```
> with(LinearAlgebra) :
> interface(rtablesize = 40) :
>
```

Simplification of minimal system extend 8

We consider the following reactions:

KR + S <-> KR_S -> KR + Sp
KT + S <-> KT_S -> KT + Sp
Sp->S
KR <-> KT
KR_S <-> KT_S

$$K^R + S \rightleftharpoons K^R S \rightarrow K^R + S_p$$
$$K^T + S \rightleftharpoons K^T S \rightarrow K^T + S_p$$
$$S_p \rightarrow S$$
$$K^R \rightleftharpoons K^T$$
$$K^R S \rightleftharpoons K^T S$$

The species of the networ are (in parentesis the order in which I consider them)

{S (1) ,Sp (2) ,KR (3) ,KT (4), KR_S (5),KT_S (6) }

There are a total of 11 reactions and 6 species.

I construct the mass-action ODE system by defining the stoichiometric matrix A, and the vector of rates "krates".
Then, the ODE system is

$$\frac{dx}{dt} = A \cdot k_{rs}$$

and hence steady states are given as $A \cdot k_{rs} = 0$.

Stoichiometric matrix:

I enter first the reactions as rows and then transpose the matrix

```
> A := Matrix(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] :
```

> $A[6,4] := 1 : A[6,2] := 1 : A[6,6] := -1 :$

> $A[7,2] := -1 : A[7,1] := 1 :$

> $A[8,3] := -1 : A[8,4] := 1 : A[9] := -A[8] :$

> $A[10,5] := -1 : A[10,6] := 1 : A[11] := -A[10] :$

> $A := Transpose(A) :$

Vector of rates:

here x_i is the concentration of the i-th species

> $ks := Vector([k_1 \cdot x_3 \cdot x_1, k_2 \cdot x_5, k_3 \cdot x_5, k_4 \cdot x_4 \cdot x_1, k_5 \cdot x_6, k_6 \cdot x_6, k_7 \cdot x_2, k_8 \cdot x_3, k_9 \cdot x_4, k_{10} \cdot x_5, k_{11} \cdot x_6])$

$$ks := \begin{bmatrix} k_1 x_3 x_1 \\ k_2 x_5 \\ k_3 x_5 \\ k_4 x_4 x_1 \\ k_5 x_6 \\ k_6 x_6 \\ k_7 x_2 \\ k_8 x_3 \\ k_9 x_4 \\ k_{10} x_5 \\ k_{11} x_6 \end{bmatrix} \tag{1}$$

Steady state equations:

> $ssEqs := A.ks$

$$ssEqs := \begin{bmatrix} -k_1 x_1 x_3 - k_4 x_1 x_4 + k_2 x_5 + k_5 x_6 + k_7 x_2 \\ k_3 x_5 + k_6 x_6 - k_7 x_2 \\ -k_1 x_1 x_3 + k_2 x_5 + k_3 x_5 - k_8 x_3 + k_9 x_4 \\ -k_4 x_1 x_4 + k_5 x_6 + k_6 x_6 + k_8 x_3 - k_9 x_4 \\ k_1 x_1 x_3 - k_2 x_5 - k_3 x_5 - k_{10} x_5 + k_{11} x_6 \\ k_4 x_1 x_4 - k_5 x_6 - k_6 x_6 + k_{10} x_5 - k_{11} x_6 \end{bmatrix} \tag{2}$$

Conservation laws:

This system has total amount of kinase and total amount of substrate conserved:

> $F := ReducedRowEchelonForm(Transpose(Matrix([op(NullSpace(Transpose(A)))])))$

$$F := \begin{bmatrix} 1 & 1 & 0 & 0 & 1 & 1 \\ 0 & 0 & 1 & 1 & 1 & 1 \end{bmatrix} \tag{3}$$

>

the conservation laws are:

$x_1 + x_2 + x_5 + x_6 - T_1, x_3 + x_4 + x_5 + x_6 - T_2$

Therefore, the steady states constrained by the conservation laws are solutions to myeqs=0
(because there are two conservation laws, two of the equations in eqs can be disregarded).

> $subsEqs := [ssEqs[2], ssEqs[4], ssEqs[5], ssEqs[6], x_1 + x_2 + x_5 + x_6 - T_1, x_3 + x_4 + x_5 + x_6 - T_2]$

$$subsEqs := [k_3 x_5 + k_6 x_6 - k_7 x_2, -k_4 x_1 x_4 + k_5 x_6 + k_6 x_6 + k_8 x_3 - k_9 x_4, k_1 x_1 x_3 - k_2 x_5 - k_3 x_5 - k_{10} x_5 + k_{11} x_6, k_4 x_1 x_4 - k_5 x_6 - k_6 x_6 + k_{10} x_5 - k_{11} x_6, x_1 + x_2 + x_5 + x_6 - T_1, x_3 + x_4 + x_5 + x_6 - T_2] \tag{4}$$

Computations

The way to find different sets of parameters is highlighted in bold. These are two steps where there is a choice.

