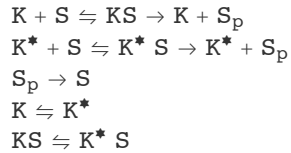


Bistable motif: parameter sampling

Finding the condition of multistationarity

We consider the following reactions:



The species of the system are:

$\{S, S_p, K, K^*, KS, K^* S\}$

In total, there are 11 reactions and 6 species.

We firstly construct the ordinary differential equations based on mass-action kinetics. Then compute the determinant of Jacobian, using the solution at critical point (steady state) to calculate the determinant. The (necessary) condition for multistationarity is to make determinant equal to zero (non-zero determinant implies injectivity).

```
A = Table[0, {11}, {6}];
A[[1]][[1]] = -1;
A[[1]][[3]] = -1;
A[[1]][[5]] = 1;
A[[2]] = -A[[1]];
A[[3]][[3]] = 1; A[[3]][[2]] = 1; A[[3]][[5]] = -1;
A[[4]][[1]] = -1;
A[[4]][[4]] = -1;
A[[4]][[6]] = 1;
A[[5]] = -A[[4]];
A[[6]][[4]] = 1;
A[[6]][[2]] = 1;
A[[6]][[6]] = -1;
A[[7]][[2]] = -1;
A[[7]][[1]] = 1;
A[[8]][[3]] = -1; A[[8]][[4]] = 1; A[[9]] = -A[[8]];
A[[10]][[5]] = -1; A[[10]][[6]] = 1; A[[11]] = -A[[10]];
stoiM = Transpose[A];
(* Now we construct the rate vector *)
ks = {k1 x x3 x x1, k2 x x5, k3 x x5, k4 x x4 x x1,
      k5 x x6, k6 x x6, k7 x x2, k8 x x3, k9 x x4, k10 x x5, k11 x x6};
ssEqns = stoiM.ks;
mC = RowReduce[NullSpace[A]];
subsEqns = {ssEqns[[2]], ssEqns[[4]],
            ssEqns[[5]], ssEqns[[6]], x1 + x2 + x5 + x6 - T1, x3 + x4 + x5 + x6 - T2};
jacobian = D[subsEqns, {{x1, x2, x3, x4, x5, x6}}];
detJ = Collect[Distribute[Det[jacobian]], {x1, x2, x3, x4, x5, x6}];
solution =
  Solve[{{subsEqns[[1]], subsEqns[[2]], subsEqns[[3]], subsEqns[[4]]} == 0},
        {x2, x4, x5, x6}];
detSubs = Replace[detJ, solution[[1]], {0, Infinity}];
(* Equilvant to detSubs=detJ/.solution[[1]]; *)
polSubs = Numerator[Together[detSubs]];
finalSubs = Collect[Distribute[polSubs], x_, FactorTerms]
```

