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[150]:=

```
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]]}]];
     ];
    ];
   ];
  ];
 ]

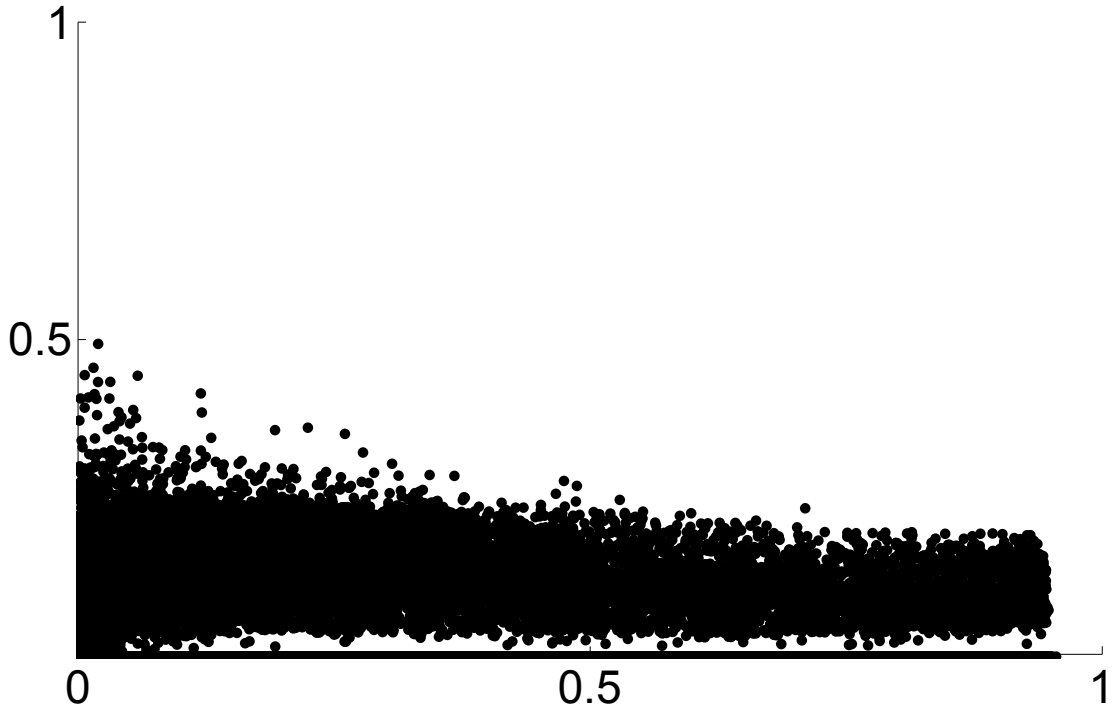
 (*Plot@@{{{(x[7][t]+x[8][t]+x[9][t]),x[4][t]}/.sol},
    Flatten@{t,x[1]["Domain"]/.sol},PlotLegends→{"Ttot","Sp"}}
  ListPlot[Transpose@{xT,x4},PlotRange→{0,10}]*)
 (*Print[pars];*)
 transPars = Transpose[pars];
 (*Export["saturationSampling.csv",transPars];*)
 Export["unsaturationSampling.csv", transPars];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

(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}
```

