```
> 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

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

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

Steady state equations:

> $ssEqs := A.ks$

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

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) :

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

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

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.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

$$finalPol := (-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) x_1^2 + (-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}$$

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

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

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

$$
\begin{aligned}
&-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 - 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 - 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} - 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:

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

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

> *factor*(*term*)

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

>

"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:

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

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

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

> *factor*(*constraintTerm*)

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

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

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 ##########################

$> bindingRate := evalf\left(seq\left(10^{-3}\cdot(10^6)^{\frac{i}{20}}, i = 0..20\right)\right):$

$> catalyticRate := seq\left(10^{-3}\cdot(10^6)^{\frac{i}{1023}}, i = 0..1023\right):$

$> switchingRate := seq\left(10^{-2}\cdot(10^4)^{\frac{i}{1023}}, i = 0..1023\right):$

$> concentration := seq\left(10^{-3}\cdot(10^6)^{\frac{i}{1023}}, i = 0..1023\right):$

> bistableSpace := fopen("bistable_parameters_low_resol.txt", APPEND, TEXT) :

> allSpace := fopen("all_parameters_low_resol.txt", APPEND, TEXT) :

> **for** p_1 **in** bindingRate **do**

for p_2 **in** bindingRate **do**

for p_3 **in** bindingRate **do**

for p_4 **in** bindingRate **do**

for p_5 **in** bindingRate **do**

for p_6 **in** bindingRate **do**

for p_7 **in** bindingRate **do**

for p_9 **in** bindingRate **do**

for p_{10} **in** bindingRate **do**

for p_{11} **in** bindingRate **do**

$params := \{k_1 = p_1, k_2 = p_2, k_3 = p_3, k_4 = p_4, k_5 = p_5, k_6 = p_6, k_7 = p_7, k_9 = p_9, k_{10} = p_{10}, k_{11} = p_{11}\};$

$critiria := subs(params, constraintTerm);$

$p_8 := evalf\left(\frac{p_1 \cdot p_{10} \cdot p_5 \cdot p_9}{p_{11} \cdot p_4 \cdot p_2}\right);$

$outParams := [p_1, p_2, p_3, p_4, p_5, p_6, p_7, p_8, p_9, p_{10}, p_{11}, critiria];$

```
if critiria > 0 and p_8 ≤ 10^3 and p_8 ≥ 10^(-3) then
  writedata(bistableSpace, outParams);
 end if;
end do;
end do;
end do;
end do;
end do;
end do;
end do;
end do;
end do;
end do;
Warning,  computation interrupted
```

```
> close(bistableSpace) :
> close(allSpace) :
```

##

#################### Orignal computation of parameters ##################################

Now **the trick resides on finding parameters of the rate constants k such that the term is positive.**

For example

> $params := \{k_1 = 10, k_2 = 0.01, k_3 = 1, k_4 = 0.01, k_5 = 10, k_6 = 100, k_7 = 0.1, k_8 = 100, k_9 = 0.01, k_{10} = 0.01, k_{11} = 1\}$:

> $subs(\text{params}, term)$

$$6.596777990 \qquad \textbf{(1.9)}$$

Once you have such a set, then substitute into the polynomial, and **find values of x1 and x3 such that the polynomial is positive**:

> $finalPol2 := subs(params, finalPol)$

$$finalPol2 := -0.035806621\, x_1^2 - 0.000102010\, x_1^3 - 1.307843255\ 10^6\, x_3 - 14.16723525\, x_1 - 1281.778575 + 6.596777990\, x_1^2\, x_3 - 4757.559908\, x_1\, x_3 \qquad \textbf{(1.10)}$$

> $finalPol2 := collect(\%, x_3)$

$$finalPol2 := \left(-1.307843255\ 10^6 + 6.596777990\, x_1^2 - 4757.559908\, x_1\right) x_3 - 0.035806621\, x_1^2 - 0.000102010\, x_1^3 - 14.16723525\, x_1 - 1281.778575 \qquad \textbf{(1.11)}$$

> $x1 := 1000$:

> $subs(x_1 = x1, finalPol2)$

$$5.31374827\ 10^5\, x_3 - 1.532656348\ 10^5 \qquad \textbf{(1.12)}$$

> $x3 := solve(\%, x_3)$

$$x3 := 0.2884322460 \quad \textbf{(1.13)}$$

>

> $subs(params, x_1 = x1, x_3 = x3, finalPol)$

$$0. \quad \textbf{(1.14)}$$

This choice of rate constants and x1 with x3 will give total amounts such that the system has three steady states.
