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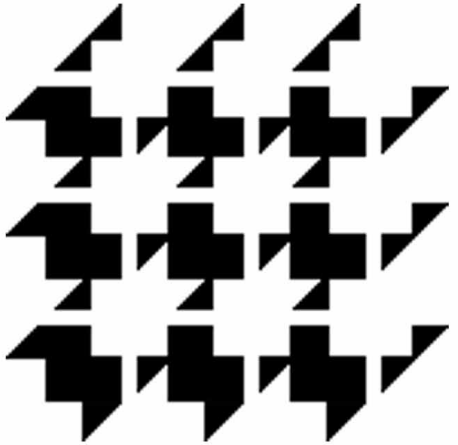

Analyzing gene regulatory networks by comparing the dynamics obtained via DSGRN (Dynamic Signatures Generated by Regulatory Networks) and RACIPE (Random Circuit Perturbation)

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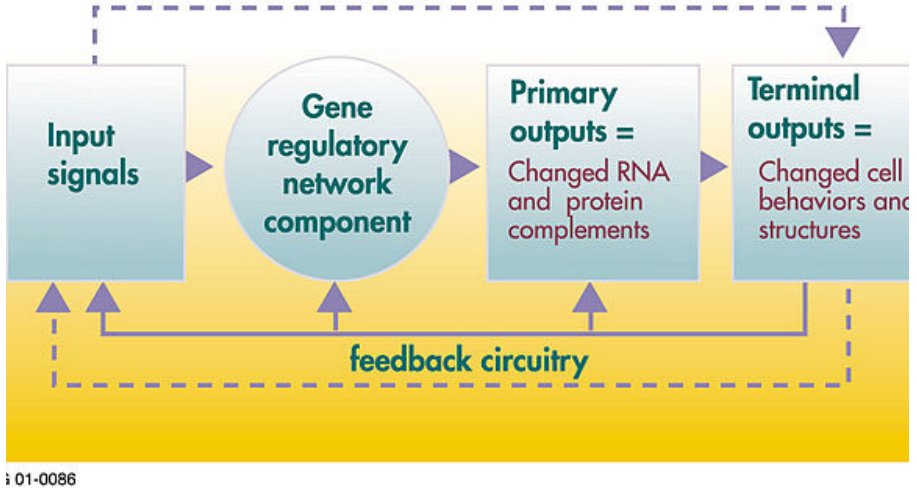
Abstract

In this research project, we are studying the analyses generated by Huang et al. using random circuit perturbation (RACIPE). After gaining a comprehensive understanding of Huang's paper, we will attempt to use RACIPE to reproduce these results. We will move from there to produce analogous results in DSGRN. After both sets of results have been generated, we will compare our RACIPE results to our DSGRN results. After completing these steps, we can take the project in a variety of directions depending on what the conclusions the comparisons yield.

Introduction

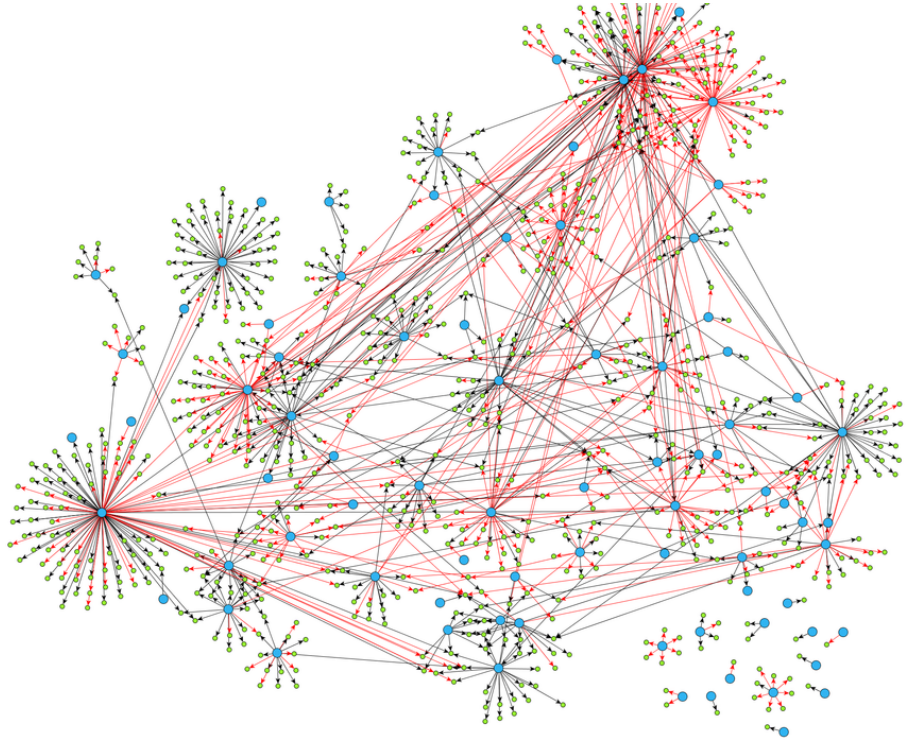
Gene Regulatory Networks



Gene Regulatory Networks (GRNs) are collections of molecular regulators that interact with each other and other substances in the cell to govern gene expression levels of mRNA and proteins.

