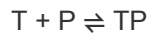
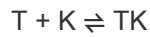


Scaffold protein titration motif

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).



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.

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

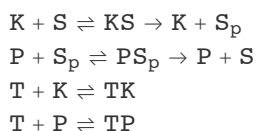
And the system need to follow these conservation equations:

$$\begin{aligned}[K] + [KS] + [TK] &= [K_{\text{tot}}], \\ [P] + [PS_p] + [TP] &= [P_{\text{tot}}], \\ [S] + [S_p] + [KS] + [PS_p] &= [S_{\text{tot}}], \\ [T] + [TK] + [TP] &= [T_{\text{tot}}].\end{aligned}$$

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:



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], -T1 + x[1] + x[5] + x[8], -T2 + x[2] + x[6] + x[9],
  -T3 + x[3] + x[4] + x[5] + x[6], -T4 + 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]}]
{ {x[3] -> (k[2] + k[3]) k[4] k[6] x[2] x[4] / (k[1] k[3] (k[5] + k[6]) x[1]), x[5] -> k[4] k[6] x[2] x[4] / (k[3] (k[5] + k[6])),
  x[6] -> k[4] x[2] x[4] / (k[5] + k[6]), x[8] -> k[7] x[1] x[7] / k[8], x[9] -> k[9] x[2] x[7] / k[10]} }

```

Here we substitute the composited parameters:

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

Then we have:

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

$$\begin{aligned} \text{solution} = \{ & x[3] \rightarrow \frac{km[1] * kcr * x[2] * x[4]}{km[2] * x[1]}, x[5] \rightarrow \frac{kcr x[2] x[4]}{km[2]}, \\ & x[6] \rightarrow \frac{x[2] x[4]}{km[2]}, x[8] \rightarrow kd[1] x[1] x[7], x[9] \rightarrow kd[2] x[2] x[7] \} \\ \{ & x[3] \rightarrow \frac{kcr km[1] x[2] x[4]}{km[2] x[1]}, x[5] \rightarrow \frac{kcr x[2] x[4]}{km[2]}, \\ & x[6] \rightarrow \frac{x[2] x[4]}{km[2]}, x[8] \rightarrow kd[1] x[1] x[7], x[9] \rightarrow kd[2] x[2] x[7] \} \end{aligned}$$

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

$$\begin{aligned} \{ & T[1] == x[1] + \frac{kcr x[2] x[4]}{km[2]} + kd[1] x[1] x[7], \\ & T[2] == x[2] + \frac{x[2] x[4]}{km[2]} + kd[2] x[2] x[7] \} \end{aligned}$$

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

$$\begin{aligned} \{ & \{ x[1] \rightarrow -((-km[2] T[1] - T[1] x[4] + kcr T[2] x[4] - kd[2] km[2] T[1] x[7]) / \\ & ((1 + kd[1] x[7]) (km[2] + x[4] + kd[2] km[2] x[7]))), \\ & x[2] \rightarrow \frac{km[2] T[2]}{km[2] + x[4] + kd[2] km[2] x[7]} \} \} \end{aligned}$$

t12Sol

$$\begin{aligned} \{ & x[1] \rightarrow -((-km[2] T[1] - T[1] x[4] + kcr T[2] x[4] - kd[2] km[2] T[1] x[7]) / \\ & ((1 + kd[1] x[7]) (km[2] + x[4] + kd[2] km[2] x[7]))), \\ & x[2] \rightarrow \frac{km[2] T[2]}{km[2] + x[4] + kd[2] km[2] x[7]} \} \end{aligned}$$

(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

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

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

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

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

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

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

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