We compute the Jacobian of myeqs (steady state equations together with the conservation laws)

> $J := VectorCalculus[Jacobian](subsEqs, [seq(x_i, i = 1..6)])$

(1.1)

$$J := \begin{bmatrix} 0 & -k_7 & 0 & 0 & k_3 & k_6 \\ -k_4 x_4 & 0 & k_8 & -k_4 x_1 - k_9 & 0 & k_5 + k_6 \\ k_1 x_3 & 0 & k_1 x_1 & 0 & -k_2 - k_3 - k_{10} & k_{11} \\ k_4 x_4 & 0 & 0 & k_4 x_1 & k_{10} & -k_5 - k_6 - k_{11} \\ 1 & 1 & 0 & 0 & 1 & 1 \\ 0 & 0 & 1 & 1 & 1 & 1 \end{bmatrix} \quad \textbf{(1.1)}$$

> $Determinant(J):$

> $detJ := collect\left(\%, \left\{seq\left(x_i, i = 1..6\right)\right\}, 'distributed'\right)$

$$detJ := \left(-k_1 k_4 k_7 k_{10} - k_1 k_4 k_7 k_{11}\right) x_1^2 + \left(-k_1 k_3 k_4 k_8 - k_1 k_3 k_4 k_{11} + k_1 k_4 k_6 k_8 - k_1 k_4 k_6 k_{10} - k_1 k_4 k_7 k_{10} - k_1 k_4 k_7 k_{11}\right) x_1 x_3 + \left(k_1 k_3 k_4 k_9 - k_1 k_3 k_4 k_{11} - k_1 k_4 k_6 k_9 - k_1 k_4 k_6 k_{10} - k_1 k_4 k_7 k_{10} - k_1 k_4 k_7 k_{11}\right) x_1 x_4 + \left(-k_1 k_5 k_7 k_9 - k_1 k_5 k_7 k_{10} - k_1 k_6 k_7 k_9 - k_1 k_6 k_7 k_{10} - k_1 k_7 k_9 k_{10} - k_1 k_7 k_9 k_{11} - k_2 k_4 k_7 k_8 - k_2 k_4 k_7 k_{11} - k_3 k_4 k_7 k_8 - k_3 k_4 k_7 k_{11} - k_4 k_7 k_8 k_{10} - k_4 k_7 k_8 k_{11}\right) x_1 + \left(-k_1 k_3 k_5 k_8 - k_1 k_3 k_5 k_9 - k_1 k_3 k_6 k_8 - k_1 k_3 k_6 k_9 - k_1 k_3 k_8 k_{11} - k_1 k_3 k_9 k_{11} - k_1 k_5 k_7 k_8 - k_1 k_5 k_7 k_9 - k_1 k_6 k_7 k_8 - k_1 k_6 k_7 k_9 - k_1 k_6 k_8 k_{10} - k_1 k_6 k_9 k_{10} - k_1 k_7 k_8 k_{10} - k_1 k_7 k_8 k_{11} - k_1 k_7 k_9 k_{10} - k_1 k_7 k_9 k_{11}\right) x_3 + \left(-k_2 k_4 k_6 k_8 - k_2 k_4 k_6 k_9 - k_2 k_4 k_7 k_8 - k_2 k_4 k_7 k_9 - k_3 k_4 k_6 k_8 - k_3 k_4 k_6 k_9 - k_3 k_4 k_7 k_8 - k_3 k_4 k_7 k_9 - k_3 k_4 k_8 k_{11} - k_3 k_4 k_9 k_{11} - k_4 k_6 k_8 k_{10} - k_4 k_6 k_9 k_{10} - k_4 k_7 k_8 k_{10} - k_4 k_7 k_8 k_{11} - k_4 k_7 k_9 k_{10} - k_4 k_7 k_9 k_{11}\right) x_4 - k_2 k_5 k_7 k_8 - k_2 k_5 k_7 k_9 - k_2 k_6 k_7 k_8 - k_2 k_6 k_7 k_9 - k_2 k_7 k_8 k_{11} - k_2 k_7 k_9 k_{11} - k_3 k_5 k_7 k_8 - k_3 k_5 k_7 k_9 - k_3 k_6 k_7 k_8 - k_3 k_6 k_7 k_9 - k_3 k_7 k_8 k_{11} - k_3 k_7 k_9 k_{11} - k_5 k_7 k_8 k_{10} - k_5 k_7 k_9 k_{10} - k_6 k_7 k_8 k_{10} - k_6 k_7 k_9 k_{10} \quad \textbf{(1.2)}$$

We parameterise the steady states as functions of x1 and x3, using the four steady state equations:
When x1 and x3 are positive, then so are the rest.

> $solution := solve\left(\left[subsEqs[2], subsEqs[3], subsEqs[4], subsEqs[1]\right], \left[x_2, x_4, x_5, x_6\right]\right)$

$$solution := \Bigg[\Bigg[x_2 = \Big(\big(k_1 k_3 k_4 k_{11} x_1 + k_1 k_4 k_6 k_{10} x_1 + k_1 k_3 k_5 k_9 + k_1 k_3 k_6 k_9 + k_1 k_3 k_9 k_{11} + k_1 k_6 k_9 k_{10} + k_2 k_4 k_6 k_8 + k_3 k_4 k_6 k_8 + k_3 k_4 k_8 k_{11} + k_4 k_6 k_8 k_{10}\big) \quad \textbf{(1.3)}$$

$x_1\,x_3\big)\Big/\big(k_7\,\big(k_2\,k_4\,k_{11}\,x_1+k_3\,k_4\,k_{11}\,x_1+k_2\,k_5\,k_9+k_2\,k_6\,k_9+k_2\,k_9\,k_{11}+k_3\,k_5\,k_9$

