Scaffold protein titration motif

The model description

This particular motif describe one phosphorylation-desphosphorylation cycle (can be generalized to any futile cycles) with both kinase (K) and phosphatase (P) can be titrated by a scaffold protein (T).

$\mathrm{K} + \mathrm{S} \rightleftharpoons \mathrm{KS} \rightarrow \mathrm{K} + S_p$
$\mathrm{P} + S_p \rightleftharpoons \mathrm{PS}_p \rightarrow \mathrm{P} + \mathrm{S}$
$\mathrm{T} + \mathrm{K} \rightleftharpoons \mathrm{TK}$
$\mathrm{T} + \mathrm{P} \rightleftharpoons \mathrm{TP}$

The above reactions show a simple system that composed of one scaffold protein, one kinase, one phosphatase and one substrate. Here we try to descibe this simple system with differential equation following the mass action kinetics.

$$\frac{d[K]}{dt} = -k[1][K][S] + k[2][\mathrm{KS}] + k[3][\mathrm{KS}] - k[7][T][K] + k[8][\mathrm{TK}],$$
$$\frac{d[P]}{dt} = -k[4][P][S_p] + k[5][\mathrm{PS}_p] + k[6][\mathrm{PS}_p] - k[9][T][P] + k[10][\mathrm{TP}],$$
$$\frac{d[S]}{dt} = -k[1][K][S] + k[2][\mathrm{KS}] + k[6][\mathrm{PS}_p],$$
$$\frac{d[S_p]}{dt} = -k[4][P][S_p] + k[3][\mathrm{KS}] + k[5][\mathrm{PS}_p],$$
$$\frac{d[\mathrm{KS}]}{dt} = k[1][K][S] - k[2][\mathrm{KS}] - k[3][\mathrm{KS}],$$
$$\frac{d[\mathrm{PS}_p]}{dt} = k[4][P][S_p] - k[5][\mathrm{PS}_p] - k[6][\mathrm{PS}_p],$$
$$\frac{d[T]}{dt} = -k[7][T][K] + k[8][\mathrm{TK}] - k[9][T][P] + k[10][\mathrm{TP}],$$
$$\frac{d[\mathrm{TK}]}{dt} = k[7][T][K] - k[8][\mathrm{TK}],$$
$$\frac{d[\mathrm{TP}]}{dt} = k[9][T][P] - k[10][\mathrm{TP}].$$

And the system need to follow these conservation equations:

$[K] + [\mathrm{KS}] + [\mathrm{TK}] = [K_{\mathrm{tot}}],$
$[P] + [\mathrm{PS}_p] + [\mathrm{TP}] = [P_{\mathrm{tot}}],$
$[S] + [S_p] + [\mathrm{KS}] + [\mathrm{PS}_p] = [S_{\mathrm{tot}}],$
$[T] + [\mathrm{TK}] + [\mathrm{TP}] = [T_{\mathrm{tot}}].$

In the following setion, we will solve the differential equations to understand the dynamics and behaviour of such system.

Understanding the dynamics of this simple system at steady states

The reactions are:

$K + S \rightleftharpoons KS \rightarrow K + S_p$
$P + S_p \rightleftharpoons PS_p \rightarrow P + S$
$T + K \rightleftharpoons TK$
$T + P \rightleftharpoons TP$

The species are:

$\{K\ (1),\ P\ (2),\ S\ (3),\ S_p\ (4),\ KS\ (5),\ PS_p\ (6),\ T\ (7),\ TK\ (8),\ TP\ (9)\}$

Here we have the differential equations:

```
Clear["Global`*"];
A = Table[0, {10}, {9}];
A[[1]][[1]] = -1;
A[[1]][[3]] = -1;
A[[1]][[5]] = 1;
A[[2]] = -A[[1]];
A[[3]][[1]] = 1;
A[[3]][[4]] = 1;
A[[3]][[5]] = -1;
A[[4]][[2]] = -1;
A[[4]][[4]] = -1;
A[[4]][[6]] = 1;
A[[5]] = -A[[4]];
A[[6]][[2]] = 1;
A[[6]][[3]] = 1;
A[[6]][[6]] = -1;
A[[7]][[1]] = -1;
A[[7]][[7]] = -1;
A[[7]][[8]] = 1;
A[[8]] = -A[[7]];
A[[9]][[2]] = -1;
A[[9]][[7]] = -1;
A[[9]][[9]] = 1;
A[[10]] = -A[[9]];
stoiM = Transpose[A];
ks = {k[1] x[1] x[3], k[2] x[5], k[3] x[5], k[4] x[2] x[4], k[5] x[6],
   k[6] x[6], k[7] x[1] x[7], k[8] x[8], k[9] x[2] x[7], k[10] x[9]};
eqns = stoiM.ks
mC = RowReduce[NullSpace[A]]
```

```
{-k[1] x[1] x[3] + k[2] x[5] + k[3] x[5] - k[7] x[1] x[7] + k[8] x[8],
 -k[4] x[2] x[4] + k[5] x[6] + k[6] x[6] - k[9] x[2] x[7] + k[10] x[9],
 -k[1] x[1] x[3] + k[2] x[5] + k[6] x[6], -k[4] x[2] x[4] + k[3] x[5] + k[5] x[6],
 k[1] x[1] x[3] - k[2] x[5] - k[3] x[5], k[4] x[2] x[4] - k[5] x[6] - k[6] x[6],
 -k[7] x[1] x[7] - k[9] x[2] x[7] + k[8] x[8] + k[10] x[9],
 k[7] x[1] x[7] - k[8] x[8], k[9] x[2] x[7] - k[10] x[9]}
```

```
{{1, 0, 0, 0, 1, 0, 0, 1, 0}, {0, 1, 0, 0, 0, 1, 0, 0, 1},
 {0, 0, 1, 1, 1, 1, 0, 0, 0}, {0, 0, 0, 0, 0, 0, 1, 1, 1}}
```

```
subsEqns =
 {eqns[[3]], eqns[[5]], eqns[[6]], eqns[[8]], eqns[[9]], x[1] + x[5] + x[8] - T1,
  x[2] + x[6] + x[9] - T2, x[3] + x[4] + x[5] + x[6] - T3, x[7] + x[8] + x[9] - T4}
```

$\{-k[1]\,x[1]\,x[3]+k[2]\,x[5]+k[6]\,x[6],\ k[1]\,x[1]\,x[3]-k[2]\,x[5]-k[3]\,x[5],\ k[4]\,x[2]\,x[4]-k[5]\,x[6]-k[6]\,x[6],\ k[7]\,x[1]\,x[7]-k[8]\,x[8],\ k[9]\,x[2]\,x[7]-k[10]\,x[9],\ -T_1+x[1]+x[5]+x[8],\ -T_2+x[2]+x[6]+x[9],\ -T_3+x[3]+x[4]+x[5]+x[6],\ -T_4+x[7]+x[8]+x[9]\}$

```
solution = Solve[{subsEqns[[1]], subsEqns[[2]], subsEqns[[3]],
    subsEqns[[4]], subsEqns[[5]]} == 0, {x[3], x[5], x[6], x[8], x[9]}]
```

$$\left\{\left\{x[3]\to\frac{(k[2]+k[3])\,k[4]\,k[6]\,x[2]\,x[4]}{k[1]\,k[3]\,(k[5]+k[6])\,x[1]},\ x[5]\to\frac{k[4]\,k[6]\,x[2]\,x[4]}{k[3]\,(k[5]+k[6])},\ x[6]\to\frac{k[4]\,x[2]\,x[4]}{k[5]+k[6]},\ x[8]\to\frac{k[7]\,x[1]\,x[7]}{k[8]},\ x[9]\to\frac{k[9]\,x[2]\,x[7]}{k[10]}\right\}\right\}$$

