

Homework 6 (Project part I)

Please answer all questions in this notebook. Email the **Mathematica notebook and a pdf** of the notebook output to beng123@gmail.com with the subject line HOMWORK 6 - YOUR NAME (s)-YOUR PID(s). If you are in a group of two, one submission is fine, but make sure both of your names are in the subject line. This homework is due at the start of class on Thursday 2/27/2014 (3:30 pm). Everything you need to know for Mathematica is in the corresponding notebook files. Remember that explanations should accompany the plots for each of the questions.

```
<< Toolbox`  
<< Toolbox`Style`
```

Problem I

Import glycolysis from the MASSToolbox sample data. Do problems 10.2 and 10.3 in the book.

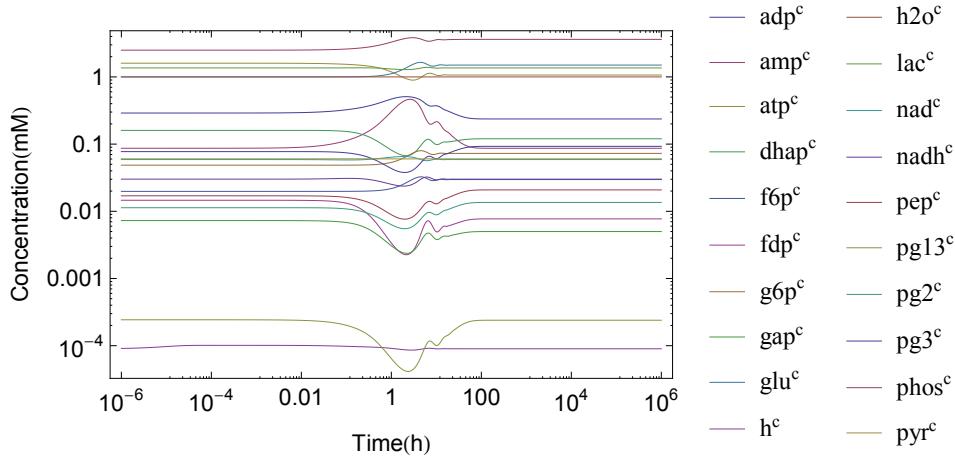
```
glycolysis = ExampleData[{"Toolbox", "Glycolysis"}]
```

The screenshot shows a Mathematica interface with an 'Overview' panel. The panel displays the following data:

Overview	
Number of species(rows):	20
Number of columns(reactions):	21
Number of exchange reactions:	7
Number of irreversible reactions:	0
Matrix rank:	18
Dimensions null space:	3
Dimensions left null space:	2
Number of parameters	49
Number of custom rate equations	0
Number of equilibrium constants:	21
Number of forward rate constants:	21
Number of initial concentrations:	20
Number of genes:	0
Number of proteins:	0

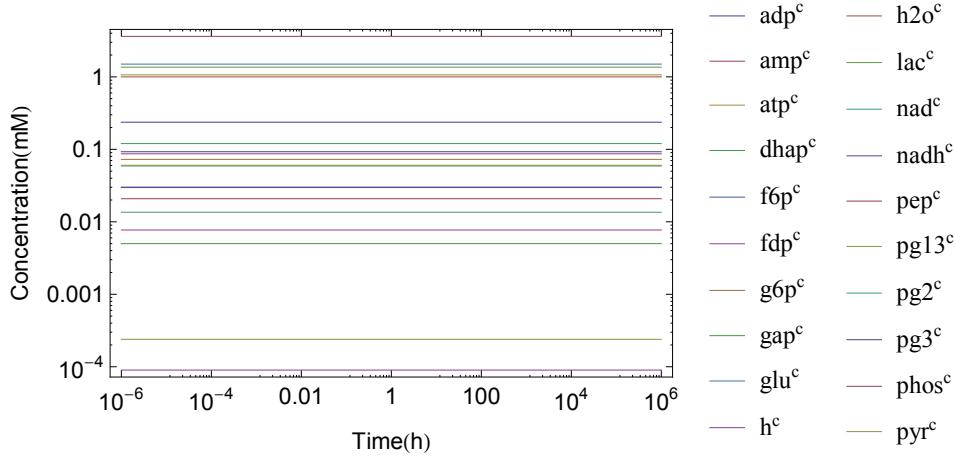
10.1)

```
{concProfilePerturbed, fluxProfilePerturbed} = simulate[glycolysis,
  {t, 0, 1*^6}, Parameters → {k["vatp"] → (1.5 * (k["vatp"] /. glycolysis))}];
plotSimulation[concProfilePerturbed, {t, 0, 1*^6}, Legend → True,
  FrameLabel → {"Time(h)", "Concentration(mM)"}]
```



This simulation shows the response of an increased Vatp at a constant glucose input rate. The system is increased by 50% at t=0 allowing more glucose to be produced by hour.

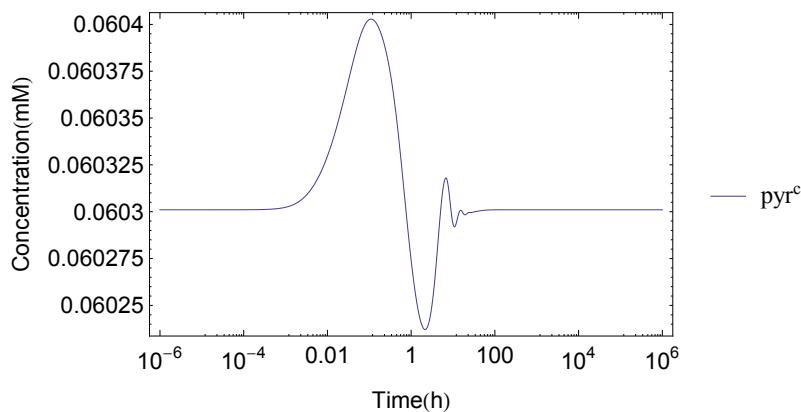
```
ssInitialConditions = concProfilePerturbed /. t → 1 000 000;
glycolysisP = glycolysis;
updateInitialConditions[glycolysisP, ssInitialConditions]
ssParameters = {k["vatp"] → (1.5 * (k["vatp"] /. glycolysis))};
updateParameters[glycolysisP, ssParameters]
plotSimulation[simulate[glycolysisP, {t, 0, 1 000 000}][[1]],
  Legend → True, FrameLabel → {"Time(h)", "Concentration(mM)"}]
```



The graph above shows glycolysis being perturbed by parameters listed in model at steady state using the concentrations from the first graph.

10.2)

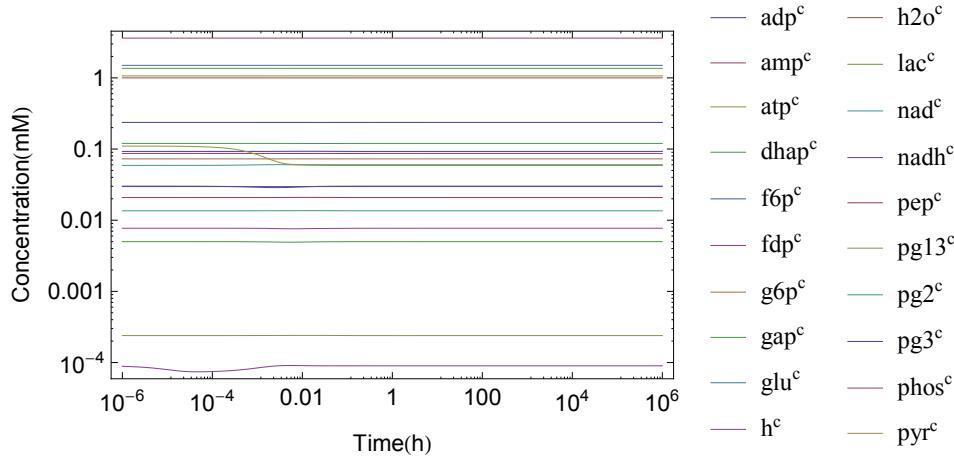
```
plotSimulation[FilterRules[concProfilePerturbed, {m["pyr", "c"]}],  
{t, 0, 1 000 000}, Legend -> True, FrameLabel -> {"Time(h)", "Concentration(mM)"}]
```



At t=0 when V_{atp} is perturbed, the concentration of pyruvate increases from the steady state concentration of 0.0603 mM accurately depicting the affects of the model. Yet as time proceeds, the concentration of pyruvate returns to steady state. This is an example of a damped oscillation.

