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).

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

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.

$$\frac{d[K]}{dt} = -k[1][K][S] + k[2][KS] + k[3][KS] - k[7][T][K] + k[8][TK] + k[11]\,k_d - k_d[K],$$
$$\frac{d[P]}{dt} = -k[4][P][S_p] + k[5][PS_p] + k[6][PS_p] - k[9][T][P] + k[10][TP],$$
$$\frac{d[S]}{dt} = -k[1][K][S] + k[2][KS] + k[6][PS_p],$$
$$\frac{d[S_p]}{dt} = -k[4][P][S_p] + k[3][KS] + k[5][PS_p],$$
$$\frac{d[KS]}{dt} = k[1][K][S] - k[2][KS] - k[3][KS],$$
$$\frac{d[PS_p]}{dt} = k[4][P][S_p] - k[5][PS_p] - k[6][PS_p],$$
$$\frac{d[T]}{dt} = -k[7][T][K] + k[8][TK] - k[9][T][P] + k[10][TP],$$
$$\frac{d[TK]}{dt} = k[7][T][K] - k[8][TK],$$
$$\frac{d[TP]}{dt} = k[9][T][P] - k[10][TP].$$

And the system need to follow these conservation equations:

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

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

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.

(NewKern) In[278]:=

```
Clear["Global`*"];
SetDirectory[NotebookDirectory[]];
kd = 10;
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] + k11[t] * kd - kd * x[1][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], 0};

init = {totK, totP, totS, 0, 0, 0, totT, 0, 0, 1. * 10^-4};
(*init={tot[1],tot[2],tot[3],0.00001,0.00001,0.00001,totT,0.00001,0.00001};*)
```

(NewKern) In[155]:=

```
AbsoluteTiming[
 totK = 0.0001; totP = 0.1; totS = 0.1;
 stepNum = 5;
 sampleSize = 100 000;

 pars = {};
 vars = Array[x, 9]; AppendTo[vars, k11];
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 = 1. * 10^(RandomReal[] * 4 - 3);

    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]]},
```

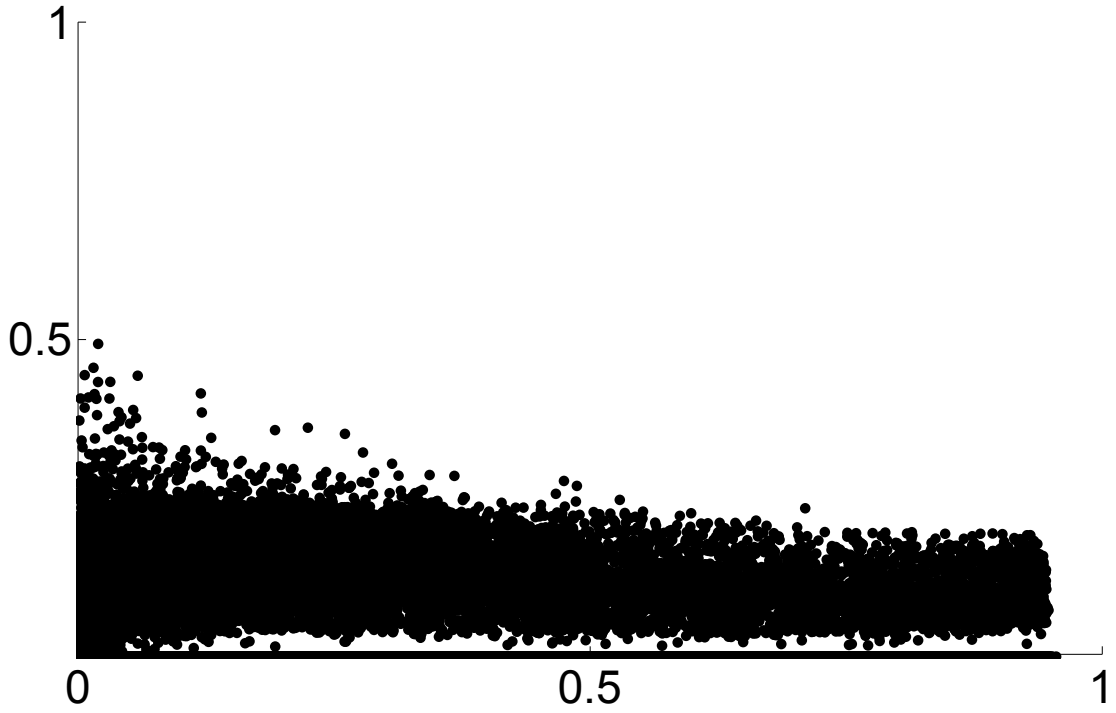
```
        WhenEvent[Norm[df] < ssthreshold, {AppendTo[tPer, t], step = step + 1,
          If[step > stepNum, "StopIntegration"], k11[t] → 10 * k11[t]}]],
       vars, {t, 0, 200 000}, MaxSteps → 10 000];
     ts = tPer;
     If[Length[ts] == stepNum + 1 && AllTrue[ts, Positive],
      x4 = Evaluate[x[4][ts - 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[[4]] - x4[[3]])] / totS) *
          Min[((Abs[(x4[[4]] - x4[[3]])] / Max[Abs[(x4[[3]] - x4[[1]])], 0.001] +
                Abs[(x4[[4]] - x4[[3]])] / Max[
                 Abs[(x4[[stepNum + 1]] - x4[[4]])], 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]]] / (0.2 * totS)), 1.0] *
            ((0.01) / (Max[Abs[(x4[[i + 1]] - x4[[i]]) / totS], 0.01])))];
      ];
      ad = (ad / 0.0001) ^ (1 / (stepNum));

      ks = Array[k, 10];
      AppendTo[pars, Join[ks, {totT, totK, totP, totS, 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];
```

(NewKern) Out[155]=

```
{16 190., Null}
```

(NewKern) In[215]:=
```
ListPlot[Transpose[{transPars[[15]], transPars[[16]]}],
 PlotRange → {{0, 1}, {0, 1}},
 (*AxesLabel→{"Ultrasensitive score","Adaptive score"},*)
 Ticks → {{0, 0.5, 1}, {0.5, 1}}, PlotStyle → {Thick, PointSize[0.01]},
 PlotTheme → "Monochrome", PlotLabel → None,
 LabelStyle → {24, GrayLevel[0]}, ImageSize → Large]
```

(NewKern) Out[215]=



(NewKern) In[159]:=
```
maxAndIndex[a_] :=
 {#, First@SparseArray[UnitStep[a - #]]["AdjacencyLists"]} &@Max@a
```

(NewKern) In[160]:=
```
maxAndIndex[transPars[[15]]]
```

(NewKern) Out[160]=
```
{0.954394, 46 581}
```

(NewKern) In[162]:=
```
maxAndIndex[transPars[[16]]]
```

(NewKern) Out[162]=
```
{0.494328, 69 663}
```

(NewKern) In[163]:=
```
usIndex = maxAndIndex[transPars[[15]]] // Last;
adIndex = maxAndIndex[transPars[[16]]] // Last;
pars[[usIndex]]
```

(NewKern) Out[165]=
```
{0.00824242, 0.0142975, 0.389576, 0.00995311, 107.866, 0.00631495,
 2.75791, 0.00442517, 124.866, 0.0176944, 0.00634784, 0.0001, 0.1,
 0.1, 0.954394, 0., 47 503, 48.9994, 10 838.1, 0.00160454, 0.000141707}
```

(NewKern) In[166]:=
```
pars[[adIndex]]
```

(NewKern) Out[166]=
```
{0.735571, 118.646, 582.997, 706.839, 0.00242219, 59.3703, 0.58786,
 0.00121274, 151.948, 0.165247, 7.60963, 0.0001, 0.1, 0.1, 0.0184361,
 0.494328, 71 037, 953.876, 0.0839974, 0.00206297, 0.00108753}
```