They are often assembled into pathways and networks to be studied under the umbrellas of systems and computational biology.

Entirely understanding these networks would allow us to target diseases, namely cancer, accurately without the devastating side effects on healthy cells that mark today's drugs.



DSGRN (Dynamic Signatures Generated by Regulatory Networks)

- Difficulty in knowing the many kinetic parameters required in popular ODE models
- DSGRN: computing coarse information without solving the ODE system
- ”Coarse” information and invariant sets
- Gives information about the dynamics for all possible parameter values
- Instantaneous

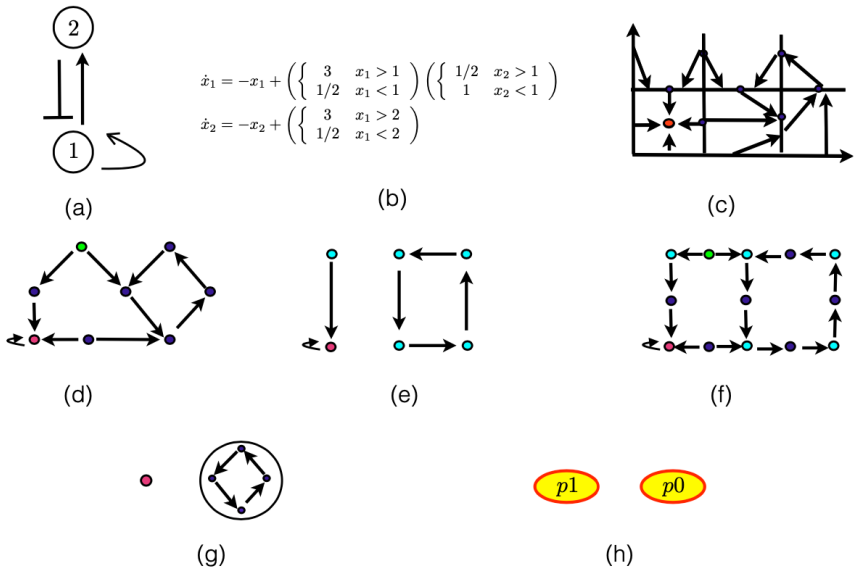
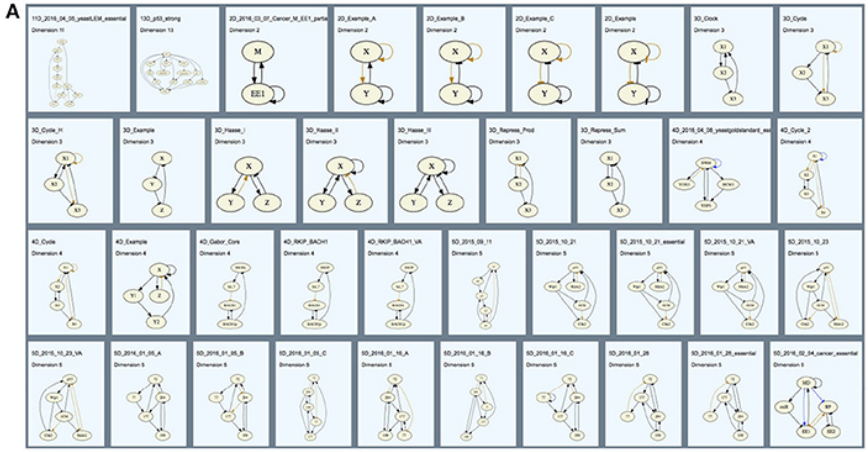
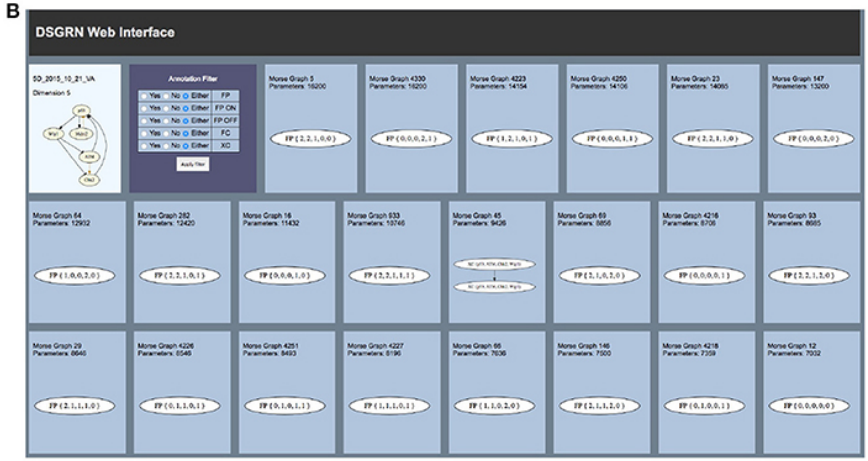
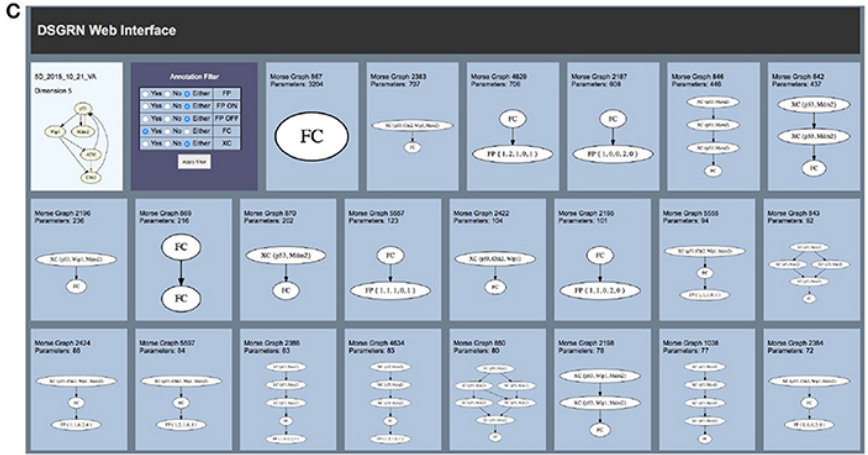


