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ORDINARY DIFFERENTIAL EQUATIONS MODEL OF THE EPITHELIAL TO MESENCHYMAL TRANSITION IN HUMAN MAMMARY EPITHELIAL CELLS

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Cellular resistance to chemotherapy treatments usually develop via genetic changes, including mutations and acquisitions of new resistance genes. However, when resistance develops without this genetic component, it is called phenotypic plasticity. Phenotypic plasticity is the idea that one genotype can produce multiple phenotypes dependent on the environmental conditions. As a result, chemo agents are stimulating cancer cells in a way that modifies their gene regulatory network (GRN). These changes to the GRN decrease the effectiveness of the chemo agents in killing the cancer cells.

There are multiple processes which fall under phenotypic plasticity, but we are specifically interested in the epithelial to mesenchymal transition (EMT). EMT promotes cellular resistance by reducing therapy efficiency. When cells undergo EMT, they are said to gain 'stem cell-like' properties. These properties make specific targeted drug therapy difficult by creating a dichotomy where the drugs kill cancer cells but induce EMT. For example, this process can down-regulate apoptotic pathways or reduce the amount of drug in a cell, both leading to a decrease in cancer cell death.

The EMT pathway is complex and not well understood. However, we believe that the pathway includes transcription factors snail family transcriptional repressor 1 (SNAIL1), twist family BHLH transcription factor 1 (TWIST1), and zinc finger E-box binding homeobox 1 (ZEB1), as well as their respective mRNAs and micro RNAs. Together, the transcription factor, mRNA, and microRNA form a positive feedback loop. All of these transcription factors upregulate the forward direction of EMT, repressing expression of E-cadherin (CDH1) and promoting expression of N-cadherin (CHD2). We use TGF-β to force the system into EMT.

To model the EMT pathway, we use a system of ordinary differential equations (ODEs), where each equation models a different component of the gene regulatory network shown in Figure 1. Using X. Tian et al's model as a jumping off point, we began by adding in TWIST1. We make an assumption that SNAIL1 and TWIST1 have the same function in the EMT pathway, and thus we model them with the same equation and parameters. Additionally, the fastest terms, as determined by their basal production rates, are the transcription factors SNAIL1, TWIST1, and ZEB1. We put these terms into quasi-steady state. Tian's model includes a differential equation for TFG-β, but we omitted that term. The final change we made was to modify the functional form of E-cadherin from a sum of effects to a multiplication of effects.

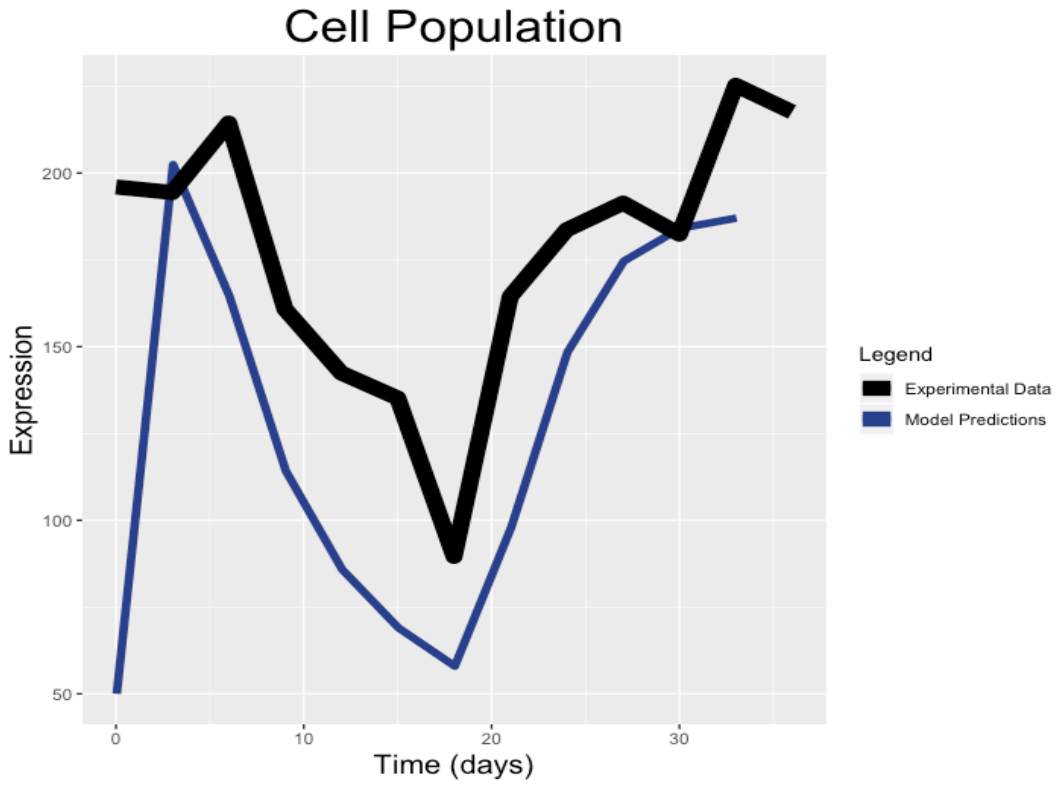
To study EMT, we will be using data collected from an experiment done by Jeff Chang's group where EMT was induced in human mammary epithelial (HMLE) cells. For 18 days, the cells were treated with tamoxifen, during which time the cells underwent EMT. The tamoxifen was then stopped, and the cells were allowed to go through the reverse process, the mesenchymal to epithelial transition (MET), for an additional 18 days. During this 36-day period, samples were collected every three days. The population of the cells that went back into the experiment,

i.e. the ones that were not sent for sampling, was kept track of, and we used this to test the accuracy of our model.

Using our population ODE,

$$\frac{dP}{dt} = 0.04P\left[\frac{1 - 0.004P}{1 + \left(\frac{Z}{J_P}\right)^2}\right]$$

we were able to plot the model predictions against the cell population from the experiment.



As seen above, our model has the general shape of the population curve correct, but the parameter values need some fine tuning. Additionally, the major jump in the blue, model prediction line between days 0 and 3 can be corrected by changing our initial conditions. In general, we see the same pattern in the differences between the model predictions and experimental data.

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