

# Sensitivity Analysis of Biochemical Systems Using Bond Graphs: Additional Material for Pentose Phosphate Pathway

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## 1 Introduction

This notebook generates the figures for the paper: Sensitivity Analysis of Biochemical Systems Using Bond Graphs - Pentose Phosphate Pathway Example

## 2 Set up the code

### 2.1 Import packages

```
[1]: ## Some useful imports
import BondGraphTools as bgt
import numpy as np
```

```

import sympy as sp
import matplotlib.pyplot as plt
import control as con
import copy
import importlib
import time

## For reimporting: use imp.reload(module)
import importlib as imp

# ## For path etc: sys.path
import sys
sys.path.append("/home/peterg/WORK/Research/SystemsBiology/lib/python")

#
## Stoichiometric analysis
import stoich as st

## SVG
import svgBondGraph as sbg

## Stoichiometry to BG
import stoichBondGraph as stbg

## Sloppy parameters
import sloppy as slp

## Display (eg disp.SVG(), disp.
import IPython.display as disp

##
quiet = True
Plotting = False
Titles = True

```

Warning - scikit.odes not found. Simulations are disabled.

```

[2]: def tfProps(tf,method='truncate'):

    ## Steady-state gain
    g = con.dcgain(tf)

    if not con.issiso(tf):
        g = g[0][0]

    ## Time constant
    ## Check if direct link
    direct_link = np.any(tf.D)
    ## Only set tau=0 if siso
    if direct_link and con.issiso(tf):
        ## Instant response

```

```

        tau = 0
    else:
        ## Reduce to first-order to estimate time constant
        ## Note that method='matchdc' can give a kernel crash - use 'truncate'
        tf1 = con.balred(sys,orders=1,method=method)
        poles = con.poles(tf1)
        realPoles = np.real(poles)
        tau = -1/min(realPoles)

    return g,tau

```

[3]: *## High frequency gain function (initial response to step)*

```

def hfgain(sys):

    tf = con.ss2tf(sys)
    num = tf.num[0][0]
    den = tf.den[0][0]
    n = len(den)
    m = len(num)
    # print(den)
    # print(num)
    # print(n,m)

    if n==m:
        g = num[0]/den[0]
    elif n>m:
        g = 0
    elif n<m:
        g = float('inf')

    return g

# g = hfgain(sys)
# print(g)

```

[4]: *## Optional plotting*

```

def Savefig(name):
    if Plotting:
        plotname = 'Figs/'+name+'.pdf'
        print('Saving',plotname)
        plt.rcParams.update({'font.size': 20})
        plt.tight_layout()
        plt.savefig(plotname)
        plt.clf()

```

## 2.2 Steady-state by simulation

```
[5]: ## Steady-state by simulation
def SteadyState(s,sc,sf=None,parameter={},X0=None,t_ss=1000):
    t = np.linspace(0,t_ss)
    dat = st.
    ↪sim(s,sc=sc,sf=sf,t=t,parameter=parameter,X0=X0,tol=1e-4,quiet=quiet)
    X_ss = dat['X'][-1]
    V_ss = dat['V'][-1]
    #dX_ss = sc['N']@V_ss
    dX_ss = dat['dX'][-1]
    dXc_ss = dat['dXc'][-1]
    print(f'Steady-state finder error: {np.linalg.norm(dXc_ss):.2e}')
    return X_ss,V_ss
```

## 2.3 Stoichiometry

```
[6]: def ↪
    ↪Stoichiometry(model,chemostats=[],flowstats=[],CommonSpecies=None,sensitivity=False):
    ↪
    ## Stoichiometry
    s = st.stoich(model,quiet=quiet)

    ## Unify species
    if not (CommonSpecies is None):
        commonSpecies = st.merge(s,CommonSpecies=CommonSpecies)
    #    print(commonSpecies)
    st.unify(s,commonSpecies=commonSpecies)

    ## Sensitivity
    if sensitivity:
        extra = st.stoichSensitivity(s)
    else:
        extra = []

    #    print(chemostats+extra)

    ## Chemostats and flowstats
    sc = st.statify(s,chemostats=chemostats+extra)
    sf = st.statify(s,flowstats=flowstats)

    return s,sc,sf
```

## 2.4 Linearisation

```
[7]: def Linear(s,sc,sf=None,parameter={},X0=None, invar='X', outvar = 'V',↪
    ↪quiet=False):

    ## Steady state
```

```

    if X0 is None:
        X0 = np.ones(s['n_X'])
#     print(len(X0))

    X_ss,V_ss = SteadyState(s,sc,sf=sf,parameter=parameter,X0=X0)
    dX_ss = s['N']@V_ss
#     print('X_ss =', X_ss)
    print('V_ss =', V_ss)
#     print('dX_ss =', dX_ss)

    ## Linearise
    sys = st.lin(s,sc,sf=sf,x_ss=X_ss,parameter=parameter,
                invar=invar,outvar=outvar,quiet=quiet)

    return sys,X_ss,V_ss,dX_ss

```

## 2.5 Extract subsystem from linear system

```

[8]: def Index(A,a):

    I = []
    for aa in a:
        i = A.index(aa)
        I.append(i)
    return np.array(I)

def zapSmall(x,tol=1e-10,quiet=True):

    xx = np.zeros(len(x))
    for i,val in enumerate(x):
        if abs(val)>tol:
            xx[i] = x[i]
        else:
            if not quiet:
                print(f'Setting {i}th coefficient {val:.2} to zero')
    return xx

def ↪
↪extractSubsystem(SYS,sc,sf,inp,outp,tol=1e-3,order=None,minreal=False,quiet=False):
↪

    Sys = copy.copy(SYS)
    chemostats = sc['chemostats']
    if sf is None:
        flowstats = []
    else:
        flowstats = sf['flowstats']
    species = sc['species']
    reaction = sc['reaction']

```

```

## Index of input and output
if inp[0] in chemostats:
    i_inp = Index(chemostats,inp)
#     print('Input:',i_inp,chemostats[i_inp[0]])
else:
    i_inp = Index(flowstats,inp)+len(chemostats)

#     print(i_inp)

if outp[0] in chemostats:
#     i_outp = Index(chemostats,outp)
    i_outp = Index(species,outp)
elif outp[0] in species:
    i_outp = Index(species,outp)
else:
    if outp[0] in reaction:
        i_outp = Index(reaction,outp)
    else:
        print(f'Output {outp} does not exist')

## Extract tf
n_y = len(i_outp)
n_u = len(i_inp)
nn = Sys.A.shape
n_x = nn[0]
#print(n_x)

sys = con.ss(Sys.A,
              Sys.B[:,i_inp].reshape(n_x,n_u),
              Sys.C[i_outp,:].reshape(n_y,n_x),
              Sys.D[i_outp][:,i_inp].reshape(n_y,n_u))

if minreal:
    sys = con.minreal(sys,tol=tol,verbose=True)

## Reduce order
if not (order is None):
    sys = con.balred(sys,order,method='matchdc')

return sys

```

## 2.6 Plotting

```

[9]: def ↳ plotSensitivity(dat,reactions=['r1','r2'],plotSim=True,name=None,labeling=True):
↳
    if plotSim:
        plt.plot(t,y_step,color='black')

```

```

else:
    plt.plot(t,y_step,label=label)

for reac in reactions:
    i = s['reaction'].index(reac)
    if plotSim:
#         label = reac + r' ($\tilde{\lambda}$ = ' + f'{lam-1:0.2f})'
        pc = int(round(100*(lam-1)))
        if labeling:
            label = f'{reac} ({pc}%)'
        else:
            label = None
        plt.plot(t,(dat['V'][:,i]-V_ss[i])/(lam-1),
                 lw=5,ls='dashed',label=label)

plt.grid()
if labeling:
    plt.legend()
plt.xlabel('$t$')
plt.ylabel(r'$\tilde{v}/\tilde{\lambda}$')
# plt.ylim(bottom=0)
# plt.xlim(left=0)
# plt.tight_layout()

```

```

[10]: def
→ plotSensitivitydX(dat,species=['A','C'],plotSim=True,name=None,labeling=True,setZero=False
→
    if plotSim:
        plt.plot(t,y_step,color='black')
    else:
        plt.plot(t,y_step,label=label)

    for spec in species:
        print(spec)
        i_s = s['species'].index(spec)
        if plotSim:
            pc = int(round(100*(lam-1)))
            if labeling:
                label = f'{spec} ({pc}%)'
            else:
                label=None
            plt.plot(t,(dat['dX'][:,i_s]-dX_ss[i_s])/(lam-1),
                     lw=5,ls='dashed',label=label)

    plt.grid()
    if labeling:
        plt.legend()
    plt.xlabel('$t$')
    plt.ylabel(r'$\Delta \mathbf{f} / \Delta \lambda$')

```

```

plt.ylabel(r'$\tilde{\dot{x}}/\tilde{\lambda}$')
if setZero:
    plt.ylim(bottom=0)
    plt.xlim(left=0)
# plt.tight_layout()

```

```

[11]: def plotLines(lw=4,ls='dotted'):
        plt.hlines(g,min(t),max(t),color='black',ls=ls,lw=lw)
        plt.vlines(tau,min(y_step.flatten()),1.1*max(y_step.
        ↳flatten()),color='black',ls=ls,lw=lw)

```

### 3 Normalisation constants

```

[12]: T_human = 37 # Human body temperature
K_0 = 273.15
print(f'T_human = {T_human} degC = {T_human+K_0} K')

mu_0 = RT = st.RT(T_cent=T_human)
print(f'mu_0 = {mu_0*1e-3:0.3f} kJ/mol')

F = st.F() # Faraday's constant
print(f'F = {F*1e-3:0.2f} kC/mol')

V_0 = RT/F
print(f'V_0 = {V_0*1e3:0.2f} mV')

P_0 = 1e-3

v_0 = P_0/mu_0
print(f'v_0 = {v_0*1e6:0.4f} micro mol /s')

i_0 = F*v_0
print(f'i_0 = {i_0*1e3:0.2f} mA')

```

```

T_human = 37 degC = 310.15 K
mu_0 = 2.579 kJ/mol
F = 96.49 kC/mol
V_0 = 26.73 mV
v_0 = 0.3878 micro mol /s
i_0 = 37.42 mA

```

### 4 Stoichiometric approach

```

[13]: def simSensitivity(s,sc,sf,Sys,X_ss,V_ss,dX_ss,chemostats=['A','C'],
        inp=['sr1'],outp=['r1','r2'],t_last=2,parameter={},lam=1.
        ↳2,order=None,tol=None):

        ## Extract sensitivity system

```



```

sys = extractSubsystem(Sys,sc,sf,inp=inp,outp=outp,order=order,tol=tol)

## Time
t = np.linspace(0,t_last,500)

## Sensitivity step response
step = con.step_response(sys,T=t)
y_step = step.y[:,0,:].T

## Exact simulation with changed parameter or state
X_ss_1 = copy.copy(X_ss)
parameter1 = copy.copy(parameter)
inComp = inp[0][1:]

if inComp in chemostats:
    ## Perturb state
    iComp = s['species'].index(inComp)
    X_ss_1[iComp] = lam*X_ss_1[iComp]
else:
    ## Perturb parameter
    if inComp in s['species']:
        parname = 'K_'+inComp
    else:
        parname = 'kappa_'+inComp

    print(parname)

    if parname in list(parameter.keys()):
        parameter1[parname] = lam*parameter[parname]
    else:
        parameter1[parname] = lam

dat = st.sim(s,sc=sc,sf=sf,t=t,parameter=parameter1,X0=X_ss_1,quiet=quiet)

return dat,y_step,t,sys

```

## 5 Import Pentose Phosphate Pathway information from:

Peter J. Gawthrop, Michael Pan, and Edmund J. Crampin. *Modular dynamic biomolecular modelling with bond graphs: the unification of stoichiometry, thermodynamics, kinetics and data*. Journal of The Royal Society Interface, 18(181):20210478, 2021. doi:10.1098/rsif.2021.0478.

```

[14]: ## Load data
import pickle
filename = 'GlyPPP.pic'
datafile = open(filename, 'rb')
GlyPPP = pickle.load(datafile)

s0 = GlyPPP['s']

```

```

parameter = GlyPPP['parameter']
print(parameter)

sc0 = GlyPPP['sc']
chemostats = sc0['chemostats']
print(chemostats)

conc = GlyPPP['conc']

import json
print(json.dumps(parameter, indent=2))

```

```

{'kappa_PGI': 154.38997002578546, 'kappa_PFK': 54.85043355391926, 'kappa_FBA':
160.07691981318658, 'kappa_TPI': 353.9323765134668, 'kappa_G6PDH2R':
4.667672687418436, 'kappa_PGL': 291.6414393949941, 'kappa_GND':
1.2695594575280742, 'kappa_RPI': 4206.975085828208, 'kappa_TKT2':
9.170830408091838, 'kappa_TALA': 1.6563170906188465, 'kappa_TKT1':
8.819978413932159, 'kappa_RPE': 96.07053469867635, 'K_6PGC': 6.233520699319548,
'K_6PGL': 1.0397283862123778, 'K_ADP': 5.154605959675528, 'K_ATP':
2.2539233202427162, 'K_CO2': 33.794182951886775, 'K_DHAP': 1.778985981513151,
'K_E4P': 57.93534155565906, 'K_F6P': 1.41401983409913, 'K_FDP':
0.38795235349448437, 'K_G3P': 14.902044199279699, 'K_G6P': 0.8377378837717493,
'K_H': 0.3491739027654742, 'K_H2O': 1.0397283862123778, 'K_NADP':
11747.063287701598, 'K_NADPH': 21.002665768445333, 'K_R5P': 12.241945837528652,
'K_RU5PD': 86.15506601742248, 'K_S7P': 21.751324335743256, 'K_XU5PD':
51.68293204643235}
['ADP', 'ATP', 'CO2', 'G6P', 'H', 'H2O', 'NADP', 'NADPH', 'R5P', 'G3P']
{
  "kappa_PGI": 154.38997002578546,
  "kappa_PFK": 54.85043355391926,
  "kappa_FBA": 160.07691981318658,
  "kappa_TPI": 353.9323765134668,
  "kappa_G6PDH2R": 4.667672687418436,
  "kappa_PGL": 291.6414393949941,
  "kappa_GND": 1.2695594575280742,
  "kappa_RPI": 4206.975085828208,
  "kappa_TKT2": 9.170830408091838,
  "kappa_TALA": 1.6563170906188465,
  "kappa_TKT1": 8.819978413932159,
  "kappa_RPE": 96.07053469867635,
  "K_6PGC": 6.233520699319548,
  "K_6PGL": 1.0397283862123778,
  "K_ADP": 5.154605959675528,
  "K_ATP": 2.2539233202427162,
  "K_CO2": 33.794182951886775,
  "K_DHAP": 1.778985981513151,
  "K_E4P": 57.93534155565906,
  "K_F6P": 1.41401983409913,
  "K_FDP": 0.38795235349448437,
  "K_G3P": 14.902044199279699,
  "K_G6P": 0.8377378837717493,

```

```

"K_H": 0.3491739027654742,
"K_H2O": 1.0397283862123778,
"K_NADP": 11747.063287701598,
"K_NADPH": 21.002665768445333,
"K_R5P": 12.241945837528652,
"K_RU5PD": 86.15506601742248,
"K_S7P": 21.751324335743256,
"K_XU5PD": 51.68293204643235
}

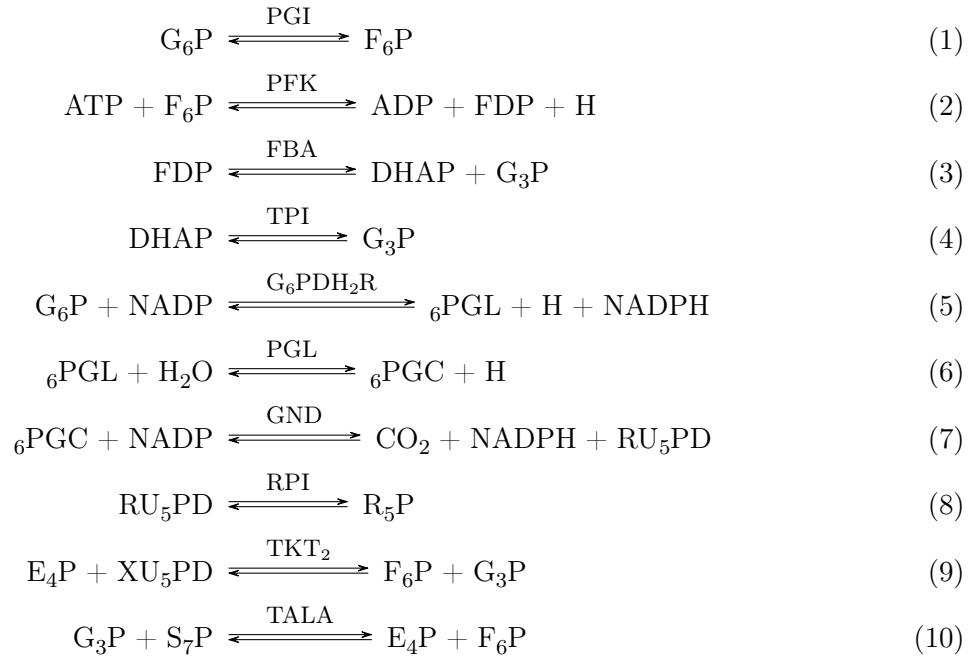
```

```

[15]: ## Reactions
disp.Latex(st.sprintrl(s0,chemformula=True))

```

[15]:

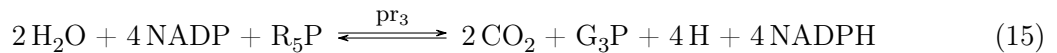
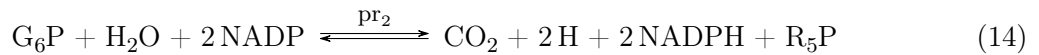


```

[16]: ## Pathway reactions
sp0 = st.path(s0,sc0)
disp.Latex(st.sprintrl(sp0,chemformula=True))

```

[16]:



## 5.1 Repeat simulations for sanity check

```
[17]: def setPath(s,path='R5P'):

    print('\n Path =', path)

    if path == 'R5P':
        chemostats = ['ADP', 'ATP', 'CO2', 'G6P', 'H', 'H2O', 'NADP',
→ 'NADPH', 'R5P']
        flowstats = ['G6PDH2R']
        dX_G6P = 5
    elif path == 'NADPH':
        chemostats = ['ADP', 'ATP', 'CO2', 'G6P', 'H', 'H2O', 'NADP', 'NADPH']
        flowstats = []
        dX_G6P = 1
    elif path == 'both':
        chemostats = ['ADP', 'ATP', 'CO2', 'G6P', 'H', 'H2O', 'NADP',
→ 'NADPH', 'R5P']
        flowstats = ['PGI', 'TKT2']
        dX_G6P = 1
    elif path == 'all':
        chemostats = ['ADP', 'ATP', 'CO2', 'G6P', 'H', 'H2O', 'NADP',
→ 'NADPH', 'R5P', 'G3P']
        flowstats = []
        dX_G6P = 10
    elif path == 'all_e4p':
        chemostats = ['ADP', 'ATP', 'CO2', 'G6P', 'H', 'H2O', 'NADP',
→ 'NADPH', 'R5P', 'G3P', 'E4P']
        flowstats = []
        dX_G6P = 10

    sc = st.statify(s,chemostats=chemostats)
    sf = st.statify(s,flowstats=flowstats)

    return sc,sf,dX_G6P
```

```
[18]: ## Data normalisation
c_0 = 7.88 # mM
f_0 = 0.9916666666666667 # mM/sec
t_0 = 7.946218487394957 # sec
```

```
[19]: ## Simulate for each path
s = copy.copy(s0) ## for compatibility
spec = s['species']
approximateFlowstats = True

Spec = ['G6P', 'R5P', 'NADPH', 'ADP', 'CO2', 'H', 'H2O']
#paths = ['all', 'both', 'R5P', 'NADPH']
#paths = ['R5P']
#paths = ['all', 'both', 'NADPH', 'R5P']
paths = ['both', 'NADPH', 'R5P', 'all_e4p', 'all']
```

```

RATIO = {}
for path in paths:
    Ratio = {}
    normalisedRatio = {}

    ## Set up pathway
    sc,sf,dX_G6P_0 = setPath(s,path=path)

    ## Print pathway
    sp = st.path(s,sc)
    print(st.sprintrl(sp))

    ## Set up parameters
    par = copy.copy(parameter)
    if approximateFlowstats:
        small = 1e-3
        par = copy.copy(parameter)
        for fs in sf['flowstats']:
            par['kappa_'+fs] = small
        sf = None

    ## Simulate
    t = np.linspace(0,3*t_0,1000)

    #     ## Find steady-state with no flowstats
    #     dat_ss = st.sim(s,sc=sc,sf=sf,t=t,parameter=parameter,X0=conc)
    #     X_ss = dat_ss['X'][-1,:]

    dat = st.sim(s,sc=sc,sf=sf,t=t,parameter=par,X0=conc)
    #st.plot(s,dat,species=[])
    #     st.plot(s,dat,reaction=[],species=Spec,dX=True)

    ## Extract some external flows
    DX = dat['dX']
    dX = {}
    for Sp in Spec:
        dX[Sp] = DX[:,spec.index(Sp)]
        Ratio[Sp] = -dX[Sp]/dX['G6P']
        normalisedRatio[Sp] = -dX_G6P_0*dX[Sp]/dX['G6P']

    RATIO[path] = normalisedRatio

    ## Print steady-state values
    for Sp in Spec:
        ratio = Ratio[Sp][-1]
        print(f'{Sp}: \t{dX[Sp][0]:3.1f} \t{dX[Sp][-1]:3.
→1f} \t{(dX_G6P_0*ratio):3.1f} \t{100*ratio:3.1f}%')

```

Path = both

```

\begin{align}
G6P + H2O + 2 NADP \&\Leftrightarrow CO2 + 2 H + 2 NADPH + R5P \\\
ADP + 4 H2O + 8 NADP + 2 R5P \&\Leftrightarrow ATP + 4 CO2 + G6P + 7 H + 8 NADPH
\end{align}

```

G6P:	-11.6	-11.6	-1.0	-100.0%
R5P:	6.2	11.5	1.0	99.4%
NADPH:	23.2	23.2	2.0	200.0%
ADP:	63.1	0.0	0.0	0.4%
CO2:	11.6	11.6	1.0	100.0%
H:	86.3	23.2	2.0	200.4%
H2O:	-11.6	-11.6	-1.0	-100.0%

```

Path = NADPH
\begin{align}
ADP + G6P + 6 H2O + 12 NADP \&\Leftrightarrow ATP + 6 CO2 + 11 H + 12 NADPH
\end{align}

```

G6P:	-71.1	-1.9	-1.0	-100.0%
R5P:	6.2	0.0	0.0	0.0%
NADPH:	23.2	23.1	12.0	1200.0%
ADP:	63.1	-1.9	-1.0	-100.0%
CO2:	11.6	11.6	6.0	600.0%
H:	86.3	21.2	11.0	1100.0%
H2O:	-11.6	-11.6	-6.0	-600.0%

```

Path = R5P
\begin{align}
G6P + H2O + 2 NADP \&\Leftrightarrow CO2 + 2 H + 2 NADPH + R5P \\\
ADP + 4 H2O + 8 NADP + 2 R5P \&\Leftrightarrow ATP + 4 CO2 + G6P + 7 H + 8 NADPH
\end{align}

```

G6P:	-59.5	-2.4	-5.0	-100.0%
R5P:	6.2	2.9	6.0	120.0%
NADPH:	11.6	0.0	0.0	0.2%
ADP:	63.1	0.5	1.0	20.0%
CO2:	11.6	0.0	0.0	0.1%
H:	74.7	0.5	1.0	20.2%
H2O:	-11.6	-0.0	-0.0	-0.1%

```

Path = all_e4p
\begin{align}
ATP + G6P \&\Leftrightarrow ADP + 2 G3P + H \\\
G6P + H2O + 2 NADP \&\Leftrightarrow CO2 + 2 H + 2 NADPH + R5P \\\
G3P + R5P \&\Leftrightarrow 2 E4P \\\
E4P + H2O + 2 NADP \&\Leftrightarrow CO2 + G3P + 2 H + 2 NADPH
\end{align}

```

G6P:	-71.1	-71.1	-10.0	-100.0%
R5P:	6.2	6.2	0.9	8.7%
NADPH:	23.2	23.2	3.3	32.6%

ADP:	63.1	63.1	8.9	88.8%
CO2:	11.6	11.6	1.6	16.3%
H:	86.3	86.3	12.1	121.3%
H2O:	-11.6	-11.6	-1.6	-16.3%

```

Path = all
\begin{align}
\text{ATP} + \text{G6P} &\rightarrow \text{ADP} + 2 \text{ G3P} + \text{H} \\
\text{G6P} + \text{H}_2\text{O} + 2 \text{ NADP} &\rightarrow \text{CO}_2 + 2 \text{ H} + 2 \text{ NADPH} + \text{R5P} \\
2 \text{ H}_2\text{O} + 4 \text{ NADP} + \text{R5P} &\rightarrow 2 \text{ CO}_2 + \text{G3P} + 4 \text{ H} + 4 \text{ NADPH}
\end{align}

```

G6P:	-71.1	-71.1	-10.0	-100.0%
R5P:	6.2	6.2	0.9	8.7%
NADPH:	23.2	23.2	3.3	32.6%
ADP:	63.1	63.1	8.9	88.8%
CO2:	11.6	11.6	1.6	16.3%
H:	86.3	86.3	12.1	121.3%
H2O:	-11.6	-11.6	-1.6	-16.3%

```

[20]: ## Set up chemostats to correspond to above path
chemostats = sc['chemostats']
Chemostats = copy.copy(sc['chemostats'])
print(path)
print(chemostats)

```

```

all
['ADP', 'ATP', 'CO2', 'G6P', 'H', 'H2O', 'NADP', 'NADPH', 'R5P', 'G3P']

```

```

[21]: ## Plot ratios
plottingRatios = False
if plottingRatios:
    name = ['i', 'ii', 'iii']
    for sp in ['R5P', 'NADPH']:
        BigFont = 24
        plt.rcParams.update({'font.size': BigFont})
        for i, path in enumerate(['both', 'R5P', 'NADPH']):
            Ratio = RATIO[path]
            label = f'Path {name[i]} ({path})'
            plt.plot(t/t_0, Ratio[sp], label=label, linewidth=5)
        if sp == 'R5P':
            ylim = 8
        else:
            ylim = 15
        plt.ylim((0, ylim))
        ylabel = r'$\rho_{'+sp+'}$'
        plt.ylabel(ylabel)
        plt.xlabel('$t/t_0$')
        plt.legend()
        plt.grid()
    # if SaveFig:

```

```
# plt.savefig(f'Figs/{sp}.pdf',bbox_inches='tight')

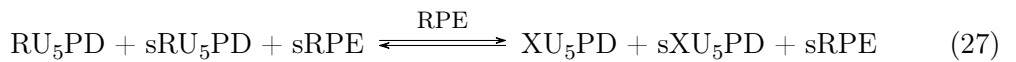
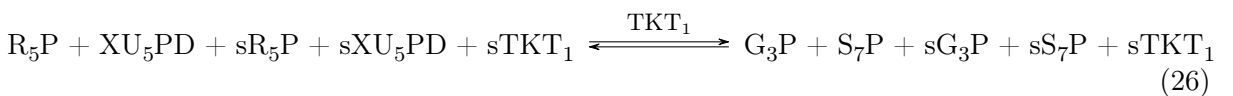
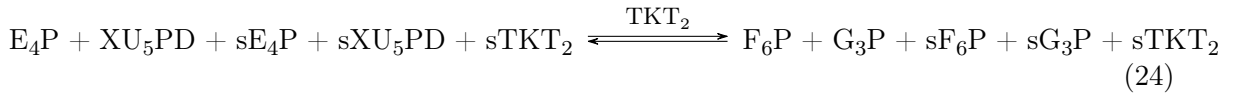
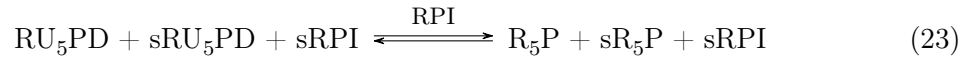
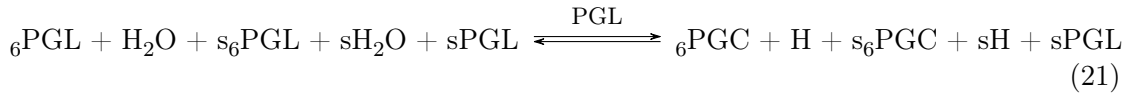
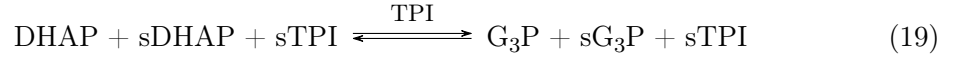
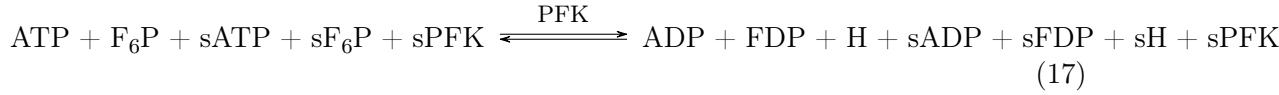
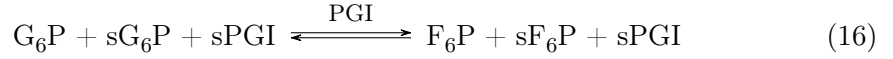
# plt.show()
```