$$\begin{aligned}
& -k_2^2 k_5^2 k_7 k_8 k_9 - 2 k_2 k_3 k_5^2 k_7 k_8 k_9 - k_3^2 k_5^2 k_7 k_8 k_9 - 2 k_2^2 k_5 k_6 k_7 k_8 k_9 - 4 k_2 k_3 k_5 k_6 k_7 k_8 k_9 - \\
& 2 k_3^2 k_5 k_6 k_7 k_8 k_9 - k_2^2 k_6^2 k_7 k_8 k_9 - 2 k_2 k_3 k_6^2 k_7 k_8 k_9 - k_3^2 k_6^2 k_7 k_8 k_9 - k_2^2 k_5^2 k_7 k_9^2 - \\
& 2 k_2 k_3 k_5^2 k_7 k_9^2 - k_3^2 k_5^2 k_7 k_9^2 - 2 k_2^2 k_5 k_6 k_7 k_9^2 - 4 k_2 k_3 k_5 k_6 k_7 k_9^2 - 2 k_3^2 k_5 k_6 k_7 k_9^2 - \\
& k_2^2 k_6^2 k_7 k_9^2 - 2 k_2 k_3 k_6^2 k_7 k_9^2 - k_3^2 k_6^2 k_7 k_9^2 - 2 k_2 k_5^2 k_7 k_8 k_9 k_{10} - 2 k_3 k_5^2 k_7 k_8 k_9 k_{10} - \\
& 4 k_2 k_5 k_6 k_7 k_8 k_9 k_{10} - 4 k_3 k_5 k_6 k_7 k_8 k_9 k_{10} - 2 k_2 k_6^2 k_7 k_8 k_9 k_{10} - 2 k_3 k_6^2 k_7 k_8 k_9 k_{10} - \\
& 2 k_2 k_5^2 k_7 k_9^2 k_{10} - 2 k_3 k_5^2 k_7 k_9^2 k_{10} - 4 k_2 k_5 k_6 k_7 k_9^2 k_{10} - 4 k_3 k_5 k_6 k_7 k_9^2 k_{10} - 2 k_2 k_6^2 k_7 k_9^2 k_{10} - \\
& 2 k_3 k_6^2 k_7 k_9^2 k_{10} - k_2^2 k_7 k_8 k_9 k_{10}^2 - 2 k_5 k_6 k_7 k_8 k_9 k_{10}^2 - k_6^2 k_7 k_8 k_9 k_{10}^2 - k_5^2 k_7 k_9^2 k_{10}^2 - \\
& 2 k_5 k_6 k_7 k_9^2 k_{10}^2 - k_6^2 k_7 k_9^2 k_{10}^2 - 2 k_2^2 k_5 k_7 k_8 k_9 k_{11} - 4 k_2 k_3 k_5 k_7 k_8 k_9 k_{11} - 2 k_3^2 k_5 k_7 k_8 k_9 k_{11} - \\
& 2 k_2^2 k_6 k_7 k_8 k_9 k_{11} - 4 k_2 k_3 k_6 k_7 k_8 k_9 k_{11} - 2 k_3^2 k_6 k_7 k_8 k_9 k_{11} - 2 k_2^2 k_5 k_7 k_9^2 k_{11} - \\
& 4 k_2 k_3 k_5 k_7 k_9^2 k_{11} - 2 k_3^2 k_5 k_7 k_9^2 k_{11} - 2 k_2^2 k_6 k_7 k_9^2 k_{11} - 4 k_2 k_3 k_6 k_7 k_9^2 k_{11} - 2 k_3^2 k_6 k_7 k_9^2 k_{11} - \\
& 2 k_2 k_5 k_7 k_8 k_9 k_{10} k_{11} - 2 k_3 k_5 k_7 k_8 k_9 k_{10} k_{11} - 2 k_2 k_6 k_7 k_8 k_9 k_{10} k_{11} - 2 k_3 k_6 k_7 k_8 k_9 k_{10} k_{11} - \\
& 2 k_2 k_5 k_7 k_9^2 k_{10} k_{11} - 2 k_3 k_5 k_7 k_9^2 k_{10} k_{11} - 2 k_2 k_6 k_7 k_9^2 k_{10} k_{11} - 2 k_3 k_6 k_7 k_9^2 k_{10} k_{11} - \\
& k_2^2 k_7 k_8 k_9 k_{11}^2 - 2 k_2 k_3 k_7 k_8 k_9 k_{11}^2 - k_3^2 k_7 k_8 k_9 k_{11}^2 - k_2^2 k_7 k_9^2 k_{11}^2 - 2 k_2 k_3 k_7 k_9^2 k_{11}^2 - \\
& k_3^2 k_7 k_9^2 k_{11}^2 + (-k_1 k_2 k_4^2 k_7 k_{10} k_{11} - k_1 k_3 k_4^2 k_7 k_{10} k_{11} - k_1 k_2 k_4^2 k_7 k_{11}^2 - k_1 k_3 k_4^2 k_7 k_{11}^2) x_1^3 + \\
& (-k_2^2 k_4 k_5 k_6 k_8^2 - 2 k_2 k_3 k_4 k_5 k_6 k_8^2 - k_3^2 k_4 k_5 k_6 k_8^2 - k_2^2 k_4 k_6^2 k_8^2 - 2 k_2 k_3 k_4 k_6^2 k_8^2 - k_3^2 k_4 k_6^2 k_8^2 - \\
& k_2^2 k_4 k_5 k_7 k_8^2 - 2 k_2 k_3 k_4 k_5 k_7 k_8^2 - k_3^2 k_4 k_5 k_7 k_8^2 - k_2^2 k_4 k_6 k_7 k_8^2 - 2 k_2 k_3 k_4 k_6 k_7 k_8^2 - \\
& k_3^2 k_4 k_6 k_7 k_8^2 - k_1 k_2 k_3 k_5^2 k_8 k_9 - k_1 k_3^2 k_5^2 k_8 k_9 - 2 k_1 k_2 k_3 k_5 k_6 k_8 k_9 - 2 k_1 k_3^2 k_5 k_6 k_8 k_9 - \\
& k_2^2 k_4 k_5 k_6 k_8 k_9 - 2 k_2 k_3 k_4 k_5 k_6 k_8 k_9 - k_3^2 k_4 k_5 k_6 k_8 k_9 - k_1 k_2 k_3 k_6^2 k_8 k_9 - \\
& k_1 k_3^2 k_6^2 k_8 k_9 - k_2^2 k_4 k_6^2 k_8 k_9 - 2 k_2 k_3 k_4 k_6^2 k_8 k_9 - k_3^2 k_4 k_6^2 k_8 k_9 - k_2^2 k_4 k_5 k_7 k_8 k_9 - \\
& 2 k_2 k_3 k_4 k_5 k_7 k_8 k_9 - k_3^2 k_4 k_5 k_7 k_8 k_9 - k_1 k_2 k_5^2 k_7 k_8 k_9 - k_1 k_3 k_5^2 k_7 k_8 k_9 - \\
& k_2^2 k_4 k_6 k_7 k_8 k_9 - 2 k_2 k_3 k_4 k_6 k_7 k_8 k_9 - k_3^2 k_4 k_6 k_7 k_8 k_9 - 2 k_1 k_2 k_5 k_6 k_7 k_8 k_9 - \\
& 2 k_1 k_3 k_5 k_6 k_7 k_8 k_9 - k_1 k_2 k_6^2 k_7 k_8 k_9 - k_1 k_3 k_6^2 k_7 k_8 k_9 - k_1 k_2 k_3 k_5^2 k_9^2 - k_1 k_3^2 k_5^2 k_9^2 - \\
& 2 k_1 k_2 k_3 k_5 k_6 k_9^2 - 2 k_1 k_3^2 k_5 k_6 k_9^2 - k_1 k_2 k_3 k_6^2 k_9^2 - k_1 k_3^2 k_6^2 k_9^2 - k_1 k_2 k_5^2 k_7 k_9^2 - \\
& k_1 k_3 k_5^2 k_7 k_9^2 - 2 k_1 k_2 k_5 k_6 k_7 k_9^2 - 2 k_1 k_3 k_5 k_6 k_7 k_9^2 - k_1 k_2 k_6^2 k_7 k_9^2 - k_1 k_3 k_6^2 k_7 k_9^2 - \\
& 2 k_2 k_4 k_5 k_6 k_8^2 k_{10} - 2 k_3 k_4 k_5 k_6 k_8^2 k_{10} - 2 k_2 k_4 k_6^2 k_8^2 k_{10} - 2 k_3 k_4 k_6^2 k_8^2 k_{10} - \\
& 2 k_2 k_4 k_5 k_7 k_8^2 k_{10} - 2 k_3 k_4 k_5 k_7 k_8^2 k_{10} - 2 k_2 k_4 k_6 k_7 k_8^2 k_{10} - 2 k_3 k_4 k_6 k_7 k_8^2 k_{10} - \\
& k_1 k_3 k_5^2 k_8 k_9 k_{10} - k_1 k_2 k_5 k_6 k_8 k_9 k_{10} - 3 k_1 k_3 k_5 k_6 k_8 k_9 k_{10} - 2 k_2 k_4 k_5 k_6 k_8 k_9 k_{10} - \\
& 2 k_3 k_4 k_5 k_6 k_8 k_9 k_{10} - k_1 k_2 k_6^2 k_8 k_9 k_{10} - 2 k_1 k_3 k_6^2 k_8 k_9 k_{10} - 2 k_2 k_4 k_6^2 k_8 k_9 k_{10} - \\
& 2 k_3 k_4 k_6^2 k_8 k_9 k_{10} - k_1 k_2 k_5 k_7 k_8 k_9 k_{10} - k_1 k_3 k_5 k_7 k_8 k_9 k_{10} - 2 k_2 k_4 k_5 k_7 k_8 k_9 k_{10} - \\
& 2 k_3 k_4 k_5 k_7 k_8 k_9 k_{10} - k_1 k_5^2 k_7 k_8 k_9 k_{10} - k_1 k_2 k_6 k_7 k_8 k_9 k_{10} - k_1 k_3 k_6 k_7 k_8 k_9 k_{10} - \\
& 2 k_2 k_4 k_6 k_7 k_8 k_9 k_{10} - 2 k_3 k_4 k_6 k_7 k_8 k_9 k_{10} - 2 k_1 k_5 k_6 k_7 k_8 k_9 k_{10} - k_1 k_6^2 k_7 k_8 k_9 k_{10} - \\
& k_1 k_3 k_5^2 k_9^2 k_{10} - k_1 k_2 k_5 k_6 k_9^2 k_{10} - 3 k_1 k_3 k_5 k_6 k_9^2 k_{10} - k_1 k_2 k_6^2 k_9^2 k_{10} - 2 k_1 k_3 k_6^2 k_9^2 k_{10} - \\
& k_1 k_2 k_5 k_7 k_9^2 k_{10} - k_1 k_3 k_5 k_7 k_9^2 k_{10} - k_1 k_5^2 k_7 k_9^2 k_{10} - k_1 k_2 k_6 k_7 k_9^2 k_{10} - k_1 k_3 k_6 k_7 k_9^2 k_{10} - \\
& 2 k_1 k_5 k_6 k_7 k_9^2 k_{10} - k_1 k_6^2 k_7 k_9^2 k_{10} - k_4 k_5 k_6 k_8^2 k_{10}^2 - k_4 k_5 k_7 k_8^2 k_{10}^2 - \\
& k_4 k_6 k_7 k_8^2 k_{10}^2 - k_1 k_5 k_6 k_8 k_9 k_{10}^2 - k_4 k_5 k_6 k_8 k_9 k_{10}^2 - k_1 k_6^2 k_8 k_9 k_{10}^2 - k_4 k_6^2 k_8 k_9 k_{10}^2 - \\
& k_1 k_5 k_7 k_8 k_9 k_{10}^2 - k_4 k_5 k_7 k_8 k_9 k_{10}^2 - k_1 k_6 k_7 k_8 k_9 k_{10}^2 - k_4 k_6 k_7 k_8 k_9 k_{10}^2 - \\
& k_1 k_5 k_6 k_9^2 k_{10}^2 - k_1 k_6^2 k_9^2 k_{10}^2 - k_1 k_5 k_7 k_9^2 k_{10}^2 - k_1 k_6 k_7 k_9^2 k_{10}^2 - k_2 k_3 k_4 k_5 k_8^2 k_{11} - \\
& k_3^2 k_4 k_5 k_8^2 k_{11} - k_2^2 k_4 k_6 k_8^2 k_{11} - 3 k_2 k_3 k_4 k_6 k_8^2 k_{11} - 2 k_3^2 k_4 k_6 k_8^2 k_{11} - k_2^2 k_4 k_7 k_8^2 k_{11} - \\
& 2 k_2 k_3 k_4 k_7 k_8^2 k_{11} - k_3^2 k_4 k_7 k_8^2 k_{11} - k_2 k_4 k_5 k_7 k_8^2 k_{11} - k_3 k_4 k_5 k_7 k_8^2 k_{11} - \\
& k_2 k_4 k_6 k_7 k_8^2 k_{11} - k_3 k_4 k_6 k_7 k_8^2 k_{11} - 2 k_1 k_2 k_3 k_5 k_8 k_9 k_{11} - 2 k_1 k_3^2 k_5 k_8 k_9 k_{11} - \\
& k_2 k_3 k_4 k_5 k_8 k_9 k_{11} - k_3^2 k_4 k_5 k_8 k_9 k_{11} - 2 k_1 k_2 k_3 k_6 k_8 k_9 k_{11} - 2 k_1 k_3^2 k_6 k_8 k_9 k_{11} - \\
& k_2^2 k_4 k_6 k_8 k_9 k_{11} - 3 k_2 k_3 k_4 k_6 k_8 k_9 k_{11} - 2 k_3^2 k_4 k_6 k_8 k_9 k_{11} - k_2^2 k_4 k_7 k_8 k_9 k_{11} - \\
& 2 k_2 k_3 k_4 k_7 k_8 k_9 k_{11} - k_3^2 k_4 k_7 k_8 k_9 k_{11} - 2 k_1 k_2 k_5 k_7 k_8 k_9 k_{11} - 2 k_1 k_3 k_5 k_7 k_8 k_9 k_{11} - \\
& k_2 k_4 k_5 k_7 k_8 k_9 k_{11} - k_3 k_4 k_5 k_7 k_8 k_9 k_{11} - 2 k_1 k_2 k_6 k_7 k_8 k_9 k_{11} - 2 k_1 k_3 k_6 k_7 k_8 k_9 k_{11} - \\
& k_2 k_4 k_6 k_7 k_8 k_9 k_{11} - k_3 k_4 k_6 k_7 k_8 k_9 k_{11} - 2 k_1 k_2 k_3 k_5 k_9^2 k_{11} - 2 k_1 k_3^2 k_5 k_9^2 k_{11} - \\
& 2 k_1 k_2 k_3 k_6 k_9^2 k_{11} - 2 k_1 k_3^2 k_6 k_9^2 k_{11} - 2 k_1 k_2 k_5 k_7 k_9^2 k_{11} - 2 k_1 k_3 k_5 k_7 k_9^2 k_{11} - \\
& 2 k_1 k_2 k_6 k_7 k_9^2 k_{11} - 2 k_1 k_3 k_6 k_7 k_9^2 k_{11} - k_3 k_4 k_5 k_8^2 k_{10} k_{11} - k_2 k_4 k_6 k_8^2 k_{10} k_{11} - \\
& 2 k_3 k_4 k_6 k_8^2 k_{10} k_{11} - k_2 k_4 k_7 k_8^2 k_{10} k_{11} - k_3 k_4 k_7 k_8^2 k_{10} k_{11} - k_4 k_5 k_7 k_8^2 k_{10} k_{11} - \\
& k_4 k_6 k_7 k_8^2 k_{10} k_{11} - k_1 k_3 k_5 k_8 k_9 k_{10} k_{11} - k_3 k_4 k_5 k_8 k_9 k_{10} k_{11} - k_1 k_2 k_6 k_8 k_9 k_{10} k_{11} - \\
& 2 k_1 k_3 k_6 k_8 k_9 k_{10} k_{11} - k_2 k_4 k_6 k_8 k_9 k_{10} k_{11} - 2 k_3 k_4 k_6 k_8 k_9 k_{10} k_{11} - \\
& k_1 k_2 k_7 k_8 k_9 k_{10} k_{11} - k_1 k_3 k_7 k_8 k_9 k_{10} k_{11} - k_2 k_4 k_7 k_8 k_9 k_{10} k_{11} - k_3 k_4 k_7 k_8 k_9 k_{10} k_{11} - \\
& k_1 k_5 k_7 k_8 k_9 k_{10} k_{11} - k_4 k_5 k_7 k_8 k_9 k_{10} k_{11} - k_1 k_6 k_7 k_8 k_9 k_{10} k_{11} - k_4 k_6 k_7 k_8 k_9 k_{10} k_{11} - \\
& k_1 k_3 k_5 k_9^2 k_{10} k_{11} - k_1 k_2 k_6 k_9^2 k_{10} k_{11} - 2 k_1 k_3 k_6 k_9^2 k_{10} k_{11} - k_1 k_2 k_7 k_9^2 k_{10} k_{11} - \\
& k_1 k_3 k_7 k_9^2 k_{10} k_{11} - k_1 k_5 k_7 k_9^2 k_{10} k_{11} - k_1 k_6 k_7 k_9^2 k_{10} k_{11} - k_2 k_3 k_4 k_8^2 k_{11}^2 - \\
& k_3^2 k_4 k_8^2 k_{11}^2 - k_2 k_4 k_7 k_8^2 k_{11}^2 - k_3 k_4 k_7 k_8^2 k_{11}^2 - k_1 k_2 k_3 k_8 k_9 k_{11}^2 - k_1 k_3^2 k_8 k_9 k_{11}^2 - \\
& k_2 k_3 k_4 k_8 k_9 k_{11}^2 - k_3^2 k_4 k_8 k_9 k_{11}^2 - k_1 k_2 k_7 k_8 k_9 k_{11}^2 - k_1 k_3 k_7 k_8 k_9 k_{11}^2 - k_2 k_4 k_7 k_8 k_9 k_{11}^2 - \\
& k_3 k_4 k_7 k_8 k_9 k_{11}^2 - k_1 k_2 k_3 k_9^2 k_{11}^2 - k_1 k_3^2 k_9^2 k_{11}^2 - k_1 k_2 k_7 k_9^2 k_{11}^2 - k_1 k_3 k_7 k_9^2 k_{11}^2) x_3 + \\
& x_1^2 (-k_1 k_2 k_4 k_5 k_7 k_9 k_{10} - k_1 k_3 k_4 k_5 k_7 k_9 k_{10} - k_1 k_2 k_4 k_6 k_7 k_9 k_{10} - k_1 k_3 k_4 k_6 k_7 k_9 k_{10} -
\end{aligned}$$