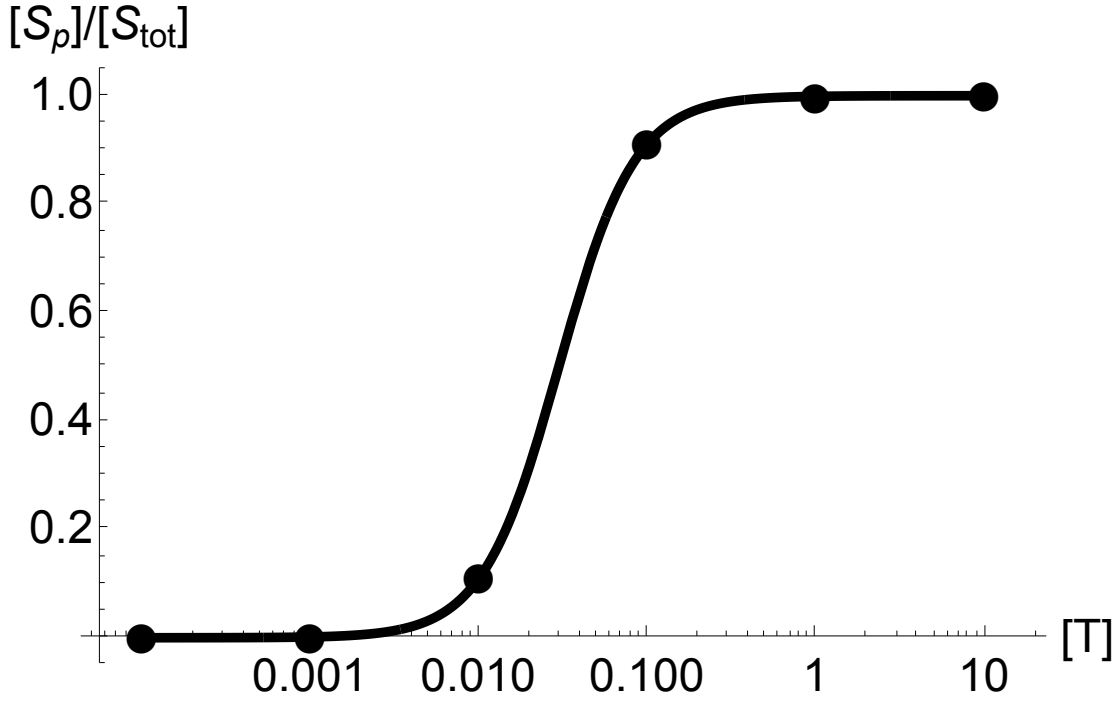
(NewKern) In[167]:=

```
init = {totK, totP, totS, 0, 0, 0, totT, 0, 0, 1. * 10^-4};
maxAndIndex[a_] :=
 {#, First@SparseArray[UnitStep[a - #]]["AdjacencyLists"]} &@Max@a
usIndex = maxAndIndex[transPars[[15]]] // Last;
adIndex = maxAndIndex[transPars[[16]]] // Last;
stepNum = 5;
maxPars = Solve[Array[k, 10] == pars[[usIndex]][[Range[10]]]];
totT = pars[[usIndex]][[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"], k11[t] → 10 * k11[t]}]]} /.
    maxPars, vars, {t, 0, 200 000}, MaxSteps → 10 000];
  ts = tPer;
  x4 = Evaluate[x[4][ts - 0.001] /. sol] / totS;
  k11t = Evaluate[(k11[ts - 0.001]) /. sol];
 ];
fittedHill = FindFit[Transpose@{k11t, x4},
  a + (b - a) * hillK / (hillK + x^(-n)), {a, b, hillK, n}, x]
Show[LogLinearPlot[a + (b - a) * hillK / (hillK + x^(-n)) /. fittedHill,
  {x, 10^-4, 10}, (*Ticks→{Automatic,{0,0.5,1}},*) PlotRange → {-0.05, 1.05},
  AxesLabel → {"[T]", "[Sp]/[Stot]"}, PlotTheme → "Monochrome",
  PlotStyle → {Thickness[0.01]}], ListLogLinearPlot[Transpose@{k11t, x4},
  PlotTheme → "Monochrome", PlotMarkers → {Automatic, 24}],
 PlotLabel → None, LabelStyle → {24, GrayLevel[0]}, ImageSize → Large]
```

(NewKern) Out[174]=

$$\{a \to -0.000757508,\ b \to 0.998489,\ hillK \to 864.572,\ n \to 1.9195\}$$

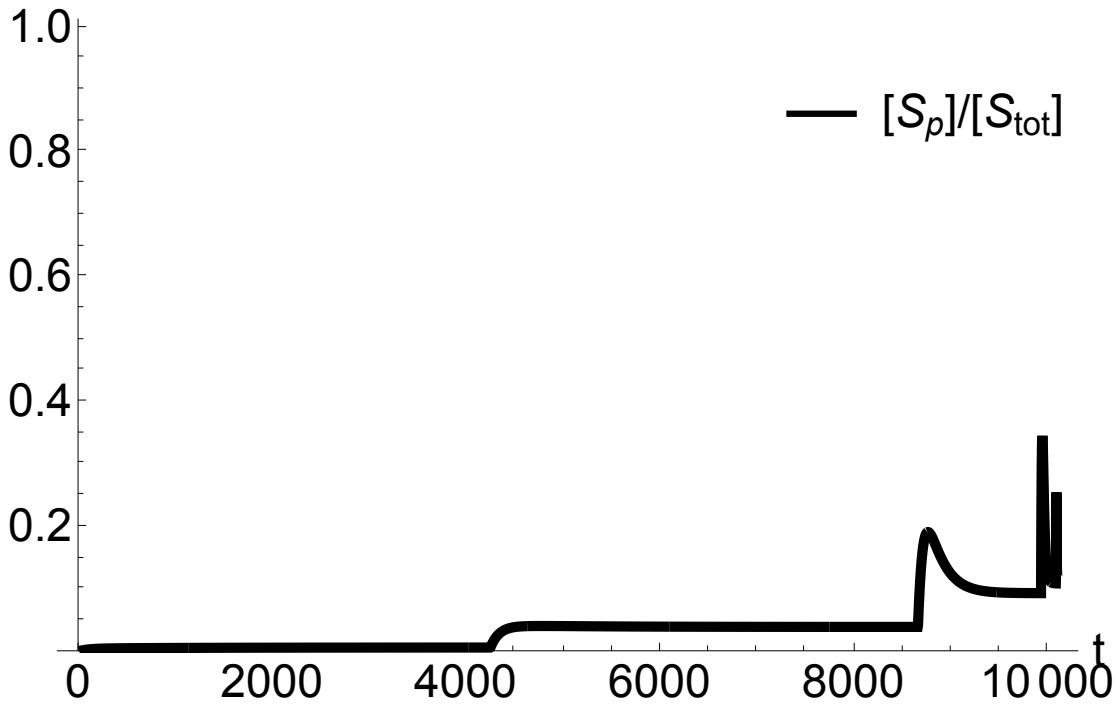
(NewKern) Out[175]=



(NewKern) In[180]:=

```
init = {totK, totP, totS, 0, 0, 0, totT, 0, 0, 1. * 10^-4};
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"], k11[t] → 10 * k11[t]}]]} /.
     maxPars, vars, {t, 0, 200 000}, MaxSteps → 10 000];
  ts = tPer;
  x4 = Evaluate[x[4][ts - 0.001] /. sol];
  k11t = Evaluate[(k11[ts - 0.001]) /. sol];
 ];
Plot[{{x[4][t] / totS} /. sol}, {t, 0, ts[[stepNum]] - 0.01},
 PlotLegends → Placed[{"[Sp]/[Stot]"}, {0.85, 0.85}], PlotRange → {0, 1.01},
 AxesLabel → {"t"}, PlotTheme → "Monochrome", PlotStyle → {Thickness[0.01]},
 PlotLabel → None, LabelStyle → {24, GrayLevel[0]}, ImageSize → Large]
```

