Bistable motif: parameter sampling

Finding the condition of multistationarity

We consider the following reactions:

$K + S \leftrightharpoons KS \to K + S_p$
$K^* + S \leftrightharpoons K^* S \to K^* + S_p$
$S_p \to S$
$K \leftrightharpoons K^*$
$KS \leftrightharpoons K^* S$

The species of the system are:

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

In total, there are 11 reations 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 implys 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 × x3 × x1, k2 × x5, k3 × x5, k4 × x4 × x1,
   k5 × x6, k6 × x6, k7 × x2, k8 × x3, k9 × x4, k10 × x5, k11 × 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]
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$$
\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_5^2 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 + \left(-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\right) x_1^3 + \\
&\Big(-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 - \\
&\quad 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 - \\
&\quad 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 - \\
&\quad 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 - \\
&\quad 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 - \\
&\quad 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 - \\
&\quad 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 - \\
&\quad 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 - \\
&\quad 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 -
\end{aligned}
$$

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

$$
\begin{aligned}
&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_3^2\, 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} + \\
&\quad 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} + \\
&\quad 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} + \\
&\quad 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} + \\
&\quad 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 + \\
&\quad 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 + \\
&\quad 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} + \\
&\quad 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} + \\
&\quad 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} + \\
&\quad 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} + \\
&\quad 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 \\
&\qquad 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} + \\
&\quad 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 \\
&\qquad 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} + \\
&\quad 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 + \\
&\quad 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}
$$

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

Factor[factor]

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

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

simpTerm = FullSimplify[term]

$$
\begin{aligned}
& -(k_2 + k_3)\; k_4\, k_{11}\; (k_6\; (-k_8 + k_{10}) + k_3\; (k_8 + k_{11}) + k_7\; (k_{10} + k_{11})) - \\
&\; k_1\; (k_5 + k_6)\; k_{10}\; (k_6\; (k_9 + k_{10}) + k_3\; (-k_9 + k_{11}) + k_7\; (k_{10} + k_{11}))
\end{aligned}
$$

```
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 mannual simplying the term, we can have:

```
simpleCond = (k3 - k6) * (M2 * k9 * k10 - M1 * k8 * k11) >
   (k11 * M1 + k10 * M2) * ((k6 * k10 + k3 * k11) + k7 * (k10 + k11))
```

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

```
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}
```

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

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

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

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

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

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

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

Necessarily:
$k_3 > k_6$ and $k_2 > k_5$
or
$k_3 < k_6$ and $k_5 > k_2$
With additional (sufficiently):
k_8, $k_9 \gg k_{10}$, k_{11} and k_7, k_{10}, $k_{11} \approx 0$

Sampling the parameters

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

Sampling the parameters related to thermodynamic constraint k1, k2, k4, k5, k8, k9, k10, k11. Using Gamma distribution with $\alpha = 7$, $\beta = 2$, and then uniformly sample 4 random numbers that sum to 1, these are for k1, k5, k9, k10. Sample anther four uniform random number for k2, k4, k8, k11.

For other parameters:

(NewKernel) In[254]:=

```
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 × x3 × x1, k2 × x5, k3 × x5, k4 × x4 × x1,
    k5 × x6, k6 × x6, k7 × x2, k8 × x3, k9 × x4, k10 × x5, k11 × 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*)
```

```
bistableKs = {};
bistableParSets = {};
SeedRandom[];
Timing[
 Do[{
    gamma = RandomVariate[GammaDistribution[2, 7]];
    rand13 = RandomVariate[DirichletDistribution[{1, 1, 1, 1}]];
    rand11 = 1 - Total@rand13;
    rand23 = RandomVariate[DirichletDistribution[{1, 1, 1, 1}]];
    rand21 = 1 - Total@rand23;
    k1 = Exp[-gamma * rand13[[1]]] * 1.*^3;
    k2 = Exp[-gamma * rand23[[3]]] * 1.*^3;
    k3 =
     Exp[-RandomVariate[ExponentialDistribution[Log[2] / (-Log[0.001])]]] * 1000;
    k4 = Exp[-gamma * rand23[[1]]] * 1.*^3;
    k5 = Exp[-gamma * rand13[[3]]] * 1.*^3;
    k6 =
     Exp[-RandomVariate[ExponentialDistribution[Log[2] / (-Log[0.001])]]] * 1000;
    k7 = Exp[-RandomVariate[ExponentialDistribution[Log[2] / (-Log[0.001])]]] *
      1000;
    k8 = Exp[-gamma * rand23[[2]]] * 1.*^3;
    k9 = Exp[-gamma * rand11] * 1.*^3;
    k10 = Exp[-gamma * rand13[[2]]] * 1.*^3;
    k11 = Exp[-gamma * rand21] * 1.*^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;
      While[hitQ == 0 && counter ≤ 1000, {
        x1 = Exp[-RandomVariate[
             ExponentialDistribution[Log[2] / (-Log[0.0001])]]] * 1000;
        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[0.0001 ≤ T1 ≤ 1000 && 0.0001 ≤ T2 ≤ 1000, {
          AppendTo[bistableParSets,
           {k1, k2, k3, k4, k5, k6, k7, k8, k9, k10, k11, T1, T2, left, right}];
          hitQ = 1;
         }];
        counter++;
       }];
     }];
   }, {i, 10000}];
]
```

(NewKernel) Out[276]=