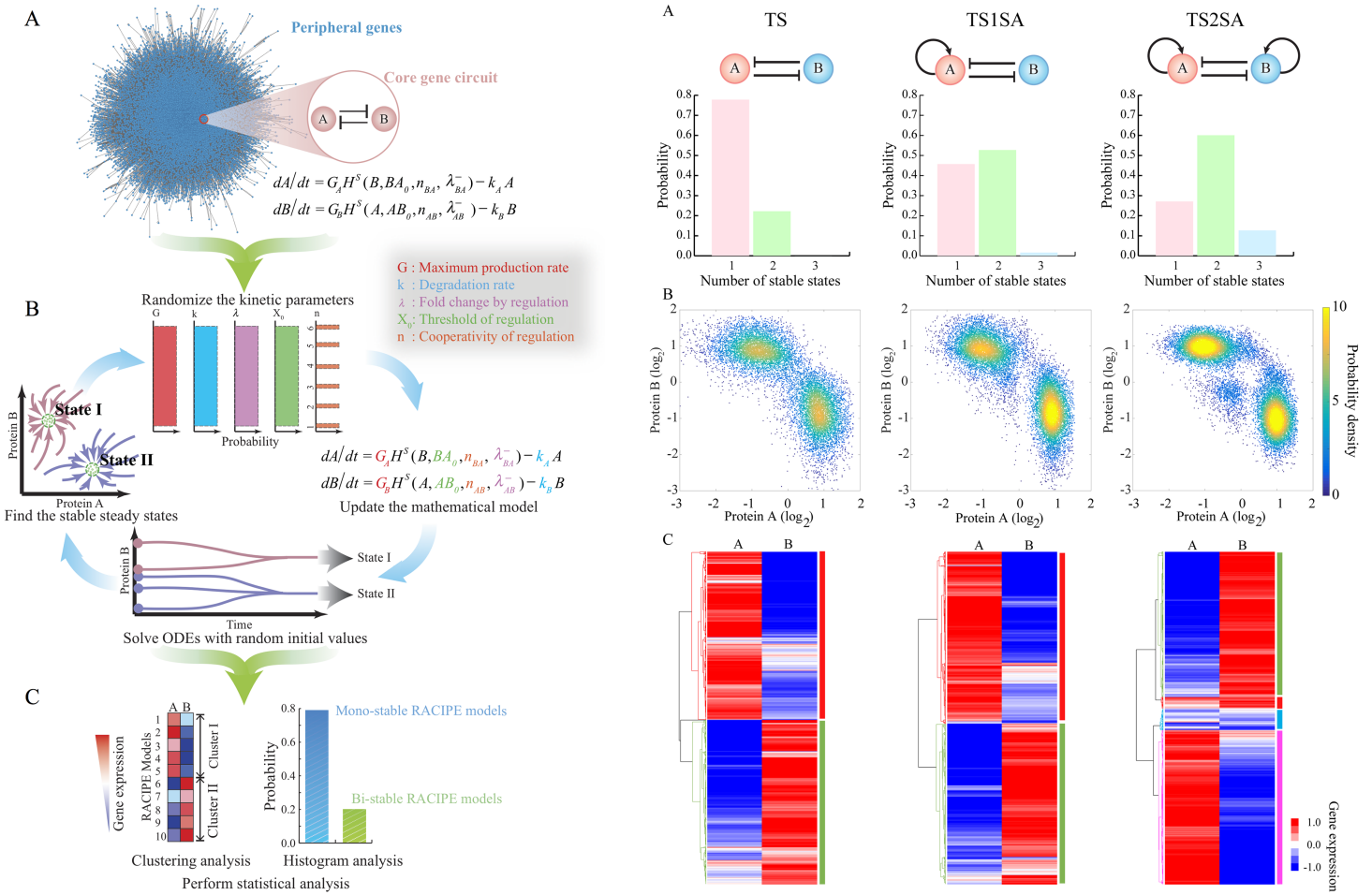
Figure 1. (a) *Regulatory network* **RN**; (b) *a set of equations with a particular choice of parameters for* **RN**; (c) *phase space*; (d) *wall graph*; (e) *domain graph*; (f) *wall-domain graph*; (g) *a set of strongly connected components of the wall, domain, or wall-domain graph*; (h) *Morse graph representing strongly connected components.*







