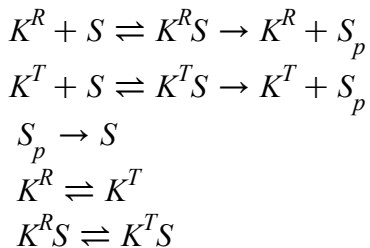
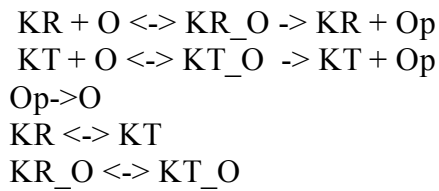


```
[> with(LinearAlgebra) :
[> interface(rtablesize = 40) :
[>
```

### 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)

{O (1), Op (2), KR (3), KT (4), KR\_O (5), KT\_O (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

$$dx/dt = A.krates$$

and hence steady states are given as  $A.krates = 0$ .

*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

```

> krates := Vector([k1·x3·x1, k2·x5, k3·x5, k4·x4·x1, k5·x6, k6·x6, k7·x2, k8·x3, k9·x4, k10·x5, k11
·x6])

```

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

Steady state equations:

```

> eqs := A.krates

```

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

Conservation laws:

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

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

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  $\text{eqs}$  can be disregarded).

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

##### Original computed paramters #####

The following set of parameters give three steady states, two stable and one unstable:

$$\begin{aligned} \text{params} &:= \{k_1 = 0.1, k_2 = 0.1, k_3 = 0.1, k_4 = 0.1, k_5 = 0.1, k_7 = 0.1, k_9 = 0.1, k_{10} = 0.1, k_{11} = 0.1, k_6 \\ &= 10, k_8 = 10000, T_1 := 3.081835511 \cdot 10^6, T_2 := 41216.17056\} : \end{aligned}$$

These parameters are for sure not reasonable, but one can play to change them. To do that, look at the Computations section.

There are three positive steady states for some total amounts if and only if the following expression on the rate constants is positive

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

As I said, the theory supporting this claim is not yet published, but the procedure above gives a way to generate parameters with three steady states.

```
##### Original computed parameters #####
#####
```

## 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)

$$\begin{aligned} &> J := \text{VectorCalculus}[\text{Jacobian}](\text{myeqs}, [\text{seq}(x_i, i = 1..6)]) \\ J := &\begin{bmatrix} 0 & -k_7 & 0 & 0 & k_3 & k_6 \\ -k_4 x_4 & 0 & k_8 & -k_4 x_1 - k_9 & 0 & k_5 + k_6 \\ k_1 x_3 & 0 & k_1 x_1 & 0 & -k_2 - k_3 - k_{10} & k_{11} \\ k_4 x_4 & 0 & 0 & k_4 x_1 & k_{10} & -k_5 - k_6 - k_{11} \\ 1 & 1 & 0 & 0 & 1 & 1 \\ 0 & 0 & 1 & 1 & 1 & 1 \end{bmatrix} \end{aligned} \quad (1.1)$$

> Determinant(J) :

> mydet := collect(%, {seq(x\_i, i = 1..6)}, 'distributed')

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

$$\begin{aligned}
& -k_4 k_7 k_8 k_{11} - k_4 k_7 k_9 k_{10} - k_4 k_7 k_9 k_{11}) x_4 - k_2 k_5 k_7 k_8 - k_2 k_5 k_7 k_9 - k_2 k_6 k_7 k_8 \\
& - k_2 k_6 k_7 k_9 - k_2 k_7 k_8 k_{11} - k_2 k_7 k_9 k_{11} - k_3 k_5 k_7 k_8 - k_3 k_5 k_7 k_9 - k_3 k_6 k_7 k_8 \\
& - k_3 k_6 k_7 k_9 - k_3 k_7 k_8 k_{11} - k_3 k_7 k_9 k_{11} - k_5 k_7 k_8 k_{10} - k_5 k_7 k_9 k_{10} - k_6 k_7 k_8 k_{10} \\
& - k_6 k_7 k_9 k_{10}
\end{aligned}$$

We parameterise the steady states as functions of  $x_1$  and  $x_3$ , using the four steady state equations:  
When  $x_1$  and  $x_3$  are positive, then so are the rest.