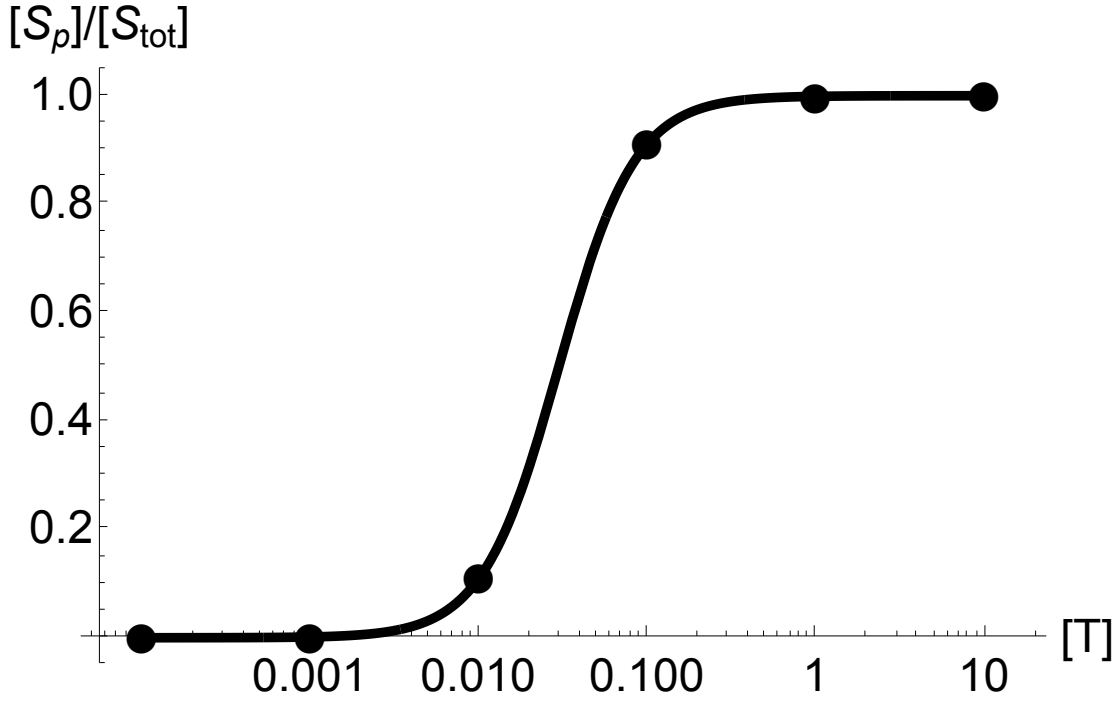
(NewKern) In[167]:=

```
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]=

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

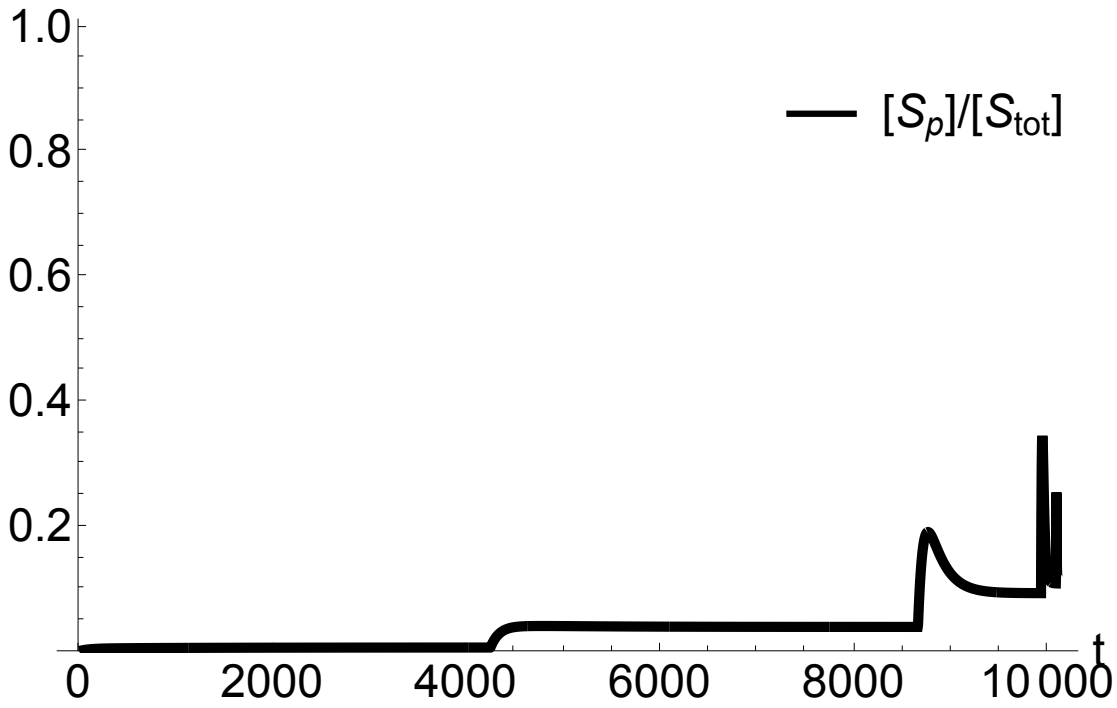
(NewKern) Out[175]=



(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]=



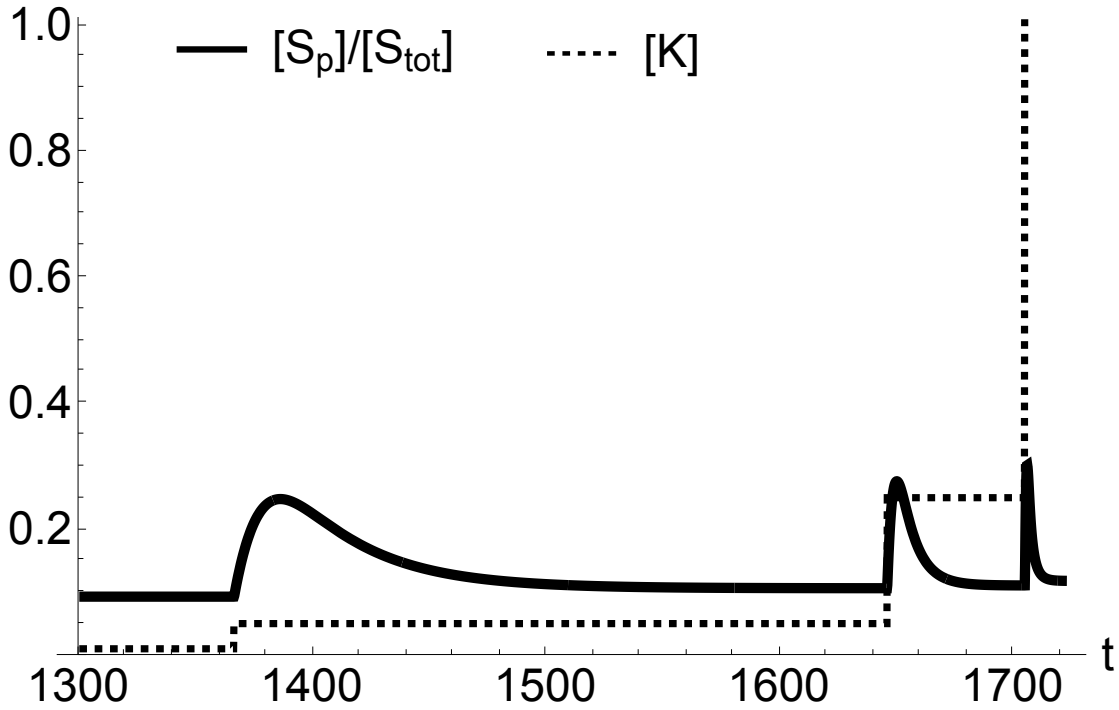
(NewKern) In[204]:=

```
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
```

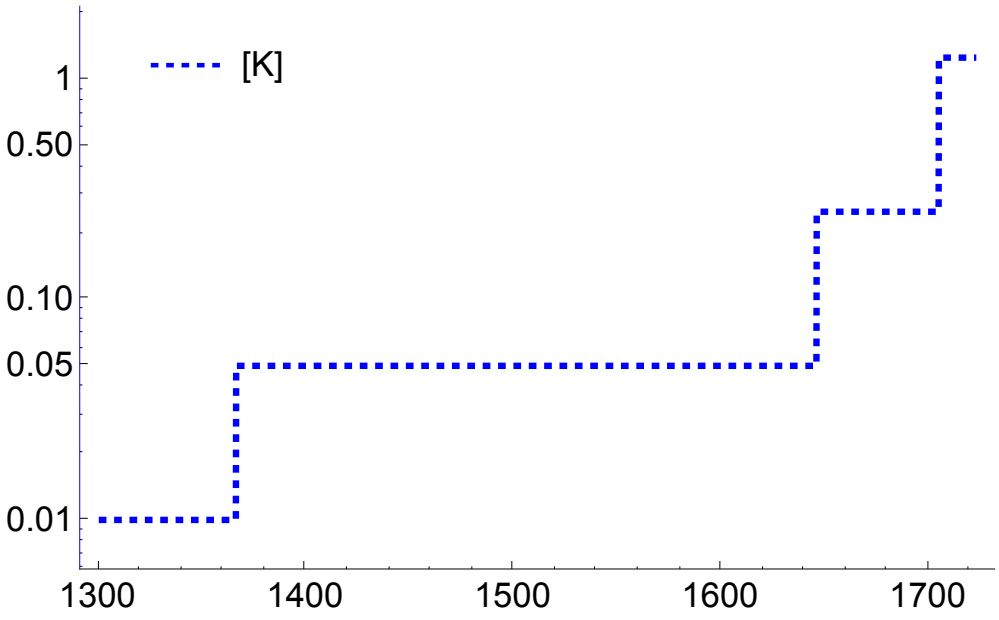
(NewKern) Out[208]=



(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}]
```

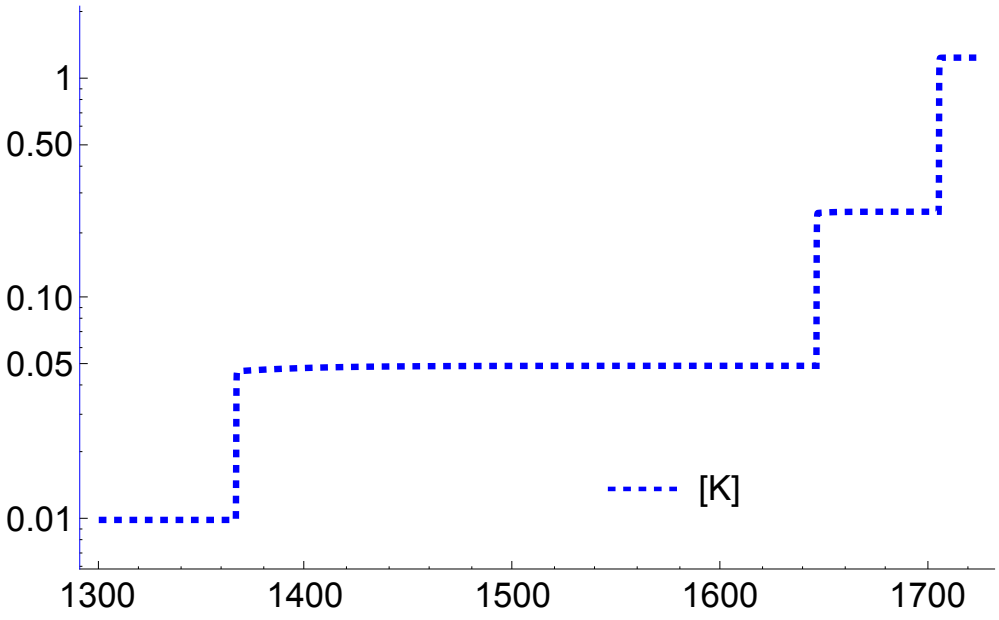
(NewKern) Out[209]=