Here we substitue the composited parameters:

$$\left\{\frac{k[2]+k[3]}{k[1]}\to km[1],\ \frac{k[5]+k[6]}{k[4]}\to km[2],\ \frac{k[6]}{k[3]}\to kcr,\ \frac{k[7]}{k[8]}\to kd[1],\ \frac{k[9]}{k[10]}\to kd[2]\right\}$$

Then we have:

```
(* Following the current solution, and substitute the T1,T2,T3,T4 *)
```

$$\text{solution} = \left\{x[3]\to\frac{km[1]*kcr*x[2]*x[4]}{km[2]*x[1]},\ x[5]\to\frac{kcr\,x[2]\,x[4]}{km[2]},\ x[6]\to\frac{x[2]\,x[4]}{km[2]},\ x[8]\to kd[1]\,x[1]\,x[7],\ x[9]\to kd[2]\,x[2]\,x[7]\right\}$$

$$\left\{x[3]\to\frac{kcr\,km[1]\,x[2]\,x[4]}{km[2]\,x[1]},\ x[5]\to\frac{kcr\,x[2]\,x[4]}{km[2]},\ x[6]\to\frac{x[2]\,x[4]}{km[2]},\ x[8]\to kd[1]\,x[1]\,x[7],\ x[9]\to kd[2]\,x[2]\,x[7]\right\}$$

```
t12 = {T[1] == x[1] + x[5] + x[8], T[2] == x[2] + x[6] + x[9]} /. solution
```

$$\left\{T[1]==x[1]+\frac{kcr\,x[2]\,x[4]}{km[2]}+kd[1]\,x[1]\,x[7],\ T[2]==x[2]+\frac{x[2]\,x[4]}{km[2]}+kd[2]\,x[2]\,x[7]\right\}$$

```
{t12Sol} = Solve[t12, {x[1], x[2]}]
```

$$\{\{x[1]\to-((-km[2]\,T[1]-T[1]\,x[4]+kcr\,T[2]\,x[4]-kd[2]\,km[2]\,T[1]\,x[7])\,/\,((1+kd[1]\,x[7])\,(km[2]+x[4]+kd[2]\,km[2]\,x[7]))),\ x[2]\to\frac{km[2]\,T[2]}{km[2]+x[4]+kd[2]\,km[2]\,x[7]}\}\}$$

```
t12Sol
```

$$\{x[1]\to-((-km[2]\,T[1]-T[1]\,x[4]+kcr\,T[2]\,x[4]-kd[2]\,km[2]\,T[1]\,x[7])\,/\,((1+kd[1]\,x[7])\,(km[2]+x[4]+kd[2]\,km[2]\,x[7]))),\ x[2]\to\frac{km[2]\,T[2]}{km[2]+x[4]+kd[2]\,km[2]\,x[7]}\}$$

```
(x[7] + x[8] + x[9]) /. solution
```

$x[7]+kd[1]\,x[1]\,x[7]+kd[2]\,x[2]\,x[7]$

```
x[3] + x[4] + x[5] + x[6] /. solution
```

$$x[4]+\frac{x[2]\,x[4]}{km[2]}+\frac{kcr\,x[2]\,x[4]}{km[2]}+\frac{kcr\,km[1]\,x[2]\,x[4]}{km[2]\,x[1]}$$

$$t3=\left\{T[3]==x[4]+\frac{x[2]\,x[4]}{km[2]}+\frac{kcr\,x[2]\,x[4]}{km[2]}+\frac{kcr\,km[1]\,x[2]\,x[4]}{km[2]\,x[1]}\right\}\ /.\ t12Sol$$

$$\left\{T[3]==x[4]+\frac{T[2]\,x[4]}{km[2]+x[4]+kd[2]\,km[2]\,x[7]}+\frac{kcr\,T[2]\,x[4]}{km[2]+x[4]+kd[2]\,km[2]\,x[7]}-(kcr\,km[1]\,T[2]\,x[4]\,(1+kd[1]\,x[7]))\,/\,(-km[2]\,T[1]-T[1]\,x[4]+kcr\,T[2]\,x[4]-kd[2]\,km[2]\,T[1]\,x[7])\right\}$$

```
t32 = {(km[2] + x[4] + kd[2] km[2] x[7]) * (km[2] + x[4] + kd[2] km[2] x[7]) *
     (-km[2] T[1] - T[1] x[4] + kcr T[2] x[4] - kd[2] km[2] T[1] x[7]) * T[3] ==
    (-km[2] T[1] - T[1] x[4] + kcr T[2] x[4] - kd[2] km[2] T[1] x[7]) *
      (km[2] + x[4] + kd[2] km[2] x[7]) * (km[2] + x[4] + kd[2] km[2] x[7]) * x[4] +
     (-km[2] T[1] - T[1] x[4] + kcr T[2] x[4] - kd[2] km[2] T[1] x[7]) *
      (km[2] + x[4] + kd[2] km[2] x[7]) * T[2] x[4] +
     (-km[2] T[1] - T[1] x[4] + kcr T[2] x[4] - kd[2] km[2] T[1] x[7]) *
      (km[2] + x[4] + kd[2] km[2] x[7]) * kcr T[2] x[4] -
     (km[2] + x[4] + kd[2] km[2] x[7]) * (km[2] + x[4] + kd[2] km[2] x[7]) *
      kcr km[1] T[2] x[4] (1 + kd[1] x[7])}
```

```
t4 = {T[4] == x[7] + kd[1] x[1] x[7] + kd[2] x[2] x[7]} /. t12Sol
```

