

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



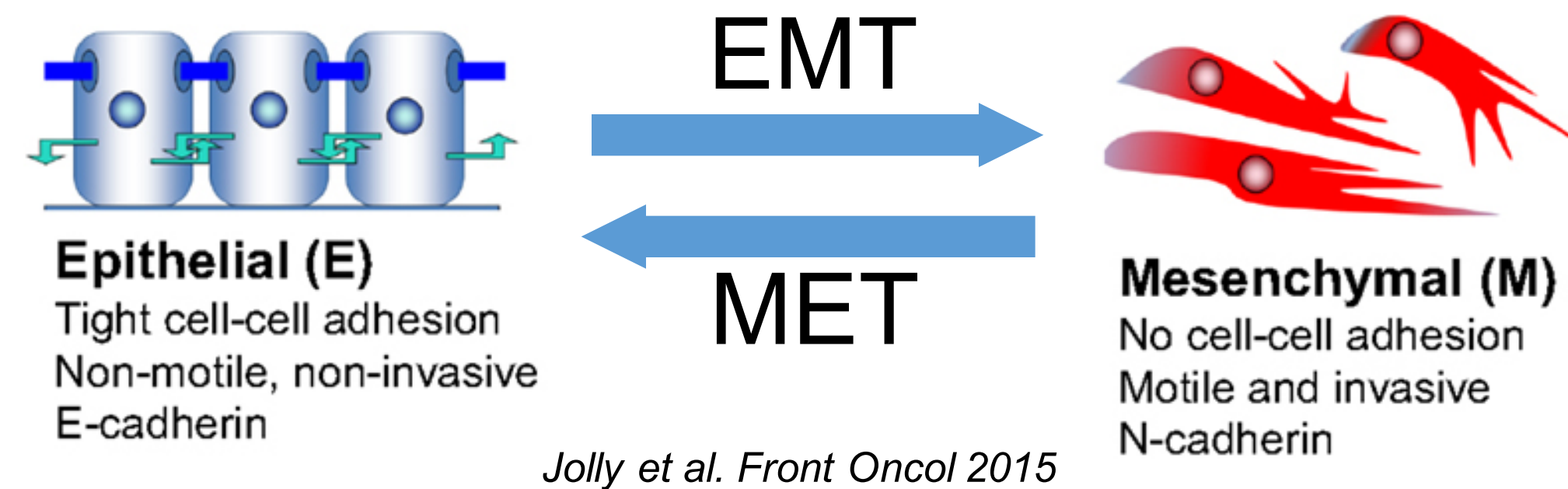
M Hisamatsu^{1,2}, S Tripathi³, MW Deem³, MK Jolly³, H Levine³

¹Department of Physics, Osaka University, Osaka, Japan, ²Nakatani RIES: Research & International experiences for Students