$$\left\{ x[7] \rightarrow \frac{(-kd[1] km[2] - kd[2] km[2] - kd[1] kd[2] km[2] T[1] - kd[1] kd[2] km[2] T[2] + \\ kd[1] kd[2] km[2] T[4] - kd[1] x[4]) / (3 kd[1] kd[2] km[2]) + \\ (2^{1/3} (-(-kd[1] km[2] - kd[2] km[2] - kd[1] kd[2] km[2] T[1] - \\ kd[1] kd[2] km[2] T[2] + kd[1] kd[2] km[2] T[4] - kd[1] x[4])^2 - \\ 3 kd[1] kd[2] km[2] (-km[2] - kd[1] km[2] T[1] - kd[2] km[2] T[2] + \\ kd[1] km[2] T[4] + kd[2] km[2] T[4] - x[4] - \\ kd[1] T[1] x[4] + kcr kd[1] T[2] x[4] + kd[1] T[4] x[4]))}{(3 kd[1] kd[2] km[2] (2 kd[1]^3 km[2]^3 - 3 kd[1]^2 kd[2] km[2]^3 - \\ 3 kd[1] kd[2]^2 km[2]^3 + 2 kd[2]^3 km[2]^3 - 3 kd[1]^3 kd[2] km[2]^3 T[1] - \\ 6 kd[1]^2 kd[2]^2 km[2]^3 T[1] + 6 kd[1] kd[2]^3 km[2]^3 T[1] - \\ 3 kd[1]^3 kd[2]^2 km[2]^3 T[1]^2 + 6 kd[1]^2 kd[2]^3 km[2]^3 T[1]^2 + \\ 2 kd[1]^3 kd[2]^3 km[2]^3 T[1]^3 + 6 kd[1]^3 kd[2] km[2]^3 T[2] - \\ 6 kd[1]^2 kd[2]^2 km[2]^3 T[2] - 3 kd[1] kd[2]^3 km[2]^3 T[2] + \\ 3 kd[1]^3 kd[2]^2 km[2]^3 T[1] T[2] + 3 kd[1]^2 kd[2]^3 km[2]^3 T[1] T[2] + \\ 6 kd[1]^3 kd[2]^3 km[2]^3 T[1]^2 T[2] + 6 kd[1]^3 kd[2]^2 km[2]^3 T[2]^2 - \\ 3 kd[1]^2 kd[2]^3 km[2]^3 T[2]^2 + 6 kd[1]^3 kd[2]^3 km[2]^3 T[1] T[2]^2 + \\ 2 kd[1]^3 kd[2]^3 km[2]^3 T[2]^3 + 3 kd[1]^3 kd[2] km[2]^3 T[4] - \\ 12 kd[1]^2 kd[2]^2 km[2]^3 T[4] + 3 kd[1] kd[2]^3 km[2]^3 T[4] + \\ 6 kd[1]^3 kd[2]^2 km[2]^3 T[1] T[4] - 3 kd[1]^2 kd[2]^3 km[2]^3 T[1] T[4] - \\ 6 kd[1]^3 kd[2]^3 km[2]^3 T[1]^2 T[4] - 3 kd[1]^3 kd[2]^2 km[2]^3 T[2] T[4] + \\ 6 kd[1]^2 kd[2]^3 km[2]^3 T[2] T[4] - 12 kd[1]^3 kd[2]^3 km[2]^3 T[1] T[2] T[4] - \\ 6 kd[1]^3 kd[2]^3 km[2]^3 T[2]^2 T[4] - 3 kd[1]^3 kd[2]^2 km[2]^3 T[4]^2 - \\ 3 kd[1]^2 kd[2]^3 km[2]^3 T[4]^2 + 6 kd[1]^3 kd[2]^3 km[2]^3 T[1] T[4]^2 + \\ 6 kd[1]^3 kd[2]^3 km[2]^3 T[2] T[4]^2 - 2 kd[1]^3 kd[2]^3 km[2]^3 T[4]^3 +}$$

$$\begin{aligned} &6 \text{kd}[1]^3 \text{km}[2] x[4] - 6 \text{kd}[1]^2 \text{kd}[2] \text{km}[2]^2 x[4] - \\ &3 \text{kd}[1] \text{kd}[2]^2 \text{km}[2]^2 x[4] - 6 \text{kd}[1]^3 \text{kd}[2] \text{km}[2]^2 T[1] x[4] - \\ &6 \text{kd}[1]^2 \text{kd}[2]^2 \text{km}[2]^2 T[1] x[4] - 3 \text{kd}[1]^3 \text{kd}[2]^2 \text{km}[2]^2 T[1]^2 x[4] + \\ &12 \text{kd}[1]^3 \text{kd}[2] \text{km}[2]^2 T[2] x[4] + 9 \text{kcr kd}[1]^3 \text{kd}[2] \text{km}[2]^2 T[2] x[4] - \\ &6 \text{kd}[1]^2 \text{kd}[2]^2 \text{km}[2]^2 T[2] x[4] + 9 \text{kcr kd}[1]^2 \text{kd}[2]^2 \text{km}[2]^2 T[2] x[4] + \\ &3 \text{kd}[1]^3 \text{kd}[2]^2 \text{km}[2]^2 T[1] T[2] x[4] + 9 \text{kcr kd}[1]^3 \text{kd}[2]^2 \\ &\quad \text{km}[2]^2 T[1] T[2] x[4] + 6 \text{kd}[1]^3 \text{kd}[2]^2 \text{km}[2]^2 T[2]^2 x[4] + \\ &9 \text{kcr kd}[1]^3 \text{kd}[2]^2 \text{km}[2]^2 T[2]^2 x[4] + 6 \text{kd}[1]^3 \text{kd}[2] \text{km}[2]^2 T[4] x[4] - \\ &12 \text{kd}[1]^2 \text{kd}[2]^2 \text{km}[2]^2 T[4] x[4] + 6 \text{kd}[1]^3 \text{kd}[2]^2 \text{km}[2]^2 T[1] T[4] x[4] - \\ &3 \text{kd}[1]^3 \text{kd}[2]^2 \text{km}[2]^2 T[2] T[4] x[4] - 9 \text{kcr kd}[1]^3 \text{kd}[2]^2 \text{km}[2]^2 T[2] \\ &\quad T[4] x[4] - 3 \text{kd}[1]^3 \text{kd}[2]^2 \text{km}[2]^2 T[4]^2 x[4] + 6 \text{kd}[1]^3 \text{km}[2] x[4]^2 - \\ &3 \text{kd}[1]^2 \text{kd}[2] \text{km}[2] x[4]^2 - 3 \text{kd}[1]^3 \text{kd}[2] \text{km}[2] T[1] x[4]^2 + \\ &6 \text{kd}[1]^3 \text{kd}[2] \text{km}[2] T[2] x[4]^2 + 9 \text{kcr kd}[1]^3 \text{kd}[2] \text{km}[2] T[2] x[4]^2 + \\ &3 \text{kd}[1]^3 \text{kd}[2] \text{km}[2] T[4] x[4]^2 + 2 \text{kd}[1]^3 x[4]^3 + \\ &\sqrt{\left((2 \text{kd}[1]^3 \text{km}[2]^3 - 3 \text{kd}[1]^2 \text{kd}[2] \text{km}[2]^3 - 3 \text{kd}[1] \text{kd}[2]^2 \text{km}[2]^3 + 2 \text{kd}[2]^3 \right.