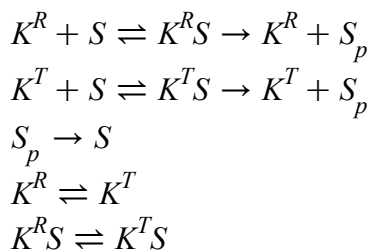
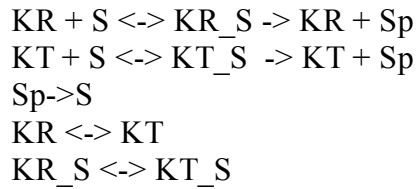


```
[> with(LinearAlgebra) :
[> interface(rtablesize = 40) :
[>
```

Simplification of minimal system extend 8

We consider the following reactions:



The species of the network are (in parenthesis 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

$$\begin{aligned}
 & \text{ks} := \text{Vector}([k_1 \cdot x_3 \cdot x_1, k_2 \cdot x_5, k_3 \cdot x_5, k_4 \cdot x_4 \cdot x_1, k_5 \cdot x_6, k_6 \cdot x_6, k_7 \cdot x_2, k_8 \cdot x_3, k_9 \cdot x_4, k_{10} \cdot x_5, k_{11} \cdot x_6]) \\
 & \text{ks} := \begin{bmatrix} k_1 x_3 x_1 \\ k_2 x_5 \\ k_3 x_5 \\ k_4 x_4 x_1 \\ k_5 x_6 \\ k_6 x_6 \\ k_7 x_2 \\ k_8 x_3 \\ k_9 x_4 \\ k_{10} x_5 \\ k_{11} x_6 \end{bmatrix} \quad (1)
 \end{aligned}$$

Steady state equations:

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

Conservation laws:

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

$$\begin{aligned} & \text{> } F := \text{ReducedRowEchelonForm}(\text{Transpose}(\text{Matrix}([\text{op}(\text{NullSpace}(\text{Transpose}(A)))]))) \\ & \quad F := \begin{bmatrix} 1 & 1 & 0 & 0 & 1 & 1 \\ 0 & 0 & 1 & 1 & 1 & 1 \end{bmatrix} \end{aligned} \quad (3)$$

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 $\text{myeqs}=0$ (because there are two conservation laws, two of the equations in eqs can be disregarded).

$$\begin{aligned} & \text{> } \text{subsEqs} := [\text{ssEqs}[2], \text{ssEqs}[4], \text{ssEqs}[5], \text{ssEqs}[6], x_1 + x_2 + x_5 + x_6 - T_1, x_3 + x_4 + x_5 \\ & \quad + x_6 - T_2] \\ & \text{subsEqs} := [k_3 x_5 + k_6 x_6 - k_7 x_2, -k_4 x_1 x_4 + k_5 x_6 + k_6 x_6 + k_8 x_3 - k_9 x_4, k_1 x_1 x_3 - k_2 x_5 \\ & \quad - k_3 x_5 - k_{10} x_5 + k_{11} x_6, k_4 x_1 x_4 - k_5 x_6 - k_6 x_6 + k_{10} x_5 - k_{11} x_6, x_1 + x_2 + x_5 + x_6 \\ & \quad - T_1, x_3 + x_4 + x_5 + x_6 - T_2] \end{aligned} \quad (4)$$

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)

$$\text{> } J := \text{VectorCalculus}[\text{Jacobian}](\text{subsEqs}, [\text{seq}(x_i, i = 1..6)]) \quad (1.1)$$

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

> Determinant(J) :

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

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

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]], [x₂, x₄, x₅, x₆])

$$\begin{aligned} \text{solution} := & \left[\begin{aligned} x_2 = & ((k_1 k_3 k_4 k_{11} x_1 + k_1 k_4 k_6 k_{10} x_1 + k_1 k_3 k_5 k_9 + k_1 k_3 k_6 k_9 \\ & + k_1 k_3 k_9 k_{11} + k_1 k_6 k_9 k_{10} + k_2 k_4 k_6 k_8 + k_3 k_4 k_6 k_8 + k_3 k_4 k_8 k_{11} + k_4 k_6 k_8 k_{10}) \end{aligned} \right] \quad (1.3) \end{aligned}$$