$$\begin{aligned}
& \text{sol} := \text{solve}([myeqs[2], myeqs[3], myeqs[4], myeqs[1]], [x_2, x_4, x_5, x_6]) \\
& \text{sol} := \left[ \left[ x_2 = \left( (k_1 k_3 k_4 k_{11} x_1 + k_1 k_4 k_6 k_{10} x_1 + k_1 k_3 k_5 k_9 + k_1 k_3 k_6 k_9 + k_1 k_3 k_9 k_{11} \right. \right. \right. \quad (1.3) \\
& \quad \left. \left. \left. + k_1 k_6 k_9 k_{10} + k_2 k_4 k_6 k_8 + k_3 k_4 k_6 k_8 + k_3 k_4 k_8 k_{11} + k_4 k_6 k_8 k_{10} \right) x_1 x_3 \right) / \right. \\
& \quad \left( k_7 (k_2 k_4 k_{11} x_1 + k_3 k_4 k_{11} x_1 + k_2 k_5 k_9 + k_2 k_6 k_9 + k_2 k_9 k_{11} + k_3 k_5 k_9 + k_3 k_6 k_9 \right. \\
& \quad \left. \left. + k_3 k_9 k_{11} + k_5 k_9 k_{10} + k_6 k_9 k_{10} \right) \right), x_4 = (x_3 (k_1 k_5 k_{10} x_1 + k_1 k_6 k_{10} x_1 \\
& \quad \left. + k_2 k_5 k_8 + k_2 k_6 k_8 + k_2 k_8 k_{11} + k_3 k_5 k_8 + k_3 k_6 k_8 + k_3 k_8 k_{11} + k_5 k_8 k_{10} \right. \\
& \quad \left. \left. + k_6 k_8 k_{10} \right) \right) / (k_2 k_4 k_{11} x_1 + k_3 k_4 k_{11} x_1 + k_2 k_5 k_9 + k_2 k_6 k_9 + k_2 k_9 k_{11} + k_3 k_5 k_9 \\
& \quad \left. + k_3 k_6 k_9 + k_3 k_9 k_{11} + k_5 k_9 k_{10} + k_6 k_9 k_{10} \right), x_5 = (x_1 x_3 (k_1 k_4 k_{11} x_1 + k_1 k_5 k_9 \\
& \quad \left. + k_1 k_6 k_9 + k_1 k_9 k_{11} + k_4 k_8 k_{11} \right) \right) / (k_2 k_4 k_{11} x_1 + k_3 k_4 k_{11} x_1 + k_2 k_5 k_9 + k_2 k_6 k_9 \\
& \quad \left. + k_2 k_9 k_{11} + k_3 k_5 k_9 + k_3 k_6 k_9 + k_3 k_9 k_{11} + k_5 k_9 k_{10} + k_6 k_9 k_{10} \right), x_6 \\
& = \left( (k_1 k_4 k_{10} x_1 + k_1 k_9 k_{10} + k_2 k_4 k_8 + k_3 k_4 k_8 + k_4 k_8 k_{10}) x_1 x_3 \right) / (k_2 k_4 k_{11} x_1 \\
& \quad + k_3 k_4 k_{11} x_1 + k_2 k_5 k_9 + k_2 k_6 k_9 + k_2 k_9 k_{11} + k_3 k_5 k_9 + k_3 k_6 k_9 + k_3 k_9 k_{11} \\
& \quad \left. + k_5 k_9 k_{10} + k_6 k_9 k_{10} \right) ] ]
\end{aligned}$$

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

x1 and x3

**>** *detsubs* := *subs(sol[1], mydet)*

$$\begin{aligned} \text{detsubs} := & \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 \right. \\ & - k_1 k_4 k_6 k_{10} - k_1 k_4 k_7 k_{10} - k_1 k_4 k_7 k_{11} \left. \right) x_1 x_3 + \left( \left( k_1 k_3 k_4 k_9 - k_1 k_3 k_4 k_{11} \right. \right. \\ & - 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} \left. \right) x_1 x_3 \left( k_1 k_5 k_{10} x_1 \right. \\ & + 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} \left. \right) \left. \right) / \left( 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} \right. \\ & + 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} \left. \right) + \left( -k_1 k_5 k_7 k_9 \right. \\ & - 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} \left. \right) x_1 + \left( \right. \\ & - 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} \left. \right) x_3 + \left( \left( -k_2 k_4 k_6 k_8 \right. \right. \\ & - 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} \left. \right) x_3 \left( k_1 k_5 k_{10} x_1 + k_1 k_6 k_{10} x_1 + k_2 k_5 k_8 \right. \\ & + 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} \left. \right) \left. \right) / \\ & \left( 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 \right. \\ & + k_3 k_9 k_{11} + k_5 k_9 k_{10} + k_6 k_9 k_{10} \left. \right) - 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 (1.4)$$