$$\left\{T[4]==x[7]+\frac{kd[2]\,km[2]\,T[2]\,x[7]}{km[2]+x[4]+kd[2]\,km[2]\,x[7]}-(kd[1]\,x[7]\,(-km[2]\,T[1]-T[1]\,x[4]+kcr\,T[2]\,x[4]-kd[2]\,km[2]\,T[1]\,x[7]))\,/\,((1+kd[1]\,x[7])\,(km[2]+x[4]+kd[2]\,km[2]\,x[7]))\right\}$$

```
t4Sol = {Solve[t4, x[7]]}[[1]][[1]]
```

```
{x[7] → (-kd[1] km[2] - kd[2] km[2] - kd[1] kd[2] km[2] T[1] - kd[1] kd[2] km[2] T[2] +
      kd[1] kd[2] km[2] T[4] - kd[1] x[4]) / (3 kd[1] kd[2] km[2]) +
   (2^(1/3) (-(-kd[1] km[2] - kd[2] km[2] - kd[1] kd[2] km[2] T[1] -
            kd[1] kd[2] km[2] T[2] + kd[1] kd[2] km[2] T[4] - kd[1] x[4])^2 -
         3 kd[1] kd[2] km[2] (-km[2] - kd[1] km[2] T[1] - kd[2] km[2] T[2] +
            kd[1] km[2] T[4] + kd[2] km[2] T[4] - x[4] -
            kd[1] T[1] x[4] + kcr kd[1] T[2] x[4] + kd[1] T[4] x[4]))) /
    (3 kd[1] kd[2] km[2] (2 kd[1]^3 km[2]^3 - 3 kd[1]^2 kd[2] km[2]^3 -
          3 kd[1] kd[2]^2 km[2]^3 + 2 kd[2]^3 km[2]^3 - 3 kd[1]^3 kd[2] km[2]^3 T[1] -
          6 kd[1]^2 kd[2]^2 km[2]^3 T[1] + 6 kd[1] kd[2]^3 km[2]^3 T[1] -
          3 kd[1]^3 kd[2]^2 km[2]^3 T[1]^2 + 6 kd[1]^2 kd[2]^3 km[2]^3 T[1]^2 +
          2 kd[1]^3 kd[2]^3 km[2]^3 T[1]^3 + 6 kd[1]^3 kd[2] km[2]^3 T[2] -
          6 kd[1]^2 kd[2]^2 km[2]^3 T[2] - 3 kd[1] kd[2]^3 km[2]^3 T[2] +
          3 kd[1]^3 kd[2]^2 km[2]^3 T[1] T[2] + 3 kd[1]^2 kd[2]^3 km[2]^3 T[1] T[2] +
          6 kd[1]^3 kd[2]^3 km[2]^3 T[1]^2 T[2] + 6 kd[1]^3 kd[2]^2 km[2]^3 T[2]^2 -
          3 kd[1]^2 kd[2]^3 km[2]^3 T[2]^2 + 6 kd[1]^3 kd[2]^3 km[2]^3 T[1] T[2]^2 +
          2 kd[1]^3 kd[2]^3 km[2]^3 T[2]^3 + 3 kd[1]^3 kd[2] km[2]^3 T[4] -
          12 kd[1]^2 kd[2]^2 km[2]^3 T[4] + 3 kd[1] kd[2]^3 km[2]^3 T[4] +
          6 kd[1]^3 kd[2]^2 km[2]^3 T[1] T[4] - 3 kd[1]^2 kd[2]^3 km[2]^3 T[1] T[4] -
          6 kd[1]^3 kd[2]^3 km[2]^3 T[1]^2 T[4] - 3 kd[1]^3 kd[2]^2 km[2]^3 T[2] T[4] +
          6 kd[1]^2 kd[2]^3 km[2]^3 T[2] T[4] - 12 kd[1]^3 kd[2]^3 km[2]^3 T[1] T[2] T[4] -
          6 kd[1]^3 kd[2]^3 km[2]^3 T[2]^2 T[4] - 3 kd[1]^3 kd[2]^2 km[2]^3 T[4]^2 -
          3 kd[1]^2 kd[2]^3 km[2]^3 T[4]^2 + 6 kd[1]^3 kd[2]^3 km[2]^3 T[1] T[4]^2 +
          6 kd[1]^3 kd[2]^3 km[2]^3 T[2] T[4]^2 - 2 kd[1]^3 kd[2]^3 km[2]^3 T[4]^3 +
```