## 6 Sensitivity System

```
[22]: ## Create sensitivity system
s = copy.copy(s0)
extra = st.stoichSensitivity(s)
chemostats += extra
sc = st.statify(s,chemostats=chemostats)
```

```
[23]: ## Reactions
disp.Latex(st.sprintrl(s,all=True,chemformula=True))
```

[23]:





```
[24]: ## Initial conditions
X0 = np.hstack((conc,np.ones(s0['n_X']),np.ones(s0['n_V'])))
# print(X0)
print(X0.shape)
```

(50,)

```
[25]: ## Linearise
# Sys,X_ss,V_ss,dX_ss = Linear(s,sc,X0=X0)
# Sys,X_ss,V_ss,dX_ss = Linear(s,sc,parameter=parameter,X0=X0, invar='X',
→outvar = 'V', quiet=False)
```

```
[26]: # species = s['species']
# reaction = s['reaction']
```

```
[27]: # print(chemostats)
# print(reaction)
# print(species)
# # print(s0['Z'])
```

```
[28]: # sys = extractSubsystem(Sys,sc,sf,inp=['sG6P'],outp=['RPI'],order=3)
```

## 6.1 Linearise sensitivity system

```
[29]: ## Linearise dX as outvar
Sys,X_ss,V_ss,dX_ss = Linear(s,sc,parameter=parameter,X0=X0, invar='X',
→outvar = 'dX', quiet=False)
```

Steady-state finder error: 2.10e-14

V\_ss = [59.52330023 63.11688312 63.11688312 63.11688312 11.57830405 11.57830405  
11.57830405 7.98472116 1.79679144 1.79679144 1.79679144 3.59358289]

Setting K\_6PGC to 6.233520699319548

Setting K\_6PGL to 1.0397283862123778

Setting K\_ADG to 5.154605959675528

Setting K\_ATP to 2.2539233202427162

Setting K\_CO2 to 33.794182951886775

Setting K\_DHAP to 1.778985981513151

Setting K\_E4P to 57.93534155565906

Setting K\_F6P to 1.41401983409913

Setting K\_FDP to 0.38795235349448437

Setting K\_G3P to 14.902044199279699

Setting K\_G6P to 0.8377378837717493

Setting K\_H to 0.3491739027654742

Setting K\_H2O to 1.0397283862123778

Setting K\_NADP to 11747.063287701598

Setting K\_NADPH to 21.002665768445333

Setting K\_R5P to 12.241945837528652

Setting K\_RU5PD to 86.15506601742248

Setting K\_S7P to 21.751324335743256

Setting K\_XU5PD to 51.68293204643235

Setting kappa\_PGI to 154.38997002578546

Setting kappa\_PFK to 54.85043355391926  
 Setting kappa\_FBA to 160.07691981318658  
 Setting kappa\_TPI to 353.9323765134668  
 Setting kappa\_G6PDH2R to 4.667672687418436  
 Setting kappa\_PGL to 291.6414393949941  
 Setting kappa\_GND to 1.2695594575280742  
 Setting kappa\_RPI to 4206.975085828208  
 Setting kappa\_TKT2 to 9.170830408091838  
 Setting kappa\_TALA to 1.6563170906188465  
 Setting kappa\_TKT1 to 8.819978413932159  
 Setting kappa\_RPE to 96.07053469867635

## 6.2 Compute chemostat sensitivities

```
[30]: ## Chemostat sensitivities
# Inp = ['sG6P', 'sR5P', 'sNADPH', 'sG3P']
Outp = ['G6P', 'R5P', 'NADPH', 'G3P']
Inp = []
for chemo in sc['chemostats']:
    if not chemo[0] in ['s', 'H']:
        Inp.append('s'+chemo)
print(Inp)
Inp_chemo = Inp
# Inp = []
# for reac in s['reaction']:
#     Inp.append('s'+reac)
# Inp = ['sG6PDH2R']

t_last=1
lam = 1.1 # Perturbation parameter

dcgain = {}
Tau = {}
for outp in Outp:
    for inp in Inp:
        print('Doing:', inp)
        sf = None
        order = None
        dat, y_step, t, sys = □
        →simSensitivity(s, sc, sf, Sys, X_ss, V_ss, dX_ss, chemostats=Chemostats, parameter=parameter,
                        □
        →inp=[inp], outp=[outp], lam=lam, t_last=t_last, order=order)

        g = con.dcgain(sys)
        g, tau = tfProps(sys)
        print('g =', g)
        name = inp[1:]

        if outp=='G6P':
            dcgain[name] = -g
```

```

        ylabel = '$-g_{\infty}$'
    else:
        dcgain[name] = g
        ylabel = '$g_{\infty}$'

    Tau[name] = tau

    dlam = int((lam-1)*100)
    print('dlam =', dlam)
    if Titles:
        plt.title(f'{name}'+r' ($\tilde{\lambda}$ = ' + f'{dlam}%; g={g:.
→2f})')
    plotSensitivitydX(dat, species=[outp], labeling=False)
#     plt.hlines(g, min(t), max(t), color='black', ls='dashed')
    plotLines()
    Savefig('PPPdX_'+name+'_'+outp)
    plt.show()

    ## Barcharts
    ## DC gain
    if Titles:
        plt.title(outp)
    plt.tick_params(axis='x', rotation=90)
    plt.grid()
    plt.bar(range(len(dcgain)), dcgain.values(), align='center')
    plt.xticks(range(len(dcgain)), list(dcgain.keys()))
    plt.ylabel(ylabel)
    Savefig(f'PPPdX_{outp}_chem_bar')
    plt.show()

    ## Time constant
    if Titles:
        plt.title(outp)
    plt.tick_params(axis='x', rotation=90)
    plt.grid()
    plt.bar(range(len(Tau)), Tau.values(), align='center')
    plt.xticks(range(len(Tau)), list(Tau.keys()))
    plt.ylabel(r'$\tau$')
    Savefig(f'PPPdX_{outp}_chem_tau_bar')
    plt.show()

```

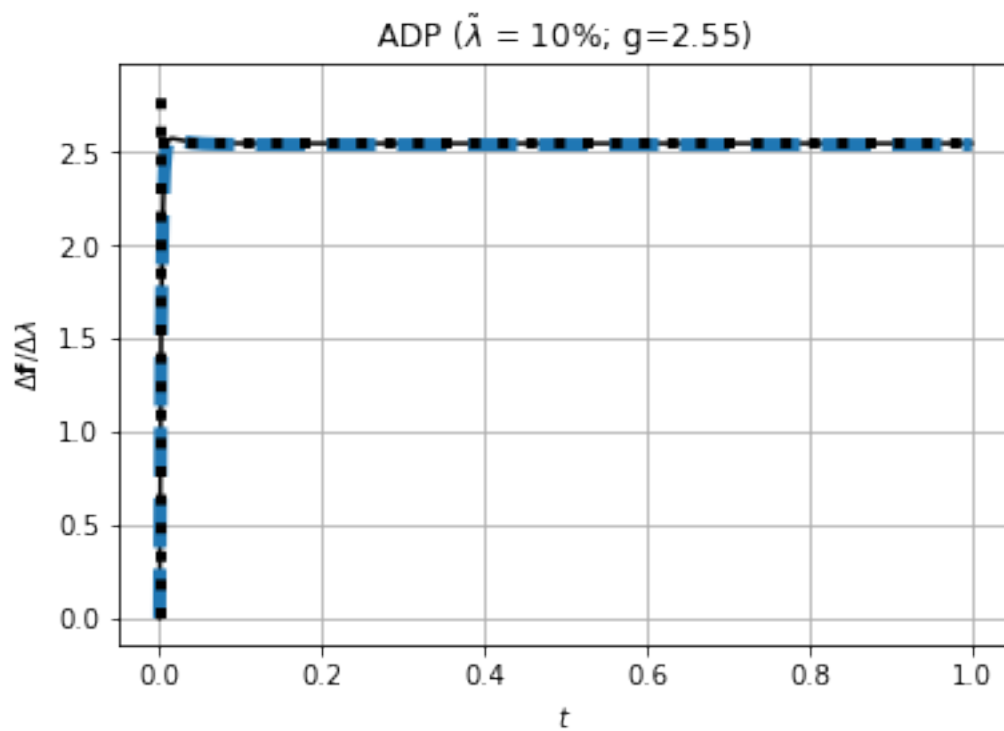
['sADP', 'sATP', 'sCO2', 'sG6P', 'sNADP', 'sNADPH', 'sR5P', 'sG3P']

Doing: sADP

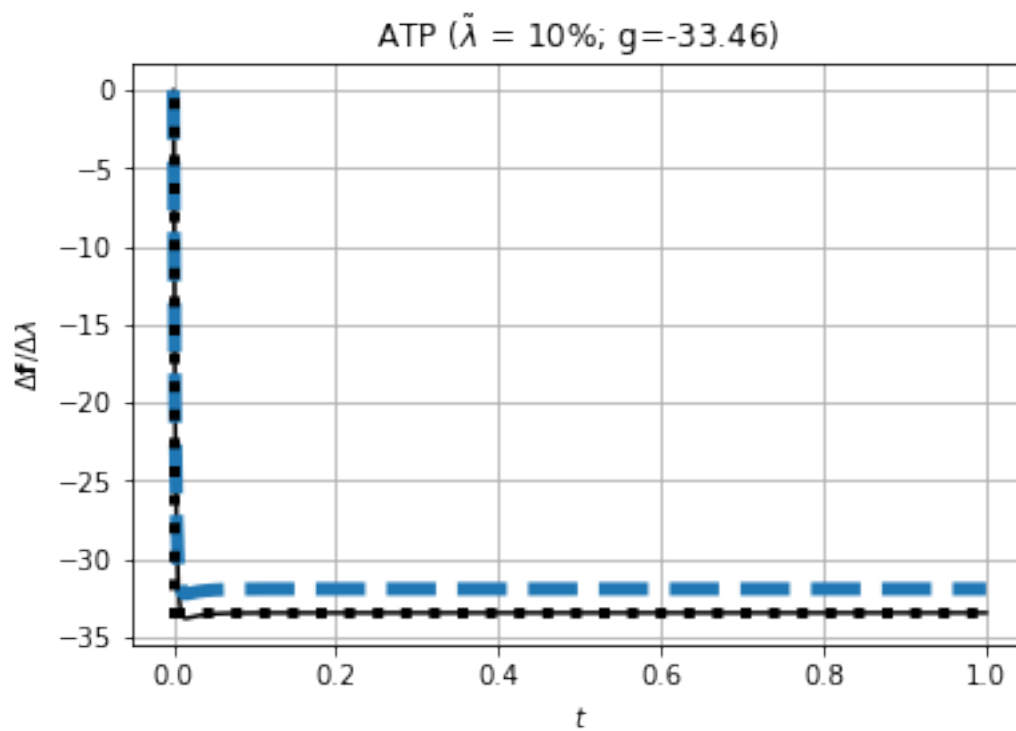
g = 2.5484963469688147

dlam = 10

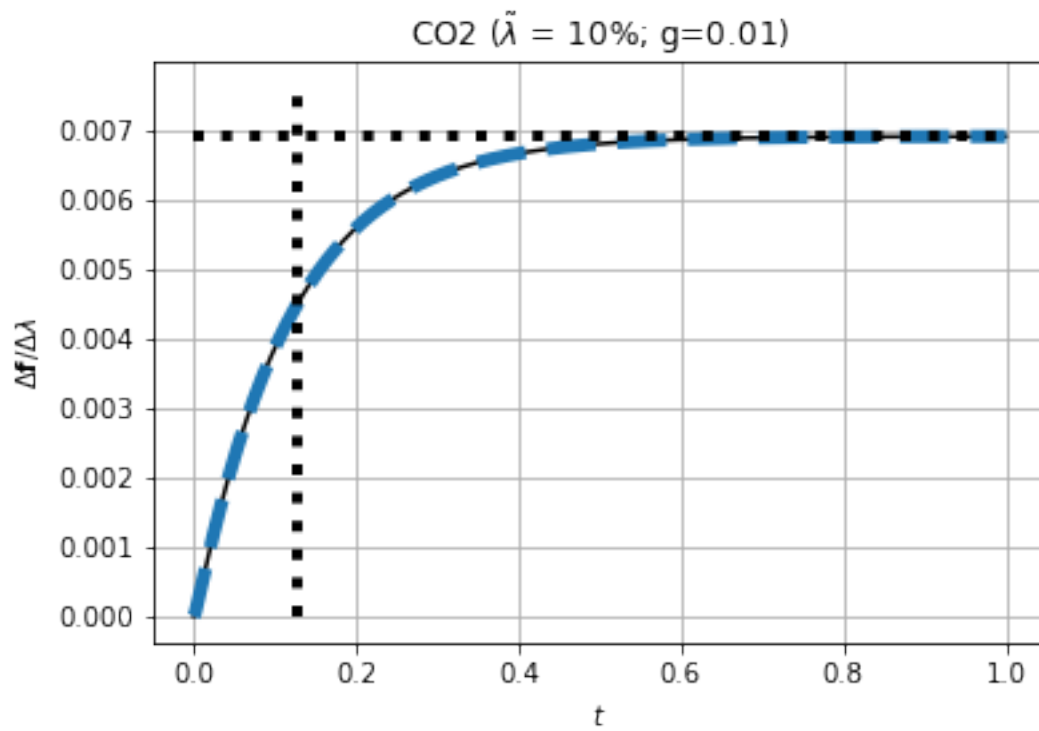
G6P



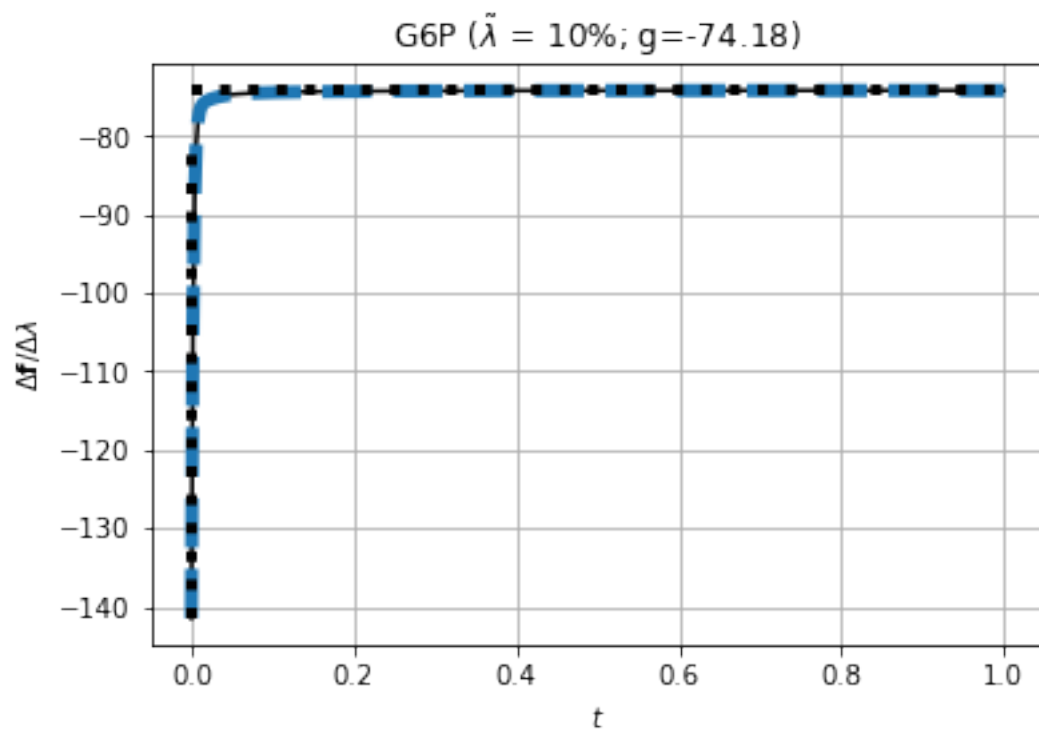
Doing: sATP  
 $g = -33.46210603034223$   
 $d\lambda = 10$   
 G6P



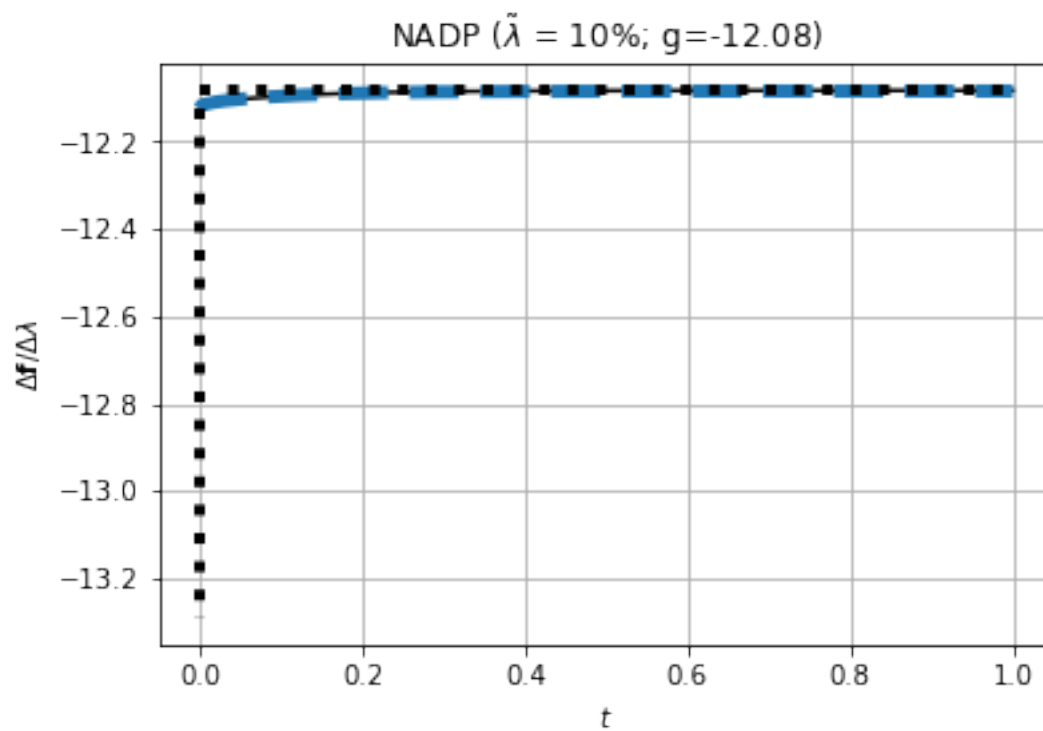
Doing: sCO2  
 $g = 0.006924942429813596$   
 $d\lambda = 10$   
 G6P



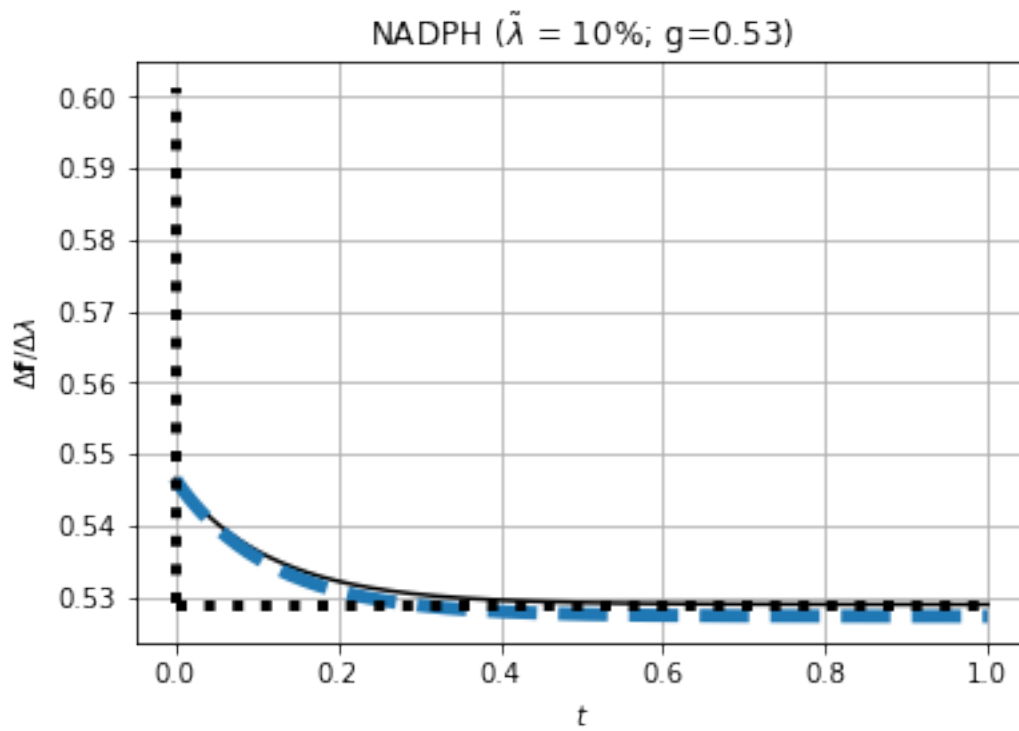
Doing: sG6P  
 $g = -74.1814457534691$   
 $d\lambda = 10$   
 G6P



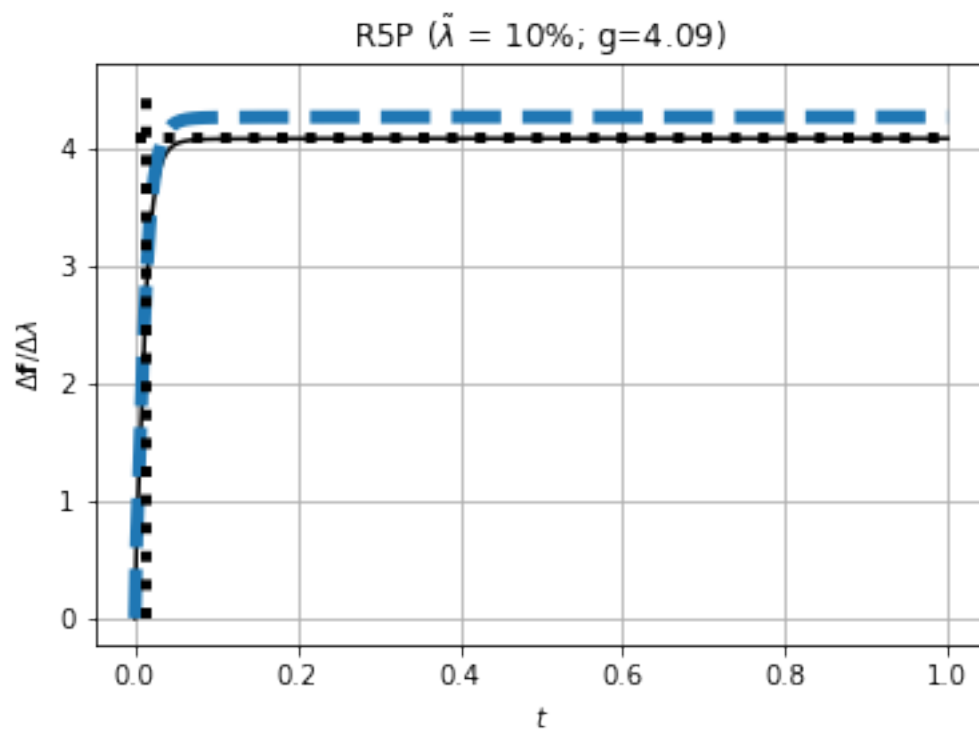
Doing: sNADP  
 $g = -12.083105188911864$   
 $d\lambda = 10$   
 G6P



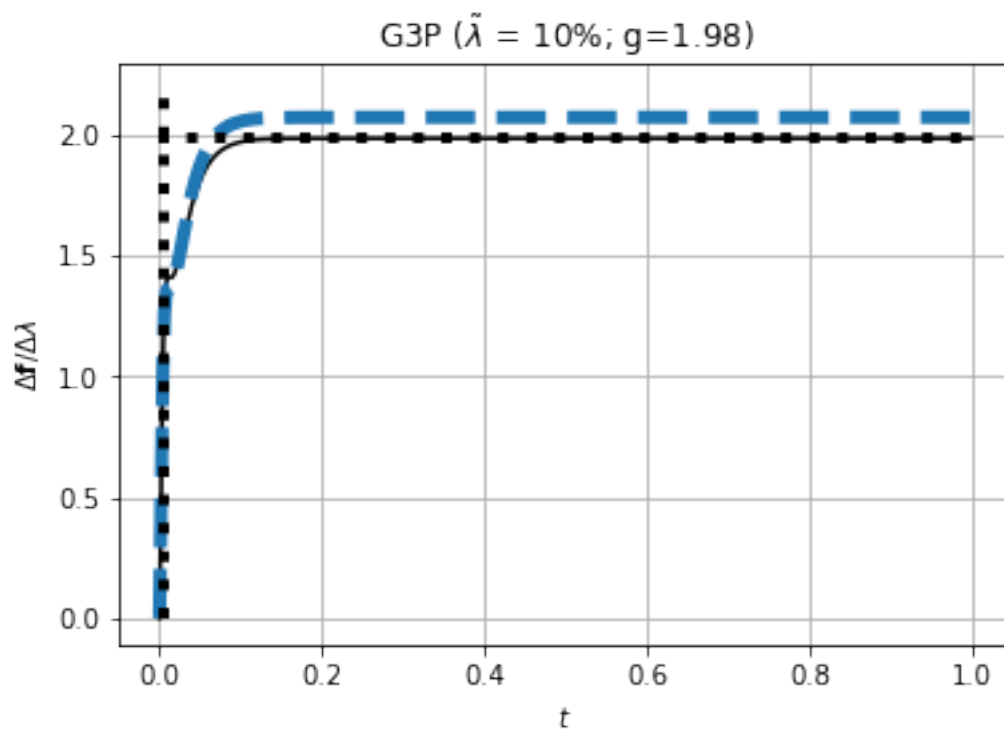
Doing: sNADPH  
 $g = 0.5288892968979394$   
 $d\lambda = 10$   
 G6P