(NewKern) Out[183]=



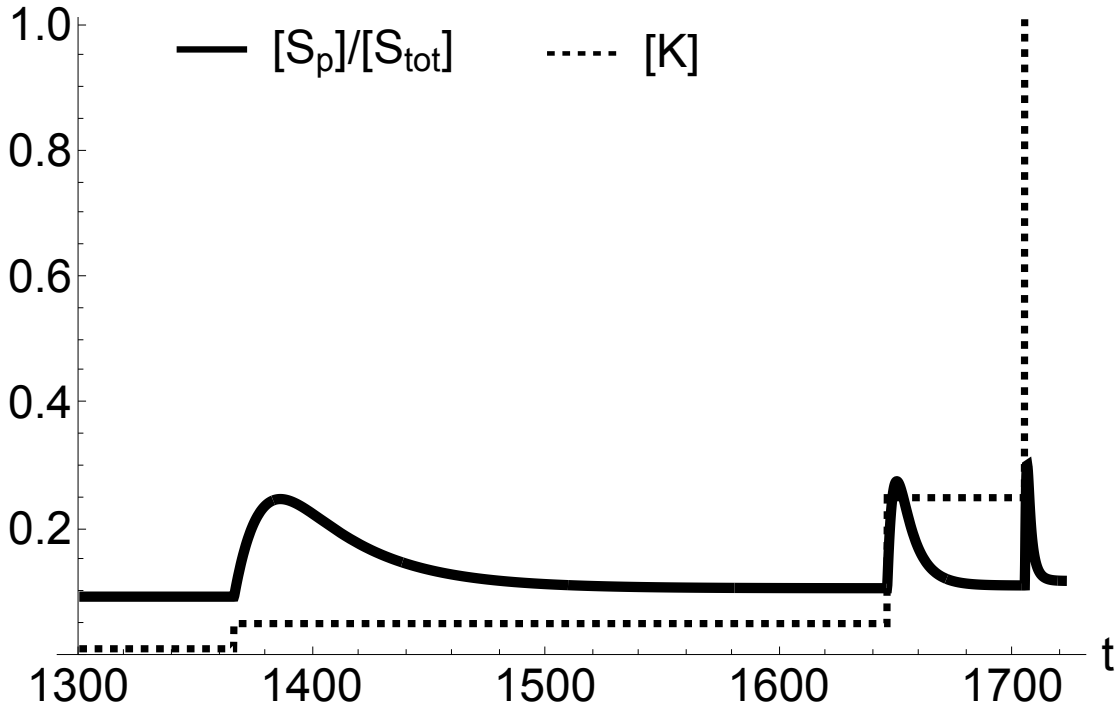
(NewKern) In[204]:=

```
init = {totK, totP, totS, 0, 0, 0, totT, 0, 0, 0.01};
stepNum = 3;
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"], k11[t] → 5 * k11[t]}]]} /.
    maxPars, vars, {t, 0, 200 000}, MaxSteps → 10 000];
  ts = tPer;
  x4 = Evaluate[x[4][ts - 0.001] /. sol];
  k11t = Evaluate[(k11[ts - 0.001]) /. sol];
 ];
Show[Plot[{{x[4][t] / totS} /. sol}, {t, 1300, ts[[stepNum + 1]] - 0.01},
  PlotLegends → Placed[{"[Sp]/[Stot]"}, {0.25, 0.95}], PlotRange → {0, 1.01},
  AxesLabel → {"t"}, PlotTheme → "Monochrome", PlotStyle → {Thickness[0.01]},
  PlotLabel → None, LabelStyle → {24, GrayLevel[0]}, ImageSize → Large],
 Plot[{{k11[t]} /. sol}, {t, 1300, ts[[stepNum + 1]] - 0.01},
  PlotLegends → Placed[{"[K]"}, {0.55, 0.95}],
  PlotRange → {0, 1.01}, AxesLabel → {"t"}, PlotTheme → "Monochrome",
  PlotStyle → {Dashed, Thickness[0.007]}, PlotLabel → None,
  LabelStyle → {24, GrayLevel[0]}, ImageSize → Large]]
```

(NewKern) Out[206]=

```
7.60963
```

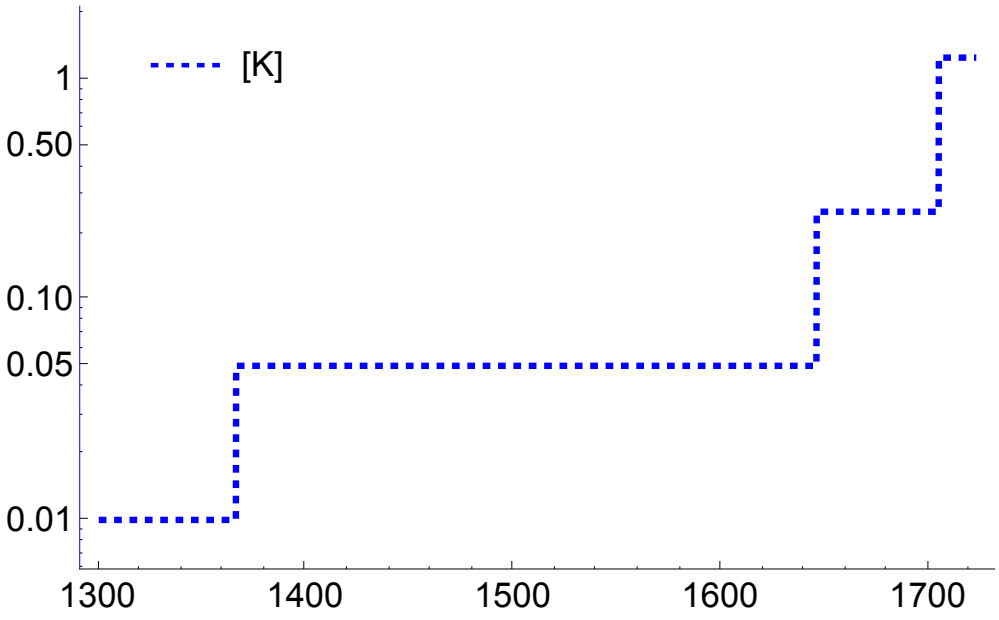
(NewKern) Out[208]=



(NewKern) In[209]:=

```
input = LogPlot[{{k11[t]} /. sol}, {t, 1300, ts[[stepNum + 1]] - 0.01},
  PlotLegends → Placed[{"[K]"}, {0.15, 0.9}], PlotTheme → "Monochrome",
  PlotStyle → {Blue, Dashed, Thickness[0.007]}, Ticks → {},
  LabelStyle → {18, GrayLevel[0]}, ImageSize → Large,
  ImagePadding → 50, Frame → {True, True, False, False},
  FrameStyle → {Automatic, Blue, Automatic, Automatic}]
```

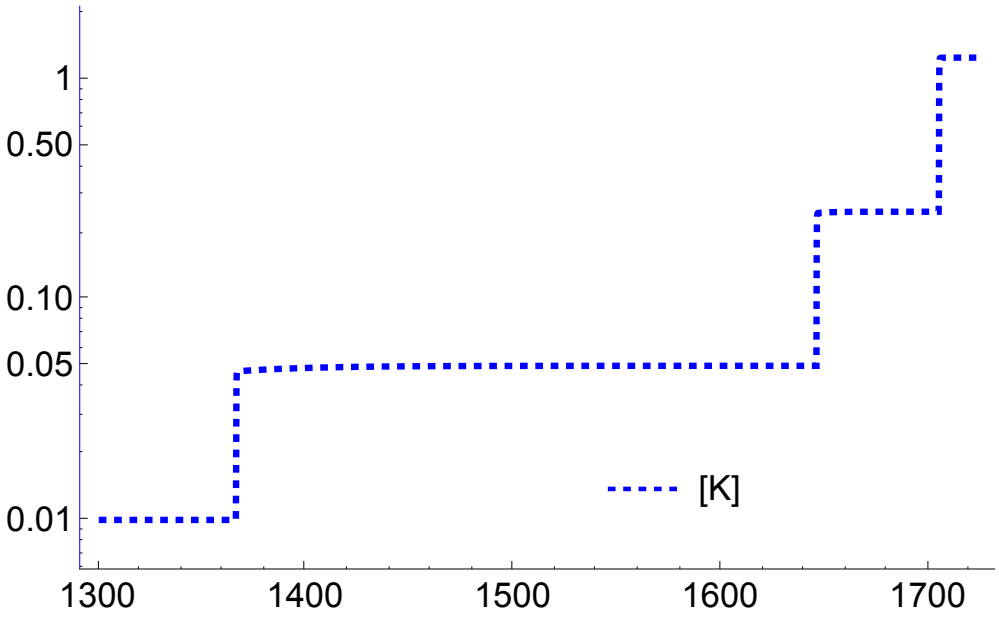
(NewKern) Out[209]=



(NewKern) In[210]:=

```
actualInput = LogPlot[{{x[1][t]} /. sol}, {t, 1300, ts[[stepNum + 1]] - 0.01},
  PlotLegends → Placed[{"[K]"}, {0.65, 0.15}], PlotTheme → "Monochrome",
  PlotStyle → {Blue, Dashed, Thickness[0.007]}, Ticks → {},
  LabelStyle → {18, GrayLevel[0]}, ImageSize → Large,
  ImagePadding → 50, Frame → {True, True, False, False},
  FrameStyle → {Automatic, Blue, Automatic, Automatic}]
```