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

We evaluate the determinant of the Jacobian at the parameterisation. We then write it as a polynomial in x_1 and x_3

$$\begin{aligned}
& \text{detSubs} := \text{subs}(\text{solution}[1], \text{detJ}) \\
& \text{detSubs} := (-k_1 k_4 k_7 k_{10} - k_1 k_4 k_7 k_{11}) x_1^2 + (-k_1 k_3 k_4 k_8 - k_1 k_3 k_4 k_{11} + k_1 k_4 k_6 k_8 \\
& - k_1 k_4 k_6 k_{10} - k_1 k_4 k_7 k_{10} - k_1 k_4 k_7 k_{11}) x_1 x_3 + ((k_1 k_3 k_4 k_9 - k_1 k_3 k_4 k_{11} \\
& - k_1 k_4 k_6 k_9 - k_1 k_4 k_6 k_{10} - k_1 k_4 k_7 k_{10} - k_1 k_4 k_7 k_{11}) x_1 x_3 (k_1 k_5 k_{10} x_1 \\
& + k_1 k_6 k_{10} x_1 + k_2 k_5 k_8 + k_2 k_6 k_8 + k_2 k_8 k_{11} + k_3 k_5 k_8 + k_3 k_6 k_8 + k_3 k_8 k_{11} \\
& + k_5 k_8 k_{10} + k_6 k_8 k_{10})) / (k_2 k_4 k_{11} x_1 + k_3 k_4 k_{11} x_1 + k_2 k_5 k_9 + k_2 k_6 k_9 + k_2 k_9 k_{11} \\
& + k_3 k_5 k_9 + k_3 k_6 k_9 + k_3 k_9 k_{11} + k_5 k_9 k_{10} + k_6 k_9 k_{10}) + (-k_1 k_5 k_7 k_9 \\
& - k_1 k_5 k_7 k_{10} - k_1 k_6 k_7 k_9 - k_1 k_6 k_7 k_{10} - k_1 k_7 k_9 k_{10} - k_1 k_7 k_9 k_{11} - k_2 k_4 k_7 k_8 \\
& - k_2 k_4 k_7 k_{11} - k_3 k_4 k_7 k_8 - k_3 k_4 k_7 k_{11} - k_4 k_7 k_8 k_{10} - k_4 k_7 k_8 k_{11}) x_1 + (\\
& -k_1 k_3 k_5 k_8 - k_1 k_3 k_5 k_9 - k_1 k_3 k_6 k_8 - k_1 k_3 k_6 k_9 - k_1 k_3 k_8 k_{11} - k_1 k_3 k_9 k_{11} \\
& - k_1 k_5 k_7 k_8 - k_1 k_5 k_7 k_9 - k_1 k_6 k_7 k_8 - k_1 k_6 k_7 k_9 - k_1 k_6 k_8 k_{10} - k_1 k_6 k_9 k_{10}
\end{aligned} \tag{1.4}$$

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

\triangleright *polSubs* := *numer*(*detSubs*) :

\triangleright *finalPol* := *collect*(*polSubs*, {*x*₁, *x*₃}, 'distributed')

$$finalPol := (-k_1 k_2 k_4^2 k_7 k_{10} k_{11} - k_1 k_2 k_4^2 k_7 k_{11}^2 - k_1 k_3 k_4^2 k_7 k_{10} k_{11} - k_1 k_3 k_4^2 k_7 k_{11}^2) x_1^3 \quad (1.5)$$

