```
> 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]·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]])
```

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

Steady state equations:

```
> ssEqs := A.ks
```

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

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.

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

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

$$x_1\,x_3)\Big/\big(k_7\,(k_2\,k_4\,k_{11}\,x_1 + k_3\,k_4\,k_{11}\,x_1 + k_2\,k_5\,k_9 + k_2\,k_6\,k_9 + k_2\,k_9\,k_{11} + k_3\,k_5\,k_9 + k_3\,k_6\,k_9 + k_3\,k_9\,k_{11} + k_5\,k_9\,k_{10} + k_6\,k_9\,k_{10})\big), x_4 = \big(x_3\,(k_1\,k_5\,k_{10}\,x_1 + k_1\,k_6\,k_{10}\,x_1 + k_2\,k_5\,k_8 + k_2\,k_6\,k_8 + k_2\,k_8\,k_{11} + k_3\,k_5\,k_8 + k_3\,k_6\,k_8 + k_3\,k_8\,k_{11} + k_5\,k_8\,k_{10} + k_6\,k_8\,k_{10})\big)\Big/\big(k_2\,k_4\,k_{11}\,x_1 + k_3\,k_4\,k_{11}\,x_1 + k_2\,k_5\,k_9 + k_2\,k_6\,k_9 + k_2\,k_9\,k_{11} + k_3\,k_5\,k_9 + k_3\,k_6\,k_9 + k_3\,k_9\,k_{11} + k_5\,k_9\,k_{10} + k_6\,k_9\,k_{10}\big), x_5 = \big(x_1\,x_3\,(k_1\,k_4\,k_{11}\,x_1 + k_1\,k_5\,k_9 + k_1\,k_6\,k_9 + k_1\,k_9\,k_{11} + k_4\,k_8\,k_{11})\big)\Big/\big(k_2\,k_4\,k_{11}\,x_1 + k_3\,k_4\,k_{11}\,x_1 + k_2\,k_5\,k_9 + k_2\,k_6\,k_9 + k_2\,k_9\,k_{11} + k_3\,k_5\,k_9 + k_3\,k_6\,k_9 + k_3\,k_9\,k_{11} + k_5\,k_9\,k_{10} + k_6\,k_9\,k_{10}\big), x_6 = \big((k_1\,k_4\,k_{10}\,x_1 + k_1\,k_9\,k_{10} + k_2\,k_4\,k_8 + k_3\,k_4\,k_8 + k_4\,k_8\,k_{10})\,x_1\,x_3\big)\Big/\big(k_2\,k_4\,k_{11}\,x_1 + k_3\,k_4\,k_{11}\,x_1 + k_2\,k_5\,k_9 + k_2\,k_6\,k_9 + k_2\,k_9\,k_{11} + k_3\,k_5\,k_9 + k_3\,k_6\,k_9 + k_3\,k_9\,k_{11} + k_5\,k_9\,k_{10} + k_6\,k_9\,k_{10}\big)]]$$

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

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

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

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

```
> polSubs := numer(detSubs) :
> finalPol := collect(polSubs, {x_1, x_3},'distributed')
```

