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

**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:

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

$$F := \begin{bmatrix} 1 & 1 & 0 & 0 & 1 & 1 \\ 0 & 0 & 1 & 1 & 1 & 1 \end{bmatrix} \quad \textbf{(3)}$$

>

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).

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

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

# 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)**

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

> $Determinant(J)$ :

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

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

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.

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

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

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

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

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

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

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

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

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

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

$+ k_3\, k_4\, k_{11}\, x_1 + k_2\, k_5\, k_9 + k_2\, k_6\, k_9 + k_2\, k_9\, k_{11} + k_3\, k_5\, k_9 + k_3\, k_6\, k_9 + k_3\, k_9\, k_{11}$

$+ k_5\, k_9\, k_{10} + k_6\, k_9\, k_{10})]]$

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)**

$- k_1\, k_4\, k_6\, k_{10} - k_1\, k_4\, k_7\, k_{10} - k_1\, k_4\, k_7\, k_{11})\, x_1\, x_3 + ((k_1\, k_3\, k_4\, k_9 - k_1\, k_3\, k_4\, k_{11}$

$- k_1\, k_4\, k_6\, k_9 - k_1\, k_4\, k_6\, k_{10} - k_1\, k_4\, k_7\, k_{10} - k_1\, k_4\, k_7\, k_{11})\, x_1\, x_3\, (k_1\, k_5\, k_{10}\, x_1$

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

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

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

$- k_1\, k_5\, k_7\, k_{10} - k_1\, k_6\, k_7\, k_9 - k_1\, k_6\, k_7\, k_{10} - k_1\, k_7\, k_9\, k_{10} - k_1\, k_7\, k_9\, k_{11} - k_2\, k_4\, k_7\, k_8$

$- k_2\, k_4\, k_7\, k_{11} - k_3\, k_4\, k_7\, k_8 - k_3\, k_4\, k_7\, k_{11} - k_4\, k_7\, k_8\, k_{10} - k_4\, k_7\, k_8\, k_{11})\, x_1 + ($

$-k_1\, k_3\, k_5\, k_8 - k_1\, k_3\, k_5\, k_9 - k_1\, k_3\, k_6\, k_8 - k_1\, k_3\, k_6\, k_9 - k_1\, k_3\, k_8\, k_{11} - k_1\, k_3\, k_9\, k_{11}$

$- k_1\, k_5\, k_7\, k_8 - k_1\, k_5\, k_7\, k_9 - k_1\, k_6\, k_7\, k_8 - k_1\, k_6\, k_7\, k_9 - k_1\, k_6\, k_8\, k_{10} - k_1\, k_6\, k_9\, k_{10}$

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

> *polSubs* := *numer*(*detSubs*) :

> *finalPol* := *collect*(*polSubs*, {$x_1$, $x_3$},'*distributed*')