RACIPE (*ra*ndom *ci*rcuit *pe*rturbation)



- Core gene regulatory circuitry
- Many random kinetic models generated from a fixed circuit topology
- Randomizes all key parameters in set ranges, except the threshold values
- Solves the rate equations, which are comprised of Hill functions and additional (G, k) parameters
- Finds steady states and repeats the process
- Statistical analysis employed to determine robust dynamical properties
- Topology, not parameters
- Average simulation time per model scales linearly with the total number of parameters in the model

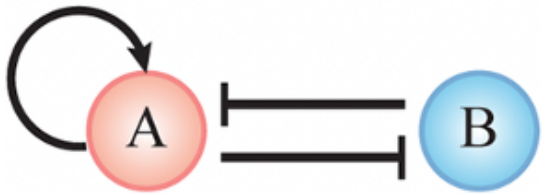
Huang, B., Lu, M., Jia, D., Ben-Jacob, E., Levine, H., & Onuchic, J. N. (2017). Interrogating the topological robustness of gene regulatory circuits by randomization. PLOS Comput Biol, 13(3), e1005456–21. http://doi.org/10.1371/journal.pcbi.1005456

Toggle Switches

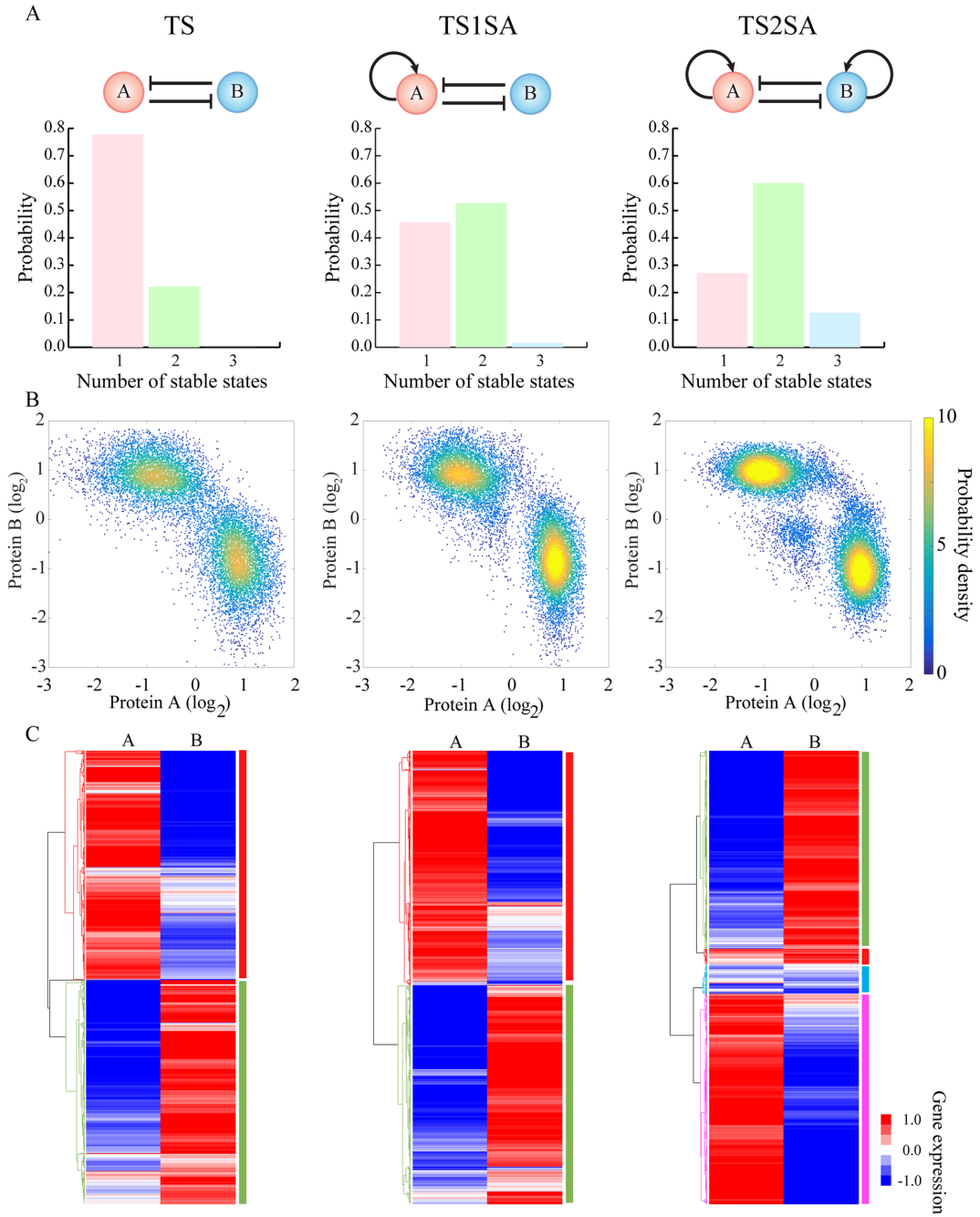
Toggle Switches in RACIPE

TS

TS1SA

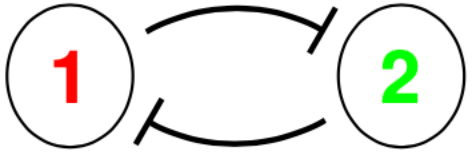


TS2SA



Huang, B., Lu, M., Jia, D., Ben-Jacob, E., Levine, H., & Onuchic, J. N. (2017). Interrogating the topological robustness of gene regulatory circuits by randomization. PLOS Comput Biol, 13(3), e1005456–21. http://doi.org/10.1371/journal.pcbi.1005456