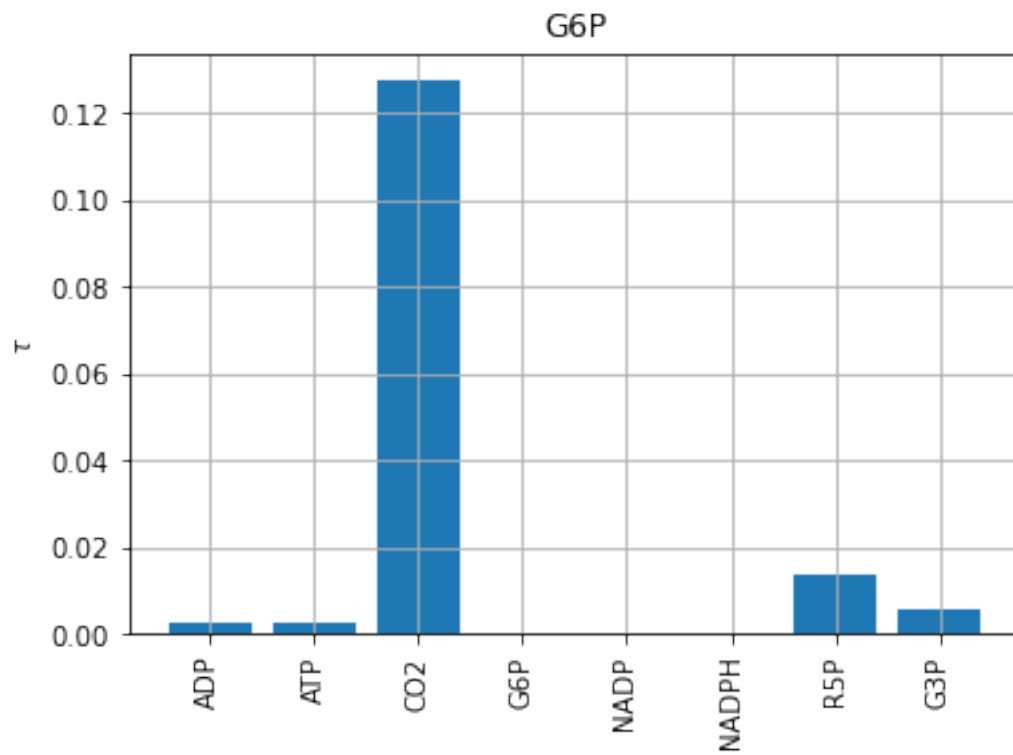
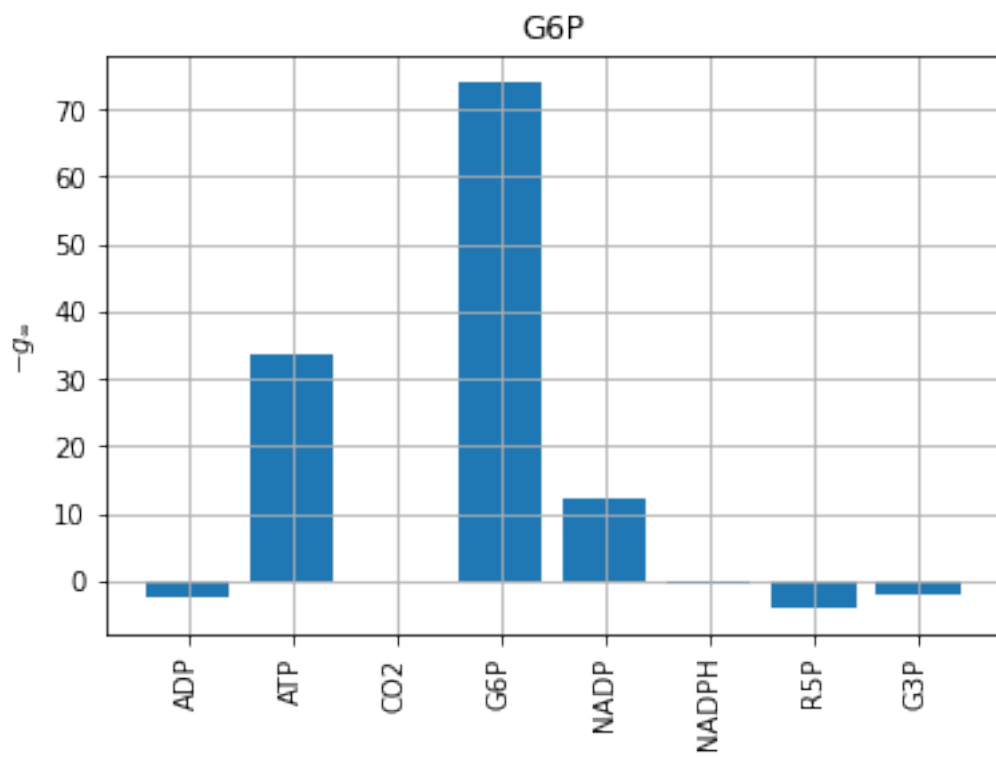
Doing: sR5P  
 $g = 4.08711120268265$   
 $d\lambda = 10$   
 G6P



Doing: sG3P  
 $g = 1.984521369029551$   
 $d\lambda = 10$   
 G6P

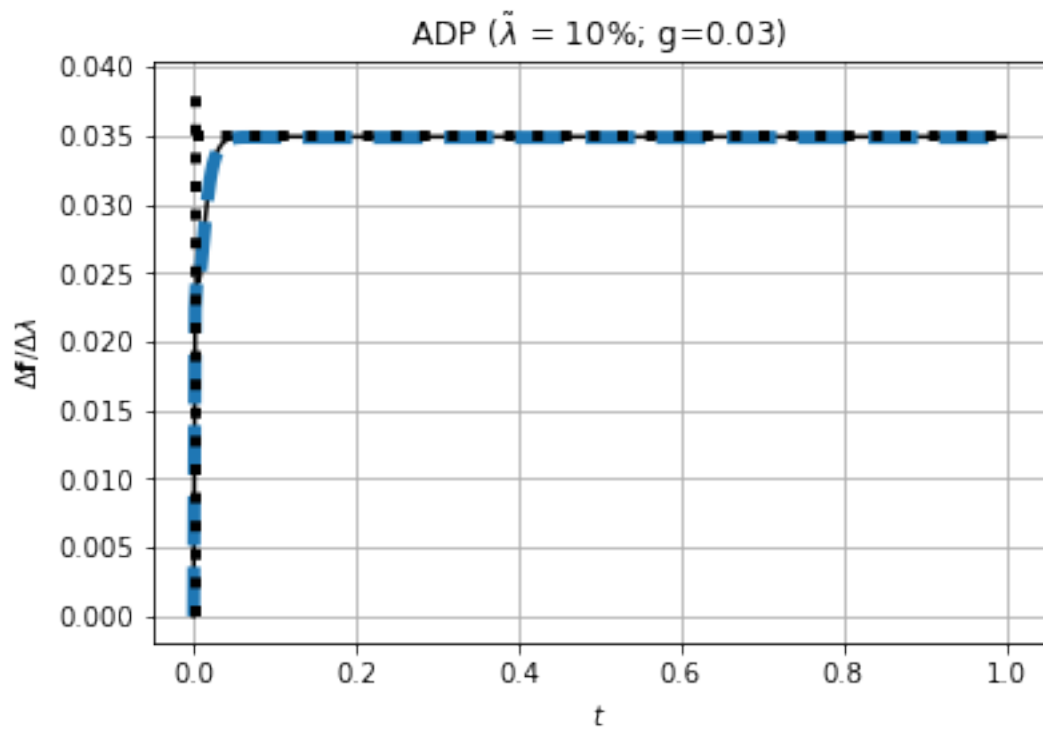




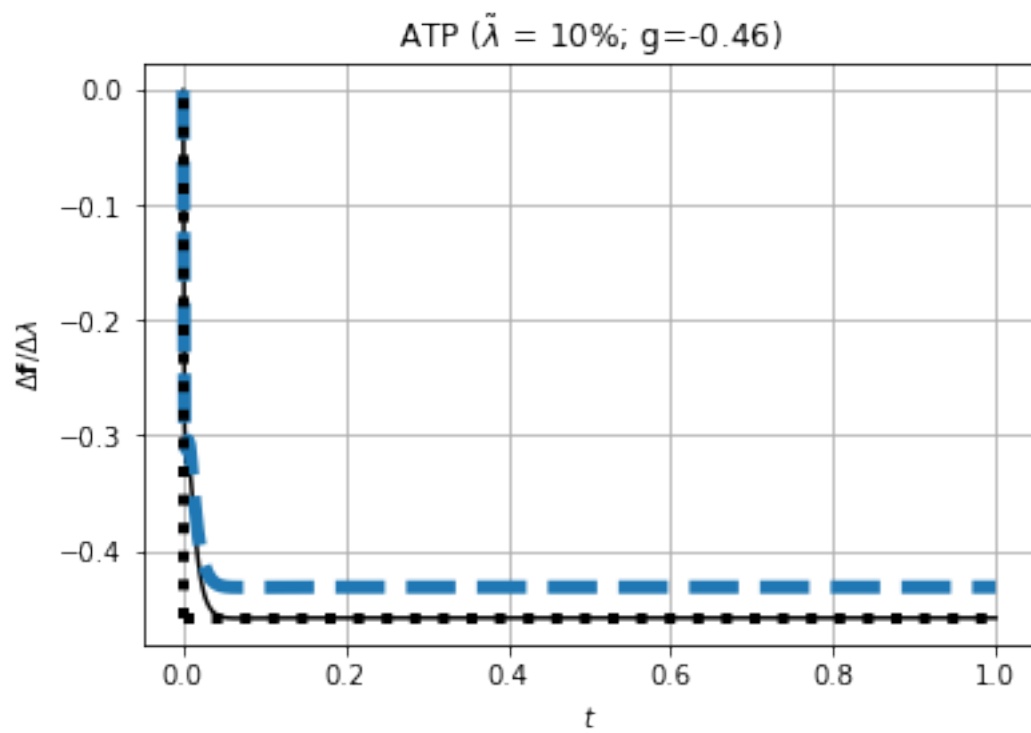


Doing: sADP

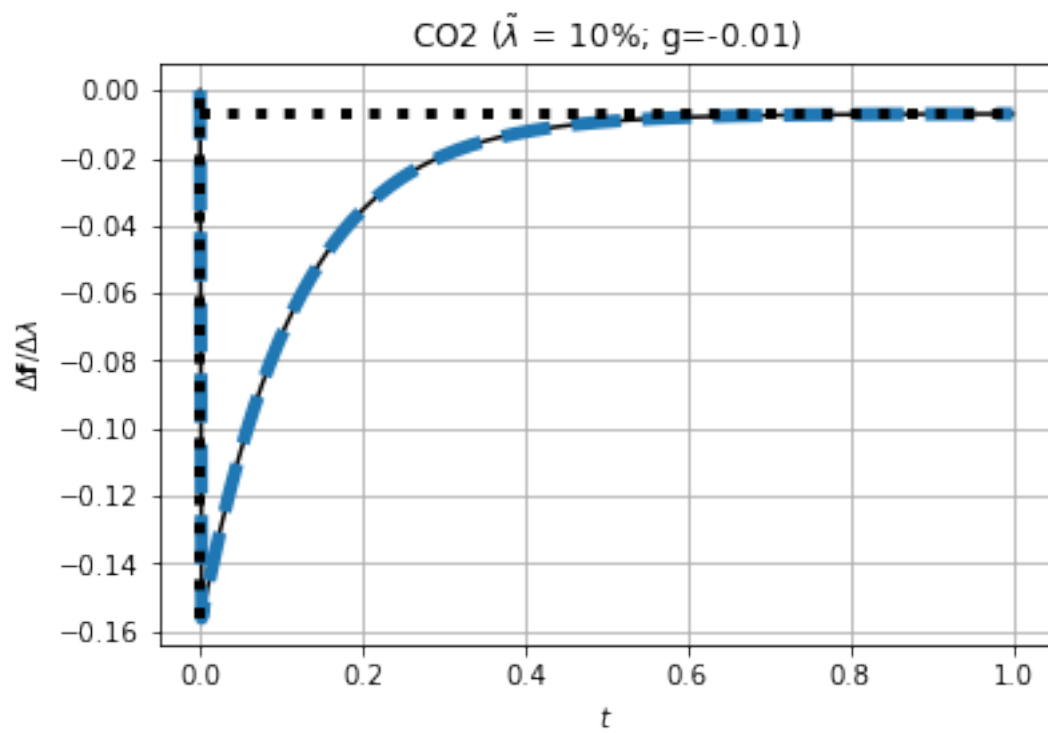
$g = 0.0349248023890647$   
 $d\lambda = 10$   
R5P



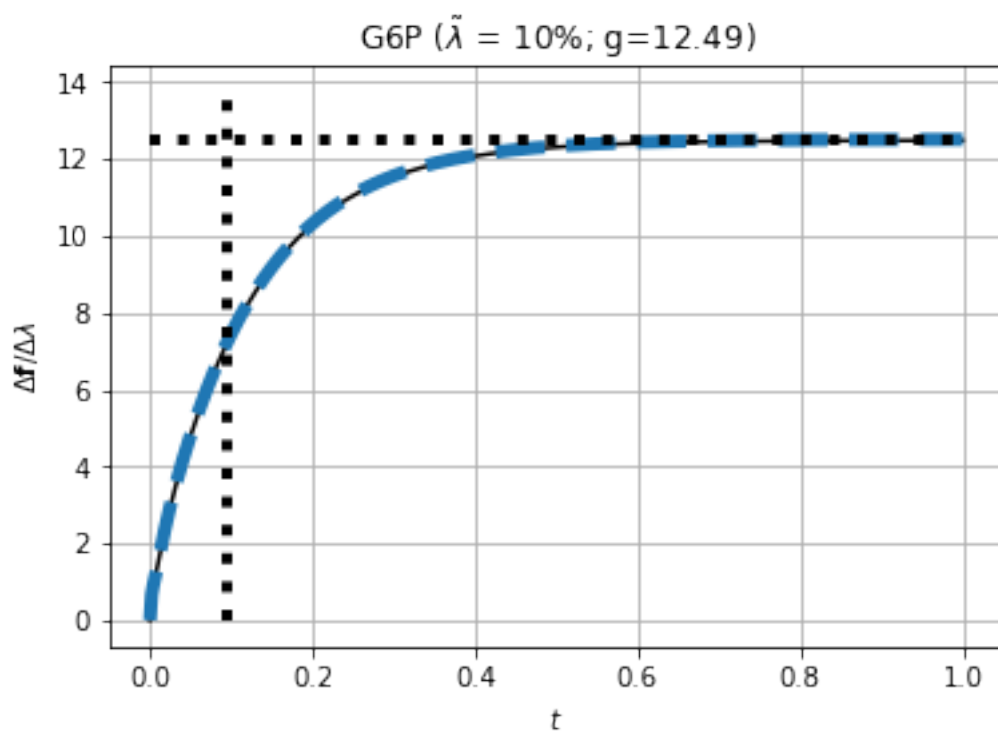
Doing: sATP  
 $g = -0.4585674380195499$   
 $d\lambda = 10$   
R5P



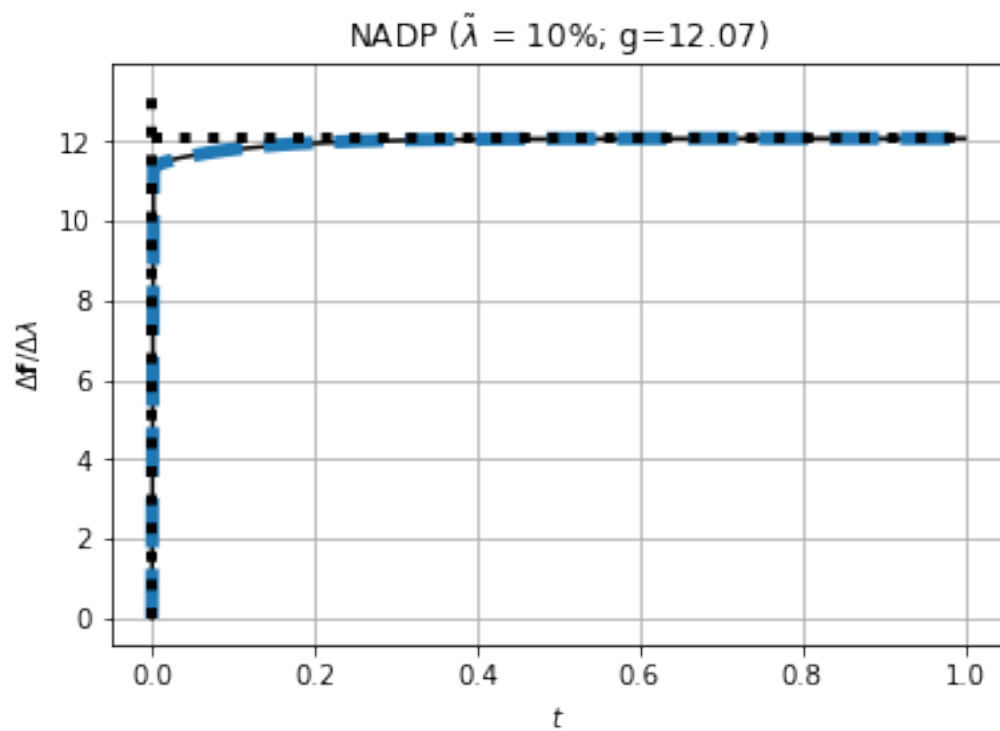
Doing: sCO2  
 $g = -0.006919387119948707$   
 $d\lambda = 10$   
 R5P



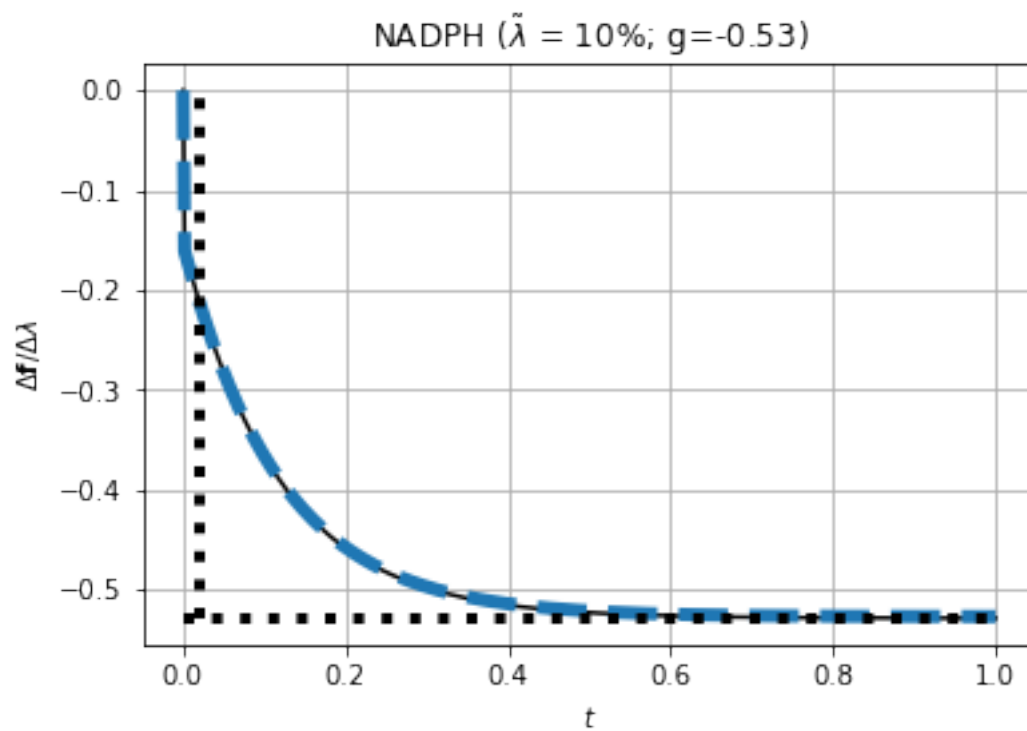
Doing: sG6P  
g = 12.485591708850293  
dlam = 10  
R5P



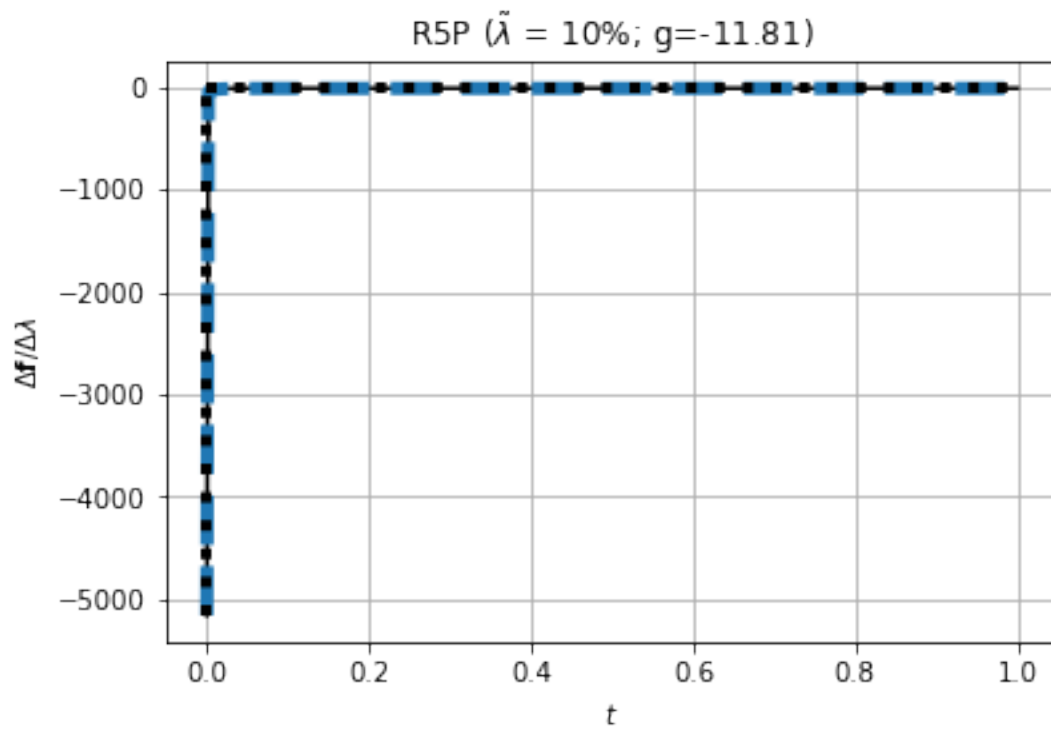
Doing: sNADP  
g = 12.07341191065308  
dlam = 10  
R5P



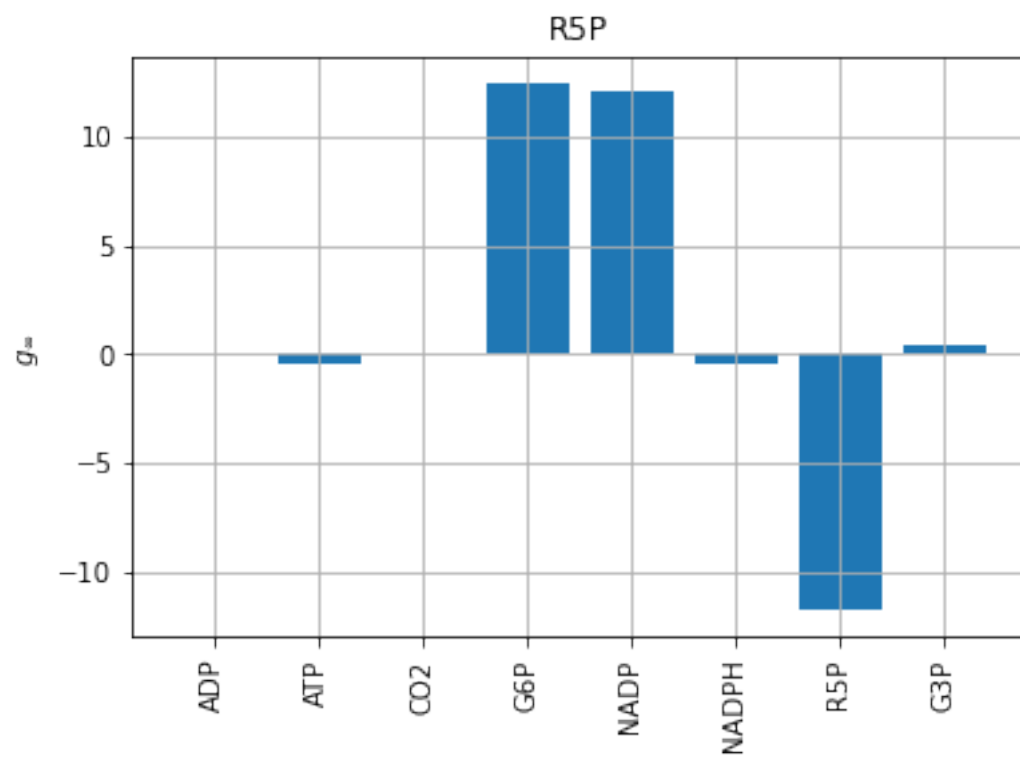
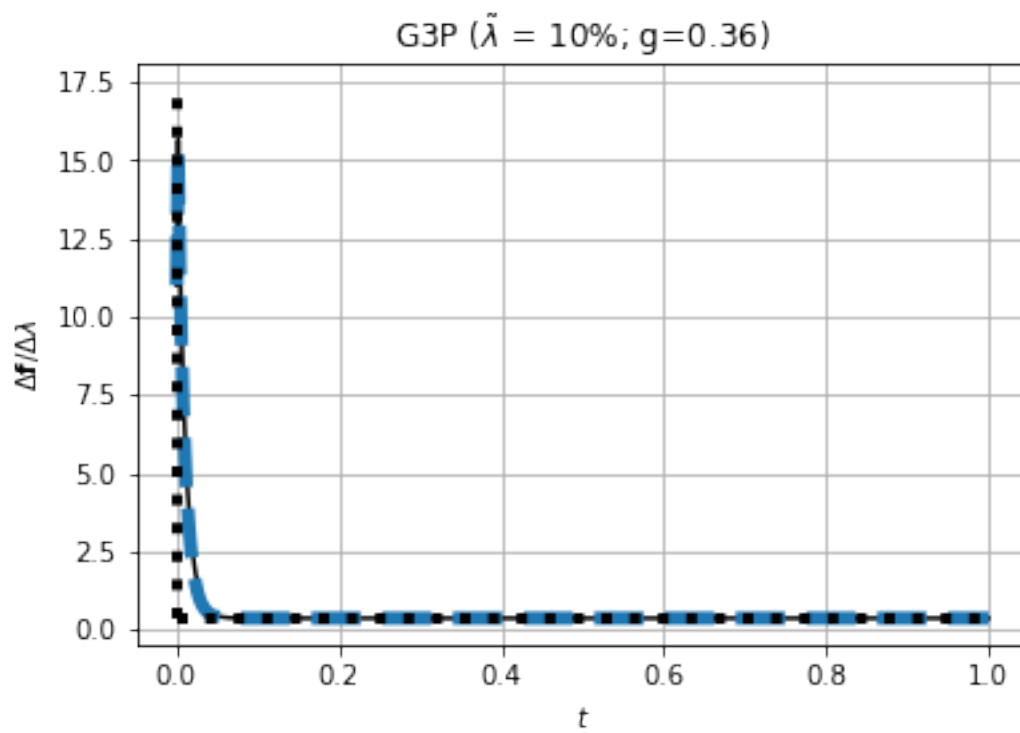
Doing: sNADPH  
 $g = -0.5284650126561967$   
 $d\lambda = 10$   
 R5P