(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}]
```

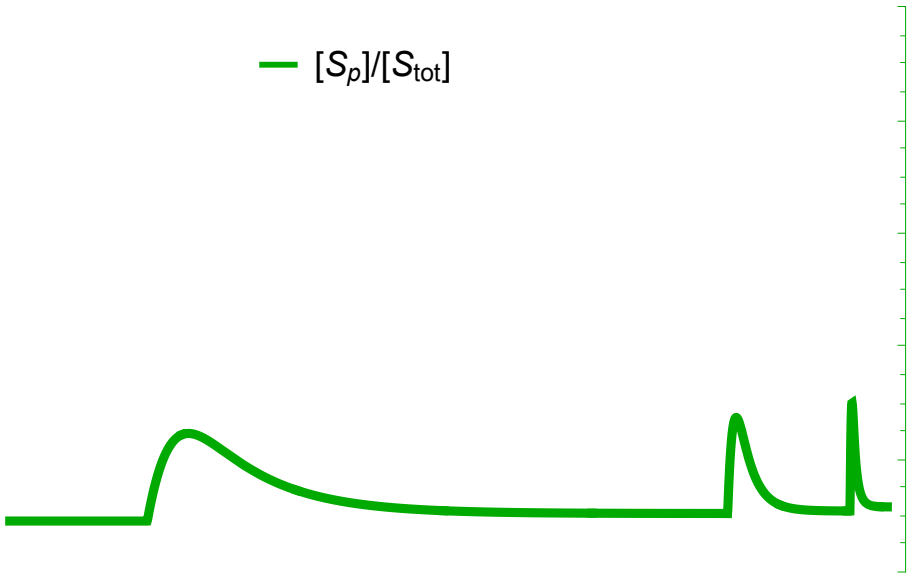
(NewKern) Out[210]=



(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]}]
```

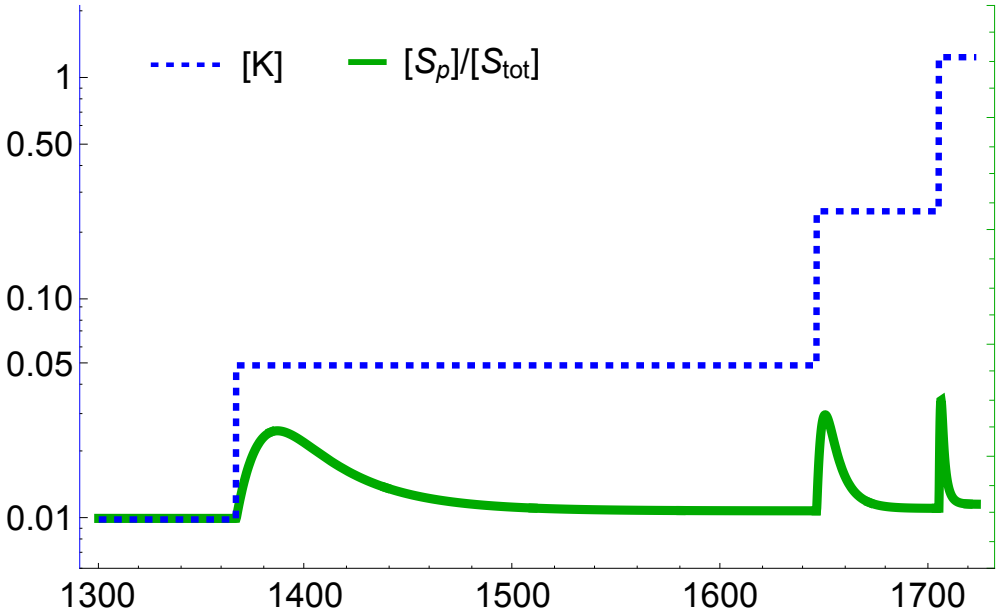
(NewKern) Out[211]=



(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,
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 {1.95101, 121.837, 177.418, 663.364, 0.295517, 170.85, 2.66429,
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  0.456537, 55 807, 153.385, 0.257996, 0.00159415, 0.000316449},
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 {3.33141, 0.0187469, 5.62504, 203.725, 0.175379, 479.252, 3.97671,
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  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,
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  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,
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(NewKern) In[223]:=

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    2.7579126947038177`, 0.004425168723158293`, 124.86588613940748`,
    0.017694402307212805`, 0.0063478384949193474`, 0.0001`, 0.1`,
    0.1`, 0.9543938503067778`, 0.`, 47 503, 48.99935091067816`,
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    0.005166697684825859`, 465.8452236367559`, 388.3893982720522`,
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    0.1`, 0.9504024006847739`, 0.`, 87 739, 9.534112493466903`,
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    0.002438333353593688`, 909.1470323607329`, 3.6740507654320447`,
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   {0.006988922196113958`, 0.0016736661716845922`, 318.12838095689193`,
    0.0038768972135044114`, 75.93982400090636`, 0.007134599728375874`,
    0.0012982914730214718`, 0.016636934080863704`, 12.661534720214746`,
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