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/Project Description

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.

DSGRN (Dynamic Signatures Generated by Regulatory Networks)

- The current state of modeling GRNs
- Difficulty in knowing the many kinetic parameters required in popular ODE models
- People turn to Boolean models, which have serious flaws for studying GRNs
- DSGRN: computing coarse information without solving the ODE system
- "Coarse" and invariant sets
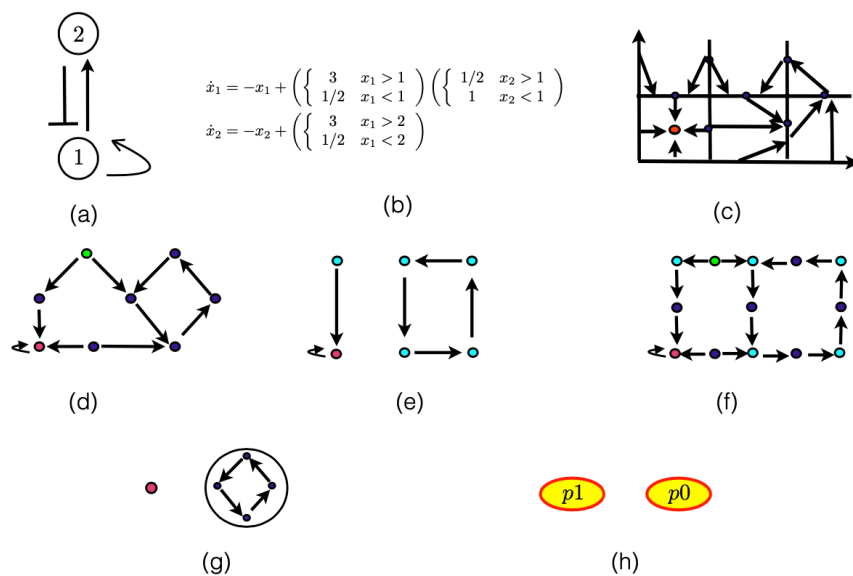- Gives information about the dynamics for all possible parameter values

$$\dot{x}_1 = -x_1 + \left(\left\{ \begin{array}{ll} 3 & x_1 > 1 \\ 1/2 & x_1 < 1 \end{array} \right\} \right) \left(\left\{ \begin{array}{ll} 1/2 & x_2 > 1 \\ 1 & x_2 < 1 \end{array} \right\} \right)$$

$$\dot{x}_2 = -x_2 + \left(\left\{ \begin{array}{ll} 3 & x_1 > 2 \\ 1/2 & x_1 < 2 \end{array} \right\} \right)$$