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

$$\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}$$

$$\begin{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
\end{aligned}$$

$$\begin{aligned}
& -2k_3k_4k_5k_6k_8^2k_{10} - 2k_3k_4k_5k_6k_8k_9k_{10} - 2k_3k_4k_5k_7k_8^2k_{10} - k_3k_4k_5k_7k_8^2k_{11} \\
& - 2k_3k_4k_5k_7k_8k_9k_{10} - k_3k_4k_5k_7k_8k_9k_{11} - k_3k_4k_5k_8^2k_{10}k_{11} \\
& - k_3k_4k_5k_8k_9k_{10}k_{11} - 2k_3k_4k_6^2k_8^2k_{10} - 2k_3k_4k_6^2k_8k_9k_{10} - 2k_3k_4k_6k_7k_8^2k_{10} \\
& - k_3k_4k_6k_7k_8^2k_{11} - 2k_3k_4k_6k_7k_8k_9k_{10} - k_3k_4k_6k_7k_8k_9k_{11} - 2k_3k_4k_6 \\
& k_8^2k_{10}k_{11} - 2k_3k_4k_6k_8k_9k_{10}k_{11} - k_3k_4k_7k_8^2k_{10}k_{11} - k_3k_4k_7k_8^2k_{11}^2 \\
& - k_3k_4k_7k_8k_9k_{10}k_{11} - k_3k_4k_7k_8k_9k_{11}^2 - k_4k_5k_6k_8^2k_{10}^2 - k_4k_5k_6k_8k_9k_{10}^2 \\
& - k_4k_5k_7k_8^2k_{10}^2 - k_4k_5k_7k_8^2k_{10}k_{11} - k_4k_5k_7k_8k_9k_{10}^2 - k_4k_5k_7k_8k_9k_{10}k_{11} - k_4 \\
& k_6^2k_8^2k_{10}^2 - k_4k_6^2k_8k_9k_{10}^2 - k_4k_6k_7k_8^2k_{10}^2 - k_4k_6k_7k_8^2k_{10}k_{11} - k_4k_6k_7k_8k_9k_{10}^2 \\
& - k_4k_6k_7k_8k_9k_{10}k_{11} \Big) x_3 - k_2^2k_6^2k_7k_8k_9 - 2k_2^2k_6k_7k_9^2k_{11} - k_2^2k_7k_8k_9k_{11}^2 \\
& - 2k_2k_3k_5^2k_7k_9^2 - 2k_2k_3k_6^2k_7k_9^2 - 2k_2k_3k_7k_9^2k_{11}^2 - 2k_2k_5^2k_7k_9^2k_{10} - 2k_2k_6^2k_7 \\
& k_9^2k_{10} - k_3^2k_5^2k_7k_8k_9 - 2k_3^2k_5k_6k_7k_9^2 - 2k_3^2k_5k_7k_9^2k_{11} - k_3^2k_6^2k_7k_8k_9 - 2k_3^2k_6k_7 \\
& k_9^2k_{11} - k_3^2k_7k_8k_9k_{11}^2 - 2k_3k_5^2k_7k_9^2k_{10} - 2k_3k_6^2k_7k_9^2k_{10} - k_5^2k_7k_8k_9k_{10}^2 \\
& - 2k_5k_6k_7k_9^2k_{10}^2 - k_6^2k_7k_8k_9k_{10}^2 - k_2^2k_5^2k_7k_8k_9 - 2k_2^2k_5k_6k_7k_9^2 - 2k_2^2k_5k_7 \\
& k_9^2k_{11} - 4k_2k_5k_6k_7k_9^2k_{10} - 2k_2k_5k_7k_9^2k_{10}k_{11} - 2k_2k_6^2k_7k_8k_9k_{10} - 2k_2k_6k_7 \\
& k_9^2k_{10}k_{11} - 2k_3^2k_5k_6k_7k_8k_9 - 2k_3^2k_5k_7k_8k_9k_{11} - 2k_3^2k_6k_7k_8k_9k_{11} - 2k_3 \\
& k_5^2k_7k_8k_9k_{10} - 4k_3k_5k_6k_7k_9^2k_{10} - 2k_3k_5k_7k_9^2k_{10}k_{11} - 2k_3k_6^2k_7k_8k_9k_{10} \\
& - 2k_3k_6k_7k_9^2k_{10}k_{11} - 2k_5k_6k_7k_8k_9k_{10}^2 - 2k_2^2k_5k_6k_7k_8k_9 - 2k_2^2k_5k_7k_8k_9k_{11} \\
& - 2k_2^2k_6k_7k_8k_9k_{11} - 2k_2k_3k_5^2k_7k_8k_9 - 4k_2k_3k_5k_6k_7k_9^2 - 4k_2k_3k_5k_7k_9^2k_{11} \\
& - 2k_2k_3k_6^2k_7k_8k_9 - 4k_2k_3k_6k_7k_9^2k_{11} - 2k_2k_3k_7k_8k_9k_{11}^2 - 2k_2k_5^2k_7k_8k_9k_{10} \\
& + \left(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} - \right. \\
& 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_4 \\
& k_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_1k_2k_4^2k_6k_8k_{11} - k_1k_2k_4^2k_6k_{10}k_{11} - k_1k_2k_4^2k_7k_{10}k_{11} - k_1k_2 \\
& k_4^2k_7k_{11}^2 - k_1k_3^2k_4^2k_8k_{11} - k_1k_3^2k_4^2k_{11}^2 + k_1k_3k_4^2k_6k_8k_{11} - k_1k_3k_4^2k_6k_{10}k_{11} \\
& - k_1k_3k_4^2k_7k_{10}k_{11} - k_1k_3k_4^2k_7k_{11}^2 \Big) x_1^2x_3 + \left(-2k_1k_2k_3k_4k_5k_8k_{11} \right. \\
& - 2k_1k_2k_3k_4k_5k_9k_{11} - 2k_1k_2k_3k_4k_6k_8k_{11} - 2k_1k_2k_3k_4k_6k_9k_{11} \\
& \left. - 2k_1k_2k_3k_4k_8k_{11}^2 - 2k_1k_2k_3k_4k_9k_{11}^2 - 2k_1k_2k_4k_5k_6k_8k_{10} \right.
\end{aligned}$$

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

>

We look at the coefficients of mypol in x1 and x3 that do not have necessarily negative sign. (????)