$finalPol := -2 k_2^2 k_5 k_6 k_7 k_8 k_9 - 2 k_2^2 k_5 k_7 k_8 k_9 k_{11} - 2 k_2^2 k_6 k_7 k_8 k_9 k_{11} - 2 k_2 k_3$ **(1.5)**
$k_5^2 k_7 k_8 k_9 - 4 k_2 k_3 k_5 k_6 k_7 k_9^2 - 4 k_2 k_3 k_5 k_7 k_9^2 k_{11} - 2 k_2 k_3 k_6^2 k_7 k_8 k_9$
$- 4 k_2 k_3 k_6 k_7 k_9^2 k_{11} - 2 k_2 k_3 k_7 k_8 k_9 k_{11}^2 - 2 k_2 k_5^2 k_7 k_8 k_9 k_{10} - 4 k_2 k_5 k_6 k_7 k_9^2 k_{10}$
$- 2 k_2 k_5 k_7 k_9^2 k_{10} k_{11} - 2 k_2 k_6^2 k_7 k_8 k_9 k_{10} - 2 k_2 k_6 k_7 k_9^2 k_{10} k_{11} - 2 k_3^2 k_5 k_6 k_7 k_8 k_9$
$- 2 k_3^2 k_5 k_7 k_8 k_9 k_{11} - 2 k_3^2 k_6 k_7 k_8 k_9 k_{11} - 2 k_3 k_5^2 k_7 k_8 k_9 k_{10} - 4 k_3 k_5 k_6 k_7 k_9^2 k_{10}$
$- 2 k_3 k_5 k_7 k_9^2 k_{10} k_{11} - 2 k_3 k_6^2 k_7 k_8 k_9 k_{10} - 2 k_3 k_6 k_7 k_9^2 k_{10} k_{11} - 2 k_5 k_6 k_7 k_8 k_9$
$k_{10}^2 + \big(-k_1 k_2 k_4 k_5 k_7 k_9 k_{10} - 2 k_1 k_2 k_4 k_5 k_7 k_9 k_{11} - k_1 k_2 k_4 k_5 k_7 k_{10} k_{11}$
$- k_1 k_2 k_4 k_6 k_7 k_9 k_{10} - 2 k_1 k_2 k_4 k_6 k_7 k_9 k_{11} - k_1 k_2 k_4 k_6 k_7 k_{10} k_{11}$
$- 2 k_1 k_2 k_4 k_7 k_9 k_{10} k_{11} - 2 k_1 k_2 k_4 k_7 k_9 k_{11}^2 - k_1 k_3 k_4 k_5 k_7 k_9 k_{10}$
$- 2 k_1 k_3 k_4 k_5 k_7 k_9 k_{11} - k_1 k_3 k_4 k_5 k_7 k_{10} k_{11} - k_1 k_3 k_4 k_6 k_7 k_9 k_{10}$
$- 2 k_1 k_3 k_4 k_6 k_7 k_9 k_{11} - k_1 k_3 k_4 k_6 k_7 k_{10} k_{11} - 2 k_1 k_3 k_4 k_7 k_9 k_{10} k_{11}$
$- 2 k_1 k_3 k_4 k_7 k_9 k_{11}^2 - k_1 k_4 k_5 k_7 k_9 k_{10}^2 - k_1 k_4 k_5 k_7 k_9 k_{10} k_{11} - k_1 k_4 k_6 k_7 k_9 k_{10}^2$
$- k_1 k_4 k_6 k_7 k_9 k_{10} k_{11} - k_2^2 k_4^2 k_7 k_8 k_{11} - k_2^2 k_4^2 k_7 k_{11}^2 - 2 k_2 k_3 k_4^2 k_7 k_8 k_{11} - 2 k_2 k_3$
$k_4^2 k_7 k_{11}^2 - k_2 k_4^2 k_7 k_8 k_{10} k_{11} - k_2 k_4^2 k_7 k_8 k_{11}^2 - k_3^2 k_4^2 k_7 k_8 k_{11} - k_3^2 k_4^2 k_7 k_{11}^2 - k_3$
$k_4^2 k_7 k_8 k_{10} k_{11} - k_3 k_4^2 k_7 k_8 k_{11}^2 \big) x_1^2 + \big(-k_1 k_2 k_5^2 k_7 k_9^2 - k_1 k_2 k_5^2 k_7 k_9 k_{10}$
$- 2 k_1 k_2 k_5 k_6 k_7 k_9^2 - 2 k_1 k_2 k_5 k_6 k_7 k_9 k_{10} - k_1 k_2 k_5 k_7 k_9^2 k_{10} - 2 k_1 k_2 k_5 k_7 k_9^2 k_{11}$
$- k_1 k_2 k_5 k_7 k_9 k_{10} k_{11} - k_1 k_2 k_6^2 k_7 k_9^2 - k_1 k_2 k_6^2 k_7 k_9 k_{10} - k_1 k_2 k_6 k_7 k_9^2 k_{10}$