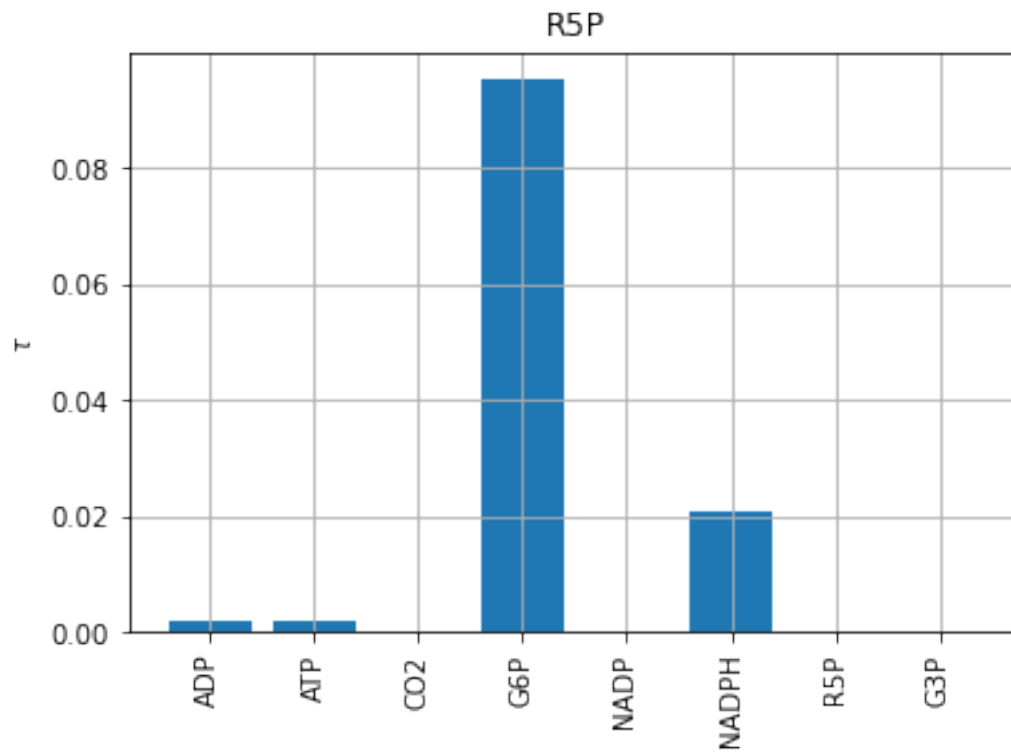


Doing: sR5P  
g = -11.81229752462059  
dlam = 10  
R5P

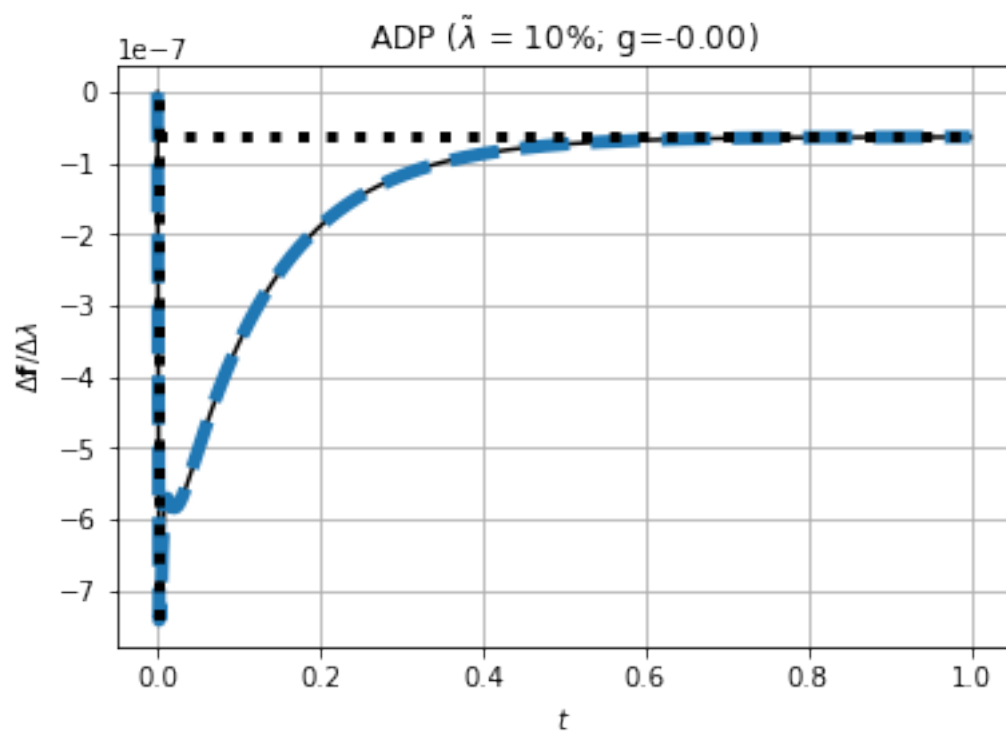


Doing: sG3P  
g = 0.3634389561691993  
dlam = 10  
R5P



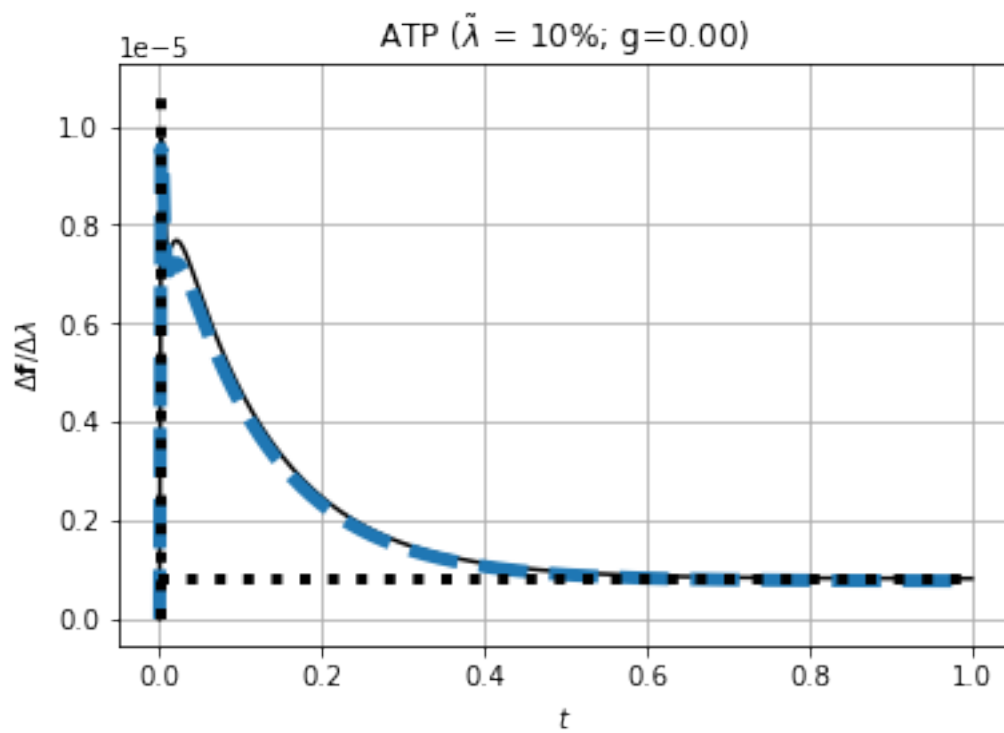


Doing: sADP  
 $g = -6.262253882820029e-08$   
 $d\lambda = 10$   
 NADPH

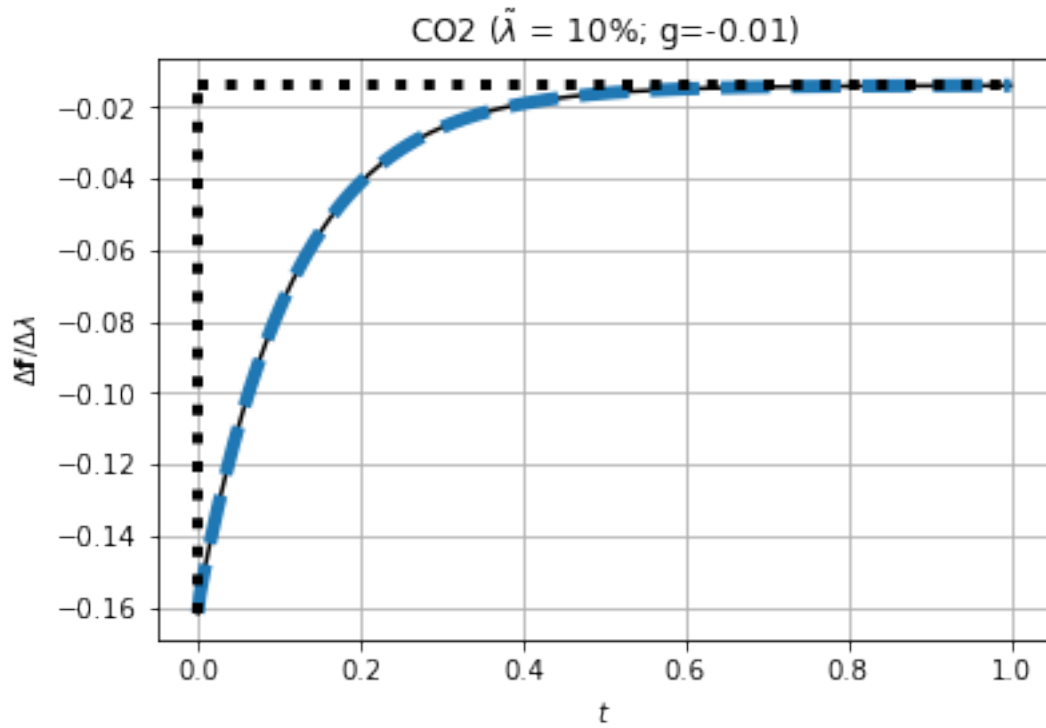




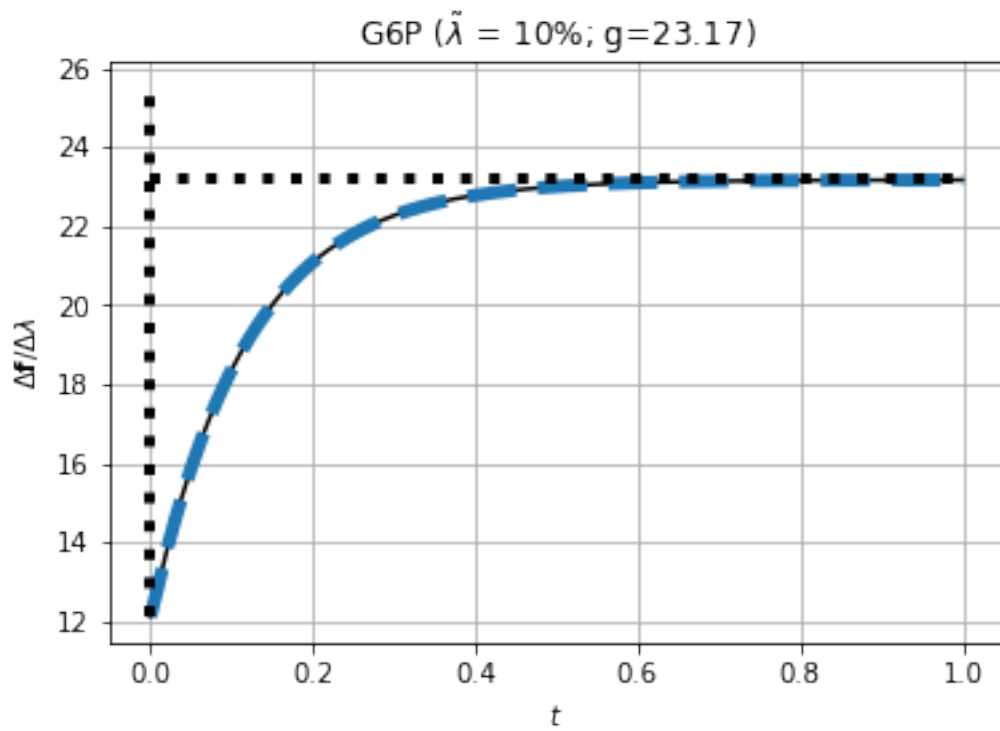
Doing: sATP  
 $g = 8.22242510439288e-07$   
 $d\lambda = 10$   
 NADPH



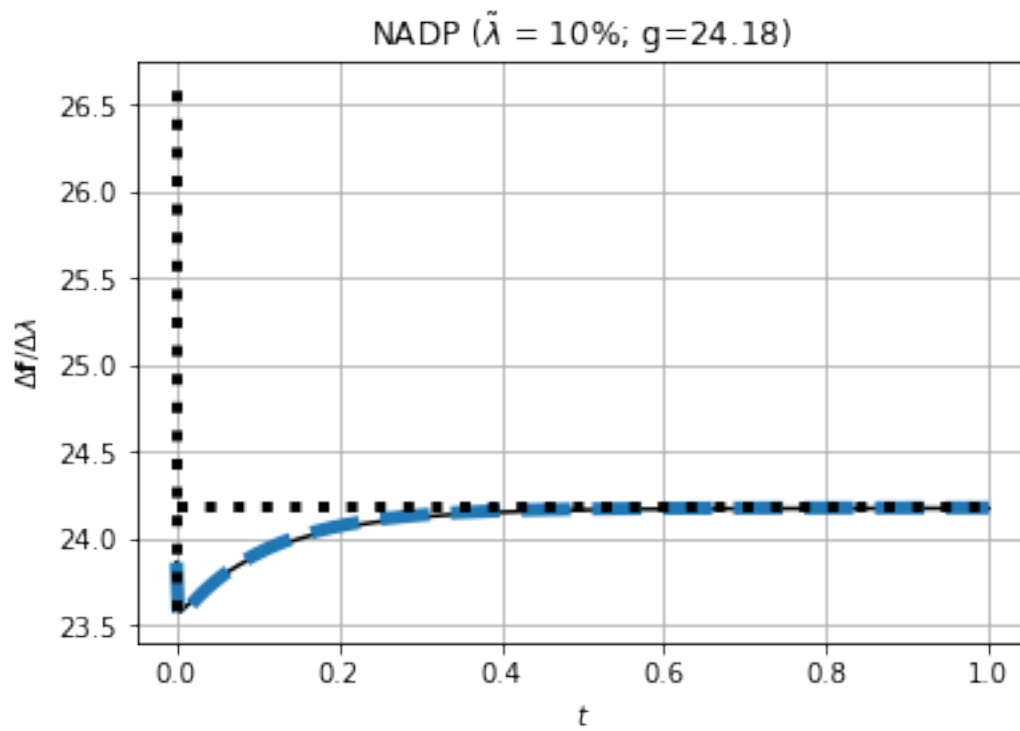
Doing: sC02  
 $g = -0.013855753145603666$   
 $d\lambda = 10$   
 NADPH



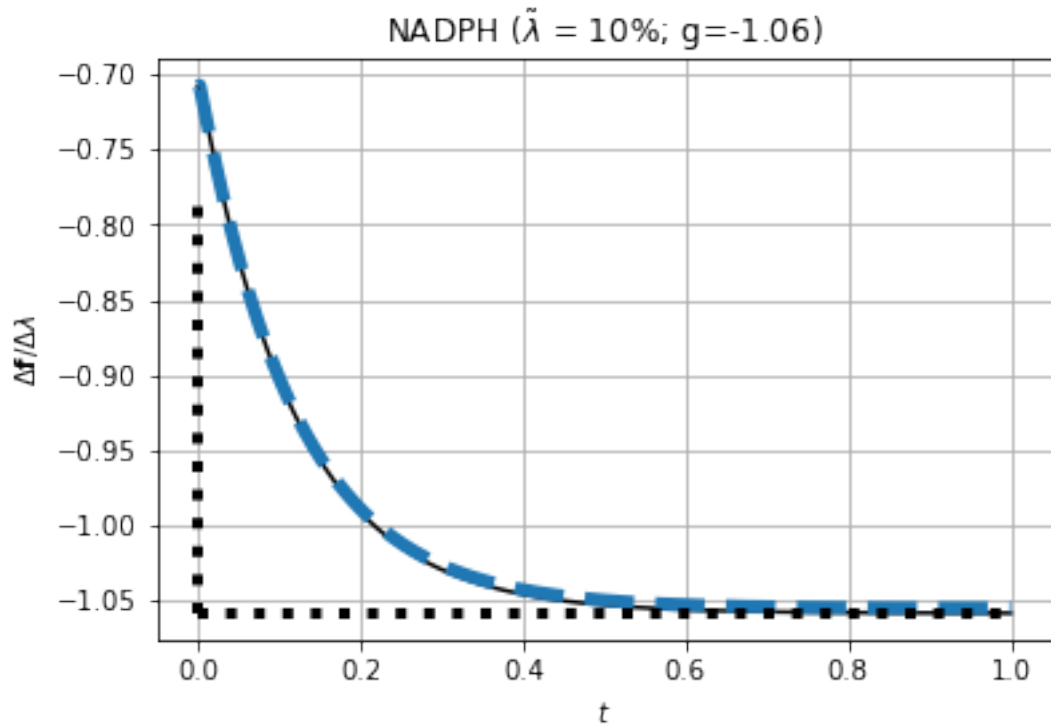
Doing: sG6P  
 $g = 23.170431095483337$   
 $d\lambda = 10$   
 NADPH



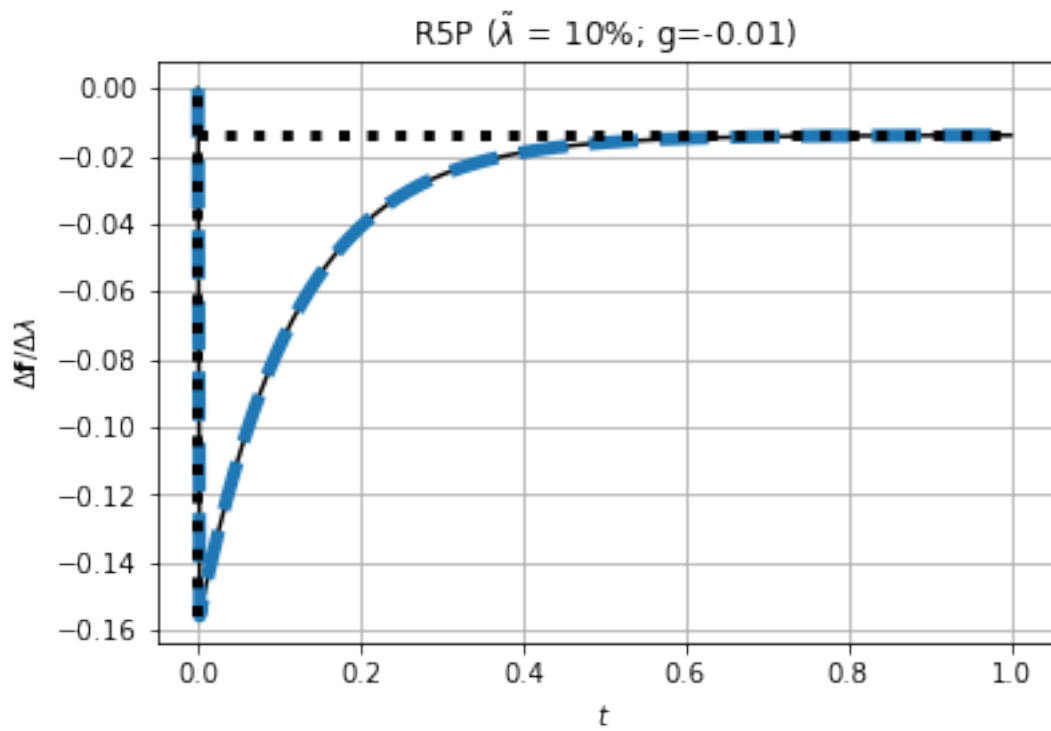
Doing: sNADP  
g = 24.176449757783388  
dlam = 10  
NADPH



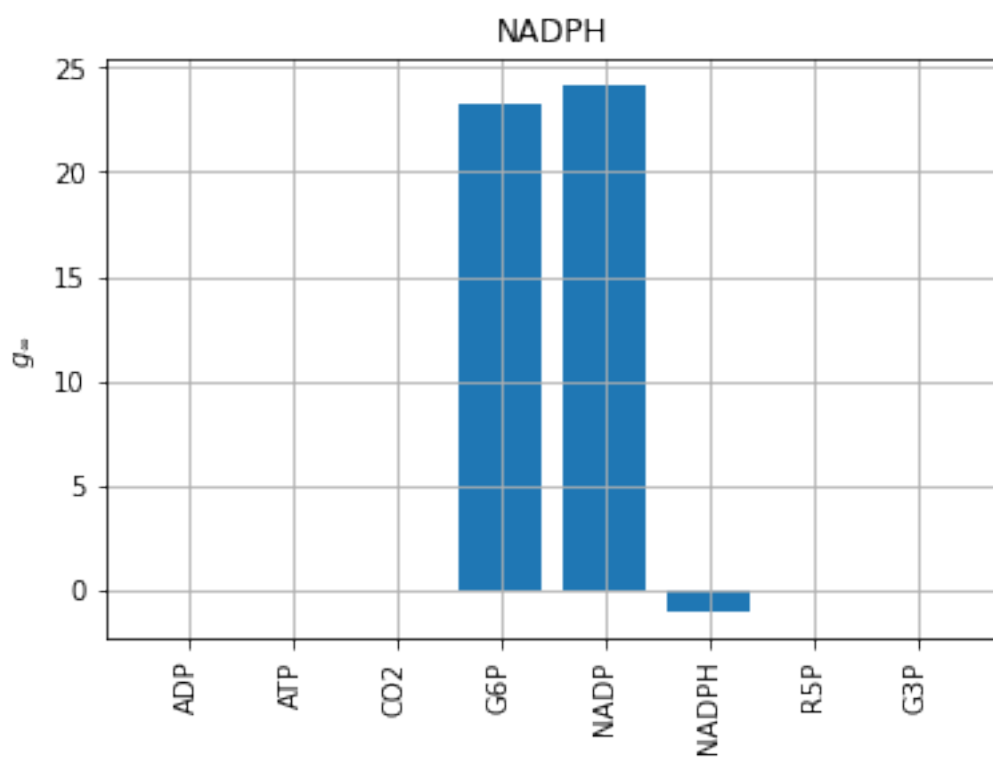
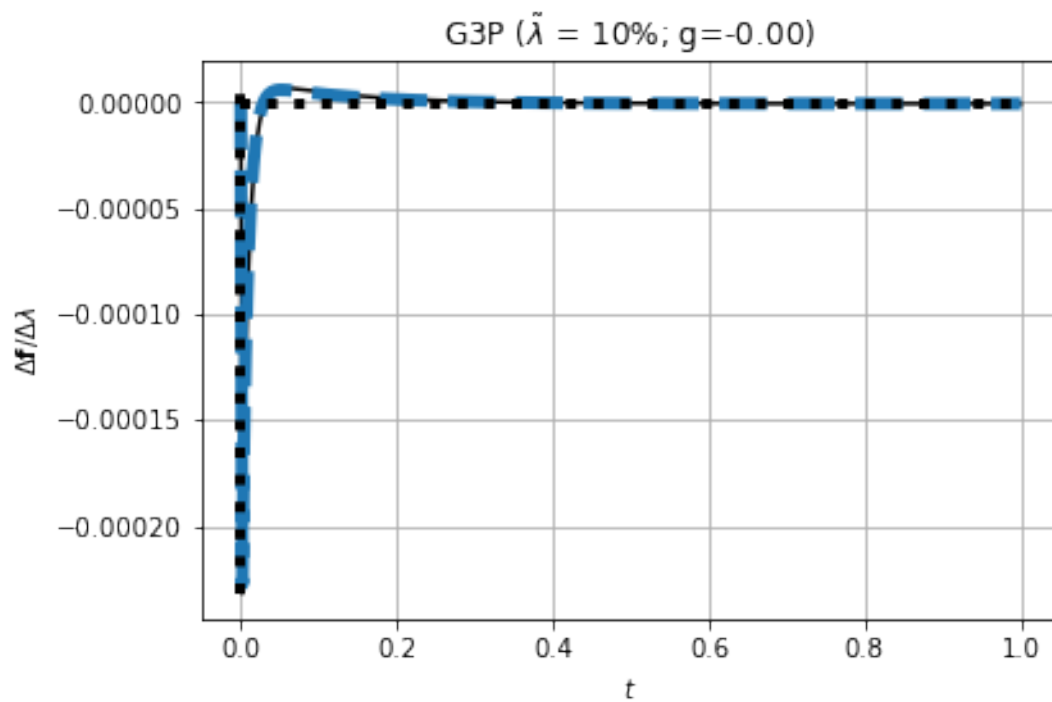
Doing: sNADPH  
g = -1.058226781441594  
dlam = 10  
NADPH