} \\ &\quad \text{km}[2]^3 - 3 \text{kd}[1]^3 \text{kd}[2] \text{km}[2]^3 T[1] - 6 \text{kd}[1]^2 \text{kd}[2]^2 \text{km}[2]^3 T[1] + \\ &\quad 6 \text{kd}[1] \text{kd}[2]^3 \text{km}[2]^3 T[1] - 3 \text{kd}[1]^3 \text{kd}[2]^2 \text{km}[2]^3 T[1]^2 + \\ &\quad 6 \text{kd}[1]^2 \text{kd}[2]^3 \text{km}[2]^3 T[1]^2 + 2 \text{kd}[1]^3 \text{kd}[2]^3 \text{km}[2]^3 T[1]^3 + \\ &\quad 6 \text{kd}[1]^3 \text{kd}[2] \text{km}[2]^3 T[2] - 6 \text{kd}[1]^2 \text{kd}[2]^2 \text{km}[2]^3 T[2] - \\ &\quad 3 \text{kd}[1] \text{kd}[2]^3 \text{km}[2]^3 T[2] + 3 \text{kd}[1]^3 \text{kd}[2]^2 \text{km}[2]^3 T[1] T[2] + \\ &\quad 3 \text{kd}[1]^2 \text{kd}[2]^3 \text{km}[2]^3 T[1] T[2] + 6 \text{kd}[1]^3 \text{kd}[2]^3 \text{km}[2]^3 T[1]^2 \\ &\quad T[2] + 6 \text{kd}[1]^3 \text{kd}[2]^2 \text{km}[2]^3 T[2]^2 - 3 \text{kd}[1]^2 \text{kd}[2]^3 \text{km}[2]^3 T[2]^2 + \\ &\quad 6 \text{kd}[1]^3 \text{kd}[2]^3 \text{km}[2]^3 T[1] T[2]^2 + 2 \text{kd}[1]^3 \text{kd}[2]^3 \text{km}[2]^3 T[2]^3 + \\ &\quad 3 \text{kd}[1]^3 \text{kd}[2] \text{km}[2]^3 T[4] - 12 \text{kd}[1]^2 \text{kd}[2]^2 \text{km}[2]^3 T[4] + \\ &\quad 3 \text{kd}[1] \text{kd}[2]^3 \text{km}[2]^3 T[4] + 6 \text{kd}[1]^3 \text{kd}[2]^2 \text{km}[2]^3 T[1] T[4] - 3 \\ &\quad \text{kd}[1]^2 \text{kd}[2]^3 \text{km}[2]^3 T[1] T[4] - 6 \text{kd}[1]^3 \text{kd}[2]^3 \text{km}[2]^3 T[1]^2 T[4] - \\ &\quad 3 \text{kd}[1]^3 \text{kd}[2]^2 \text{km}[2]^3 T[2] T[4] + 6 \text{kd}[1]^2 \text{kd}[2]^3 \text{km}[2]^3 T[2] T[4] - \\ &\quad 12 \text{kd}[1]^3 \text{kd}[2]^3 \text{km}[2]^3 T[1] T[2] T[4] - 6 \text{kd}[1]^3 \text{kd}[2]^3 \text{km}[2]^3 \\ &\quad T[2]^2 T[4] - 3 \text{kd}[1]^3 \text{kd}[2]^2 \text{km}[2]^3 T[4]^2 - 3 \text{kd}[1]^2 \text{kd}[2]^3 \text{km}[2]^3 \\ &\quad T[4]^2 + 6 \text{kd}[1]^3 \text{kd}[2]^3 \text{km}[2]^3 T[1] T[4]^2 + 6 \text{kd}[1]^3 \text{kd}[2]^3 \text{km}[2]^3 \\ &\quad T[2] T[4]^2 - 2 \text{kd}[1]^3 \text{kd}[2]^3 \text{km}[2]^3 T[4]^3 + 6 \text{kd}[1]^3 \text{km}[2]^2 x[4] - \\ &\quad 6 \text{kd}[1]^2 \text{kd}[2] \text{km}[2]^2 x[4] - 3 \text{kd}[1] \text{kd}[2]^2 \text{km}[2]^2 x[4] - \\ &\quad 6 \text{kd}[1]^3 \text{kd}[2] \text{km}[2]^2 T[1] x[4] - 6 \text{kd}[1]^2 \text{kd}[2]^2 \text{km}[2]^2 T[1] x[4] - \\ &\quad 3 \text{kd}[1]^3 \text{kd}[2]^2 \text{km}[2]^2 T[1]^2 x[4] + 12 \text{kd}[1]^3 \text{kd}[2] \text{km}[2]^2 T[2] \\ &\quad x[4] + 9 \text{kcr kd}[1]^3 \text{kd}[2] \text{km}[2]^2 T[2] x[4] - 6 \text{kd}[1]^2 \text{kd}[2]^2 \text{km}[2]^2 \\ &\quad T[2] x[4] + 9 \text{kcr kd}[1]^2 \text{kd}[2]^2 \text{km}[2]^2 T[2] x[4] + 3 \text{kd}[1]^3 \text{kd}[2]^2 \\ &\quad \text{km}[2]^2 T[1] T[2] x[4] + 9 \text{kcr kd}[1]^3 \text{kd}[2]^2 \text{km}[2]^2 T[1] T[2] x[4] + \\ &\quad 6 \text{kd}[1]^3 \text{kd}[2]^2 \text{km}[2]^2 T[2]^2 x[4] + 9 \text{kcr kd}[1]^3 \text{kd}[2]^2 \text{km}[2]^2 T[2]^2 \\ &\quad x[4] + 6 \text{kd}[1]^3 \text{kd}[2] \text{km}[2]^2 T[4] x[4] - 12 \text{kd}[1]^2 \text{kd}[2]^2 \text{km}[2]^2 \\ &\quad T[4] x[4] + 6 \text{kd}[1]^3 \text{kd}[2]^2 \text{km}[2]^2 T[1] T[4] x[4] - 3 \text{kd}[1]^3 \text{kd}[2]^2 \\ &\quad \text{km}[2]^2 T[2] T[4] x[4] - 9 \text{kcr kd}[1]^3 \text{kd}[2]^2 \text{km}[2]^2 T[2] T[4] x[4] - \\ &\quad 3 \text{kd}[1]^3 \text{kd}[2]^2 \text{km}[2]^2 T[4]^2 x[4] + 6 \text{kd}[1]^3 \text{km}[2] x[4]^2 - \\ &\quad 3 \text{kd}[1]^2 \text{kd}[2] \text{km}[2] x[4]^2 - 3 \text{kd}[1]^3 \text{kd}[2] \text{km}[2] T[1] x[4]^2 + \\ &\quad 6 \text{kd}[1]^3 \text{kd}[2] \text{km}[2] T[2] x[4]^2 + 9 \text{kcr kd}[1]^3 \text{kd}[2] \text{km}[2] T[2] \\ &\quad x[4]^2 + 3 \text{kd}[1]^3 \text{kd}[2] \text{km}[2] T[4] x[4]^2 + 2 \text{kd}[1]^3 x[4]^3)^2 + \\ &4 (-(-\text{kd}[1] \text{km}[2] - \text{kd}[2] \text{km}[2] - \text{kd}[1] \text{kd}[2] \text{km}[2] T[1] - \text{kd}[1] \\ &\quad \text{kd}[2] \text{km}[2] T[2] + \text{kd}[1] \text{kd}[2] \text{km}[2] T[4] - \text{kd}[1] x[4])^2 - \\ &\quad 3 \text{kd}[1] \text{kd}[2] \text{km}[2] (-\text{km}[2] - \text{kd}[1] \text{km}[2] T[1] - \text{kd}[2] \text{km}[2] \\ &\quad T[2] + \text{kd}[1] \text{km}[2] T[4] + \text{kd}[2] \text{km}[2] T[4] - x[4] - \text{kd}[1] \\ &\quad T[1] x[4] + \text{kcr kd}[1] T[2] x[4] + \text{kd}[1] T[4] x[4]))^3) \Big)^{1/3} - \\ &\frac{1}{3 \times 2^{1/3} \text{kd}[1] \text{kd}[2] \text{km}[2]} \left(2 \text{kd}[1]^3 \text{km}[2]^3 - 3 \text{kd}[1]^2 \text{kd}[2] \text{km}[2]^3 - \right. \\ &\quad 3 \text{kd}[1] \text{kd}[2]^2 \text{km}[2]^3 + \\ &\quad 2 \text{kd}[2]^3 \text{km}[2]^3 - \\ &\quad \left. 3 \text{kd}[1]^3 \text{kd}[2] \text{km}[2]^3 T[1] - \right. \end{aligned}$$

[illegible]

$$\sqrt{\left(\begin{aligned} & (2 \text{kd}[1]^3 \text{km}[2]^3 - 3 \text{kd}[1]^2 \text{kd}[2] \text{km}[2]^3 - 3 \text{kd}[1] \text{kd}[2]^2 \text{km}[2]^3 + 2 \text{kd}[2]^3 \\ & \text{km}[2]^3 - 3 \text{kd}[1]^3 \text{kd}[2] \text{km}[2]^3 \text{T}[1] - 6 \text{kd}[1]^2 \text{kd}[2]^2 \text{km}[2]^3 \text{T}[1] + 6 \\ & \text{kd}[1] \text{kd}[2]^3 \text{km}[2]^3 \text{T}[1] - 3 \text{kd}[1]^3 \text{kd}[2]^2 \text{km}[2]^3 \text{T}[1]^2 + 6 \text{kd}[1]^2 \\ & \text{kd}[2]^3 \text{km}[2]^3 \text{T}[1]^2 + 2 \text{kd}[1]^3 \text{kd}[2]^3 \text{km}[2]^3 \text{T}[1]^3 + 6 \text{kd}[1]^3 \text{kd}[2] \\ & \text{km}[2]^3 \text{T}[2] - 6 \text{kd}[1]^2 \text{kd}[2]^2 \text{km}[2]^3 \text{T}[2] - 3 \text{kd}[1] \text{kd}[2]^3 \text{km}[2]^3 \\ & \text{T}[2] + 3 \text{kd}[1]^3 \text{kd}[2]^2 \text{km}[2]^3 \text{T}[1] \text{T}[2] + 3 \text{kd}[1]^2 \text{kd}[2]^3 \text{km}[2]^3 \text{T}[1] \\ & \text{T}[2] + 6 \text{kd}[1]^3 \text{kd}[2]^3 \text{km}[2]^3 \text{T}[1]^2 \text{T}[2] + 6 \text{kd}[1]^3 \text{kd}[2]^2 \text{km}[2]^3 \\ & \text{T}[2]^2 - 3 \text{kd}[1]^2 \text{kd}[2]^3 \text{km}[2]^3 \text{T}[2]^2 + 6 \text{kd}[1]^3 \text{kd}[2]^3 \text{km}[2]^3 \text{T}[1] \\ & \text{T}[2]^2 + 2 \text{kd}[1]^3 \text{kd}[2]^3 \text{km}[2]^3 \text{T}[2]^3 + 3 \text{kd}[1]^3 \text{kd}[2] \text{km}[2]^3 \text{T}[4] - 12 \\ & \text{kd}[1]^2 \text{kd}[2]^2 \text{km}[2]^3 \text{T}[4] + 3 \text{kd}[1] \text{kd}[2]^3 \text{km}[2]^3 \text{T}[4] + 6 \text{kd}[1]^3 \\ & \text{kd}[2]^2 \text{km}[2]^3 \text{T}[1] \text{T}[4] - 3 \text{kd}[1]^2 \text{kd}[2]^3 \text{km}[2]^3 \text{T}[1] \text{T}[4] - 6 \text{kd}[1]^3 \\ & \text{kd}[2]^3 \text{km}[2]^3 \text{T}[1]^2 \text{T}[4] - 3 \text{kd}[1]^3 \text{kd}[2]^2 \text{km}[2]^3 \text{T}[2] \text{T}[4] + 6 \\ & \text{kd}[1]^2 \text{kd}[2]^3 \text{km}[2]^3 \text{T}[2] \text{T}[4] - 12 \text{kd}[1]^3 \text{kd}[2]^3 \text{km}[2]^3 \text{T}[1] \text{T}[2] \\ & \text{T}[4] - 6 \text{kd}[1]^3 \text{kd}[2]^3 \text{km}[2]^3 \text{T}[2]^2 \text{T}[4] - 3 \text{kd}[1]^3 \text{kd}[2]^2 \text{km}[2]^3 \\ & \text{T}[4]^2 - 3 \text{kd}[1]^2 \text{kd}[2]^3 \text{km}[2]^3 \text{T}[4]^2 + 6 \text{kd}[1]^3 \text{kd}[2]^3 \text{km}[2]^3 \text{T}[1] \\ & \text{T}[4]^2 + 6 \text{kd}[1]^3 \text{kd}[2]^3 \text{km}[2]^3 \text{T}[2] \text{T}[4]^2 - 2 \text{kd}[1]^3 \text{kd}[2]^3 \text{km}[2]^3 \\ & \text{T}[4]^3 + 6 \text{kd}[1]^3 \text{km}[2]^2 \text{x}[4] - 6 \text{kd}[1]^2 \text{kd}[2] \text{km}[2]^2 \text{x}[4] - 3 \text{kd}[1] \\ & \text{kd}[2]^2 \text{km}[2]^2 \text{x}[4] - 6 \text{kd}[1]^3 \text{kd}[2] \text{km}[2]^2 \text{T}[1] \text{x}[4] - 6 \text{kd}[1]^2 \text{kd}[2]^2 \\ & \text{km}[2]^2 \text{T}[1] \text{x}[4] - 3 \text{kd}[1]^3 \text{kd}[2]^2 \text{km}[2]^2 \text{T}[1]^2 \text{x}[4] + 12 \text{kd}[1]^3 \\ & \text{kd}[2] \text{km}[2]^2 \text{T}[2] \text{x}[4] + 9 \text{kcr} \text{kd}[1]^3 \text{kd}[2] \text{km}[2]^2 \text{T}[2] \text{x}[4] - 6 \\ & \text{kd}[1]^2 \text{kd}[2]^2 \text{km}[2]^2 \text{T}[2] \text{x}[4] + 9 \text{kcr} \text{kd}[1]^2 \text{kd}[2]^2 \text{km}[2]^2 \text{T}[2] \\ & \text{x}[4] + 3 \text{kd}[1]^3 \text{kd}[2]^2 \text{km}[2]^2 \text{T}[1] \text{T}[2] \text{x}[4] + 9 \text{kcr} \text{kd}[1]^3 \text{kd}[2]^2 \\ & \text{km}[2]^2 \text{T}[1] \text{T}[2] \text{x}[4] + 6 \text{kd}[1]^3 \text{kd}[2]^2 \text{km}[2]^2 \text{T}[2]^2 \text{x}[4] + 9 \text{kcr} \\ & \text{kd}[1]^3 \text{kd}[2]^2 \text{km}[2]^2 \text{T}[2]^2 \text{x}[4] + 6 \text{kd}[1]^3 \text{kd}[2] \text{km}[2]^2 \text{T}[4] \text{x}[4] - 12 \\ & \text{kd}[1]^2 \text{kd}[2]^2 \text{km}[2]^2 \text{T}[4] \text{x}[4] + 6 \text{kd}[1]^3 \text{kd}[2]^2 \text{km}[2]^2 \text{T}[1] \text{T}[4] \\ & \text{x}[4] - 3 \text{kd}[1]^3 \text{kd}[2]^2 \text{km}[2]^2 \text{T}[2] \text{T}[4] \text{x}[4] - 9 \text{kcr} \text{kd}[1]^3 \text{kd}[2]^2 \\ & \text{km}[2]^2 \text{T}[2] \text{T}[4] \text{x}[4] - 3 \text{kd}[1]^3 \text{kd}[2]^2 \text{km}[2]^2 \text{T}[4]^2 \text{x}[4] + 6 \text{kd}[1]^3 \\ & \text{km}[2] \text{x}[4]^2 - 3 \text{kd}[1]^2 \text{kd}[2] \text{km}[2] \text{x}[4]^2 - 3 \text{kd}[1]^3 \text{kd}[2] \text{km}[2] \text{T}[1] \\ & \text{x}[4]^2 + 6 \text{kd}[1]^3 \text{kd}[2] \text{km}[2] \text{T}[2] \text{x}[4]^2 + 9 \text{kcr} \text{kd}[1]^3 \text{kd}[2] \text{km}[2] \\ & \text{T}[2] \text{x}[4]^2 + 3 \text{kd}[1]^3 \text{kd}[2] \text{km}[2] \text{T}[4] \text{x}[4]^2 + 2 \text{kd}[1]^3 \text{x}[4]^3)^2 + \\ & 4 \left(-(-\text{kd}[1] \text{km}[2] - \text{kd}[2] \text{km}[2] - \text{kd}[1] \text{kd}[2] \text{km}[2] \text{T}[1] - \text{kd}[1] \right. \\ & \quad \left. \text{kd}[2] \text{km}[2] \text{T}[2] + \text{kd}[1] \text{kd}[2] \text{km}[2] \text{T}[4] - \text{kd}[1] \text{x}[4])^2 - \right. \\ & \quad \left. 3 \text{kd}[1] \text{kd}[2] \text{km}[2] (-\text{km}[2] - \text{kd}[1] \text{km}[2] \text{T}[1] - \text{kd}[2] \right. \\ & \quad \left. \text{km}[2] \text{T}[2] + \text{kd}[1] \text{km}[2] \text{T}[4] + \text{kd}[2] \text{km}[2] \text{T}[4] - \text{x}[4] - \right. \\ & \quad \left. \text{kd}[1] \text{T}[1] \text{x}[4] + \text{kcr} \text{kd}[1] \text{T}[2] \text{x}[4] + \text{kd}[1] \text{T}[4] \text{x}[4]) \right)^3 \Big)^{1/3} \end{aligned} \right\}$$

t3 /. t4Sol

$$\left\{ \text{T}[3] == \text{x}[4] + \frac{\text{T}[2] \text{x}[4]}{\text{km}[2] + \text{x}[4] + \text{kd}[2] \text{km}[2]} \left(\frac{\dots 1 \dots}{3 \dots 2 \dots \text{km}[2]} + \dots 1 \dots - \frac{\dots 1 \dots}{\dots 1 \dots} \right) + \right. \\ \left. \frac{\text{kcr} \text{T}[2] \text{x}[4]}{\text{km}[2] + \text{x}[4] + \text{kd}[2] \text{km}[2]} \left(\frac{\dots 1 \dots}{\dots 1 \dots} \right) - \frac{1}{\dots 1 \dots} \text{kcr} \text{km}[1] \text{T}[2] \text{x}[4] \right. \\ \left. \left(1 + \text{kd}[1] \left(\frac{\dots 1 \dots}{3 \text{kd}[1] \text{kd}[2] \text{km}[2]} + \frac{2 \dots 1 \dots (\dots 1 \dots (\dots 1 \dots \dots 1 \dots)}{3 \dots 4 \dots} - \frac{(\dots 1 \dots)^{1/3}}{3 \times 2^{1/3} \text{kd}[1] \text{kd}[2] \text{km}[2]} \right) \right) \right\}$$

largeoutput

showless

showmore

showall

setsizelimit..

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::vars: Equations may not give solution for all "solve" variables>>

$$\left\{ \left\{ x[3][t] \rightarrow \frac{(k[2] + k[3]) x[5][t]}{k[1] x[1][t]}, x[4][t] \rightarrow \frac{k[3] (k[5] + k[6]) x[5][t]}{k[4] k[6] x[2][t]}, \right. \right.$$

$$x[6][t] \rightarrow \frac{k[3] x[5][t]}{k[6]}, x[8][t] \rightarrow \frac{k[7] x[1][t] x[7][t]}{k[8]},$$

$$x[9][t] \rightarrow \frac{k[9] x[2][t] x[7][t]}{k[10]} \left. \right\}, \left\{ x[1][t] \rightarrow 0, x[4][t] \rightarrow 0, \right.$$

$$x[5][t] \rightarrow 0, x[6][t] \rightarrow 0, x[8][t] \rightarrow 0, x[9][t] \rightarrow \frac{k[9] x[2][t] x[7][t]}{k[10]} \left. \right\},$$

$$\left\{ x[1][t] \rightarrow 0, x[2][t] \rightarrow 0, x[5][t] \rightarrow 0, x[6][t] \rightarrow 0, x[8][t] \rightarrow 0, x[9][t] \rightarrow 0, \right.$$

$$\left\{ x[2][t] \rightarrow 0, x[3][t] \rightarrow 0, x[5][t] \rightarrow 0, x[6][t] \rightarrow 0, \right.$$

$$x[8][t] \rightarrow \frac{k[7] x[1][t] x[7][t]}{k[8]}, x[9][t] \rightarrow 0 \left. \right\}$$

Here we substitute the composited parameters:

$$\left\{ \frac{k[2] + k[3]}{k[1]} \rightarrow km[1], \frac{k[5] + k[6]}{k[4]} \rightarrow km[2], \right.$$

$$\left. \frac{k[3]}{k[6]} \rightarrow kcr, \frac{k[7]}{k[8]} \rightarrow kd[1], \frac{k[9]}{k[10]} \rightarrow kd[2] \right\}$$

Then we have:


