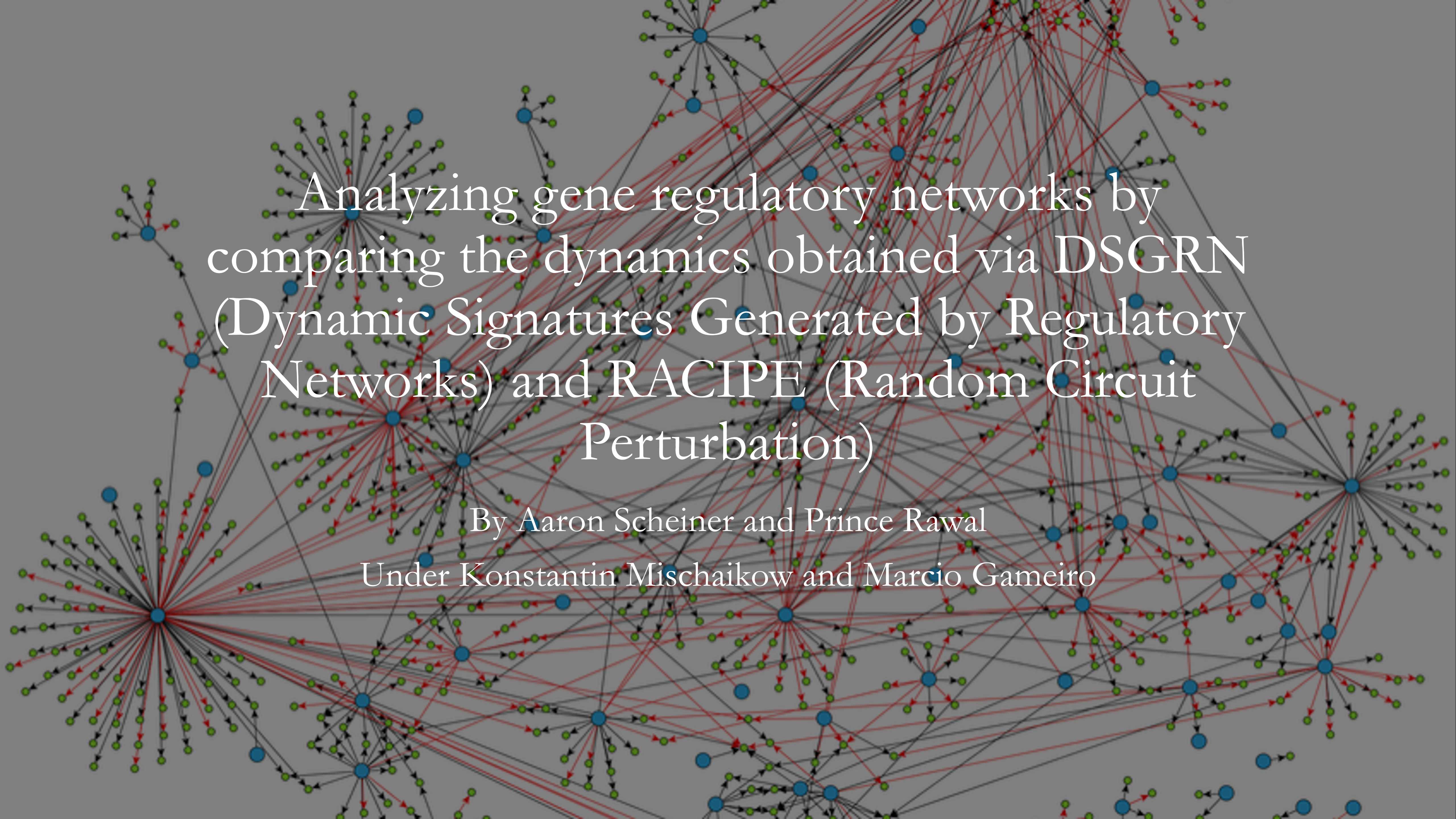

Analyzing gene regulatory networks by comparing the dynamics obtained via DSGRN (Dynamic Signatures Generated by Regulatory Networks) and RACIPE (Random Circuit Perturbation)