$$
\begin{array}{l}
6\,kd[1]^3\,km[2]^2\,x[4] - 6\,kd[1]^2\,kd[2]\,km[2]^2\,x[4] - \\
3\,kd[1]\,kd[2]^2\,km[2]^2\,x[4] - 6\,kd[1]^3\,kd[2]\,km[2]^2\,T[1]\,x[4] - \\
6\,kd[1]^2\,kd[2]^2\,km[2]^2\,T[1]\,x[4] - 3\,kd[1]^3\,kd[2]^2\,km[2]^2\,T[1]^2\,x[4] + \\
12\,kd[1]^3\,kd[2]\,km[2]^2\,T[2]\,x[4] + 9\,kcr\,kd[1]^3\,kd[2]\,km[2]^2\,T[2]\,x[4] - \\
6\,kd[1]^2\,kd[2]^2\,km[2]^2\,T[2]\,x[4] + 9\,kcr\,kd[1]^2\,kd[2]^2\,km[2]^2\,T[2]\,x[4] + \\
3\,kd[1]^3\,kd[2]^2\,km[2]^2\,T[1]\,T[2]\,x[4] + 9\,kcr\,kd[1]^3\,kd[2]^2 \\
\quad km[2]^2\,T[1]\,T[2]\,x[4] + 6\,kd[1]^3\,kd[2]^2\,km[2]^2\,T[2]^2\,x[4] + \\
9\,kcr\,kd[1]^3\,kd[2]^2\,km[2]^2\,T[2]^2\,x[4] + 6\,kd[1]^3\,kd[2]\,km[2]^2\,T[4]\,x[4] - \\
12\,kd[1]^2\,kd[2]^2\,km[2]^2\,T[4]\,x[4] + 6\,kd[1]^3\,kd[2]^2\,km[2]^2\,T[1]\,T[4]\,x[4] - \\
3\,kd[1]^3\,kd[2]^2\,km[2]^2\,T[2]\,T[4]\,x[4] - 9\,kcr\,kd[1]^3\,kd[2]^2\,km[2]^2\,T[2] \\
\quad T[4]\,x[4] - 3\,kd[1]^3\,kd[2]^2\,km[2]^2\,T[4]^2\,x[4] + 6\,kd[1]^3\,km[2]\,x[4]^2 - \\
3\,kd[1]^2\,kd[2]\,km[2]\,x[4]^2 - 3\,kd[1]^3\,kd[2]\,km[2]\,T[1]\,x[4]^2 + \\
6\,kd[1]^3\,kd[2]\,km[2]\,T[2]\,x[4]^2 + 9\,kcr\,kd[1]^3\,kd[2]\,km[2]\,T[2]\,x[4]^2 + \\
3\,kd[1]^3\,kd[2]\,km[2]\,T[4]\,x[4]^2 + 2\,kd[1]^3\,x[4]^3 + \\
\surd\Big(\Big(2\,kd[1]^3\,km[2]^3 - 3\,kd[1]^2\,kd[2]\,km[2]^3 - 3\,kd[1]\,kd[2]^2\,km[2]^3 + 2\,kd[2]^3 \\
\qquad km[2]^3 - 3\,kd[1]^3\,kd[2]\,km[2]^3\,T[1] - 6\,kd[1]^2\,kd[2]^2\,km[2]^3\,T[1] + \\
\qquad 6\,kd[1]\,kd[2]^3\,km[2]^3\,T[1] - 3\,kd[1]^3\,kd[2]^2\,km[2]^3\,T[1]^2 + \\
\qquad 6\,kd[1]^2\,kd[2]^3\,km[2]^3\,T[1]^2 + 2\,kd[1]^3\,kd[2]^3\,km[2]^3\,T[1]^3 + \\
\qquad 6\,kd[1]^3\,kd[2]\,km[2]^3\,T[2] - 6\,kd[1]^2\,kd[2]^2\,km[2]^3\,T[2] - \\
\qquad 3\,kd[1]\,kd[2]^3\,km[2]^3\,T[2] + 3\,kd[1]^3\,kd[2]^2\,km[2]^3\,T[1]\,T[2] + \\
\qquad 3\,kd[1]^2\,kd[2]^3\,km[2]^3\,T[1]\,T[2] + 6\,kd[1]^3\,kd[2]^3\,km[2]^3\,T[1]^2 \\
\qquad T[2] + 6\,kd[1]^3\,kd[2]^2\,km[2]^3\,T[2]^2 - 3\,kd[1]^2\,kd[2]^3\,km[2]^3\,T[2]^2 + \\
\qquad 6\,kd[1]^3\,kd[2]^3\,km[2]^3\,T[1]\,T[2]^2 + 2\,kd[1]^3\,kd[2]^3\,km[2]^3\,T[2]^3 + \\
\qquad 3\,kd[1]^3\,kd[2]\,km[2]^3\,T[4] - 12\,kd[1]^2\,kd[2]^2\,km[2]^3\,T[4] + \\
\qquad 3\,kd[1]\,kd[2]^3\,km[2]^3\,T[4] + 6\,kd[1]^3\,kd[2]^2\,km[2]^3\,T[1]\,T[4] - 3 \\
\qquad kd[1]^2\,kd[2]^3\,km[2]^3\,T[1]\,T[4] - 6\,kd[1]^3\,kd[2]^3\,km[2]^3\,T[1]^2\,T[4] - \\
\qquad 3\,kd[1]^3\,kd[2]^2\,km[2]^3\,T[2]\,T[4] + 6\,kd[1]^2\,kd[2]^3\,km[2]^3\,T[2]\,T[4] - \\
\qquad 12\,kd[1]^3\,kd[2]^3\,km[2]^3\,T[1]\,T[2]\,T[4] - 6\,kd[1]^3\,kd[2]^3\,km[2]^3 \\
\qquad T[2]^2\,T[4] - 3\,kd[1]^3\,kd[2]^2\,km[2]^3\,T[4]^2 - 3\,kd[1]^2\,kd[2]^3\,km[2]^3 \\
\qquad T[4]^2 + 6\,kd[1]^3\,kd[2]^3\,km[2]^3\,T[1]\,T[4]^2 + 6\,kd[1]^3\,kd[2]^3\,km[2]^3 \\
\qquad T[2]\,T[4]^2 - 2\,kd[1]^3\,kd[2]^3\,km[2]^3\,T[4]^3 + 6\,kd[1]^3\,km[2]^2\,x[4] - \\
\qquad 6\,kd[1]^2\,kd[2]\,km[2]^2\,x[4] - 3\,kd[1]\,kd[2]^2\,km[2]^2\,x[4] - \\
\qquad 6\,kd[1]^3\,kd[2]\,km[2]^2\,T[1]\,x[4] - 6\,kd[1]^2\,kd[2]^2\,km[2]^2\,T[1]\,x[4] - \\
\qquad 3\,kd[1]^3\,kd[2]^2\,km[2]^2\,T[1]^2\,x[4] + 12\,kd[1]^3\,kd[2]\,km[2]^2\,T[2] \\
\qquad x[4] + 9\,kcr\,kd[1]^3\,kd[2]\,km[2]^2\,T[2]\,x[4] - 6\,kd[1]^2\,kd[2]^2\,km[2]^2 \\
\qquad T[2]\,x[4] + 9\,kcr\,kd[1]^2\,kd[2]^2\,km[2]^2\,T[2]\,x[4] + 3\,kd[1]^3\,kd[2]^2 \\
\qquad km[2]^2\,T[1]\,T[2]\,x[4] + 9\,kcr\,kd[1]^3\,kd[2]^2\,km[2]^2\,T[1]\,T[2]\,x[4] + \\
\qquad 6\,kd[1]^3\,kd[2]^2\,km[2]^2\,T[2]^2\,x[4] + 9\,kcr\,kd[1]^3\,kd[2]^2\,km[2]^2\,T[2]^2 \\
\qquad x[4] + 6\,kd[1]^3\,kd[2]\,km[2]^2\,T[4]\,x[4] - 12\,kd[1]^2\,kd[2]^2\,km[2]^2 \\
\qquad T[4]\,x[4] + 6\,kd[1]^3\,kd[2]^2\,km[2]^2\,T[1]\,T[4]\,x[4] - 3\,kd[1]^3\,kd[2]^2 \\
\qquad km[2]^2\,T[2]\,T[4]\,x[4] - 9\,kcr\,kd[1]^3\,kd[2]^2\,km[2]^2\,T[2]\,T[4]\,x[4] - \\
\qquad 3\,kd[1]^3\,kd[2]^2\,km[2]^2\,T[4]^2\,x[4] + 6\,kd[1]^3\,km[2]\,x[4]^2 - \\
\qquad 3\,kd[1]^2\,kd[2]\,km[2]\,x[4]^2 - 3\,kd[1]^3\,kd[2]\,km[2]\,T[1]\,x[4]^2 + \\
\qquad 6\,kd[1]^3\,kd[2]\,km[2]\,T[2]\,x[4]^2 + 9\,kcr\,kd[1]^3\,kd[2]\,km[2]\,T[2] \\
\qquad x[4]^2 + 3\,kd[1]^3\,kd[2]\,km[2]\,T[4]\,x[4]^2 + 2\,kd[1]^3\,x[4]^3\Big)^2 + \\
\quad 4\,\Big(-(-kd[1]\,km[2] - kd[2]\,km[2] - kd[1]\,kd[2]\,km[2]\,T[1] - kd[1] \\
\qquad\qquad kd[2]\,km[2]\,T[2] + kd[1]\,kd[2]\,km[2]\,T[4] - kd[1]\,x[4])^2 - \\
\qquad 3\,kd[1]\,kd[2]\,km[2]\,(-km[2] - kd[1]\,km[2]\,T[1] - kd[2]\,km[2] \\
\qquad\qquad T[2] + kd[1]\,km[2]\,T[4] + kd[2]\,km[2]\,T[4] - x[4] - kd[1] \\
\qquad\qquad T[1]\,x[4] + kcr\,kd[1]\,T[2]\,x[4] + kd[1]\,T[4]\,x[4])\Big)^3\Big)\Big)^{1/3}\Big) - \\
\frac{1}{3\times 2^{1/3}\,kd[1]\,kd[2]\,km[2]}\Big(2\,kd[1]^3\,km[2]^3 - 3\,kd[1]^2\,kd[2]\,km[2]^3 - \\
\quad 3\,kd[1]\,kd[2]^2\,km[2]^3 + \\
\quad 2\,kd[2]^3\,km[2]^3 - \\
\quad 3\,kd[1]^3\,kd[2]\,km[2]^3\,T[1] -
\end{array}
$$