³Center for Theoretical Biological Physics, Rice University, Houston, TX



EMT / MET : Engine of Cellular Plasticity



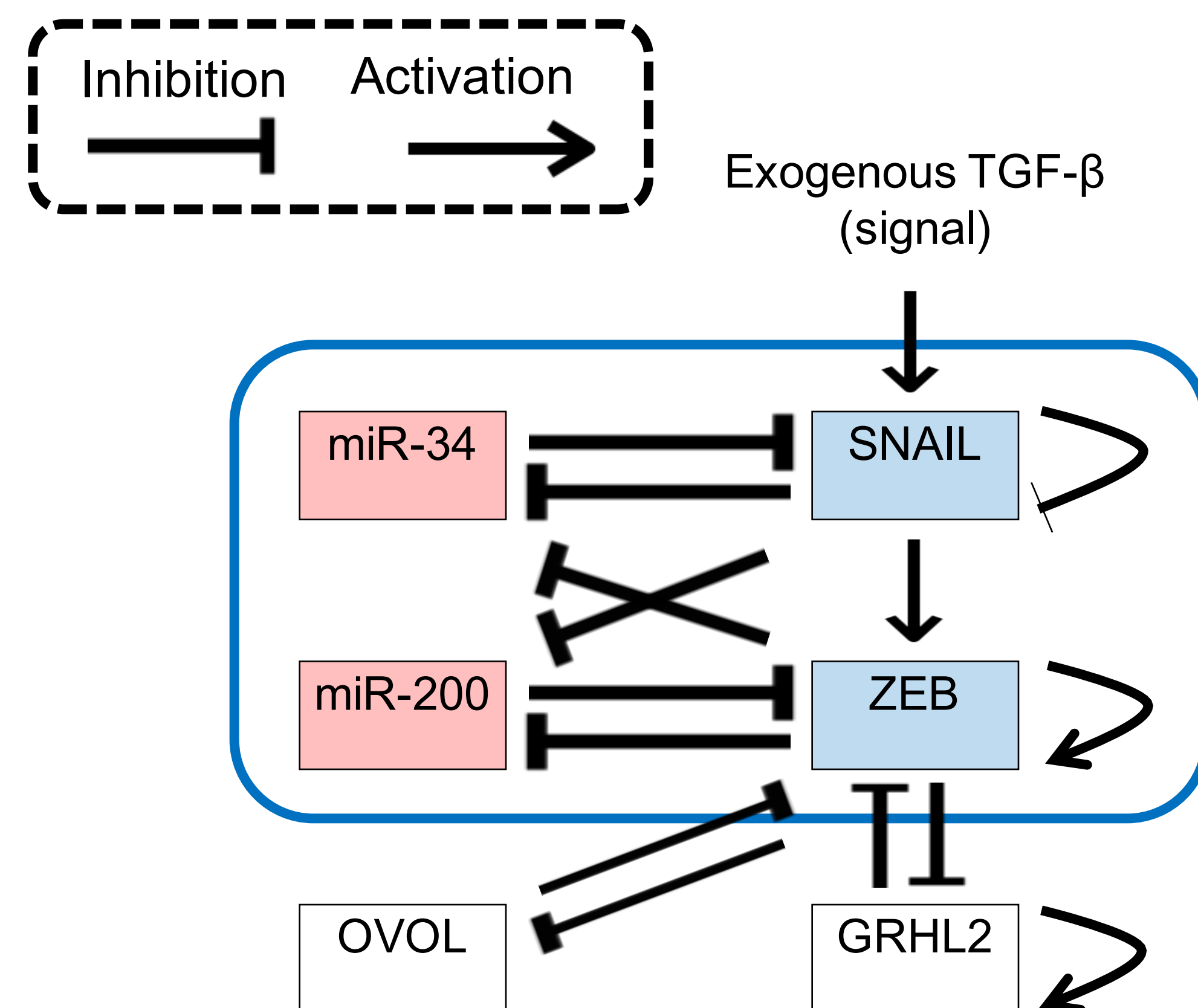
EMT/MET is critical for cancer metastasis and therapy resistance that claim nearly all of cancer-related deaths. The dynamics of EMT/MET is not well-studied, hence limiting our ability to identify new therapeutic targets.

Goal: Understand the nonlinear dynamics of EMT/MET

Boolean model for a core EMT network

Boolean network simulation:

- Uses 0 and 1 to represent expression level of genes - 0 means OFF and 1 means ON.
- Updates the next state of a gene depending on the number of activators, inhibitors, and Boolean update rule.
- Can be synchronous (the state of all genes are updated together in one time step) or asynchronous (only one gene updated in a given time step)



Red nodes are epithelial genes, blue ones are mesenchymal genes.

Core EMT network (shown in box) coupled with GRHL2 and OVOL.