10.3)

```
plotSimulation[simulate[glycolysisP, {t, 0, 1 000 000},  
InitialConditions -> {m["pyr", "c"] -> .11 Millimole Liter-1}][[1]],  
Legend -> True, FrameLabel -> {"Time(h)", "Concentration(mM)"}]
```



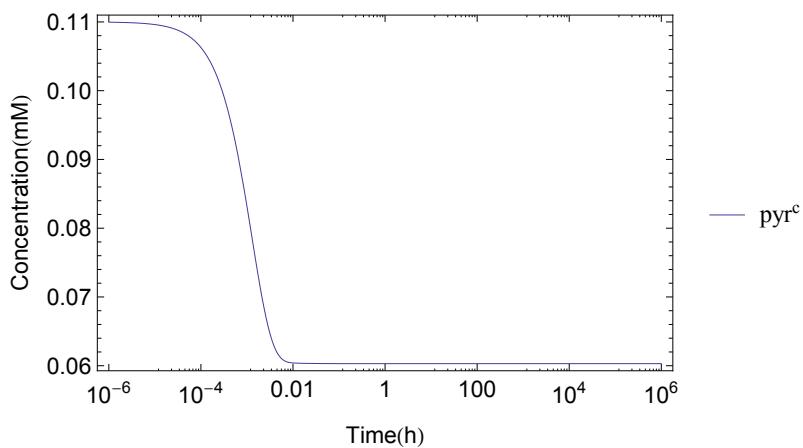
This graph shows concentration versus time of all the metabolites after the concentration of pyruvate is changed to 0.11 mM.

```

{concProfilePerturbed2, fluxProfilePerturbed2} = simulate[glycolysisP, {t, 0, 1*^6},
  InitialConditions -> {metabolite["pyr", "c"] -> .11 Millimole Liter-1}];

plotSimulation[FilterRules[concProfilePerturbed2, {metabolite["pyr", "c"]}],
  FrameLabel -> {"Time(h)", "Concentration(mM)"}, Legend -> True, PlotFunction -> LogLinearPlot]

```

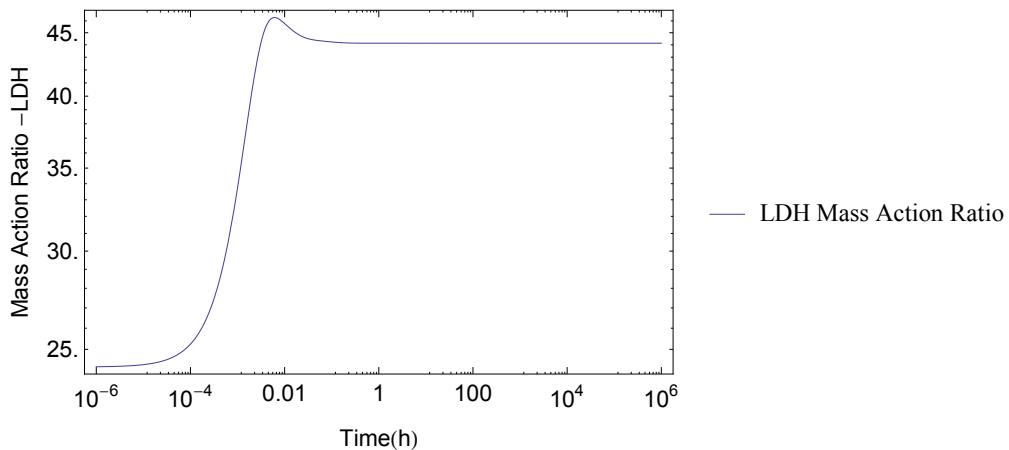


This graph is an example of a smooth landing where no oscillation exists. The concentration of pyruvate changes from 0.11 mM at $t=0$ to the initial steady state concentration of 0.063 mM.

```

massactionratioLDH = {"LDH Mass Action Ratio" ->
  (m["lac", "c"] * m["nad", "c"]) / (m["nad", "c"] * m["pyr", "c"])};
plotSimulation[Flatten[{massactionratioLDH /. concProfilePerturbed2}], FrameLabel -> {"Time(h)", "Mass Action Ratio -LDH"}, Legend -> True]

```



The equilibrium constant for LDH is 26300. Compared to the steady state mass action ratio calculated above, their ratio is always small because the highest value that gamma reaches is around 45, with γ/K_{eq} . In this perturbed state, because the gamma is smaller, the reactions should proceed in the forward direction, using up more Pyruvate to reach equilibrium.

Problem 2

Combine the glycolysis (pre-perturbation) and pentose phosphate pathways ONLY. Simulate a doubling in the rate of GSH utilization as shown in Figure 11.7. Plot the concentrations of GL6P and GO6P as a function of time and explain what you observe.

```

glycolysis = ExampleData[{"Toolbox", "Glycolysis"}];
ppp = ExampleData[{"Toolbox", "PentosePhosphatePathway"}];
combi = Union[glycolysis, ppp];
getExchanges @ {glycolysis, ppp}

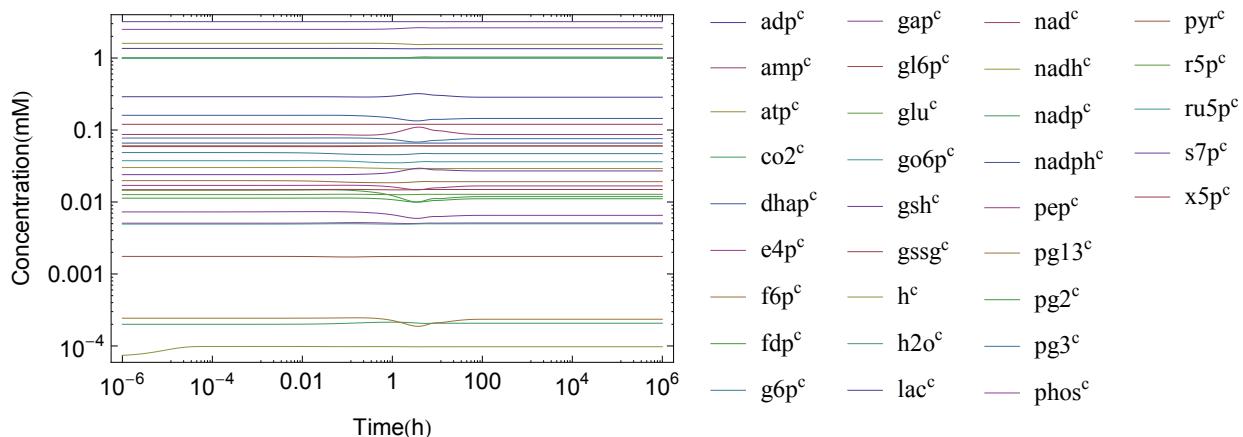
{vamp, vpyr, vlac, vgluin, vampin, vh, vh2o} \[Element] 
  {amp^c \[Rightarrow] \[EmptySet], pyr^c \[Rightarrow] \[EmptySet], lac^c \[Rightarrow] \[EmptySet], 
   \[EmptySet] \[Rightarrow] glu^c, \[EmptySet] \[Rightarrow] amp^c, h^c \[Rightarrow] \[EmptySet], 
   h2o^c \[Rightarrow] \[EmptySet]}, 
{vco2, EX_g6p_c, EX_f6p_c, EX_r5p_c, EX_h_c, EX_h2o_c, EX_gap_c} \[Element] 
  {co2^c \[Rightarrow] \[EmptySet], g6p^c \[Rightarrow] \[EmptySet], f6p^c \[Rightarrow] \[EmptySet], r5p^c \[Rightarrow] \[EmptySet], 
   h^c \[Rightarrow] \[EmptySet], h2o^c \[Rightarrow] \[EmptySet], gap^c \[Rightarrow] \[EmptySet]}

combi = deleteReactions[combi,
  {"EX_g6p_c", "EX_f6p_c", "EX_gap_c", "EX_h_c", "EX_h2o_c", "EX_r5p_c"}];
getExchanges[
  combi]

{amp^c \[Rightarrow] \[EmptySet], \[EmptySet] \[Rightarrow] amp^c, co2^c \[Rightarrow] \[EmptySet], 
 \[EmptySet] \[Rightarrow] glu^c, h^c \[Rightarrow] \[EmptySet], h2o^c \[Rightarrow] \[EmptySet], 
 lac^c \[Rightarrow] \[EmptySet], pyr^c \[Rightarrow] \[EmptySet]}

{concSolCombiGP, fluxSolCombiGP} = simulate[combi, {t, 0, 1000000}];
plotSimulation[simulate[combi, {t, 0, 1000000}]][[1]],
Legend \[Rule] True, FrameLabel \[Rule] {"Time(h)", "Concentration(mM)"}]