$$
\begin{aligned}
&6\,kd[1]^2\,kd[2]^2\,km[2]^3\,T[1]\,+\\
&6\,kd[1]\,kd[2]^3\,km[2]^3\,T[1]\,-\\
&3\,kd[1]^3\,kd[2]^2\,km[2]^3\,T[1]^2\,+\\
&6\,kd[1]^2\,kd[2]^3\,km[2]^3\,T[1]^2\,+\\
&2\,kd[1]^3\,kd[2]^3\,km[2]^3\,T[1]^3\,+\\
&6\,kd[1]^3\,kd[2]\,km[2]^3\,T[2]\,-\\
&6\,kd[1]^2\,kd[2]^2\,km[2]^3\,T[2]\,-\\
&3\,kd[1]\,kd[2]^3\,km[2]^3\,T[2]\,+\\
&3\,kd[1]^3\,kd[2]^2\,km[2]^3\,T[1]\,T[2]\,+\\
&3\,kd[1]^2\,kd[2]^3\,km[2]^3\,T[1]\,T[2]\,+\\
&6\,kd[1]^3\,kd[2]^3\,km[2]^3\,T[1]^2\,T[2]\,+\\
&6\,kd[1]^3\,kd[2]^2\,km[2]^3\,T[2]^2\,-\\
&3\,kd[1]^2\,kd[2]^3\,km[2]^3\,T[2]^2\,+\\
&6\,kd[1]^3\,kd[2]^3\,km[2]^3\,T[1]\,T[2]^2\,+\\
&2\,kd[1]^3\,kd[2]^3\,km[2]^3\,T[2]^3\,+\\
&3\,kd[1]^3\,kd[2]\,km[2]^3\,T[4]\,-\\
&12\,kd[1]^2\,kd[2]^2\,km[2]^3\,T[4]\,+\\
&3\,kd[1]\,kd[2]^3\,km[2]^3\,T[4]\,+\\
&6\,kd[1]^3\,kd[2]^2\,km[2]^3\,T[1]\,T[4]\,-\\
&3\,kd[1]^2\,kd[2]^3\,km[2]^3\,T[1]\,T[4]\,-\\
&6\,kd[1]^3\,kd[2]^3\,km[2]^3\,T[1]^2\,T[4]\,-\\
&3\,kd[1]^3\,kd[2]^2\,km[2]^3\,T[2]\,T[4]\,+\\
&6\,kd[1]^2\,kd[2]^3\,km[2]^3\,T[2]\,T[4]\,-\\
&12\,kd[1]^3\,kd[2]^3\,km[2]^3\,T[1]\,T[2]\,T[4]\,-\\
&6\,kd[1]^3\,kd[2]^3\,km[2]^3\,T[2]^2\,T[4]\,-\\
&3\,kd[1]^3\,kd[2]^2\,km[2]^3\,T[4]^2\,-\\
&3\,kd[1]^2\,kd[2]^3\,km[2]^3\,T[4]^2\,+\\
&6\,kd[1]^3\,kd[2]^3\,km[2]^3\,T[1]\,T[4]^2\,+\\
&6\,kd[1]^3\,kd[2]^3\,km[2]^3\,T[2]\,T[4]^2\,-\\
&2\,kd[1]^3\,kd[2]^3\,km[2]^3\,T[4]^3\,+\\
&6\,kd[1]^3\,km[2]^2\,x[4]\,-\\
&6\,kd[1]^2\,kd[2]\,km[2]^2\,x[4]\,-\\
&3\,kd[1]\,kd[2]^2\,km[2]^2\,x[4]\,-\\
&6\,kd[1]^3\,kd[2]\,km[2]^2\,T[1]\,x[4]\,-\\
&6\,kd[1]^2\,kd[2]^2\,km[2]^2\,T[1]\,x[4]\,-\\
&3\,kd[1]^3\,kd[2]^2\,km[2]^2\,T[1]^2\,x[4]\,+\\
&12\,kd[1]^3\,kd[2]\,km[2]^2\,T[2]\,x[4]\,+\\
&9\,kcr\,kd[1]^3\,kd[2]\,km[2]^2\,T[2]\,x[4]\,-\\
&6\,kd[1]^2\,kd[2]^2\,km[2]^2\,T[2]\,x[4]\,+\\
&9\,kcr\,kd[1]^2\,kd[2]^2\,km[2]^2\,T[2]\,x[4]\,+\\
&3\,kd[1]^3\,kd[2]^2\,km[2]^2\,T[1]\,T[2]\,x[4]\,+\\
&9\,kcr\,kd[1]^3\,kd[2]^2\,km[2]^2\,T[1]\,T[2]\,x[4]\,+\\
&6\,kd[1]^3\,kd[2]^2\,km[2]^2\,T[2]^2\,x[4]\,+\\
&9\,kcr\,kd[1]^3\,kd[2]^2\,km[2]^2\,T[2]^2\,x[4]\,+\\
&6\,kd[1]^3\,kd[2]\,km[2]^2\,T[4]\,x[4]\,-\\
&12\,kd[1]^2\,kd[2]^2\,km[2]^2\,T[4]\,x[4]\,+\\
&6\,kd[1]^3\,kd[2]^2\,km[2]^2\,T[1]\,T[4]\,x[4]\,-\\
&3\,kd[1]^3\,kd[2]^2\,km[2]^2\,T[2]\,T[4]\,x[4]\,-\\
&9\,kcr\,kd[1]^3\,kd[2]^2\,km[2]^2\,T[2]\,T[4]\,x[4]\,-\\
&3\,kd[1]^3\,kd[2]^2\,km[2]^2\,T[4]^2\,x[4]\,+\\
&6\,kd[1]^3\,km[2]\,x[4]^2 - 3\,kd[1]^2\,kd[2]\,km[2]\,x[4]^2\,-\\
&3\,kd[1]^3\,kd[2]\,km[2]\,T[1]\,x[4]^2\,+\\
&6\,kd[1]^3\,kd[2]\,km[2]\,T[2]\,x[4]^2\,+\\
&9\,kcr\,kd[1]^3\,kd[2]\,km[2]\,T[2]\,x[4]^2\,+\\
&3\,kd[1]^3\,kd[2]\,km[2]\,T[4]\,x[4]^2 + 2\,kd[1]^3\,x[4]^3\,+
\end{aligned}
$$

```
√((2 kd[1]^3 km[2]^3 - 3 kd[1]^2 kd[2] km[2]^3 - 3 kd[1] kd[2]^2 km[2]^3 + 2 kd[2]^3
    km[2]^3 - 3 kd[1]^3 kd[2] km[2]^3 T[1] - 6 kd[1]^2 kd[2]^2 km[2]^3 T[1] + 6
    kd[1] kd[2]^3 km[2]^3 T[1] - 3 kd[1]^3 kd[2]^2 km[2]^3 T[1]^2 + 6 kd[1]^2
    kd[2]^3 km[2]^3 T[1]^2 + 2 kd[1]^3 kd[2]^3 km[2]^3 T[1]^3 + 6 kd[1]^3 kd[2]
    km[2]^3 T[2] - 6 kd[1]^2 kd[2]^2 km[2]^3 T[2] - 3 kd[1] kd[2]^3 km[2]^3
    T[2] + 3 kd[1]^3 kd[2]^2 km[2]^3 T[1] T[2] + 3 kd[1]^2 kd[2]^3 km[2]^3 T[1]
    T[2] + 6 kd[1]^3 kd[2]^3 km[2]^3 T[1]^2 T[2] + 6 kd[1]^3 kd[2]^2 km[2]^3
    T[2]^2 - 3 kd[1]^2 kd[2]^3 km[2]^3 T[2]^2 + 6 kd[1]^3 kd[2]^3 km[2]^3 T[1]
    T[2]^2 + 2 kd[1]^3 kd[2]^3 km[2]^3 T[2]^3 + 3 kd[1]^3 kd[2] km[2]^3 T[4] - 12
    kd[1]^2 kd[2]^2 km[2]^3 T[4] + 3 kd[1] kd[2]^3 km[2]^3 T[4] + 6 kd[1]^3
    kd[2]^2 km[2]^3 T[1] T[4] - 3 kd[1]^2 kd[2]^3 km[2]^3 T[1] T[4] - 6 kd[1]^3
    kd[2]^3 km[2]^3 T[1]^2 T[4] - 3 kd[1]^3 kd[2]^2 km[2]^3 T[2] T[4] + 6
    kd[1]^2 kd[2]^3 km[2]^3 T[2] T[4] - 12 kd[1]^3 kd[2]^3 km[2]^3 T[1] T[2]
    T[4] - 6 kd[1]^3 kd[2]^3 km[2]^3 T[2]^2 T[4] - 3 kd[1]^3 kd[2]^2 km[2]^3
    T[4]^2 - 3 kd[1]^2 kd[2]^3 km[2]^3 T[4]^2 + 6 kd[1]^3 kd[2]^3 km[2]^3 T[1]
    T[4]^2 + 6 kd[1]^3 kd[2]^3 km[2]^3 T[2] T[4]^2 - 2 kd[1]^3 kd[2]^3 km[2]^3
    T[4]^3 + 6 kd[1]^3 km[2]^2 x[4] - 6 kd[1]^2 kd[2] km[2]^2 x[4] - 3 kd[1]
    kd[2]^2 km[2]^2 x[4] - 6 kd[1]^3 kd[2] km[2]^2 T[1] x[4] - 6 kd[1]^2 kd[2]^2
    km[2]^2 T[1] x[4] - 3 kd[1]^3 kd[2]^2 km[2]^2 T[1]^2 x[4] + 12 kd[1]^3
    kd[2] km[2]^2 T[2] x[4] + 9 kcr kd[1]^3 kd[2] km[2]^2 T[2] x[4] - 6
    kd[1]^2 kd[2]^2 km[2]^2 T[2] x[4] + 9 kcr kd[1]^2 kd[2]^2 km[2]^2 T[2]
    x[4] + 3 kd[1]^3 kd[2]^2 km[2]^2 T[1] T[2] x[4] + 9 kcr kd[1]^3 kd[2]^2
    km[2]^2 T[1] T[2] x[4] + 6 kd[1]^3 kd[2]^2 km[2]^2 T[2]^2 x[4] + 9 kcr
    kd[1]^3 kd[2]^2 km[2]^2 T[2]^2 x[4] + 6 kd[1]^3 kd[2] km[2]^2 T[4] x[4] - 12
    kd[1]^2 kd[2]^2 km[2]^2 T[4] x[4] + 6 kd[1]^3 kd[2]^2 km[2]^2 T[1] T[4]
    x[4] - 3 kd[1]^3 kd[2]^2 km[2]^2 T[2] T[4] x[4] - 9 kcr kd[1]^3 kd[2]^2
    km[2]^2 T[2] T[4] x[4] - 3 kd[1]^3 kd[2]^2 km[2]^2 T[4]^2 x[4] + 6 kd[1]^3
    km[2] x[4]^2 - 3 kd[1]^2 kd[2] km[2] x[4]^2 - 3 kd[1]^3 kd[2] km[2] T[1]
    x[4]^2 + 6 kd[1]^3 kd[2] km[2] T[2] x[4]^2 + 9 kcr kd[1]^3 kd[2] km[2]
    T[2] x[4]^2 + 3 kd[1]^3 kd[2] km[2] T[4] x[4]^2 + 2 kd[1]^3 x[4]^3)^2 +
  4 (-(-kd[1] km[2] - kd[2] km[2] - kd[1] kd[2] km[2] T[1] - kd[1]
        kd[2] km[2] T[2] + kd[1] kd[2] km[2] T[4] - kd[1] x[4])^2 -
    3 kd[1] kd[2] km[2] (-km[2] - kd[1] km[2] T[1] - kd[2]
      km[2] T[2] + kd[1] km[2] T[4] + kd[2] km[2] T[4] - x[4] -
      kd[1] T[1] x[4] + kcr kd[1] T[2] x[4] + kd[1] T[4] x[4]))^3))^(1/3)}
```