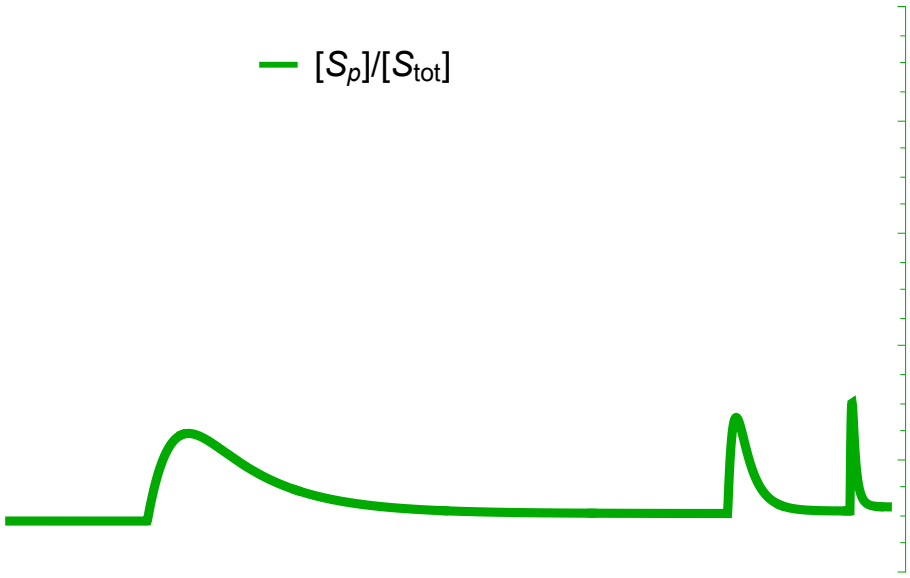
(NewKern) Out[210]=



(NewKern) In[211]:=

```
output = Plot[{{x[4][t] / totS} /. sol}, {t, 1300, ts[[stepNum + 1]] - 0.01},
  PlotLegends → Placed[{"[Sp]/[Stot]"}, {0.4, 0.9}], PlotRange → {0, 1},
  PlotStyle → {Darker[Green], Thickness[0.01]}, Ticks → {0, 0.5, 1},
  LabelStyle → {18, GrayLevel[0]}, ImageSize → Large, ImagePadding → 50,
  (*Axes→False,*)Frame → {False, False, False, True},
  FrameTicks → {None, None, None, {0, 0.5, 1}},
  FrameStyle → {Automatic, Automatic, Automatic, Darker[Green]}]
```

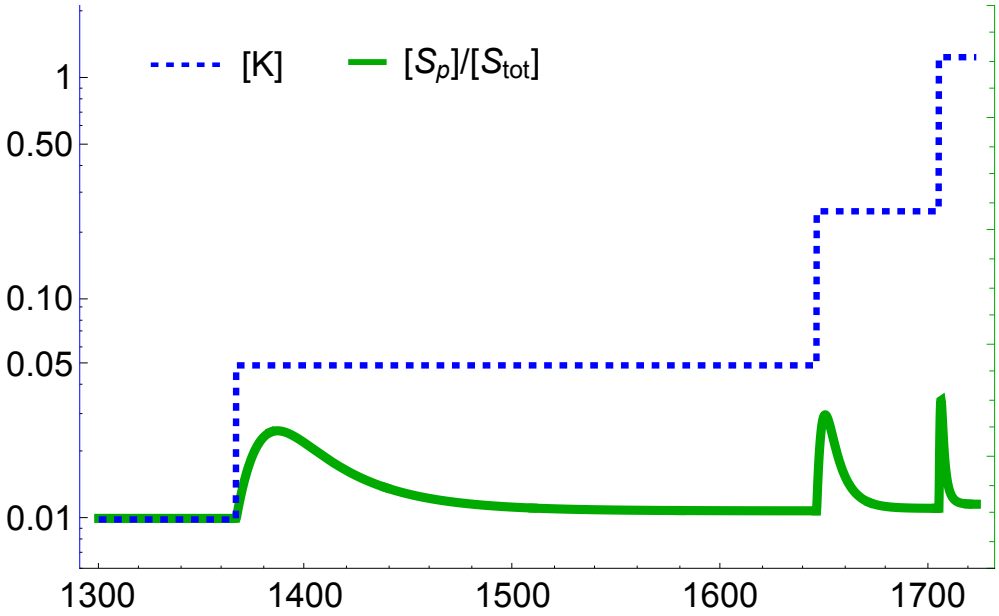
(NewKern) Out[211]=



(NewKern) In[212]:=

```
adPlot = Overlay[{output, input}]
Export["scaffoldTitrationUnsaturatedVaringKAd.eps", adPlot];
Export["scaffoldTitrationUnsaturatedVaringKAd.pdf", adPlot];
```

(NewKern) Out[212]=



(NewKern) In[216]:=

```
us10index = Reverse[Ordering[transPars[[15]], -10]]
```

(NewKern) Out[216]=

```
{46 581, 86 053, 55 163, 22 701, 73 649, 35 579, 78 074, 83 646, 35 959, 96 101}
```

(NewKern) In[217]:=

```
ad10index = Reverse[Ordering[transPars[[16]], -10]]
```

(NewKern) Out[217]=

```
{69 663, 54 715, 21 683, 47 613, 38 276, 15 415, 96 639, 73 216, 46 486, 3761}
```

(NewKern) In[218]:=

```
us10pars = pars[[us10index]]
```

(NewKern) Out[218]=

```
{{0.00824242, 0.0142975, 0.389576, 0.00995311, 107.866, 0.00631495,
  2.75791, 0.00442517, 124.866, 0.0176944, 0.00634784, 0.0001, 0.1,
  0.1, 0.954394, 0., 47503, 48.9994, 10838.1, 0.00160454, 0.000141707},
 {81.81, 779.915, 0.0709024, 0.0236294, 1.48281, 0.00181968,
  0.0051667, 465.845, 388.389, 25.7394, 4.51435, 0.0001, 0.1, 0.1,
  0.950402, 0., 87739, 9.53411, 62.8297, 90163.1, 0.0662722},
 {0.00743688, 0.0113029, 0.671015, 0.00492874, 566.87, 103.834,
  0.00243833, 909.147, 3.67405, 0.00932696, 2.14538, 0.0001, 0.1,
  0.1, 0.950329, 0., 56261, 91.7478, 136080., 372856., 0.00253861},
 {0.00698892, 0.00167367, 318.128, 0.0038769, 75.9398, 0.0071346,
  0.00129829, 0.0166369, 12.6615, 4.64243, 0.0212571, 0.0001, 0.1,
  0.1, 0.947997, 0., 23144, 45519.2, 19589.6, 12.8145, 0.366656},
 {6.10743, 649.535, 0.752426, 0.00147295, 8.05263, 0.0284595,
  0.0154783, 1.51283, 2.46765, 0.111024, 0.00668883, 0.0001, 0.1,
  0.1, 0.947944, 0., 75112, 106.475, 5486.33, 97.739, 0.0449916},
 {0.00709114, 0.00549381, 0.565582, 0.00590914, 0.198451, 13.464,
  0.644136, 74.2185, 254.25, 0.351952, 1.67155, 0.0001, 0.1, 0.1,
  0.947933, 0., 36286, 80.5337, 2312.08, 115.222, 0.00138427},
 {0.00695203, 0.0156043, 154.269, 0.00139535, 1.37544, 0.0023542,
  0.938676, 81.4574, 1.10378, 0.0248065, 0.549622, 0.0001, 0.1,
  0.1, 0.947673, 0., 79621, 22192.8, 987.415, 86.779, 0.022474},
 {0.00740196, 0.0417947, 0.679874, 0.0909913, 264.63, 0.0128765,
  0.324899, 54.7032, 0.00591257, 94.04, 0.705696, 0.0001, 0.1,
  0.1, 0.947585, 0., 85293, 97.4969, 2908.44, 168.37, 15905.1},
 {0.00696942, 0.130711, 16.19, 0.00115111, 269.693, 0.0455591,
  0.0527405, 5.51065, 310.695, 0.0375332, 0.0493036, 0.0001, 0.1,
  0.1, 0.947438, 0., 36673, 2341.76, 234329., 104.486, 0.000120804},
 {0.00707415, 4.41596, 185.361, 0.00390312, 0.00318256, 0.060568,
  0.321758, 32.2432, 280.976, 0.117636, 4.58475, 0.0001, 0.1, 0.1,
  0.947386, 0., 97997, 26826.8, 16.3332, 100.21, 0.000418669}}
```

