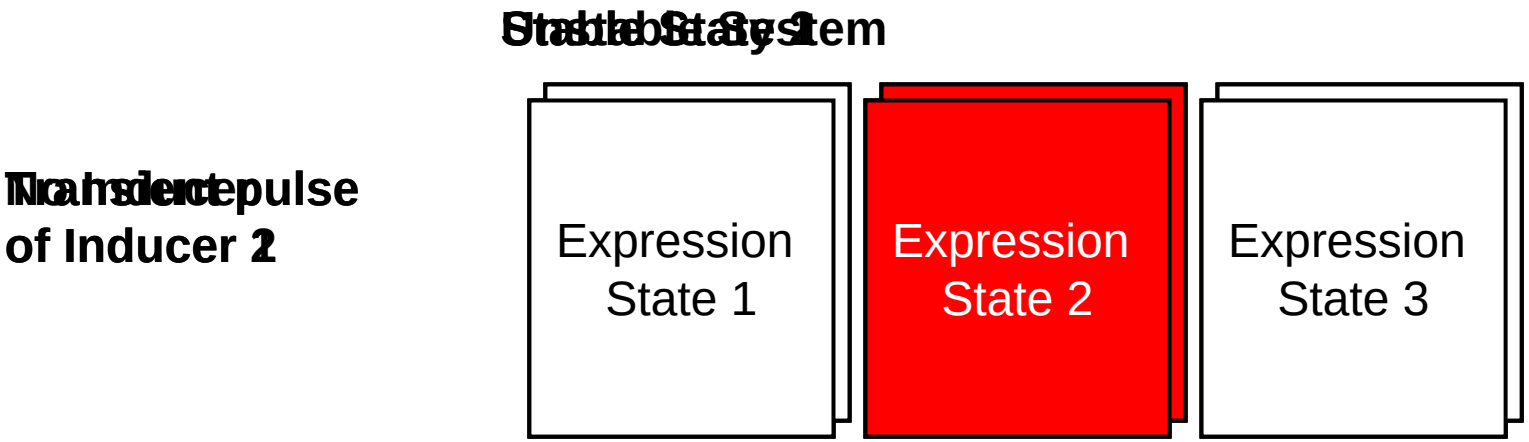
Tristable Concept

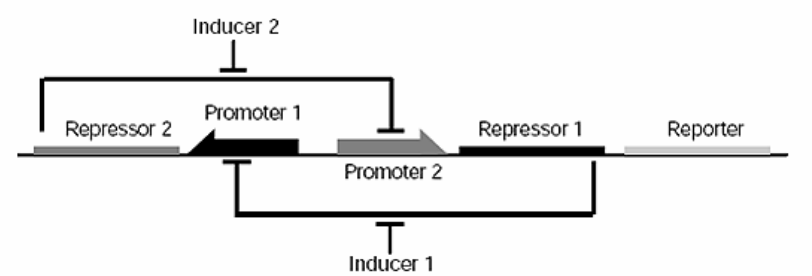
Want to create a system capable of switching among three stable states following transient pulse of inducers.



etc...