Simulation Results

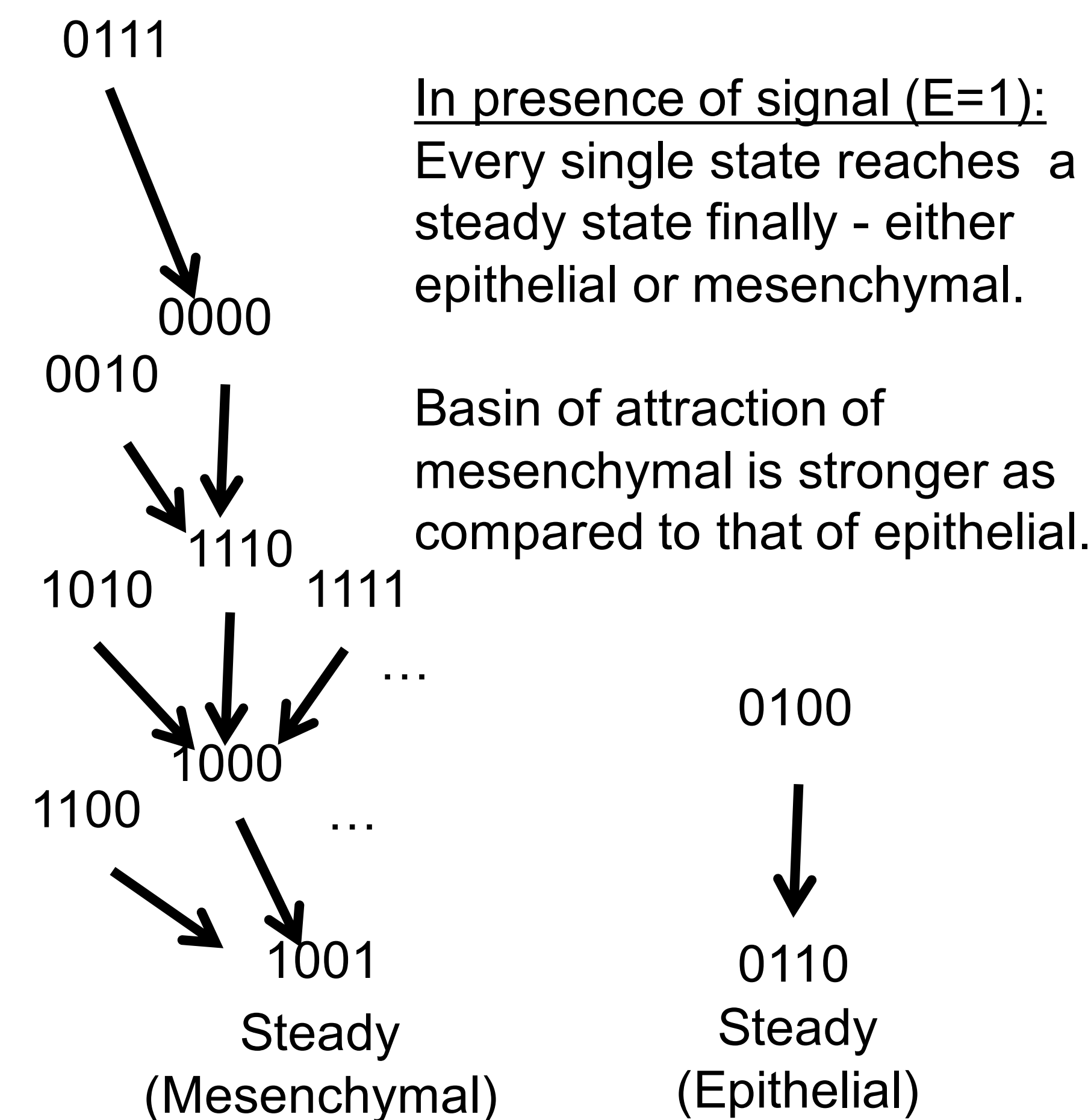
1. Core EMT network is bistable

Boolean rules:

- *SNAIL = (signal AND SNAIL) or (NOT SNAIL AND (signal AND NOT miR-34))
- *miR-34 = (NOT SNAIL) AND (NOT ZEB)
- *miR-200 = (NOT SNAIL) AND (NOT ZEB)
- *ZEB = (SNAIL OR ZEB) AND (NOT miR-200)