$finalPol := (-k_1 k_2 k_4^2 k_7 k_{10} k_{11} - k_1 k_2 k_4^2 k_7 k_{11}^2 - k_1 k_3 k_4^2 k_7 k_{10} k_{11} - k_1 k_3 k_4^2 k_7 k_{11}^2) x_1^3$ **(1.5)**
$+ (-k_1 k_2 k_5^2 k_7 k_9^2 - k_1 k_2 k_5^2 k_7 k_9 k_{10} - 2 k_1 k_2 k_5 k_6 k_7 k_9^2 - 2 k_1 k_2 k_5 k_6 k_7 k_9 k_{10}$
$- k_1 k_2 k_5 k_7 k_9^2 k_{10} - 2 k_1 k_2 k_5 k_7 k_9^2 k_{11} - k_1 k_2 k_5 k_7 k_9 k_{10} k_{11} - k_1 k_2 k_6^2 k_7 k_9^2$
$- k_1 k_2 k_6^2 k_7 k_9 k_{10} - k_1 k_2 k_6 k_7 k_9^2 k_{10} - 2 k_1 k_2 k_6 k_7 k_9^2 k_{11} - k_1 k_2 k_6 k_7 k_9 k_{10} k_{11}$
$- k_1 k_2 k_7 k_9^2 k_{10} k_{11} - k_1 k_2 k_7 k_9^2 k_{11}^2 - k_1 k_3 k_5^2 k_7 k_9^2 - k_1 k_3 k_5^2 k_7 k_9 k_{10}$
$- 2 k_1 k_3 k_5 k_6 k_7 k_9^2 - 2 k_1 k_3 k_5 k_6 k_7 k_9 k_{10} - k_1 k_3 k_5 k_7 k_9^2 k_{10} - 2 k_1 k_3 k_5 k_7 k_9^2 k_{11}$
$- k_1 k_3 k_5 k_7 k_9 k_{10} k_{11} - k_1 k_3 k_6^2 k_7 k_9^2 - k_1 k_3 k_6^2 k_7 k_9 k_{10} - k_1 k_3 k_6 k_7 k_9^2 k_{10}$
$- 2 k_1 k_3 k_6 k_7 k_9^2 k_{11} - k_1 k_3 k_6 k_7 k_9 k_{10} k_{11} - k_1 k_3 k_7 k_9^2 k_{10} k_{11} - k_1 k_3 k_7 k_9^2 k_{11}^2$
$- k_1 k_5^2 k_7 k_9^2 k_{10} - k_1 k_5^2 k_7 k_9 k_{10}^2 - 2 k_1 k_5 k_6 k_7 k_9^2 k_{10} - 2 k_1 k_5 k_6 k_7 k_9 k_{10}^2$
$- k_1 k_5 k_7 k_9^2 k_{10}^2 - k_1 k_5 k_7 k_9^2 k_{10} k_{11} - k_1 k_6^2 k_7 k_9^2 k_{10} - k_1 k_6^2 k_7 k_9 k_{10}^2 - k_1 k_6 k_7 k_9^2$
$k_{10}^2 - k_1 k_6 k_7 k_9^2 k_{10} k_{11} - k_2^2 k_4 k_5 k_7 k_8 k_9 - k_2^2 k_4 k_5 k_7 k_8 k_{11} - 2 k_2^2 k_4 k_5 k_7 k_9 k_{11} -$
$k_2^2 k_4 k_6 k_7 k_8 k_9 - k_2^2 k_4 k_6 k_7 k_8 k_{11} - 2 k_2^2 k_4 k_6 k_7 k_9 k_{11} - k_2^2 k_4 k_7 k_8 k_9 k_{11} -$
$k_2^2 k_4 k_7 k_8 k_{11}^2 - 2 k_2^2 k_4 k_7 k_9 k_{11}^2 - 2 k_2 k_3 k_4 k_5 k_7 k_8 k_9 - 2 k_2 k_3 k_4 k_5 k_7 k_8 k_{11}$
$- 4 k_2 k_3 k_4 k_5 k_7 k_9 k_{11} - 2 k_2 k_3 k_4 k_6 k_7 k_8 k_9 - 2 k_2 k_3 k_4 k_6 k_7 k_8 k_{11}$
$- 4 k_2 k_3 k_4 k_6 k_7 k_9 k_{11} - 2 k_2 k_3 k_4 k_7 k_8 k_9 k_{11} - 2 k_2 k_3 k_4 k_7 k_8 k_{11}^2$
$- 4 k_2 k_3 k_4 k_7 k_9 k_{11}^2 - 2 k_2 k_4 k_5 k_7 k_8 k_9 k_{10} - k_2 k_4 k_5 k_7 k_8 k_9 k_{11}$
$- k_2 k_4 k_5 k_7 k_8 k_{10} k_{11} - 2 k_2 k_4 k_5 k_7 k_9 k_{10} k_{11} - 2 k_2 k_4 k_6 k_7 k_8 k_9 k_{10}$

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

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

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

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

>

***<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* $:= \Big(k_1^2 k_3 k_4 k_5 k_9 k_{10} - k_1^2 k_3 k_4 k_5 k_{10} k_{11} + k_1^2 k_3 k_4 k_6 k_9 k_{10} - k_1^2 k_3 k_4 k_6 k_{10} k_{11} -$
$k_1^2 k_4 k_5 k_6 k_9 k_{10} - k_1^2 k_4 k_5 k_6 k_{10}^2 - k_1^2 k_4 k_5 k_7 k_{10}^2 - k_1^2 k_4 k_5 k_7 k_{10} k_{11} - k_1^2 k_4 k_6^2 k_9 k_{10}$
$- k_1^2 k_4 k_6^2 k_{10}^2 - k_1^2 k_4 k_6 k_7 k_{10}^2 - k_1^2 k_4 k_6 k_7 k_{10} k_{11} - k_1 k_2 k_3 k_4^2 k_8 k_{11} - k_1 k_2 k_3 k_4^2 k_{11}^2$