t3 /. t4Sol

```
{T[3] == x[4] + T[2] x[4] / (km[2] + x[4] + kd[2] km[2] ((…1…)/(3 (…2…) km[2]) + (…1…) - (…1…)/(…1…))) +
    kcr T[2] x[4] / (km[2] + x[4] + kd[2] km[2] (…1…)) - 1/(…1…) kcr km[1] T[2] x[4]
    (1 + kd[1] ((…1…)/(3 kd[1] kd[2] km[2]) + 2^(…1…) (…1…) ((…1…) (…1…))/(3 (…4…)) - ((…1…))^(1/3)/(3 × 2^(1/3) kd[1] kd[2] km[2])))}

large output   show less   show more   show all   set size limit...
```

Solve[t3 /. t4Sol, x[4]]

```
$Aborted
```

Here we have the solution for the system we can plug in the values of total concentrations.

```
(*The following commented region is merely show
 that there is only one steady state for this system*)
(*jacobian=D[subsEqns,{{x[1],x[2],x[3],x[4],x[5],x[6],x[7],x[8],x[9]}}];
detJ=Collect[Distribute[Det[jacobian]],
  {x[1],x[2],x[3],x[4],x[5],x[6],x[7],x[8],x[9]}];
detSubs=Replace[detJ,solution[[1]],{0,Infinity}];
polSubs=Numerator[Together[detSubs]];
finalSubs=Collect[Distribute[polSubs],x_,FactorTerms];*)
```

Here we directly solve the system with *Mathematica's Solve function.*

```
Clear["Global`*"];

des = {x[1]'[t], x[2]'[t], x[3]'[t], x[4]'[t],
    x[5]'[t], x[6]'[t], x[7]'[t], x[8]'[t], x[9]'[t]} ==
   {-k[1] x[1][t] x[3][t] + k[2] x[5][t] + k[3] x[5][t] - k[7] x[1][t] x[7][t] +
     k[8] x[8][t], -k[4] x[2][t] x[4][t] + k[5] x[6][t] + k[6] x[6][t] -
     k[9] x[2][t] x[7][t] + k[10] x[9][t], -k[1] x[1][t] x[3][t] + k[2] x[5][t] +
     k[6] x[6][t], -k[4] x[2][t] x[4][t] + k[3] x[5][t] + k[5] x[6][t],
    k[1] x[1][t] x[3][t] - k[2] x[5][t] - k[3] x[5][t],
    k[4] x[2][t] x[4][t] - k[5] x[6][t] - k[6] x[6][t],
    -k[7] x[1][t] x[7][t] - k[9] x[2][t] x[7][t] + k[8] x[8][t] + k[10] x[9][t],
    k[7] x[1][t] x[7][t] - k[8] x[8][t], k[9] x[2][t] x[7][t] - k[10] x[9][t]};

init = {T[1], T[2], T[3], 0, 0, 0, T[4], 0, 0};

solution = Solve[Table[0, {i, Length[des[[1]]]}] == des[[2]],
  Table[x[i][t], {i, Length[des[[1]]]}]]
```