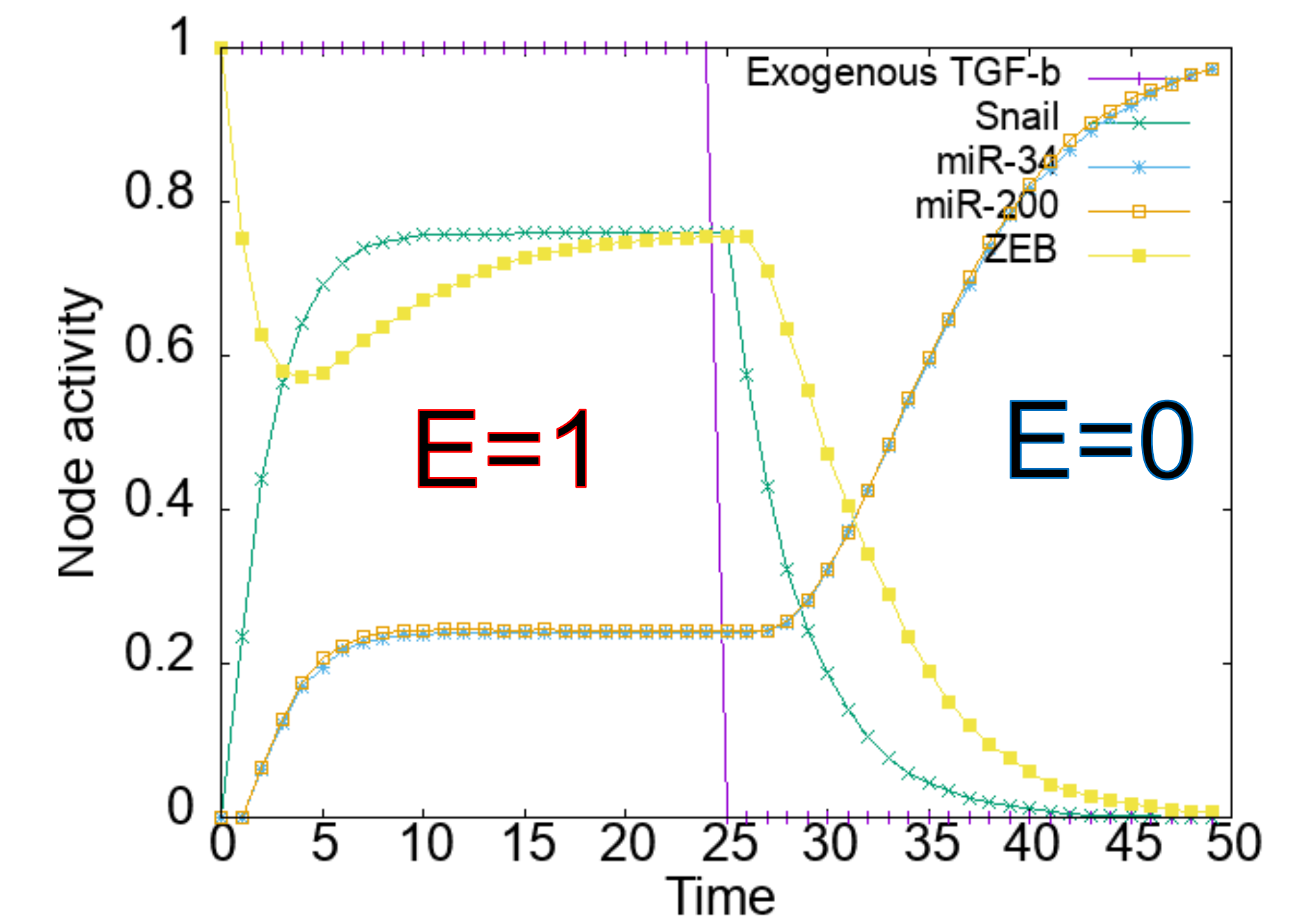
- Sequence of the network nodes as shown: (SNAIL, miR-34, miR-200, ZEB)
- Signal is exogenous TGF-β. (E)