$$-2 k_1 k_2 k_6 k_7 k_9^2 k_{11} - k_1 k_2 k_6 k_7 k_9 k_{10} k_{11} - k_1 k_2 k_7 k_9^2 k_{10} k_{11} - k_1 k_2 k_7 k_9^2 k_{11}^2$$

$$-k_1 k_3 k_5^2 k_7 k_9^2 - k_1 k_3 k_5^2 k_7 k_9 k_{10} - 2 k_1 k_3 k_5 k_6 k_7 k_9^2 - 2 k_1 k_3 k_5 k_6 k_7 k_9 k_{10}$$

$$-k_1 k_3 k_5 k_7 k_9^2 k_{10} - 2 k_1 k_3 k_5 k_7 k_9^2 k_{11} - k_1 k_3 k_5 k_7 k_9 k_{10} k_{11} - k_1 k_3 k_6^2 k_7 k_9^2$$

$$-k_1 k_3 k_6^2 k_7 k_9 k_{10} - k_1 k_3 k_6 k_7 k_9^2 k_{10} - 2 k_1 k_3 k_6 k_7 k_9^2 k_{11} - k_1 k_3 k_6 k_7 k_9 k_{10} k_{11}$$

$$-k_1 k_3 k_7 k_9^2 k_{10} k_{11} - k_1 k_3 k_7 k_9^2 k_{11}^2 - k_1 k_5^2 k_7 k_9^2 k_{10} - k_1 k_5^2 k_7 k_9 k_{10}^2 - 2 k_1 k_5 k_6 k_7$$

$$k_9^2 k_{10} - 2 k_1 k_5 k_6 k_7 k_9 k_{10}^2 - k_1 k_5 k_7 k_9^2 k_{10}^2 - k_1 k_5 k_7 k_9^2 k_{10} k_{11} - k_1 k_6^2 k_7 k_9^2 k_{10} - k_1$$

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

$$-2 k_2^2 k_4 k_5 k_7 k_9 k_{11} - k_2^2 k_4 k_6 k_7 k_8 k_9 - k_2^2 k_4 k_6 k_7 k_8 k_{11} - 2 k_2^2 k_4 k_6 k_7 k_9 k_{11} -$$

$$k_2^2 k_4 k_7 k_8 k_9 k_{11} - k_2^2 k_4 k_7 k_8 k_{11}^2 - 2 k_2^2 k_4 k_7 k_9 k_{11}^2 - 2 k_2 k_3 k_4 k_5 k_7 k_8 k_9$$

$$-2 k_2 k_3 k_4 k_5 k_7 k_8 k_{11} - 4 k_2 k_3 k_4 k_5 k_7 k_9 k_{11} - 2 k_2 k_3 k_4 k_6 k_7 k_8 k_9$$

$$-2 k_2 k_3 k_4 k_6 k_7 k_8 k_{11} - 4 k_2 k_3 k_4 k_6 k_7 k_9 k_{11} - 2 k_2 k_3 k_4 k_7 k_8 k_9 k_{11}$$

$$-2 k_2 k_3 k_4 k_7 k_8 k_{11}^2 - 4 k_2 k_3 k_4 k_7 k_9 k_{11}^2 - 2 k_2 k_4 k_5 k_7 k_8 k_9 k_{10}$$

$$-k_2 k_4 k_5 k_7 k_8 k_9 k_{11} - k_2 k_4 k_5 k_7 k_8 k_{10} k_{11} - 2 k_2 k_4 k_5 k_7 k_9 k_{10} k_{11}$$

$$-2 k_2 k_4 k_6 k_7 k_8 k_9 k_{10} - k_2 k_4 k_6 k_7 k_8 k_9 k_{11} - k_2 k_4 k_6 k_7 k_8 k_{10} k_{11}$$