Solve::svars : Equations may not give solutions for all "solve" variables ≫

$$\left\{\left\{x[3][t]\to\frac{(k[2]+k[3])\,x[5][t]}{k[1]\,x[1][t]},\ x[4][t]\to\frac{k[3]\,(k[5]+k[6])\,x[5][t]}{k[4]\,k[6]\,x[2][t]},\ x[6][t]\to\frac{k[3]\,x[5][t]}{k[6]},\ x[8][t]\to\frac{k[7]\,x[1][t]\,x[7][t]}{k[8]},\ x[9][t]\to\frac{k[9]\,x[2][t]\,x[7][t]}{k[10]}\right\},\ \left\{x[1][t]\to 0,\ x[4][t]\to 0,\ x[5][t]\to 0,\ x[6][t]\to 0,\ x[8][t]\to 0,\ x[9][t]\to\frac{k[9]\,x[2][t]\,x[7][t]}{k[10]}\right\},\ \{x[1][t]\to 0,\ x[2][t]\to 0,\ x[5][t]\to 0,\ x[6][t]\to 0,\ x[8][t]\to 0,\ x[9][t]\to 0\},\ \left\{x[2][t]\to 0,\ x[3][t]\to 0,\ x[5][t]\to 0,\ x[6][t]\to 0,\ x[8][t]\to\frac{k[7]\,x[1][t]\,x[7][t]}{k[8]},\ x[9][t]\to 0\right\}\right\}$$

Here we substitue the composited parameters:

$$\left\{\frac{k[2]+k[3]}{k[1]}\to km[1],\ \frac{k[5]+k[6]}{k[4]}\to km[2],\ \frac{k[3]}{k[6]}\to kcr,\ \frac{k[7]}{k[8]}\to kd[1],\ \frac{k[9]}{k[10]}\to kd[2]\right\}$$

Then we have:

```
solution =
  {x[3][t] -> km[1] x[5][t] / x[1][t], x[4][t] -> kcr * km[2] x[5][t] / x[2][t], x[6][t] -> kcr x[5][t],
   x[8][t] -> kd[1] x[1][t] x[7][t], x[9][t] -> kd[2] x[2][t] x[7][t]}
```

```
{x[3][t] → km[1] x[5][t] / x[1][t], x[4][t] → kcr km[2] x[5][t] / x[2][t], x[6][t] → kcr x[5][t],
 x[8][t] → kd[1] x[1][t] x[7][t], x[9][t] → kd[2] x[2][t] x[7][t]}
```

Understanding the dynamics of the simple system with input pertubations (numerical study)

Since, it is a bit difficult to solve the differential equations analytically. Here we try to study them numerically. By defining two different way to characterising the dynamics with scoring their tempral dynamics when presented with input signal perturbation (the changing of [T]). The quantification can be derived from the actually fitness funcitons for ultrasensitive response and adaptive response. Then we save all the parameter sets as well as their score on ultrasensitivity and adaptation.

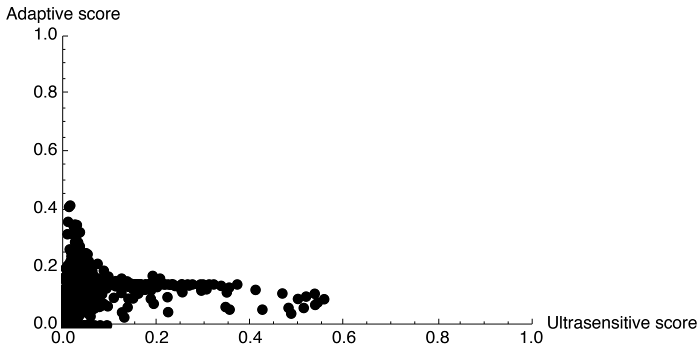
```
Clear["Global`*"];
SetDirectory[NotebookDirectory[]];
AbsoluteTiming[
 des = {-k[1] * x[1][t] * x[3][t] + k[2] * x[5][t] + k[3] * x[5][t] -
     k[7] * x[1][t] * x[7][t] + k[8] * x[8][t], -k[4] * x[2][t] * x[4][t] +
     k[5] * x[6][t] + k[6] * x[6][t] - k[9] * x[2][t] * x[7][t] + k[10] * x[9][t],
    -k[1] * x[1][t] * x[3][t] + k[2] * x[5][t] + k[6] * x[6][t],
    -k[4] * x[2][t] * x[4][t] + k[3] * x[5][t] + k[5] * x[6][t],
    k[1] * x[1][t] * x[3][t] - k[2] * x[5][t] - k[3] * x[5][t],
    k[4] * x[2][t] * x[4][t] - k[5] * x[6][t] - k[6] * x[6][t],
    -k[7] * x[1][t] * x[7][t] - k[9] * x[2][t] * x[7][t] +
     k[8] * x[8][t] + k[10] * x[9][t],
    k[7] * x[1][t] * x[7][t] - k[8] * x[8][t],
    k[9] * x[2][t] * x[7][t] - k[10] * x[9][t]};


init = {totK, totP, totS, 0, 0, 0, totT, 0, 0};
 (*init=
   {tot[1],tot[2],tot[3],0.00001,0.00001,0.00001,totT,0.00001,0.00001};*)

 totK = 1; totP = 1; totS = 10;
 stepNum = 6;
 sampleSize = 20000;

 pars = {};
 vars = Array[x, 9];
dvars = Thread[Derivative[1][vars]];
 SeedRandom[IntegerPart[SessionTime[]]];
 ts = {};
 For[num = 1, num ≤ sampleSize, num++,
  Block[{k, T, ssthreshold}, k[n_] := k[n] = 10^(RandomReal[] * 6 - 3);
    (*tot[n_]:=tot[n]=10^(RandomReal[]*4-3);*)
    (*ksTest1=Array[k,10];*)
    (*totT=1.*^-3;*)
    totT = 0.01;

    Block[{tPer, step},
```

```
        step = 0;
        tPer = {};
        ssthreshold = 1.*^-5;
        (* Print[des]; *)
        {sol} = NDSolve[{Through[dvars[t]] == des, Through[vars[0]] == init,
           With[{df = Through[dvars[t]]}, WhenEvent[Norm[df] < ssthreshold,
              {AppendTo[tPer, t], step = step + 1, If[step ≥ stepNum,
                 "StopIntegration"], x[7][t] → x[7][t] + 10 / (stepNum - 1)}]]},
          vars, {t, 0, 200000}, MaxSteps → 10000];
        ts = tPer;
        If[Length[ts] == stepNum && AllTrue[ts, Positive],
         x4 = Evaluate[x[4][ts - 0.001] /. sol];
         xT = Evaluate[(x[7][ts - 0.001] + x[8][ts - 0.001] + x[9][ts - 0.001]) /. sol];

         us = Sqrt[
            ((Abs[(x4[[stepNum - IntegerPart[stepNum / 2] + 1]] - x4[[stepNum / 2]])] /
                totS) * Min[((Abs[(x4[[stepNum - IntegerPart[stepNum / 2] + 1]] -
                        x4[[stepNum / 2]])] / Max[Abs[(x4[[IntegerPart[
                            stepNum / 2]]] - x4[[1]])], 0.001] + Abs[(x4[[stepNum -
                          IntegerPart[stepNum / 2] + 1]] - x4[[stepNum / 2]])] /
                     Max[Abs[(x4[[stepNum]] - x4[[stepNum - IntegerPart[
                            stepNum / 2] + 1]])], 0.001]) / 2) / 10.0, 1.0])];
         ad = 0.0001;
         For[i = 1, i < stepNum, i++,
          ad = ad * Sqrt[
               (Min[(Max[Abs[Evaluate[x[4][Range[ts[[i]], ts[[i + 1]], 1]] /. sol] -
                        Evaluate[x[4][ts[[i]]] /. sol]]] / (0.5 * totS)), 1.0] *
                 Min[(0.1) / (Max[Abs[x4[[i + 1]] - x4[[i]]], 0.001]), 1.0])];
         ];
         ad = (ad / 0.0001) ^ (1 / (stepNum - 1));

         ks = Array[k, 10];
         AppendTo[pars, Join[ks, {us, ad, num,
             (ks[[2]] + ks[[3]]) / ks[[1]], (ks[[5]] + ks[[6]]) / ks[[4]], ks[[8]] / ks[[7]], ks[[10]] / ks[[9]]}]];
        ];
       ];
      ];
    ];
  ]

  (*Plot@@{{{(x[7][t]+x[8][t]+x[9][t]),x[4][t]}/.sol},
     Flatten@{t,x[1]["Domain"]/.sol},PlotLegends→{"Ttot","Sp"}}
   ListPlot[Transpose@{xT,x4},PlotRange→{0,10}]*)
  (*Print[pars];*)
  transPars = Transpose[pars];
  Export["saturationSampling.csv", transPars];
  (*Export["unsaturationSampling.csv",transPars];*)
```