```

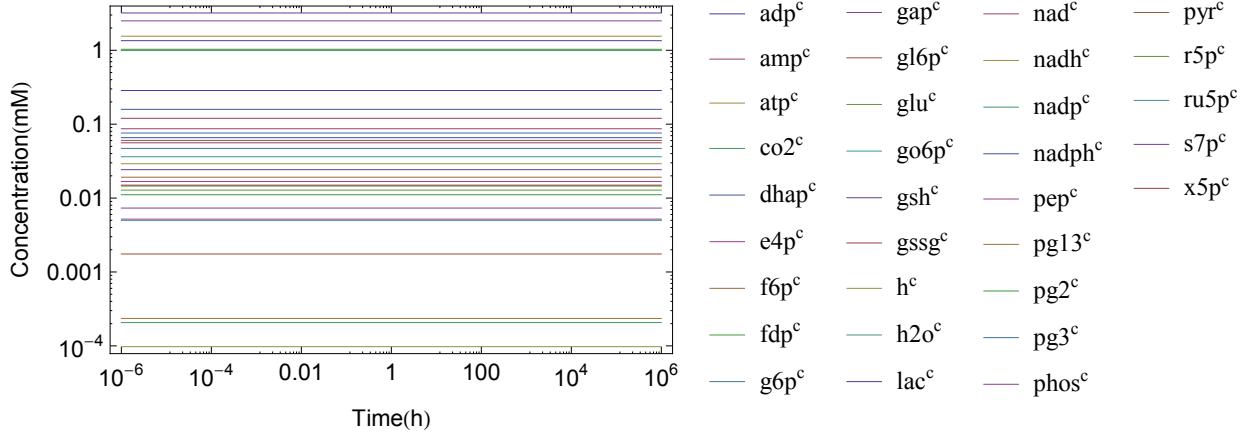


This graph shows the concentration versus time of the combined glycolysis and pentose phosphate pathways before perturbation. This is not in steady state.

```

combiRelaxed = combi;
updateInitialConditions[combiRelaxed, Flatten[findSteadyState[combi]]];
plotSimulation[simulate[combiRelaxed, {t, 0, 1*^6}][[1]],
  Legend -> True, FrameLabel -> {"Time(h)", "Concentration(mM)"}]

```

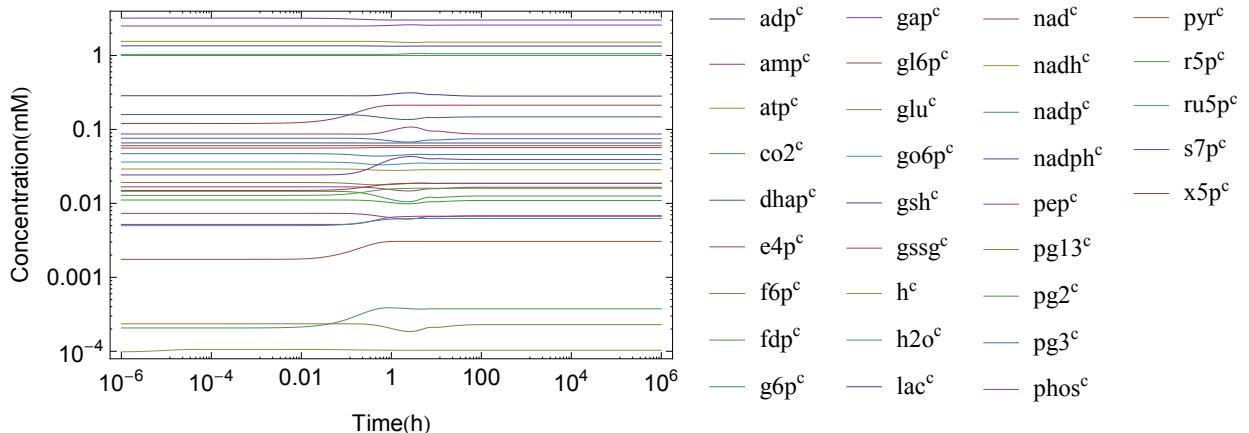


This plot demonstrates the updated initial conditions as well as the concentrations in steady state.

```

combiRelaxedP = combiRelaxed;
{concSolCombiP, fluxSolCombiP} = simulate[combiRelaxedP, {t, 0, 1 000 000},
  Parameters -> {k["vgshr"] -> (2 * (k["vgshr"]) /. combiRelaxed)};
plotSimulation[concSolCombiP, {t, 0, 1*^6}, Legend -> True,
  FrameLabel -> {"Time(h)", "Concentration(mM)"}]

```

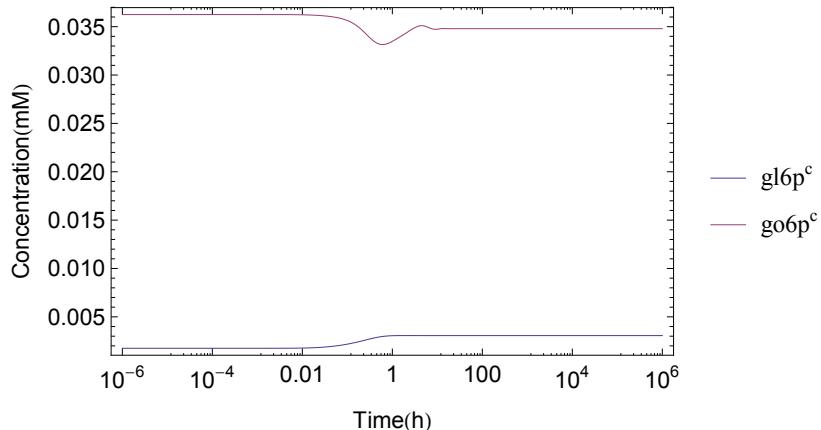


This plot shows that the system has been perturbed by doubling the value of vgshr.

```

yo = FilterRules[concSolCombiP,
  {metabolite["gl6p", "c"], metabolite["go6p", "c"]}];
plotSimulation[yo, FrameLabel -> {"Time(h)", "Concentration(mM)" },
  Legend -> True, PlotFunction -> LogLinearPlot]
yo /. t -> 0
yo /. t -> 1*^6

```



$$\{ \text{gl6p}^c \rightarrow 0.00175051 \text{ Millimole Liter}^{-1}, \text{go6p}^c \rightarrow 0.0362506 \text{ Millimole Liter}^{-1} \}$$

$$\{ \text{gl6p}^c \rightarrow 0.0030607 \text{ Millimole Liter}^{-1}, \text{go6p}^c \rightarrow 0.0347936 \text{ Millimole Liter}^{-1} \}$$

This plot shows the isolated concentrations of GL6P and GOP6. Increasing vgshr increases the rate at which NADP is produced which therefore leads an increase in GL6P which counter balanced this. GO6P is not as greatly affected by the increase in vgshr since it is not “local” but “distant” in comparison to GL6P in the perturbation.