**>** *polsubs* := *numer(detsubs)* :

**>** *mypol* := *collect(polsubs, {x1, x3}, 'distributed')* :

**>** *mypol*

$$\begin{aligned} & -2 k_2^2 k_5 k_6 k_7 k_8 k_9 - 2 k_2^2 k_5 k_7 k_8 k_9 k_{11} - 2 k_2^2 k_6 k_7 k_8 k_9 k_{11} - 2 k_2 k_3 k_5^2 k_7 k_8 k_9 \\ & - 4 k_2 k_3 k_5 k_6 k_7 k_9^2 - 4 k_2 k_3 k_5 k_7 k_9^2 k_{11} - 2 k_2 k_3 k_6^2 k_7 k_8 k_9 - 4 k_2 k_3 k_6 k_7 k_9^2 k_{11} \\ & - 2 k_2 k_3 k_7 k_8 k_9 k_{11}^2 - 2 k_2 k_5^2 k_7 k_8 k_9 k_{10} - 4 k_2 k_5 k_6 k_7 k_9^2 k_{10} - 2 k_2 k_5 k_7 k_9^2 k_{10} k_{11} \\ & - 2 k_2 k_6^2 k_7 k_8 k_9 k_{10} - 2 k_2 k_6 k_7 k_9^2 k_{10} k_{11} - 2 k_3^2 k_5 k_6 k_7 k_8 k_9 - 2 k_3^2 k_5 k_7 k_8 k_9 k_{11} \\ & - 2 k_3^2 k_6 k_7 k_8 k_9 k_{11} - 2 k_3 k_5^2 k_7 k_8 k_9 k_{10} - 4 k_3 k_5 k_6 k_7 k_9^2 k_{10} - 2 k_3 k_5 k_7 k_9^2 k_{10} k_{11} \end{aligned} \quad (1.5)$$

$$\begin{aligned}
& -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 + ( \\
& -k_1k_2k_4k_5k_7k_9k_{10} - 2k_1k_2k_4k_5k_7k_9k_{11} - k_1k_2k_4k_5k_7k_{10}k_{11} \\
& - k_1k_2k_4k_6k_7k_9k_{10} - 2k_1k_2k_4k_6k_7k_9k_{11} - k_1k_2k_4k_6k_7k_{10}k_{11} \\
& - 2k_1k_2k_4k_7k_9k_{10}k_{11} - 2k_1k_2k_4k_7k_9k_{11}^2 - k_1k_3k_4k_5k_7k_9k_{10} \\
& - 2k_1k_3k_4k_5k_7k_9k_{11} - k_1k_3k_4k_5k_7k_{10}k_{11} - k_1k_3k_4k_6k_7k_9k_{10} \\
& - 2k_1k_3k_4k_6k_7k_9k_{11} - k_1k_3k_4k_6k_7k_{10}k_{11} - 2k_1k_3k_4k_7k_9k_{10}k_{11} \\
& - 2k_1k_3k_4k_7k_9k_{11}^2 - k_1k_4k_5k_7k_9k_{10}^2 - k_1k_4k_5k_7k_9k_{10}k_{11} - k_1k_4k_6k_7k_9k_{10}^2 \\
& - k_1k_4k_6k_7k_9k_{10}k_{11} - k_2^2k_4^2k_7k_8k_{11} - k_2^2k_4^2k_7k_{11}^2 - 2k_2k_3k_4^2k_7k_8k_{11} - 2k_2k_3 \\
& k_4^2k_7k_{11}^2 - k_2k_4^2k_7k_8k_{10}k_{11} - k_2k_4^2k_7k_8k_{11}^2 - k_3^2k_4^2k_7k_8k_{11} - k_3^2k_4^2k_7k_{11}^2 - k_3 \\
& k_4^2k_7k_8k_{10}k_{11} - k_3k_4^2k_7k_8k_{11}^2) x_1^2 + (-k_1k_2k_4^2k_7k_{10}k_{11} - k_1k_2k_4^2k_7k_{11}^2 - k_1k_3 \\
