Modeling EMT-Stemness Interplay and Testing the Tristable Switch Hypothesis

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1 Background

Metastisis is driven by transitions from epithelial phenotypes to mesenchymal phenotypes (EMT), which are characterized by increased motility. More critically, this can result in hybrid **"partial EMT phenotypes"** (E/M) which have a greater potential to metastasize. This occurrence of EMT can allow tumor relapse, which is thought to relate to the idea of stemness. Here, we aim to investigate the stabilization of stemness in EMT-prone cells, as there has been an associated link between cancer stemness and the EMT-regulatory circuit [2]. Here, we explore the link between the coupled up-regulation of metabolism in cancer cells through a HIF-1/AMPK complex. Given that phenotypic plasticity and metabolic dysregulation are hallmarks of cancer [1], this should help us better understand the dynamics at play.

2 Aims

look into when metabolic activity peaks can we observe metabolic changes as precursor for EMT

- **Aim 1. Test the tristable switch hypothesis:** Recreate the phase plane from the paper and demonstrate the tristable behavior of the system.[2] Verify the existence of three stable steady states (E, E/M, and M) by solving the system using Ordinary Differential Equations (ODEs).
- **Aim 2. Extend the model:** Introduce and analyze the effects of a new regulatory molecule on the EMT-stemness interplay. This will involve adding a new variable such as TNF-α and AMPK and exploring how it affects the stemness window and EMT axis positioning.

3 Approach

- **ODE Formulation:** We will use Ordinary Differential Equations (ODEs) with shifted Hill functions to model the coupled gene regulatory networks from the paper.
- **Simulating the Phase Plane:** We will use numerical solvers (e.g., SciPy odeint in Python) to solve the system of ODEs for varying values of the coupling parameters (α_1 and α_2), reproduce the phase plane, and identify the regions where tristability occurs. We can visualize the system behavior by plotting bifurcation diagrams and/or phenotypic maps.
- **Extending the Model:** We will introduce two new regulatory molecules, HIF-1 and AMPK, into the system. AMPK is a key regulator of cellular energy balance and works in complex with HIF-1. We will explore how these molecules influence the EMT-stemness coupling and the stemness window. The metabolic state, such as the ATP/AMP ratio, will influence AMPK expression, linking metabolic dysregulation to stemness and EMT dynamics. We expect that the coupling of the metabolic input through HIF-1 and AMPK, will result in a greater population of cells in mesenchymal states since EMT is induced by metabolism [3].

4 Possible pitfalls

Introduction of a new regulatory molecule may require parameter estimation, which could be difficult if experimental data in the literature is scarce. We will start by using literature values for similar pathways or reasonable assumptions based on prior knowledge. Also, adding a new regulatory molecule introduces more complexity, which may lead to challenges in simulating the system's behavior.

References

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[3] H. Kang, H. Kim, S. Lee, H. Youn, and B. Youn. Role of metabolic reprogramming in epithelial–mesenchymal transition (EMT). 20(8):2042.