$+k_3\,k_6\,k_9+k_3\,k_9\,k_{11}+k_5\,k_9\,k_{10}+k_6\,k_9\,k_{10}\big)\big),x_4=\big(x_3\,\big(k_1\,k_5\,k_{10}\,x_1$

$+k_1\,k_6\,k_{10}\,x_1+k_2\,k_5\,k_8+k_2\,k_6\,k_8+k_2\,k_8\,k_{11}+k_3\,k_5\,k_8+k_3\,k_6\,k_8+k_3\,k_8\,k_{11}$

$+k_5\,k_8\,k_{10}+k_6\,k_8\,k_{10}\big)\big)\Big/\big(k_2\,k_4\,k_{11}\,x_1+k_3\,k_4\,k_{11}\,x_1+k_2\,k_5\,k_9+k_2\,k_6\,k_9+k_2\,k_9\,k_{11}$

$+k_3\,k_5\,k_9+k_3\,k_6\,k_9+k_3\,k_9\,k_{11}+k_5\,k_9\,k_{10}+k_6\,k_9\,k_{10}\big),x_5=\big(x_1\,x_3\,\big(k_1\,k_4\,k_{11}\,x_1$

$+k_1\,k_5\,k_9+k_1\,k_6\,k_9+k_1\,k_9\,k_{11}+k_4\,k_8\,k_{11}\big)\big)\Big/\big(k_2\,k_4\,k_{11}\,x_1+k_3\,k_4\,k_{11}\,x_1+k_2\,k_5\,k_9$

$+k_2\,k_6\,k_9+k_2\,k_9\,k_{11}+k_3\,k_5\,k_9+k_3\,k_6\,k_9+k_3\,k_9\,k_{11}+k_5\,k_9\,k_{10}+k_6\,k_9\,k_{10}\big),x_6$

$=\big(\big(k_1\,k_4\,k_{10}\,x_1+k_1\,k_9\,k_{10}+k_2\,k_4\,k_8+k_3\,k_4\,k_8+k_4\,k_8\,k_{10}\big)\,x_1\,x_3\big)\Big/\big(k_2\,k_4\,k_{11}\,x_1$
$+k_3\,k_4\,k_{11}\,x_1+k_2\,k_5\,k_9+k_2\,k_6\,k_9+k_2\,k_9\,k_{11}+k_3\,k_5\,k_9+k_3\,k_6\,k_9+k_3\,k_9\,k_{11}$
$+k_5\,k_9\,k_{10}+k_6\,k_9\,k_{10}\big)\big]\big]$

We evaluate the determinant of the Jacobian at the parameterisation. We then write it as a polynomial in x1 and x3

> $detSubs := subs(solution[1], detJ)$

$detSubs := \big(-k_1\,k_4\,k_7\,k_{10}-k_1\,k_4\,k_7\,k_{11}\big)\,x_1^2+\big(-k_1\,k_3\,k_4\,k_8-k_1\,k_3\,k_4\,k_{11}+k_1\,k_4\,k_6\,k_8$ **(1.4)**
$-k_1\,k_4\,k_6\,k_{10}-k_1\,k_4\,k_7\,k_{10}-k_1\,k_4\,k_7\,k_{11}\big)\,x_1\,x_3+\big(\big(k_1\,k_3\,k_4\,k_9-k_1\,k_3\,k_4\,k_{11}$
$-k_1\,k_4\,k_6\,k_9-k_1\,k_4\,k_6\,k_{10}-k_1\,k_4\,k_7\,k_{10}-k_1\,k_4\,k_7\,k_{11}\big)\,x_1\,x_3\,\big(k_1\,k_5\,k_{10}\,x_1$
$+k_1\,k_6\,k_{10}\,x_1+k_2\,k_5\,k_8+k_2\,k_6\,k_8+k_2\,k_8\,k_{11}+k_3\,k_5\,k_8+k_3\,k_6\,k_8+k_3\,k_8\,k_{11}$
$+k_5\,k_8\,k_{10}+k_6\,k_8\,k_{10}\big)\big)\Big/\big(k_2\,k_4\,k_{11}\,x_1+k_3\,k_4\,k_{11}\,x_1+k_2\,k_5\,k_9+k_2\,k_6\,k_9+k_2\,k_9\,k_{11}$
$+k_3\,k_5\,k_9+k_3\,k_6\,k_9+k_3\,k_9\,k_{11}+k_5\,k_9\,k_{10}+k_6\,k_9\,k_{10}\big)+\big(-k_1\,k_5\,k_7\,k_9$
$-k_1\,k_5\,k_7\,k_{10}-k_1\,k_6\,k_7\,k_9-k_1\,k_6\,k_7\,k_{10}-k_1\,k_7\,k_9\,k_{10}-k_1\,k_7\,k_9\,k_{11}-k_2\,k_4\,k_7\,k_8$
$-k_2\,k_4\,k_7\,k_{11}-k_3\,k_4\,k_7\,k_8-k_3\,k_4\,k_7\,k_{11}-k_4\,k_7\,k_8\,k_{10}-k_4\,k_7\,k_8\,k_{11}\big)\,x_1+\big($
$-k_1\,k_3\,k_5\,k_8-k_1\,k_3\,k_5\,k_9-k_1\,k_3\,k_6\,k_8-k_1\,k_3\,k_6\,k_9-k_1\,k_3\,k_8\,k_{11}-k_1\,k_3\,k_9\,k_{11}$
$-k_1\,k_5\,k_7\,k_8-k_1\,k_5\,k_7\,k_9-k_1\,k_6\,k_7\,k_8-k_1\,k_6\,k_7\,k_9-k_1\,k_6\,k_8\,k_{10}-k_1\,k_6\,k_9\,k_{10}$