(a)　　　　　　(b)　　　　　　(c)
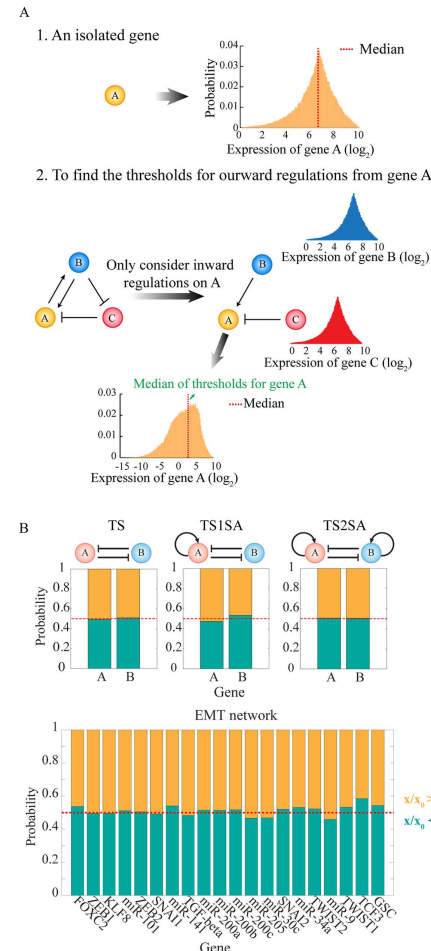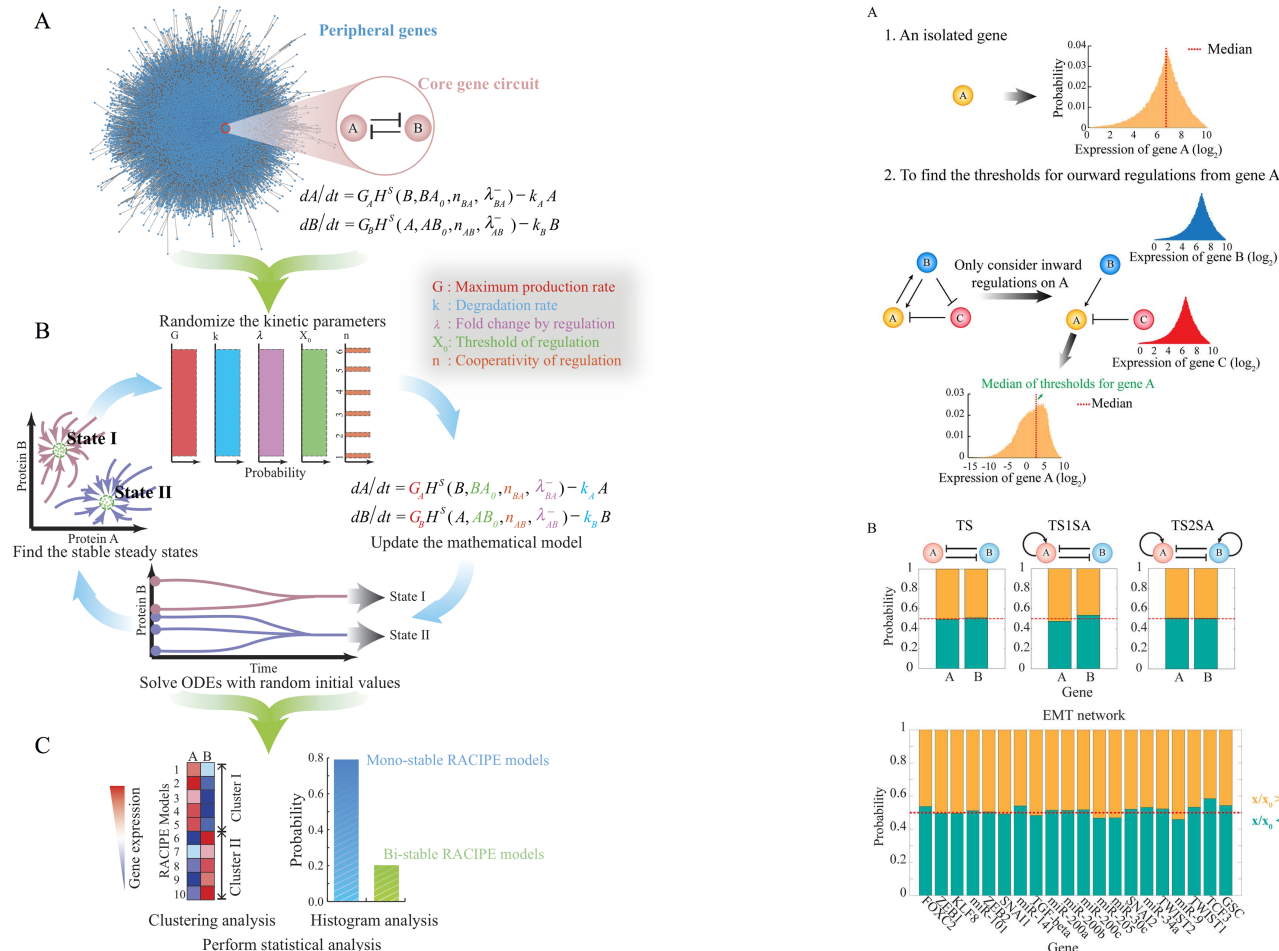
(d)　　　　　　(e)　　　　　　(f)

(g)　　　　　　(h)