(NewKern) In[219]:=

```
ad10pars = pars[[ad10index]]
```

(NewKern) Out[219]=

```
{{0.735571, 118.646, 582.997, 706.839, 0.00242219, 59.3703, 0.58786,
  0.00121274, 151.948, 0.165247, 7.60963, 0.0001, 0.1, 0.1, 0.0184361,
  0.494328, 71 037, 953.876, 0.0839974, 0.00206297, 0.00108753},
 {1.95101, 121.837, 177.418, 663.364, 0.295517, 170.85, 2.66429,
  0.00424728, 363.467, 0.115019, 1.58205, 0.0001, 0.1, 0.1, 0.0138765,
  0.456537, 55 807, 153.385, 0.257996, 0.00159415, 0.000316449},
 {0.36069, 1.5341, 135.513, 428.197, 0.00305221, 0.113468, 11.0447,
  0.00370085, 137.291, 0.00948276, 0.212784, 0.0001, 0.1, 0.1, 0.00525981,
  0.444976, 22 107, 379.959, 0.00027212, 0.000335079, 0.0000690704},
 {3.33141, 0.0187469, 5.62504, 203.725, 0.175379, 479.252, 3.97671,
  0.00175581, 88.8423, 0.00153736, 0.11137, 0.0001, 0.1, 0.1, 0.0570813,
  0.443989, 48 557, 1.69411, 2.35331, 0.000441523, 0.0000173044},
 {0.426371, 3.09422, 55.6686, 227.293, 0.00159084, 0.0266362, 179.437,
  0.96391, 0.782552, 0.0158895, 9.14562, 0.0001, 0.1, 0.1, 0.0302836,
  0.434335, 39 037, 137.821, 0.000124188, 0.00537185, 0.0203047},
 {17.0937, 3.41101, 0.301565, 72.2851, 2.83121, 4.31268, 261.866,
  0.144543, 6.41265, 0.0022489, 0.253744, 0.0001, 0.1, 0.1, 0.0183213,
  0.434083, 15 707, 0.217189, 0.0988294, 0.000551975, 0.000350698},
 {259.822, 0.022446, 56.5581, 58.2245, 0.134017, 2.74127, 367.653,
  0.002858, 195.294, 0.0230284, 0.505971, 0.0001, 0.1, 0.1, 0.118749,
  0.416015, 98 542, 0.217766, 0.0493828, 7.77363 × 10^-6, 0.000117916},
 {0.0472267, 0.0935084, 0.15388, 74.0217, 0.0316643, 0.559788, 10.5727,
  0.00112543, 85.2736, 0.00113777, 1.04593, 0.0001, 0.1, 0.1, 0.0148946,
  0.414948, 74 671, 5.23832, 0.00799026, 0.000106446, 0.0000133426},
 {0.180744, 111.871, 351.439, 406.631, 0.148401, 476.674, 3.73393,
  0.00363532, 220.459, 0.0118537, 1.9494, 0.0001, 0.1, 0.1, 0.00891086,
  0.40966, 47 406, 2563.34, 1.17262, 0.00097359, 0.0000537682},
 {116.352, 2.01487, 12.9521, 243.552, 0.00116233, 14.4008, 450.646,
  0.13848, 41.2994, 0.0229058, 0.332521, 0.0001, 0.1, 0.1, 0.00123906,
  0.408018, 3837, 0.128636, 0.059133, 0.000307293, 0.000554629}}
```

(NewKern) In[283]:=

```
us10pars = {{0.008242419051215819`, 0.014297548563237405`, 0.38957563488014546`,
    0.009953109596179146`, 107.8661008438542`, 0.006314953758460749`,
    2.7579126947038177`, 0.004425168723158293`, 124.86588613940748`,
    0.017694402307212805`, 0.0063478384949193474`, 0.0001`, 0.1`,
    0.1`, 0.9543938503067778`, 0.`, 47 503, 48.99935091067816`,
    10838.061688683034`, 0.0016045354632350055`, 0.00014170725771695366`},
   {81.80999118688213`, 779.9147566804214`, 0.07090238484877774`,
    0.023629370047937814`, 1.4828071618957515`, 0.0018196786959553148`,
    0.005166697684825859`, 465.8452236367559`, 388.3893982720522`,
    25.739414637152606`, 4.514347828776098`, 0.0001`, 0.1`,
    0.1`, 0.9504024006847739`, 0.`, 87 739, 9.534112493466903`,
    62.829725785316626`, 90163.05037643343`, 0.06627218650062923`},
   {0.007436884564263904`, 0.011302916513155986`, 0.6710146976607011`,
    0.004928737708475768`, 566.8697056759694`, 103.8344293843366`,
    0.002438333353593688`, 909.1470323607329`, 3.6740507654320447`,
    0.009326964883691391`, 2.145377995148467`, 0.0001`, 0.1`,
    0.1`, 0.9503290174951521`, 0.`, 56 261, 91.7477753322358`,
    136080.30589798294`, 372855.92268210783`, 0.002538605337587`},
   {0.006988922196113958`, 0.0016736661716845922`, 318.12838095689193`,
    0.0038768972135044114`, 75.93982400090636`, 0.007134599728375874`,
    0.0012982914730214718`, 0.016636934080863704`, 12.661534720214746`,
    4.642433150565979`, 0.021257093058109425`, 0.0001`, 0.1`,
    0.1`, 0.9479971029049556`, 0.`, 23 144, 45519.18674956106`,
    19589.62397457647`, 12.814483054521729`, 0.3666564325060936`},
```

```
        {6.107425037429362`, 649.5353552592625`, 0.7524260920765895`,
         0.0014729497141937231`, 8.052633347726365`, 0.02845947181373509`,
         0.015478298783216222`, 1.5128329994165866`, 2.4676545739184803`,
         0.11102367043959017`, 0.006688833524495067`, 0.0001`, 0.1`,
         0.1`, 0.9479441576758459`, 0.`, 75 112, 106.47495095986437`,
         5486.3331325357585`, 97.7389712270586`, 0.044991576865351775`},
        {0.007091142109866954`, 0.005493811788922619`, 0.5655818097924644`,
         0.005909143440224084`, 0.19845111705829294`, 13.46397169306408`,
         0.6441363015506287`, 74.2184912184464`, 254.2504103533836`,
         0.3519518924650007`, 1.6715460955512464`, 0.0001`, 0.1`,
         0.1`, 0.9479331300630189`, 0.`, 36 286, 80.53365913888048`,
         2312.081767574129`, 115.22171788762766`, 0.0013842726624347292`},
        {0.006952033584603749`, 0.015604271163729836`, 154.2691402400409`,
         0.001395354228516014`, 1.3754389380406353`, 0.0023541971467900594`,
         0.9386755333546533`, 81.45736642754734`, 1.1037849990246893`,
         0.024806469768168832`, 0.5496221885500605`, 0.0001`, 0.1`,
         0.1`, 0.9476731015134761`, 0.`, 79 621, 22192.750169229592`,
         987.4145984082729`, 86.77904508327147`, 0.022474005164128855`},
        {0.007401960884046088`, 0.04179474538192852`, 0.6798736666393617`,
         0.09099126158417799`, 264.62954656186565`, 0.012876495300717751`,
         0.3248988406197796`, 54.70317785569333`, 0.00591257184529494`,
         94.04004332816972`, 0.7056955303863556`, 0.0001`, 0.1`,
         0.1`, 0.9475847674835752`, 0.`, 85 293, 97.49692322432392`,
         2908.4377823725404`, 168.36987707109427`, 15905.099470884934`},
        {0.006969416194173042`, 0.13071090665252838`, 16.18998053451299`,
         0.0011511100049083453`, 269.69306331568555`, 0.04555911640342133`,
         0.052740489526546266`, 5.510645994323729`, 310.69539698143484`,
         0.03753319708675017`, 0.04930363704868246`, 0.0001`, 0.1`,
         0.1`, 0.9474380184157137`, 0.`, 36 673, 2341.758762349542`,
         234329.1442884873`, 104.4860607816318`, 0.00012080384019655403`},
        {0.007074145703139318`, 4.415959837084385`, 185.36101347734967`,
         0.0039031213188464313`, 0.003182560277136155`, 0.060568034295841795`,
         0.3217580470903207`, 32.24322799746911`, 280.9757311687689`,
         0.11763574585579659`, 4.5847530834562225`, 0.0001`, 0.1`,
         0.1`, 0.9473864338646523`, 0.`, 97 997, 26826.839773771706`,
         16.333234190071103`, 100.20954654917495`, 0.00041866870624900456`}};
```