Problem 3

Now combine glycolysis, PPP and the nucleotide salvage pathway. Do question 12.2 in the book. Make sure to compare to the simulation done in problem 2.

```

glycolysis = ExampleData[{"Toolbox", "Glycolysis"}];
ppp = ExampleData[{"Toolbox", "PentosePhosphatePathway"}];
salvage = ExampleData[{"Toolbox", "NucleotideSalvagePathway"}];
combiGP = Union[{glycolysis, ppp, salvage}]

```

Overview	
Number of species(rows):	40
Number of columns(reactions):	54
Number of exchange reactions:	20
Number of irreversible reactions:	0
Matrix rank:	37
Dimensions null space:	17
Dimensions left null space:	3
Number of parameters	126
Number of custom rate equations	0
Number of equilibrium constants:	54
Number of forward rate constants:	54
Number of initial concentrations:	40
Number of genes:	0
Number of proteins:	0

```

getExchanges /@ {glycolysis, ppp, salvage}

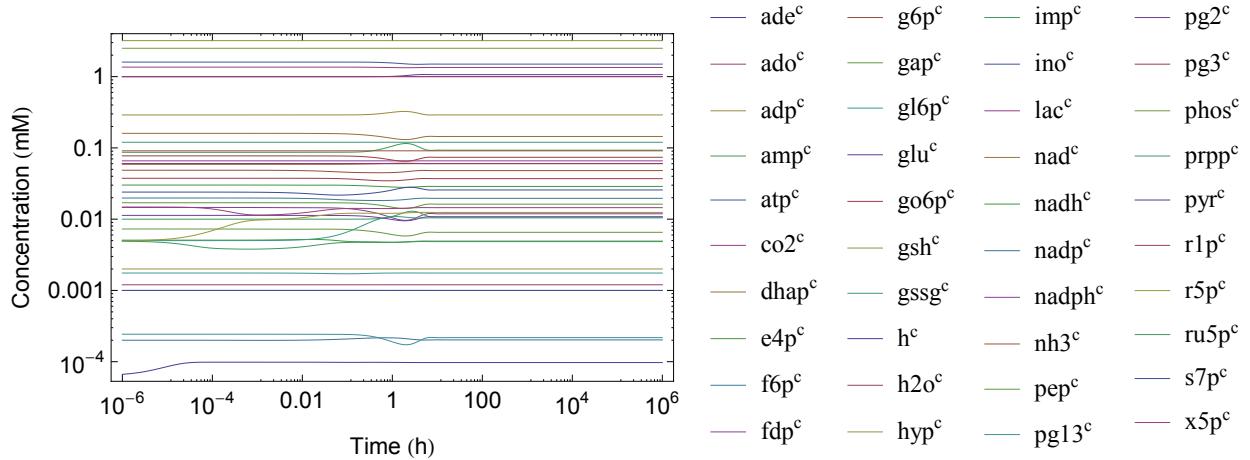
{ {amp^c <=> \emptyset, pyr^c <=> \emptyset, lac^c <=> \emptyset, \emptyset <=> glu^c, \emptyset <=> amp^c, h^c <=> \emptyset, h2o^c <=> \emptyset}, 
{co2^c <=> \emptyset, EX_g6p_c <=> \emptyset, EX_f6p_c <=> \emptyset, EX_r5p_c <=> \emptyset, EX_h_c <=> \emptyset, EX_h2o_c <=> \emptyset, EX_gap_c <=> \emptyset}, 
{ade^c <=> \emptyset, ado^c <=> \emptyset, hyp^c <=> \emptyset, ino^c <=> \emptyset, nh3^c <=> \emptyset, phos^c <=> \emptyset, amp^c <=> \emptyset, h^c <=> \emptyset, h2o^c <=> \emptyset} }

combiGP = deleteReactions[combiGP, {"EX_g6p_c", "EX_f6p_c",
"EX_gap_c", "EX_h_c", "EX_h2o_c", "EX_r5p_c", "vamp", "vampin"}];
getExchanges[
combiGP]

{ {ade^c <=> \emptyset, ado^c <=> \emptyset, co2^c <=> \emptyset, \emptyset <=> gluc^c, h^c <=> \emptyset, h2o^c <=> \emptyset,
hyp^c <=> \emptyset, ino^c <=> \emptyset, lac^c <=> \emptyset, nh3^c <=> \emptyset, phos^c <=> \emptyset, pyr^c <=> \emptyset} }

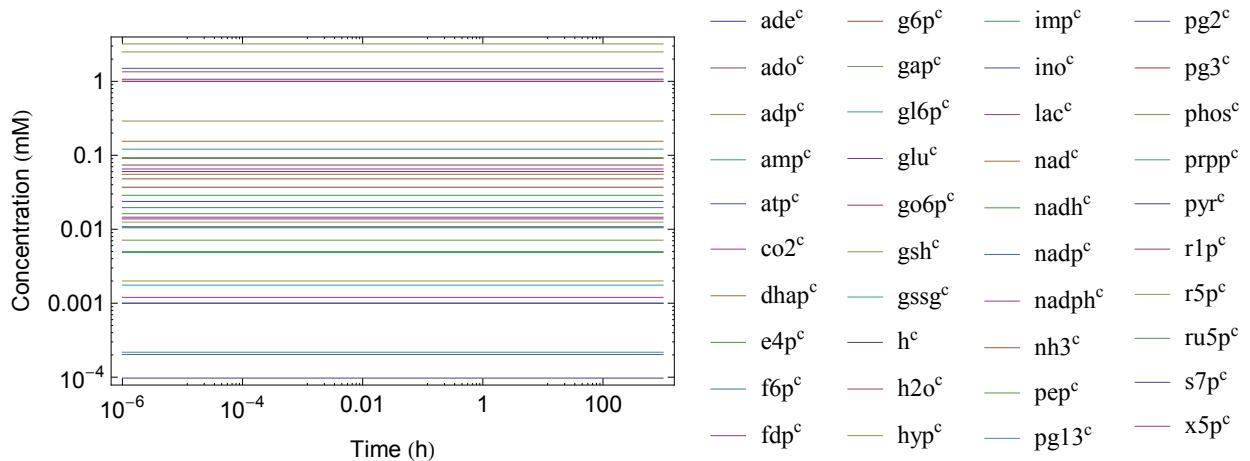
```

```
plotSimulation[simulate[combiGP, {t, 0, 1 000 000}][[1]],
FrameLabel -> {"Time (h)", "Concentration (mM)"}, Legend -> True]
```



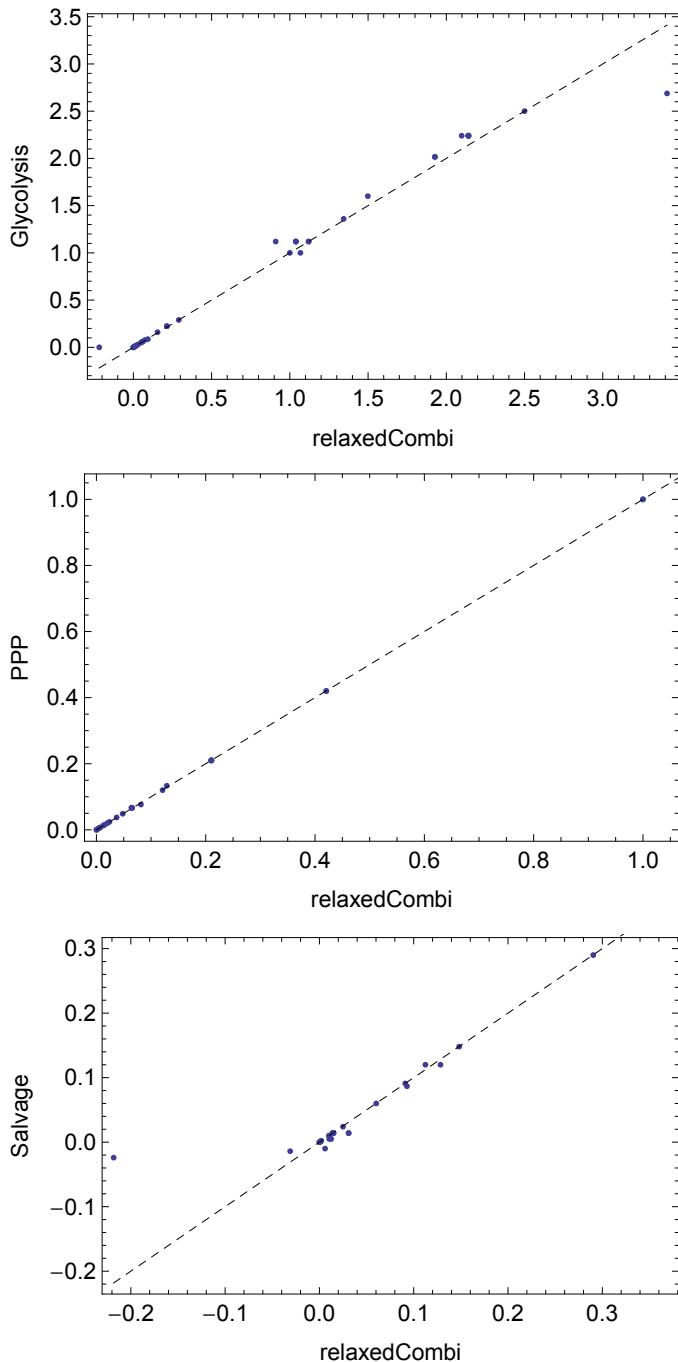
```
combiGPRelaxed = combiGP;
updateInitialConditions[combiGPRelaxed, Flatten[findSteadyState[combiGP]]]

plotSimulation[simulate[combiGPRelaxed, {t, 0, 1000}][[1]],
FrameLabel -> {"Time (h)", "Concentration (mM)"}, Legend -> True]
```