$$\begin{aligned}
& k_1 k_4 k_5 k_7 k_9 k_{10}^2 - k_1 k_4 k_6 k_7 k_9 k_{10}^2 - k_2^2 k_4^2 k_7 k_8 k_{11} - 2 k_2 k_3 k_4^2 k_7 k_8 k_{11} - \\
& k_3^2 k_4^2 k_7 k_8 k_{11} - 2 k_1 k_2 k_4 k_5 k_7 k_9 k_{11} - 2 k_1 k_3 k_4 k_5 k_7 k_9 k_{11} - 2 k_1 k_2 k_4 k_6 k_7 k_9 k_{11} - \\
& 2 k_1 k_3 k_4 k_6 k_7 k_9 k_{11} - k_1 k_2 k_4 k_5 k_7 k_{10} k_{11} - k_1 k_3 k_4 k_5 k_7 k_{10} k_{11} - \\
& k_1 k_2 k_4 k_6 k_7 k_{10} k_{11} - k_1 k_3 k_4 k_6 k_7 k_{10} k_{11} - k_2 k_4^2 k_7 k_8 k_{10} k_{11} - k_3 k_4^2 k_7 k_8 k_{10} k_{11} - \\
& 2 k_1 k_2 k_4 k_7 k_9 k_{10} k_{11} - 2 k_1 k_3 k_4 k_7 k_9 k_{10} k_{11} - k_1 k_4 k_5 k_7 k_9 k_{10} k_{11} - \\
& k_1 k_4 k_6 k_7 k_9 k_{10} k_{11} - k_2^2 k_4^2 k_7 k_{11}^2 - 2 k_2 k_3 k_4^2 k_7 k_{11}^2 - k_3^2 k_4^2 k_7 k_{11}^2 - \\
& k_2 k_4^2 k_7 k_8 k_{11}^2 - k_3 k_4^2 k_7 k_8 k_{11}^2 - 2 k_1 k_2 k_4 k_7 k_9 k_{11}^2 - 2 k_1 k_3 k_4 k_7 k_9 k_{11}^2 + \\
& (k_1^2 k_3 k_4 k_5 k_9 k_{10} + k_1^2 k_3 k_4 k_6 k_9 k_{10} - k_1^2 k_4 k_5 k_6 k_9 k_{10} - k_1^2 k_4 k_6^2 k_9 k_{10} - k_1^2 k_4 k_5 k_6 k_{10}^2 - \\
& k_1^2 k_4 k_6^2 k_{10}^2 - k_1^2 k_4 k_5 k_7 k_{10}^2 - k_1^2 k_4 k_6 k_7 k_{10}^2 - k_1 k_2 k_3 k_4^2 k_8 k_{11} - k_1 k_3^2 k_4^2 k_8 k_{11} + k_1 k_2 \\
& k_4^2 k_6 k_8 k_{11} + k_1 k_3 k_4^2 k_6 k_8 k_{11} - k_1^2 k_3 k_4 k_5 k_{10} k_{11} - k_1^2 k_3 k_4 k_6 k_{10} k_{11} - k_1 k_2 k_4^2 k_6 k_{10} \\
& k_{11} - k_1 k_3 k_4^2 k_6 k_{10} k_{11} - k_1 k_2 k_4^2 k_7 k_{10} k_{11} - k_1 k_3 k_4^2 k_7 k_{10} k_{11} - k_1^2 k_4 k_5 k_7 k_{10} k_{11} - \\
& k_1^2 k_4 k_6 k_7 k_{10} k_{11} - k_1 k_2 k_3 k_4^2 k_{11}^2 - k_1 k_3^2 k_4^2 k_{11}^2 - k_1 k_2 k_4^2 k_7 k_{11}^2 - k_1 k_3 k_4^2 k_7 k_{11}^2) x_3) + \\
x_1 & (-k_2^2 k_4 k_5 k_7 k_8 k_9 - 2 k_2 k_3 k_4 k_5 k_7 k_8 k_9 - k_3^2 k_4 k_5 k_7 k_8 k_9 - k_2^2 k_4 k_6 k_7 k_8 k_9 - \\
& 2 k_2 k_3 k_4 k_6 k_7 k_8 k_9 - k_3^2 k_4 k_6 k_7 k_8 k_9 - k_1 k_2 k_5^2 k_7 k_9^2 - k_1 k_3 k_5^2 k_7 k_9^2 - \\
& 2 k_1 k_2 k_5 k_6 k_7 k_9^2 - 2 k_1 k_3 k_5 k_6 k_7 k_9^2 - k_1 k_2 k_6^2 k_7 k_9^2 - k_1 k_3 k_6^2 k_7 k_9^2 - k_1 k_2 k_5^2 k_7 k_9 k_{10} - \\
& k_1 k_3 k_5^2 k_7 k_9 k_{10} - 2 k_1 k_2 k_5 k_6 k_7 k_9 k_{10} - 2 k_1 k_3 k_5 k_6 k_7 k_9 k_{10} - k_1 k_2 k_6^2 k_7 k_9 k_{10} - \\
& k_1 k_3 k_6^2 k_7 k_9 k_{10} - 2 k_2 k_4 k_5 k_7 k_8 k_9 k_{10} - 2 k_3 k_4 k_5 k_7 k_8 k_9 k_{10} - 2 k_2 k_4 k_6 k_7 k_8 k_9 k_{10} - \\
& 2 k_3 k_4 k_6 k_7 k_8 k_9 k_{10} - k_1 k_2 k_5 k_7 k_9^2 k_{10} - k_1 k_3 k_5 k_7 k_9^2 k_{10} - k_1 k_5^2 k_7 k_9^2 k_{10} - \\
& k_1 k_2 k_6 k_7 k_9^2 k_{10} - k_1 k_3 k_6 k_7 k_9^2 k_{10} - 2 k_1 k_5 k_6 k_7 k_9^2 k_{10} - k_1 k_6^2 k_7 k_9^2 k_{10} - k_1 k_5^2 k_7 k_9 k_{10}^2 - \\
& 2 k_1 k_5 k_6 k_7 k_9 k_{10}^2 - k_1 k_6^2 k_7 k_9 k_{10}^2 - k_4 k_5 k_7 k_8 k_9 k_{10}^2 - k_4 k_6 k_7 k_8 k_9 k_{10}^2 - \\
& k_1 k_5 k_7 k_9^2 k_{10}^2 - k_1 k_6 k_7 k_9^2 k_{10}^2 - k_2^2 k_4 k_5 k_7 k_8 k_{11} - 2 k_2 k_3 k_4 k_5 k_7 k_8 k_{11} - \\
& k_3^2 k_4 k_5 k_7 k_8 k_{11} - k_2^2 k_4 k_6 k_7 k_8 k_{11} - 2 k_2 k_3 k_4 k_6 k_7 k_8 k_{11} - k_3^2 k_4 k_6 k_7 k_8 k_{11} - \\
& 2 k_2^2 k_4 k_5 k_7 k_9 k_{11} - 4 k_2 k_3 k_4 k_5 k_7 k_9 k_{11} - 2 k_3^2 k_4 k_5 k_7 k_9 k_{11} - 2 k_2^2 k_4 k_6 k_7 k_9 k_{11} - \\
& 4 k_2 k_3 k_4 k_6 k_7 k_9 k_{11} - 2 k_3^2 k_4 k_6 k_7 k_9 k_{11} - k_2^2 k_4 k_7 k_8 k_9 k_{11} - 2 k_2 k_3 k_4 k_7 k_8 k_9 k_{11} - \\
& k_3^2 k_4 k_7 k_8 k_9 k_{11} - k_2 k_4 k_5 k_7 k_8 k_9 k_{11} - k_3 k_4 k_5 k_7 k_8 k_9 k_{11} - k_2 k_4 k_6 k_7 k_8 k_9 k_{11} - \\
& k_3 k_4 k_6 k_7 k_8 k_9 k_{11} - 2 k_1 k_2 k_5 k_7 k_9^2 k_{11} - 2 k_1 k_3 k_5 k_7 k_9^2 k_{11} - 2 k_1 k_2 k_6 k_7 k_9^2 k_{11} - \\
& 2 k_1 k_3 k_6 k_7 k_9^2 k_{11} - k_2 k_4 k_5 k_7 k_8 k_{10} k_{11} - k_3 k_4 k_5 k_7 k_8 k_{10} k_{11} - k_2 k_4 k_6 k_7 k_8 k_{10} k_{11} - \\
& k_3 k_4 k_6 k_7 k_8 k_{10} k_{11} - k_1 k_2 k_5 k_7 k_9 k_{10} k_{11} - k_1 k_3 k_5 k_7 k_9 k_{10} k_{11} - 2 k_2 k_4 k_5 k_7 k_9 k_{10} k_{11} - \\
& 2 k_3 k_4 k_5 k_7 k_9 k_{10} k_{11} - k_1 k_2 k_6 k_7 k_9 k_{10} k_{11} - k_1 k_3 k_6 k_7 k_9 k_{10} k_{11} - \\
& 2 k_2 k_4 k_6 k_7 k_9 k_{10} k_{11} - 2 k_3 k_4 k_6 k_7 k_9 k_{10} k_{11} - k_2 k_4 k_7 k_8 k_9 k_{10} k_{11} - \\
& k_3 k_4 k_7 k_8 k_9 k_{10} k_{11} - k_4 k_5 k_7 k_8 k_9 k_{10} k_{11} - k_4 k_6 k_7 k_8 k_9 k_{10} k_{11} - k_1 k_2 k_7 k_9^2 k_{10} k_{11} - \\
& k_1 k_3 k_7 k_9^2 k_{10} k_{11} - k_1 k_5 k_7 k_9^2 k_{10} k_{11} - k_1 k_6 k_7 k_9^2 k_{10} k_{11} - k_2^2 k_4 k_7 k_8 k_{11}^2 - \\
& 2 k_2 k_3 k_4 k_7 k_8 k_{11}^2 - k_3^2 k_4 k_7 k_8 k_{11}^2 - 2 k_2^2 k_4 k_7 k_9 k_{11}^2 - 4 k_2 k_3 k_4 k_7 k_9 k_{11}^2 - \\
& 2 k_2 k_3 k_4 k_7 k_9 k_{11}^2 - k_2 k_4 k_7 k_8 k_9 k_{11}^2 - k_3 k_4 k_7 k_8 k_9 k_{11}^2 - k_1 k_2 k_7 k_9^2 k_{11}^2 - k_1 k_3 k_7 k_9^2 k_{11}^2 - \\
& 2 (k_1 k_2 k_4 k_5 k_6 k_8 k_{10} + k_1 k_3 k_4 k_5 k_6 k_8 k_{10} + k_1 k_2 k_4 k_6^2 k_8 k_{10} + k_1 k_3 k_4 k_6^2 k_8 k_{10} + \\
& k_1 k_2 k_4 k_5 k_7 k_8 k_{10} + k_1 k_3 k_4 k_5 k_7 k_8 k_{10} + k_1 k_2 k_4 k_6 k_7 k_8 k_{10} + k_1 k_3 k_4 k_6 k_7 k_8 k_{10} + \\
& k_1 k_2 k_4 k_5 k_6 k_9 k_{10} + k_1 k_3 k_4 k_5 k_6 k_9 k_{10} + k_1 k_2 k_4 k_6^2 k_9 k_{10} + k_1 k_3 k_4 k_6^2 k_9 k_{10} + \\
& k_1 k_2 k_4 k_5 k_7 k_9 k_{10} + k_1 k_3 k_4 k_5 k_7 k_9 k_{10} + k_1 k_2 k_4 k_6 k_7 k_9 k_{10} + k_1 k_3 k_4 k_6 k_7 k_9 k_{10} + \\
& k_1 k_4 k_5 k_6 k_8 k_{10}^2 + k_1 k_4 k_6^2 k_8 k_{10}^2 + k_1 k_4 k_5 k_7 k_8 k_{10}^2 + k_1 k_4 k_6 k_7 k_8 k_{10}^2 + \\
& k_1 k_4 k_5 k_6 k_9 k_{10}^2 + k_1 k_4 k_6^2 k_9 k_{10}^2 + k_1 k_4 k_5 k_7 k_9 k_{10}^2 + k_1 k_4 k_6 k_7 k_9 k_{10}^2 + \\
& k_1 k_2 k_3 k_4 k_5 k_8 k_{11} + k_1 k_3^2 k_4 k_5 k_8 k_{11} + k_1 k_2 k_3 k_4 k_6 k_8 k_{11} + k_1 k_3^2 k_4 k_6 k_8 k_{11} + \\
& k_1 k_2 k_4 k_5 k_7 k_8 k_{11} + k_1 k_3 k_4 k_5 k_7 k_8 k_{11} + k_1 k_2 k_4 k_6 k_7 k_8 k_{11} + k_1 k_3 k_4 k_6 k_7 k_8 k_{11} + \\
& k_1 k_2 k_3 k_4 k_5 k_9 k_{11} + k_1 k_3^2 k_4 k_5 k_9 k_{11} + k_1 k_2 k_3 k_4 k_6 k_9 k_{11} + k_1 k_3^2 k_4 k_6 k_9 k_{11} + \\
& k_1 k_2 k_4 k_5 k_7 k_9 k_{11} + k_1 k_3 k_4 k_5 k_7 k_9 k_{11} + k_1 k_2 k_4 k_6 k_7 k_9 k_{11} + k_1 k_3 k_4 k_6 k_7 k_9 k_{11} + \\
& k_1 k_3 k_4 k_5 k_8 k_{10} k_{11} + k_1 k_2 k_4 k_6 k_8 k_{10} k_{11} + 2 k_1 k_3 k_4 k_6 k_8 k_{10} k_{11} + k_1 k_2 k_4 k_7 \\
& k_8 k_{10} k_{11} + k_1 k_3 k_4 k_7 k_8 k_{10} k_{11} + k_1 k_4 k_5 k_7 k_8 k_{10} k_{11} + k_1 k_4 k_6 k_7 k_8 k_{10} k_{11} + \\
& k_1 k_3 k_4 k_5 k_9 k_{10} k_{11} + k_1 k_2 k_4 k_6 k_9 k_{10} k_{11} + 2 k_1 k_3 k_4 k_6 k_9 k_{10} k_{11} + k_1 k_2 k_4 k_7 \\
& k_7 k_9 k_{10} k_{11} + k_1 k_3 k_4 k_7 k_9 k_{10} k_{11} + k_1 k_4 k_5 k_7 k_9 k_{10} k_{11} + k_1 k_4 k_6 k_7 k_9 k_{10} k_{11} + \\
& k_1 k_2 k_3 k_4 k_8 k_{11}^2 + k_1 k_3^2 k_4 k_8 k_{11}^2 + k_1 k_2 k_4 k_7 k_8 k_{11}^2 + k_1 k_3 k_4 k_7 k_8 k_{11}^2 + \\
& k_1 k_2 k_3 k_4 k_9 k_{11}^2 + k_1 k_3^2 k_4 k_9 k_{11}^2 + k_1 k_2 k_4 k_7 k_9 k_{11}^2 + k_1 k_3 k_4 k_7 k_9 k_{11}^2) x_3)
\end{aligned}$$