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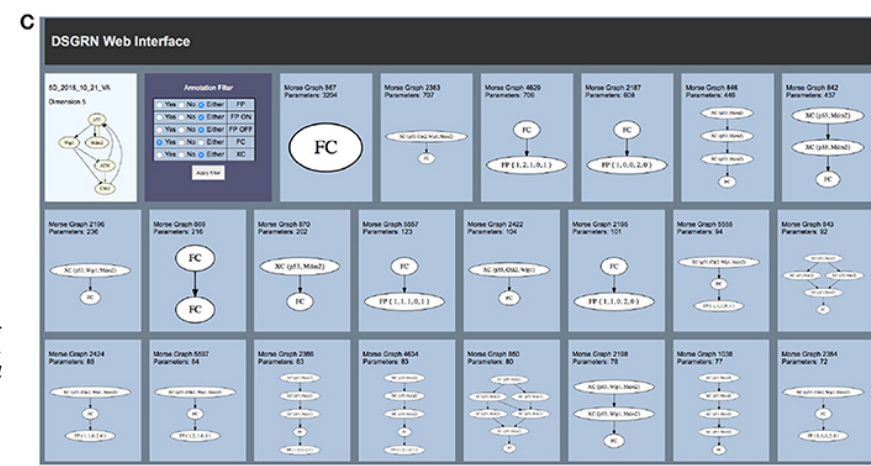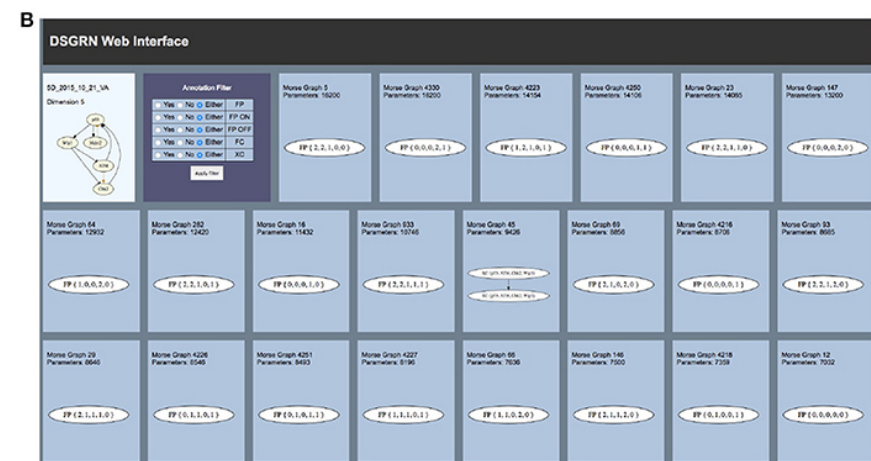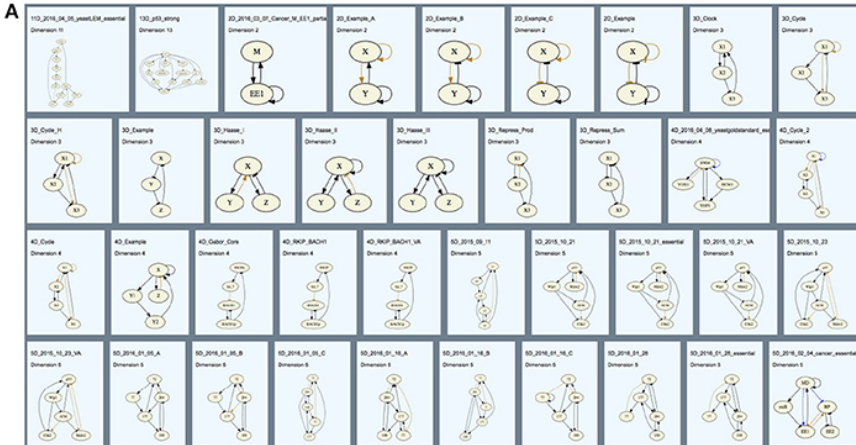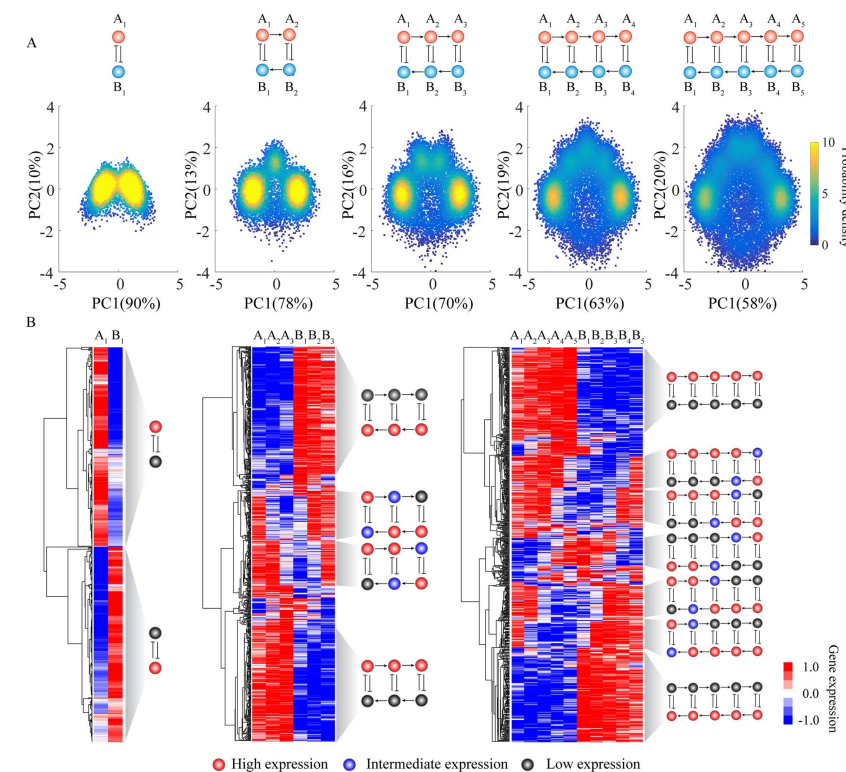
RACIPE (*ra*ndom *ci*rcuit *pe*rturbation)