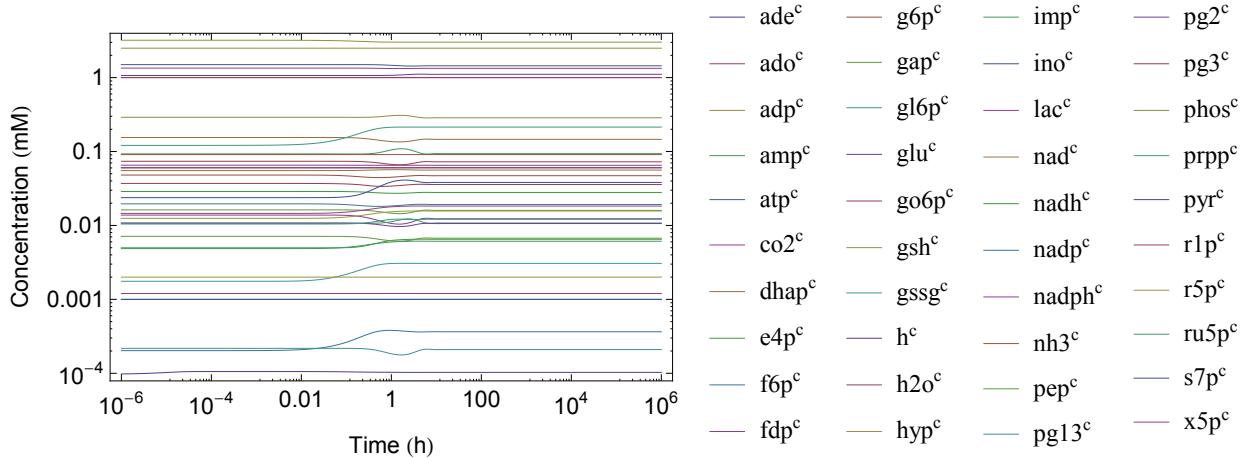
The merged model, combined relaxed, with the new initial conditions is in a steady-state.

```
comparisonPlot = Show[ListPlot[Thread[Tooltip[#[[All, 2]], #[[All, 1]]]], ##2],
Graphics[{Dashed, Line[{Min[#[[All, 2]]], Min[#[[All, 2]]]}, {Max[#[[All, 2]]], Max[#[[All, 2]]]}]}, PlotRange -> Automatic] &;
comparisonPlot[stripUnits[scatterFromDicts[combiGPRelaxed["InitialConditions"],
glycolysis["InitialConditions"]]],
FrameLabel -> {"relaxedCombi", "Glycolysis"}]
comparisonPlot[stripUnits[scatterFromDicts[combiGPRelaxed["InitialConditions"],
ppp["InitialConditions"]]], FrameLabel -> {"relaxedCombi", "PPP"}]
comparisonPlot[stripUnits[scatterFromDicts[combiGPRelaxed["InitialConditions"],
salvage["InitialConditions"]]], FrameLabel -> {"relaxedCombi", "Salvage"}]
```



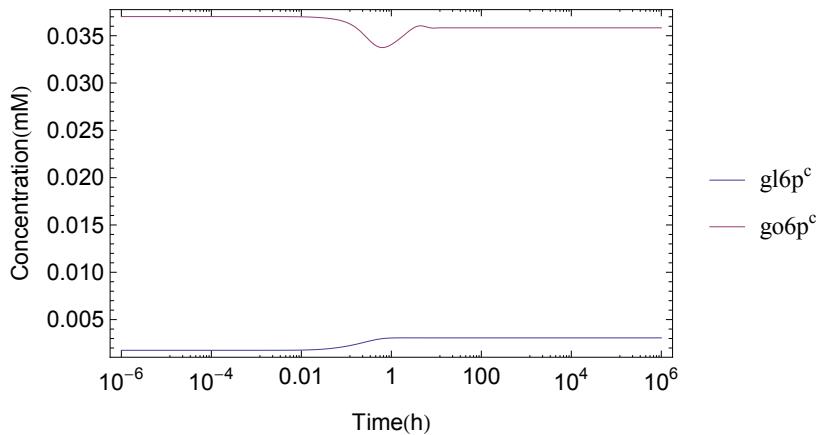
The graphs above are concerned with comparing the initial conditions of the individual pathways with the newly obtained steady state reveals that fluxes and concentration are not dramatically different.

```
{concSolCombiGPP, fluxSolCombiGPP} = simulate[combiGPRelaxed, {t, 0, 1 000 000},
  Parameters → {k["vgshr"] → (k["vgshr"] /. combiGPRelaxed) 2}];
plotSimulation[concSolCombiGPP, {t, 0, 1 000 000},
  FrameLabel → {"Time (h)", "Concentration (mM)"}, Legend → True]
```



The merged model, combined relaxed, perturbed by doubling vgshr.

```
ko = FilterRules[concSolCombiGPP,
  {metabolite["gl6p", "c"], metabolite["go6p", "c"]}];
plotSimulation[ko, FrameLabel → {"Time(h)", "Concentration(mM)"},
  Legend → True, PlotFunction → LogLinearPlot]
ko /. t → 0
ko /. t → 1*^6
```



$$\{ \text{gl6p}^c \rightarrow 0.00175609 \text{ Millimole Liter}^{-1}, \text{go6p}^c \rightarrow 0.0370211 \text{ Millimole Liter}^{-1} \}$$

$$\{ \text{gl6p}^c \rightarrow 0.00306838 \text{ Millimole Liter}^{-1}, \text{go6p}^c \rightarrow 0.0358325 \text{ Millimole Liter}^{-1} \}$$

Compared to the simulated plot of glycolysis and the pentose phosphate pathways in Problem 2, this plot of glycolysis, the pentose phosphate, and salvage pathways is the same. This shows that the addition of the AMP sub-network does not have an effect on the concentrations of GL6P and GO6P when vgshr is doubled.

