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

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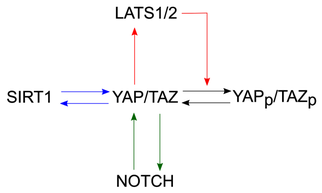
Motivation

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 WWRT 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], $[YT_{up}]$, $[YT_p]$, [S], and [N] denote the concentrations of endogenous LATS1/2, unphosphorylated YAP/TAZ, phosphorylated YAP/TAZ, SIRT1, and NOTCH, respectively.

$$\frac{d[L]}{dt} = k_{L1} + k_{L2}\cdot\frac{[YT_{up}]^n}{[YT_{up}]^n + J_L^n} - k_{L3}\cdot[L] \quad (1)$$

$$\frac{d[YT_{up}]}{dt} = k_{YTup0} + k_{YTup1}\cdot\frac{[S]^n}{[S]^n + J_{YTup1}^n} + k_{YTup2}\cdot\frac{[N]^n}{[N]^n + J_{YTup2}^n} + k_{YTup3}\cdot\frac{[YT_{up}]\cdot[L]}{[YT_{up}] + J_{YTup3}} + k_{YTup4}\cdot\frac{[YT_p]}{[YT_p] + J_{YTup4}} - k_{YTup5}\cdot[YT_{up}] \quad (2)$$

$$\frac{d[YT_p]}{dt} = k_{YTup3}\cdot\frac{[YT_{up}]\cdot[L]}{[YT_{up}] + J_{YTup3}} - k_{YTup4}\cdot\frac{[YT_p]}{[YT_p] + J_{YTup4}} - k_{YTp1}\cdot[YTp] \quad (3)$$

$$\frac{d[S]}{dt} = k_{S1} + k_{S2}\cdot\frac{[YT_{up}]^n}{[YT_{up}]^n + J_S^n} - k_{S3}\cdot[S] \quad (4)$$

$$\frac{d[N]}{dt} = k_{N1} + k_{N2}\cdot\frac{[YT_{up}]^n}{[YT_{up}]^n + J_N^n} - k_{N3}\cdot[N] \quad (5)$$

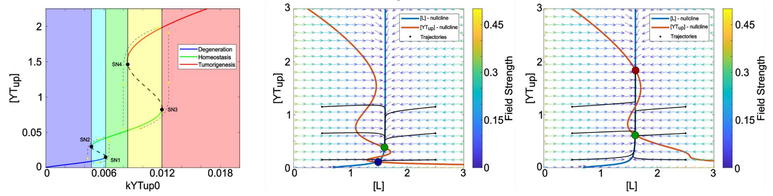
To plot the nullclines when the value of k_{YTup0} changes, we reduced the 5-ODE model to a 2-ODE model. To do so, we set d[YT_p]/dt, d[S]/dt and d[N]/dt to 0. The pseudo-steady states, [YT_p*], [S*] and [N*], were used to plot d[L]/dt = 0 and d[YT_{up}]/dt = 0.

$$\frac{d[L]}{dt} = k_{L1} + k_{L2}\cdot\frac{[YT_{up}]^n}{[YT_{up}]^n + J_L^n} - k_{L3}\cdot[L] \quad (6)$$

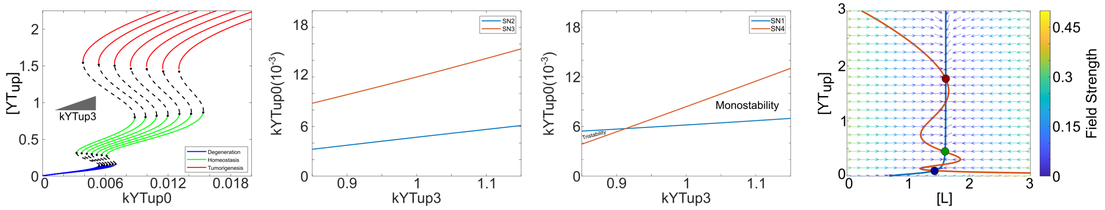
$$\frac{d[YT_{up}]}{dt} = k_{YTup0} + k_{YTup1}\cdot\frac{[S^*]^n}{[S^*]^n + J_{YTup1}^n} + k_{YTup2}\cdot\frac{[N^*]^n}{[N^*]^n + J_{YTup2}^n} + k_{YTup3}\cdot\frac{[YT_{up}]\cdot[L]}{[YT_{up}] + J_{YTup3}} + k_{YTup4}\cdot\frac{[YT_p^*]}{[YT_p^*] + J_{YTup4}} - k_{YTup5}\cdot[YT_{up}] \quad (7)$$

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_{YTup0} that were within the bistable regions.

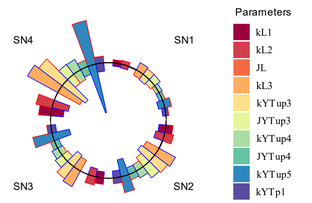


The parameter kYTup3 was used to characterize the strength of the YAP/TAZ-LATS1/2 negative feedback loop. The bifurcation diagram shows the possibility of a tristable region and how the transition thresholds change with increasing or decreasing kYTup3. The nullclines were plotted again to show the three stable state states when kYTup3 was 85% of its original parameter value.

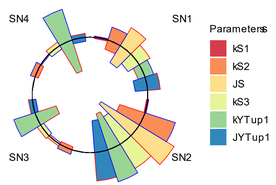


Data from 2-parameter bifurcation diagrams were used to calculate the percent changes in the transition thresholds with increases and decreases in their original parameter values by 15%. This circular barplots allows better visualization for determining which parameters from the feedback loops have greater control over the transition thresholds.

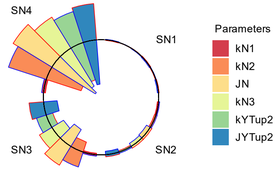
YAP/TAZ-LATS1/2 Feedback Loop



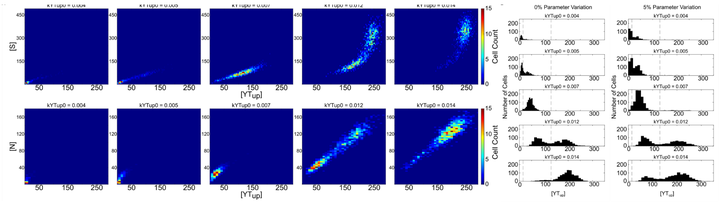
YAP/TAZ-SIRT1 Feedback Loop



YAP/TAZ-NOTCH Feedback Loop



Results(continued)



These heatmaps show the cell counts with specific [S], [N], and $[YT_{up}]$ concentrations after running simulations with intrinsic noise by using the Tau-leap based Gillespie algorithm and changing the value of k_{YTup0}. The cells can be better visualized by using the distribution of $[YT_{up}]$ as k_{YTup0} changes. Including extrinsic noise, in addition to the intrinsic noise, make the distributions within each state wider.

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.

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References

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