```

solution =
{
  {x[3][t] ->  $\frac{km[1] x[5][t]}{x[1][t]}$ , x[4][t] ->  $\frac{kcr * km[2] x[5][t]}{x[2][t]}$ , 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] ->  $\frac{km[1] x[5][t]}{x[1][t]}$ , x[4][t] ->  $\frac{kcr km[2] x[5][t]}{x[2][t]}$ , 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 perturbations (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 temporal dynamics when presented with input signal perturbation (the changing of [T]). The quantification can be derived from the actually fitness functions for ultrasensitive response and adaptive response. Then we save all the parameter sets as well as their score on ultrasensitivity and adaptation.

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In[433]:= Clear["Global`*"];
SetDirectory[NotebookDirectory[]];

des = {-k[1] * x[1][t] * x[3][t] + k[2] * x[5][t] + k3[t] * 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] + k3[t] * x[5][t] + k[5] * x[6][t],
  k[1] * x[1][t] * x[3][t] - k[2] * x[5][t] - k3[t] * 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], 0};

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

In[437]:= AbsoluteTiming[
  totK = 1; totP = 1; totS = 10;
  stepNum = 6;
  sampleSize = 2000;

  pars = {};
  vars = Array[x, 9]; AppendTo[vars, k3];
  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 = 10^(RandomReal[] * 4 - 3);

      Block[{tPer, step},
        step = 0;

```

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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"], k3[t] → 10 * k3[t]}]}],
  vars, {t, 0, 200 000}, MaxSteps → 10 000];
ts = tPer;
If[Length[ts] == stepNum + 1 && 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];

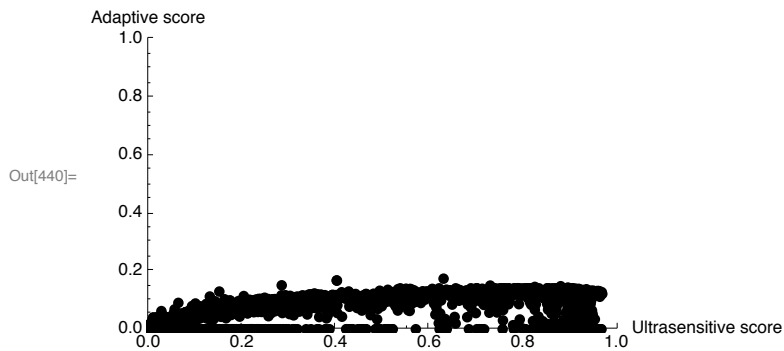
  us = Sqrt[(Abs[(x4[[5]] - x4[[3]])] / totS) * Min[(Abs[(x4[[5]] - x4[[3]])] /
    Max[Abs[(x4[[3]] - x4[[1]])], 0.001] + Abs[(x4[[5]] - x4[[3]])] /
    Max[Abs[(x4[[stepNum]] - x4[[5]])], 0.001]) / 2) / 10.0, 1.0)];
  ad = 0.0001;
  For[i = 1, i < stepNum, i++,
    ad = ad * Sqrt[
      (Min[(Max[Abs[Evaluate[x[4][Range[ts[[i]], 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, {totT, totK, totP, totS, us, ad, num,
     $\frac{ks[[2]] + ks[[3]]}{ks[[1]]}$ ,  $\frac{ks[[5]] + ks[[6]]}{ks[[4]]}$ ,  $\frac{ks[[8]]}{ks[[7]]}$ ,  $\frac{ks[[10]]}{ks[[9]]}$ }]]];
  ];
  ];
  ];
  ];

(*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];*)

In[440]:= ListPlot[Transpose[{transPars[[15]], transPars[[16]]}],
  PlotRange → {{0, 1}, {0, 1}},
  AxesLabel → {"Ultrasensitive score", "Adaptive score"},
  PlotStyle → {Thick, PointSize[0.01]}, PlotTheme → "Monochrome"]

