Boolean modeling of regulatory circuit governing Epithelial-Mesenchymal Transition (EMT)

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**EMT / MET : Engine of Cellular Plasticity**

EMT/MET is critical for cancer metastasis and therapy resistance that claim nearly all of cancer-related deaths. The dynamics of EMT/MET is not well-studied, hence limiting our ability to identify new therapeutic targets.

**Goal:** Understand the nonlinear dynamics of EMT/MET

1. Core EMT network is bistable

Boolean rules:
- $\text{SNAIL} = (\text{signal AND SNAIL})$ or $(\text{NOT SNAIL AND (signal AND NOT miR-34)})$
- $\text{miR-34} = (\text{NOT SNAIL})$ AND $(\text{NOT ZEB})$
- $\text{miR-200} = (\text{NOT SNAIL})$ AND $(\text{NOT ZEB})$
- $\text{ZEB} = (\text{SNAIL OR ZEB})$ AND $(\text{NOT miR-200})$

- Sequence of the network nodes as shown: (SNAIL, miR-34, miR-200, ZEB)
- Signal is exogenous TGF-β (E)

**Simulation Results**

2. Asynchronous simulations reveal the co-existence of two states

- The diagram here shows the average of 5000 asynchronous simulations, each starting from the same initial state.
- The value of each node can be 0 or 1. Average values represent that both steady states are attained with a certain probability.
- In absence of signal (E=0), cells attain epithelial state.

3. GRHL2 and OVOL stabilize epithelial state

New rules for GRHL2, OVOL, and ZEB:
- $\text{GRHL2} = (\text{NOT miR-200})$ and GHRL
- $\text{OVOL} = \text{NOT ZEB}$
- $\text{ZEB} = (\text{NOT GRHL2})$ AND $(\text{NOT OVOL})$ AND $(\text{NOT miR-200})$ AND $(\text{ZEB OR SNAIL})$

**Conclusion**

- Core EMT network can have two stable states - epithelial (high miR-34 and miR-200, low ZEB and SNAIL), and mesenchymal (low miR-34 and miR-200, high ZEB and SNAIL)
- Relative stability of states depend on EMT-inducing signal, GRHL2 and OVOL.
- GRHL2 and OVOL can stabilize epithelial state, and maintain it even in presence of EMT-inducing signal as well as when the signal is taken away.

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