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

```
> polSubs := numer(detSubs) :
> finalPol := collect(polSubs, {x[1], x[3]},'distributed')
```

$$finalPol := -2 k_2^2 k_5 k_6 k_7 k_8 k_9 - 2 k_2^2 k_5 k_7 k_8 k_9 k_{11} - 2 k_2^2 k_6 k_7 k_8 k_9 k_{11} - 2 k_2 k_3 k_5^2 k_7 k_8 k_9 - 4 k_2 k_3 k_5 k_6 k_7 k_9^2 - 4 k_2 k_3 k_5 k_7 k_9^2 k_{11} - 2 k_2 k_3 k_6^2 k_7 k_8 k_9 - 4 k_2 k_3 k_6 k_7 k_9^2 k_{11} - 2 k_2 k_3 k_7 k_8 k_9 k_{11}^2 - 2 k_2 k_5^2 k_7 k_8 k_9 k_{10} - 4 k_2 k_5 k_6 k_7 k_9^2 k_{10} - 2 k_2 k_5 k_7 k_9^2 k_{10} k_{11} - 2 k_2 k_6^2 k_7 k_8 k_9 k_{10} - 2 k_2 k_6 k_7 k_9^2 k_{10} k_{11} - 2 k_3^2 k_5 k_6 k_7 k_8 k_9 - 2 k_3^2 k_5 k_7 k_8 k_9 k_{11} - 2 k_3^2 k_6 k_7 k_8 k_9 k_{11} - 2 k_3 k_5^2 k_7 k_8 k_9 k_{10} - 4 k_3 k_5 k_6 k_7 k_9^2 k_{10} - 2 k_3 k_5 k_7 k_9^2 k_{10} k_{11} - 2 k_3 k_6^2 k_7 k_8 k_9 k_{10} - 2 k_3 k_6 k_7 k_9^2 k_{10} k_{11} - 2 k_5 k_6 k_7 k_8 k_9 k_{10}^2 + (-k_1 k_2 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_{10} k_{11} - k_1 k_3 k_4^2 k_7 k_{11}^2) x_1^3 + (-k_1 k_2 k_3 k_5^2 k_8 k_9 - k_1 k_2 k_3 k_5^2 k_9^2 - 2 k_1 k_2 k_3 k_5 k_6 k_8 k_9 - 2 k_1 k_2 k_3 k_5 k_6 k_9^2 - 2 k_1 k_2 k_3 k_5 k_8 k_9 k_{11} - 2 k_1 k_2 k_3 k_5 k_9^2 k_{11} - k_1 k_2 k_3 k_6^2 k_8 k_9 - k_1 k_2 k_3 k_6^2 k_9^2 - 2 k_1 k_2 k_3 k_6 k_8 k_9 k_{11} - 2 k_1 k_2 k_3 k_6 k_9^2 k_{11} - k_1 k_2 k_3 k_8 k_9 k_{11}^2 - k_1 k_2 k_3 k_9^2 k_{11}^2 - k_1 k_2 k_5^2 k_7 k_8 k_9 - k_1 k_2 k_5^2 k_7 k_9^2 - 2 k_1 k_2 k_5 k_6 k_7 k_8 k_9 - 2 k_1 k_2 k_5 k_6 k_7 k_9^2 - k_1 k_2 k_5 k_6 k_8 k_9 k_{10} - k_1 k_2 k_5 k_6 k_9^2 k_{10} - k_1 k_2 k_5 k_7 k_8 k_9 k_{10} - 2 k_1 k_2 k_5 k_7 k_8 k_9 k_{11} - k_1 k_2 k_5 k_7 k_9^2 k_{10} - 2 k_1 k_2 k_5 k_7 k_9^2 k_{11} - k_1 k_2 k_6^2 k_7 k_8 k_9 - k_1 k_2 k_6^2 k_7 k_9^2 - k_1 k_2 k_6^2 k_8 k_9 k_{10} - k_1 k_2 k_6^2 k_9^2 k_{10} - k_1 k_2 k_6 k_7 k_8 k_9 k_{10} - 2 k_1 k_2 k_6 k_7 k_8 k_9 k_{11} - k_1 k_2 k_6 k_7 k_9^2 k_{10} - 2 k_1 k_2 k_6 k_7 k_9^2 k_{11} - k_1 k_2 k_6 k_8 k_9 k_{10} k_{11} - k_1 k_2 k_6 k_9^2 k_{10} k_{11} - k_1 k_2 k_7 k_8 k_9 k_{10} k_{11} - k_1 k_2 k_7 k_8 k_9 k_{11}^2 - k_1 k_2 k_7 k_9^2 k_{10} k_{11} - k_1 k_2 k_7 k_9^2 k_{11}^2 - k_1 k_3^2 k_5^2 k_8 k_9 - k_1 k_3^2 k_5^2 k_9^2 - 2 k_1 k_3^2 k_5 k_6 k_8 k_9$$