- Core gene regulatory circuitry
- Without detailed kinetic parameters
- Many random kinetic models all from a fixed circuit topology
- Statistical analysis employed to determine robust dynamical properties
- Topology, not parameters

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 Motifs in RACIPE
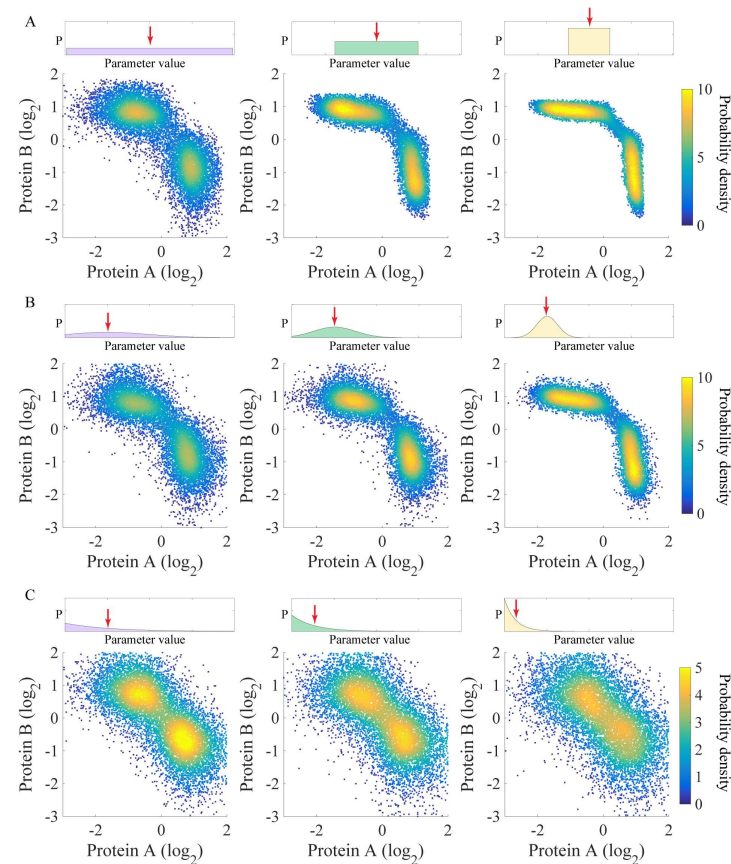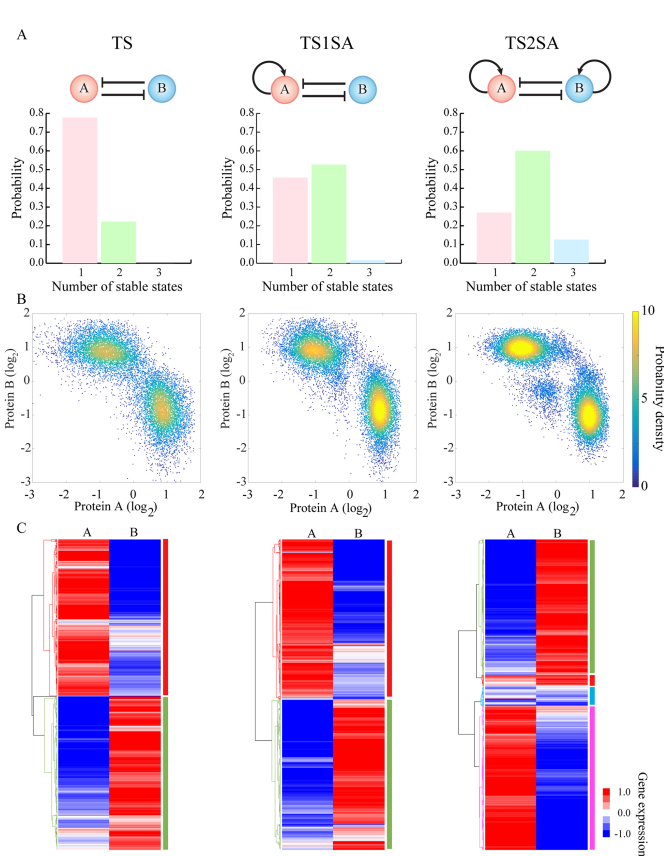
Toggle Switch Motifs in DSGRN
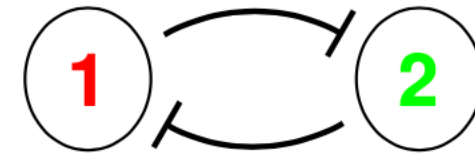
Identifying Sign of $-\gamma_2 x_2 + \lambda_{2,1}(x_1)$