(NewKern) In[284]:=

```
ad10pars = {{0.735571222241763`, 118.64642205965505`, 582.9971400470964`,
     706.8394378169739`, 0.002422186552963498`, 59.37025775545801`,
     0.5878600457124783`, 0.0012127352844165504`, 151.94773728590604`,
     0.16524734571475494`, 7.609634626396518`, 0.0001`, 0.1`, 0.1`,
     0.01843606088092748`, 0.4943283032183251`, 71 037, 953.8757646994238`,
     0.08399740700006708`, 0.002062965995497673`, 0.001087527518779857`},
    {1.9510092320017631`, 121.83725928120194`, 177.41759263832117`,
     663.3635861616302`, 0.2955173181857165`, 170.84963961593652`,
     2.664287015821727`, 0.004247279212263593`, 363.46711701346464`,
     0.11501887482620801`, 1.5820469188948103`, 0.0001`, 0.1`, 0.1`,
     0.013876464021015205`, 0.45653676798203247`, 55 807, 153.38464165670985`,
     0.2579960077766799`, 0.0015941522767784968`, 0.0003164491901531415`},
    {0.3606895529509488`, 1.534103107697038`, 135.51328873200438`,
     428.19653077185984`, 0.003052211073389339`, 0.11346843652385563`,
     11.044705447359437`, 0.003700851807618234`, 137.29122248645643`,
     0.009482758367214558`, 0.2127838614419442`, 0.0001`, 0.1`, 0.1`,
     0.005259805474808121`, 0.4449755951280263`, 22 107, 379.959415842407`,
     0.0002721195507754508`, 0.00033507926718888024`, 0.0000690703906300347 6`},
    {3.3314111834820537`, 0.01874688007545478`, 5.62503583285114`,
     203.72521708429753`, 0.17537882173838426`, 479.2524500380064`,
     3.976706503079339`, 0.0017558092879061632`, 88.84226481994725`,
     0.0015373628546780326`, 0.11137016049474194`, 0.0001`, 0.1`, 0.1`,
```

```
  0.05708129990082774`, 0.4439885965921797`, 48 557, 1.6941117148522045`,
  2.353306260861005`, 0.000441523478422801`, 0.000017304408636967314`},
 {0.4263712958128932`, 3.094221616489053`, 55.66855280989356`,
  227.29294234821705`, 0.0015908403954287436`, 0.026636246655785505`,
  179.4373522429962`, 0.9639102346112335`, 0.7825520587634579`,
  0.015889462525724322`, 9.145624166899875`, 0.0001`, 0.1`, 0.1`,
  0.030283611858450087`, 0.4343354873088408`, 39 037, 137.82066242135073`,
  0.00012418813694606417`, 0.005371848294472684`, 0.020304671552243955`},
 {17.093740671561175`, 3.4110104554820273`, 0.30156520059711117`,
  72.28509472942149`, 2.8312131539517034`, 4.312677838284476`,
  261.8657186740548`, 0.14454341959708286`, 6.412653361393108`,
  0.0022489030884043633`, 0.2537436236561277`, 0.0001`, 0.1`, 0.1`,
  0.01832132842854263`, 0.4340831475771345`, 15 707, 0.217189187984801`,
  0.0988293785735121`, 0.000551975341900 3141`, 0.000350697747354272`},
 {259.8224990012565`, 0.022446000141571533`, 56.558067727518896`,
  58.22453893726362`, 0.13401710647030238`, 2.7412742760945514`,
  367.65303670461117`, 0.0028579974427508114`, 195.2944476702128`,
  0.023028381160966737`, 0.5059707885483982`, 0.0001`, 0.1`, 0.1`,
  0.11874911685269912`, 0.41601545293856546`, 98 542, 0.21776602852005836`,
  0.04938281066790332`, 7.773626646383596`*^-6, 0.00011791621029520508`},
 {0.0472267405408226`, 0.0935083874368316`, 0.15388018935405978`,
  74.02173822499718`, 0.03166428360267055`, 0.5597883119001384`,
  10.572728095393058`, 0.0011254266640571104`, 85.2735713860022`,
  0.0011377720978641365`, 1.0459271759021924`, 0.0001`, 0.1`, 0.1`,
  0.014894558619941321`, 0.4149478777602289`, 74 671, 5.238315707539667`,
  0.007990255426115827`, 0.0001064461938208268`, 0.000013342611073645071`},
 {0.18074448632237966`, 111.87094401000431`, 351.43867615111185`,
  406.63090789001194`, 0.14840084999571837`, 476.6737337341944`,
  3.7339281238515465`, 0.003635315435596232`, 220.45933748214983`,
  0.011853700004796342`, 1.9493981488480692`, 0.0001`, 0.1`, 0.1`,
  0.008910858616333062`, 0.4096603696865107`, 47 406, 2563.340268840884`,
  1.1726165555353307`, 0.0009735900946712399`, 0.000053768192085563686`},
 {116.35183658620625`, 2.0148718617952834`, 12.9521322749468`,
  243.55229354986727`, 0.0011623264113556947`, 14.400815211493702`,
  450.64565227537145`, 0.13848031079436982`, 41.29942858615112`,
  0.022905845947735887`, 0.33252083629741697`, 0.0001`, 0.1`, 0.1`,
  0.001239058727798742`, 0.40801760540357`, 3837, 0.12863573602169037`,
  0.0591329990286306`, 0.0003072931250865593`, 0.0005546286409254794`}};
```

Here we sample [T] to explore that the effect of changing [T] on both adaptive level and ultrasensitive level.