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

$$-k_3^2 k_4 k_5 k_7 k_8 k_{11} - 2 k_3^2 k_4 k_5 k_7 k_9 k_{11} - k_3^2 k_4 k_6 k_7 k_8 k_9 - k_3^2 k_4 k_6 k_7 k_8 k_{11} - 2$$

$$k_3^2 k_4 k_6 k_7 k_9 k_{11} - k_3^2 k_4 k_7 k_8 k_9 k_{11} - k_3^2 k_4 k_7 k_8 k_{11}^2 - 2 k_3^2 k_4 k_7 k_9 k_{11}^2$$

$$-2 k_3 k_4 k_5 k_7 k_8 k_9 k_{10} - k_3 k_4 k_5 k_7 k_8 k_9 k_{11} - k_3 k_4 k_5 k_7 k_8 k_{10} k_{11}$$

$$-2 k_3 k_4 k_5 k_7 k_9 k_{10} k_{11} - 2 k_3 k_4 k_6 k_7 k_8 k_9 k_{10} - k_3 k_4 k_6 k_7 k_8 k_9 k_{11}$$

$$-k_3 k_4 k_6 k_7 k_8 k_{10} k_{11} - 2 k_3 k_4 k_6 k_7 k_9 k_{10} k_{11} - k_3 k_4 k_7 k_8 k_9 k_{10} k_{11}$$

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

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

$$-2 k_1 k_2 k_3 k_5 k_6 k_8 k_9 - 2 k_1 k_2 k_3 k_5 k_6 k_9^2 - 2 k_1 k_2 k_3 k_5 k_8 k_9 k_{11} - 2 k_1 k_2 k_3 k_5$$

$$k_9^2 k_{11} - k_1 k_2 k_3 k_6^2 k_8 k_9 - k_1 k_2 k_3 k_6^2 k_9^2 - 2 k_1 k_2 k_3 k_6 k_8 k_9 k_{11} - 2 k_1 k_2 k_3 k_6 k_9^2 k_{11}$$

$$-k_1 k_2 k_3 k_8 k_9 k_{11}^2 - k_1 k_2 k_3 k_9^2 k_{11}^2 - k_1 k_2 k_5^2 k_7 k_8 k_9 - k_1 k_2 k_5^2 k_7 k_9^2$$

$$-2 k_1 k_2 k_5 k_6 k_7 k_8 k_9 - 2 k_1 k_2 k_5 k_6 k_7 k_9^2 - k_1 k_2 k_5 k_6 k_8 k_9 k_{10} - k_1 k_2 k_5 k_6 k_9^2 k_{10}$$

$$-k_1 k_2 k_5 k_7 k_8 k_9 k_{10} - 2 k_1 k_2 k_5 k_7 k_8 k_9 k_{11} - k_1 k_2 k_5 k_7 k_9^2 k_{10} - 2 k_1 k_2 k_5 k_7 k_9^2 k_{11}$$

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

$$- k_{2} k_{4} k_{6} k_{7} k_{8} k_{9} k_{11} - k_{2} k_{4} k_{6} k_{8}^{2} k_{10} k_{11} - k_{2} k_{4} k_{6} k_{8} k_{9} k_{10} k_{11} - k_{2} k_{4} k_{7} k_{8}^{2} k_{10} k_{11}$$

$$- k_{2} k_{4} k_{7} k_{8}^{2} k_{11}^{2} - k_{2} k_{4} k_{7} k_{8} k_{9} k_{10} k_{11} - k_{2} k_{4} k_{7} k_{8} k_{9} k_{11}^{2} - k_{3}^{2} k_{4} k_{5} k_{6} k_{8}^{2} -$$

$$k_{3}^{2} k_{4} k_{5} k_{6} k_{8} k_{9} - k_{3}^{2} k_{4} k_{5} k_{7} k_{8}^{2} - k_{3}^{2} k_{4} k_{5} k_{7} k_{8} k_{9} - k_{3}^{2} k_{4} k_{5} k_{8}^{2} k_{11} - k_{3}^{2} k_{4} k_{5} k_{8} k_{9} k_{11}$$

$$- k_{3}^{2} k_{4} k_{6}^{2} k_{8}^{2} - k_{3}^{2} k_{4} k_{6}^{2} k_{8} k_{9} - k_{3}^{2} k_{4} k_{6} k_{7} k_{8}^{2} - k_{3}^{2} k_{4} k_{6} k_{7} k_{8} k_{9} - 2 k_{3}^{2} k_{4} k_{6} k_{8}^{2} k_{11} - 2$$

