TGF-β-induced epithelial-to-mesenchymal transition

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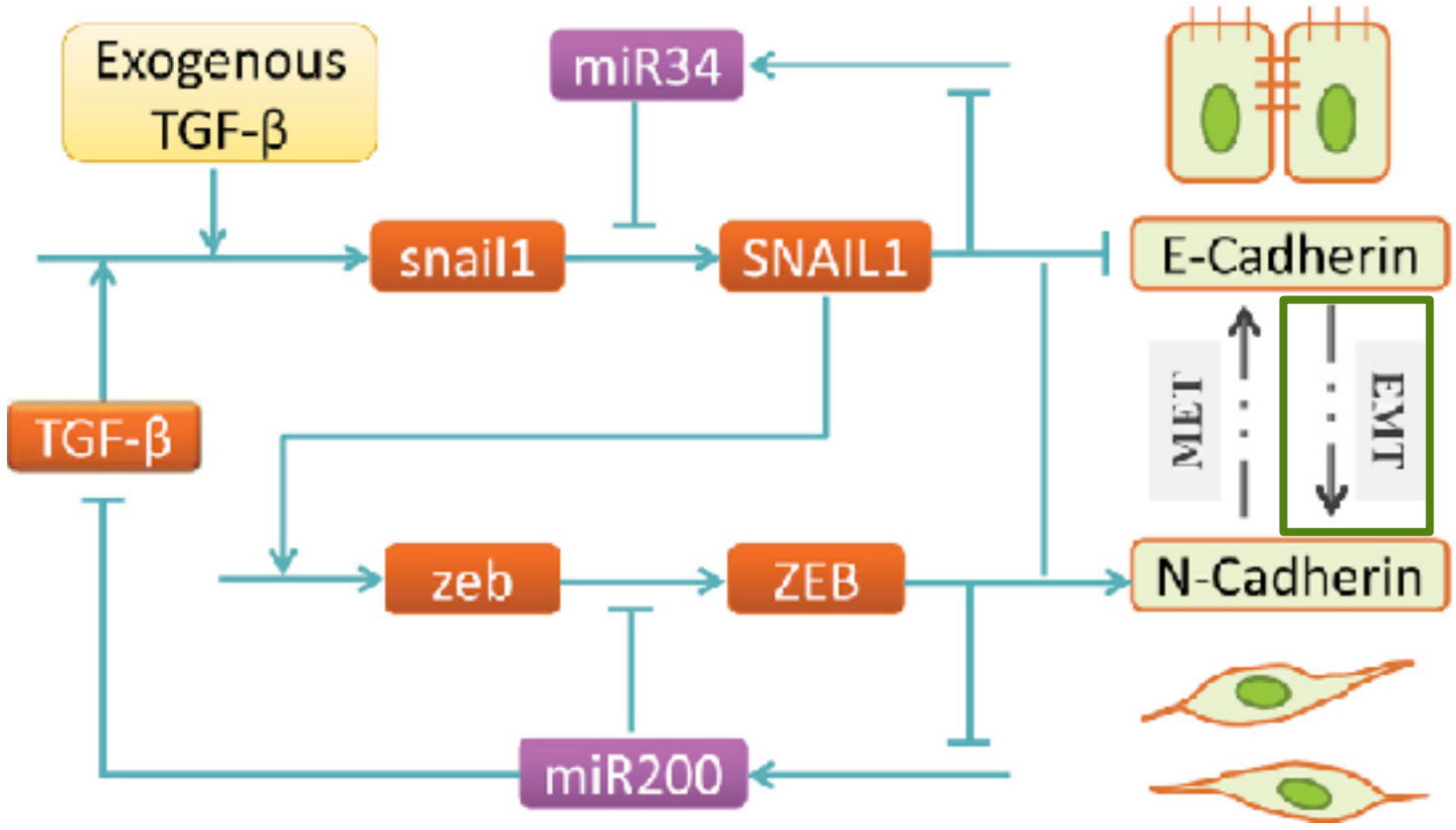
Introduction
Epithelial-to-mesenchymal transition

- “Cancer stem cells”
- Mesenchymal cells
  - *Lack apical polarity*
  - *Lose intercellular tight junctions*
  - *Release ECM-degrading enzymes*