Problem 4

To the integrated glycolysis/ppp/salvage pathway model, add the hemoglobin module. Assume O_2^{xt} is constant. Simulate a 1.5x increase in ATP usage (for example, when exercising). Define and plot the oxygen charge ratio as well as the hemoglobin T/R ratio. Explain what this means physiologically and if this is realistic.

```
hemoglobin = ExampleData[{"Toolbox", "Hemoglobin"}];
glycolysis = ExampleData[{"Toolbox", "Glycolysis"}];
ppp = ExampleData[{"Toolbox", "PentosePhosphatePathway"}];
salvage = ExampleData[{"Toolbox", "NucleotideSalvagePathway"}];
combiHb = Union[glycolysis, ppp, salvage, hemoglobin]
```

Overview	
Number of species(rows):	48
Number of columns(reactions):	62
Number of exchange reactions:	21
Number of irreversible reactions:	0
Matrix rank:	44
Dimensions null space:	18
Dimensions left null space:	4
Number of parameters	143
Number of custom rate equations	0
Number of equilibrium constants:	62
Number of forward rate constants:	62
Number of initial concentrations:	48
Number of genes:	0
Number of proteins:	0

```
getExchanges /@ {glycolysis, ppp, salvage, hemoglobin}

{ {amp^c ⇌∅, pyr^c ⇌∅, lac^c ⇌∅, ∅ ⇌glu^c, ∅ ⇌amp^c, h^c ⇌∅, h2o^c ⇌∅}, {co2^c ⇌∅, g6p^c ⇌∅, f6p^c ⇌∅, r5p^c ⇌∅, h^c ⇌∅, h2o^c ⇌∅, gap^c ⇌∅}, {ade^c ⇌∅, ado^c ⇌∅, hyp^c ⇌∅, ino^c ⇌∅, nh3^c ⇌∅, phos^c ⇌∅, amp^c ⇌∅, h^c ⇌∅, h2o^c ⇌∅}, {o2^c ⇌∅} }
```

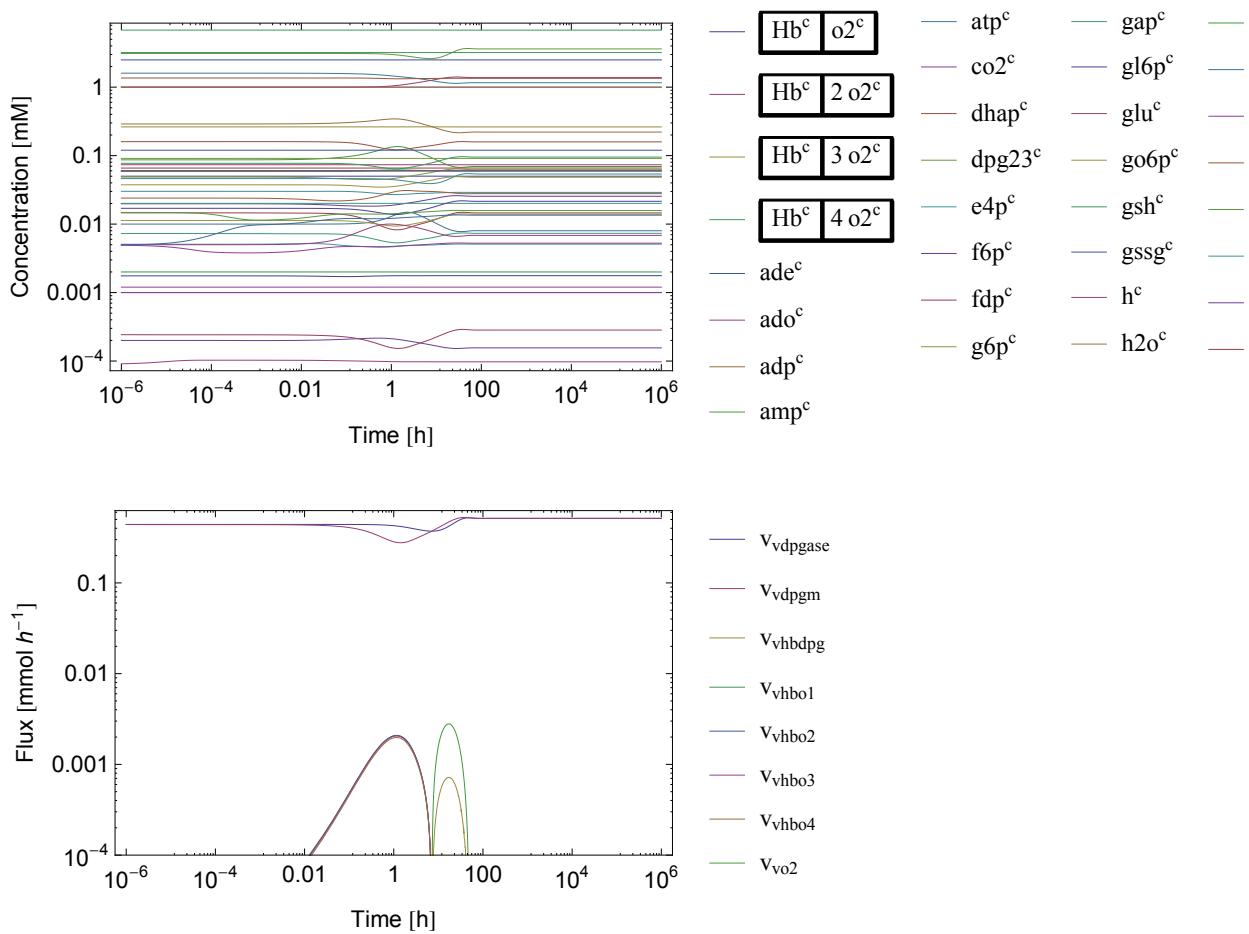
```

combiHb = deleteReactions[combiHb, {"EX_g6p_c", "EX_f6p_c",
    "EX_gap_c", "EX_h_c", "EX_h2o_c", "EX_r5p_c", "vamp", "vampin"}];
getExchanges[
  combiHb]

{adevade $\rightleftharpoons$   $\emptyset$ , adovado $\rightleftharpoons$   $\emptyset$ , co2vco2 $\rightleftharpoons$   $\emptyset$ ,  $\emptyset$  $\rightleftharpoons$  gluvgluin, hvh $\rightleftharpoons$   $\emptyset$ , h2ovh2o $\rightleftharpoons$   $\emptyset$ ,
hypvhyp $\rightleftharpoons$   $\emptyset$ , inovino $\rightleftharpoons$   $\emptyset$ , lacvlac $\rightleftharpoons$   $\emptyset$ , nh3vnh3 $\rightleftharpoons$   $\emptyset$ , o2vo2 $\rightleftharpoons$   $\emptyset$ , phosvphos $\rightleftharpoons$   $\emptyset$ , pyrvpyr $\rightleftharpoons$   $\emptyset$ }

{concSolHbPreSS, fluxSolHbPreSS} = simulate[combiHb, {t, 0, 1 000 000}];
plotSimulation[concSolHbPreSS, Legend -> True,
  FrameLabel -> {"Time [h]", "Concentration [mM]"}]
plotSimulation[FilterRules[fluxSolHbPreSS, hemoglobin["Fluxes"]], 
  FrameLabel -> {"Time [h]", "Flux [mmol h-1]"}, 
  PlotRange -> {All, {1*^-4, All}}, Legend -> True]

```

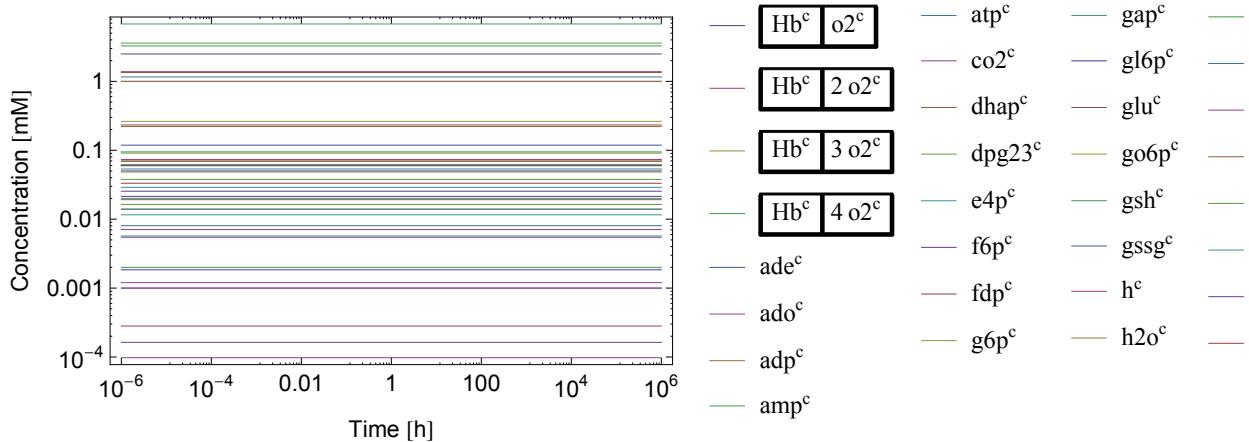


Both plots are simulated before the system is perturbed. The first plot shows that the merged model is not in steady state. The second plot compares the fluxes with respect of time of different rates presented in the system.

```

combiHbRelaxed = combiHb;
updateInitialConditions[combiHbRelaxed, Flatten[findSteadyState[combiHb]]];
plotSimulation[simulate[combiHbRelaxed, {t, 0, 1000000}][[1]],
  Legend → True, FrameLabel → {"Time [h]", "Concentration [mM]"}]