$$\begin{aligned}
\text{factor} &= k_1^2 k_3 k_4 k_5 k_9 k_{10} + k_1^2 k_3 k_4 k_6 k_9 k_{10} - k_1^2 k_4 k_5 k_6 k_9 k_{10} - \\
& k_1^2 k_4 k_6^2 k_9 k_{10} - k_1^2 k_4 k_5 k_6 k_{10}^2 - k_1^2 k_4 k_6^2 k_{10}^2 - k_1^2 k_4 k_5 k_7 k_{10}^2 - k_1^2 k_4 k_6 k_7 k_{10}^2 - \\
& k_1 k_2 k_3 k_4^2 k_8 k_{11} - k_1 k_3^2 k_4^2 k_8 k_{11} + k_1 k_2 k_4^2 k_6 k_8 k_{11} + k_1 k_3 k_4^2 k_6 k_8 k_{11} - \\
& k_1^2 k_3 k_4 k_5 k_{10} k_{11} - k_1^2 k_3 k_4 k_6 k_{10} k_{11} - k_1 k_2 k_4^2 k_6 k_{10} k_{11} - k_1 k_3 k_4^2 k_6 k_{10} k_{11} - \\
& k_1 k_2 k_4^2 k_7 k_{10} k_{11} - k_1 k_3 k_4^2 k_7 k_{10} k_{11} - k_1^2 k_4 k_5 k_7 k_{10} k_{11} - k_1^2 k_4 k_6 k_7 k_{10} k_{11} - \\
& k_1 k_2 k_3 k_4^2 k_{11}^2 - k_1 k_3^2 k_4^2 k_{11}^2 - k_1 k_2 k_4^2 k_7 k_{11}^2 - k_1 k_3 k_4^2 k_7 k_{11}^2;
\end{aligned}$$