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

> *factor*(*term*)

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

> $K_1 := \frac{k_1}{k_2 + k_3}$

$$K_1 := \frac{k_1}{k_2 + k_3} \tag{1.7}$$

>

> $K_2 := \frac{k_4}{k_5 + k_6}$

$$K_2 := \frac{k_4}{k_5 + k_6} \tag{1.8}$$

>

>

**"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*)

$$constraintTerm := -k_1^2 k_3 k_4 k_5 k_{10} k_{11} + k_1^2 k_3 k_4 k_6 k_9 k_{10} - k_1^2 k_3 k_4 k_6 k_{10} k_{11} - k_1^2 k_4 k_5 k_6 k_{10}^2 - k_1^2 k_4 k_5 k_7 k_{10}^2 - k_1^2 k_4 k_5 k_7 k_{10} k_{11} - k_1^2 k_4 k_6^2 k_9 k_{10} - k_1^2 k_4 k_6^2 k_{10}^2 - k_1^2 k_4 k_6 k_7 k_{10}^2 - k_1^2 k_4 k_6 k_7 k_{10} k_{11} - k_1 k_2 k_3 k_4^2 k_{11}^2 - k_1 k_2 k_4^2 k_6 k_{10} k_{11} - k_1 k_2 k_4^2 k_7 k_{10} k_{11} \tag{1.9}$$

$$- k_1 k_2 k_4^2 k_7 k_{11}^2 - \frac{k_1^2 k_3^2 k_4 k_{10} k_5 k_9}{k_2} - k_1 k_3^2 k_4^2 k_{11}^2 + \frac{k_1^2 k_3 k_4 k_6 k_{10} k_5 k_9}{k_2} - k_1 k_3 k_4^2 k_6 k_{10} k_{11} - k_1 k_3 k_4^2 k_7 k_{10} k_{11} - k_1 k_3 k_4^2 k_7 k_{11}^2$$

> $factor(constraintTerm)$

$$-\frac{1}{k_2}\Big(k_1 k_4 \big(k_1 k_2 k_3 k_5 k_{10} k_{11} - k_1 k_2 k_3 k_6 k_9 k_{10} + k_1 k_2 k_3 k_6 k_{10} k_{11} + k_1 k_2 k_5 k_6 k_{10}^2 + k_1 k_2 k_5 k_7 k_{10}^2 + k_1 k_2 k_5 k_7 k_{10} k_{11} + k_1 k_2 k_6^2 k_9 k_{10} + k_1 k_2 k_6^2 k_{10}^2 + k_1 k_2 k_6 k_7 k_{10}^2 + k_1 k_2 k_6 k_7 k_{10} k_{11} + k_1 k_3^2 k_5 k_9 k_{10} - k_1 k_3 k_5 k_6 k_9 k_{10} + k_2^2 k_3 k_4 k_{11}^2 + k_2^2 k_4 k_6 k_{10} k_{11} + k_2^2 k_4 k_7 k_{10} k_{11} + k_2^2 k_4 k_7 k_{11}^2 + k_2 k_3^2 k_4 k_{11}^2 + k_2 k_3 k_4 k_6 k_{10} k_{11} + k_2 k_3 k_4 k_7 k_{10} k_{11} + k_2 k_3 k_4 k_7 k_{11}^2\big)\Big) \tag{1.10}$$