Toggle Switches in DSGRN



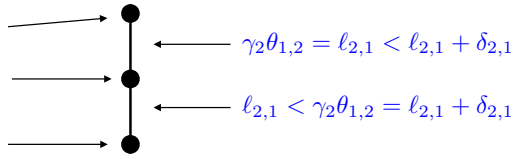
Identifying Sign of $-\gamma_2 x_2 + \lambda_{2,1}(x_1)$

Remark: the only explicit value of x_2 is $\theta_{1,2}$ arising from definition of $\lambda^-_{1,2}$. Therefore, we focus on sign of

$$-\gamma_2\theta_{1,2} + \lambda^-_{2,1}(x_1) = -\gamma_2\theta_{1,2} + \begin{cases} \ell_{2,1} + \delta_{2,1} & \text{if } x_1 < \theta_{2,1} \\ \ell_{2,1} & \text{if } x_1 > \theta_{2,1} \end{cases}$$

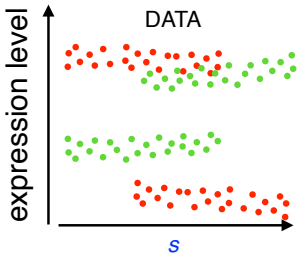
Three Possibilities:

$$\gamma_2\theta_{1,2} < \ell_{2,1} < \ell_{2,1} + \delta_{2,1}$$
$$\ell_{2,1} < \gamma_2\theta_{1,2} < \ell_{2,1} + \delta_{2,1}$$
$$\ell_{2,1} < \ell_{2,1} + \delta_{2,1} < \gamma_2\theta_{1,2}$$

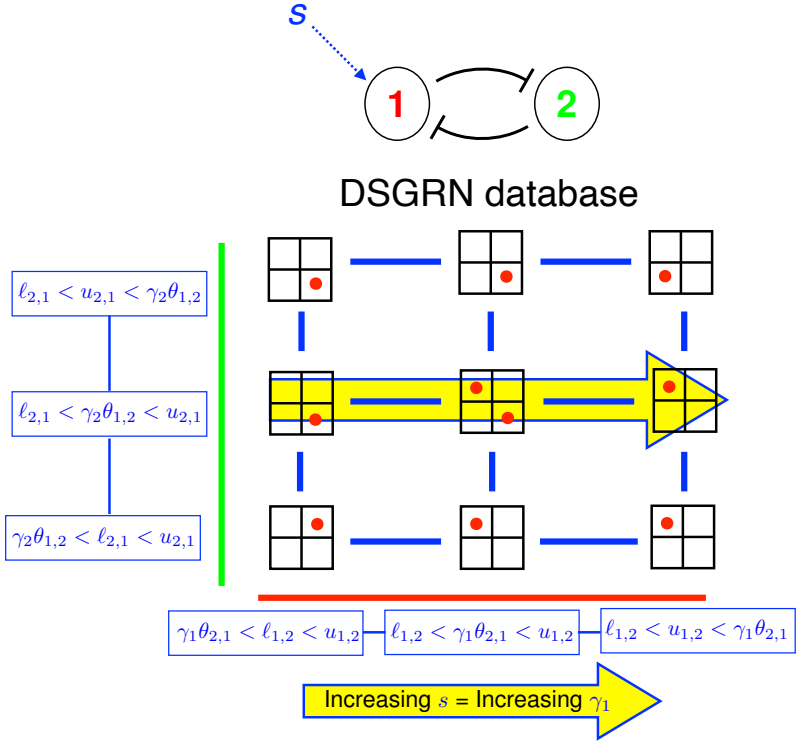


Remark: This defines a semi-algebraic decomposition of the associated parameter space $(0, \infty)^4$.

Data Analysis



Levels of expression of two genes at various levels of a compound *s* that increases degradation rate of product of gene 1.



We cannot get such a qualitative match with  or  .