Leads to enhanced migration = metastasis

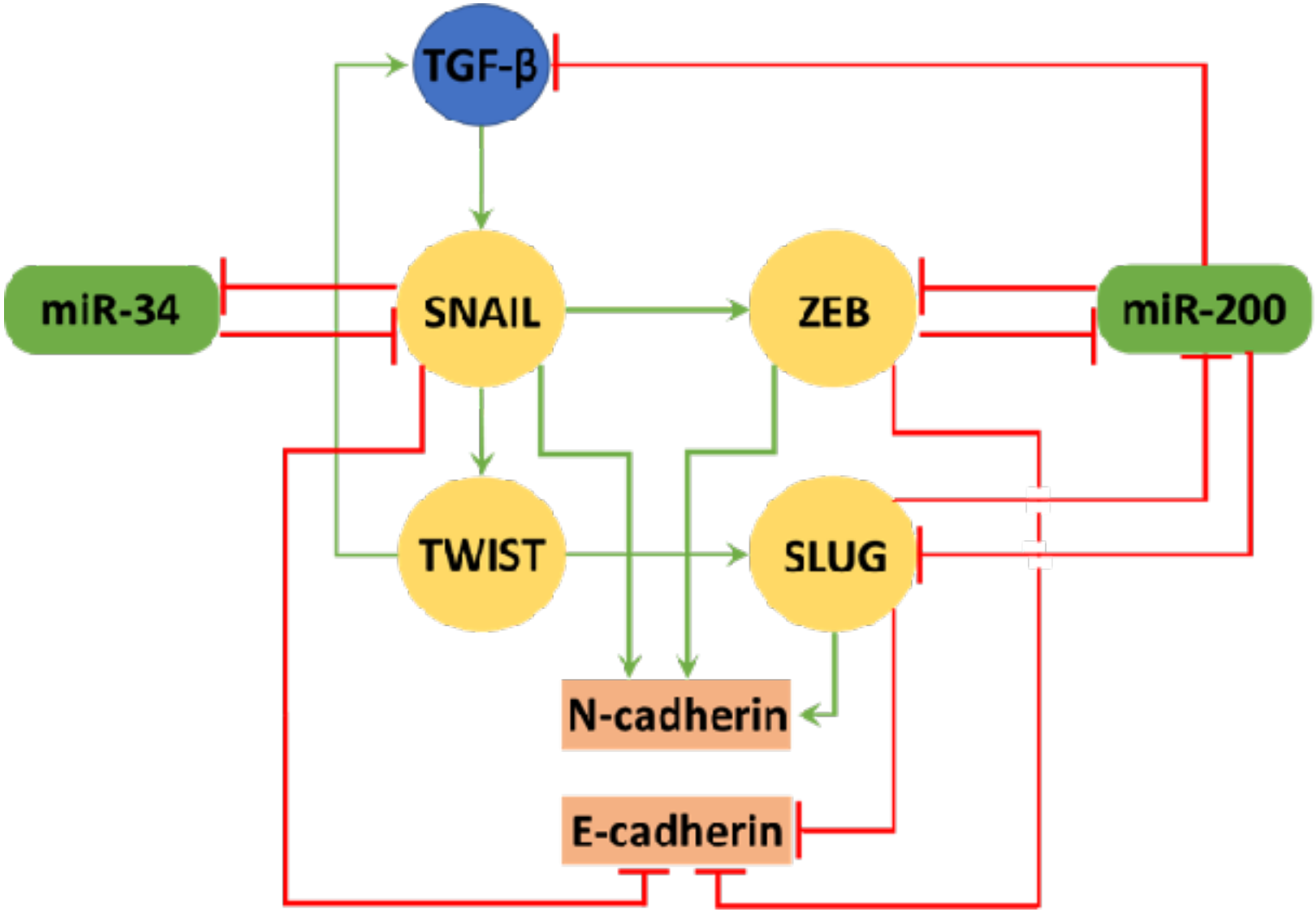
Introduction
TGF-β and previous work

- E-cadherin:
  - *Epithelial*
- N-cadherin:
  - *Mesenchymal*
- "Partial" EMT state exists