(1.5)

$$- 2 k_1 k_3^2 k_5 k_6 k_9^2 - 2 k_1 k_3^2 k_5 k_8 k_9 k_{11} - 2 k_1 k_3^2 k_5 k_9^2 k_{11} - k_1 k_3^2 k_6^2 k_8 k_9 - k_1 k_3^2 k_6^2 k_9^2$$
$$- 2 k_1 k_3^2 k_6 k_8 k_9 k_{11} - 2 k_1 k_3^2 k_6 k_9^2 k_{11} - k_1 k_3^2 k_8 k_9 k_{11}^2 - k_1 k_3^2 k_9^2 k_{11}^2 - k_1 k_3$$
$$k_5^2 k_7 k_8 k_9 - k_1 k_3 k_5^2 k_7 k_9^2 - k_1 k_3 k_5^2 k_8 k_9 k_{10} - k_1 k_3 k_5^2 k_9^2 k_{10} - 2 k_1 k_3 k_5 k_6 k_7 k_8 k_9$$
$$- 2 k_1 k_3 k_5 k_6 k_7 k_9^2 - 3 k_1 k_3 k_5 k_6 k_8 k_9 k_{10} - 3 k_1 k_3 k_5 k_6 k_9^2 k_{10}$$
$$- k_1 k_3 k_5 k_7 k_8 k_9 k_{10} - 2 k_1 k_3 k_5 k_7 k_8 k_9 k_{11} - k_1 k_3 k_5 k_7 k_9^2 k_{10} - 2 k_1 k_3 k_5 k_7 k_9^2 k_{11}$$
$$- k_1 k_3 k_5 k_8 k_9 k_{10} k_{11} - k_1 k_3 k_5 k_9^2 k_{10} k_{11} - k_1 k_3 k_6^2 k_7 k_8 k_9 - k_1 k_3 k_6^2 k_7 k_9^2$$
$$- 2 k_1 k_3 k_6^2 k_8 k_9 k_{10} - 2 k_1 k_3 k_6^2 k_9^2 k_{10} - k_1 k_3 k_6 k_7 k_8 k_9 k_{10} - 2 k_1 k_3 k_6 k_7 k_8 k_9 k_{11}$$
$$- k_1 k_3 k_6 k_7 k_9^2 k_{10} - 2 k_1 k_3 k_6 k_7 k_9^2 k_{11} - 2 k_1 k_3 k_6 k_8 k_9 k_{10} k_{11} - 2 k_1 k_3 k_6$$
$$k_9^2 k_{10} k_{11} - k_1 k_3 k_7 k_8 k_9 k_{10} k_{11} - k_1 k_3 k_7 k_8 k_9 k_{11}^2 - k_1 k_3 k_7 k_9^2 k_{10} k_{11} - k_1 k_3 k_7 k_9^2$$
$$k_{11}^2 - k_1 k_5^2 k_7 k_8 k_9 k_{10} - k_1 k_5^2 k_7 k_9^2 k_{10} - 2 k_1 k_5 k_6 k_7 k_8 k_9 k_{10} - 2 k_1 k_5 k_6 k_7 k_9^2 k_{10}$$
$$- k_1 k_5 k_6 k_8 k_9 k_{10}^2 - k_1 k_5 k_6 k_9^2 k_{10}^2 - k_1 k_5 k_7 k_8 k_9 k_{10}^2 - k_1 k_5 k_7 k_8 k_9 k_{10} k_{11}$$
$$- k_1 k_5 k_7 k_9^2 k_{10}^2 - k_1 k_5 k_7 k_9^2 k_{10} k_{11} - k_1 k_6^2 k_7 k_8 k_9 k_{10} - k_1 k_6^2 k_7 k_9^2 k_{10} - k_1$$
$$k_6^2 k_8 k_9 k_{10}^2 - k_1 k_6^2 k_9^2 k_{10}^2 - k_1 k_6 k_7 k_8 k_9 k_{10}^2 - k_1 k_6 k_7 k_8 k_9 k_{10} k_{11} - k_1 k_6 k_7 k_9^2 k_{10}^2$$
$$- k_1 k_6 k_7 k_9^2 k_{10} k_{11} - k_2^2 k_4 k_5 k_6 k_8^2 - k_2^2 k_4 k_5 k_6 k_8 k_9 - k_2^2 k_4 k_5 k_7 k_8^2 -$$
$$k_2^2 k_4 k_5 k_7 k_8 k_9 - k_2^2 k_4 k_6^2 k_8^2 - k_2^2 k_4 k_6^2 k_8 k_9 - k_2^2 k_4 k_6 k_7 k_8^2 - k_2^2 k_4 k_6 k_7 k_8 k_9 -$$
$$k_2^2 k_4 k_6 k_8^2 k_{11} - k_2^2 k_4 k_6 k_8 k_9 k_{11} - k_2^2 k_4 k_7 k_8^2 k_{11} - k_2^2 k_4 k_7 k_8 k_9 k_{11}$$
$$- 2 k_2 k_3 k_4 k_5 k_6 k_8^2 - 2 k_2 k_3 k_4 k_5 k_6 k_8 k_9 - 2 k_2 k_3 k_4 k_5 k_7 k_8^2 - 2 k_2 k_3 k_4 k_5 k_7 k_8 k_9$$
$$- k_2 k_3 k_4 k_5 k_8^2 k_{11} - k_2 k_3 k_4 k_5 k_8 k_9 k_{11} - 2 k_2 k_3 k_4 k_6^2 k_8^2 - 2 k_2 k_3 k_4 k_6^2 k_8 k_9$$
$$- 2 k_2 k_3 k_4 k_6 k_7 k_8^2 - 2 k_2 k_3 k_4 k_6 k_7 k_8 k_9 - 3 k_2 k_3 k_4 k_6 k_8^2 k_{11}$$
$$- 3 k_2 k_3 k_4 k_6 k_8 k_9 k_{11} - 2 k_2 k_3 k_4 k_7 k_8^2 k_{11} - 2 k_2 k_3 k_4 k_7 k_8 k_9 k_{11} - k_2 k_3 k_4 k_8^2 k_{11}^2$$
$$- k_2 k_3 k_4 k_8 k_9 k_{11}^2 - 2 k_2 k_4 k_5 k_6 k_8^2 k_{10} - 2 k_2 k_4 k_5 k_6 k_8 k_9 k_{10} - 2 k_2 k_4 k_5 k_7 k_8^2 k_{10}$$
$$- k_2 k_4 k_5 k_7 k_8^2 k_{11} - 2 k_2 k_4 k_5 k_7 k_8 k_9 k_{10} - k_2 k_4 k_5 k_7 k_8 k_9 k_{11} - 2 k_2 k_4 k_6^2 k_8^2 k_{10}$$
$$- 2 k_2 k_4 k_6^2 k_8 k_9 k_{10} - 2 k_2 k_4 k_6 k_7 k_8^2 k_{10} - k_2 k_4 k_6 k_7 k_8^2 k_{11} - 2 k_2 k_4 k_6 k_7 k_8 k_9 k_{10}$$
$$- k_2 k_4 k_6 k_7 k_8 k_9 k_{11} - k_2 k_4 k_6 k_8^2 k_{10} k_{11} - k_2 k_4 k_6 k_8 k_9 k_{10} k_{11} - k_2 k_4 k_7 k_8^2 k_{10} k_{11}$$
$$- k_2 k_4 k_7 k_8^2 k_{11}^2 - k_2 k_4 k_7 k_8 k_9 k_{10} k_{11} - k_2 k_4 k_7 k_8 k_9 k_{11}^2 - k_3^2 k_4 k_5 k_6 k_8^2 -$$
$$k_3^2 k_4 k_5 k_6 k_8 k_9 - k_3^2 k_4 k_5 k_7 k_8^2 - k_3^2 k_4 k_5 k_7 k_8 k_9 - k_3^2 k_4 k_5 k_8^2 k_{11} - k_3^2 k_4 k_5 k_8 k_9 k_{11}$$
$$- k_3^2 k_4 k_6^2 k_8^2 - k_3^2 k_4 k_6^2 k_8 k_9 - k_3^2 k_4 k_6 k_7 k_8^2 - k_3^2 k_4 k_6 k_7 k_8 k_9 - 2 k_3^2 k_4 k_6 k_8^2 k_{11} - 2$$

