Control of Tissue Homeostasis, Tumorigenesis, and Degeneration by Coupled Bidirectional Bistable Switches

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Motivation
The Hippo signaling pathway is responsible for organ size control, tissue homeostasis, and regeneration[1]. Dysfunction of this pathway has been associated with tumorigenesis and degenerative diseases[1-3]. This pathway consist of several kinases that target two transcriptional co-activators, Yes-associated protein 1 (YAP) and WWTR1 PDZ binding motif (TAZ)[1-3]. YAP/TAZ and its targets form complex regulatory network with many feedback loops. The roles of these feedbacks loops remain underexplored.

Methods
We used the following ODE system to describe the deterministic behavior of this regulatory network. \([L] \), \([YT\text{}_{\text{up}}]\), \([YT\text{ }p]\), \([S]\), and \([N]\) denote the concentrations of endogenous LATS1/2, unphosphorylated YAP/TAZ, phosphorylated YAP/TAZ, SIRT1, and NOTCH, respectively.

\[
\begin{align*}
\frac{d[L]}{dt} &= -k_{L}\cdot [L] - k_{LATS1/2}\cdot [L] \cdot [S] + k_{S}\cdot [S] - k_{T}\cdot [L] \cdot [Y]\cdot [P] - k_{S}\cdot [S] + k_{N}\cdot [N] \\
\frac{d[YT\text{ }\text{p}]}{dt} &= k_{LATS1/2}\cdot [L] \cdot [S] - k_{S}\cdot [S] + k_{Y}\cdot [Y] \cdot [T] \cdot [P] \\
\frac{d[Y\cdot T]}{dt} &= k_{S}\cdot [S] - k_{T}\cdot [L] \cdot [Y]\cdot [P] - k_{Y}\cdot [Y] \cdot [T] \cdot [P] + [T] \cdot [P] \\
\frac{d[S]}{dt} &= k_{S}\cdot [S] - k_{T}\cdot [L] \cdot [Y]\cdot [P] - k_{S}\cdot [S] + k_{N}\cdot [N] \\
\frac{d[N]}{dt} &= k_{S}\cdot [S] - k_{T}\cdot [L] \cdot [Y]\cdot [P] - k_{S}\cdot [S] + k_{N}\cdot [N] \\
\end{align*}
\]

To plot the nullclines when the value of \(k_{YT\text{up}}\) changes, we reduced the 5-ODE model to a 2-ODE model. To do so, we set \(d[YT\text{ }\text{p}]/dt, d[S]/dt\) and \(d[N]/dt\) to 0. The pseudo-steady states, \([YT\text{ }\text{p},*], [S,*] \) and \([N,*]\), were used to plot \(d[YT\text{ }\text{p}]/dt = 0\) and \(d[YT\text{ }\text{p}]/dt = 0\).

Results
The lower blue branch, middle green branch, and upper red branch are defined as the degenerative state, homeostatic state, and tumorigenic state. Each color shaded region shows different types of stability ranges within each state. Most important is the green shaded region representing the monostable region of the homeostatic state. The nullclines were also plotted for values of \(k_{YT\text{up}}\) that were within the bistable regions.

Conclusion and Future Works
Hippo pathway can regulate transition between physiological and pathological states using coupled bidirectional bistable switches. Expanding the monostability range within the homeostatic state by targeting the strength of the YAP/TAZ-LATS1/2 negative feedback loop had a tradeoff in also making at least of the one of the transitions easier to occur. Future work includes experimental work for verification of this regulatory network.

Acknowledgements
I would like to thank Dr. Tian for his guidance on this project. I would also like to thank Juan Melendez-Alvarez for helping me understand some of the concepts and methods used.

References