Tian, et al., 2013

Model


TGF-β
miR-34
SNAIL
ZEB
miR-200
TWIST
SLUG
N-cadherin
E-cadherin

Model

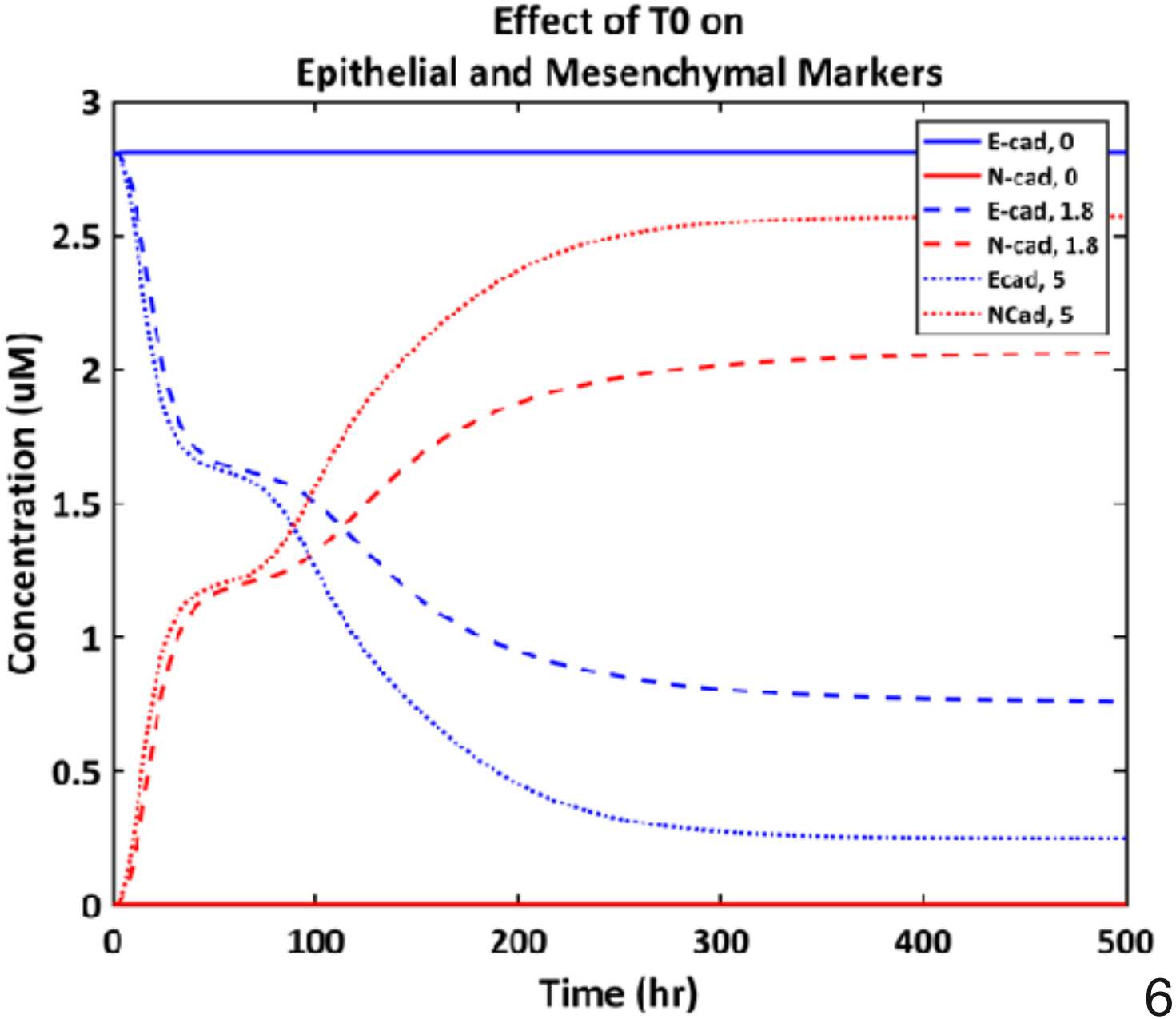
- 13 ODEs (simplified models not accurate)

$$\frac{d[slug]}{dt} = k0_{sl} + k_{sl}\frac{\left(\frac{[TWIST]}{M_{sl}}\right)^2}{1+\left(\frac{[TWIST]}{M_{sl}}\right)^2} - kd_{sl}[slug]$$

$$\frac{d[SLUG]}{dt} = \frac{k_{SL}[slug]}{1+\left(\frac{[mR200]}{M_{SL2}}\right)^2} - kd_{SL}[SLUG]$$