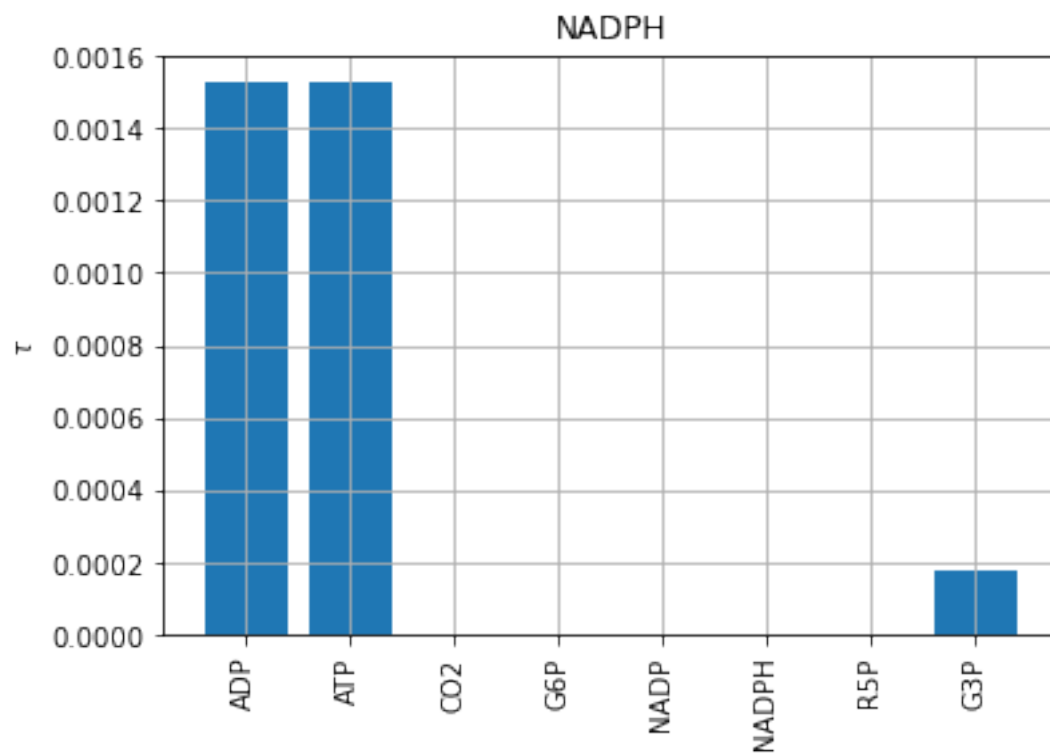


Doing: sR5P  
 $g = -0.013813109583456041$   
 $d\lambda = 10$   
 NADPH

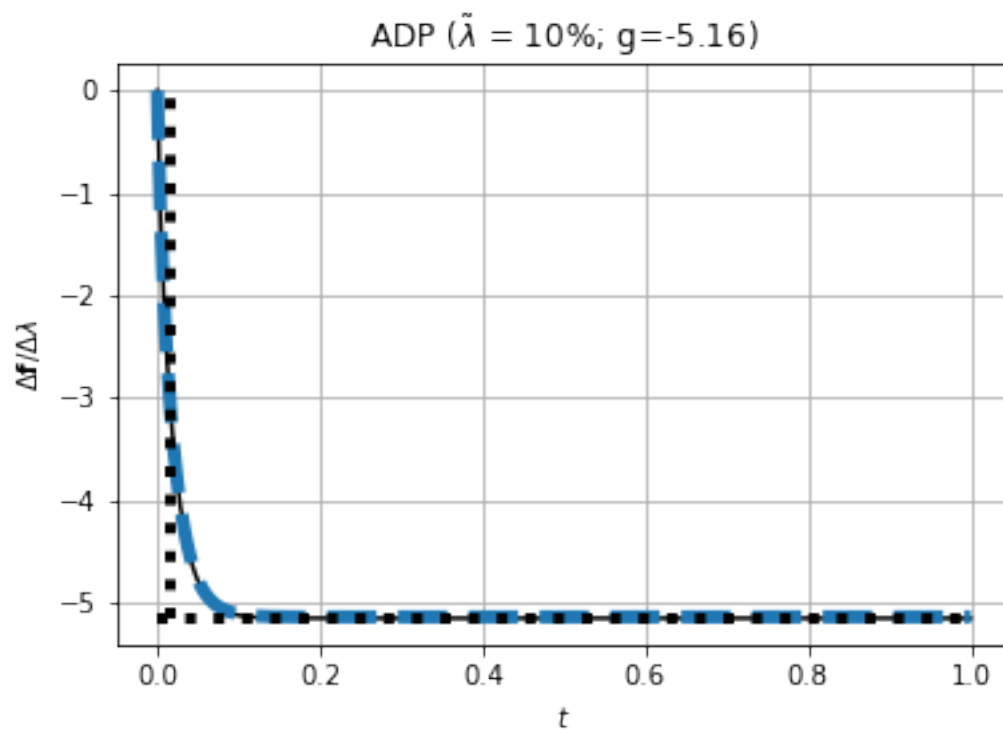


Doing: sG3P  
 $g = -6.516705662261944\text{e-}07$   
 $d\lambda = 10$   
 NADPH

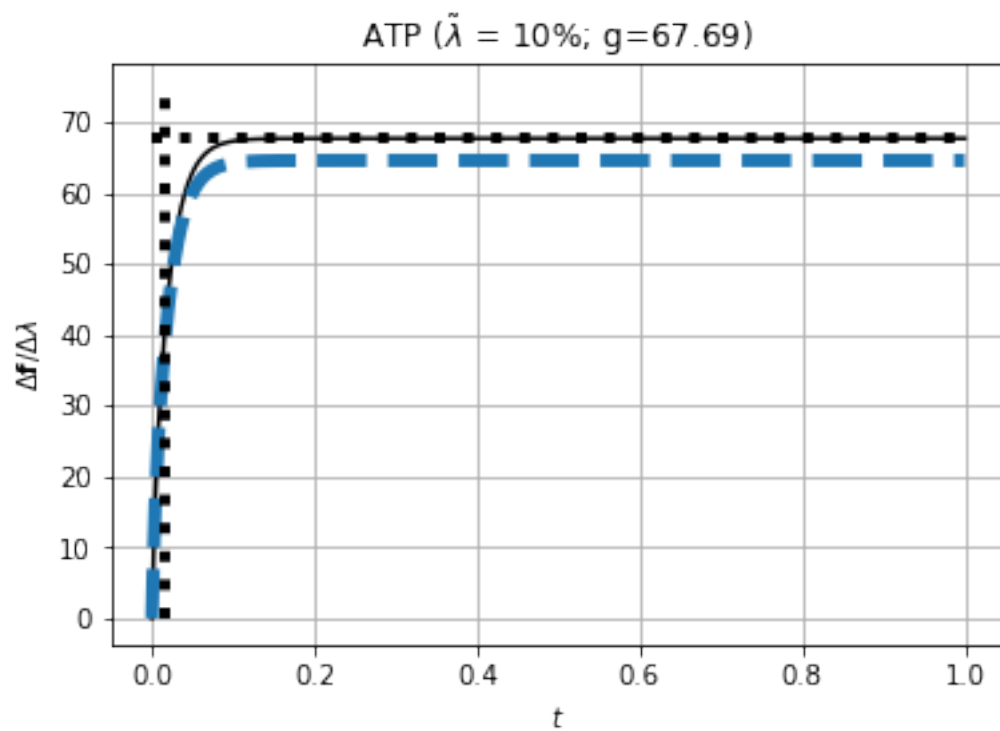




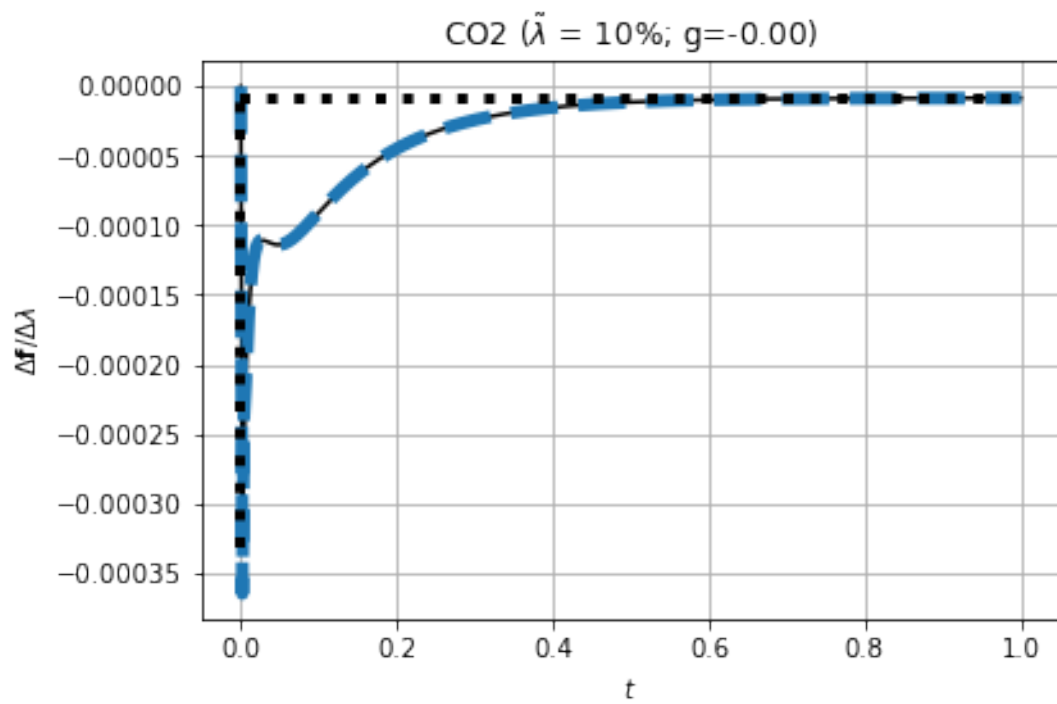
Doing: sADP  
 $g = -5.155200687482189$   
 $d_{lam} = 10$   
 G3P



Doing: sATP  
 $g = 67.68849098700832$   
 $d\lambda = 10$   
 G3P

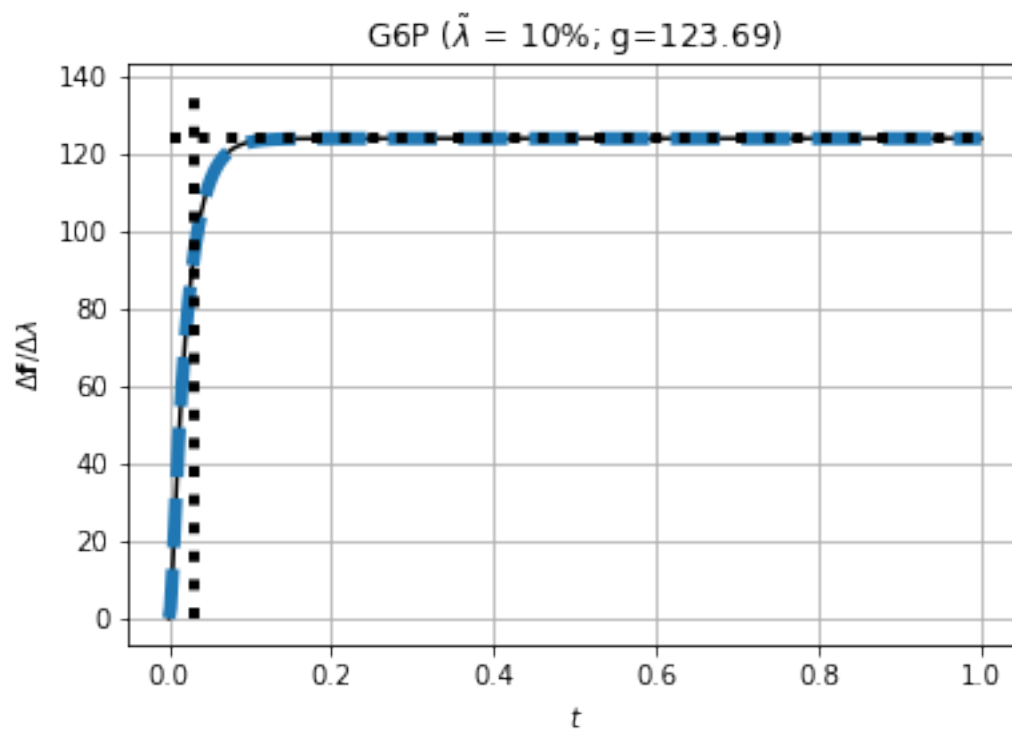


Doing: sC02  
g = -8.280802207064823e-06  
dlam = 10  
G3P

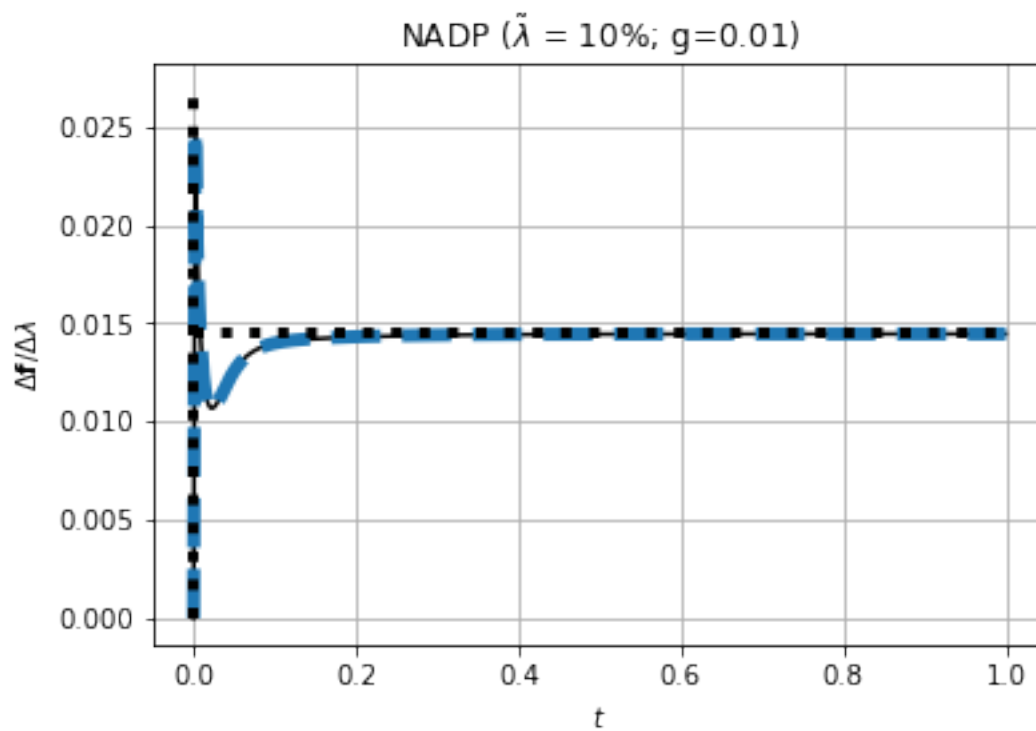


Doing: sG6P  
g = 123.69183347627043  
dlam = 10  
G3P

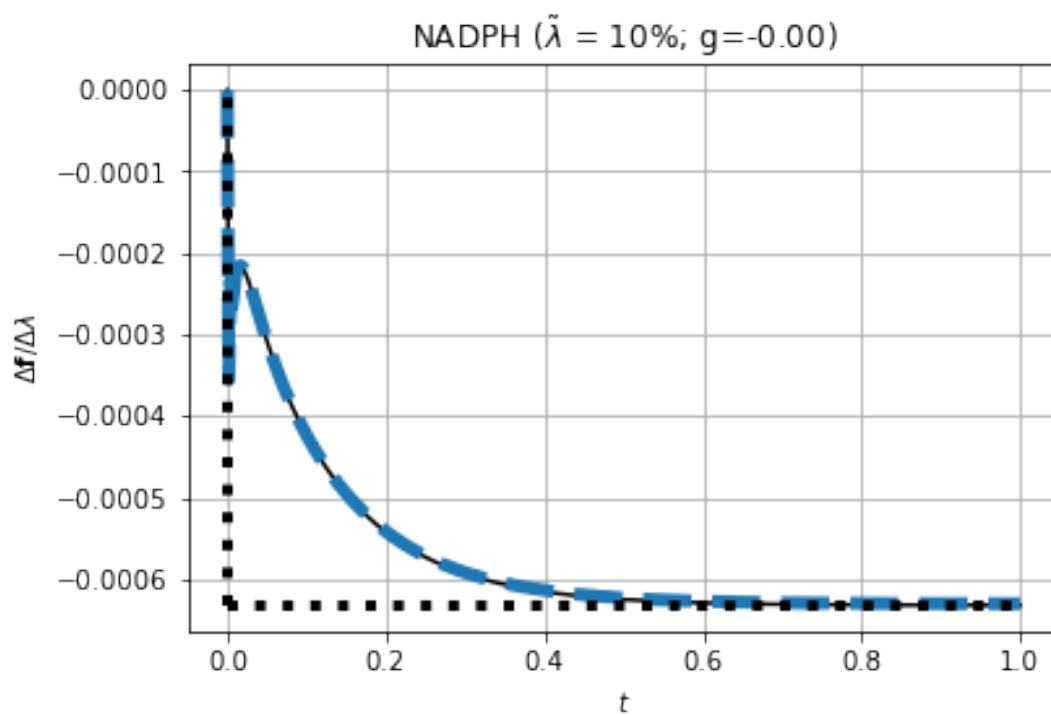




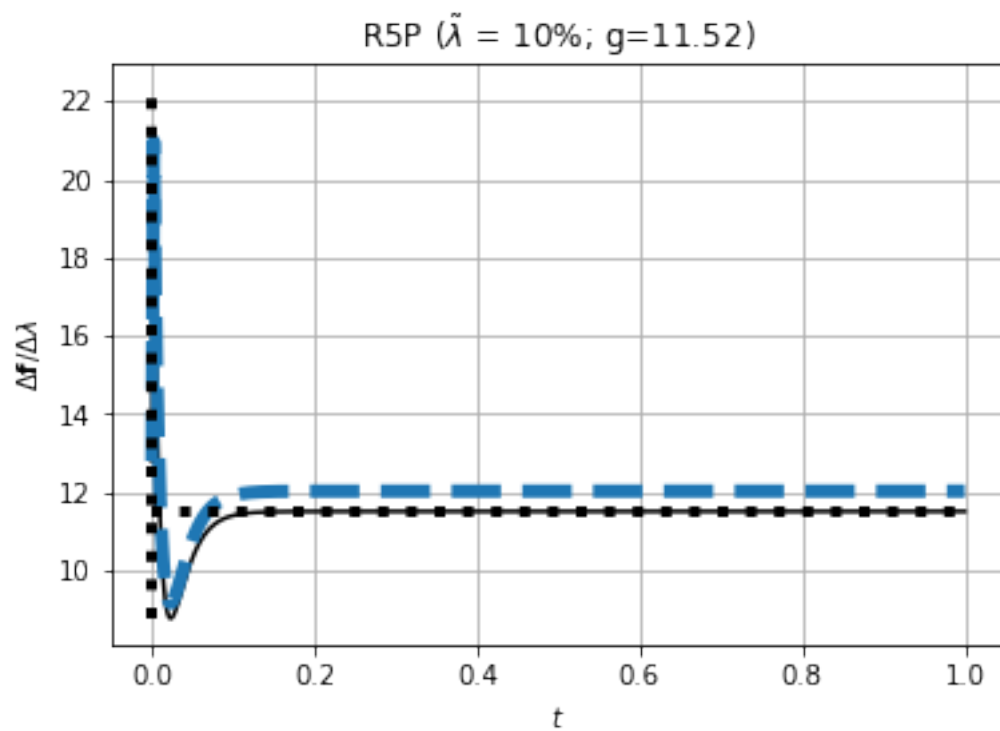
Doing: sNADP  
 $g = 0.014448900437827383$   
 $d\lambda = 10$   
 G3P



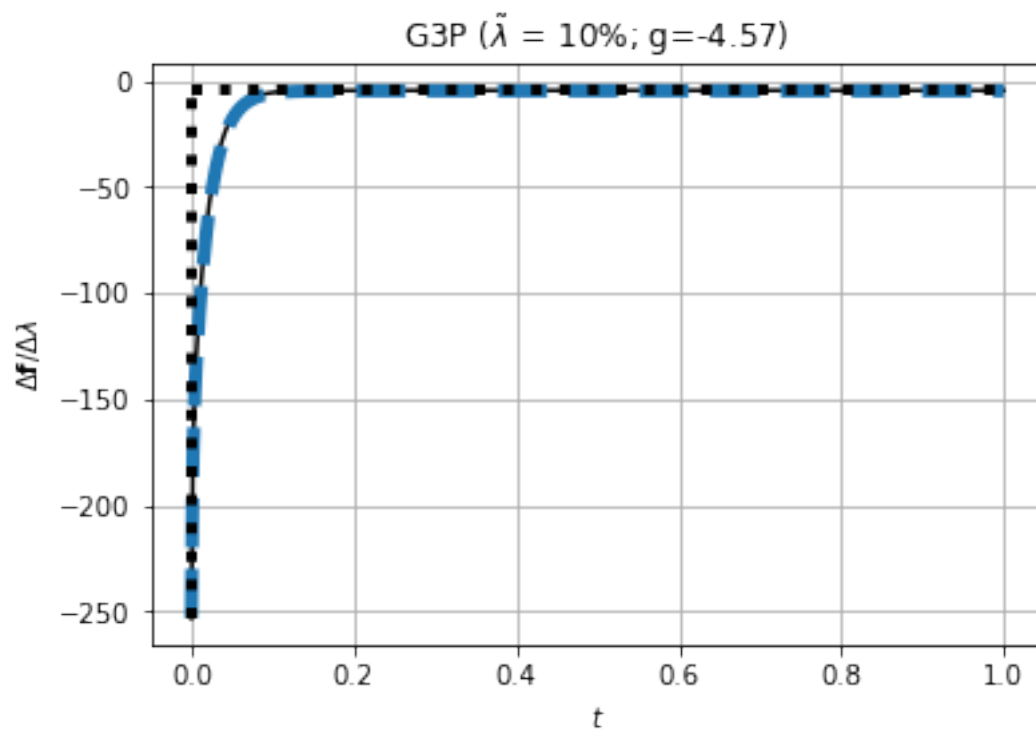
Doing: sNADPH  
g = -0.0006324424618591407  
dlam = 10  
G3P

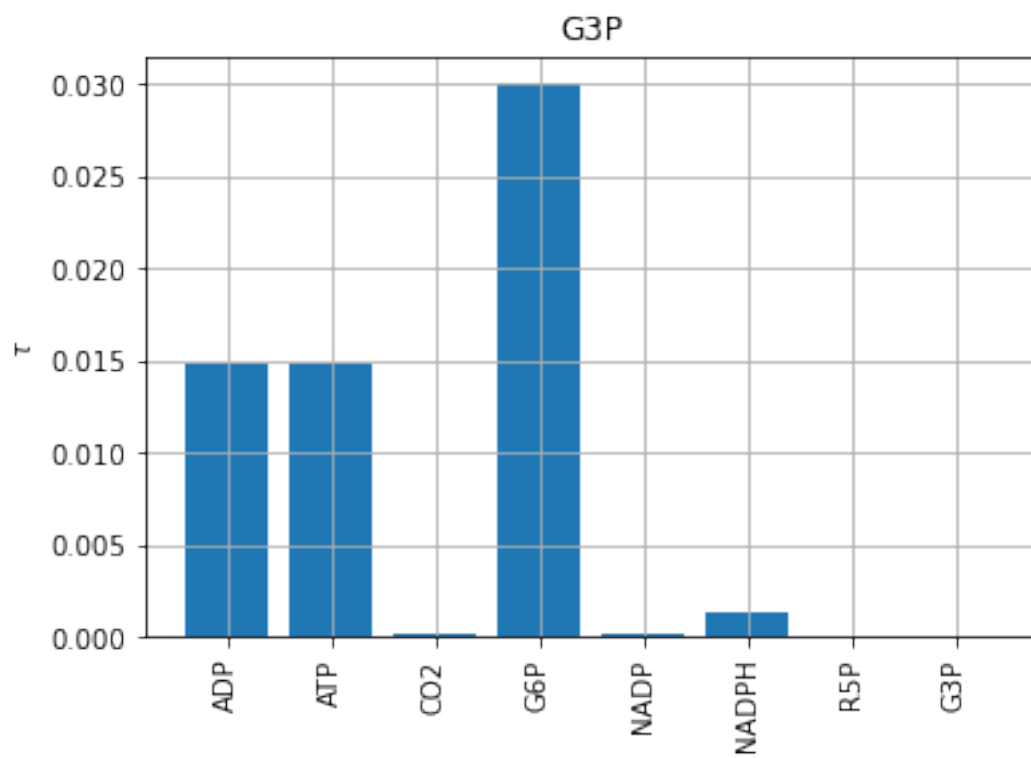
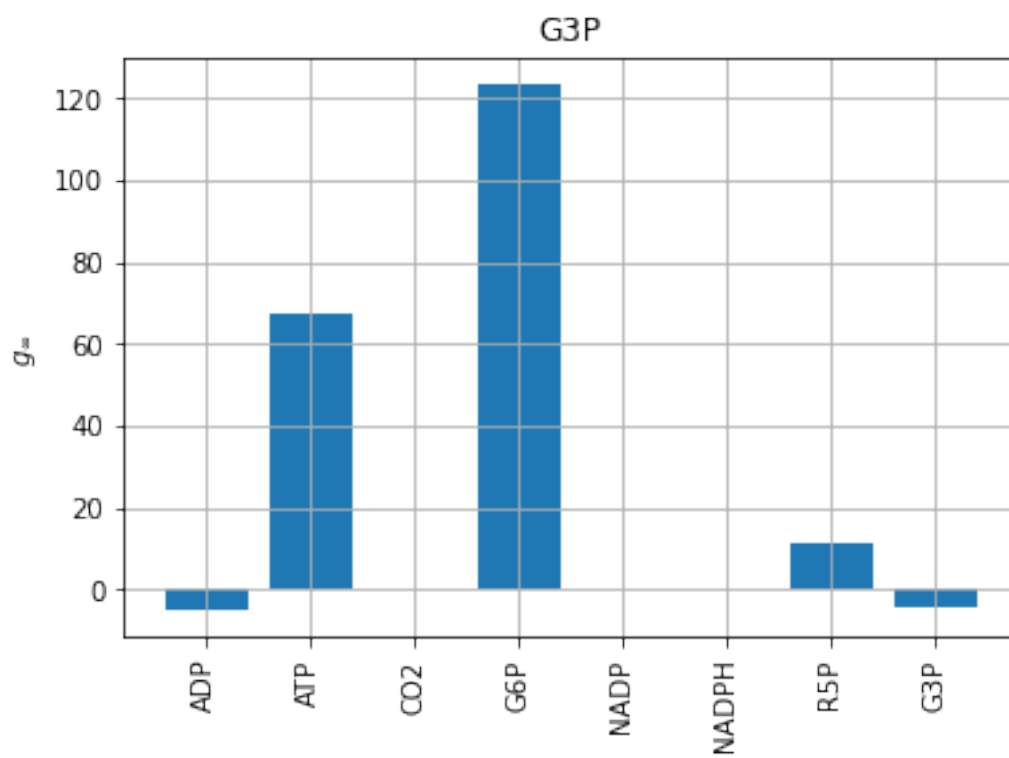


Doing: sR5P  
g = 11.515242320596151  
dlam = 10  
G3P



Doing: sG3P  
 $g = -4.574774223072097$   
 $d\lambda = 10$   
 G3P



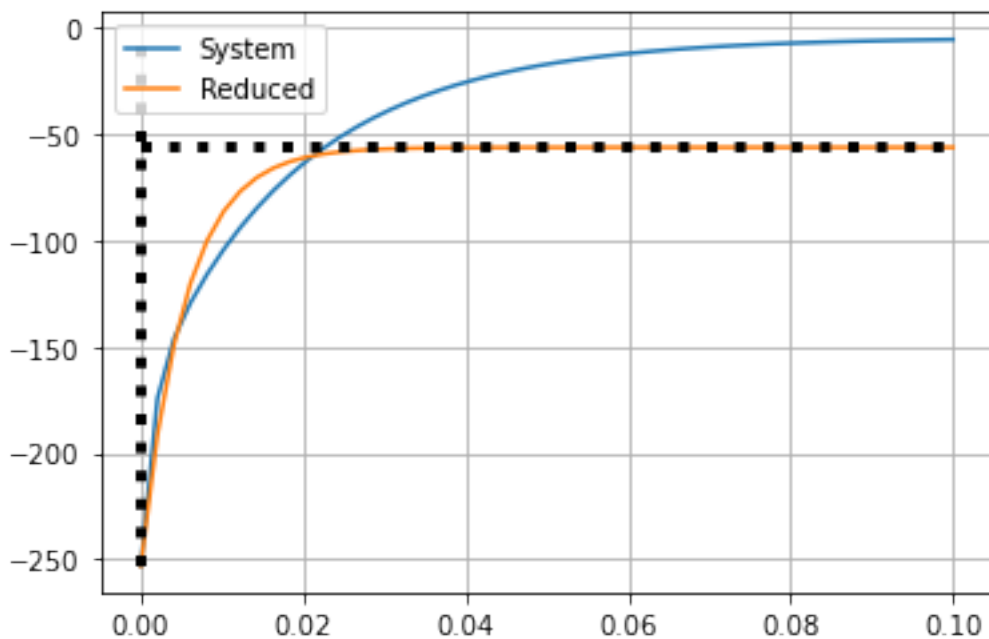


### 6.3 Test model reduction

```
[31]: ## Test model reduction
g,tau = tfProps(sys)
print(f'g = {g:.2f}, tau = {tau:.2f}')
sys1 = con.balred(sys,orders=1,method='truncate')
# print(con.dcgain(sys))
# print(con.dcgain(sys1))
con.tf(sys1)
g,tau = tfProps(sys1)
print(f'g = {g:.2f}, tau = {tau:.2f}')

t = np.linspace(0,0.1)
step = con.step_response(sys,T=t)
step1 = con.step_response(sys1,T=t)
plt.plot(t,step.outputs.T,label='System')
plt.plot(t,step1.outputs.T,label='Reduced')
plt.legend()
plt.grid()
plotLines()
```

```
g = -4.57, tau = 0.00
g = -56.31, tau = 0.00
```



```
[32]: print(Tau)
```

```
{'ADP': 0.014866156765752257, 'ATP': 0.01486615676575225, 'CO2':  
0.00017684665624202378, 'G6P': 0.03004139008090118, 'NADP':  
0.00017642871957648497, 'NADPH': 0.0013662874711383617, 'R5P': 0, 'G3P': 0}
```

## 6.4 Compute reaction sensitivities

```
[33]: ## Reaction sensitivities
Outp = ['G6P', 'R5P', 'NADPH', 'G3P']
Inp = []
for reac in s['reaction']:
    Inp.append('s'+reac)

Inp_reac = Inp
# Inp = []
# for reac in s['reaction']:
#     Inp.append('s'+reac)
# Inp = ['sG6PDH2R']

t_last=1
lam = 1.1 # Perturbation parameter

dcgain = {}
Tau = {}
for outp in Outp:
    for inp in Inp:
        print('Doing:', inp)
        sf = None
        order = None
        dat, y_step, t, sys =   

        →simSensitivity(s, sc, sf, Sys, X_ss, V_ss, dX_ss, chemostats=Chemostats, parameter=parameter,   

        →inp=[inp], outp=[outp], lam=lam, t_last=t_last, order=order, tol=None)

#     g = con.dcgain(sys)
#     g, tau = tfProps(sys)
#     print('g =', g, 'tau =', tau)
#     poles = con.poles(sys)
#     print('Poles:', poles)
#     print('Zeros:', con.zeros(sys))
#     print(con.ss2tf(sys))
name = inp[1:]
if name == 'G6PDH2R':
    name = 'G6PD.'
if outp == 'G6P':
    dcgain[name] = -g
    ylabel = '$-g_{\infty}$'
else:
    dcgain[name] = g
    ylabel = '$g_{\infty}$'

Tau[name] = tau

dlam = int((lam-1)*100)
print('dlam =', dlam)
plt.title(f'Order = {poles.size}')
```

```

        if Titles:
            plt.title(f'{name}'+r' ($\tilde{\lambda}$ = ' + f'{dlam}%'; g={g:.
→2f})')
            plotSensitivitydX(dat,species=[outp],labeling=False)
#         plt.hlines(g,min(t),max(t),color='black',ls='dashed')
            plotLines()
            Savefig('PPPdX_'+name+'_'+outp)

            plt.show()
            #print(con.tf(sys))

## Bar chart of gains
if Titles:
    plt.title(outp)
    plt.tick_params(axis='x', rotation=90)
    plt.grid()
    plt.bar(range(len(dcgain)), dcgain.values(), align='center')
    plt.xticks(range(len(dcgain)), list(dcgain.keys()))
    plt.ylabel(ylabel)
    Savefig(f'PPPdX_{outp}_reac_bar')
    plt.show()

## Time constant
if Titles:
    plt.title(outp)
    plt.tick_params(axis='x', rotation=90)
    plt.grid()
    plt.bar(range(len(Tau)), Tau.values(), align='center')
    plt.xticks(range(len(Tau)), list(Tau.keys()))
    plt.ylabel(r'$\tau$')
    Savefig(f'PPPdX_{outp}_reac_tau_bar')
    plt.show()