```
{968.207, Null}
```

(NewKernel) In[277]:=

```
Length[bistableParSets]
```

(NewKernel) Out[277]=

```
10
```

(NewKernel) In[278]:=

```
InputForm[bistableParSets]
```

(NewKernel) Out[278]//InputForm=

```
{{79.96925401169008, 0.029162755292384164, 0.1140572889623974, 339.9710565197557, 233.8
  0.0026653378838017924, 848.0814624988211, 98.0763198422986, 0.12619325577159665, 27.5
  0.21784454128365366, 3334.951424572326, 3.1583906774386863}, {7.0407389028226355, 0.0
  0.022012926151557918, 401.15438043780716, 25.357045093495817, 406.19014937715247, 2.9
  20.559244834670906, 0.21704069940157816, 44.99183701772713, 862.318382770165, 0.00012
  33.824226747395265}, {305.1991093062434, 784.3737124091133, 619.82637855117, 50.91681
  103.1422207651505, 0.00009615735390542761, 9.355029822594844, 223.8514742126822, 160.
  199.7173004058969, 0.00011587014463072953, 3.7690401551549785*^7, 5.743178555595361*^
 {36.81864149905964, 659.041896529781, 96.5118740002914, 35.82392226394757, 0.005916307
  1.7108210874551764, 0.26414718929071834, 267.16821436188894, 0.26444478905548685, 0.0
  144.0991423332005, 4.879648082213135, 0.0357089768834993}, {32.149478677994004, 256.1
  48.533459200047446, 0.00020842276281625365, 0.006943163800317498, 0.00038305252460814
  267.0058657606572, 4.499352192086573, 0.002774965596024407, 18.43824828699346, 0.193
  0.0018042719455556141}, {149.89233556195757, 95.12174637165315, 69.3654470782759, 291
  2.519161939397978, 0.0001309302464138583, 0.7911846442410612, 18.160496573316713, 3.
  10.01342676756553, 0.00021131381998175917, 30.200820078745593, 1.0831531801853953},
 {20.127872532643252, 0.0003133225443978319, 30.74274557763445, 493.62928939657775, 134
  0.000017784752489717836, 267.0791729419947, 84.44730358642785, 0.01936476924412682, 1
  0.00012110711056150803, 3.286041766641667*^6, 540935.372451751}, {168.27980540288368,
  659.5321083666223, 37.06870237804975, 280.1944486830178, 34.705991369127666, 303.7385
  12.30372914830827, 152.91459483003842, 270.0539849225215, 99.98676017351923, 2.197546
 {345.49429827326423, 0.05247863362064721, 0.38809790650294373, 191.03720181629416, 314
  0.022644355878415345, 103.25951825834322, 1.891799857799716, 0.33653343852317413, 66.
  19.74058395159674, 479.7438053589221, 36.8815398730932}, {66.4018838052063, 0.0028507
  208.46562662075124, 1.3580023088499898*^-9, 94.86939488594105, 61.51216015207017, 0.0
  48.578349561777564, 9.13224655803779, 786.9979175109088, 166.91082732711357, 1.064225
```

(NewKernel) In[279]:=