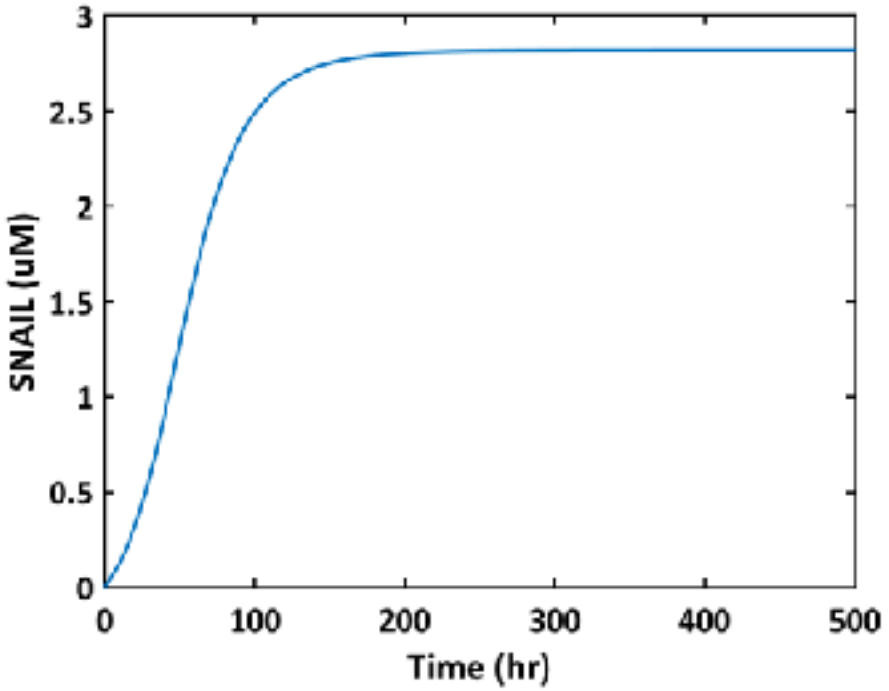
Model Results

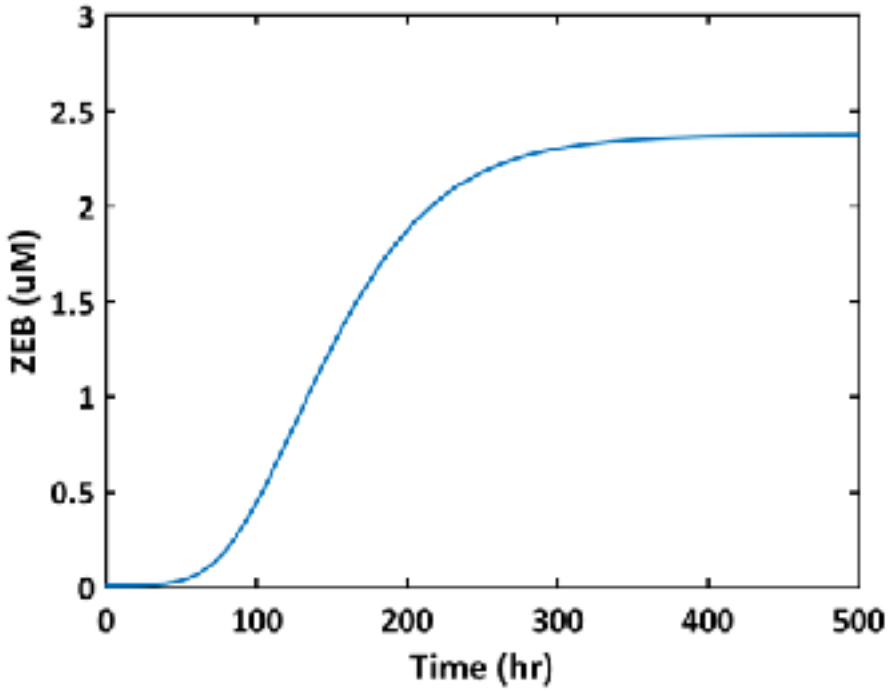
- E-cadherin:
  - *Epithelial*
- N-cadherin:
  - *Mesenchymal*