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

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

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

>

<u>We look at the coefficients of mypol in x1 and x3 that do not have necessarily negative sign.   (????)</u>
I did it manually, but I only see one such term:

$$
\begin{aligned}
> term := \big(& k_1^2 k_3 k_4 k_5 k_9 k_{10} - k_1^2 k_3 k_4 k_5 k_{10} k_{11} + k_1^2 k_3 k_4 k_6 k_9 k_{10} - k_1^2 k_3 k_4 k_6 k_{10} k_{11} - \\
& k_1^2 k_4 k_5 k_6 k_9 k_{10} - k_1^2 k_4 k_5 k_6 k_{10}^2 - k_1^2 k_4 k_5 k_7 k_{10}^2 - k_1^2 k_4 k_5 k_7 k_{10} k_{11} - k_1^2 k_4 k_6^2 k_9 k_{10} \\
& - k_1^2 k_4 k_6^2 k_{10}^2 - k_1^2 k_4 k_6 k_7 k_{10}^2 - k_1^2 k_4 k_6 k_7 k_{10} k_{11} - k_1 k_2 k_3 k_4^2 k_8 k_{11} - k_1 k_2 k_3 k_4^2 k_{11}^2
\end{aligned}
$$

$$+ k_1 k_2 k_4^2 k_6 k_8 k_{11} - k_1 k_2 k_4^2 k_6 k_{10} k_{11} - k_1 k_2 k_4^2 k_7 k_{10} k_{11} - k_1 k_2 k_4^2 k_7 k_{11}^2 - k_1 k_3^2 k_4^2 k_8 k_{11} - k_1 k_3^2 k_4^2 k_{11}^2 + k_1 k_3 k_4^2 k_6 k_8 k_{11} - k_1 k_3 k_4^2 k_6 k_{10} k_{11} - k_1 k_3 k_4^2 k_7 k_{10} k_{11} - k_1 k_3 k_4^2 k_7 k_{11}^2\Big) :$$

> $factor(term)$

$$k_1 k_4 \big(k_1 k_3 k_5 k_9 k_{10} - k_1 k_3 k_5 k_{10} k_{11} + k_1 k_3 k_6 k_9 k_{10} - k_1 k_3 k_6 k_{10} k_{11} - k_1 k_5 k_6 k_9 k_{10} - k_1 k_5 k_6 k_{10}^2 - k_1 k_5 k_7 k_{10}^2 - k_1 k_5 k_7 k_{10} k_{11} - k_1 k_6^2 k_9 k_{10} - k_1 k_6^2 k_{10}^2 - k_1 k_6 k_7 k_{10}^2 - k_1 k_6 k_7 k_{10} k_{11} - k_2 k_3 k_4 k_8 k_{11} - k_2 k_3 k_4 k_{11}^2 + k_2 k_4 k_6 k_8 k_{11} - k_2 k_4 k_6 k_{10} k_{11} - k_2 k_4 k_7 k_{10} k_{11} - k_2 k_4 k_7 k_{11}^2 - k_3^2 k_4 k_8 k_{11} - k_3^2 k_4 k_{11}^2 + k_3 k_4 k_6 k_8 k_{11} - k_3 k_4 k_6 k_{10} k_{11} - k_3 k_4 k_7 k_{10} k_{11} - k_3 k_4 k_7 k_{11}^2\big) \quad \textbf{(1.6)}$$

>

"Now the trick resides on finding parameters of the rate constants k such that the term is positive." Thus we try to search parameter set that make *term* positive.