Synchronous simulation



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

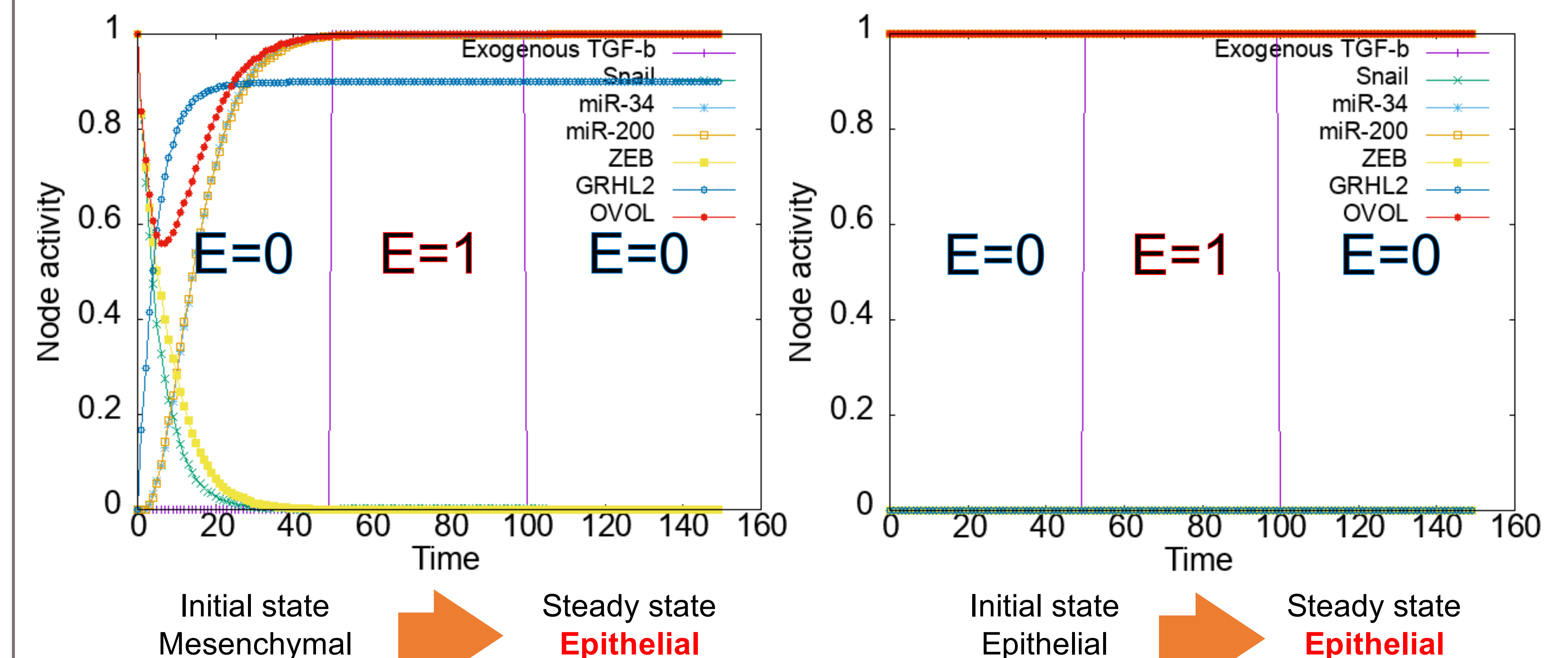
- The diagram here shows the average of 5000 asynchronous simulations, each starting from the same initial state.
- The value of each node can be 0 or 1. Average values represent that both steady states are attained with a certain probability.
- In absence of signal (E=0), cells attain epithelial state.



3. GRHL2 and OVOL stabilize epithelial state

New rules for GRHL2, OVOL, and ZEB:

- *GRHL2 = (NOT miR-200) and GRHL
- *OVOL = NOT ZEB
- *ZEB = (NOT GRHL2) AND (NOT OVOL) AND (NOT miR-200) AND (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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