```



```
In[441]:= maxAndIndex[a_] :=  
          {#, First@SparseArray[UnitStep[a - #]]["AdjacencyLists"]} &@Max@a
```

```
In[442]:= maxAndIndex[transPars[[15]]]
```

```
Out[442]= {0.96715, 548}
```

```
In[443]:= maxAndIndex[transPars[[16]]]
```

```
Out[443]= {0.174748, 1120}
```

```
In[444]:= usIndex = maxAndIndex[transPars[[15]]] // Last;  
          adIndex = maxAndIndex[transPars[[16]]] // Last;  
          pars[[usIndex]]
```

```
Out[446]= {372.643, 0.0324246, 0.0829501, 0.590869, 502.727, 575.843,  
          10.3571, 0.0547431, 6.6491, 1.48785, 0.0313374, 1, 1, 10, 0.96715,  
          0.121975, 577, 0.000309612, 1825.4, 0.00528557, 0.223767}
```

```
In[447]:= pars[[adIndex]]
```

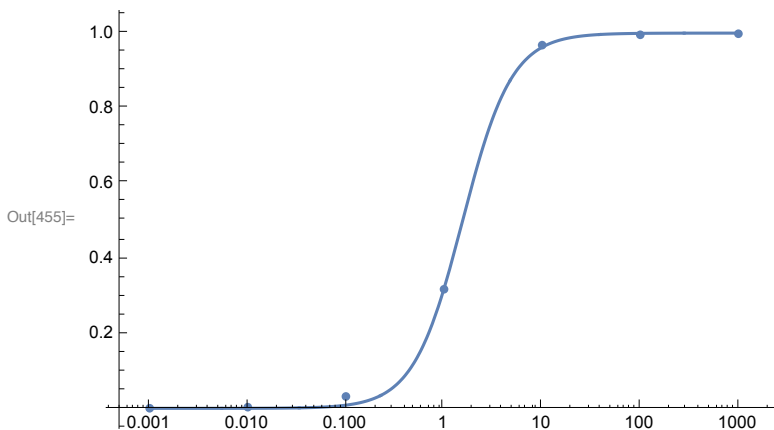
```
Out[447]= {142.87, 0.0618893, 12.62, 10.0135, 2.2853, 136.868, 0.615872,  
          0.00513072, 15.9154, 0.0917951, 4.70921, 1, 1, 10, 0.628087,  
          0.174748, 1180, 0.0887653, 13.8966, 0.00833083, 0.0057677}
```

```

In[448]:= maxAndIndex[a_] :=
  {#, First@SparseArray[UnitStep[a - #]]["AdjacencyLists"]} &@Max@a
usIndex = maxAndIndex[transPars[[15]]] // Last;
adIndex = maxAndIndex[transPars[[16]]] // Last;
stepNum = 6;
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"], k3[t] → 10 * k3[t]}]}] /.
    maxPars, vars, {t, 0, 200 000}, MaxSteps → 10 000];
  ts = tPer;
  x4 = Evaluate[x[4][ts - 0.001] /. sol] / totS;
  k3t = Evaluate[(k3[ts - 0.001]) /. sol];
];
(*Show[LogLinearPlot[Interpolation[(Transpose@{k3t, x4})][x],
  {x, 1.*^-3, 1.*^3}, PlotRange → {0, 1}, AxesLabel → {"k3", "[Sp] / [Stot]"}],
  ListLogLinearPlot[Transpose@{k3t, x4}]] *)
(*ListLogLinearPlot[Transpose@{k3t, x4}, Joined → True] *)
fittedHill = FindFit[Transpose@{k3t, x4}, x^n / (hillK + x^n), {hillK, n}, x]
Show[LogLinearPlot[x^n / (hillK + x^n) /. fittedHill, {x, 10^-3, 10^3}],
  ListLogLinearPlot[Transpose@{k3t, x4}]]

```

Out[454]= {hillK → 2.13242, n → 1.73629}



```

In[456]:= maxPars = Solve[Array[k, 10] == pars[[adIndex]][[Range[10]]]];
totT = pars[[adIndex]][[11]]
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", k3[t] → 10 * k3[t]}]}] /.
    maxPars, vars, {t, 0, 200 000}, MaxSteps → 10 000];
  ts = tPer;
  x4 = Evaluate[x[4][ts - 0.001] /. sol];
  k3t = Evaluate[(k3[ts - 0.001]) /. sol];
];
Plot@{{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[456]= 4.70921

