How-To

This document gives step-by-step instructions on how to implement and interpret our code to find control targets in pancreatic cancer.

Find controls using Macaulay2 -- use files "*pcc_mutation_edge_control.m2*" and "*pcc_mutation_node_control_public.m2*"

1) To find node controls
    a. The code already has the model nodes, edges, and functions available
        i. Within the *functions* portion, the mutations have their alternate functions commented out. To induce a mutation, switch the unmutated function with its mutated counterpart
    b. Under "*encoding the edge controls*", one can choose edge deletion or expression, simply uncomment the preferred method
    c. Define good/bad states according to mutation presence and fixed-point/attractor preference
    d. Use "*for blocking*" to block regions (aka. BADSTATE(s)), or use "*for creating a new fixed point*" to find controls leading to a GOODSTATE(s)

*The output will be a string of **potential** edge controls that can be tested in the simulator. These outputs are not guaranteed to be good controls*

2) To find edge controls:
    a. The code already has the model nodes and functions available
        i. Within the *functions* portion, the mutations have their alternate functions commented out. To induce a mutation, switch the unmutated function with its mutated counterpart
    b. Under "*create equations*" one can define restrictions of which nodes can be controls and the states of nodes. Due to the size of the system, we elected to use all nodes except for cytokines, and we excluded the four potentially mutated genes (unless inducing their mutation)
    c. If one wishes to search for strictly knockout or strictly expressed nodes, use sections *"### ONLY UP ###"* or *"### ONLY DOWN ###"*

*The output will be a string of **potential** edge controls that can be tested in the simulator. These outputs are not guaranteed to be good controls*

Now that the list of potential controls is identified, use our MATLAB simulator "*comb_pcc_DP.m*" to parse the good/bad controls. Below is the step-by-step instructions for running simulations:

1) Under "*Inductions and Control*", use the *Mutation Functions* `F1-F4` to induce the desired mutation.
    a. Node and parameters are already set, all one needs to do is uncomment the desired gene and maintain order when compounding mutations. For example(s)

    KRAS can be induced by using

    ```
    F1 = TruthTable_del_n_temp(F,nv,varF,p, 43,1);
    ```

    KRAS/TP53 can be induced by using

    ```
    F1 = TruthTable_del_n_temp(F,nv,varF,p, 43,1);

    F2 = TruthTable_del_n_temp(F1,nv,varF,p, 64,0);
    ```

    TP53/CDKN2A can be induced by using

    ```
    F2 = TruthTable_del_n_temp(F,nv,varF,p, 64,0);

    F3 = TruthTable_del_n_temp(F2,nv,varF,p, 56,0);
    ```

2) Also under "*Inductions and Control*", use Node/Edge Control Functions `F5-F8` to implement the desired control strategy.
    a. Specific gene numbers are provided in the code for reference
    b. One must continue to compound functions as before in Step 1 if multiple controls are desired
    c. Note that the MATLAB functions for inducing node/edge control are:
    `TruthTable_del_n_temp(F,nv,varF,p, node,v)`

    `TruthTable_del_a_temp(F,nv,varF,p,tail,head,v)`

    (Here `v` indicates the sign of the action where knockout=0, expression =1)
3) Under "*Simulation*", set the desired noise level and choose either the noisy or silent simulation.
    a. Make sure the function being used in the simulation matches the last function being used (aka. `F-F8`, depending on the scenario being simulated)
    b. The variable `Phen` will print the ending phenotype levels, which indicate long term probability of expression.
4) To visually represent the full trajectories of the simulation, use section "*Graphing*". See that the final expression levels are those from Step 3.
    a. Notice that over time, expression levels will appear to converge.

To determine the efficacy of controls, we compare uncontrolled simulations with the appropriate targeted control simulations. Inducing mutations will result in high levels of diseased phenotypes. Thus, a good control will produce low disease levels and high health levels (apoptosis in our case).