(NewKern) In[245]:=

```
AbsoluteTiming[

 SetDirectory[NotebookDirectory[]];
 vars = Array[x, 9]; AppendTo[vars, k11];
 dvars = Thread[Derivative[1][vars]];
 SeedRandom[IntegerPart[SessionTime[]]];
 ts = {};
 Block[{points, iPar, num, usToAdPars, maxPars, transPars},
  totK = 0.0001; totP = 0.1; totS = 0.1;
  stepNum = 5;
  sampleSize = 1000;
  points = 10;

  For[iPar = 1, iPar ≤ points, iPar++,
   maxPars = Solve[Array[k, 10] == us10pars[[iPar]][[Range[10]]]];
   usToAdPars = {};
```

```
For[num = 1, num ≤ sampleSize, num++,
 Block[{ssthreshold},
   (*tot[n_]:=tot[n]=10^(RandomReal[]*4-3);*)
   (*ksTest1=Array[k,10];*)
   (*totT=1.*^-3;*)
   totT = 1. * 10 ^ (RandomReal[] * 4 - 3);

   Block[{tPer, step, us, ad, x4, sol},
    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"], k11[t] → 10 * k11[t]}]]} /.
       maxPars, 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[[4]] - x4[[3]])] / totS) *
         Min[((Abs[(x4[[4]] - x4[[3]])] / Max[Abs[(x4[[3]] - x4[[1]])], 0.001] +
             Abs[(x4[[4]] - x4[[3]])] / Max[Abs[
                 (x4[[stepNum + 1]] - x4[[4]])], 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]]] / (0.2 * totS)), 1.0] *
         ((0.01) / (Max[Abs[(x4[[i + 1]] - x4[[i]]) / totS], 0.01])))];
     ];
     ad = (ad / 0.0001) ^ (1 / (stepNum));

     AppendTo[usToAdPars, {totT, us, ad, num}];
    ];
   ];
  ];
 ];
 transUsToAdPars = Transpose[usToAdPars];
 vsPlot = ListPlot[Transpose[{transUsToAdPars[[2]], transUsToAdPars[[3]]}],
   PlotRange → {{0, 1}, {0, 1}},
   (*AxesLabel→{"Ultrasensitive score","Adaptive score"},*)
   Ticks → {{0, 0.5, 1}, {0.5, 1}}, PlotStyle → {Thick, PointSize[0.01]},
   PlotTheme → "Monochrome", PlotLabel → None,
   LabelStyle → {24, GrayLevel[0]}, ImageSize → Large];
 Export[NotebookDirectory[] <> "unsaturatedUsToAd" <>
   ToString[iPar] <> ".pdf", vsPlot];
 Export[NotebookDirectory[] <> "unsaturatedUsToAd" <>
   ToString[iPar] <> ".eps", vsPlot];
 (*Print[vsPlot]*)
];
```

(NewKern) Out[245]=

```
{1615.8, Null}
```

(NewKern) In[253]:=

```
AbsoluteTiming[

 SetDirectory[NotebookDirectory[]];
 vars = Array[x, 9]; AppendTo[vars, k11];
 dvars = Thread[Derivative[1][vars]];
 SeedRandom[IntegerPart[SessionTime[]]];
 ts = {};
 totK = 0.0001; totP = 0.1; totS = 0.1;
 stepNum = 5;
 sampleSize = 1000;

 Block[{points, iPar, num, usToAdPars, maxPars, transPars},

  points = 10;

  For[iPar = 1, iPar ≤ points, iPar++,
   maxPars = Solve[Array[k, 10] == ad10pars[[iPar]][[Range[10]]]];
   adToUsPars = {};

   For[num = 1, num ≤ sampleSize, num++,
    Block[{ssthreshold},
     (*tot[n_]:=tot[n]=10^(RandomReal[]*4-3);*)
     (*ksTest1=Array[k,10];*)
     (*totT=1.*^-3;*)
     totT = 1. * 10 ^ (RandomReal[] * 4 - 3);

     Block[{tPer, step, us, ad, x4, sol},
      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"], k11[t] → 10 * k11[t]}]]} /.
        maxPars, 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[[4]] - x4[[3]])] / totS) *
            Min[((Abs[(x4[[4]] - x4[[3]])] / Max[Abs[(x4[[3]] - x4[[1]])], 0.001] +
                  Abs[(x4[[4]] - x4[[3]])] / Max[Abs[
                      (x4[[stepNum + 1]] - x4[[4]])], 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]]] / (0.2 * totS)), 1.0] *
            ((0.01) / (Max[Abs[(x4[[i + 1]] - x4[[i]]) / totS], 0.01])))];
```

```
          ];
          ad = (ad / 0.0001) ^ (1 / (stepNum));

          AppendTo[adToUsPars, {totT, us, ad, num}];
         ];
        ];
       ];
      ];
      transAdToUsPars = Transpose[adToUsPars];
      vsPlot = ListPlot[Transpose[{transAdToUsPars[[2]], transAdToUsPars[[3]]}],
        PlotRange → {{0, 1}, {0, 1}},
        (*AxesLabel→{"Ultrasensitive score","Adaptive score"},*)
        Ticks → {{0, 0.5, 1}, {0.5, 1}}, PlotStyle → {Thick, PointSize[0.01]},
        PlotTheme → "Monochrome", PlotLabel → None,
        LabelStyle → {24, GrayLevel[0]}, ImageSize → Large];
      Export[NotebookDirectory[] <> "unsaturatedAdToUs" <>
        ToString[iPar] <> ".pdf", vsPlot];
      Export[NotebookDirectory[] <> "unsaturatedAdToUs" <>
        ToString[iPar] <> ".eps", vsPlot];
      (*Print[vsPlot]*)
     ];
    ];
   ]
```

(NewKern) Out[253]=

```
{2003.78, Null}
```

Here, we alternatively sample k_s of T interacting K and P.

```
AbsoluteTiming[

 SetDirectory[NotebookDirectory[]];
 vars = Array[x, 9]; AppendTo[vars, k11];
 dvars = Thread[Derivative[1][vars]];
 SeedRandom[IntegerPart[SessionTime[]]];
 ts = {};
 totK = 0.0001; totP = 0.1; totS = 0.1;
 stepNum = 5;
 sampleSize = 1000;

 Block[{points, iPar, num, usToAdPars, maxPars, transPars},
  points = 10;

  For[iPar = 1, iPar ≤ points, iPar++,
   totT = us10pars[[iPar]][[11]];
   usToAdPars = {};

   For[num = 1, num ≤ sampleSize, num++,
    Block[{ssthreshold},
     (*tot[n_]:=tot[n]=10^(RandomReal[]*4-3);*)
     (*ksTest1=Array[k,10];*)
     (*totT=1.*^-3;*)
     (*totT=1.*10^(RandomReal[]*4-3);*)
     {maxPars} = Solve[Array[k, 10] == Join[us10pars[[iPar]][[Range[6]]],
         Table[1. * 10^(RandomReal[] * 6 - 3), {i, 1, 4}]]];

     Block[{tPer, step, us, ad, x4, sol},
      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"], k11[t] → 10 * k11[t]}]]} /.
           maxPars, 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[[4]] - x4[[3]])] / totS) *
             Min[((Abs[(x4[[4]] - x4[[3]])] / Max[Abs[(x4[[3]] - x4[[1]])], 0.001] +
                   Abs[(x4[[4]] - x4[[3]])] / Max[Abs[
                       (x4[[stepNum + 1]] - x4[[4]])], 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]]] / (0.2 * totS)), 1.0] *
                ((0.01) / (Max[Abs[(x4[[i + 1]] - x4[[i]]) / totS], 0.01])))];
         ];
         ad = (ad / 0.0001) ^ (1 / (stepNum));

         AppendTo[usToAdPars,
          Join[{totT, us, ad, num}, {k[7], k[8], k[9], k[10]} /. maxPars]];
        ];
       ];
      ];
     ];
     transUsToAdPars = Transpose[usToAdPars];
     vsPlot = ListPlot[Transpose[{transUsToAdPars[[2]], transUsToAdPars[[3]]}],
       PlotRange → {{0, 1}, {0, 1}},
       (*AxesLabel→{"Ultrasensitive score","Adaptive score"},*)
       Ticks → {{0, 0.5, 1}, {0.5, 1}}, PlotStyle → {Thick, PointSize[0.01]},
       PlotTheme → "Monochrome", PlotLabel → None,
       LabelStyle → {24, GrayLevel[0]}, ImageSize → Large];
     Export[NotebookDirectory[] <> "unsaturatedUsToAdSampleKs" <>
       ToString[iPar] <> ".pdf", vsPlot];
     Export[NotebookDirectory[] <> "unsaturatedUsToAdSampleKs" <>
       ToString[iPar] <> ".eps", vsPlot];
     (*Print[vsPlot]*)
    ];
   ];
  ]
```