Factor[factor]

$$k_1 k_4 \left(k_1 k_3 k_5 k_9 k_{10} + k_1 k_3 k_6 k_9 k_{10} - k_1 k_5 k_6 k_9 k_{10} - k_1 k_6^2 k_9 k_{10} - \right. \\ \left. k_1 k_5 k_6 k_{10}^2 - k_1 k_6^2 k_{10}^2 - k_1 k_5 k_7 k_{10}^2 - k_1 k_6 k_7 k_{10}^2 - k_2 k_3 k_4 k_8 k_{11} - k_3^2 k_4 k_8 k_{11} + \right. \\ \left. k_2 k_4 k_6 k_8 k_{11} + k_3 k_4 k_6 k_8 k_{11} - k_1 k_3 k_5 k_{10} k_{11} - k_1 k_3 k_6 k_{10} k_{11} - k_2 k_4 k_6 k_{10} k_{11} - \right. \\ \left. k_3 k_4 k_6 k_{10} k_{11} - k_2 k_4 k_7 k_{10} k_{11} - k_3 k_4 k_7 k_{10} k_{11} - k_1 k_5 k_7 k_{10} k_{11} - \right. \\ \left. k_1 k_6 k_7 k_{10} k_{11} - k_2 k_3 k_4 k_{11}^2 - k_3^2 k_4 k_{11}^2 - k_2 k_4 k_7 k_{11}^2 - k_3 k_4 k_7 k_{11}^2 \right)$$