$$k_{3}^{2} k_{4} k_{6} k_{8} k_{9} k_{11} - k_{3}^{2} k_{4} k_{7} k_{8}^{2} k_{11} - k_{3}^{2} k_{4} k_{7} k_{8} k_{9} k_{11} - k_{3}^{2} k_{4} k_{8}^{2} k_{11}^{2} - k_{3}^{2} k_{4} k_{8} k_{9} k_{11}^{2}$$

$$- 2 k_{3} k_{4} k_{5} k_{6} k_{8}^{2} k_{10} - 2 k_{3} k_{4} k_{5} k_{6} k_{8} k_{9} k_{10} - 2 k_{3} k_{4} k_{5} k_{7} k_{8}^{2} k_{10} - k_{3} k_{4} k_{5} k_{7} k_{8}^{2} k_{11}$$

$$- 2 k_{3} k_{4} k_{5} k_{7} k_{8} k_{9} k_{10} - k_{3} k_{4} k_{5} k_{7} k_{8} k_{9} k_{11} - k_{3} k_{4} k_{5} k_{8}^{2} k_{10} k_{11}$$

$$- k_{3} k_{4} k_{5} k_{8} k_{9} k_{10} k_{11} - 2 k_{3} k_{4} k_{6}^{2} k_{8}^{2} k_{10} - 2 k_{3} k_{4} k_{6}^{2} k_{8} k_{9} k_{10} - 2 k_{3} k_{4} k_{6} k_{7} k_{8}^{2} k_{10}$$

$$- k_{3} k_{4} k_{6} k_{7} k_{8}^{2} k_{11} - 2 k_{3} k_{4} k_{6} k_{7} k_{8} k_{9} k_{10} - k_{3} k_{4} k_{6} k_{7} k_{8} k_{9} k_{11} - 2 k_{3} k_{4} k_{6}$$

$$k_{8}^{2} k_{10} k_{11} - 2 k_{3} k_{4} k_{6} k_{8} k_{9} k_{10} k_{11} - k_{3} k_{4} k_{7} k_{8}^{2} k_{10} k_{11} - k_{3} k_{4} k_{7} k_{8}^{2} k_{11}^{2}$$

$$- k_{3} k_{4} k_{7} k_{8} k_{9} k_{10} k_{11} - k_{3} k_{4} k_{7} k_{8} k_{9} k_{11}^{2} - k_{4} k_{5} k_{6} k_{8}^{2} k_{10}^{2} - k_{4} k_{5} k_{6} k_{8} k_{9} k_{10}^{2}$$

$$- k_{4} k_{5} k_{7} k_{8}^{2} k_{10}^{2} - k_{4} k_{5} k_{7} k_{8}^{2} k_{10} k_{11} - k_{4} k_{5} k_{7} k_{8} k_{9} k_{10}^{2} - k_{4} k_{5} k_{7} k_{8} k_{9} k_{10} k_{11} - k_{4}$$

$$k_{6}^{2} k_{8}^{2} k_{10}^{2} - k_{4} k_{6}^{2} k_{8} k_{9} k_{10}^{2} - k_{4} k_{6} k_{7} k_{8}^{2} k_{10}^{2} - k_{4} k_{6} k_{7} k_{8}^{2} k_{10} k_{11} - k_{4} k_{6} k_{7} k_{8} k_{9} k_{10}^{2}$$

$$- k_{4} k_{6} k_{7} k_{8} k_{9} k_{10} k_{11} \Big) x_{3} + \Big(-k_{1} k_{2} k_{4}^{2} k_{7} k_{10} k_{11} - k_{1} k_{2} k_{4}^{2} k_{7} k_{11}^{2} - k_{1} k_{3}$$

$$k_{4}^{2} k_{7} k_{10} k_{11} - k_{1} k_{3} k_{4}^{2} k_{7} k_{11}^{2} \Big) x_{1}^{3} - k_{2}^{2} k_{5}^{2} k_{7} k_{8} k_{9} - 2 k_{2}^{2} k_{5} k_{6} k_{7} k_{9}^{2} - 2 k_{2}^{2} k_{5} k_{7} k_{9}^{2} k_{11}$$