& k_4^2k_7k_{10}k_{11} - k_1k_3k_4^2k_7k_{11}^2) x_1^3 + (-k_1k_2k_5^2k_7k_9^2 - k_1k_2k_5^2k_7k_9k_{10} \\
& - 2k_1k_2k_5k_6k_7k_9^2 - 2k_1k_2k_5k_6k_7k_9k_{10} - k_1k_2k_5k_7k_9^2k_{10} - 2k_1k_2k_5k_7k_9^2k_{11} \\
& - k_1k_2k_5k_7k_9k_{10}k_{11} - k_1k_2k_6^2k_7k_9^2 - k_1k_2k_6^2k_7k_9k_{10} - k_1k_2k_6k_7k_9^2k_{10} \\
& - 2k_1k_2k_6k_7k_9^2k_{11} - k_1k_2k_6k_7k_9k_{10}k_{11} - k_1k_2k_7k_9^2k_{10}k_{11} - k_1k_2k_7k_9^2k_{11}^2 \\
& - k_1k_3k_5^2k_7k_9^2 - k_1k_3k_5^2k_7k_9k_{10} - 2k_1k_3k_5k_6k_7k_9^2 - 2k_1k_3k_5k_6k_7k_9k_{10} \\
& - k_1k_3k_5k_7k_9^2k_{10} - 2k_1k_3k_5k_7k_9^2k_{11} - k_1k_3k_5k_7k_9k_{10}k_{11} - k_1k_3k_6^2k_7k_9^2 \\
& - k_1k_3k_6^2k_7k_9k_{10} - k_1k_3k_6k_7k_9^2k_{10} - 2k_1k_3k_6k_7k_9^2k_{11} - k_1k_3k_6k_7k_9k_{10}k_{11} \\
& - k_1k_3k_7k_9^2k_{10}k_{11} - k_1k_3k_7k_9^2k_{11}^2 - k_1k_5^2k_7k_9^2k_{10} - k_1k_5^2k_7k_9k_{10}^2 - 2k_1k_5k_6k_7 \\
& k_9^2k_{10} - 2k_1k_5k_6k_7k_9k_{10}^2 - k_1k_5k_7k_9^2k_{10}^2 - k_1k_5k_7k_9^2k_{10}k_{11} - k_1k_6^2k_7k_9^2k_{10} - k_1 \\
& k_6^2k_7k_9k_{10}^2 - k_1k_6k_7k_9^2k_{10}^2 - k_1k_6k_7k_9^2k_{10}k_{11} - k_2^2k_4k_5k_7k_8k_9 - k_2^2k_4k_5k_7k_8k_{11} \\
& - 2k_2^2k_4k_5k_7k_9k_{11} - k_2^2k_4k_6k_7k_8k_9 - k_2^2k_4k_6k_7k_8k_{11} - 2k_2^2k_4k_6k_7k_9k_{11} - \\
& k_2^2k_4k_7k_8k_9k_{11} - k_2^2k_4k_7k_8k_{11}^2 - 2k_2^2k_4k_7k_9k_{11}^2 - 2k_2k_3k_4k_5k_7k_8k_9 \\
& - 2k_2k_3k_4k_5k_7k_8k_{11} - 4k_2k_3k_4k_5k_7k_9k_{11} - 2k_2k_3k_4k_6k_7k_8k_9 \\
& - 2k_2k_3k_4k_6k_7k_8k_{11} - 4k_2k_3k_4k_6k_7k_9k_{11} - 2k_2k_3k_4k_7k_8k_9k_{11} \\
& - 2k_2k_3k_4k_7k_8k_{11}^2 - 4k_2k_3k_4k_7k_9k_{11}^2 - 2k_2k_4k_5k_7k_8k_9k_{10} \\
& - k_2k_4k_5k_7k_8k_9k_{11} - k_2k_4k_5k_7k_8k_{10}k_{11} - 2k_2k_4k_5k_7k_9k_{10}k_{11} \\
& - 2k_2k_4k_6k_7k_8k_9k_{10} - k_2k_4k_6k_7k_8k_9k_{11} - k_2k_4k_6k_7k_8k_{10}k_{11}
\end{aligned}$$