$$\text{term} = k_1 k_3 k_5 k_9 k_{10} + k_1 k_3 k_6 k_9 k_{10} - k_1 k_5 k_6 k_9 k_{10} - k_1 k_6^2 k_9 k_{10} - \\ k_1 k_5 k_6 k_{10}^2 - k_1 k_6^2 k_{10}^2 - k_1 k_5 k_7 k_{10}^2 - k_1 k_6 k_7 k_{10}^2 - k_2 k_3 k_4 k_8 k_{11} - k_3^2 k_4 k_8 k_{11} + \\ k_2 k_4 k_6 k_8 k_{11} + k_3 k_4 k_6 k_8 k_{11} - k_1 k_3 k_5 k_{10} k_{11} - k_1 k_3 k_6 k_{10} k_{11} - k_2 k_4 k_6 k_{10} k_{11} - \\ k_3 k_4 k_6 k_{10} k_{11} - k_2 k_4 k_7 k_{10} k_{11} - k_3 k_4 k_7 k_{10} k_{11} - k_1 k_5 k_7 k_{10} k_{11} - \\ k_1 k_6 k_7 k_{10} k_{11} - k_2 k_3 k_4 k_{11}^2 - k_3^2 k_4 k_{11}^2 - k_2 k_4 k_7 k_{11}^2 - k_3 k_4 k_7 k_{11}^2;$$

simpTerm = FullSimplify[term]

$$- (k_2 + k_3) k_4 k_{11} (k_6 (-k_8 + k_{10}) + k_3 (k_8 + k_{11}) + k_7 (k_{10} + k_{11})) - \\ k_1 (k_5 + k_6) k_{10} (k_6 (k_9 + k_{10}) + k_3 (-k_9 + k_{11}) + k_7 (k_{10} + k_{11}))$$

simplerTerm = Distribute[simpTerm / (k1 * k4)] /. {(k2 + k3) / k1 → M1, (k5 + k6) / k4 → M2}

$$- k_{11} (k_6 (-k_8 + k_{10}) + k_3 (k_8 + k_{11}) + k_7 (k_{10} + k_{11})) M_1 - \\ k_{10} (k_6 (k_9 + k_{10}) + k_3 (-k_9 + k_{11}) + k_7 (k_{10} + k_{11})) M_2$$

This above term larger than 0 should be the necessary condition.

condition = simplerTerm > 0

$$- k_{11} (k_6 (-k_8 + k_{10}) + k_3 (k_8 + k_{11}) + k_7 (k_{10} + k_{11})) M_1 - \\ k_{10} (k_6 (k_9 + k_{10}) + k_3 (-k_9 + k_{11}) + k_7 (k_{10} + k_{11})) M_2 > 0$$

By manual simplifying the term, we can have:

$$\text{simpleCond} = (k_3 - k_6) * (M_2 * k_9 * k_{10} - M_1 * k_8 * k_{11}) > \\ (k_{11} * M_1 + k_{10} * M_2) * ((k_6 * k_{10} + k_3 * k_{11}) + k_7 * (k_{10} + k_{11})) \\ (k_3 - k_6) (-k_8 k_{11} M_1 + k_9 k_{10} M_2) > (k_6 k_{10} + k_3 k_{11} + k_7 (k_{10} + k_{11})) (k_{11} M_1 + k_{10} M_2)$$

left = (k3 - k6) * (M2 * k9 * k10 - M1 * k8 * k11) /. {M1 → (k2 + k3) / k1, M2 → (k5 + k6) / k4}

$$(k_3 - k_6) \left(\frac{(k_5 + k_6) k_9 k_{10}}{k_4} - \frac{(k_2 + k_3) k_8 k_{11}}{k_1} \right)$$

right = (k11 * M1 + k10 * M2) * ((k6 * k10 + k3 * k11) + k7 * (k10 + k11)) /. {M1 → (k2 + k3) / k1, M2 → (k5 + k6) / k4}

$$\left(\frac{(k_5 + k_6) k_{10}}{k_4} + \frac{(k_2 + k_3) k_{11}}{k_1} \right) (k_6 k_{10} + k_3 k_{11} + k_7 (k_{10} + k_{11}))$$

To fullfile the assumption of thermodynamic conditions for the reversible reactions, we have the the constraint:

$$\frac{k_1 k_{10}}{k_2 k_{11}} = \frac{k_4 k_8}{k_5 k_9}.$$

This will give us a even simple condition. Then we will example how will this condition result in the parameter space for multistationarity.

oriCond = simpleCond /. {M1 → (k2 + k3) / k1, M2 → (k5 + k6) / k4}

$$(k_3 - k_6) \left(\frac{(k_5 + k_6) k_9 k_{10}}{k_4} - \frac{(k_2 + k_3) k_8 k_{11}}{k_1} \right) > \\ \left(\frac{(k_5 + k_6) k_{10}}{k_4} + \frac{(k_2 + k_3) k_{11}}{k_1} \right) (k_6 k_{10} + k_3 k_{11} + k_7 (k_{10} + k_{11}))$$

$$\text{Simplify}\left[\text{oriCond}, \text{Assumptions} \rightarrow \frac{k_1 k_{10}}{k_2 k_{11}} == \frac{k_4 k_8}{k_5 k_9}\right]$$

$$\frac{(k_3 - k_6) (k_1 k_6 k_9 k_{10} - k_3 k_4 k_8 k_{11})}{k_1 k_4} >$$

$$\left(\frac{(k_5 + k_6) k_{10}}{k_4} + \frac{(k_2 + k_3) k_{11}}{k_1} \right) ((k_6 + k_7) k_{10} + (k_3 + k_7) k_{11})$$

Better to do it manually, then we have the condition with thermodynamic constraint:

thermoCond =

$$(k_3 - k_6) (k_6 k_2 - k_3 k_5) > \left(\frac{k_2}{k_9} \times \frac{k_5^2 + k_6}{k_5} + \frac{k_5}{k_8} \times \frac{k_2^2 + k_3}{k_2} \right) ((k_6 + k_7) k_{10} + (k_3 + k_7) k_{11})$$

$$(k_3 - k_6) (-k_3 k_5 + k_2 k_6) > \left(\frac{(k_2^2 + k_3) k_5}{k_2 k_8} + \frac{k_2 (k_5^2 + k_6)}{k_5 k_9} \right) ((k_6 + k_7) k_{10} + (k_3 + k_7) k_{11})$$

From the above condition, we can get some general idea that in order to satisfy the thermodynamic condition we should have:

Necessarily:

$$k_3 > k_6 \text{ and } k_2 > k_5$$

or

$$k_3 < k_6 \text{ and } k_5 > k_2$$

With additional (sufficiently):

$$k_8, k_9 \gg k_{10}, k_{11} \text{ and } k_7, k_{10}, k_{11} \approx 0$$

Sampling the parameters

Here we try to sampling the parameters by enforcing the thermodynamic constraint. The parameters are sampled in biologically meaningful ranges.