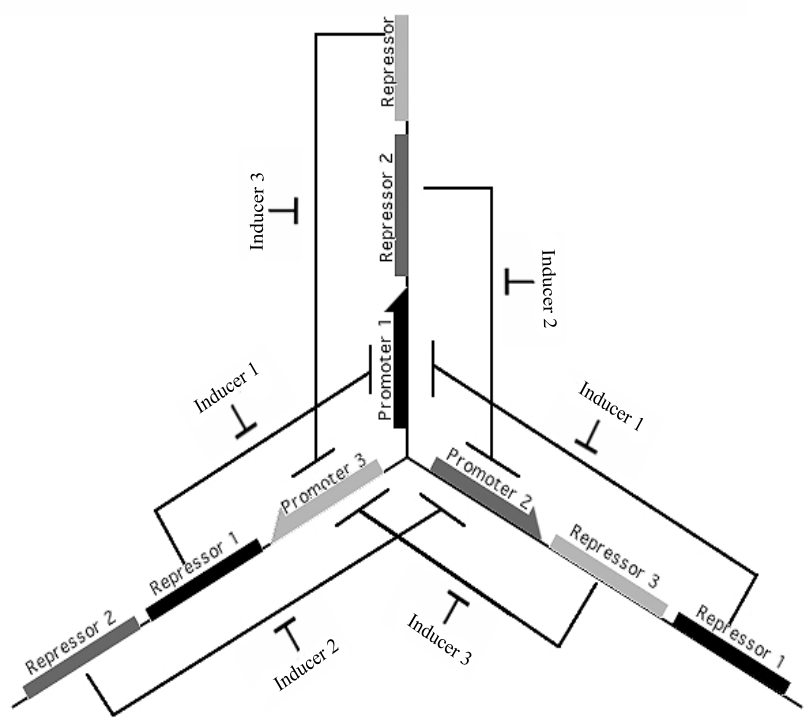
Design

Bistable Toggle Switch Design



Gardner TS, Cantor CR, Collins JJ. “Construction of a genetic toggle Switch in Escherichia coli.” **Nature** 2000 Jan, 20.

Tristable Toggle Switch Design



Brown iGEM et al.

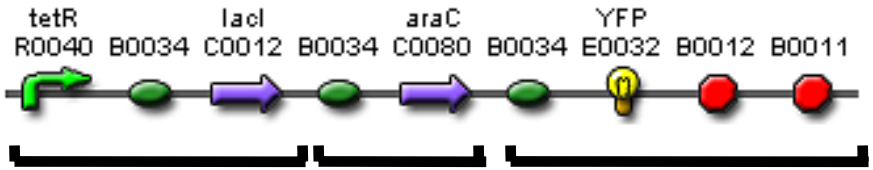
Components of the Tristable Toggle Switch

pTetR construct

Inducers: Tetracycline, aTc

Reporter Gene: YFP

Status: *Under construction*



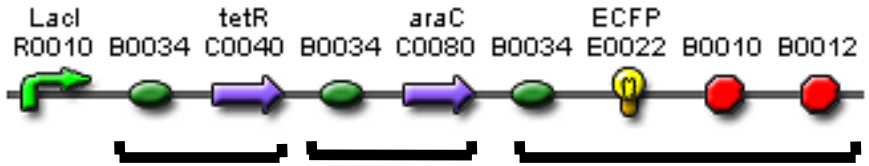
Completed Composites

pLacI construct

Inducers: Lactose, IPTG

Reporter Gene: ECFP

Status: *Under construction*



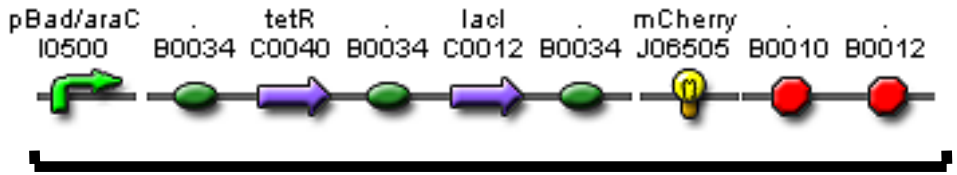
Completed Composites

pBad construct

Inducers: Arabinose

Reporter Gene: mCherry

Status: *Construction Complete!*



Part:BBa_J24676

Model: Extension to Three

Bistable

$$\frac{du}{dt} = \frac{\alpha_1}{1+v^{\beta}} - u$$

$$\frac{dv}{dt} = \frac{\alpha_2}{1+u^{\gamma}} - v$$

vs.

Tristable

$$\frac{du}{dt} = \frac{\alpha_{12}}{1+v^{\beta_{12}}} + \boxed{\frac{\alpha_{13}}{1+z^{\beta_{13}}}} - u$$

$$\frac{dv}{dt} = \frac{\alpha_{21}}{1+u^{\beta_{21}}} + \boxed{\frac{\alpha_{23}}{1+z^{\beta_{23}}}} - v$$

$$\boxed{\frac{dz}{dt} = \frac{\alpha_{31}}{1+u^{\beta_{31}}} + \frac{\alpha_{32}}{1+v^{\beta_{32}}} - z}$$

The key difference is the addition of z. Notice how terms are of the same format.