```
transposedBiKs = Transpose[bistableParSets];
```

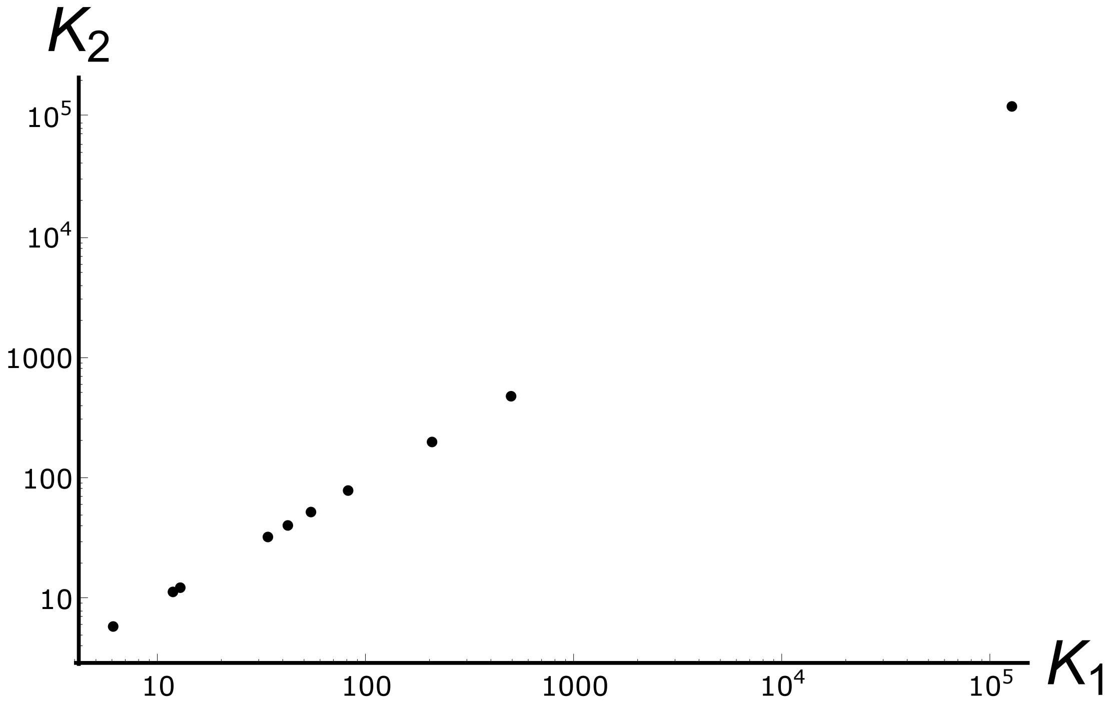
$$\text{biParK1} = \frac{\text{transposedBiKs[[1]]} * \text{transposedBiKs[[10]]}}{\text{transposedBiKs[[2]]} * \text{transposedBiKs[[11]]}};$$

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

(NewKernel) In[280]:=

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

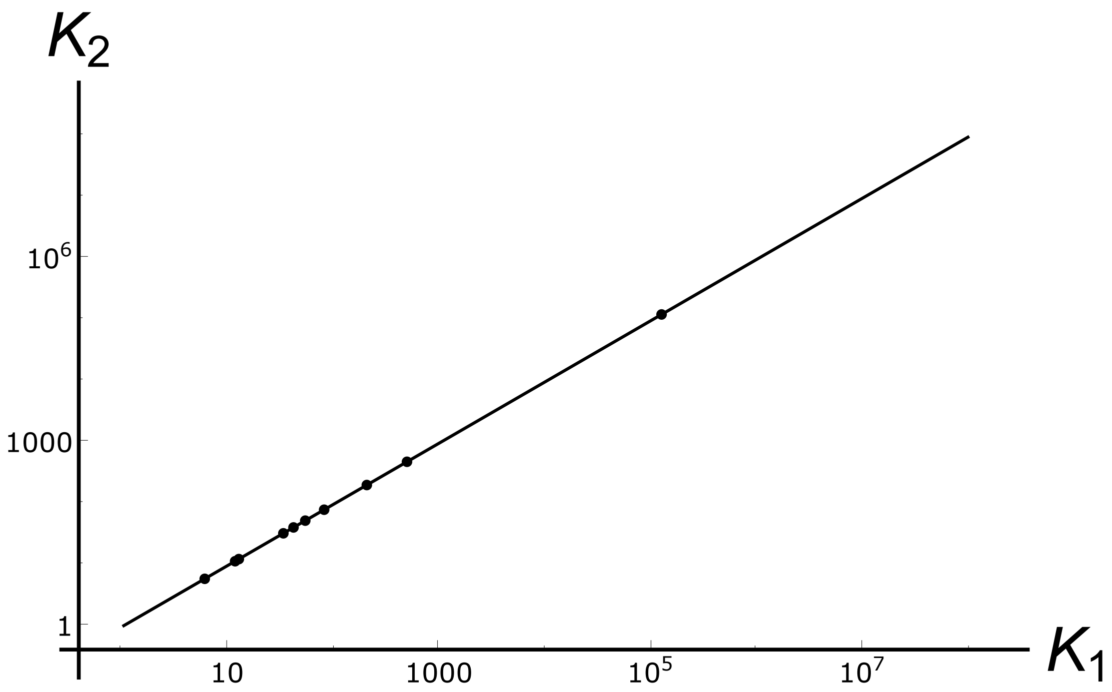
(NewKernel) Out[280]=



(NewKernel) In[281]:=