Hill Functions and Rook Fields

Toggle Switch (TS) Hill Function

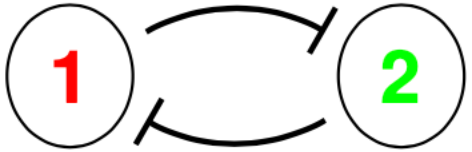
$$\dot{A} = g_A H^S(B, BA_0, n_{BA}, \lambda^-_{BA}) - k_A A$$
$$\dot{B} = g_B H^S(A, AB_0, n_{AB}, \lambda^-_{AB}) - k_B B \quad ,$$

$$\dot{A} = g_A(\lambda^-_{BA} + (1 - \lambda^-_{BA})(1/(1+(B/BA_0)^{n_{BA}}))) - k_A A$$

$$\dot{B} = g_B(\lambda^-_{AB} + (1 - \lambda^-_{AB})(1/(1+(A/AB_0)^{n_{AB}}))) - k_B B$$

Huang, B., Lu, M., Jia, D., Ben-Jacob, E., Levine, H., & Onuchic, J. N. (2017). Interrogating the topological robustness of gene regulatory circuits by randomization. PLOS Comput Biol, 13(3), e1005456–21. http://doi.org/10.1371/journal.pcbi.1005456

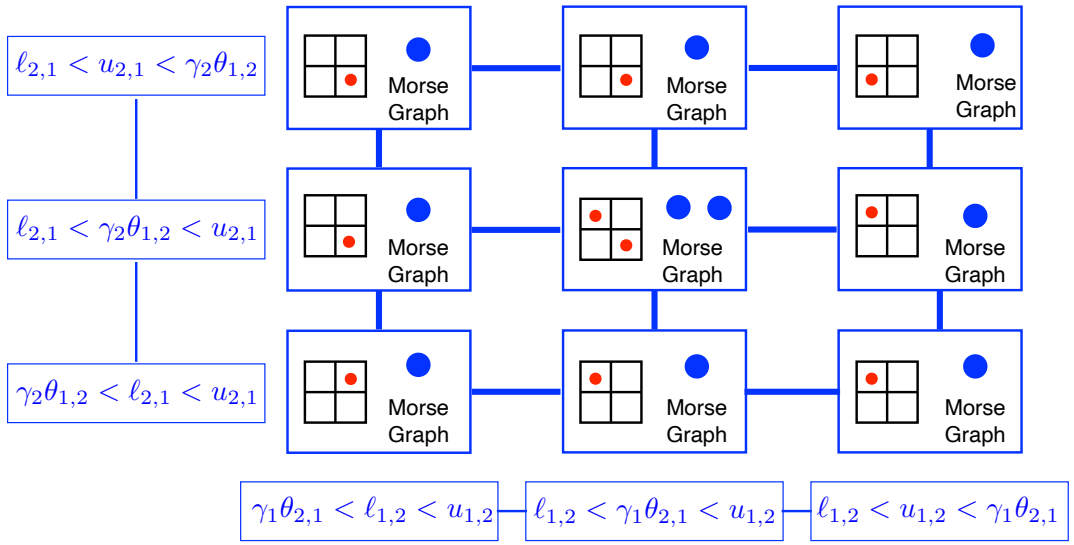
Toggle Switch Parameter Space in DSGRN



Organizing the Information

DSGRN database

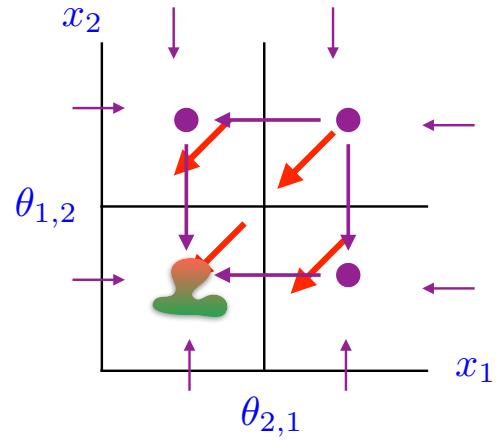
Parameter Graph: Region of Parameter Space & Dynamics



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



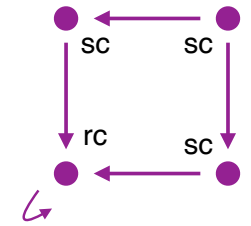
Assume $\ell_{1,2} < u_{1,2} < \gamma_1\theta_{2,1}$, $\ell_{2,1} < u_{2,1} < \gamma_2\theta_{1,2}$

Rook Field

$$-\gamma_1 x_1 + \begin{cases} \ell_{1,2} + \delta_{1,2} & \text{if } x_2 < \theta_{1,2} \\ \ell_{1,2} & \text{if } x_2 > \theta_{1,2} \end{cases}$$

$$-\gamma_2 x_2 + \begin{cases} \ell_{2,1} + \delta_{2,1} & \text{if } x_1 < \theta_{2,1} \\ \ell_{2,1} & \text{if } x_1 > \theta_{2,1} \end{cases}$$

State Transition Graph



Morse Graph (poset)