```

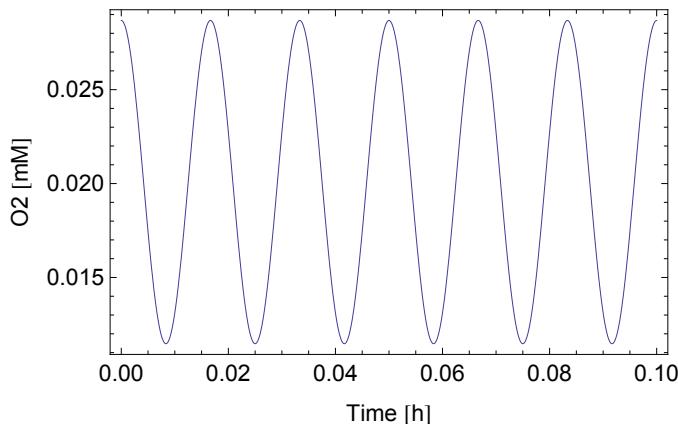
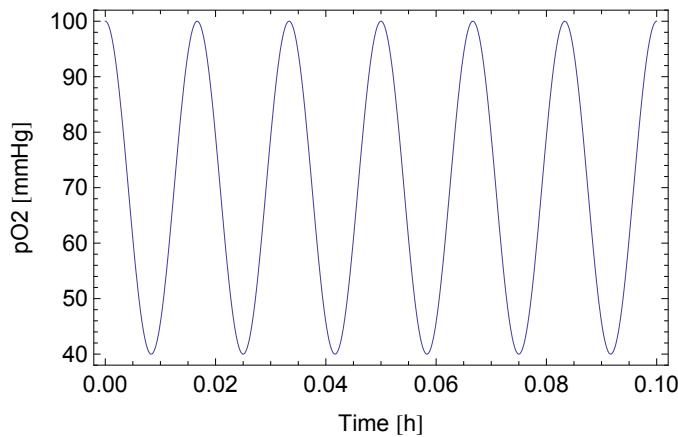


The merged model is not in steady state.

```

Plot[70 + 30 Cos[120 Pi t], {t, 0, .1}, FrameLabel → {"Time [h]", "pO2 [mmHg]"}]
Plot[(70 + 30 Cos[120 Pi t]) 2.8684 * 10^-4,
 {t, 0, .1}, FrameLabel → {"Time [h]", "O2 [mM]"}]

```

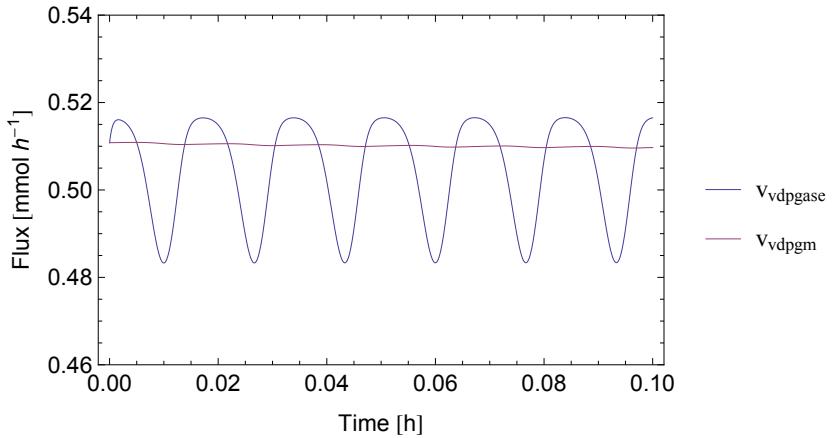
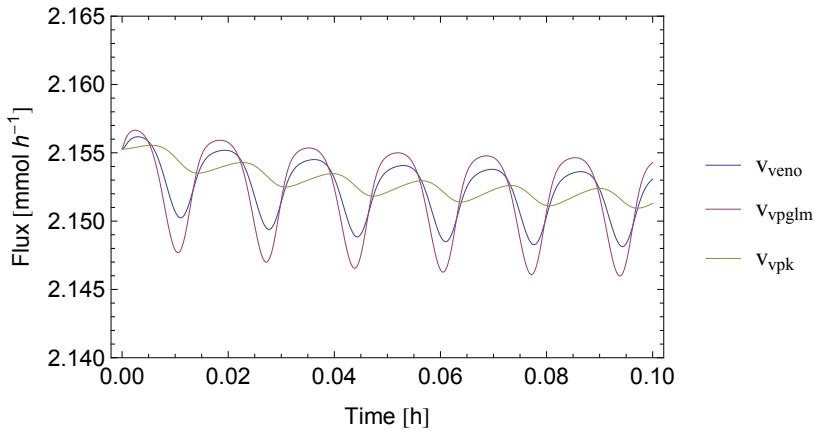


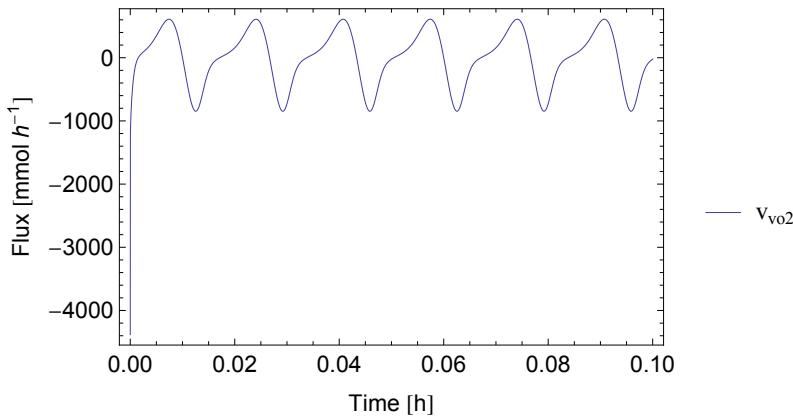
The two graphs show the changed in oxygen concentration over a period of time, this shows typical oxygen circulation. This graph is an example of a sustained oscillation.

```
{concSolHb, fluxSolHb} = simulate[combiHbRelaxed, {t, 0, .1},
  Parameters → {m["o2", "Xt"] → (70 + 30 Cos[120 Pi t]) 2.8684 * 10^-4];
plotSimulation[FilterRules[fluxSolHb, {v["veno"], v["vpk"], v["vpglm"]}],,
PlotFunction → Plot, PlotRange → {All, {2.14, 2.165}},
Legend → True, FrameLabel → {"Time [h]", "Flux [mmol h^-1]"}]

plotSimulation[FilterRules[fluxSolHb, {v["vdpgm"], v["vdpgase"]}],,
PlotFunction → Plot, PlotRange → {All, {.46, .54}},
Legend → True, FrameLabel → {"Time [h]", "Flux [mmol h^-1]"}]

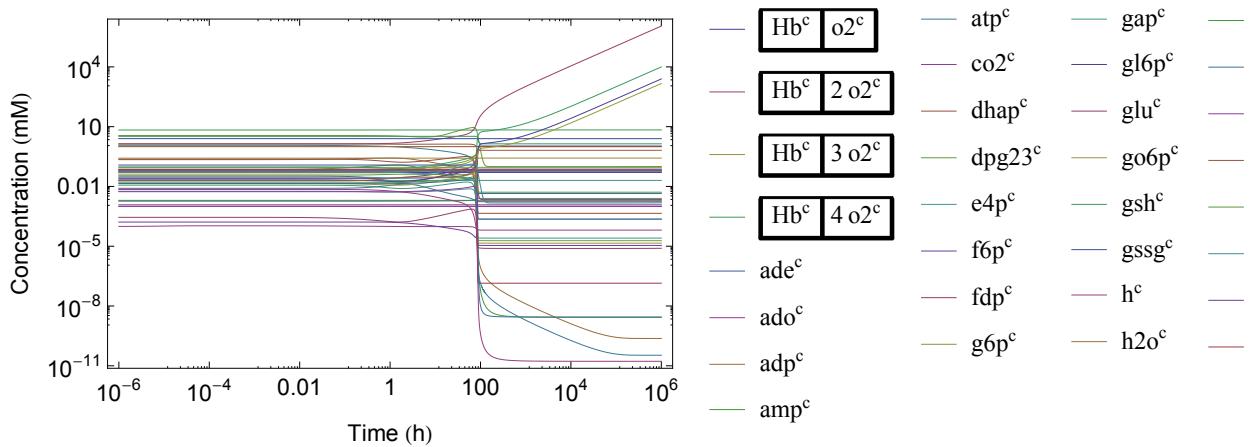
plotSimulation[filter[fluxSolHb, {v["vo2"]}],, PlotFunction → Plot,
FrameLabel → {"Time [h]", "Flux [mmol h^-1]"}, Legend → True]
```