$$- k_{2}^{2} k_{6}^{2} k_{7} k_{8} k_{9} - 2 k_{2}^{2} k_{6} k_{7} k_{9}^{2} k_{11} - k_{2}^{2} k_{7} k_{8} k_{9} k_{11}^{2} - 2 k_{2} k_{3} k_{5}^{2} k_{7} k_{9}^{2} - 2 k_{2} k_{3} k_{6}^{2} k_{7} k_{9}^{2}$$

$$- 2 k_{2} k_{3} k_{7} k_{9}^{2} k_{11}^{2} - 2 k_{2} k_{5}^{2} k_{7} k_{9}^{2} k_{10} - 2 k_{2} k_{6}^{2} k_{7} k_{9}^{2} k_{10} - k_{3}^{2} k_{5}^{2} k_{7} k_{8} k_{9} - 2$$

$$k_{3}^{2} k_{5} k_{6} k_{7} k_{9}^{2} - 2 k_{3}^{2} k_{5} k_{7} k_{9}^{2} k_{11} - k_{3}^{2} k_{6}^{2} k_{7} k_{8} k_{9} - 2 k_{3}^{2} k_{6} k_{7} k_{9}^{2} k_{11} - k_{3}^{2} k_{7} k_{8} k_{9} k_{11}^{2}$$

$$- 2 k_{3} k_{5}^{2} k_{7} k_{9}^{2} k_{10} - 2 k_{3} k_{6}^{2} k_{7} k_{9}^{2} k_{10} - k_{5}^{2} k_{7} k_{8} k_{9} k_{10}^{2} - 2 k_{5} k_{6} k_{7} k_{9}^{2} k_{10}^{2} - k_{6}^{2} k_{7} k_{8} k_{9}$$

$$k_{10}^{2} + \Big(k_{1}^{2} k_{3} k_{4} k_{5} k_{9} k_{10} - k_{1}^{2} k_{3} k_{4} k_{5} k_{10} k_{11} + k_{1}^{2} k_{3} k_{4} k_{6} k_{9} k_{10} - k_{1}^{2} k_{3} k_{4} k_{6} k_{10} k_{11}$$

$$- k_{1}^{2} k_{4} k_{5} k_{6} k_{9} k_{10} - k_{1}^{2} k_{4} k_{5} k_{6} k_{10}^{2} - k_{1}^{2} k_{4} k_{5} k_{7} k_{10}^{2} - k_{1}^{2} k_{4} k_{5} k_{7} k_{10} k_{11} - k_{1}^{2} k_{4}$$

$$k_{6}^{2} k_{9} k_{10} - k_{1}^{2} k_{4} k_{6}^{2} k_{10}^{2} - k_{1}^{2} k_{4} k_{6} k_{7} k_{10}^{2} - k_{1}^{2} k_{4} k_{6} k_{7} k_{10} k_{11} - k_{1} k_{2} k_{3} k_{4}^{2} k_{8} k_{11}$$

$$- k_{1} k_{2} k_{3} k_{4}^{2} k_{11}^{2} + k_{1} k_{2} k_{4}^{2} k_{6} k_{8} k_{11} - k_{1} k_{2} k_{4}^{2} k_{6} k_{10} k_{11} - k_{1} k_{2} k_{4}^{2} k_{7} k_{10} k_{11} - k_{1} k_{2}$$

$$k_{4}^{2} k_{7} k_{11}^{2} - k_{1} k_{3}^{2} k_{4}^{2} k_{8} k_{11} - k_{1} k_{3}^{2} k_{4}^{2} k_{11}^{2} + k_{1} k_{3} k_{4}^{2} k_{6} k_{8} k_{11} - k_{1} k_{3} k_{4}^{2} k_{6} k_{10} k_{11}$$

$$- k_{1} k_{3} k_{4}^{2} k_{7} k_{10} k_{11} - k_{1} k_{3} k_{4}^{2} k_{7} k_{11}^{2} \Big) x_{1}^{2} x_{3} + \Big(-2 k_{1} k_{2} k_{3} k_{4} k_{5} k_{8} k_{11}$$