$$\begin{aligned}
& -2k_2k_4k_6k_7k_9k_{10}k_{11} - k_2k_4k_7k_8k_9k_{10}k_{11} - k_2k_4k_7k_8k_9k_{11}^2 - k_3^2k_4k_5k_7k_8k_9 \\
& - k_3^2k_4k_5k_7k_8k_{11} - 2k_3^2k_4k_5k_7k_9k_{11} - k_3^2k_4k_6k_7k_8k_9 - k_3^2k_4k_6k_7k_8k_{11} - 2 \\
& k_3^2k_4k_6k_7k_9k_{11} - k_3^2k_4k_7k_8k_9k_{11} - k_3^2k_4k_7k_8k_{11}^2 - 2k_3^2k_4k_7k_9k_{11}^2 \\
& - 2k_3k_4k_5k_7k_8k_9k_{10} - k_3k_4k_5k_7k_8k_9k_{11} - k_3k_4k_5k_7k_8k_{10}k_{11} \\
& - 2k_3k_4k_5k_7k_9k_{10}k_{11} - 2k_3k_4k_6k_7k_8k_9k_{10} - k_3k_4k_6k_7k_8k_9k_{11} \\
& - k_3k_4k_6k_7k_8k_{10}k_{11} - 2k_3k_4k_6k_7k_9k_{10}k_{11} - k_3k_4k_7k_8k_9k_{10}k_{11} \\
& - k_3k_4k_7k_8k_9k_{11}^2 - k_4k_5k_7k_8k_9k_{10}^2 - k_4k_5k_7k_8k_9k_{10}k_{11} - k_4k_6k_7k_8k_9k_{10}^2 \\
& - k_4k_6k_7k_8k_9k_{10}k_{11} \Big) x_1 + \Big( -k_1k_2k_3k_5^2k_8k_9 - k_1k_2k_3k_5^2k_9^2 \\
& - 2k_1k_2k_3k_5k_6k_8k_9 - 2k_1k_2k_3k_5k_6k_9^2 - 2k_1k_2k_3k_5k_8k_9k_{11} - 2k_1k_2k_3k_5 \\
& k_9^2k_{11} - k_1k_2k_3k_6^2k_8k_9 - k_1k_2k_3k_6^2k_9^2 - 2k_1k_2k_3k_6k_8k_9k_{11} - 2k_1k_2k_3k_6k_9^2k_{11} \\
& - k_1k_2k_3k_8k_9k_{11}^2 - k_1k_2k_3k_9^2k_{11}^2 - k_1k_2k_5^2k_7k_8k_9 - k_1k_2k_5^2k_7k_9^2 \\
& - 2k_1k_2k_5k_6k_7k_8k_9 - 2k_1k_2k_5k_6k_7k_9^2 - k_1k_2k_5k_6k_8k_9k_{10} - k_1k_2k_5k_6k_9^2k_{10} \\
& - k_1k_2k_5k_7k_8k_9k_{10} - 2k_1k_2k_5k_7k_8k_9k_{11} - k_1k_2k_5k_7k_9^2k_{10} - 2k_1k_2k_5k_7k_9^2k_{11} \\
& - k_1k_2k_6^2k_7k_8k_9 - k_1k_2k_6^2k_7k_9^2 - k_1k_2k_6^2k_8k_9k_{10} - k_1k_2k_6^2k_9^2k_{10} \\
& - k_1k_2k_6k_7k_8k_9k_{10} - 2k_1k_2k_6k_7k_8k_9k_{11} - k_1k_2k_6k_7k_9^2k_{10} - 2k_1k_2k_6k_7k_9^2k_{11} \\
& - k_1k_2k_6k_8k_9k_{10}k_{11} - k_1k_2k_6k_9^2k_{10}k_{11} - k_1k_2k_7k_8k_9k_{10}k_{11} - k_1k_2k_7k_8k_9k_{11}^2 \\
& - k_1k_2k_7k_9^2k_{10}k_{11} - k_1k_2k_7k_9^2k_{11}^2 - k_1k_3^2k_5^2k_8k_9 - k_1k_3^2k_5^2k_9^2 - 2k_1k_3^2k_5k_6k_8k_9 \\
& - 2k_1k_3^2k_5k_6k_9^2 - 2k_1k_3^2k_5k_8k_9k_{11} - 2k_1k_3^2k_5k_9^2k_{11} - k_1k_3^2k_6^2k_8k_9 - k_1k_3^2k_6^2k_9^2 \\
& - 2k_1k_3^2k_6k_8k_9k_{11} - 2k_1k_3^2k_6k_9^2k_{11} - k_1k_3^2k_8k_9k_{11}^2 - k_1k_3^2k_9^2k_{11}^2 - k_1k_3 \\
& k_5^2k_7k_8k_9 - k_1k_3k_5^2k_7k_9^2 - k_1k_3k_5^2k_8k_9k_{10} - k_1k_3k_5^2k_9^2k_{10} - 2k_1k_3k_5k_6k_7k_8k_9 \\
& - 2k_1k_3k_5k_6k_7k_9^2 - 3k_1k_3k_5k_6k_8k_9k_{10} - 3k_1k_3k_5k_6k_9^2k_{10} \\
& - k_1k_3k_5k_7k_8k_9k_{10} - 2k_1k_3k_5k_7k_8k_9k_{11} - k_1k_3k_5k_7k_9^2k_{10} - 2k_1k_3k_5k_7k_9^2k_{11} \\
& - k_1k_3k_5k_8k_9k_{10}k_{11} - k_1k_3k_5k_9^2k_{10}k_{11} - k_1k_3k_6^2k_7k_8k_9 - k_1k_3k_6^2k_7k_9^2 \\
& - 2k_1k_3k_6^2k_8k_9k_{10} - 2k_1k_3k_6^2k_9^2k_{10} - k_1k_3k_6k_7k_8k_9k_{10} - 2k_1k_3k_6k_7k_8k_9k_{11} \\
& - k_1k_3k_6k_7k_9^2k_{10} - 2k_1k_3k_6k_7k_9^2k_{11} - 2k_1k_3k_6k_8k_9k_{10}k_{11} - 2k_1k_3k_6 \\
& k_9^2k_{10}k_{11} - k_1k_3k_7k_8k_9k_{10}k_{11} - k_1k_3k_7k_8k_9k_{11}^2 - k_1k_3k_7k_9^2k_{10}k_{11} - k_1k_3k_7k_9^2 \\
& k_{11}^2 - k_1k_5^2k_7k_8k_9k_{10} - k_1k_5^2k_7k_9^2k_{10} - 2k_1k_5k_6k_7k_8k_9k_{10} - 2k_1k_5k_6k_7k_9^2k_{10}
\end{aligned}$$