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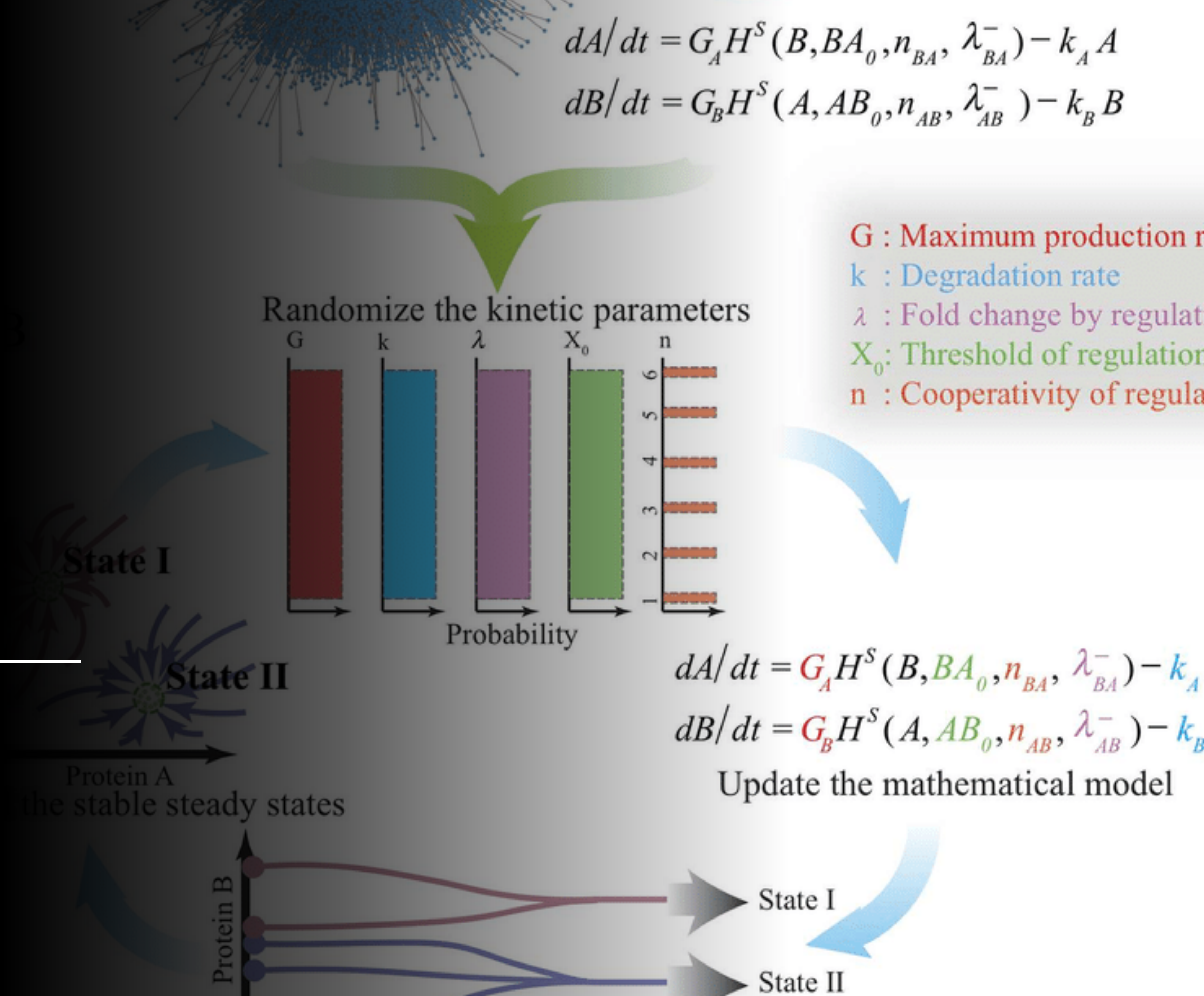
Under Konstantin Mischaikow and Marcio Gameiro