*New terms

Stability in 2D

Bistable System Monostable System

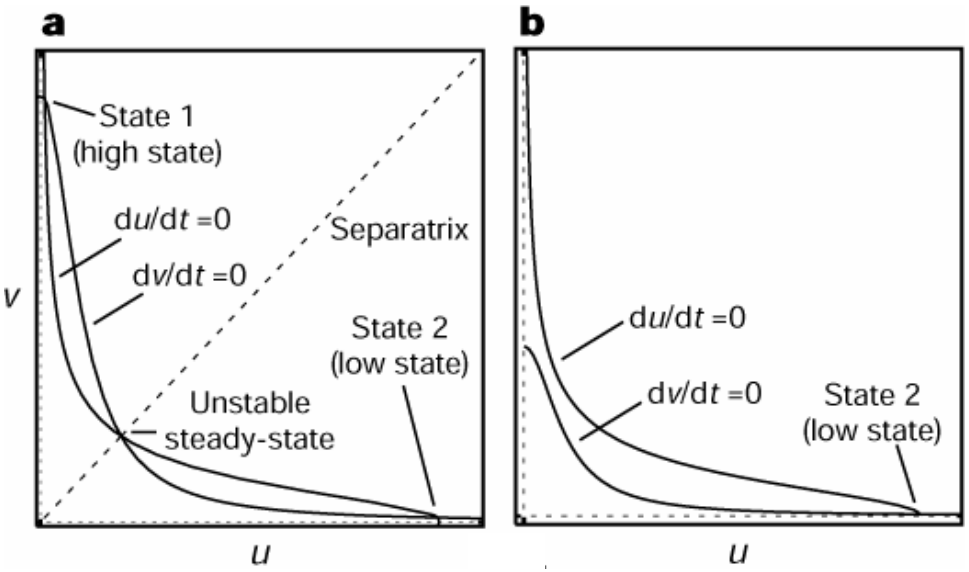


Figure 2 Geometric structure of the toggle equations. **a**, A bistable toggle network with balanced promoter strengths. **b**, A monostable toggle network with imbalanced promoter strengths.

Stability in 3D

Tristable System

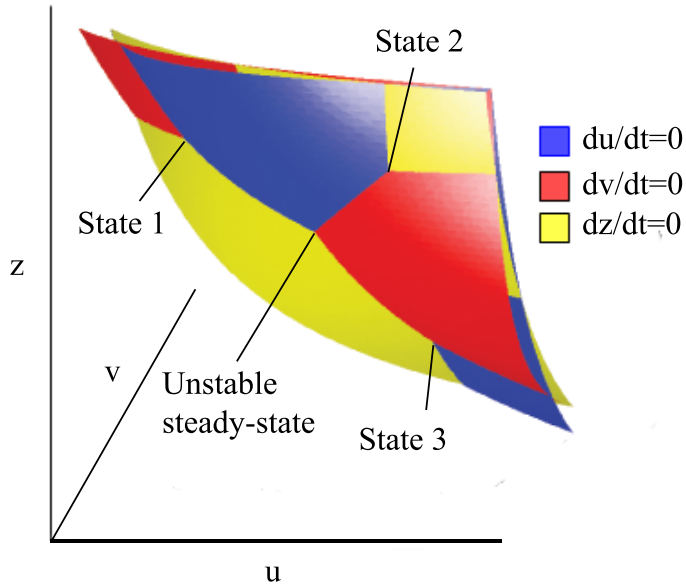


Figure 2a Plot of the null cline equations for a tristable system. Three-way intersections indicate tristable points.