```

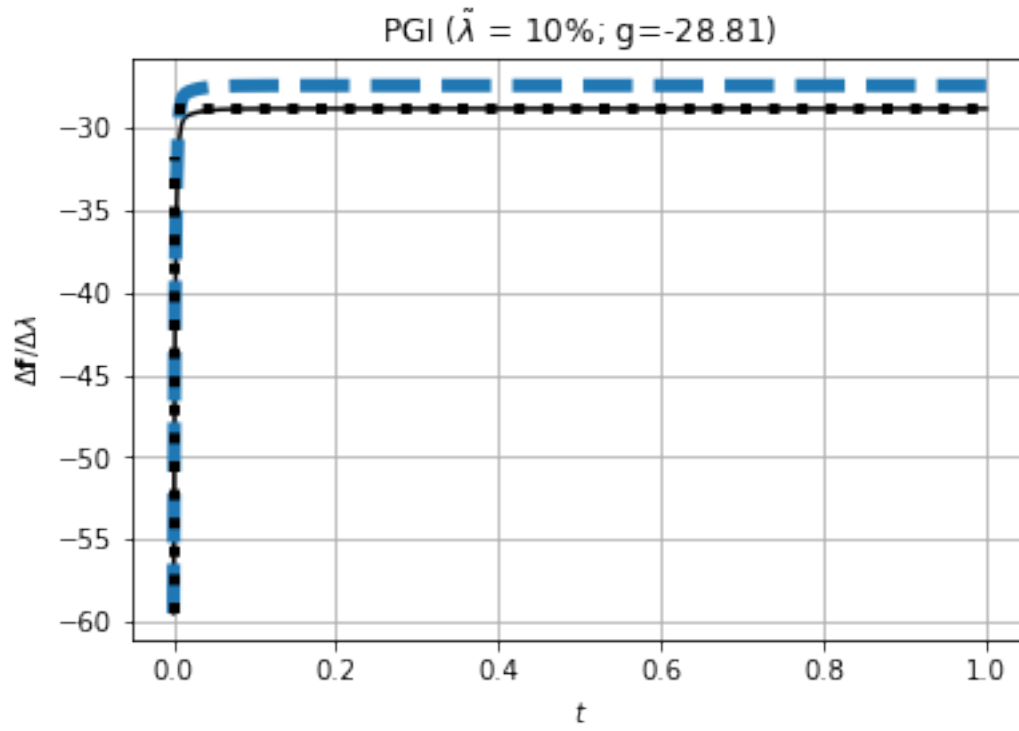
Doing: sPGI

kappa\_PGI

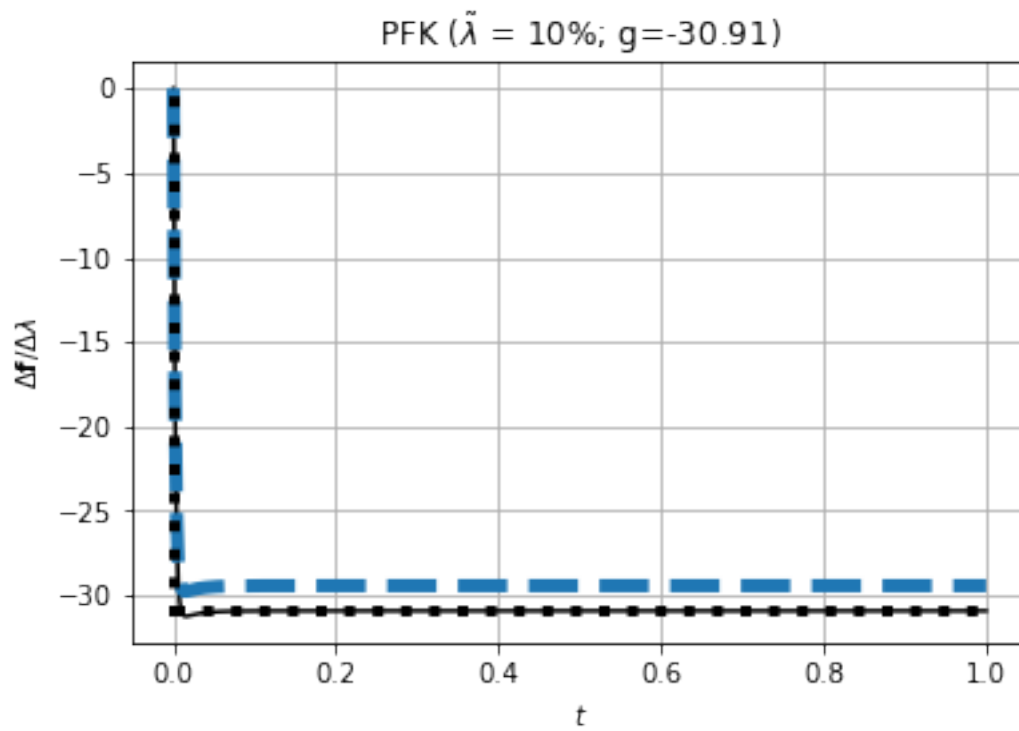
g = -28.80991511396469 tau = 0

dlam = 10

G6P



Doing: sPFK  
kappa\_PFK  
 $g = -30.913609683373416$   $\tau = 0.002278015825776077$   
 $d\lambda = 10$   
G6P





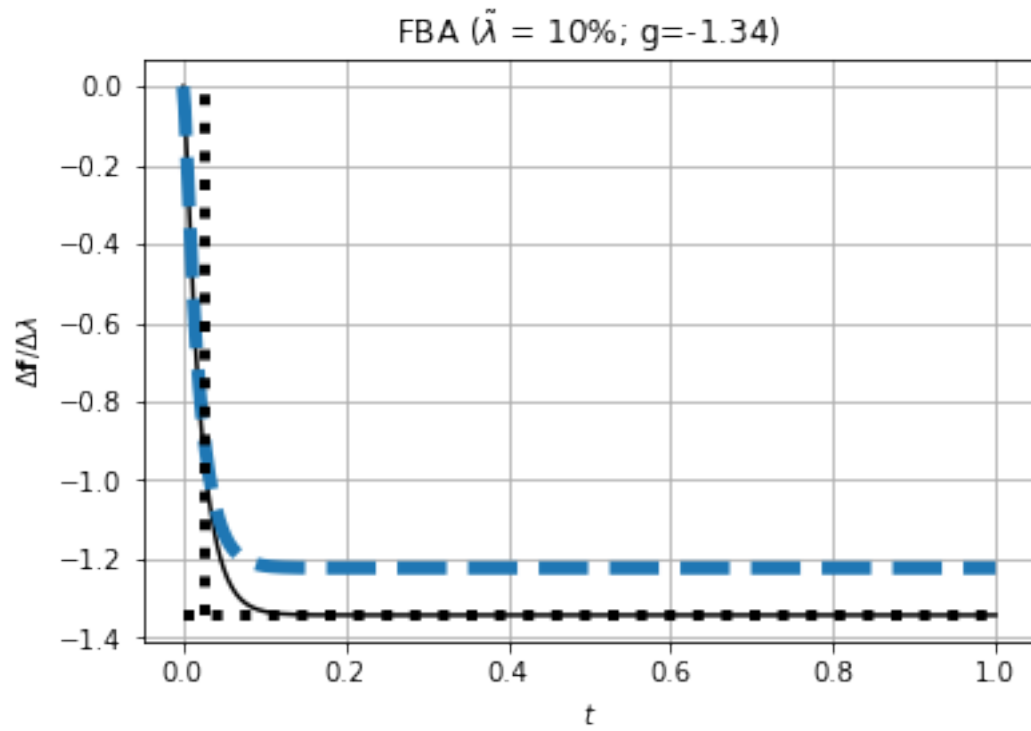
Doing: sFBA

kappa\_FBA

$g = -1.3427806651016105$   $\tau = 0.026921154867136633$

d $\lambda = 10$

G6P



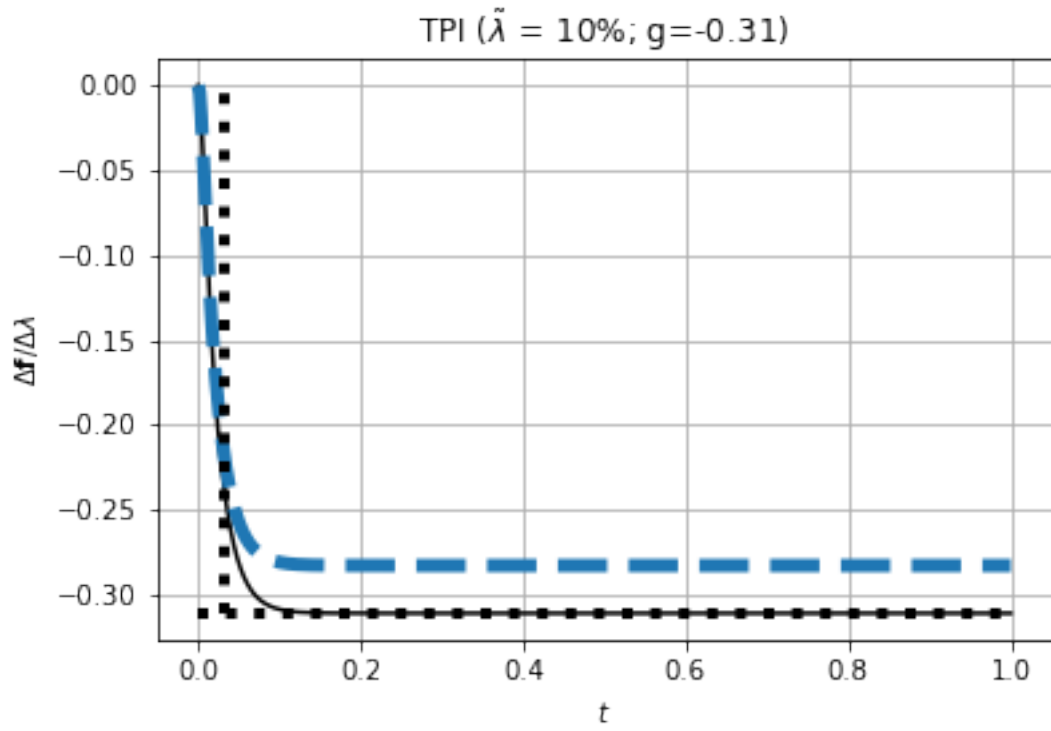
Doing: sTPI

kappa\_TPI

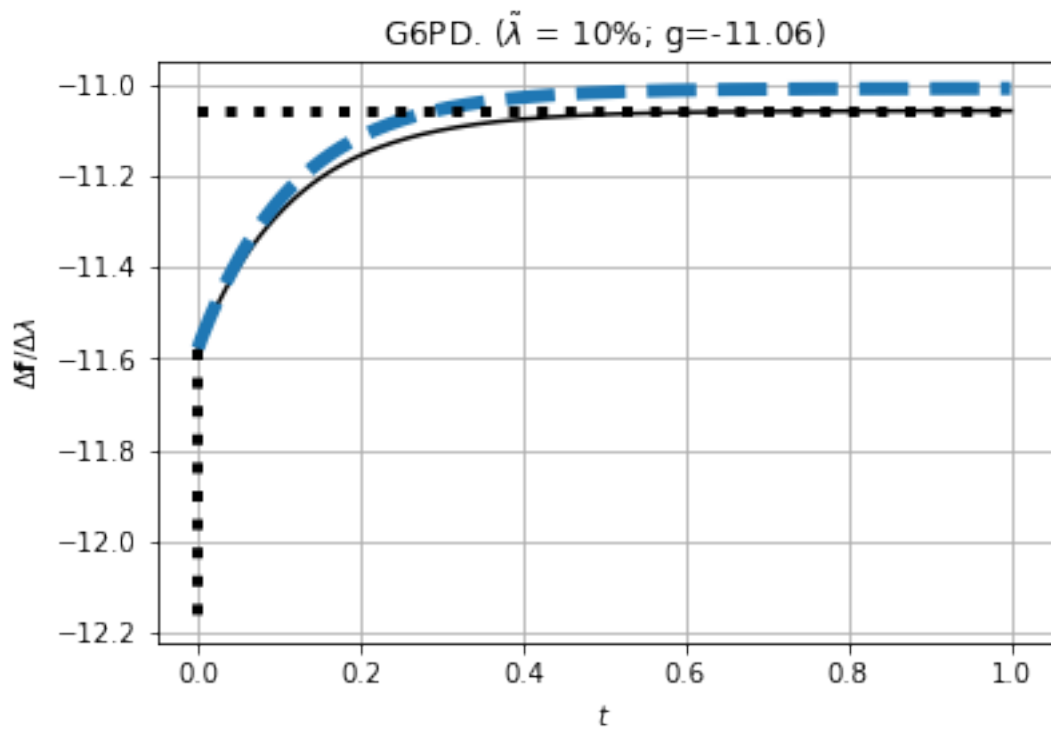
$g = -0.31124503089893363$   $\tau = 0.03292616976551729$

d $\lambda = 10$

G6P



Doing: sG6PDH2R  
 kappa\_G6PDH2R  
 $g = -11.05834536093916$   $\tau = 0$   
 $d\lambda = 10$   
 G6P



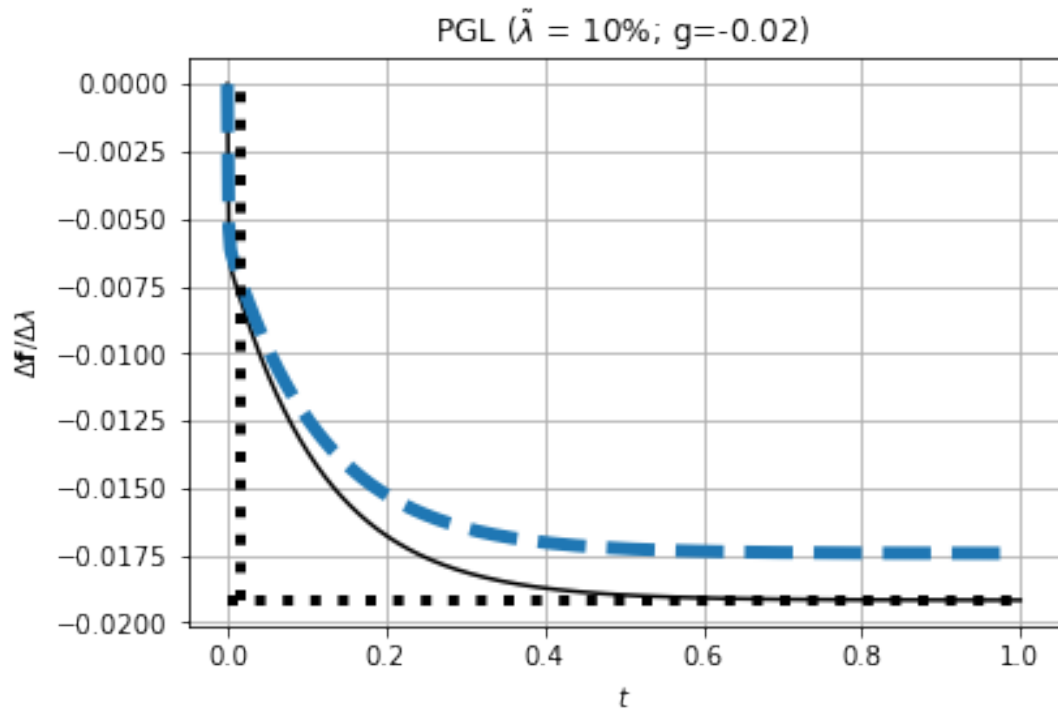
Doing: sPGL

kappa\_PGL

$g = -0.019168880963538627$   $\tau = 0.016293783108219457$

d $\lambda = 10$

G6P



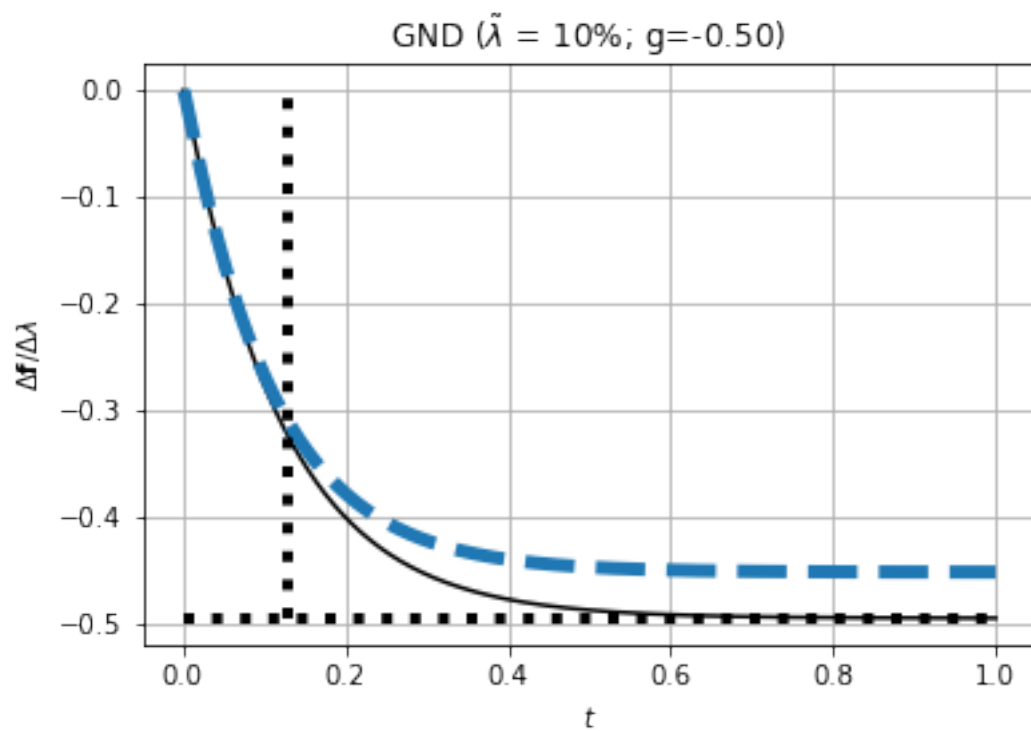
Doing: sGND

kappa\_GND

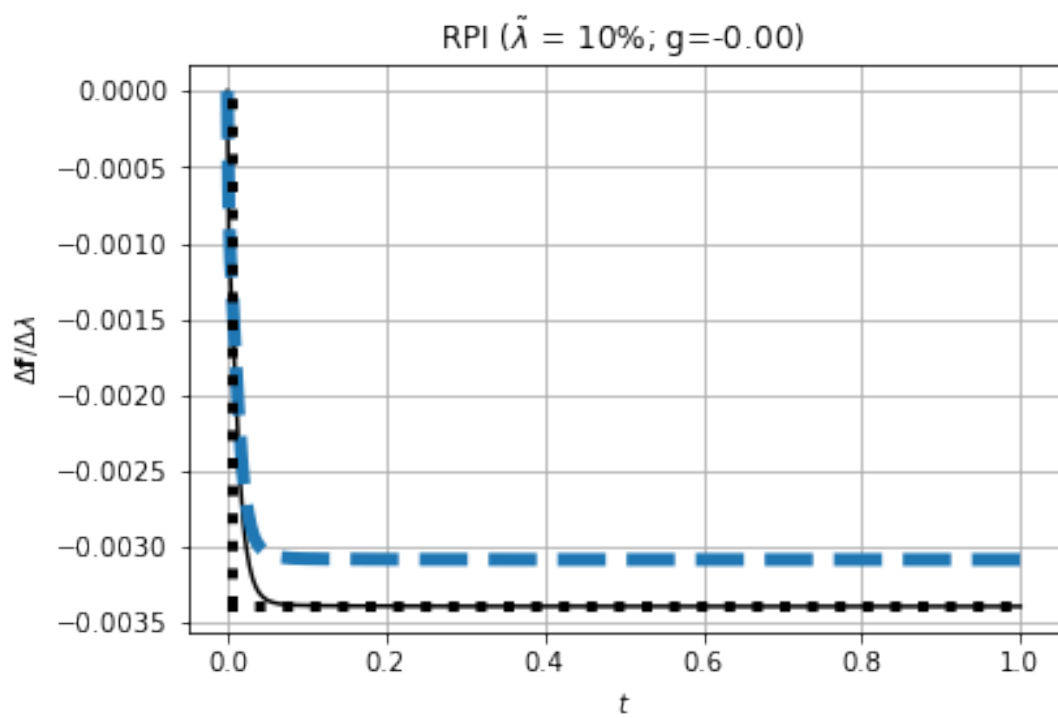
$g = -0.4958705310747634$   $\tau = 0.12751609732062125$

d $\lambda = 10$

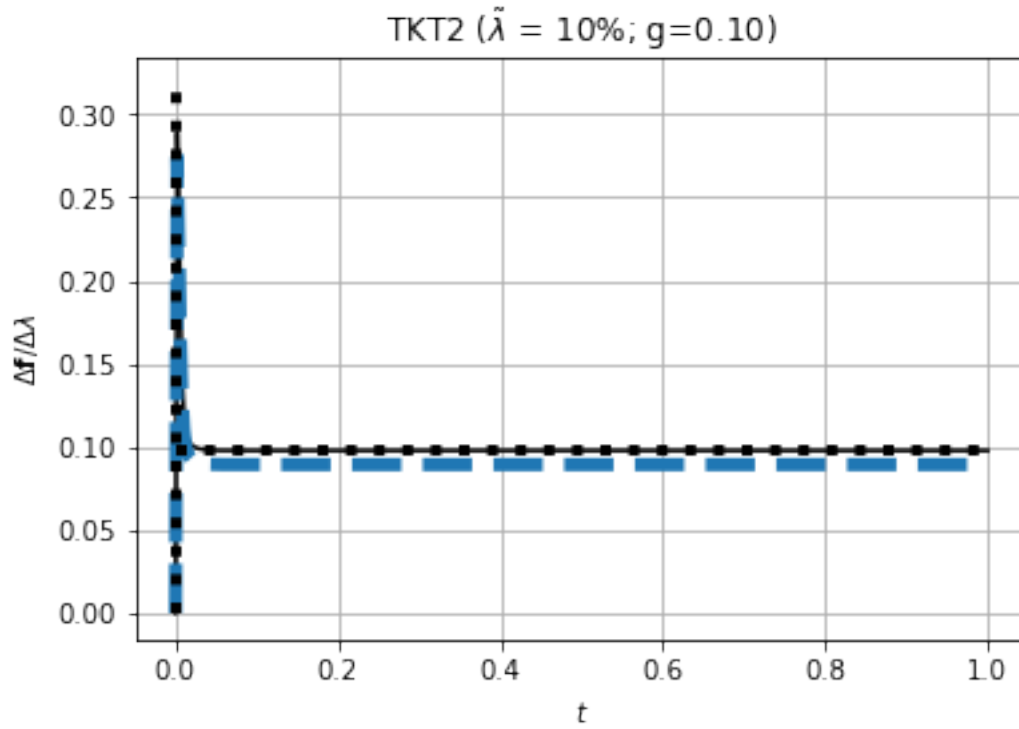
G6P



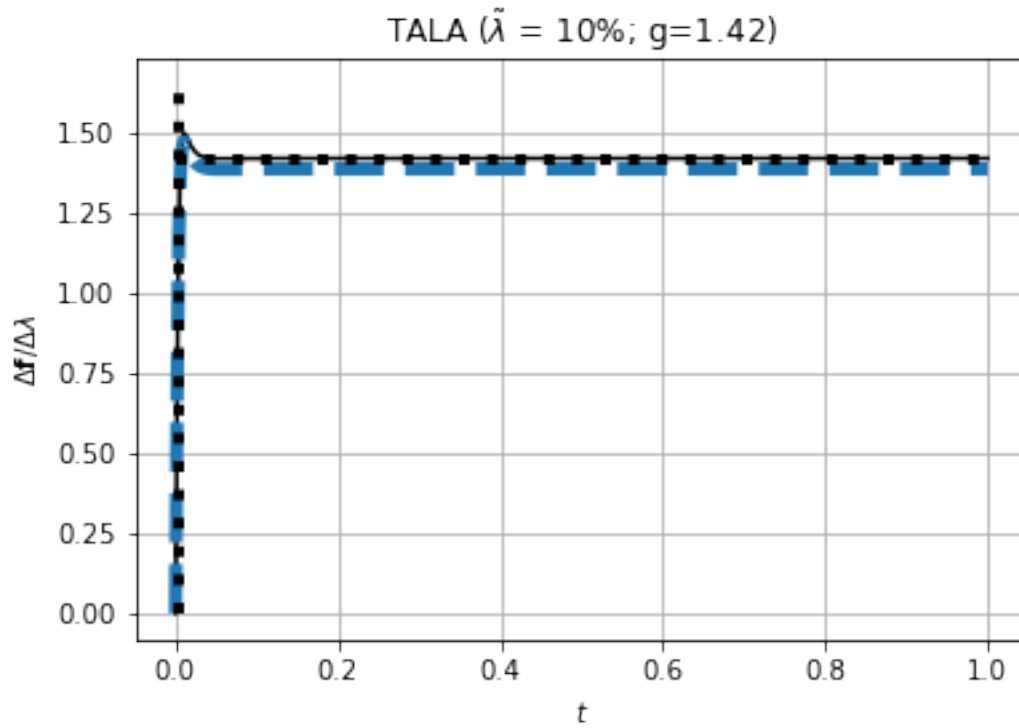
Doing: sRPI  
kappa\_RPI  
 $g = -0.00339246977181743$   $\tau = 0.00824443541241612$   
 $d\lambda = 10$   
G6P



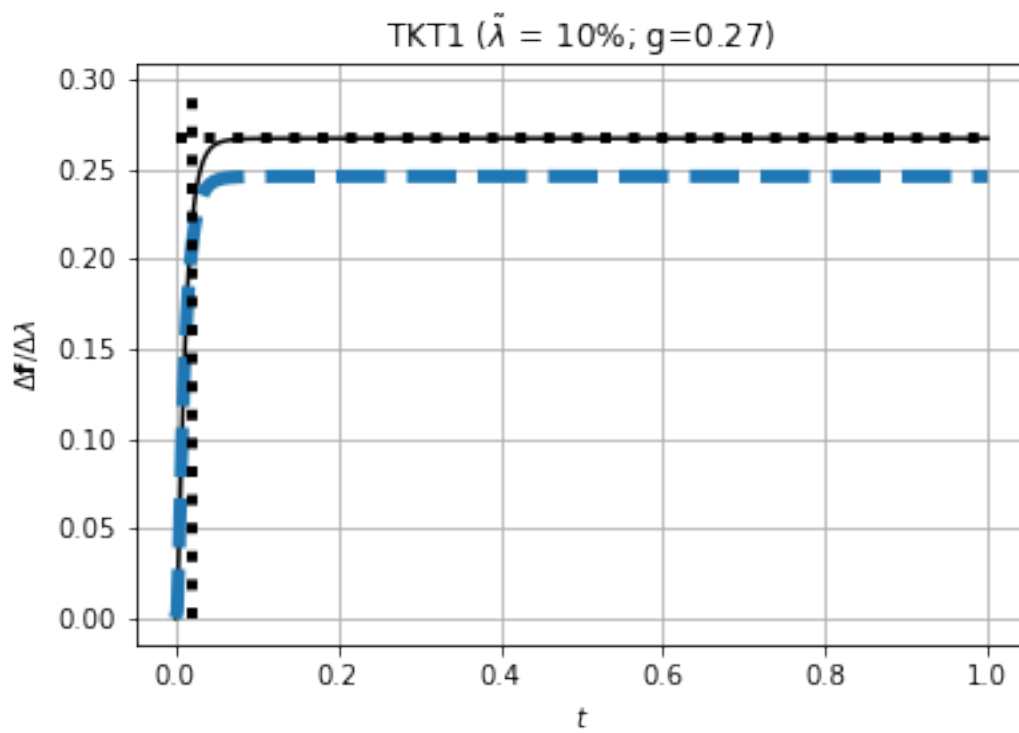
Doing: sTKT2  
kappa\_TKT2  
 $g = 0.09778496614281532$   $\tau = 0.0009111118563853957$   
 $d\lambda = 10$   
G6P



