Analyzing gene regulatory networks by comparing the dynamics obtained via DSGRN (Dynamic Signatures Generated by Regulatory Networks) and RACIPE (Random Circuit Perturbation)

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Random Sampling in RACIPE and Rook Fields

Week Three

\[
\begin{align*}
\frac{dA}{dt} &= G_A H^S(B, BA_0, n_{BA}, \lambda_{BA}^-) - k_A A \\
\frac{dB}{dt} &= G_B H^S(A, AB_0, n_{AB}, \lambda_{AB}^-) - k_B B
\end{align*}
\]

- \( G \) : Maximum production rate
- \( k \) : Degradation rate
- \( \lambda \) : Fold change by regulation
- \( X_0 \) : Threshold of regulation
- \( n \) : Cooperativity of regulation

Update the mathematical model

State I

State II

Randomize the kinetic parameters

State I

State II

Protein A and B move to the stable steady states

Probability

1 2 3 4 5 6
Progress

Over the last week, we compiled documents explaining the random sampling of RACIPE and the current literature on the computational cost of RACIPE. We analyzed the half-functional rule using the additional information files and the source code. We then moved to reproduce the results in RACIPE, particularly the ratio between the amount of monostable and bistable steady states. From there, we reproduced the rook fields seen in Konstantin’s initial DSGRN presentation. Finally, we have begun working on reproducing the toggle switch results from RACIPE in DSGRN using essential parameters and their neighbors.
The Half-Functional Rule

• Isolated gene “num” times

• Isolated genes with inward regulations ”num” times

• Multiply by Hill functions with thresholds from above

• Median outputs

Toggle-switch circuit (TS):

\[
\begin{align*}
\dot{A} &= G_A H^S(B, BA_0, n_{BA}, \lambda^-_{BA}) - k_A A \\
\dot{B} &= G_B H^S(A, AB_0, n_{AB}, \lambda^-_{AB}) - k_B B,
\end{align*}
\]

Toggle-switch circuit with one-sided self-activation (TS1SA):

\[
\begin{align*}
\dot{A} &= G_A H^S(B, BA_0, n_{BA}, \lambda^-_{BA}) H^S(A, AA_0, n_{AA}, \lambda^+_{AA}) / \lambda^+_{AA} - k_A A \\
\dot{B} &= G_B H^S(A, AB_0, n_{AB}, \lambda^-_{AB}) - k_B B,
\end{align*}
\]

Toggle-switch circuit with two-sided self-activation (TS2SA):

\[
\begin{align*}
\dot{A} &= G_A H^S(B, BA_0, n_{BA}, \lambda^-_{BA}) H^S(A, AA_0, n_{AA}, \lambda^+_{AA}) / \lambda^+_{AA} - k_A A \\
\dot{B} &= G_B H^S(A, AB_0, n_{AB}, \lambda^-_{AB}) H^S(B, BB_0, n_{BB}, \lambda^+_{BB}) / \lambda^+_{BB} - k_B B,
\end{align*}
\]

Organizing the Information
DSGRN database

Parameter Graph: Region of Parameter Space & Dynamics

$\ell_{2,1} < u_{2,1} < \gamma_2 \theta_{1,2}$

$\ell_{2,1} < \gamma_2 \theta_{1,2} < u_{2,1}$

$\gamma_2 \theta_{1,2} < \ell_{2,1} < u_{2,1}$

Database provides a complete decomposition of parameter space into explicit regions (semi-algebraic sets) and description of global dynamics over each region. Purely combinatorial representation.

$u = \ell + \delta$

Representing Dynamics

Assume

$\ell_{1,2} < u_{1,2} < \gamma_1 \theta_{2,1}$

$\ell_{2,1} < u_{2,1} < \gamma_2 \theta_{1,2}$

Rook Field

State Transition Graph

Morse Graph (poset)

$\ell_{1,2} < \theta_{1,2}$ if $x_2 < \theta_{1,2}$

$\ell_{1,2}$ if $x_2 > \theta_{1,2}$

$\ell_{2,1} + \delta_{2,1}$ if $x_1 < \theta_{2,1}$

$\ell_{2,1}$ if $x_1 > \theta_{2,1}$

Toggle Switch Parameter Space in DSGRN
Next Steps

Our next steps include understanding essential parameters, running the RACIPE simulations in DSGRN with the essential parameters, and continuing to study the mathematics that underly both DSGRN and RACIPE.
Thank You for Listening!

and

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