I did it manually, but I only see one such term:

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

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

> *factor(term)*

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

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

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

>

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

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

>

>

"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)*

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

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

$$k_4^2 k_6 k_{10} k_{11} - k_1 k_3 k_4^2 k_7 k_{10} k_{11} - k_1 k_3 k_4^2 k_7 k_{11}^2$$

> *factor(constraintTerm)*

$$- \frac{1}{k_2} \left(k_1 k_4 \left(k_1 k_2 k_3 k_5 k_{10} k_{11} - k_1 k_2 k_3 k_6 k_9 k_{10} + k_1 k_2 k_3 k_6 k_{10} k_{11} + k_1 k_2 k_5 k_6 k_{10}^2 \right. \right. \quad (1.10)$$

$$+ k_1 k_2 k_5 k_7 k_{10}^2 + k_1 k_2 k_5 k_7 k_{10} k_{11} + k_1 k_2 k_6^2 k_9 k_{10} + k_1 k_2 k_6^2 k_{10}^2 + k_1 k_2 k_6 k_7 k_{10}^2$$

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

$$k_2^2 k_4 k_6 k_{10} k_{11} + k_2^2 k_4 k_7 k_{10} k_{11} + k_2^2 k_4 k_7 k_{11}^2 + k_2 k_3^2 k_4 k_{11}^2 + k_2 k_3 k_4 k_6 k_{10} k_{11}$$

$$\left. \left. + k_2 k_3 k_4 k_7 k_{10} k_{11} + k_2 k_3 k_4 k_7 k_{11}^2 \right) \right)$$

$$> \text{finalTerm} := - \left(k_1 k_2 k_3 k_5 k_{10} k_{11} - k_1 k_2 k_3 k_6 k_9 k_{10} + k_1 k_2 k_3 k_6 k_{10} k_{11} + k_1 k_2 k_5 k_6 k_{10}^2 \right.$$

$$+ k_1 k_2 k_5 k_7 k_{10}^2 + k_1 k_2 k_5 k_7 k_{10} k_{11} + k_1 k_2 k_6^2 k_9 k_{10} + k_1 k_2 k_6^2 k_{10}^2 + k_1 k_2 k_6 k_7 k_{10}^2$$

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

$$k_2^2 k_4 k_6 k_{10} k_{11} + k_2^2 k_4 k_7 k_{10} k_{11} + k_2^2 k_4 k_7 k_{11}^2 + k_2 k_3^2 k_4 k_{11}^2 + k_2 k_3 k_4 k_6 k_{10} k_{11}$$

$$\left. \left. + k_2 k_3 k_4 k_7 k_{10} k_{11} + k_2 k_3 k_4 k_7 k_{11}^2 \right) \right)$$

$$\text{finalTerm} := -k_1 k_2 k_3 k_5 k_{10} k_{11} + k_1 k_2 k_3 k_6 k_9 k_{10} - k_1 k_2 k_3 k_6 k_{10} k_{11} - k_1 k_2 k_5 k_6 k_{10}^2 \quad (1.11)$$

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

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

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

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

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

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

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

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

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 · (106) $\frac{i}{1023}$ , i = 0 .. 1023)) :  
# association rates are considered to be 10-3 ~ 103 μM-1 · s-1  
> dissociationRate := evalf(seq(10-3 · (106) $\frac{i}{1023}$ , i = 0 .. 1023)) :  
# `dissociation rates are considered to be 10-3 ~ 103 s-1  
> catalyticRate := evalf(seq(10-3 · (106) $\frac{i}{1023}$ , i = 0 .. 1023)) : # the range is 10-3 ~ 103 s-1  
> switchingRate := evalf(seq(10-3 · (109) $\frac{i}{1023}$ , i = 0 .. 1023)) :  
# the range is assumed as 10-3 ~ 106 s-1  
> concentration := evalf(seq(10-3 · (104) $\frac{i}{1023}$ , 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  $B1 \geq 10^{-3}$  and  $B1 \leq 10$  and  $B2 \geq 10^{-3}$  and  $B2 \leq 10$  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) :

```

```

#####

```