$$- 2 k_{1} k_{2} k_{3} k_{4} k_{5} k_{9} k_{11} - 2 k_{1} k_{2} k_{3} k_{4} k_{6} k_{8} k_{11} - 2 k_{1} k_{2} k_{3} k_{4} k_{6} k_{9} k_{11}$$

$$- 2 k_{1} k_{2} k_{3} k_{4} k_{8} k_{11}^{2} - 2 k_{1} k_{2} k_{3} k_{4} k_{9} k_{11}^{2} - 2 k_{1} k_{2} k_{4} k_{5} k_{6} k_{8} k_{10}$$

$$-2k_1k_2k_4k_5k_6k_9k_{10}-2k_1k_2k_4k_5k_7k_8k_{10}-2k_1k_2k_4k_5k_7k_8k_{11}$$
$$-2k_1k_2k_4k_5k_7k_9k_{10}-2k_1k_2k_4k_5k_7k_9k_{11}-2k_1k_2k_4k_6^2k_8k_{10}-2k_1k_2k_4$$
$$k_6^2k_9k_{10}-2k_1k_2k_4k_6k_7k_8k_{10}-2k_1k_2k_4k_6k_7k_8k_{11}-2k_1k_2k_4k_6k_7k_9k_{10}$$
$$-2k_1k_2k_4k_6k_7k_9k_{11}-2k_1k_2k_4k_6k_8k_{10}k_{11}-2k_1k_2k_4k_6k_9k_{10}k_{11}$$
$$-2k_1k_2k_4k_7k_8k_{10}k_{11}-2k_1k_2k_4k_7k_8k_{11}^2-2k_1k_2k_4k_7k_9k_{10}k_{11}$$
$$-2k_1k_2k_4k_7k_9k_{11}^2-2k_1k_3^2k_4k_5k_8k_{11}-2k_1k_3^2k_4k_5k_9k_{11}-2k_1k_3^2k_4k_6k_8k_{11}$$
$$-2k_1k_3^2k_4k_6k_9k_{11}-2k_1k_3^2k_4k_8k_{11}^2-2k_1k_3^2k_4k_9k_{11}^2-2k_1k_3k_4k_5k_6k_8k_{10}$$
$$-2k_1k_3k_4k_5k_6k_9k_{10}-2k_1k_3k_4k_5k_7k_8k_{10}-2k_1k_3k_4k_5k_7k_8k_{11}$$
$$-2k_1k_3k_4k_5k_7k_9k_{10}-2k_1k_3k_4k_5k_7k_9k_{11}-2k_1k_3k_4k_5k_8k_{10}k_{11}$$
$$-2k_1k_3k_4k_5k_9k_{10}k_{11}-2k_1k_3k_4k_6^2k_8k_{10}-2k_1k_3k_4k_6^2k_9k_{10}$$
$$-2k_1k_3k_4k_6k_7k_8k_{10}-2k_1k_3k_4k_6k_7k_8k_{11}-2k_1k_3k_4k_6k_7k_9k_{10}$$
$$-2k_1k_3k_4k_6k_7k_9k_{11}-4k_1k_3k_4k_6k_8k_{10}k_{11}-4k_1k_3k_4k_6k_9k_{10}k_{11}$$
$$-2k_1k_3k_4k_7k_8k_{10}k_{11}-2k_1k_3k_4k_7k_8k_{11}^2-2k_1k_3k_4k_7k_9k_{10}k_{11}$$
$$-2k_1k_3k_4k_7k_9k_{11}^2-2k_1k_4k_5k_6k_8k_{10}^2-2k_1k_4k_5k_6k_9k_{10}^2-2k_1k_4k_5k_7k_8k_{10}^2$$
$$-2k_1k_4k_5k_7k_8k_{10}k_{11}-2k_1k_4k_5k_7k_9k_{10}^2-2k_1k_4k_5k_7k_9k_{10}k_{11}-2k_1k_4k_6^2k_8$$
$$k_{10}^2-2k_1k_4k_6^2k_9k_{10}^2-2k_1k_4k_6k_7k_8k_{10}^2-2k_1k_4k_6k_7k_8k_{10}k_{11}-2k_1k_4k_6k_7k_9$$
$$k_{10}^2-2k_1k_4k_6k_7k_9k_{10}k_{11}\big)x_1x_3-k_2^2k_5^2k_7k_9^2-k_2^2k_6^2k_7k_9^2-k_2^2k_7k_9^2k_{11}^2-k_3^2k_5^2k_7$$
$$k_9^2-k_3^2k_6^2k_7k_9^2-k_3^2k_7k_9^2k_{11}^2-k_5^2k_7k_9^2k_{10}^2-k_6^2k_7k_9^2k_{10}^2-4k_2k_3k_5k_6k_7k_8k_9$$
$$-4k_2k_3k_5k_7k_8k_9k_{11}-4k_2k_3k_6k_7k_8k_9k_{11}-4k_2k_5k_6k_7k_8k_9k_{10}$$
$$-2k_2k_5k_7k_8k_9k_{10}k_{11}-2k_2k_6k_7k_8k_9k_{10}k_{11}-4k_3k_5k_6k_7k_8k_9k_{10}$$
$$-2k_3k_5k_7k_8k_9k_{10}k_{11}-2k_3k_6k_7k_8k_9k_{10}k_{11}$$