Doing: sTALA  
kappa\_TALA  
 $g = 1.4213693479775253$   $\tau = 0.0033987149739030348$   
 $d\lambda = 10$   
G6P



Doing: sTKT1  
 kappa\_TKT1  
 $g = 0.2669211003303768$   $\tau = 0.021001174006396915$   
 $d\lambda = 10$   
 G6P



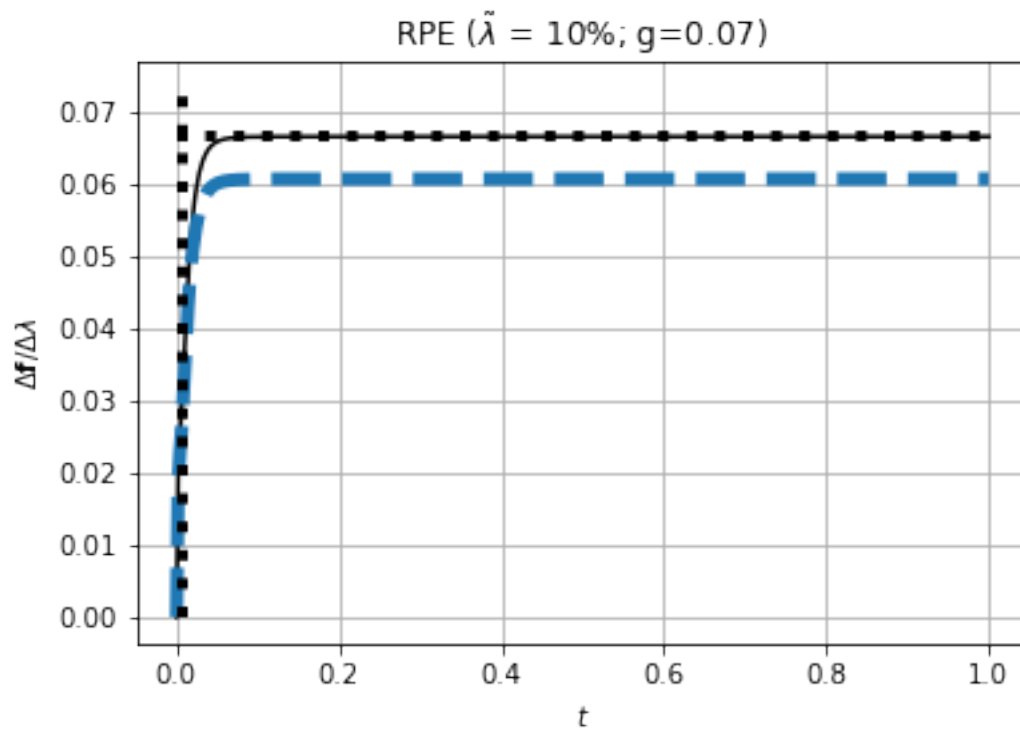
Doing: sRPE

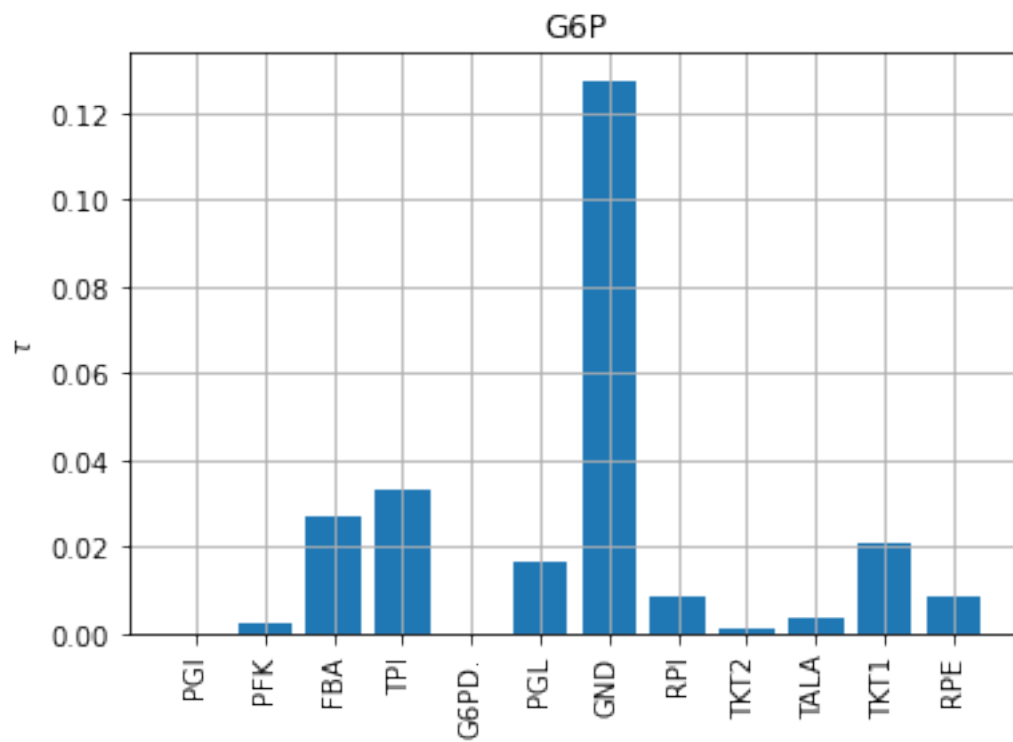
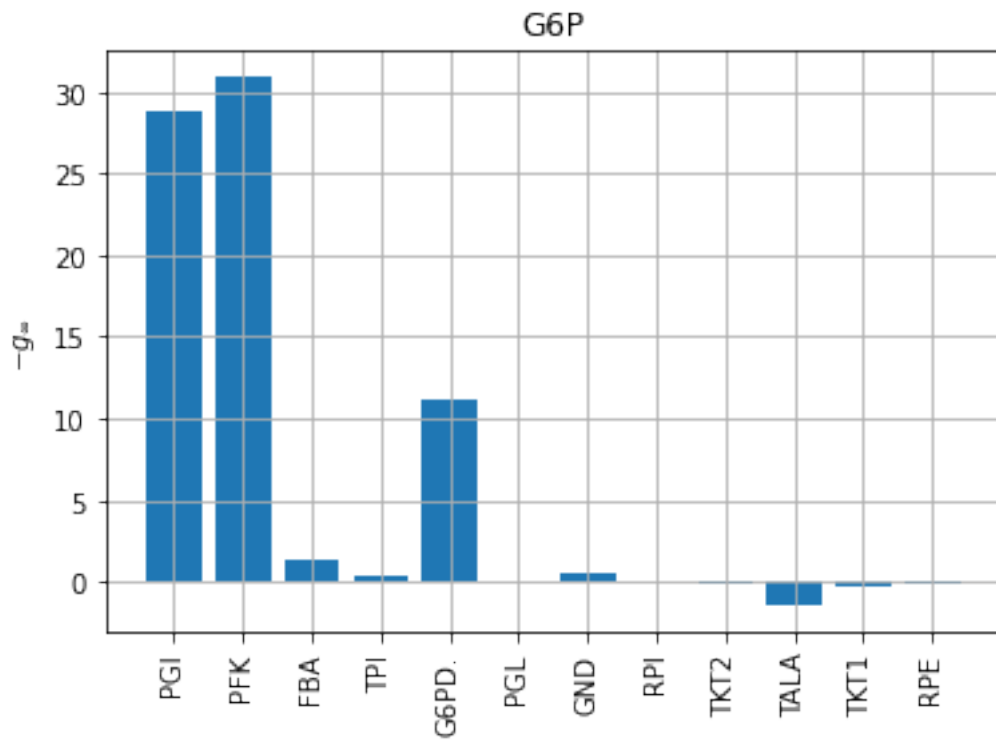
kappa\_RPE

$g = 0.06664804356236037$   $\tau = 0.008221010075271595$

$d\lambda = 10$

G6P

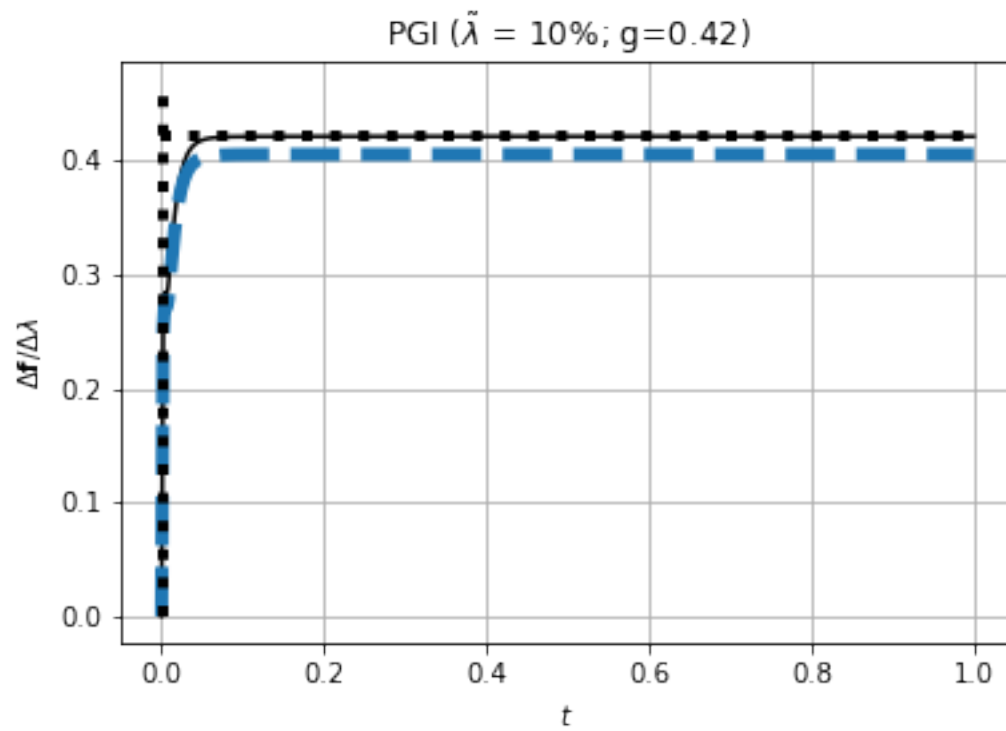




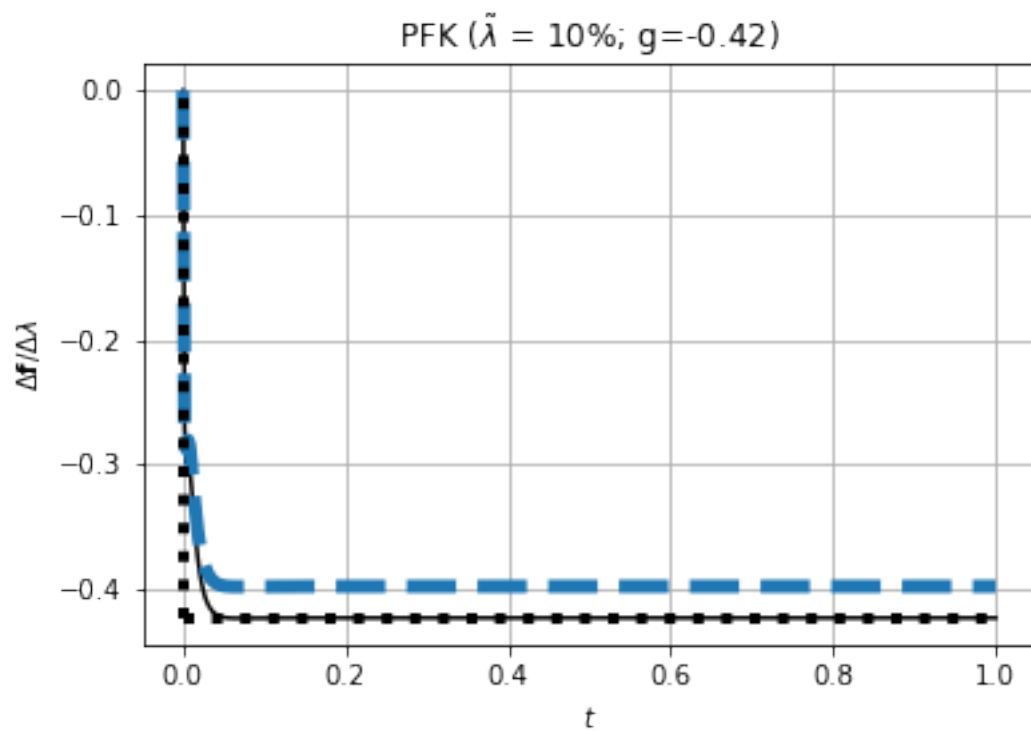
Doing: sPGI  
 kappa\_PGI  
 $g = 0.4208987417694914$   $\tau = 0.001784019116768216$



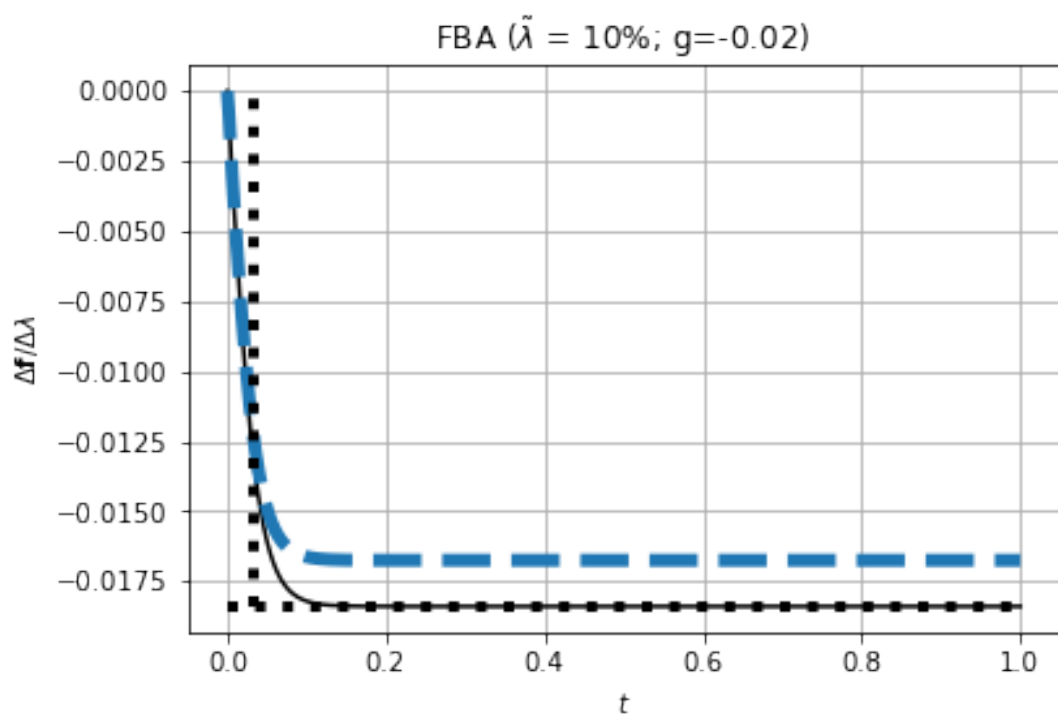
d $\lambda$  = 10  
R5P



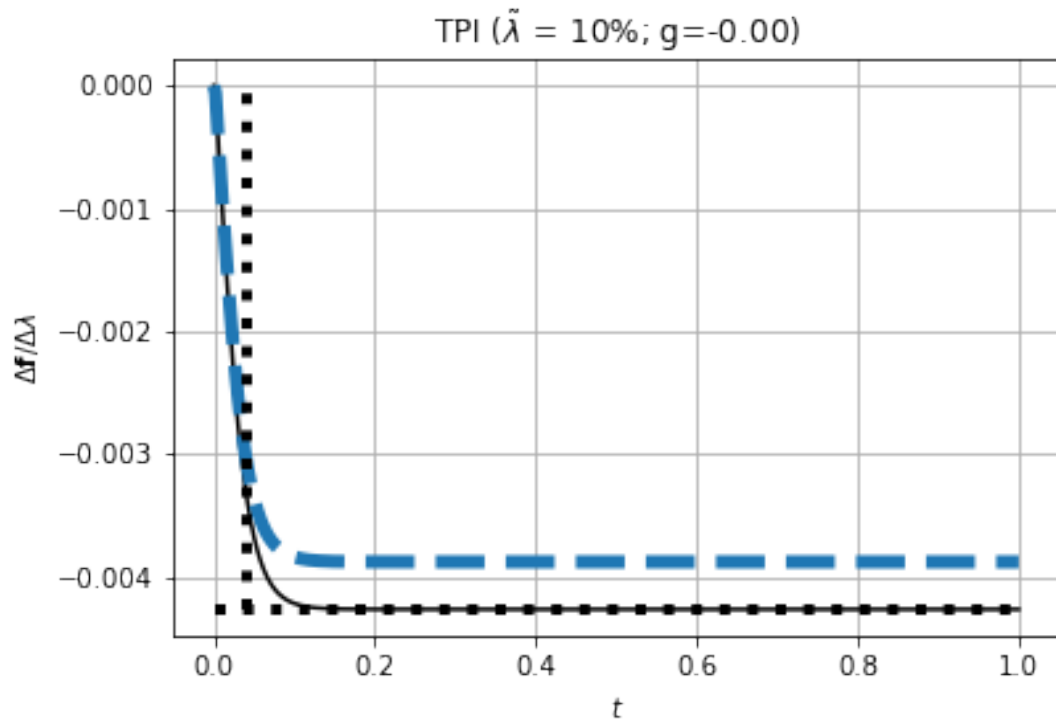
Doing: sPFK  
kappa\_PFK  
 $g = -0.42364263563046833$   $\tau = 0.001717964990211834$   
d $\lambda$  = 10  
R5P



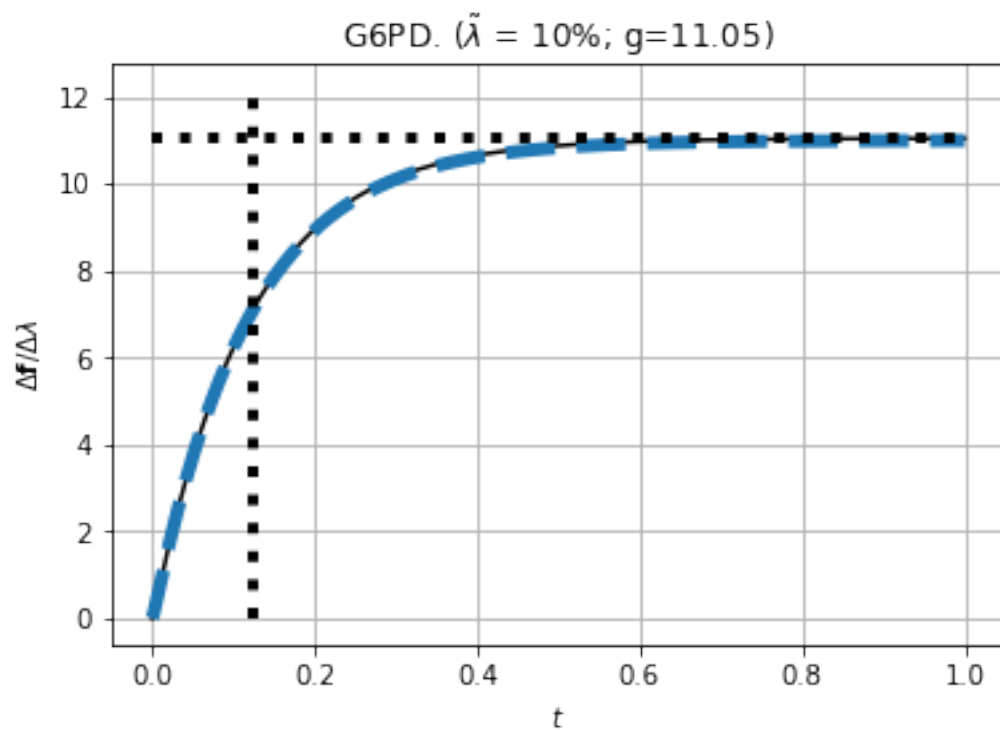
Doing: sFBA  
 kappa\_FBA  
 $g = -0.018401576065215863$   $\tau = 0.033394801269318826$   
 $d\lambda = 10$   
 R5P



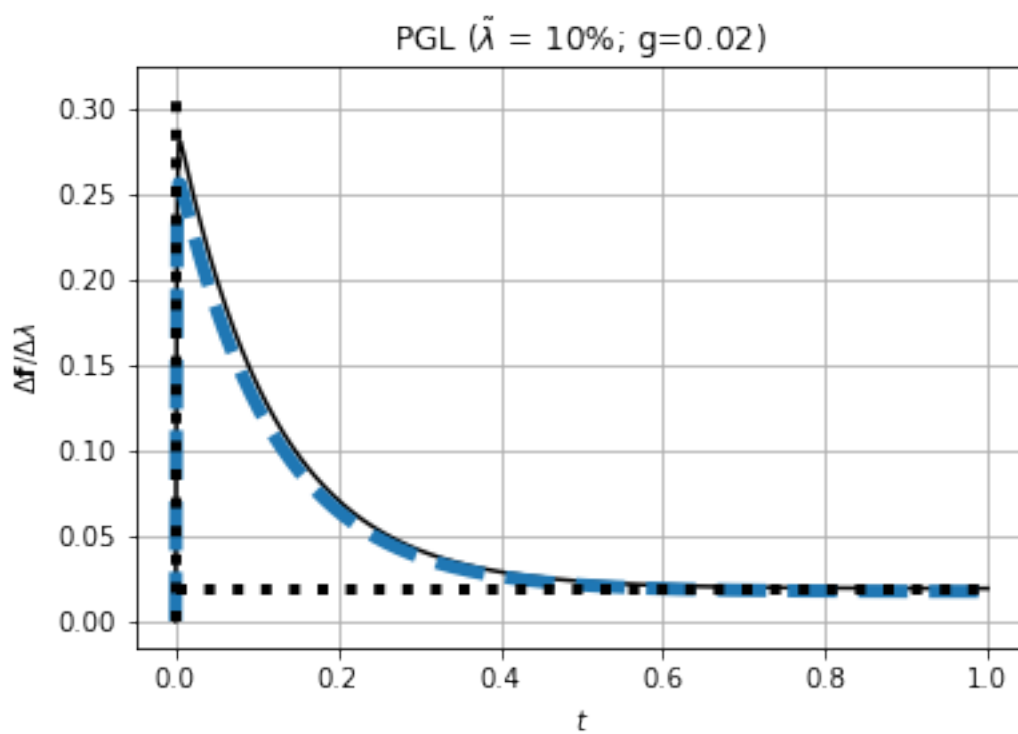
Doing: sTPI  
kappa\_TPI  
 $g = -0.004265327359156856$   $\tau = 0.039469568172793866$   
 $d\lambda = 10$   
R5P



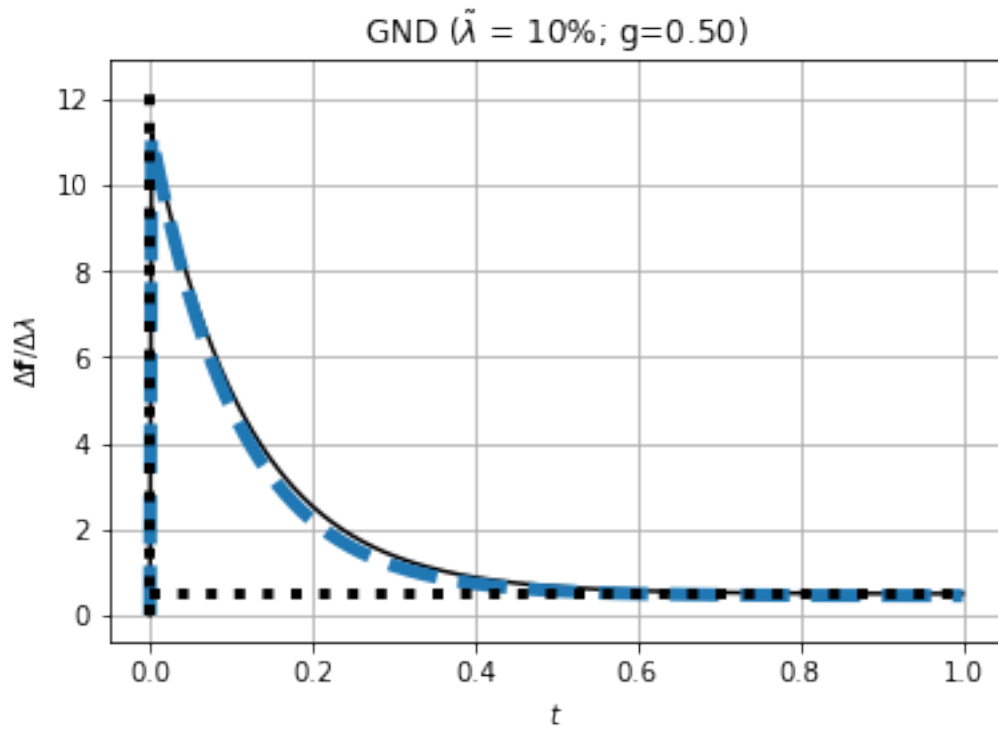
Doing: sG6PDH2R  
kappa\_G6PDH2R  
 $g = 11.049474162931$   $\tau = 0.12364579561293719$   
 $d\lambda = 10$   
R5P



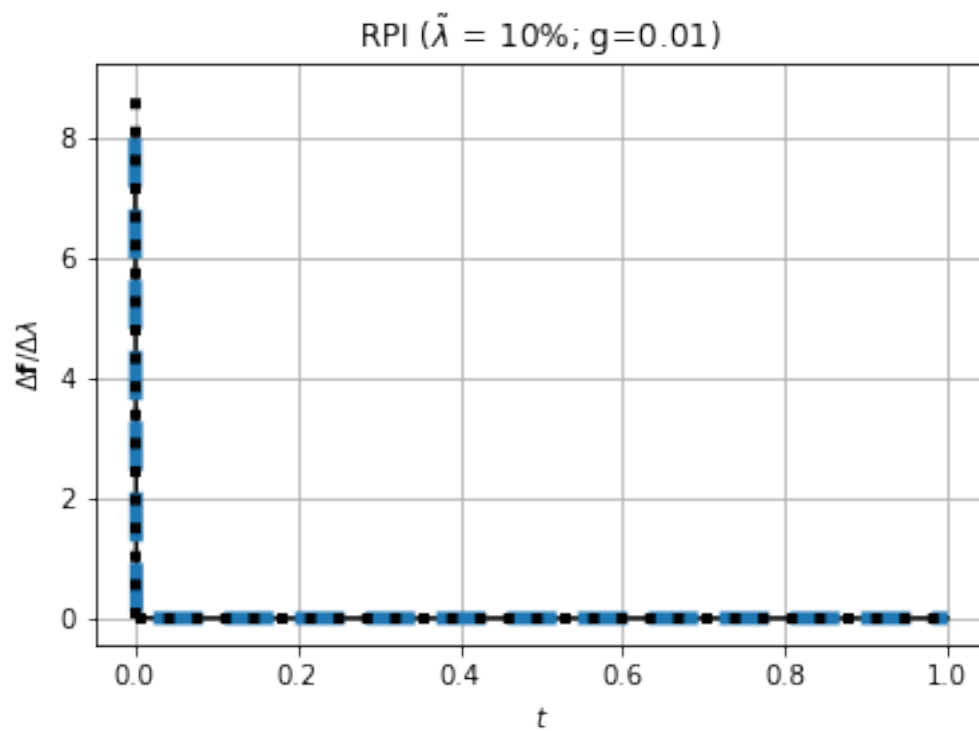
Doing: sPGL  
kappa\_PGL  
 $g = 0.01915350335214014$   $\tau = 0.0010470596032330958$   
 $d\lambda = 10$   
R5P



