthy cells. In the event of a genetic mutation, or changes in the tumor microenvironment, the epigenetic landscape can be altered, making the cancerous attractor accessible. The development of cancer can be driven by aberrant cell signaling that sends the cell into the tumorigenic attractor.

Thus, tumor reversion can be viewed as an optimal control problem in dynamical systems where the objective is to move the network state from the cancerous attractor to a normal attractor

By applying a structure-based attractor-based control method for nonlinear systems to the network, we will identify driver nodes of the system whose concerted perturbation can shift the state of the network to any desired attractor from an arbitrary initial state. In terms of the epigenetic landscape, this is equivalent to the cell moving from the tumorigenic valley to the normal-like valley.

Our goal is to develop a quantitative pipeline for the reconstruction of the CL tumorigenic signaling network and apply optimal control to identify combinations of therapeutic targets that can trigger tumor reversion. Eventually we will build a Boolean network to corroborate our findings and ultimately validate experimentally.

**Network Construction**

* Three levels: FunDEG, TF, MR
  + Talk about why we do FunDEG?
* Considered multi-omics data
* Considered mutational data
* Used available databases

**SFA**

* Algorithm that uses the topology of the network to estimate the network state
* The expression level of a node is determined by its basal activity, as well as the activity of its regulating nodes
* As time progresses, the signal flows through the network and the network state changes until it reaches a steady state
* An approximation because just using the topology of the network
* We approximated the attractor landscape
  + There are several attractors that are not of interest because they are either biologically not relevant or are not cancerous/normal

**Kmeans**

* Estimated the phenotype landscape with kmeans with 6 centroids
* Need to refine this by altering number of clusters
* Use this to define basin of normal attractor and cancerous attracotor

GOAL: perturb FC nodes so they are classified as normal

**FC**

* FC is a structure based attractor based control method for nonlinear dynamic systems such as our intracellular signaling network
* We applied it to the network to identify nodes whose concerted perturbation can shift the network state out of the tumorigenic basin of attraction and into the normal-like basin of attraction
* Identified 6 minimal FVS sets each of 14 nodes

**InSilico**

* We perturbed FC nodes by setting them equal to -1 (inhibition), 0, 1(activation)
* Because of constraints, we only tested one of the 6 FC sets, and only a sample of 100,000 instead of all possible perturbations
* Identified a perturbation that was classified as normal after doing knn with 30 neighbors using phenotype landscape as training
* Need further validation because there’s a lack of separation in the clustering
* Doesn’t make sense to upregulate MAPK
* See known oncogenes as well as unknown in this FC
* Need a subset with fewer perturbations to be able to test experimentally

**Conclusions**

* Need to revisit kmeans
* need to do more knn exploration