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

$$\begin{aligned}
& 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} - 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} + ( \\
& 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) x_1^2 x_3 + (-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
\end{aligned}$$

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

**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:

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

$> \text{factor}(\text{term})$

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

**"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:

$$\begin{aligned}
> \text{thermo} := & \left[ k[8] = \frac{k[1]k[10]k[5]k[9]}{k[11]k[4]k[2]} \right] : \\
> \text{constraintTerm} := & \text{subs}(\text{thermo}, \text{term})
\end{aligned}$$

$$\begin{aligned}
\text{constraintTerm} := & -k_1^2 k_3 k_4 k_5 k_{10} k_{11} + k_1^2 k_3 k_4 k_6 k_9 k_{10} - k_1^2 k_3 k_4 k_6 k_{10} k_{11} - k_1^2 k_4 k_5 k_6 \\
& k_{10}^2 - k_1^2 k_4 k_5 k_7 k_{10}^2 - k_1^2 k_4 k_5 k_7 k_{10} k_{11} - k_1^2 k_4 k_6^2 k_9 k_{10} - k_1^2 k_4 k_6^2 k_{10}^2 - k_1^2 k_4 k_6 k_7 \\
& k_{10}^2 - k_1^2 k_4 k_6 k_7 k_{10} k_{11} - k_1 k_2 k_3 k_4^2 k_{11}^2 - k_1 k_2 k_4^2 k_6 k_{10} k_{11} - k_1 k_2 k_4^2 k_7 k_{10} k_{11} \\
& - k_1 k_2 k_4^2 k_7 k_{11}^2 - \frac{k_1^2 k_3^2 k_4 k_{10} k_5 k_9}{k_2} - k_1 k_3^2 k_4^2 k_{11}^2 + \frac{k_1^2 k_3 k_4 k_6 k_{10} k_5 k_9}{k_2} - k_1 k_3 \\
& k_4^2 k_6 k_{10} k_{11} - k_1 k_3 k_4^2 k_7 k_{10} k_{11} - k_1 k_3 k_4^2 k_7 k_{11}^2
\end{aligned} \tag{1.7}$$

$$\begin{aligned}
& \text{factor}(\text{constraintTerm}) \\
& - \frac{1}{k_2} \left( k_1 k_4 \left( k_1 k_2 k_3 k_5 k_{10} k_{11} - k_1 k_2 k_3 k_6 k_9 k_{10} + k_1 k_2 k_3 k_6 k_{10} k_{11} + k_1 k_2 k_5 k_6 k_{10}^2 \right. \right. \\
& \quad + k_1 k_2 k_5 k_7 k_{10}^2 + k_1 k_2 k_5 k_7 k_{10} k_{11} + k_1 k_2 k_6^2 k_9 k_{10} + k_1 k_2 k_6^2 k_{10}^2 + k_1 k_2 k_6 k_7 k_{10}^2 \\
& \quad + k_1 k_2 k_6 k_7 k_{10} k_{11} + k_1 k_3^2 k_5 k_9 k_{10} - k_1 k_3 k_5 k_6 k_9 k_{10} + k_2^2 k_3 k_4 k_{11}^2 + \\
& \quad k_2^2 k_4 k_6 k_{10} k_{11} + k_2^2 k_4 k_7 k_{10} k_{11} + k_2^2 k_4 k_7 k_{11}^2 + k_2 k_3^2 k_4 k_{11}^2 + k_2 k_3 k_4 k_6 k_{10} k_{11} \\
& \quad \left. \left. + k_2 k_3 k_4 k_7 k_{10} k_{11} + k_2 k_3 k_4 k_7 k_{11}^2 \right) \right)
\end{aligned} \tag{1.8}$$

Then, we impose the biochemical reaction network parameter ranges:

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

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

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

```

> bindingRate := evalf(seq(10^-3 * (10^6)^(i/20), i = 0..20)) :
> catalyticRate := seq(10^-3 * (10^6)^(i/1023), i = 0..1023) :
> switchingRate := seq(10^-2 * (10^4)^(i/1023), i = 0..1023) :
> concentration := seq(10^-3 * (10^6)^(i/1023), i = 0..1023) :
> bistableSpace := fopen("bistable_parameters_low_resol.txt", APPEND, TEXT) :
> allSpace := fopen("all_parameters_low_resol.txt", APPEND, TEXT) :

```

```

> for  $p_1$  in bindingRate do
  for  $p_2$  in bindingRate do
    for  $p_3$  in bindingRate do
      for  $p_4$  in bindingRate do
        for  $p_5$  in bindingRate do
          for  $p_6$  in bindingRate do
            for  $p_7$  in bindingRate do
              for  $p_9$  in bindingRate do
                for  $p_{10}$  in bindingRate do
                  for  $p_{11}$  in bindingRate do
                     $params := \{k_1 = p_1, k_2 = p_2, k_3 = p_3, k_4 = p_4, k_5 = p_5, k_6 = p_6, k_7 = p_7, k_9 = p_9, k_{10}$ 
 $= p_{10}, k_{11} = p_{11}\};$ 
                     $critiria := subs(params, constraintTerm);$ 
                     $p_8 := evalf\left(\frac{p_1 \cdot p_{10} \cdot p_5 \cdot p_9}{p_{11} \cdot p_4 \cdot p_2}\right);$ 
                     $outParams := [p_1, p_2, p_3, p_4, p_5, p_6, p_7, p_8, p_9, p_{10}, p_{11}, critiria];$ 
                    if  $critiria > 0$  and  $p_8 \leq 10^3$  and  $p_8 \geq 10^{-3}$  then
                       $writedata(bistableSpace, outParams);$ 
                    end if;
                  end do;
                end do;
              end do;
            end do;
          end do;
        end do;
      end do;
    end do;
  end do;
end do;

```

Warning, computation interrupted

```

[> close(bistableSpace) :

```

```

[> close(allSpace) :