(NewKern) In[176]:=

```
ClearAll["Global`*"];
A = Table[0, {11}, {6}];
A[[1]][[1]] = -1;
A[[1]][[3]] = -1;
A[[1]][[5]] = 1;
A[[2]] = -A[[1]];
A[[3]][[3]] = 1; A[[3]][[2]] = 1; A[[3]][[5]] = -1;
A[[4]][[1]] = -1;
A[[4]][[4]] = -1;
A[[4]][[6]] = 1;
A[[5]] = -A[[4]];
A[[6]][[4]] = 1;
A[[6]][[2]] = 1;
A[[6]][[6]] = -1;
A[[7]][[2]] = -1;
A[[7]][[1]] = 1;
A[[8]][[3]] = -1; A[[8]][[4]] = 1; A[[9]] = -A[[8]];
A[[10]][[5]] = -1; A[[10]][[6]] = 1; A[[11]] = -A[[10]];
stoiM = Transpose[A];
(* Now we construct the rate vector *)
ks = {k1 x x3 x x1, k2 x x5, k3 x x5, k4 x x4 x x1,
      k5 x x6, k6 x x6, k7 x x2, k8 x x3, k9 x x4, k10 x x5, k11 x x6};
ssEqns = stoiM.ks;
mC = RowReduce[NullSpace[A]];
subsEqns = {ssEqns[[2]], ssEqns[[4]],
            ssEqns[[5]], ssEqns[[6]], x1 + x2 + x5 + x6 - T1, x3 + x4 + x5 + x6 - T2};
jacobian = D[subsEqns, {{x1, x2, x3, x4, x5, x6}}];
detJ = Collect[Distribute[Det[jacobian]], {x1, x2, x3, x4, x5, x6}];
```

```

solution =
  Solve[{{subsEqns[[1]], subsEqns[[2]], subsEqns[[3]], subsEqns[[4]]} == 0},
    {x2, x4, x5, x6}];
detSubs = Replace[detJ, solution[[1]], {0, Infinity}];
(* Equivilant to detSubs=detJ/.solution[[1]]; *)
polSubs = Numerator[Together[detSubs]];
finalSubs = Collect[Distribute[polSubs], x_, FactorTerms];
(*The above code is the same as first section*)

reactionRates = N[Array[10^(-3) * (10^6)^(#-1/1023) &, 1024]];
(* association rates are set as 10^-3~10^3μM^-1s^-1,
disassociation and catalytic rates are set as 10^-3~10^3s^-1 *)
switchingRates = N[Array[10^(-3) * (10^9)^(#-1/1535) &, 1536]];

(* The switching rate between
different conformations are set as 10^-3~10^6s^-1 *)
concentrations = N[Array[10^(-3) * (10^4)^(#-1/9) &, 10]];
(* The concentration values are set as 10^-3~
10μM (1 molecule in a cell is approximately 2nM) *)

bistableKs = {};
bistableParSets = {};
SeedRandom[];
Timing[
  Do[{
    k1 = reactionRates[[RandomInteger[1023]]];
    k2 = reactionRates[[RandomInteger[1023]]];
    k3 = reactionRates[[RandomInteger[1023]]];
    k4 = reactionRates[[RandomInteger[1023]]];
    k5 = reactionRates[[RandomInteger[1023]]];
    k6 = reactionRates[[RandomInteger[1023]]];
    k7 = reactionRates[[RandomInteger[1023]]];
    (*k8=switchingRates[[RandomInteger[1023]]];*)
    k9 = switchingRates[[RandomInteger[1535]]];
    k10 = switchingRates[[RandomInteger[1535]]];
    k11 = switchingRates[[RandomInteger[1535]]];
    k8 = (k1 × k10 × k5 × k9) / (k11 × k4 × k2);
    If[10^(-3) ≤ k8 ≤ 10^3, {
      left = (k3 - k6) ( (k5 + k6) k9 k10 / k4 - (k2 + k3) k8 k11 / k1 );
      right = ( (k5 + k6) k10 / k4 + (k2 + k3) k11 / k1 ) (k6 k10 + k3 k11 + k7 (k10 + k11));
      If[left > right, {
        AppendTo[bistableKs,
          {k1, k2, k3, k4, k5, k6, k7, k8, k9, k10, k11, left, right}];
        counter = 1; hitQ = 0;
        randCons = RandomSample[Range[10]] - 1;
        numIterations = Length[randCons];
        While[hitQ == 0 && counter ≤ numIterations, {
          x1 = concentrations[[randCons[[counter]]]];
          finalSol = NSolve[
            finalSubs == 0 /. {k1 → k1, k2 → k2, k3 → k3, k4 → k4, k5 → k5, k6 → k6,
              k7 → k7, k8 → k8, k9 → k9, k10 → k10, k11 → k11, x1 → x1}, {x3}];
          x3 = x3 /. finalSol[[1]];
          realSol = solution /. {k1 → k1, k2 → k2, k3 → k3, k4 → k4, k5 → k5, k6 → k6,
            k7 → k7, k8 → k8, k9 → k9, k10 → k10, k11 → k11, x1 → x1, x3 → x3};

```

```

T1 = (x1 + x2 + x5 + x6) /. Flatten[Append[{x1 → x1, x3 → x3},
realSol[[1]]]];
T2 = (x3 + x4 + x5 + x6) /. Flatten[Append[{x1 → x1, x3 → x3},
realSol[[1]]]];
If[10^(-3) ≤ T1 ≤ 10 && 10^(-3) ≤ T2 ≤ 10, {
AppendTo[bistableParSets,
{k1, k2, k3, k4, k5, k6, k7, k8, k9, k10, k11, T1, T2, left, right}];
hitQ = 1;
}];
counter++;
}];
}];
}, {i, 100 000}];
]
(NewKern) Out[200]=
{72.412297, Null}

(NewKern) In[201]:=
Length[bistableParSets]

(NewKern) Out[201]=
4

(NewKern) In[212]:=
InputForm[bistableParSets]

(NewKern) Out[212]/InputForm=
{{805.6721616936468, 723.1652294935797, 325.9841474641885, 18.61207189258695, 0.0044173
0.5945570708544392, 2.1336726036431073, 7.610851088488717, 22.111866678674108, 0.0208
1.584496179647185, 204.38291283628442, 2.523254300495873}, {90.36738814396949, 0.0102
143.02936809965504, 59.45570708544391, 7.329977462151208, 0.42419542706920305, 8.6171
0.0061877241514645, 0.07221574930686654, 7.841098859167478, 1.140251925887791, 0.0165
{582.6340937077745, 0.0016260866900534396, 0.19912245340072018, 54.092596673122024, 0.
0.011216396996267482, 9.46413833821489, 0.089627853732365, 0.02171739935759679, 0.076
0.06097279124533667, 0.00029695043338743134, 0.00004462888860375256}, {753.0656608133
495.4669185977836, 146.94520707580176, 0.024548746742478266, 0.44774051345422433, 0.3
1.8946300882401192, 0.41208206515902046, 0.006801008065722134, 5.995672162002269, 0.1
0.045240897699078575}}

(NewKern) In[202]:=
transposedBiKs = Transpose[bistableParSets];
biParK1 = 
$$\frac{\text{transposedBiKs}[[1]] * \text{transposedBiKs}[[10]]}{\text{transposedBiKs}[[2]] * \text{transposedBiKs}[[11]]};$$

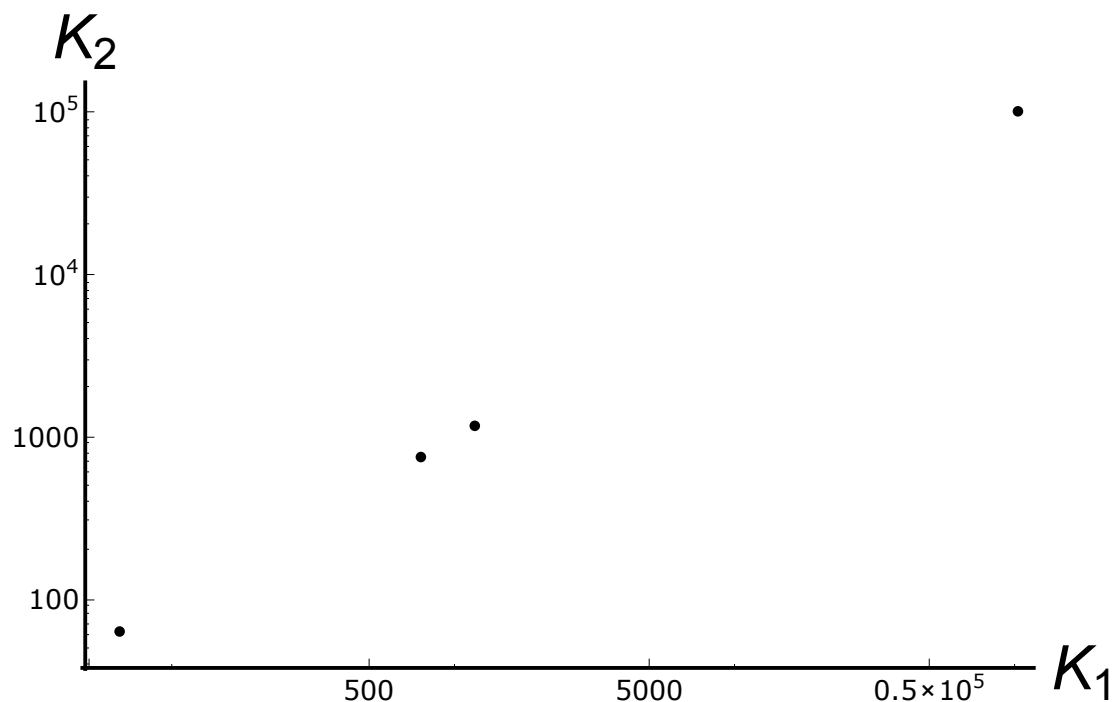
biParK2 = 
$$\frac{\text{transposedBiKs}[[4]] * \text{transposedBiKs}[[8]]}{\text{transposedBiKs}[[5]] * \text{transposedBiKs}[[9]]};$$