```
Show[LogLogPlot[x, {x, 10^(0), 10^8}, PlotRange → Full,
  ImageSize → Large, PlotTheme → "Monochrome", PlotLabel → None,
  LabelStyle → {32, GrayLevel[0]}, AxesLabel → {"K₁", "K₂"}, Ticks → Automatic,
  TicksStyle → Directive["Label", 14], AxesStyle → Thick], biPlot]
```

(NewKernel) Out[281]=



(NewKernel) In[282]:=

```
Length[bistableKs]
```

(NewKernel) Out[282]=

```
164
```

(NewKernel) In[283]:=

```
transposedKs = Transpose[bistableKs];
```

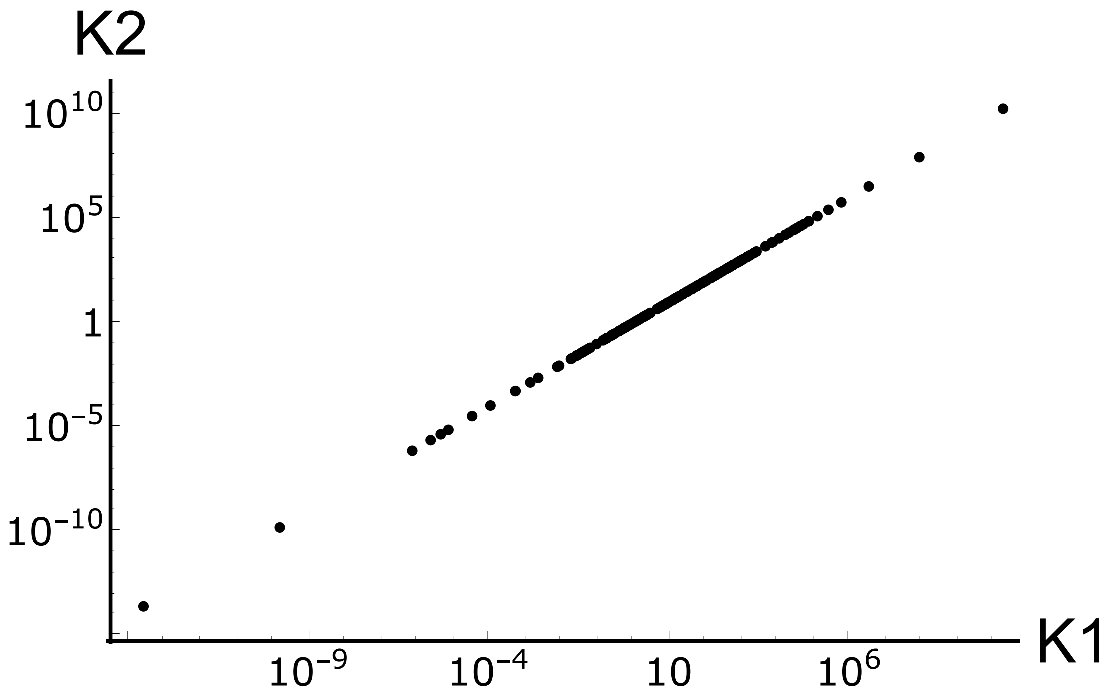
$$\text{parK1} = \frac{\text{transposedKs[[1]]} * \text{transposedKs[[10]]}}{\text{transposedKs[[2]]} * \text{transposedKs[[11]]}};$$

$$\text{parK2} = \frac{\text{transposedKs[[4]]} * \text{transposedKs[[8]]}}{\text{transposedKs[[5]]} * \text{transposedKs[[9]]}};$$

(NewKernel) In[284]:=

```
plot = ListLogLogPlot[Transpose[{parK1, parK2}],
  AxesLabel → {"K1", "K2"}, ImageSize → Large, PlotRange → Full,
  LabelStyle → {32, GrayLevel[0]}, AxesStyle → Thick, Ticks → Automatic,
  TicksStyle → Directive["Label", 20], PlotTheme → "Monochrome"]
```

(NewKernel) Out[284]=



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 paramter space is largely reduced.

Conditions	with thermo	with thermo	without ther
Sampling size	only check bistability	bistability & concentrations	only check bista
10^4	164	10	1626
10^5	□	□	□

Test