However, we need to compute some parameters with biological meaning/sense, by considering the constraint on parameter range and constraint on allosteric model (thermodynamic cycle).

First, we impose the thermodynamic cycle:

> $thermo := \left[k[8] = \dfrac{k[1]k[10]k[5]k[9]}{k[11]k[4]k[2]}\right]:$

> $constraintTerm := subs(thermo, term)$

$$constraintTerm := -k_1^2 k_3 k_4 k_5 k_{10} k_{11} + k_1^2 k_3 k_4 k_6 k_9 k_{10} - k_1^2 k_3 k_4 k_6 k_{10} k_{11} - k_1^2 k_4 k_5 k_6 k_{10}^2 - k_1^2 k_4 k_5 k_7 k_{10}^2 - k_1^2 k_4 k_5 k_7 k_{10} k_{11} - k_1^2 k_4 k_6^2 k_9 k_{10} - k_1^2 k_4 k_6^2 k_{10}^2 - k_1^2 k_4 k_6 k_7 k_{10}^2 - k_1^2 k_4 k_6 k_7 k_{10} k_{11} - k_1 k_2 k_3 k_4^2 k_{11}^2 - k_1 k_2 k_4^2 k_6 k_{10} k_{11} - k_1 k_2 k_4^2 k_7 k_{10} k_{11} - k_1 k_2 k_4^2 k_7 k_{11}^2 - \frac{k_1^2 k_3^2 k_4 k_{10} k_5 k_9}{k_2} - k_1 k_3^2 k_4^2 k_{11}^2 + \frac{k_1^2 k_3 k_4 k_6 k_{10} k_5 k_9}{k_2} - k_1 k_3 k_4^2 k_6 k_{10} k_{11} - k_1 k_3 k_4^2 k_7 k_{10} k_{11} - k_1 k_3 k_4^2 k_7 k_{11}^2 \quad \textbf{(1.7)}$$

> $factor(constraintTerm)$

$$-\frac{1}{k_2}\Big(k_1 k_4 \big(k_1 k_2 k_3 k_5 k_{10} k_{11} - k_1 k_2 k_3 k_6 k_9 k_{10} + k_1 k_2 k_3 k_6 k_{10} k_{11} + k_1 k_2 k_5 k_6 k_{10}^2 + k_1 k_2 k_5 k_7 k_{10}^2 + k_1 k_2 k_5 k_7 k_{10} k_{11} + k_1 k_2 k_6^2 k_9 k_{10} + k_1 k_2 k_6^2 k_{10}^2 + k_1 k_2 k_6 k_7 k_{10}^2 + k_1 k_2 k_6 k_7 k_{10} k_{11} + k_1 k_3^2 k_5 k_9 k_{10} - k_1 k_3 k_5 k_6 k_9 k_{10} + k_2^2 k_3 k_4 k_{11}^2 + k_2^2 k_4 k_6 k_{10} k_{11} + k_2^2 k_4 k_7 k_{10} k_{11} + k_2^2 k_4 k_7 k_{11}^2 + k_2 k_3^2 k_4 k_{11}^2 + k_2 k_3 k_4 k_6 k_{10} k_{11} \quad \textbf{(1.8)}$$

$$+ k_2 k_3 k_4 k_7 k_{10} k_{11} + k_2 k_3 k_4 k_7 k_{11}^2))$$

> $finalTerm := -(k_1 k_2 k_3 k_5 k_{10} k_{11} - k_1 k_2 k_3 k_6 k_9 k_{10} + k_1 k_2 k_3 k_6 k_{10} k_{11} + k_1 k_2 k_5 k_6 k_{10}^2 + k_1 k_2 k_5 k_7 k_{10}^2 + k_1 k_2 k_5 k_7 k_{10} k_{11} + k_1 k_2 k_6^2 k_9 k_{10} + k_1 k_2 k_6^2 k_{10}^2 + k_1 k_2 k_6 k_7 k_{10}^2 + k_1 k_2 k_6 k_7 k_{10} k_{11} + k_1 k_3^2 k_5 k_9 k_{10} - k_1 k_3 k_5 k_6 k_9 k_{10} + k_2^2 k_3 k_4 k_{11}^2 + k_2^2 k_4 k_6 k_{10} k_{11} + k_2^2 k_4 k_7 k_{10} k_{11} + k_2^2 k_4 k_7 k_{11}^2 + k_2 k_3^2 k_4 k_{11}^2 + k_2 k_3 k_4 k_6 k_{10} k_{11} + k_2 k_3 k_4 k_7 k_{10} k_{11} + k_2 k_3 k_4 k_7 k_{11}^2)$