```

(NewKern) In[203]:=

```
biPlot = ListLogLogPlot[Transpose[{biParK1, biParK2}], ImageSize → Large,
  PlotRange → All, PlotLabel → None, LabelStyle → {32, GrayLevel[0]},
  AxesLabel → {"K1", "K2"}, Ticks → Automatic, TicksStyle → Directive["Label", 14],
  AxesStyle → Thick, PlotTheme → "Monochrome"]
```

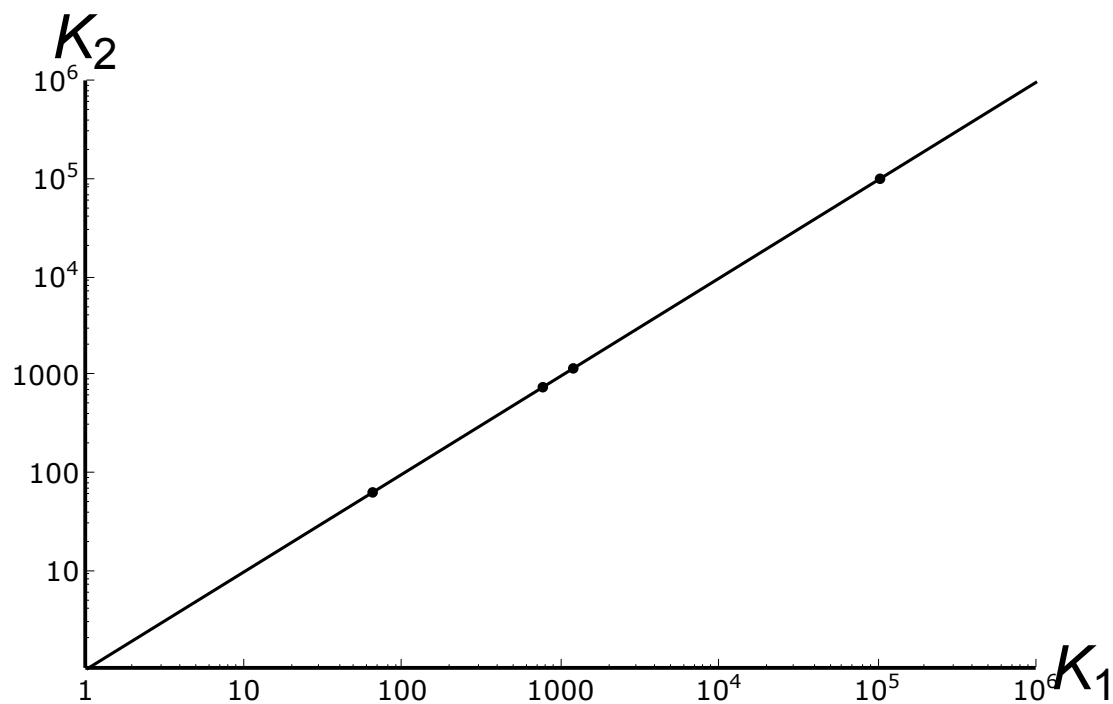
(NewKern) Out[203]=



(NewKern) In[204]:=

```
Show[LogLogPlot[x, {x, 10^(0), 10^6},
  PlotRange → {{10^(0), 10^6}, {10^(0), 10^6}},
  ImageSize → Large, PlotTheme → "Monochrome", PlotLabel → None,
  LabelStyle → {32, GrayLevel[0]}, AxesLabel → {"K1", "K2"}, Ticks → Automatic,
  TicksStyle → Directive["Label", 14], AxesStyle → Thick], biPlot]
```

(NewKern) Out[204]=



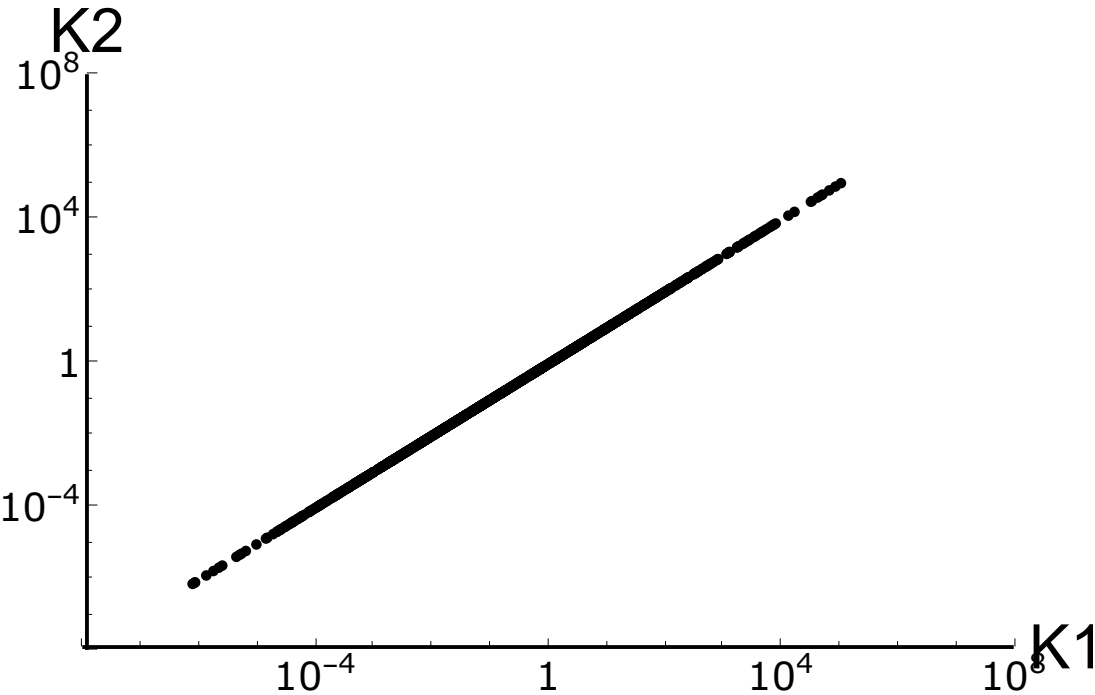

```
(NewKern) In[205]:=
Length[bistableKs]
```

```
(NewKern) Out[205]=
1054
```

```
(NewKern) In[206]:=
transposedKs = Transpose[bistableKs];
parK1 =  $\frac{\text{transposedKs}[[1]] * \text{transposedKs}[[10]]}{\text{transposedKs}[[2]] * \text{transposedKs}[[11]]}$ ;
parK2 =  $\frac{\text{transposedKs}[[4]] * \text{transposedKs}[[8]]}{\text{transposedKs}[[5]] * \text{transposedKs}[[9]]}$ ;
```

```
(NewKern) In[207]:=
plot = ListLogLogPlot[Transpose[{parK1, parK2}], AxesLabel -> {"K1", "K2"},
  ImageSize -> Large, PlotRange -> {{10^(-8), 10^8}, {10^(-8), 10^8}},
  LabelStyle -> {32, GrayLevel[0]}, AxesStyle -> Thick, Ticks -> Automatic,
  TicksStyle -> Directive["Label", 20], PlotTheme -> "Monochrome"]
```

```
(NewKern) Out[207]=
```



These above results show that the parameter set within biological meaningful ranges can be reached by increasing the sampling size even when enforcing the thermodynamic constraint. Comparing to results from the other document (without enforcing thermodynamic constraint), the parameter space is largely reduced.

□	with thermo		without ther
Sampling size	only check bistability	bistability & concentrations	only check bista
10 ⁵	1054	4	11 985
10 ⁶	10 506	52	120 345