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

$$finalTerm := -k_1 k_2 k_3 k_5 k_{10} k_{11} + k_1 k_2 k_3 k_6 k_9 k_{10} - k_1 k_2 k_3 k_6 k_{10} k_{11} - k_1 k_2 k_5 k_6 k_{10}^2 - k_1 k_2 k_5 k_7 k_{10}^2 - k_1 k_2 k_5 k_7 k_{10} k_{11} - k_1 k_2 k_6^2 k_9 k_{10} - k_1 k_2 k_6^2 k_{10}^2 - k_1 k_2 k_6 k_7 k_{10}^2 - k_1 k_2 k_6 k_7 k_{10} k_{11} - k_1 k_3^2 k_5 k_9 k_{10} + k_1 k_3 k_5 k_6 k_9 k_{10} - k_2^2 k_3 k_4 k_{11}^2 - k_2^2 k_4 k_6 k_{10} k_{11} - k_2^2 k_4 k_7 k_{10} k_{11} - k_2^2 k_4 k_7 k_{11}^2 - k_2 k_3^2 k_4 k_{11}^2 - k_2 k_3 k_4 k_6 k_{10} k_{11} - k_2 k_3 k_4 k_7 k_{10} k_{11} - k_2 k_3 k_4 k_7 k_{11}^2 \tag{1.11}$$

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

$$simpleLeft := (k_3 - k_6)\left(\frac{k_1 k_9 k_{10}}{k_2 + k_3} - \frac{k_4 k_8 k_{11}}{k_5 + k_6}\right) \tag{1.12}$$

> $simpleRight := \big((k_6 + k_7)\cdot k_{10} + k_{11}\cdot(k_3 + k_7)\big)\cdot\left(\frac{k_1}{k_2 + k_3}\cdot k_{10} + \frac{k_4}{k_5 + k_6}\cdot k_{11}\right)$

$$simpleRight := \big((k_6 + k_7) k_{10} + k_{11} (k_3 + k_7)\big)\left(\frac{k_1 k_{10}}{k_2 + k_3} + \frac{k_4 k_{11}}{k_5 + k_6}\right) \tag{1.13}$$

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(seq(10^(-3)·(10^6)^(i/1023), i = 0..1023)) :
    # association rates are considered to be 10^(-3) ~ 10^3 µM^(-1)·s^(-1)
> dissociationRate := evalf(seq(10^(-3)·(10^6)^(i/1023), i = 0..1023)) :
    #` `dissociation rates are considered to be 10^(-3) ~ 10^3 s^(-1)
> catalyticRate := evalf(seq(10^(-3)·(10^6)^(i/1023), i = 0..1023)) : # the range is 10^(-3) ~ 10^3 s^(-1)
> switchingRate := evalf(seq(10^(-3)·(10^9)^(i/1023), i = 0..1023)) :
    # the range is assumed as 10^(-3) ~ 10^6 s^(-1)
> concentration := evalf(seq(10^(-3)·(10^4)^(i/1023), i = 0..1023)) : # 1 molecule ≈ 2 nM,
    signaling protein : 10^(-3) ~ 10 µM
>
> randomize(413) :
> 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("bistable_space_rates.txt", APPEND, TEXT) :

> for number from 1 by 1 to 10000000 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]] :
    ps8 := switchingRate[rs[8]] :
    ps9 := switchingRate[rs[9]] :
```

```
    ps10 := switchingRate[rs[10]] :
    ps11 := switchingRate[rs[11]] :

    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} :
    inequalityLeft := evalf(subs(params, simpleLeft)) :
    inequalityRight := evalf(subs(params, simpleRight)) :
    monoBiSplit := [[ps1, ps2, ps3, ps4, ps5, ps6, ps7, ps8, ps9, ps10, ps11, inequalityLeft,
      inequalityRight, number]] :
    if inequalityLeft > inequalityRight then
      writedata(bistableSpaceRates, monoBiSplit) :
      finalPol2 := subs(params, finalPol) :
      #for x1 in concentration do
        x1 := concentration[roll( )] :
        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,
     inequalityLeft, inequalityRight, number]] :
          writedata(bistableSpacePositive, outParams) :
          if B1 >= 10^(-3) and B1 <= 10 and B2 >= 10^(-3) and B2 <= 10 then
            writedata(bistableSpaceRealistic, outParams) :
          end if:
        end if:
      #end do:
    #elif inequalityLeft <= inequalityRight then
    #    writedata(monostableSpaceRates, monoBiSplit) :
    end if:

  end do:
  close(bistableSpacePositive) :
  close(bistableSpaceRealistic) :
  close(bistableSpaceRates) :
  close(monostableSpaceRates) :

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