Week Three

Random Sampling in RACIPE and Rook Fields



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.

```
case 1:    // Uniform distribution
  for (i = 0; i < num; i++){
    g    = randu(minP, maxP);
    k    = randu(minK, maxK);
    A[i] = g/k;
  }

  MA = median(A, num);

  for (i = 0; i < num; i++){
    g    = randu(minP, maxP);
    k    = randu(minK, maxK);
    B[i] = g/k;

    if (numA != 0){
      for (j = 0; j < numA; j++){
        g      = randu(minP, maxP);
        k      = randu(minK, maxK);
        n      = randd(minN, maxN, dist);
        T      = randu(MA*f1, MA*f2);
        lambda = randu(minF, maxF);

        B[i] = B[i]*Hillshift(g/k, T, n, lambda)/lambda;
      }
    }

    if (numI != 0){
      for (j = 0; j < numI; j++){
        g      = randu(minP, maxP);
        k      = randu(minK, maxK);
        n      = randd(minN, maxN, dist);
        T      = randu(MA*f1, MA*f2);
        lambda = 1.0/randu(minF, maxF);

        B[i] = B[i]*Hillshift(g/k, T, n, lambda);
      }
    }
  }

  MB = median(B, num);
  minT[ID] = MB*f1;
  maxT[ID] = MB*f2;
  free(A);
  free(B);
  break;
 }
}
```

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

Huang, B., Jia, D., Feng, J. *et al.* RACIPE: a computational tool for modeling gene regulatory circuits using randomization. *BMC Syst Biol* **12,** 74 (2018). https://doi.org/10.1186/s12918-018-0594-6

Toggle-switch circuit (TS):

$$\dot{A} = G_A H^S(B, BA_0, n_{BA}, \lambda_{BA}^-) - k_A A$$
$$\dot{B} = G_B H^S(A, AB_0, n_{AB}, \lambda_{AB}^-) - k_B B \quad , (1)$$

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

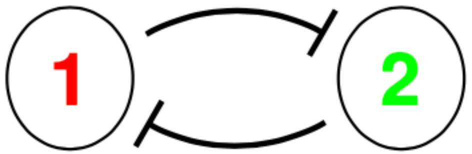
$$\dot{A} = G_A H^S(B, BA_0, n_{BA}, \lambda_{BA}^-) H^S(A, AA_0, n_{AA}, \lambda_{AA}^+) / \lambda_{AA}^+ - k_A A$$
$$\dot{B} = G_B H^S(A, AB_0, n_{AB}, \lambda_{AB}^-) - k_B B \quad , (2)$$

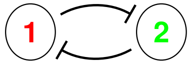
Toggle-switch circuit with two-sided self-activation (TS2SA):

$$\dot{A} = G_A H^S(B, BA_0, n_{BA}, \lambda_{BA}^-) H^S(A, AA_0, n_{AA}, \lambda_{AA}^+) / \lambda_{AA}^+ - k_A A$$
$$\dot{B} = G_B H^S(A, AB_0, n_{AB}, \lambda_{AB}^-) H^S(B, BB_0, n_{BB}, \lambda_{BB}^+) / \lambda_{BB}^+ - k_B B \quad , (3)$$