To find the total amounts, we find the values of x2, x4, x5, x6 corresponding to x1 and x3, as given by the expressions above in sol2[1].
Then we substitute these values into the conservation laws:

> $solution2 := subs(params, x_1 = x1, x_3 = x3, solution)$

$$solution2 := [[x_2 = 80684.29918, x_4 = 573.1872191, x_5 = 2878.647339, x_6 = 51.89782579]] \quad \textbf{(1.15)}$$

> $B_1 := subs(solution2[1], x_1 = x1, x_3 = x3, x_1 + x_2 + x_5 + x_6)$

$$B_1 := 84614.84435 \quad \textbf{(1.16)}$$

> $B_2 := subs(solution2[1], x_1 = x1, x_3 = x3, x_3 + x_4 + x_5 + x_6)$

$$B_2 := 3504.020816 \quad \textbf{(1.17)}$$

We now check that we have three steady states. We substitute into myeqs the values of the parameters and solve the equations:

> $subs(params, T_1 = B_1, T_2 = B_2, subsEqs)$

$$[-0.1\, x_2 + x_5 + 100\, x_6, -0.01\, x_1\, x_4 + 100\, x_3 - 0.01\, x_4 + 110\, x_6, 10\, x_1\, x_3 - 1.02\, x_5 + x_6, 0.01\, x_1\, x_4 + 0.01\, x_5 - 111\, x_6, x_1 + x_2 + x_5 + x_6 - 84614.84435, x_3 + x_4 + x_5 + x_6 - 3504.020816] \quad \textbf{(1.18)}$$

> $solutionSS := solve(\%)$

$$solutionSS := \{x_1 = 9485.350939, x_2 = 71668.95903, x_3 = 0.03641531393, x_4 = 43.45001595, x_5 = 3423.096390, x_6 = 37.43799513\}, \{x_1 = 1000.019288, x_2 = 80684.26702, x_3 = 0.2884280291, x_4 = 573.1743463, x_5 = 2878.660378, x_6 = 51.89766324\}, \{x_1 = 999.9807131, x_2 = 80684.33135, x_3 = 0.2884364628, x_4 = 573.2000917, x_5 = 2878.634300, x_6 = 51.89798835\} \quad \textbf{(1.19)}$$

We find indeed three positive steady states.

The last step is to find their asymptotic stability properties.
To do that, we compute the eigenvalues of the Jacobian of eqs evaluated at the three steady states. Two of them (because there are two conservation laws) should be zero.

Due to numerical issues, we get small numbers instead of zero. We disregard the bottom two eigenvalues.