(NewKern) Out[261]=

```
{3778.71, Null}
```

(NewKern) In[269]:=

```
SetDirectory[NotebookDirectory[]];
vars = Array[x, 9]; AppendTo[vars, k11];
dvars = Thread[Derivative[1][vars]];
SeedRandom[IntegerPart[SessionTime[]]];
```

```
ts = {};
totK = 0.0001; totP = 0.1; totS = 0.1;
stepNum = 5;
sampleSize = 1000;

Block[{points, iPar, num, adToUsPars, maxPars, transPars},
  points = 10;
  For[iPar = 1, iPar ≤ points, iPar++,
   totT = ad10pars[[iPar]][[11]];
   adToUsPars = {};
   For[num = 1, num ≤ sampleSize, num++,
    Block[{ssthreshold},
      (*tot[n_]:=tot[n]=10^(RandomReal[]*4-3);*)
      (*ksTest1=Array[k,10];*)
      (*totT=1.*^-3;*)
      (*totT=1.*10^(RandomReal[]*4-3);*)
      {maxPars} = Solve[Array[k, 10] == Join[ad10pars[[iPar]][[Range[6]]],
          Table[1. * 10^(RandomReal[] * 6 - 3), {i, 1, 4}]]];

      Block[{tPer, step, us, ad, x4, sol},
       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"], k11[t] → 10 * k11[t]}]]} /.
          maxPars, 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[[4]] - x4[[3]])] / totS) *
            Min[((Abs[(x4[[4]] - x4[[3]])] / Max[Abs[(x4[[3]] - x4[[1]])], 0.001] +
                  Abs[(x4[[4]] - x4[[3]])] / Max[Abs[
                      (x4[[stepNum + 1]] - x4[[4]])], 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]]] / (0.2 * totS)), 1.0] *
              ((0.01) / (Max[Abs[(x4[[i + 1]] - x4[[i]]) / totS], 0.01])))];
        ];
        ad = (ad / 0.0001) ^ (1 / (stepNum));

        AppendTo[adToUsPars,
         Join[{totT, us, ad, num}, {k[7], k[8], k[9], k[10]} /. maxPars]];
       ];
      ];
    ];
   ];
   transAdToUsPars = Transpose[adToUsPars];
```

```
  vsPlot = ListPlot[Transpose[{transAdToUsPars[[2]], transAdToUsPars[[3]]}],
    PlotRange → {{0, 1}, {0, 1}},
    (*AxesLabel→{"Ultrasensitive score","Adaptive score"},*)
    Ticks → {{0, 0.5, 1}, {0.5, 1}}, PlotStyle → {Thick, PointSize[0.01]},
    PlotTheme → "Monochrome", PlotLabel → None,
    LabelStyle → {24, GrayLevel[0]}, ImageSize → Large];
  Export[NotebookDirectory[] <> "unsaturatedAdToUsSampleKs" <>
    ToString[iPar] <> ".pdf", vsPlot];
  Export[NotebookDirectory[] <> "unsaturatedAdToUsSampleKs" <>
    ToString[iPar] <> ".eps", vsPlot];
  (*Print[vsPlot]*)
 ];
];
```

Now, we finally to sample both [T] and k_s.

(NewKern) In[285]:=

```
AbsoluteTiming[

 SetDirectory[NotebookDirectory[]];
 vars = Array[x, 9]; AppendTo[vars, k11];
 dvars = Thread[Derivative[1][vars]];
 SeedRandom[IntegerPart[SessionTime[]]];
 ts = {};
 totK = 0.0001; totP = 0.1; totS = 0.1;
 stepNum = 5;
 sampleSize = 1000;

 Block[{points, iPar, num, usToAdPars, maxPars, transPars},
  points = 10;

  For[iPar = 1, iPar ≤ points, iPar++,
   (*totT=us10pars[[iPar]][[11]];*)
   usToAdPars = {};

   For[num = 1, num ≤ sampleSize, num++,
    Block[{ssthreshold},
     (*tot[n_]:=tot[n]=10^(RandomReal[]*4-3);*)
     (*ksTest1=Array[k,10];*)
     (*totT=1.*^-3;*)
     totT = 1. * 10 ^ (RandomReal[] * 4 - 3);
     {maxPars} = Solve[Array[k, 10] == Join[us10pars[[iPar]][[Range[6]]],
         Table[1. * 10 ^ (RandomReal[] * 6 - 3), {i, 1, 4}]]];

     Block[{tPer, step, us, ad, x4, sol},
      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"], k11[t] → 10 * k11[t]}]]} /.
        maxPars, 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[[4]] - x4[[3]])] / totS) *
          Min[((Abs[(x4[[4]] - x4[[3]])] / Max[Abs[(x4[[3]] - x4[[1]])], 0.001] +
                Abs[(x4[[4]] - x4[[3]])] / Max[Abs[
                    (x4[[stepNum + 1]] - x4[[4]])], 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]]] / (0.2 * totS)), 1.0] *
            ((0.01) / (Max[Abs[(x4[[i + 1]] - x4[[i]]) / totS], 0.01])))];
      ];
      ad = (ad / 0.0001) ^ (1 / (stepNum));

      AppendTo[usToAdPars,
       Join[{totT, us, ad, num}, {k[7], k[8], k[9], k[10]} /. maxPars]];
     ];
    ];
   ];
  ];
  transUsToAdPars = Transpose[usToAdPars];
  vsPlot = ListPlot[Transpose[{transUsToAdPars[[2]], transUsToAdPars[[3]]}],
    PlotRange → {{0, 1}, {0, 1}},
    (*AxesLabel→{"Ultrasensitive score","Adaptive score"},*)
    Ticks → {{0, 0.5, 1}, {0.5, 1}}, PlotStyle → {Thick, PointSize[0.01]},
    PlotTheme → "Monochrome", PlotLabel → None,
    LabelStyle → {24, GrayLevel[0]}, ImageSize → Large];
  Export[NotebookDirectory[] <> "unsaturatedUsToAdSampleAll" <>
    ToString[iPar] <> ".pdf", vsPlot];
  Export[NotebookDirectory[] <> "unsaturatedUsToAdSampleAll" <>
    ToString[iPar] <> ".eps", vsPlot];
  (*Print[vsPlot]*)
 ];
];

Block[{points, iPar, num, adToUsPars, maxPars, transPars},
 points = 10;
 For[iPar = 1, iPar ≤ points, iPar++,
  (*totT=ad10pars[[iPar]][[11]];*)
  adToUsPars = {};
  For[num = 1, num ≤ sampleSize, num++,
   Block[{ssthreshold},
    (*tot[n_]:=tot[n]=10^(RandomReal[]*4-3);*)
    (*ksTest1=Array[k,10];*)
    (*totT=1.*^-3;*)
    totT = 1. * 10 ^ (RandomReal[] * 4 - 3);
    {maxPars} = Solve[Array[k, 10] == Join[ad10pars[[iPar]][[Range[6]]],
        Table[1. * 10 ^ (RandomReal[] * 6 - 3), {i, 1, 4}]]];

    Block[{tPer, step, us, ad, x4, sol},
     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"], k11[t] → 10 * k11[t]}]]} /.
       maxPars, 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[[4]] - x4[[3]])] / totS) *
          Min[((Abs[(x4[[4]] - x4[[3]])] / Max[Abs[(x4[[3]] - x4[[1]])], 0.001] +
              Abs[(x4[[4]] - x4[[3]])] / Max[Abs[
                (x4[[stepNum + 1]] - x4[[4]])], 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]]] / (0.2 * totS)), 1.0] *
         ((0.01) / (Max[Abs[(x4[[i + 1]] - x4[[i]]) / totS], 0.01])))];
      ];
      ad = (ad / 0.0001) ^ (1 / (stepNum));

      AppendTo[adToUsPars,
       Join[{totT, us, ad, num}, {k[7], k[8], k[9], k[10]} /. maxPars]];
     ];
    ];
   ];
  ];
  transAdToUsPars = Transpose[adToUsPars];
  vsPlot = ListPlot[Transpose[{transAdToUsPars[[2]], transAdToUsPars[[3]]}],
    PlotRange → {{0, 1}, {0, 1}},
    (*AxesLabel→{"Ultrasensitive score","Adaptive score"},*)
    Ticks → {{0, 0.5, 1}, {0.5, 1}}, PlotStyle → {Thick, PointSize[0.01]},
    PlotTheme → "Monochrome", PlotLabel → None,
    LabelStyle → {24, GrayLevel[0]}, ImageSize → Large];
  Export[NotebookDirectory[] <> "unsaturatedAdToUsSampleAll" <>
    ToString[iPar] <> ".pdf", vsPlot];
  Export[NotebookDirectory[] <> "unsaturatedAdToUsSampleAll" <>
    ToString[iPar] <> ".eps", vsPlot];
  (*Print[vsPlot]*)
 ];
];
]
```

(NewKern) Out[285]=

```
{3219.51, Null}
```