```

```

#####

```

```

##### Original computation of parameters #####

```

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

For example

```

[>  $params := \{k_1 = 0.1, k_2 = 0.1, k_3 = 0.1, k_4 = 0.1, k_5 = 0.1, k_7 = 0.1, k_9 = 0.1, k_{10} = 0.1, k_{11}$ 
 $= 0.1, k_6 = 10, k_8 = 10000\} :$ 

```

$$\begin{aligned} &> \text{subs}(\text{params}, \text{term}) \\ &\quad 1.9779392 \end{aligned} \quad (1.9)$$

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

$$\begin{aligned} &> \text{mypol2} := \text{subs}(\text{params}, \text{mypol}) \\ \text{mypol2} &:= -930.2593025 - 18.3063440 x_1 - 4.10^{-7} x_1^3 - 0.0801022 x_1^2 \\ &\quad - 9.302686051 10^7 x_3 + 1.9779392 x_1^2 x_3 - 628.3062830 x_1 x_3 \end{aligned} \quad (1.10)$$

$$\begin{aligned} &> \text{mypol2} := \text{collect}(\%, x_3) \\ \text{mypol2} &:= (-9.302686051 10^7 + 1.9779392 x_1^2 - 628.3062830 x_1) x_3 - 930.2593025 \\ &\quad - 18.3063440 x_1 - 4.10^{-7} x_1^3 - 0.0801022 x_1^2 \end{aligned} \quad (1.11)$$

$$\begin{aligned} &> \text{subs}(x_1 = 8000, \text{mypol2}) \\ &\quad 2.853479803 10^7 x_3 - 5.478721811 10^6 \end{aligned} \quad (1.12)$$

$$\begin{aligned} &> \text{solve}(\%, x_3) \\ &\quad 0.1920014224 \end{aligned} \quad (1.13)$$

$$\begin{aligned} &> \text{subs}(\text{params}, x_1 = 8000, x_3 = 0.2, \text{mypol}) \\ &\quad 2.28237795 10^5 \end{aligned} \quad (1.14)$$

This choice of rate constants and x1 with x3 will give total amounts such that the system has three steady states.

To find the total amounts, we find the values of x2, x4, x5, x6 corresponding to x1 and x3, as given by the expressions above in sol2[1].

Then we substitute these values into the conservation laws:

$$\begin{aligned} &> \text{sol2} := \text{subs}(\text{params}, x_1 = 8000, x_3 = 0.2, \text{sol}) \\ \text{sol2} &:= \left[ \left[ x_2 = 3.033003570 10^6, x_4 = 384.0294388, x_5 = 10607.98528, x_6 = 30223.95584 \right] \right] \end{aligned} \quad (1.15)$$

$$\begin{aligned} &> B_1 := \text{subs}(\text{sol2}[1], x_1 = 8000, x_3 = 0.2, x_1 + x_2 + x_5 + x_6) \\ &\quad B_1 := 3.081835511 10^6 \end{aligned} \quad (1.16)$$

$$\begin{aligned} &> B_2 := \text{subs}(\text{sol2}[1], x_1 = 8000, x_3 = 0.2, x_3 + x_4 + x_5 + x_6) \\ &\quad B_2 := 41216.17056 \end{aligned} \quad (1.17)$$

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

$$\begin{aligned} &> \text{subs}(\text{params}, T_1 = B_1, T_2 = B_2, \text{myeqs}) \end{aligned} \quad (1.18)$$

$$\begin{aligned} & \left[ -0.1 x_2 + 0.1 x_5 + 10 x_6, -0.1 x_1 x_4 + 10000 x_3 - 0.1 x_4 + 10.1 x_6, 0.1 x_1 x_3 - 0.3 x_5 \right. \\ & \quad + 0.1 x_6, 0.1 x_1 x_4 + 0.1 x_5 - 10.2 x_6, x_1 + x_2 + x_5 + x_6 - 3.081835511 \cdot 10^6, x_3 + x_4 \\ & \quad \left. + x_5 + x_6 - 41216.17056 \right] \end{aligned} \quad (1.18)$$

**>** `sol3 := solve(%)`

$$\begin{aligned} \text{sol3} &:= \{x_1 = 7.431949267 \cdot 10^5, x_2 = 2.297427560 \cdot 10^6, x_3 = 0.04370170866, x_4 \\ &= 3.103037458, x_5 = 18422.97800, x_6 = 22790.04582\}, \{x_1 = 7999.987798, x_2 \\ &= 3.033003583 \cdot 10^6, x_3 = 0.2000000146, x_4 = 384.0300264, x_5 = 10607.98455, x_6 \\ &= 30223.95598\}, \{x_1 = 7904.812640, x_2 = 3.033103396 \cdot 10^6, x_3 = 0.2001138793, x_4 \\ &= 388.6681412, x_5 = 10602.29126, x_6 = 30225.01105\} \end{aligned} \quad (1.19)$$

We find indeed three positive steady states.

The last step is to find their asymptotic stability properties.

To do that, we compute the eigenvalues of the Jacobian of eqs evaluated at the three steady states. Two of them (because there are two conservation laws) should be zero.