The three plots above demonstrate the binding states of hemoglobin during normal circulation in consideration to the fluxes of different rates in relation to time.

```
{concSolHbP, fluxSolHbP} = simulate[combiHbRelaxed, {t, 0, 1 000 000},
  Parameters → {k["vatp"] → (k["vatp"] /. combiHbRelaxed) 1.5}];
plotSimulation[concSolHbP, {t, 0, 1 000 000},
  FrameLabel → {"Time (h)", "Concentration (mM)"}, Legend → True]
```



The merged model is perturbed by an increase of vatp by 1.5 times. The model shows how the system changes from steady state once the concentration of vatp is increased.

```
Hb1 = (complex[species["Hb", "c"], m["o2", "c"]]);
Hb2 = (complex[species["Hb", "c"], m["o2", "c"], m["o2", "c"]]);
Hb3 = (complex[species["Hb", "c"], m["o2", "c"], m["o2", "c"], m["o2", "c"]]);
Hb4 = (complex[species["Hb", "c"],
  m["o2", "c"], m["o2", "c"], m["o2", "c"], m["o2", "c"]]);
HbTOT = 4 (Hb1 + Hb2 + Hb3 + Hb4 + species["deoxyHb", "c"] + species["Hb", "c"]);
```

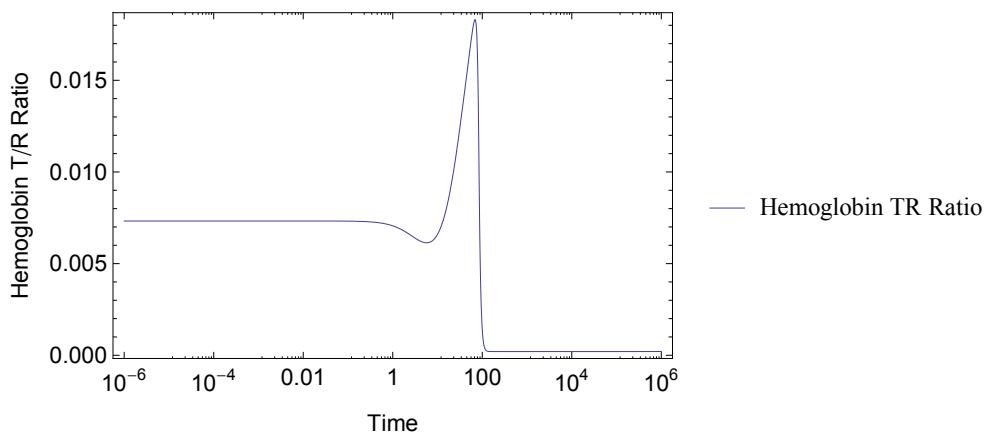
```

hemoglobinTRratio = {"Hemoglobin TR Ratio" \[Rule] (species["deoxyHb", "c"] / 
    (Hb1 + Hb2 + Hb3 + Hb4 + species["deoxyHb", "c"] + species["Hb", "c"]))}
plotSimulation[hemoglobinTRratio /. concSolHbP, {t, 0, 1*^6},
  PlotFunction \[Rule] LogLinearPlot, Legend \[Rule] True,
  FrameLabel \[Rule] {"Time", "Hemoglobin T/R Ratio"}]

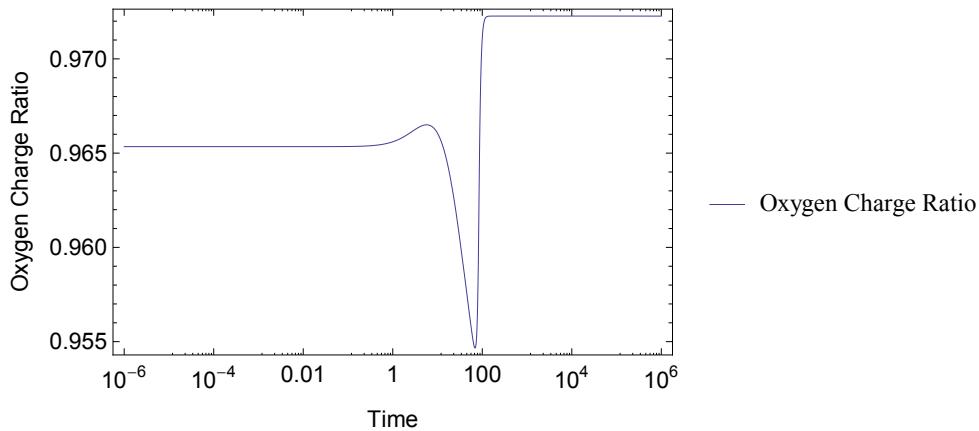
oxygenchargeratio = {"Oxygen Charge Ratio" \[Rule] (Hb1 + 2 Hb2 + 3 Hb3 + 4 Hb4) / HbTOT}
plotSimulation[oxygenchargeratio /. concSolHbP,
  {t, 0, 1*^6}, PlotFunction \[Rule] LogLinearPlot, Legend \[Rule] True,
  FrameLabel \[Rule] {"Time", "Oxygen Charge Ratio"}]

{Hemoglobin TR Ratio \[Rule]
  deoxyHb^c / (Hb^c o2^c + Hb^c 2 o2^c + Hb^c 3 o2^c + Hb^c 4 o2^c + deoxyHb^c + Hb^c)}

```



This plot shows the T/R ratio of hemoglobin which reaches a lower steady state as time proceeds. This occurs because additional oxygen must be circulated throughout the body.

$$\left\{ \text{Oxygen Charge Ratio} \rightarrow \left(\frac{\text{Hb}^c \text{o2}^c + 2 \text{Hb}^c 2 \text{o2}^c + 3 \text{Hb}^c 3 \text{o2}^c + 4 \text{Hb}^c 4 \text{o2}^c}{4 (\text{Hb}^c \text{o2}^c + \text{Hb}^c 2 \text{o2}^c + \text{Hb}^c 3 \text{o2}^c + \text{Hb}^c 4 \text{o2}^c + \text{deoxyHb}^c + \text{Hb}^c)} \right) \right\}$$


This graph shows the oxygen charge in relation to time. Increasing vapt increases the amount of oxygen which must be used to satisfy the physiological needs of the system therefore the steady state of

the plot occurs at a higher value of the oxygen charge.