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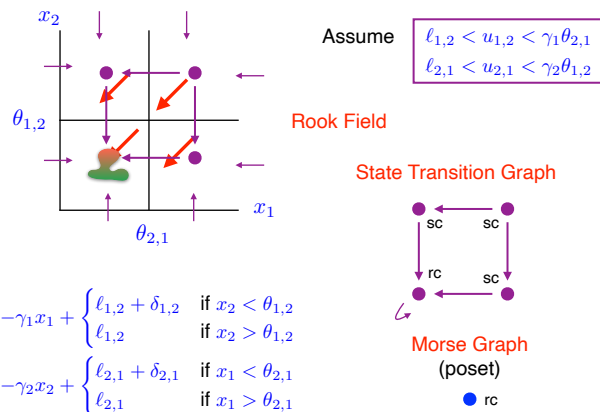
$$\gamma_2\theta_{1,2} < \ell_{2,1} < \ell_{2,1} + \delta_{2,1}$$
$$\ell_{2,1} < \gamma_2\theta_{1,2} < \ell_{2,1} + \delta_{2,1}$$
$$\ell_{2,1} < \ell_{2,1} + \delta_{2,1} < \gamma_2\theta_{1,2}$$

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

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

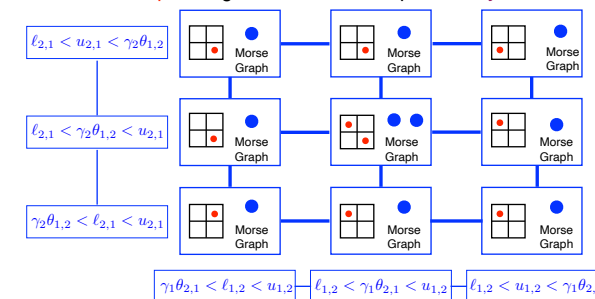**Remark:** This defines a semi-algebraic decomposition of the associated parameter space $(0,\infty)^4$.