$$finalTerm := -k_1 k_2 k_3 k_5 k_{10} k_{11} + k_1 k_2 k_3 k_6 k_9 k_{10} - k_1 k_2 k_3 k_6 k_{10} k_{11} - k_1 k_2 k_5 k_6 k_{10}^2 - k_1 k_2 k_5 k_7 k_{10}^2 - k_1 k_2 k_5 k_7 k_{10} k_{11} - k_1 k_2 k_6^2 k_9 k_{10} - k_1 k_2 k_6^2 k_{10}^2 - k_1 k_2 k_6 k_7 k_{10}^2 - k_1 k_2 k_6 k_7 k_{10} k_{11} - k_1 k_3^2 k_5 k_9 k_{10} + k_1 k_3 k_5 k_6 k_9 k_{10} - k_2^2 k_3 k_4 k_{11}^2 - k_2^2 k_4 k_6 k_{10} k_{11} - k_2^2 k_4 k_7 k_{10} k_{11} - k_2^2 k_4 k_7 k_{11}^2 - k_2 k_3^2 k_4 k_{11}^2 - k_2 k_3 k_4 k_6 k_{10} k_{11} - k_2 k_3 k_4 k_7 k_{10} k_{11} - k_2 k_3 k_4 k_7 k_{11}^2 \quad \textbf{(1.9)}$$

Then, we impose the biochemical reaction network parameter ranges:

However, the search space is very big, can not search all of them. I will try to find an alternative way to do it.

The alternative way could be Monte Carlo method try to find some reasonable parameter sets. I will implement this in MATLAB.

################################### Unpractical searching ##########################

> $associationRate := evalf\left(seq\left(10^{-6}\cdot(10^6)^{\frac{i}{1023}}, i = 0..1023\right)\right):$
association rates are considered to be $10^{-6} \sim 1\ nM^{-1}\cdot s^{-1}$

> $dissociationRate := evalf\left(seq\left(10^{-4}\cdot(10^5)^{\frac{i}{1023}}, i = 0..1023\right)\right):$
#` `dissociation rates are considered **to** be $10^{-4} \sim 10\ s^{-1}$

> $catalyticRate := evalf\left(seq\left(10^{-3}\cdot(10^6)^{\frac{i}{1023}}, i = 0..1023\right)\right):$ # the range is $10^{-3} \sim 10^3\ s^{-1}$

> $switchingRate := evalf\left(seq\left(10^{-6}\cdot(10^4)^{\frac{i}{1023}}, i = 0..1023\right)\right):$
the range is assumed as $10^{-6} \sim 10^{-2}\ s^{-1}$

> $concentration := evalf\left(seq\left(2\cdot(10^3)^{\frac{i}{1023}}, i = 0..1023\right)\right):$

```
   # 1 molecule ≈2nM, signaling protein: 10∼10^3 nM
> bistableSpace := fopen("bistable_parameters.txt", APPEND, TEXT) :
> realisticBistableSpace := fopen("bistable_realistic_parameters.txt", APPEND, TEXT) :
> randomize(1) :
> roll := rand(1 ..1023) :
> for number from 1 by 1 to 10000 do
    rs := seq(roll( ), i = 1 ..11) :
    ps1 := associationRate[rs[1]] : ps2 := dissociationRate[rs[2]] : ps3
      := catalyticRate[rs[3]] : ps4 := associationRate[rs[4]] : ps5
      := dissociationRate[rs[5]] : ps6 := catalyticRate[rs[6]] : ps7
      := catalyticRate[rs[7]] : ps9 := switchingRate[rs[9]] : ps10
      := switchingRate[rs[10]] : ps11 := switchingRate[rs[11]] :
    ps8 := evalf((ps1·ps10·ps5·ps9)/(ps11·ps4·ps2)) :
    if ps8 ≥ 10^-6 and ps8 ≤ 10^-2 then
      params := {k[1] = ps1, k[2] = ps2, k[3] = ps3, k[4] = ps4, k[5] = ps5, k[6] = ps6,
     k[7] = ps7, k[8] = ps8, k[9] = ps9, k[10] = ps10, k[11] = ps11} :
      critiria := evalf(subs(params, finalTerm)) :
      if critiria > 0 then
        finalPol2 := subs(params, finalPol) :
        x1 := concentration[roll( )] :
        finalPol3 := subs(x[1] = x1, finalPol2) :
        x3 := evalf(solve(finalPol3, x[3])) :
        if x3 ≥ 2 and x3 ≤ 10^3 then
          solution2 := subs(params, x[1] = x1, x[3] = x3, solution) :
          B1 := evalf(subs(solution2[1], x[1] = x1, x[3] = x3, x[1] + x[2] + x[5]
      + x[6])) :
          B2 := evalf(subs(solution2[1], x[1] = x1, x[3] = x3, x[3] + x[4] + x[5]
      + x[6])) :
          outParams := [[ps1, ps2, ps3, ps4, ps5, ps6, ps7, ps8, ps9, ps10, ps11, B1, B2,
     critiria, number]] :
          writedata(bistableSpace, outParams);
          if B1 ≥ 2 and B1 ≤ 10^3 and B2 ≥ 2 and B2 ≤ 10^3 then
            writedata(realisticBistableSpace, outParams);
          end if;
        end if;
      end if;
    end if;
  end do;
  close(bistableSpace) :
  close(realisticBistableSpace) :

##########################################################################################
```