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

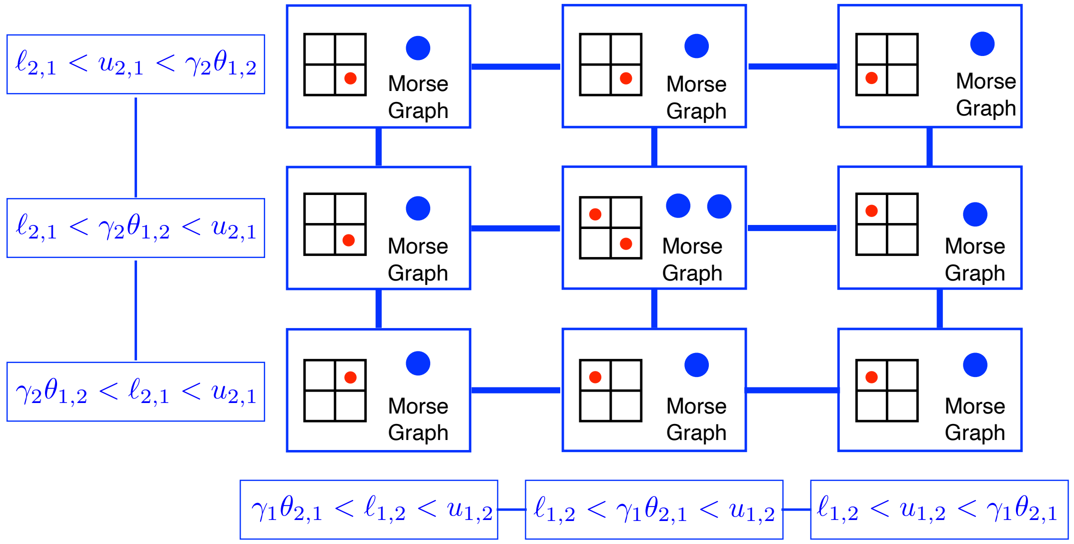




Organizing the Information

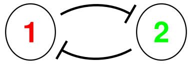
DSGRN database

Parameter Graph: Region of Parameter Space & Dynamics

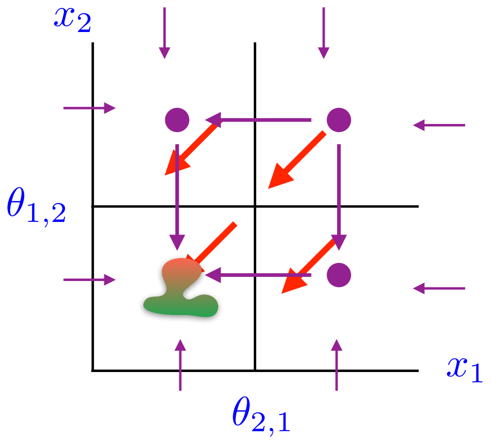


Database provides a complete decomposition of parameter space into explicit regions (semi-algebraic sets) and description of global dynamics over each region. *Purely combinatorial representation.*

$u = \ell + \delta$



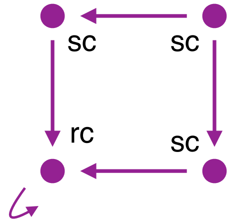
Representing Dynamics



Assume
$$\boxed{\begin{array}{l}\ell_{1,2} < u_{1,2} < \gamma_1\theta_{2,1} \\ \ell_{2,1} < u_{2,1} < \gamma_2\theta_{1,2}\end{array}}$$

Rook Field

State Transition Graph



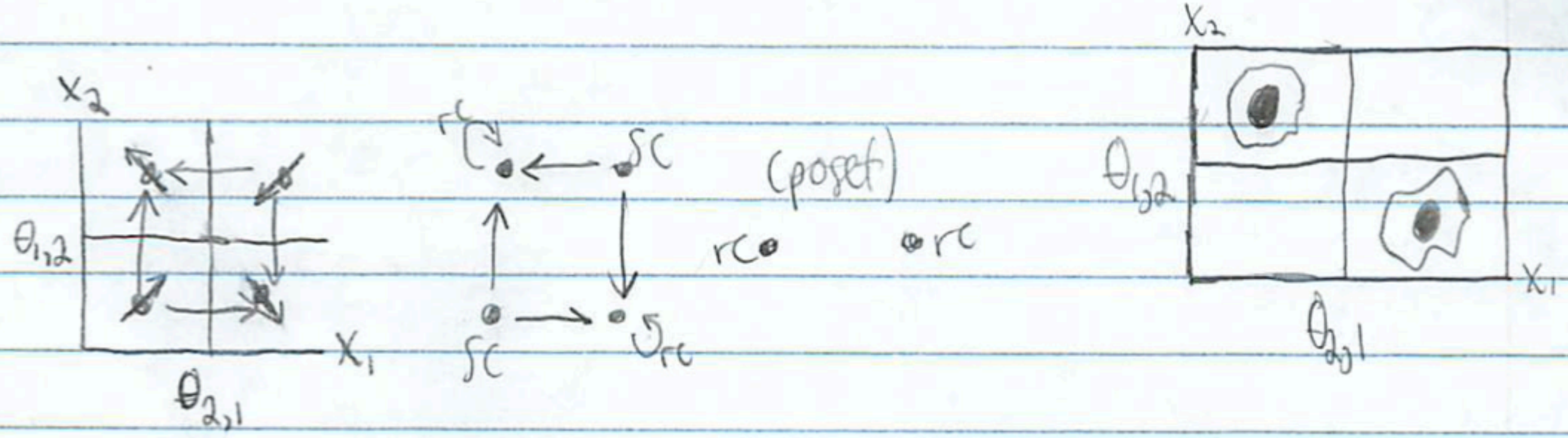
$$-\gamma_1 x_1 + \begin{cases} \ell_{1,2} + \delta_{1,2} & \text{if } x_2 < \theta_{1,2} \\ \ell_{1,2} & \text{if } x_2 > \theta_{1,2} \end{cases}$$