Unstable System

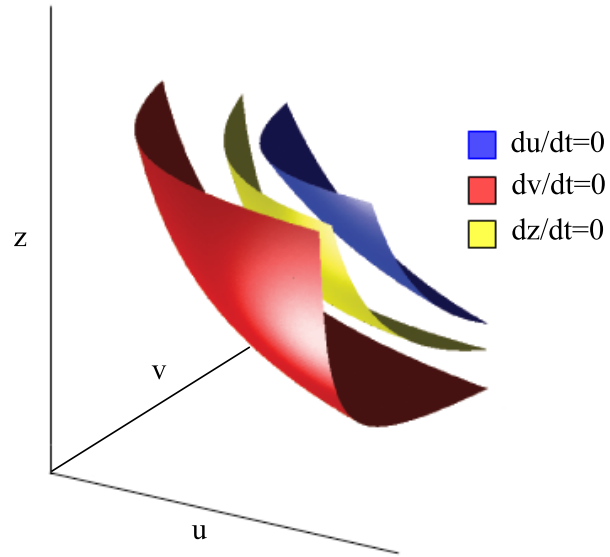
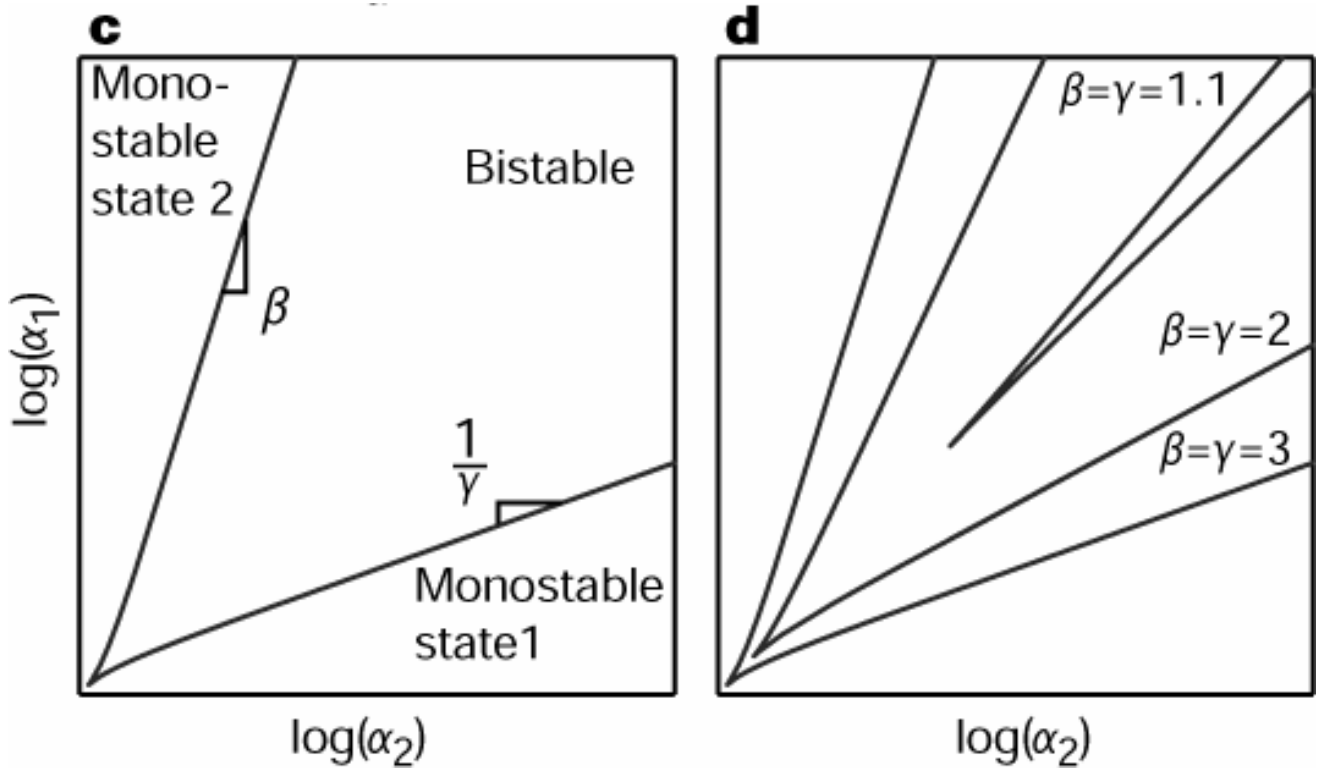


Figure 2b Plot of the null cline equations for an unstable system. There are no three-way intersection points for this system.

Bistable Parameter Space



c, The bistable region. The lines mark the transition (bifurcation) between bistability and monostability. The slopes of the bifurcation lines are determined by the exponents β and γ for large α_1 and α_2. **d**, Reducing the cooperativity of repression (β and γ) reduces the size of the bistable region. Bifurcation lines are illustrated for three different values of β and γ. The bistable region lies inside of each pair of curves.