Out[535]= {4311.04, Null}

In[538]:=
```
ListPlot[Transpose[{transPars[[11]], transPars[[12]]}],
 PlotRange → {{0, 1}, {0, 1}},
 AxesLabel → {"Ultrasensitive score", "Adaptive score"},
 PlotStyle → {Thick, PointSize[0.01]}, PlotTheme → "Monochrome"]
```

Out[538]=



In[539]:=
```
maxAndIndex[a_] :=
 {#, First@SparseArray[UnitStep[a - #]]["AdjacencyLists"]} &@Max@a
```

In[540]:=
```
maxAndIndex[transPars[[11]]]
```

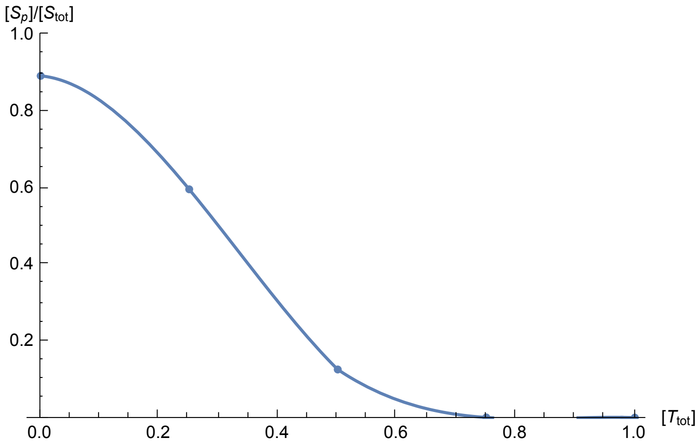
Out[540]= {0.554555, 12 278}

In[541]:=
```
maxAndIndex[transPars[[12]]]
```

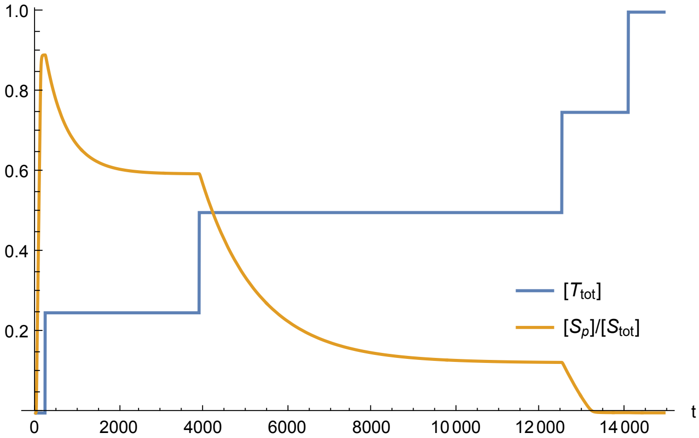
Out[541]= {0.414253, 2962}

In[692]:=
```
maxAndIndex[a_] :=
  {#, First@SparseArray[UnitStep[a - #]]["AdjacencyLists"]} &@Max@a
usIndex = maxAndIndex[transPars[[11]]] // Last;
adIndex = maxAndIndex[transPars[[12]]] // Last;
stepNum = 5;
maxPars = Solve[Array[k, 10] == pars[[usIndex]][[Range[10]]]];
Block[{tPer, step, totT},
  totT = 0.0001;
  step = 0;
  tPer = {};
  ssthreshold = 1.*^-5;
  (* Print[des]; *)
  {sol} = NDSolve[{Through[dvars[t]] == des, Through[vars[0]] == init,
       With[{df = Through[dvars[t]], delta = Through[dvars[t + 500]]},
        WhenEvent[(Norm[df] < ssthreshold && Norm[delta] < ssthreshold),
         {AppendTo[tPer, t], step = step + 1, If[step ≥ stepNum, "StopIntegration"],
          x[7][t] → x[7][t] + 10 / (stepNum - 1)}]]} /.
     maxPars, vars, {t, 0, 200 000}, MaxSteps → 10 000];
  ts = tPer;
  x4 = Evaluate[x[4][ts - 0.001] /. sol] / totS;
  xT = Evaluate[(x[7][ts - 0.001] + x[8][ts - 0.001] + x[9][ts - 0.001]) /. sol] / 10;
 ];
Show[Plot[Interpolation[(Transpose@{xT, x4})][x], {x, 0, 1}, PlotRange → {0, 1},
  AxesLabel → {"[Ttot]", "[Sp]/[Stot]"}], ListPlot[Transpose@{xT, x4}]]
Plot @@ {{{(x[7][t] + x[8][t] + x[9][t]) / 10, x[4][t] / totS} /. sol},
  Flatten@{t, 0, ts[[stepNum]] - 0.01},
  PlotLegends → Placed[{"[Ttot]", "[Sp]/[Stot]"}, {0.85, 0.25}],
  PlotRange → {0, 1.01}, AxesLabel → {"t"}}

maxPars = Solve[Array[k, 10] == pars[[adIndex]][[Range[10]]]];
Block[{tPer, step, totT},
  totT = 0.01;
  step = 0;
  tPer = {};
  ssthreshold = 1.*^-5;
  (* Print[des]; *)
  {sol} = NDSolve[{Through[dvars[t]] == des, Through[vars[0]] == init,
       With[{df = Through[dvars[t]]}, WhenEvent[Norm[df] < ssthreshold,
          {AppendTo[tPer, t], step = step + 1, If[step ≥ stepNum, "StopIntegration"],
           x[7][t] → x[7][t] + 10 / (stepNum - 1)}]]} /.
     maxPars, vars, {t, 0, 200 000}, MaxSteps → 10 000];
  ts = tPer;
  x4 = Evaluate[x[4][ts - 0.001] /. sol];
  xT = Evaluate[(x[7][ts - 0.001] + x[8][ts - 0.001] + x[9][ts - 0.001]) /. sol];
 ];
Plot @@ {{{(x[7][t] + x[8][t] + x[9][t]) / 10, x[4][t] / totS} /. sol},
  Flatten@{t, 0, ts[[stepNum]] - 0.01},
  PlotLegends → Placed[{"[Ttot]", "[Sp]/[Stot]"}, {0.85, 0.25}],
  PlotRange → {0, 1.01}, AxesLabel → {"t"}}
```

Out[698]=



Out[699]=



Out[702]=