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

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

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

Morse Graph (poset)

● rc

Organizing the Information
DSGRN database

Parameter Graph: Region of Parameter Space & Dynamics

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

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

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

$\gamma_1\theta_{2,1} < \ell_{1,2} < u_{1,2}$ — $\ell_{1,2} < \gamma_1\theta_{2,1} < u_{1,2}$ — $\ell_{1,2} < u_{1,2} < \gamma_1\theta_{2,1}$
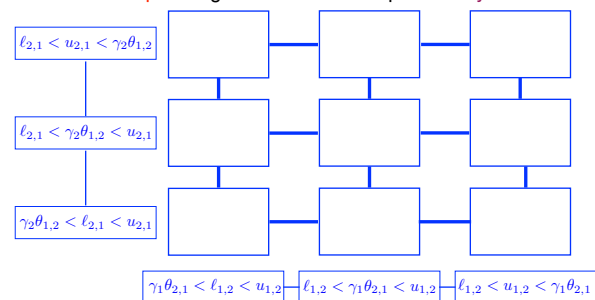
Database provides a complete decomposition of parameter space into explicit regions (semi-algebraic sets) and description of global dynamics over each region. *Purely combinatorial representation.*

$u = \ell + \delta$

Organizing the Information
DSGRN database

Parameter Graph: Region of Parameter Space & Dynamics

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

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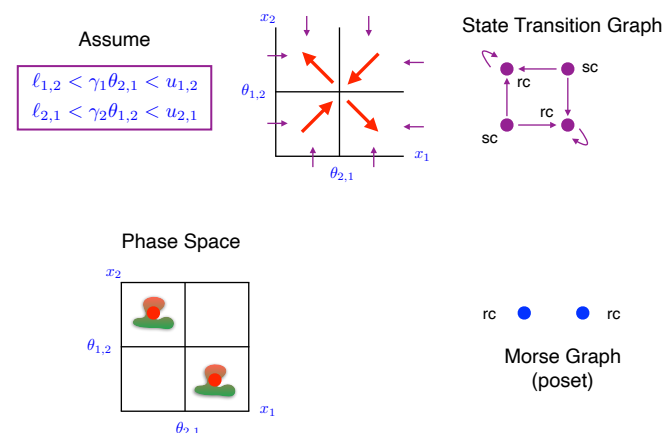
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$u = \ell + \delta$

Representing Dynamics

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

State Transition Graph

Phase Space

rc ● ● rc

Morse Graph (poset)

Data Analysis

DATA

expression level

s

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

DSGRN database

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

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

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

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

Increasing s = Increasing γ_1
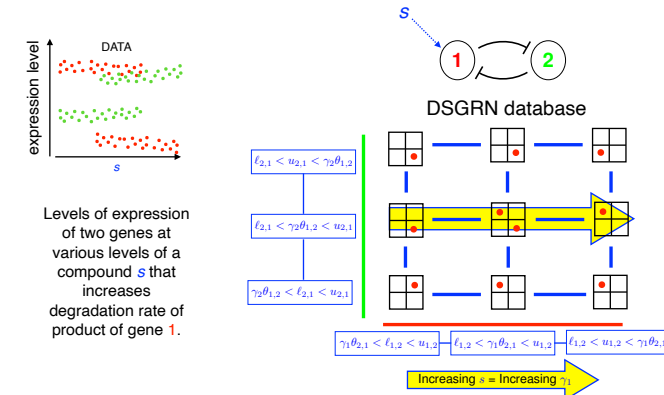
We cannot get such a qualitative match with (1)(2) or (1)(2).

Next Steps and Future Work

Next Steps: Understand the mathematics underlying RACIPE, particularly how they are doing random sampling, how they identify the region of parameter space they are sampling from, how they structured their Hill functions, and, most importantly, the notion of the half-functional rule.

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.

Thank You for Listening!

and

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