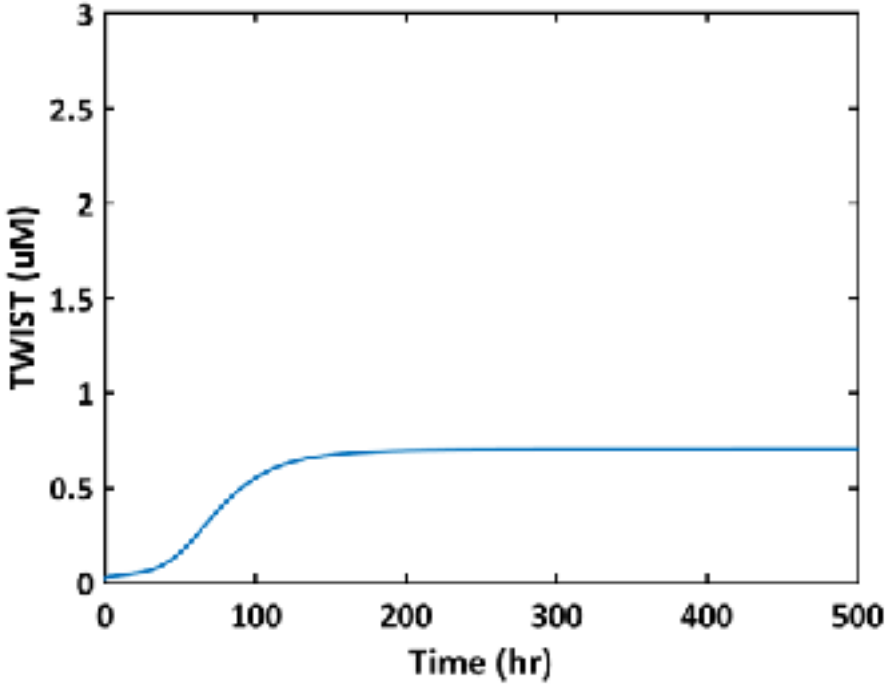


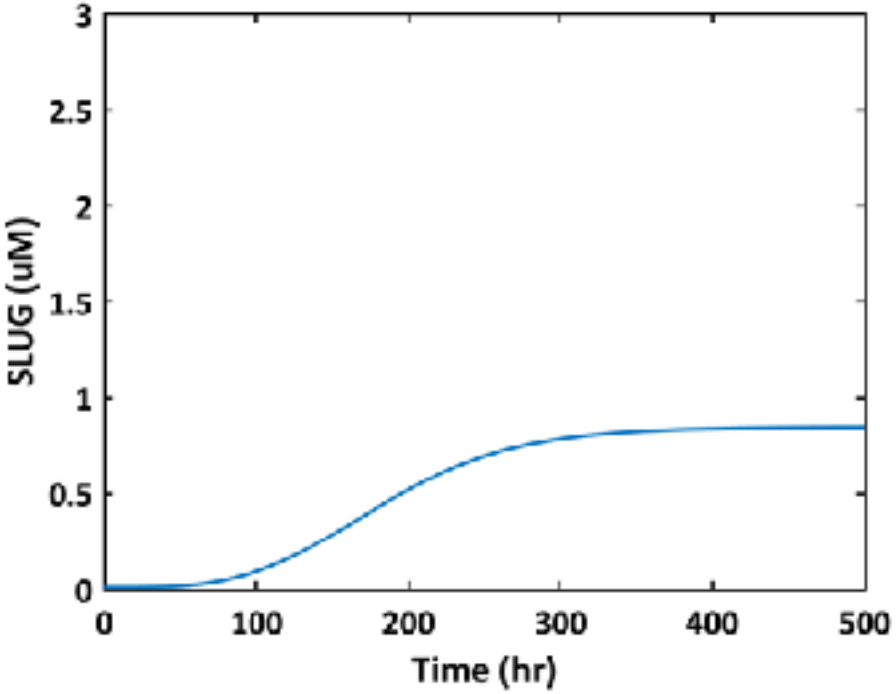
Model Result

Transcription Factors



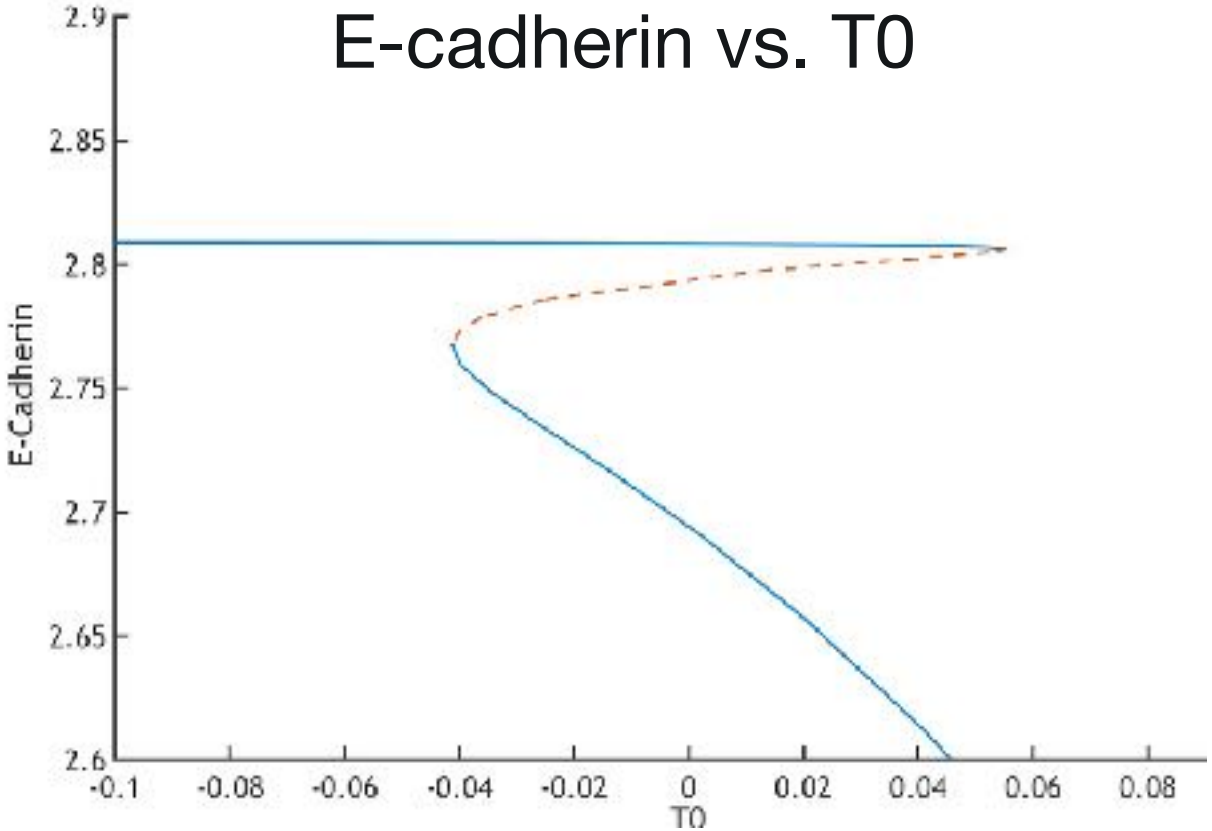




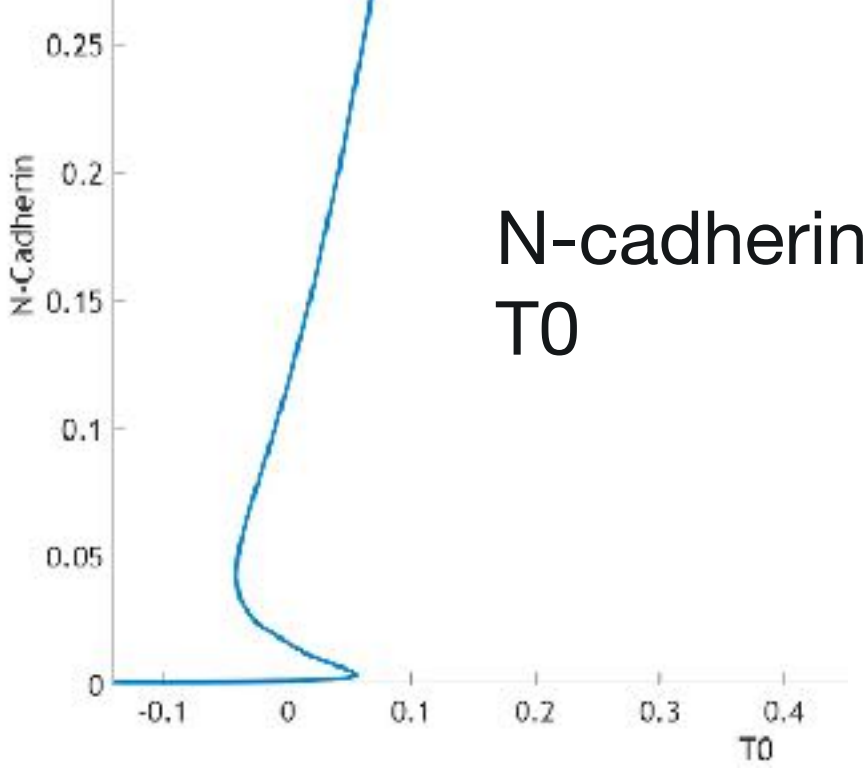


Model Results
Bifurcation

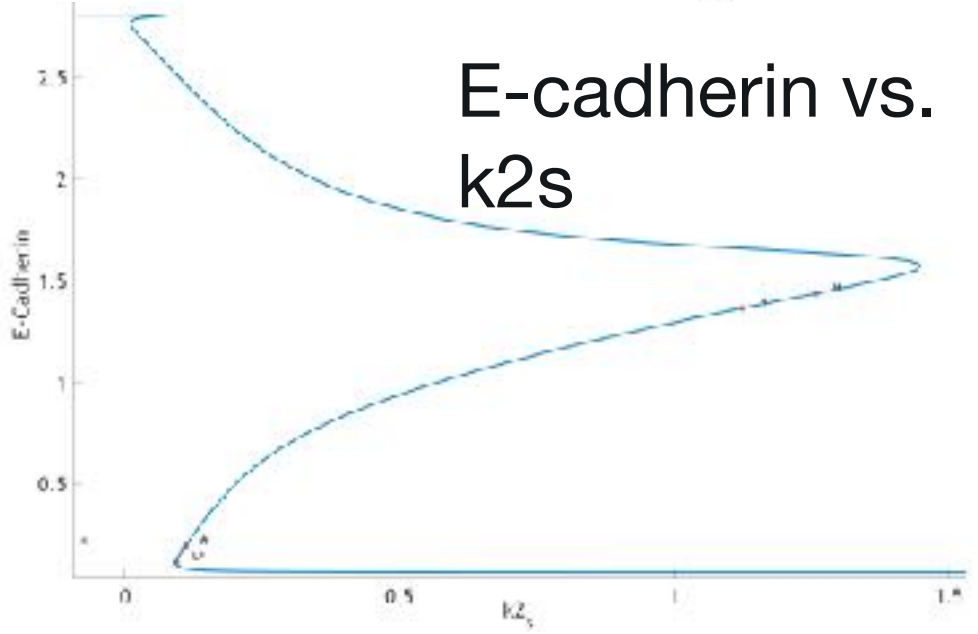
E-cadherin vs. T0



N-cadherin vs. T0



E-cadherin vs. k2s



Conclusions

- SLUG and TWIST are important TF to consider in EMT
- EMT affected by more than TGF-β input
- Modeling allows analysis of systems before experimentation

- Future research
  - *Confirm parameters through experimentation*
  - *Consider feedback loop on TWIST*
  - *Characterize stability of steady-states*
  - *Perform bifurcation analysis for species*
  - *Analyze effect of Hill coefficient*

References

- Gupta, S., & Maitra, A. (2016). EMT: Matter of Life or Death? *Cell*, 164(5), 840-842.
- Santillán, M. (2008). On the Use of the Hill Functions in Mathematical Models of Gene Regulatory Networks. *Mathematical Modelling of Natural Phenomena*, 3(2), 85-97.
- Tian, X., Zhang, H., & Xing, J. (2013). “Coupled Reversible and Irreversible Bistable Switches Underlying TGFβ-induced Epithelial to Mesenchymal Transition.” *Biophysical Journal*, 105(4), 1079-1089.