● rc

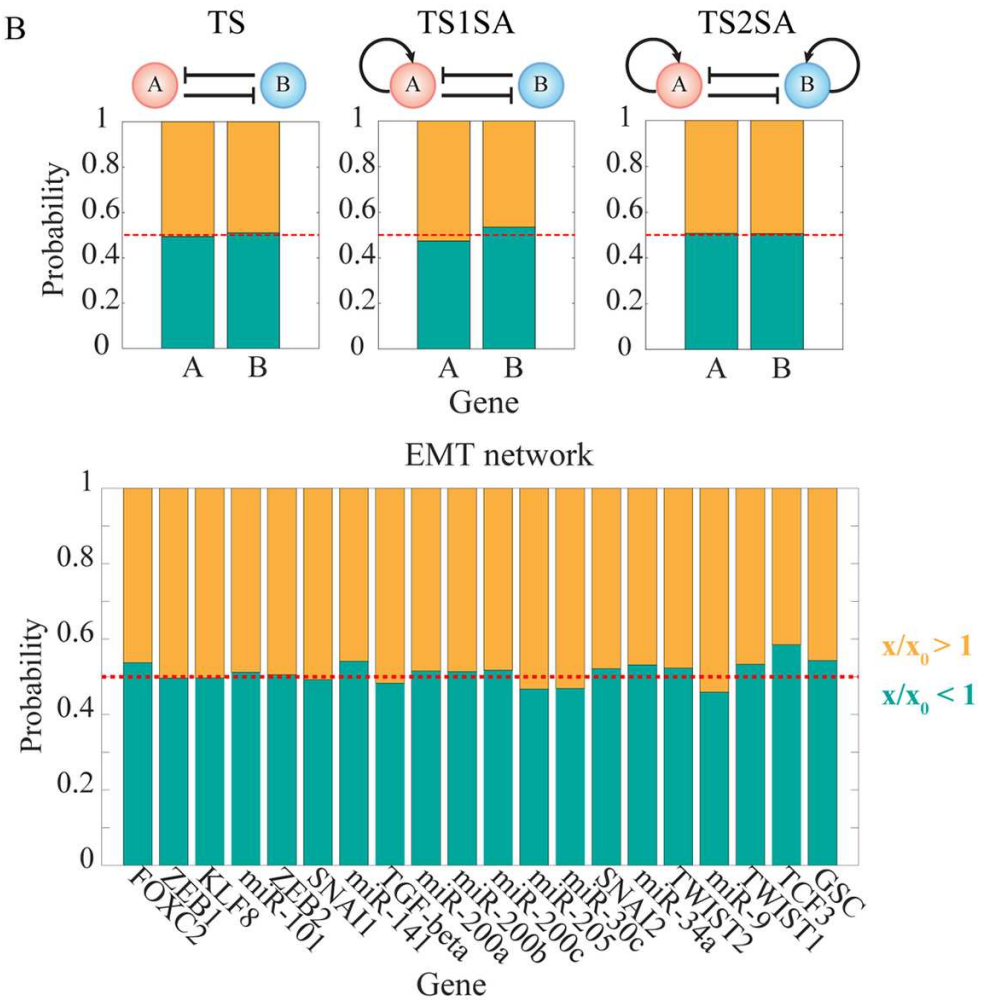
RACIPE Sampling

RACIPE Parameter Ranges for Sampling

Parameters	Min to Max Values (Uniform)	Mean, Standard Deviation (Rectified Gaussian)$^{+}$	Mean (Exponential)
Maximum production rate (G)	1-100	50.5, 49.5	50.5
Degradation rate (k)	0.1-1	0.55, 0.45	0.55
Fold change (λ)*	1-100	50.5, 49.5	50.5
Threshold (X_0)	The ranges, which depend on the inward regulations, are estimated by a Monte Carlo simulation.		
Hill coefficient (n)$^{\#}$	1-6	3.5, 2.5	3.5

Huang, B., Lu, M., Jia, D., Ben-Jacob, E., Levine, H., & Onuchic, J. N. (2017). Interrogating the topological robustness of gene regulatory circuits by randomization. PLOS Comput Biol, 13(3), e1005456–21. http://doi.org/10.1371/journal.pcbi.1005456

RACIPE's Half-Functional Rule



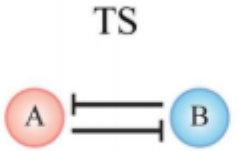
The method used in random sampling for thresholds:

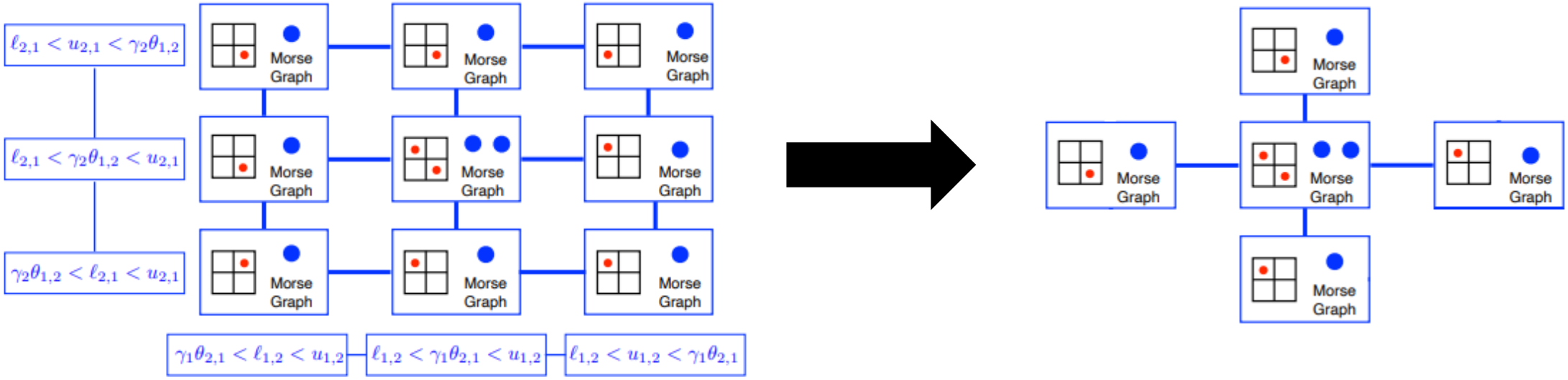
The half-functional rule is used such that the median value chosen results in 50% of the values being below the threshold and 50% being above it. This ensures that the link is active half of the time, which allows for a good understanding of each link in the circuit.

Huang, B., Lu, M., Jia, D., Ben-Jacob, E., Levine, H., & Onuchic, J. N. (2017). Interrogating the topological robustness of gene regulatory circuits by randomization. PLOS Comput Biol, 13(3), e1005456–21. http://doi.org/10.1371/journal.pcbi.1005456

Essential Parameters and Neighbors

Essential Nodes and Their Neighbors:





- Essential nodes are where the links have probability to be both active and inactive.

- Neighbors are the nodes adjacent to the essential nodes.

RACIPE Data in DSGRN

Parameter space in DSGRN corresponding to RACIPE results

- Lun Zhang's DSGRN code
- L, U, and T $\ell_{1,2} < u_{1,2} < \gamma_1\theta_{2,1}$ $\ell_{2,1} < u_{2,1} < \gamma_2\theta_{1,2}$

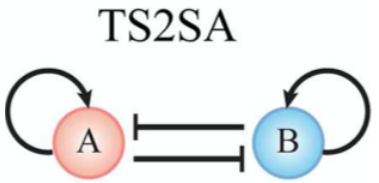
$$\dot{B} = g_B(\lambda^-_{AB} + (1 - \lambda^-_{AB})(1/(1 + (A/AB_0)^{n_{AB}}))) - k_B B$$

Inhibition: L = g*λ; U = g; T = AB_0*k
Self-Activation: L = g; U = g*λ; T = BB_0*k

- G and 1 vs. $\sqrt{G}$ and $\sqrt{G}$ in the model
- Essential parameters and their neighbors

Results Table

TS2SA Simulations



num_paras	minN/maxN	num_ode	stable: 1 #	stable: 2 #	stable: 3 #	stable: 4 #	stable: 5 #		stable: 1 %	stable: 2 %	stable: 3 %	stable: 4 %	stable: 5 %
1000	2	1000	423	535	42	0	0		42.3	53.5	4.2	0	0
1000	4	1000	156	654	183	6	1		15.6	65.4	18.3	0.6	0.1
1000	6	1000	124	584	281	9	2		12.4	58.4	28.1	0.9	0.2
1000	10	1000	115	492	360	29	4		11.5	49.2	36	2.9	0.4
1000	20	1000	77	455	426	35	7		7.7	45.5	42.6	3.5	0.7
1000	30	1000	60	468	422	40	10		6	46.8	42.2	4	1
10000	2	1000	4147	5451	398	4	0		41.47	54.51	3.98	0.04	0
10000	4	1000	1617	6398	1943	37	5		16.17	63.98	19.43	0.37	0.05
10000	6	1000	1148	5936	2793	110	13		11.48	59.36	27.93	1.1	0.13
10000	10	1000	954	5398	3394	214	40		9.54	53.98	33.94	2.14	0.4
10000	20	1000	842	4772	3970	345	71		8.42	47.72	39.7	3.45	0.71
10000	30	1000	778	4501	4179	414	128		7.78	45.01	41.79	4.14	1.28
10000	1 to 6	DSGRN Weighting							10.07	39.96	48.04	1.66	0.27
DSGRN (196 Essential)			0	46	102	28	20		0	23.469388	52.040816	14.285714	10.204082
DSGRN (756 Essential + Neighbors)			112	302	246	76	20		14.814815	39.94709	32.539683	10.05291	2.6455026
DSGRN (1600 Parameters)			560	654	262	104	20		35	40.875	16.375	6.5	1.25

Future Work

The results of the comparisons between our RACIPE and DSGRN results could potentially lead to a paper describing the results and could also lead to additional problems that could be studied during the research project or afterwards, such as applying these ideas to networks of biological interest, understanding how to sample for large networks, understanding how to apply these ideas to a broader range of dynamics, computing volumes of the DSGRN regions of parameter space, or understanding how the regions change as a function of more realistic parameters.

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Thank You for Listening!

And

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And

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