>

<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:

> $term := \big(k_1^2k_3k_4k_5k_9k_{10}-k_1^2k_3k_4k_5k_{10}k_{11}+k_1^2k_3k_4k_6k_9k_{10}-k_1^2k_3k_4k_6k_{10}k_{11}-$
$k_1^2k_4k_5k_6k_9k_{10}-k_1^2k_4k_5k_6k_{10}^2-k_1^2k_4k_5k_7k_{10}^2-k_1^2k_4k_5k_7k_{10}k_{11}-k_1^2k_4k_6^2k_9k_{10}$
$-k_1^2k_4k_6^2k_{10}^2-k_1^2k_4k_6k_7k_{10}^2-k_1^2k_4k_6k_7k_{10}k_{11}-k_1k_2k_3k_4^2k_8k_{11}-k_1k_2k_3k_4^2k_{11}^2$

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

> *factor*(*term*)

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

>

"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:

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

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

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

> *factor*(*constraintTerm*)

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

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

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

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

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: $10 \sim 10^3 nM$

```
> 
> randomize(3) :
> roll := rand(1 ..1023) :
> 
> bistableSpacePositive := fopen("bistable_space_positive_solutions.txt", APPEND, TEXT) :
> bistableSpaceRealistic := fopen("bistable_space_realistic_solutions.txt", APPEND, TEXT) :
> monostableSpaceRates := fopen("monostable_space_rates.txt", APPEND, TEXT) :
> bistableSpaceRates := fopen("monostable_space_rates.txt", APPEND, TEXT) :

> for number from 1 by 1 to 20000000 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)) :
      monoBiSplit := [[ps1, ps2, ps3, ps4, ps5, ps6, ps7, ps8, ps9, ps10, ps11, critiria,
    number]] :
      if critiria > 0 then
        writedata(bistableSpaceRates, monoBiSplit) :
        finalPol2 := subs(params, finalPol) :
        for x1 in concentration do
          finalPol3 := subs(x[1] = x1, finalPol2) :
          x3 := evalf(solve(finalPol3, x[3])) :
          if x3 > 0 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(bistableSpacePositive, outParams) :
            if B1 ≥ 2 and B1 ≤ 10^3 and B2 ≥ 2 and B2 ≤ 10^3 then
```

```
                writedata(bistableSpaceRealistic, outParams) :
              end if:
            end if:
          end do:
        else
          writedata(monostableSpaceRates, monoBiSplit) :
        end if:
      end if:
    end do:
    close(bistableSpacePositive) :
    close(bistableSpaceRealistic) :
    close(bistableSpaceRates) :
    close(monostableSpaceRates) :
>

> close(bistableSpacePositive) : close(bistableSpaceRealistic) : close(bistableSpaceRates) :
      close(monostableSpaceRates) :
####################################################################################
```