> *ssEqs*

$$\left[\begin{array}{c} -k_1 x_1 x_3 - k_4 x_1 x_4 + k_2 x_5 + k_5 x_6 + k_7 x_2 \\ k_3 x_5 + k_6 x_6 - k_7 x_2 \\ -k_1 x_1 x_3 + k_2 x_5 + k_3 x_5 - k_8 x_3 + k_9 x_4 \\ -k_4 x_1 x_4 + k_5 x_6 + k_6 x_6 + k_8 x_3 - k_9 x_4 \\ k_1 x_1 x_3 - k_2 x_5 - k_3 x_5 - k_{10} x_5 + k_{11} x_6 \\ k_4 x_1 x_4 - k_5 x_6 - k_6 x_6 + k_{10} x_5 - k_{11} x_6 \end{array}\right] \tag{1.20}$$

> $J := VectorCalculus[Jacobian]\left(ssEqs, \left[seq\left(x_i, i = 1..6\right)\right]\right)$

$$J := \left[\begin{array}{cccccc} -k_1 x_3 - k_4 x_4 & k_7 & -k_1 x_1 & -k_4 x_1 & k_2 & k_5 \\ 0 & -k_7 & 0 & 0 & k_3 & k_6 \\ -k_1 x_3 & 0 & -k_1 x_1 - k_8 & k_9 & k_2 + k_3 & 0 \\ -k_4 x_4 & 0 & k_8 & -k_4 x_1 - k_9 & 0 & k_5 + k_6 \\ k_1 x_3 & 0 & k_1 x_1 & 0 & -k_2 - k_3 - k_{10} & k_{11} \\ k_4 x_4 & 0 & 0 & k_4 x_1 & k_{10} & -k_5 - k_6 - k_{11} \end{array}\right] \tag{1.21}$$

> *subs*(*params*, *solutionSS*[1], *J*); *Eigenvalues*(%)

$$\left[\begin{array}{cccccc} -0.7986532988 & 0.1 & -94853.50939 & -94.85350939 & 0.01 & 10 \\ 0 & -0.1 & 0 & 0 & 1 & 100 \\ -0.3641531393 & 0 & -94953.50939 & 0.01 & 1.01 & 0 \\ -0.4345001595 & 0 & 100 & -94.86350939 & 0 & 110 \\ 0.3641531393 & 0 & 94853.50939 & 0 & -1.02 & 1 \\ 0.4345001595 & 0 & 0 & 94.85350939 & 0.01 & -111 \end{array}\right]$$

$$\left[\begin{array}{c} -94954.8821040290 + 0.\,I \\ -205.617900135784 + 0.\,I \\ -0.741304286052932 + 0.\,I \\ -0.0502442377746779 + 0.\,I \\ -2.29666343149062\;10^{-14} + 0.\,I \\ -1.54079147505976\;10^{-10} + 0.\,I \end{array}\right] \tag{1.22}$$

> *subs*(*params*, *solutionSS*[2], *J*); *Eigenvalues*(%)

$$\begin{bmatrix} -8.616023754 & 0.1 & -10000.19288 & -10.00019288 & 0.01 & 10 \\ 0 & -0.1 & 0 & 0 & 1 & 100 \\ -2.884280291 & 0 & -10100.19288 & 0.01 & 1.01 & 0 \\ -5.731743463 & 0 & 100 & -10.01019288 & 0 & 110 \\ 2.884280291 & 0 & 10000.19288 & 0 & -1.02 & 1 \\ 5.731743463 & 0 & 0 & 10.00019288 & 0.01 & -111 \end{bmatrix}$$

$$\begin{bmatrix} -10104.0500258180 + 0.\,I \\ -121.899052736275 + 0.\,I \\ -4.99001861764501 + 0.\,I \\ 4.81480075585683\ 10^{-7} + 0.\,I \\ 5.64073940181866\ 10^{-8} + 0.\,I \\ -3.50740692856986\ 10^{-13} + 0.\,I \end{bmatrix} \tag{1.23}$$

> *subs*(*params*, *solutionSS*[3], *J*); *Eigenvalues*(%)

$$\begin{bmatrix} -8.616365545 & 0.1 & -9999.807131 & -9.999807131 & 0.01 & 10 \\ 0 & -0.1 & 0 & 0 & 1 & 100 \\ -2.884364628 & 0 & -10099.80713 & 0.01 & 1.01 & 0 \\ -5.732000917 & 0 & 100 & -10.00980713 & 0 & 110 \\ 2.884364628 & 0 & 9999.807131 & 0 & -1.02 & 1 \\ 5.732000917 & 0 & 0 & 9.999807131 & 0.01 & -111 \end{bmatrix}$$

$$\begin{bmatrix} -10103.6643580139 + 0.\,I \\ -121.898700136404 + 0.\,I \\ -4.99024398796274 + 0.\,I \\ -0.0000071294424962440 9 + 0.\,I \\ 0.00000659269467467827 + 0.\,I \\ -9.92827049122219\ 10^{-13} + 0.\,I \end{bmatrix} \tag{1.24}$$

>