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

**>** `eqs`

$$\begin{aligned} & \begin{bmatrix} -k_1 x_1 x_3 - k_4 x_1 x_4 + k_2 x_5 + k_5 x_6 + k_7 x_2 \\ k_3 x_5 + k_6 x_6 - k_7 x_2 \\ -k_1 x_1 x_3 + k_2 x_5 + k_3 x_5 - k_8 x_3 + k_9 x_4 \\ -k_4 x_1 x_4 + k_5 x_6 + k_6 x_6 + k_8 x_3 - k_9 x_4 \\ k_1 x_1 x_3 - k_2 x_5 - k_3 x_5 - k_{10} x_5 + k_{11} x_6 \\ k_4 x_1 x_4 - k_5 x_6 - k_6 x_6 + k_{10} x_5 - k_{11} x_6 \end{bmatrix} \end{aligned} \quad (1.20)$$

**>** `J := VectorCalculus[Jacobian](eqs, [seq(x_i, i = 1..6)])`

$$J := \begin{bmatrix} -k_1 x_3 - k_4 x_4 & k_7 & -k_1 x_1 & -k_4 x_1 & k_2 & k_5 \\ 0 & -k_7 & 0 & 0 & k_3 & k_6 \\ -k_1 x_3 & 0 & -k_1 x_1 - k_8 & k_9 & k_2 + k_3 & 0 \\ -k_4 x_4 & 0 & k_8 & -k_4 x_1 - k_9 & 0 & k_5 + k_6 \\ k_1 x_3 & 0 & k_1 x_1 & 0 & -k_2 - k_3 - k_{10} & k_{11} \\ k_4 x_4 & 0 & 0 & k_4 x_1 & k_{10} & -k_5 - k_6 - k_{11} \end{bmatrix} \quad (1.21)$$

> subs(params, sol3[1], J); Eigenvalues(%)

$$\begin{bmatrix} -0.3146739167 & 0.1 & -74319.49267 & -74319.49267 & 0.1 & 0.1 \\ 0 & -0.1 & 0 & 0 & 0.1 & 10 \\ -0.004370170866 & 0 & -84319.49267 & 0.1 & 0.2 & 0 \\ -0.3103037458 & 0 & 10000 & -74319.59267 & 0 & 10.1 \\ 0.004370170866 & 0 & 74319.49267 & 0 & -0.3 & 0.1 \\ 0.3103037458 & 0 & 0 & 74319.49267 & 0.1 & -10.2 \end{bmatrix}$$

$$\begin{bmatrix} -74329.9072195618 + 0. I \\ -84319.7690349337 + 0. I \\ -0.256508871082136 + 0. I \\ -0.0672505517198567 + 0. I \\ -3.40696081225279 \cdot 10^{-11} + 0. I \\ 1.61035821374563 \cdot 10^{-9} + 0. I \end{bmatrix}$$

(1.22)

> subs(params, sol3[2], J); Eigenvalues(%)

$$\begin{bmatrix} -38.42300264 & 0.1 & -799.9987798 & -799.9987798 & 0.1 & 0.1 \\ 0 & -0.1 & 0 & 0 & 0.1 & 10 \\ -0.02000000146 & 0 & -10799.99878 & 0.1 & 0.2 & 0 \\ -38.40300264 & 0 & 10000 & -800.0987798 & 0 & 10.1 \\ 0.02000000146 & 0 & 799.9987798 & 0 & -0.3 & 0.1 \\ 38.40300264 & 0 & 0 & 799.9987798 & 0.1 & -10.2 \end{bmatrix}$$

$$\begin{bmatrix} -10800.1136024190 + 0. I \\ -848.069487381455 + 0. I \\ -0.939099629488182 + 0. I \\ 0.00162702361222828 + 0. I \\ -3.36258666518844 \cdot 10^{-8} + 0. I \\ -4.39825053240974 \cdot 10^{-11} + 0. I \end{bmatrix}$$

(1.23)

> subs(params, sol3[3], J); Eigenvalues(%)

$$\begin{bmatrix} -38.88682551 & 0.1 & -790.4812640 & -790.4812640 & 0.1 & 0.1 \\ 0 & -0.1 & 0 & 0 & 0.1 & 10 \\ -0.02001138793 & 0 & -10790.48126 & 0.1 & 0.2 & 0 \\ -38.86681412 & 0 & 10000 & -790.5812640 & 0 & 10.1 \\ 0.02001138793 & 0 & 790.4812640 & 0 & -0.3 & 0.1 \\ 38.86681412 & 0 & 0 & 790.4812640 & 0.1 & -10.2 \end{bmatrix}$$



$$\begin{bmatrix} -10790.5959189980 + 0. \text{I} \\ -839.005378502047 + 0. \text{I} \\ -0.946418509930592 + 0. \text{I} \\ -0.00163346268233688 + 0. \text{I} \\ -3.75553713329940 \cdot 10^{-8} + 0. \text{I} \\ 1.87741903112777 \cdot 10^{-10} + 0. \text{I} \end{bmatrix} \quad (1.24)$$