Reproducing the Bistable Parameter Space

Elusive derivation of parameter space in bistable paper

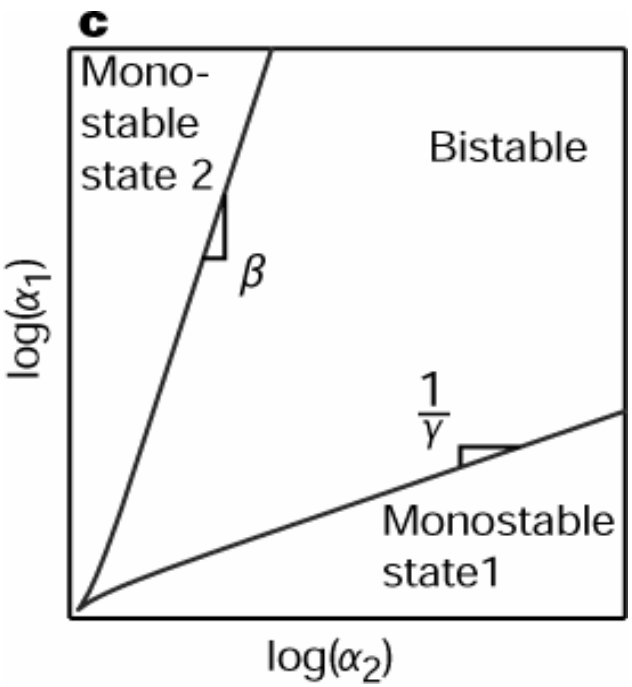
- Attempt to reproduce these figures by generating stability points for different parameter values
- Then fit a function to the boundaries of the stability regions

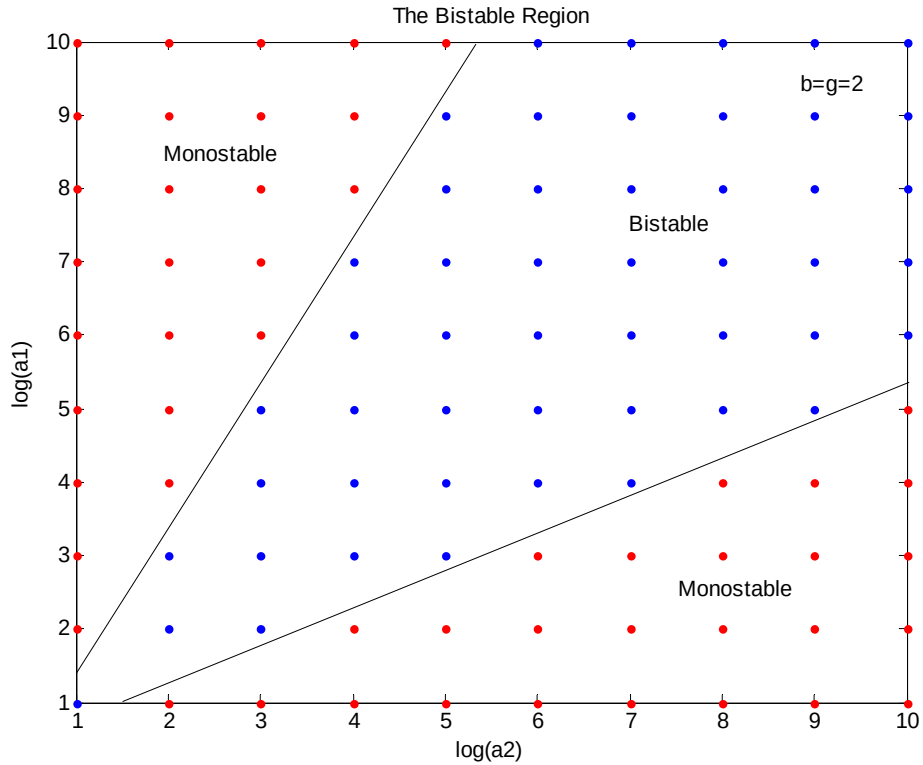
Reproducing the Bistable Parameter Space

Create MATLAB script

1. Create a “for loop” that cycles through each combination of parameters
2. For each parameter combination calculate eq. values using the solve() function
3. Calculate the Jacobian of these solutions
4. Calculate the Eigen values of the Jacobian
5. Determine stability based on Eigen value (need 2 stable solutions for bistability)
    1. + Eigen value = unstable
    2. - Eigen value = stable
6. Plot points changing color for Stable vs. Unstable