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

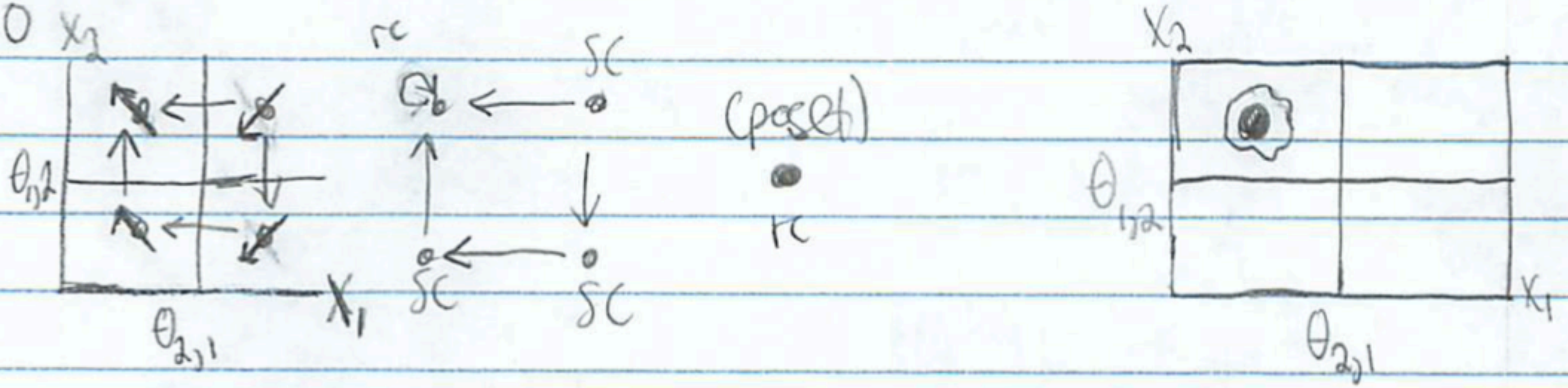
Morse Graph
(poset)

● rc

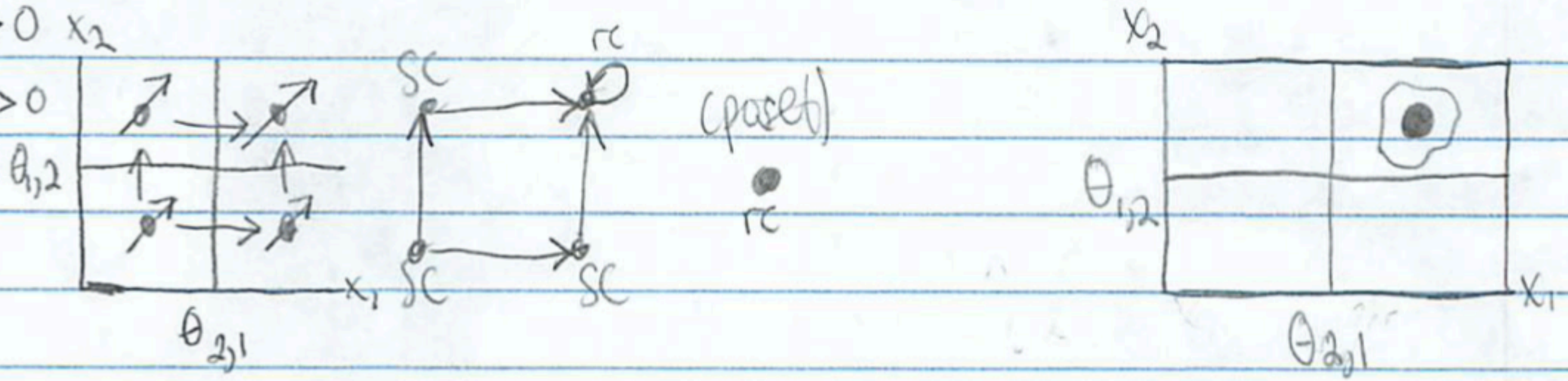
5.) $\dot{x}_1$ $\dot{x}_2$



6.) $\dot{x}_1 < 0$ $\dot{x}_2$



7.) $\dot{x}_1 > 0$ $\dot{x}_2 > 0$



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

Thank you to the 2020 David and Dorothy Bernstein Endowed Scholarship for Summer Research and Aresty Research Center for supporting our research this summer!