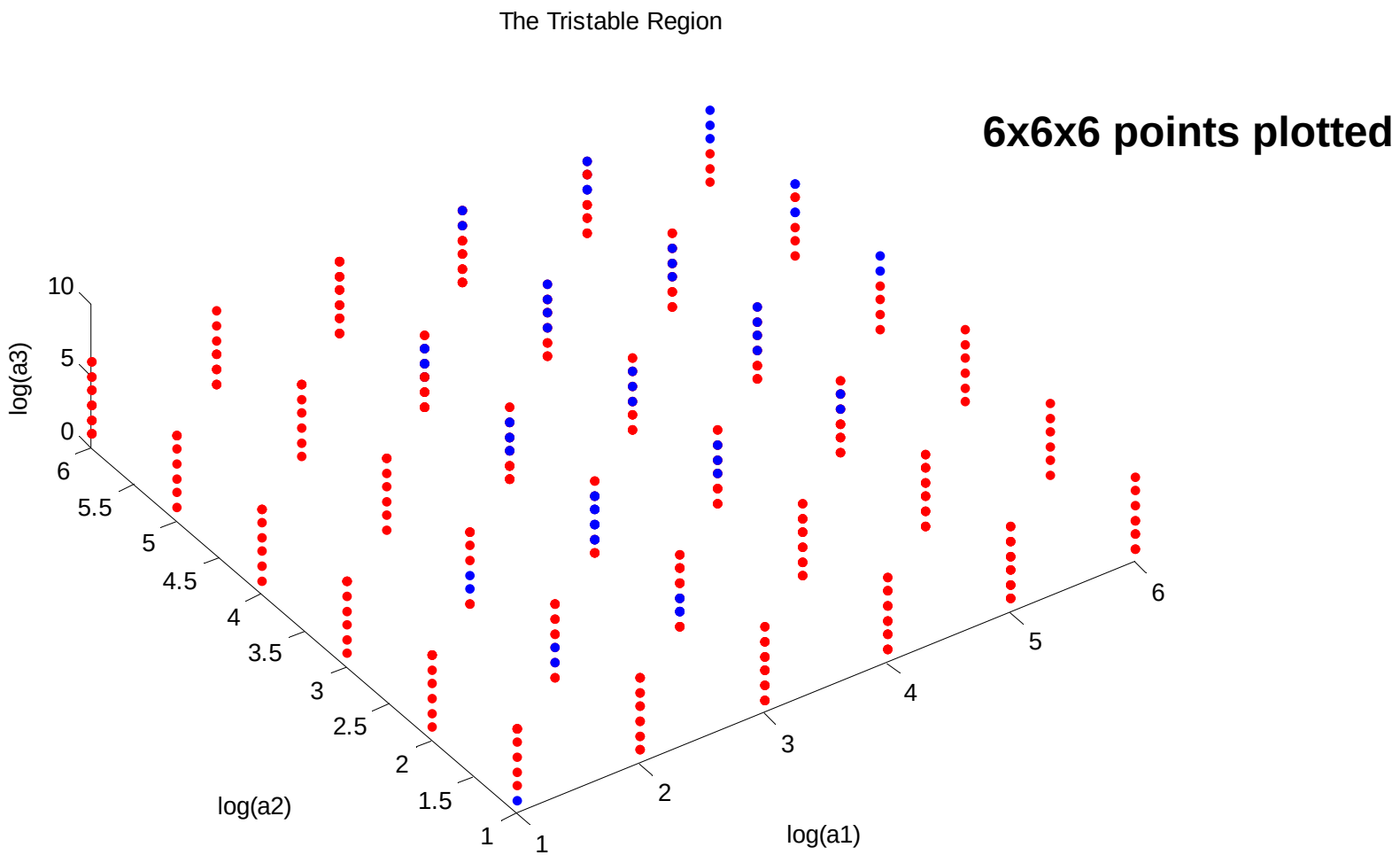
Bistable Plot





Not bad, try to extend to three…

Tristable Plot



Future Goals

- Bistable
  - Fit functions to the boundaries of the stability regions.
    - Compare with Figure 2c. in Gardner et al.
- Tristable
  - Acquire more points to better define the tristable region.
  - Fit functions to the boundaries of the stability regions.
  - Determine realistic parameters.
  - Characterize constructed systems

References

Gardner TS, Cantor CR, Collins JJ. “Construction of a genetic toggle Switch in Escherichia coli.” **Nature** 2000 Jan, 20.