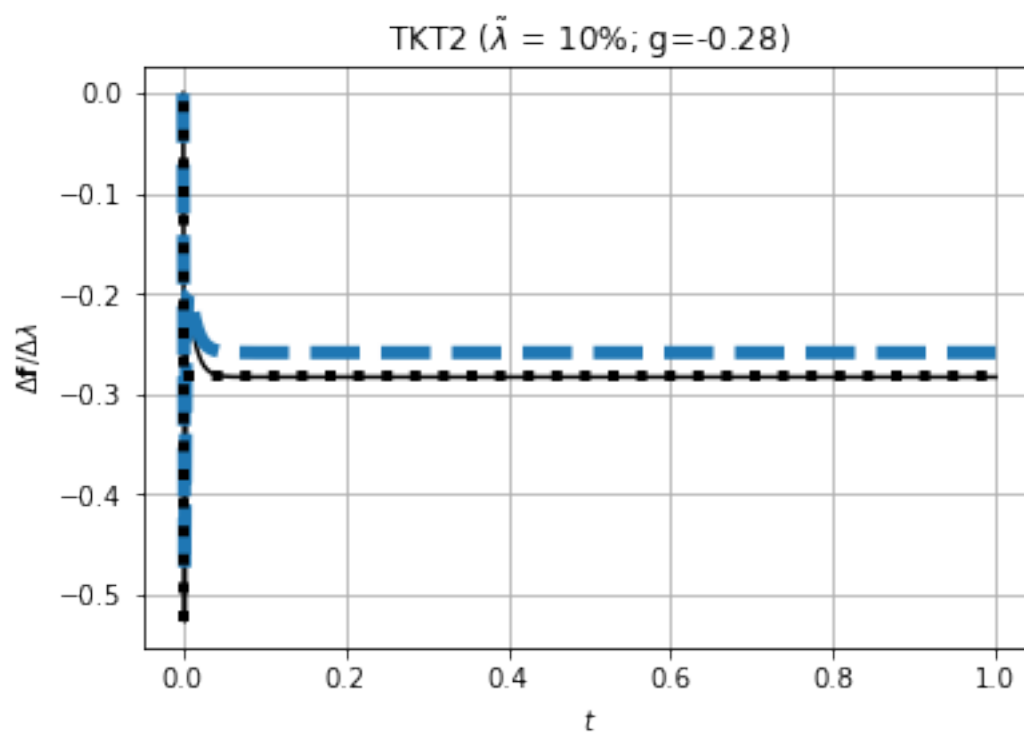
Doing: sGND  
kappa\_GND  
 $g = 0.4954727350638917$   $\tau = 2.6988194236854497\text{e-}06$   
 $d\lambda = 10$   
R5P



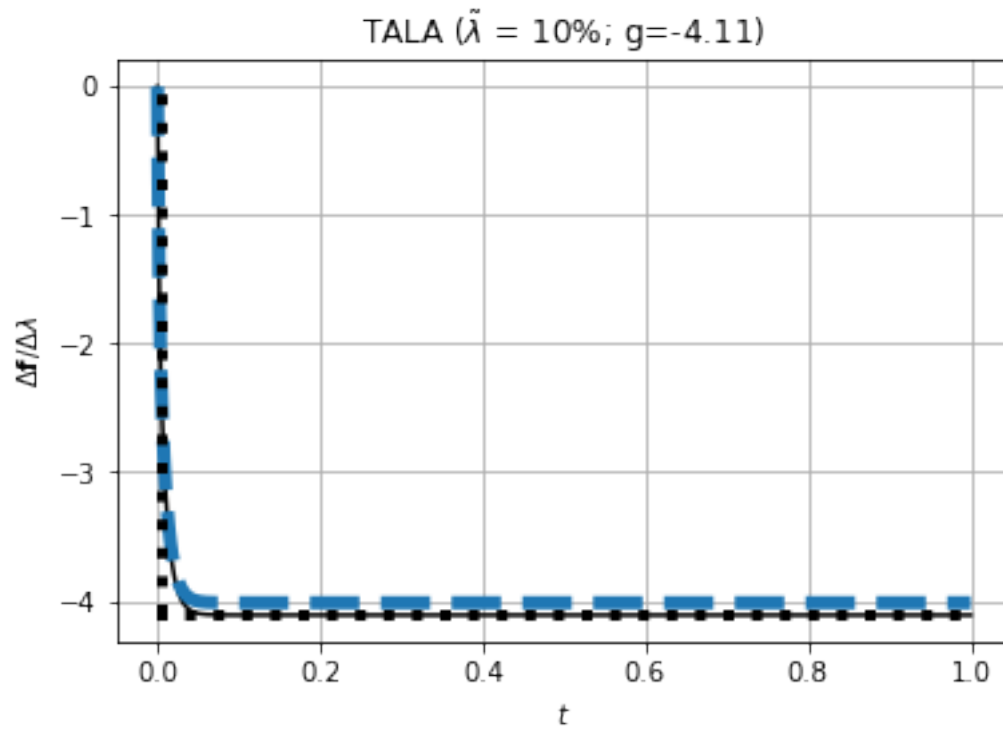
Doing: sRPI  
kappa\_RPI  
 $g = 0.009795231203673538$   $\tau = 0$   
 $d\lambda = 10$   
R5P



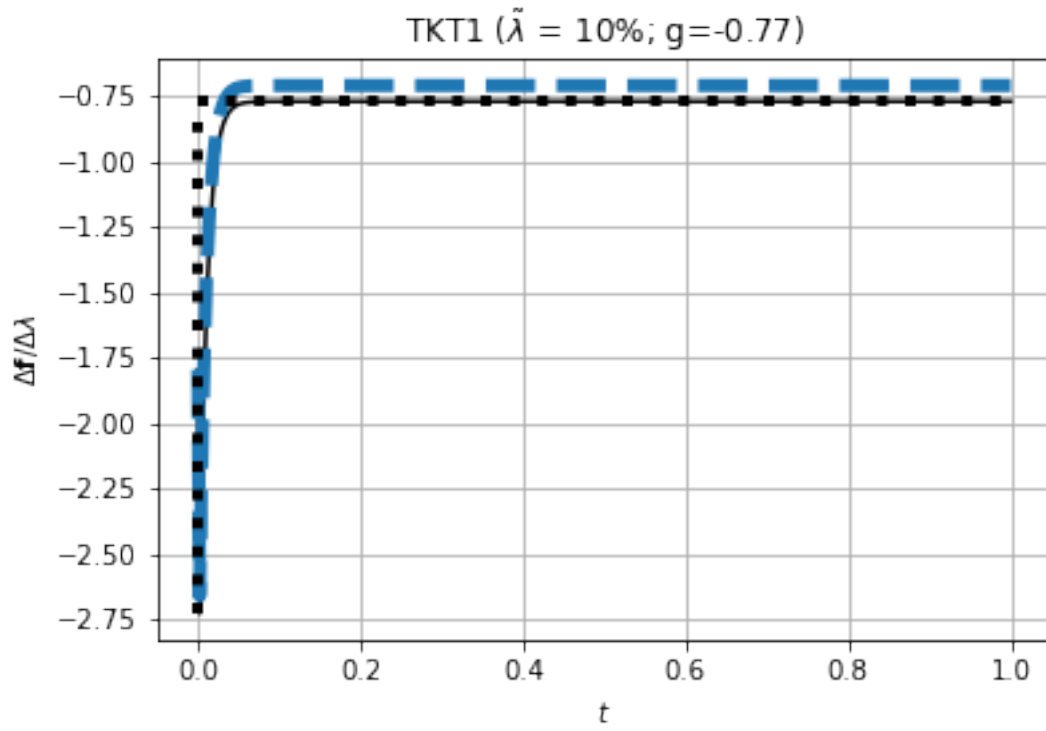
Doing: sTKT2  
 kappa\_TKT2  
 $g = -0.282924954852798$   $\tau = 0.00017126550296392315$   
 $d\lambda = 10$   
 R5P



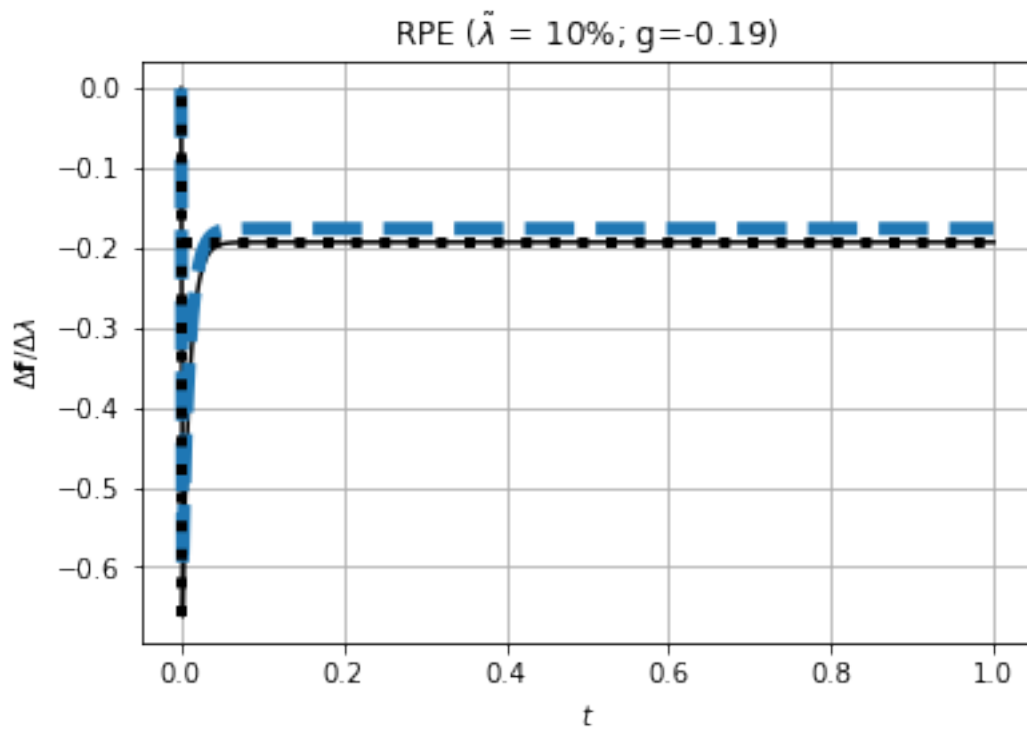
Doing: sTALA  
kappa\_TALA  
 $g = -4.1125018954178$   $\tau = 0.0045160996928807215$   
 $d\lambda = 10$   
R5P



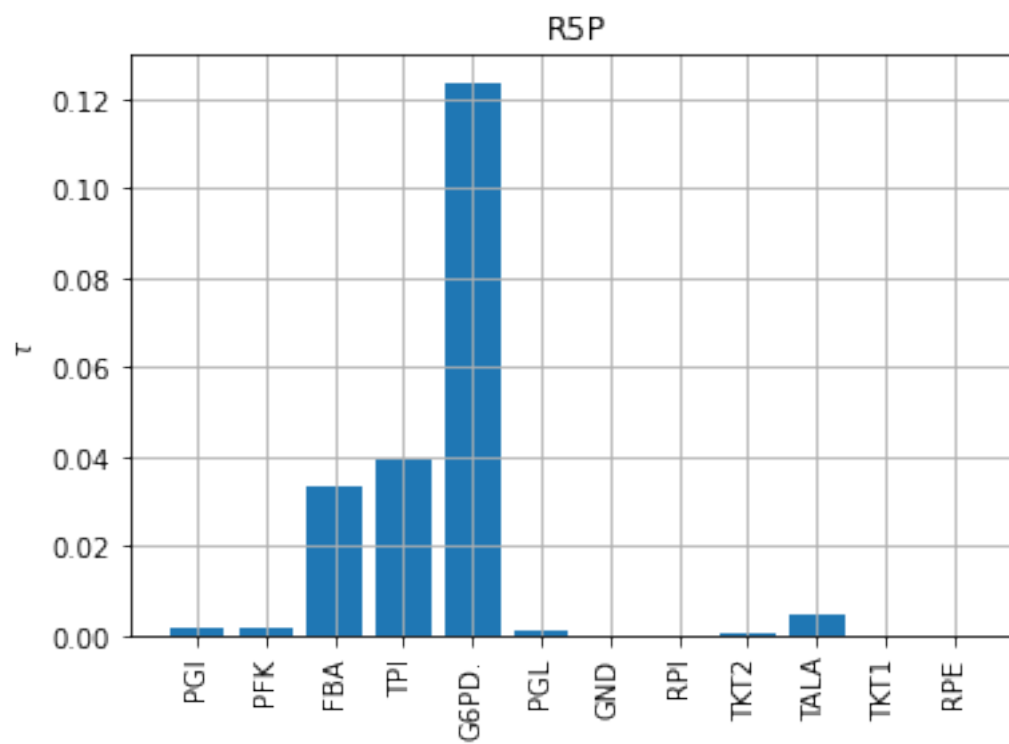
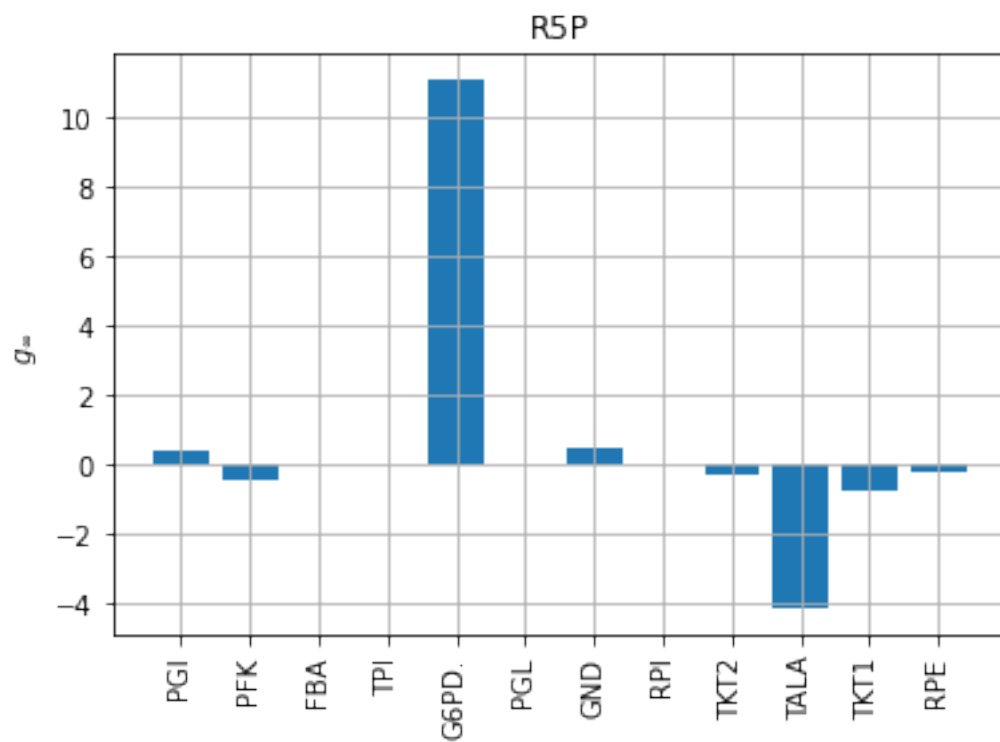
Doing: sTKT1  
kappa\_TKT1  
 $g = -0.7722929529876414$   $\tau = 0$   
 $d\lambda = 10$   
R5P



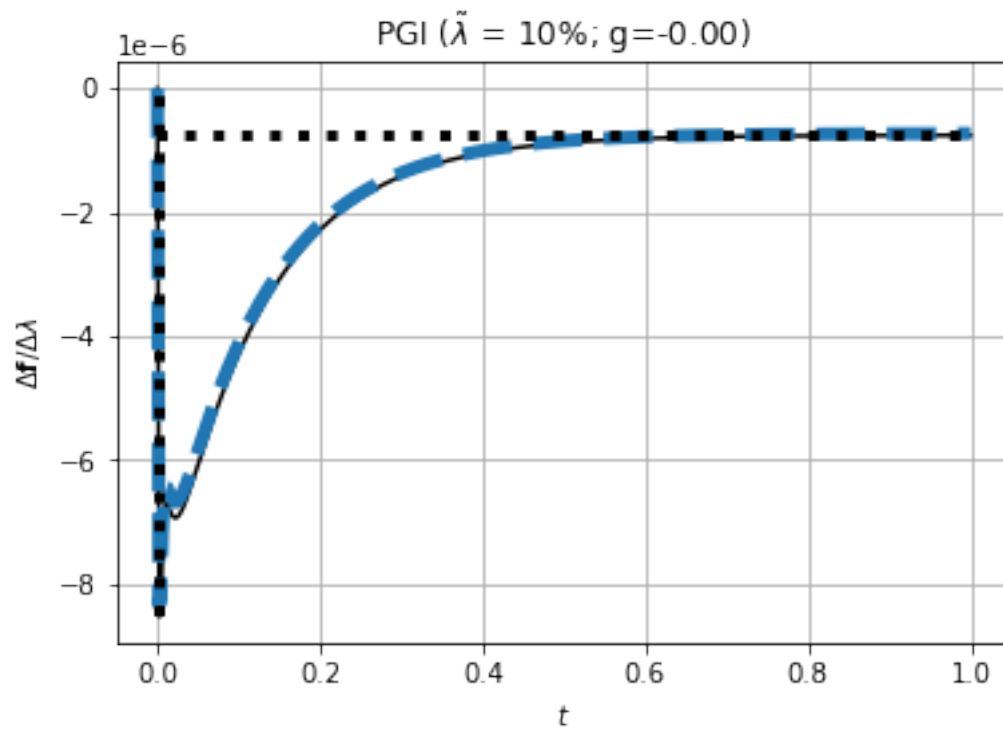
Doing: sRPE  
 kappa\_RPE  
 $g = -0.19283531466757647$   $\tau = 2.6571744064148927e-06$   
 $d\lambda = 10$   
 R5P



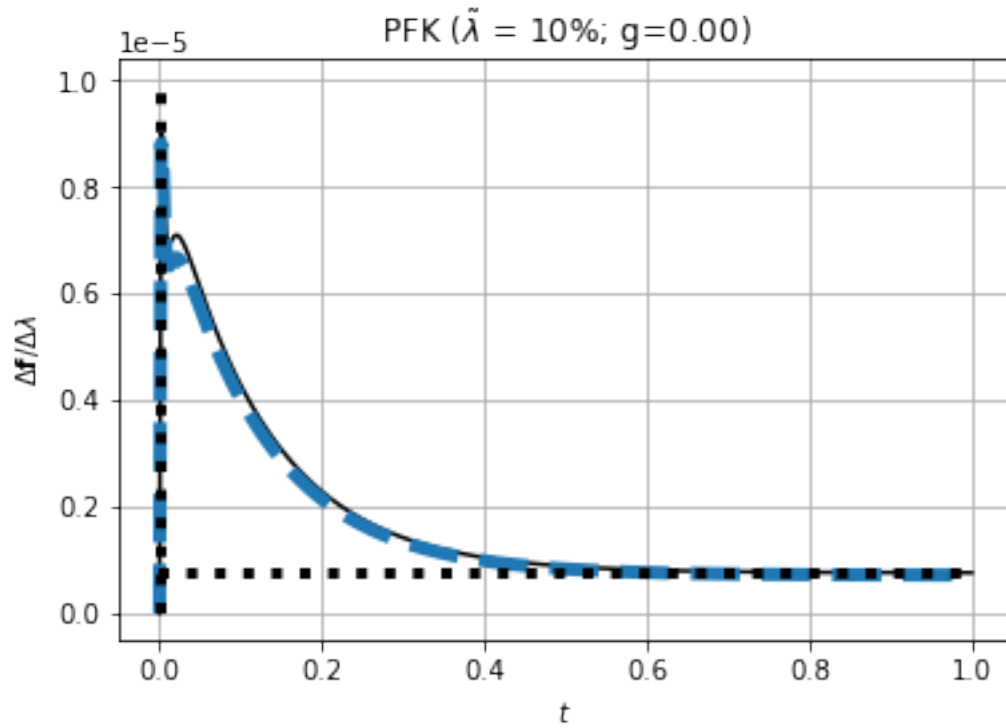




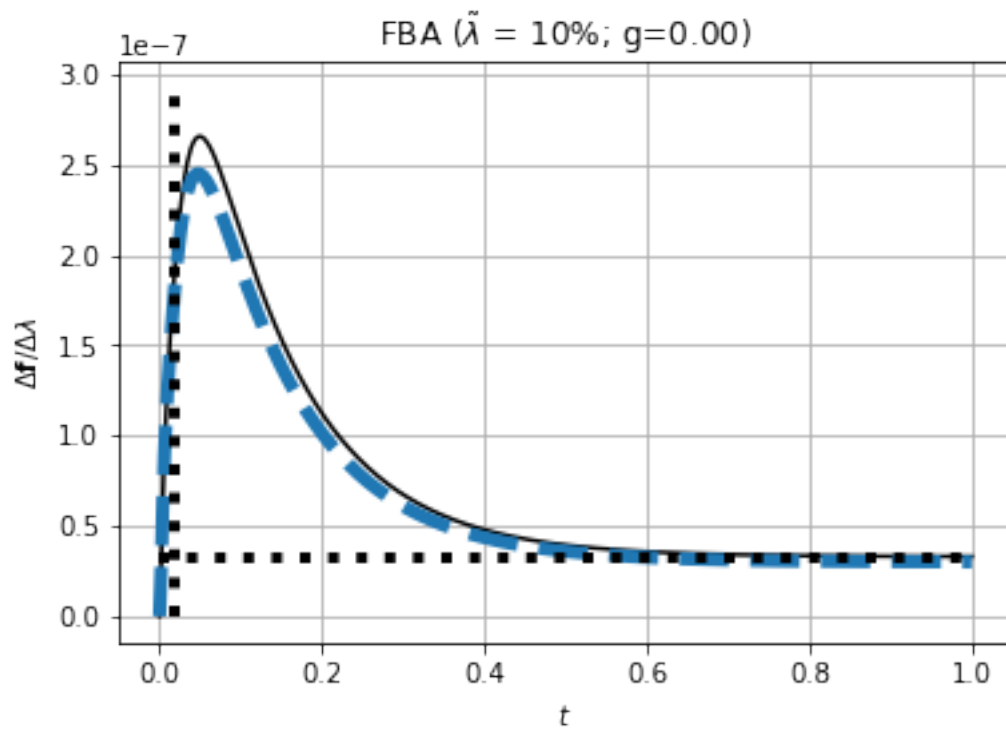
Doing: sPGI  
kappa\_PGI  
 $g = -7.546999477333997\text{e-}07$   $\tau = 0.0015271411542531847$   
dlam = 10  
NADPH



Doing: sPFK  
kappa\_PFK  
 $g = 7.596199715986058\text{e-}07$   $\tau = 0.0015261943288164277$   
dlam = 10  
NADPH



Doing: sFBA  
kappa\_FBA  
 $g = 3.299527434456363e-08$   $\tau = 0.019527507142779787$   
 $d\lambda = 10$   
NADPH



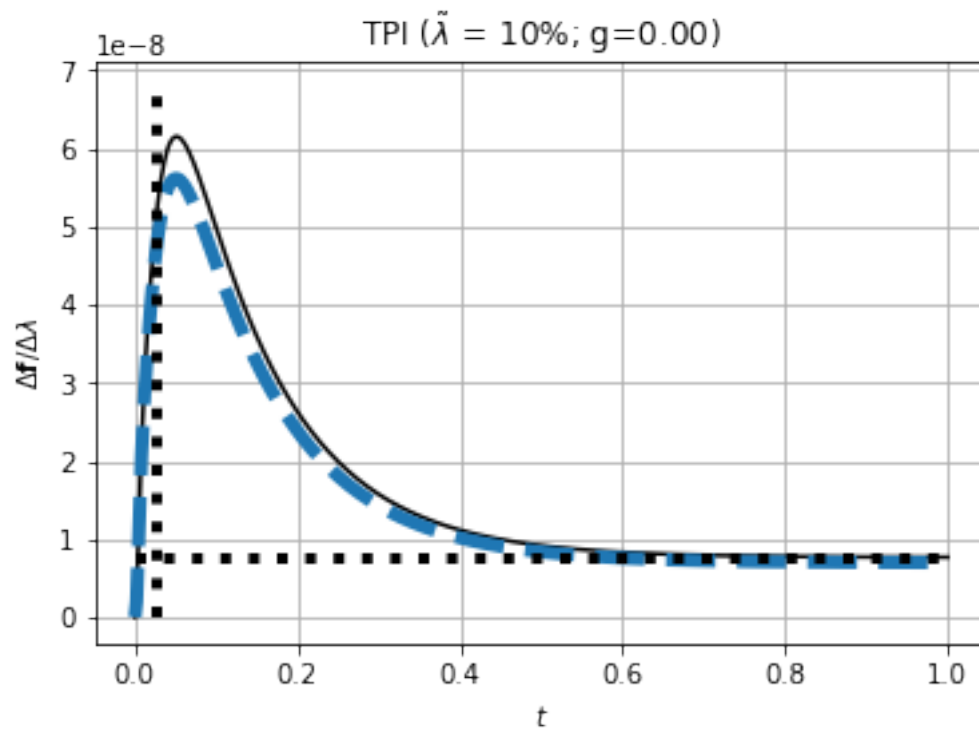
Doing: sTPI

kappa\_TPI

$g = 7.647982183374511\text{e-}09$   $\tau = 0.02541572981821223$

d $\lambda$  = 10

NADPH



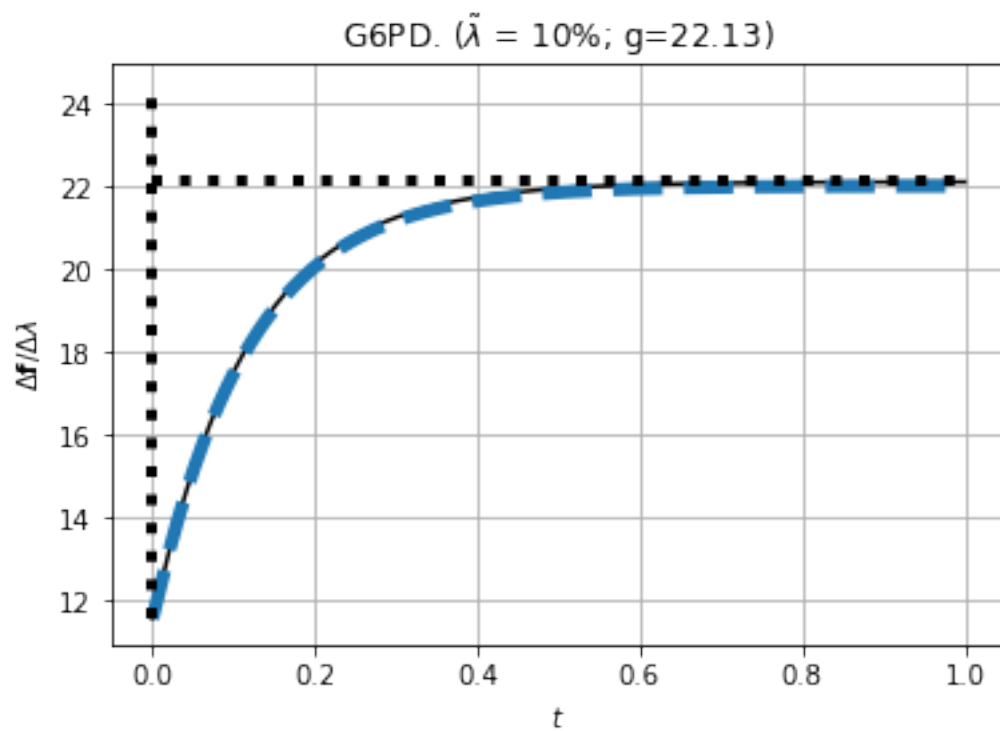
Doing: sG6PDH2R

kappa\_G6PDH2R

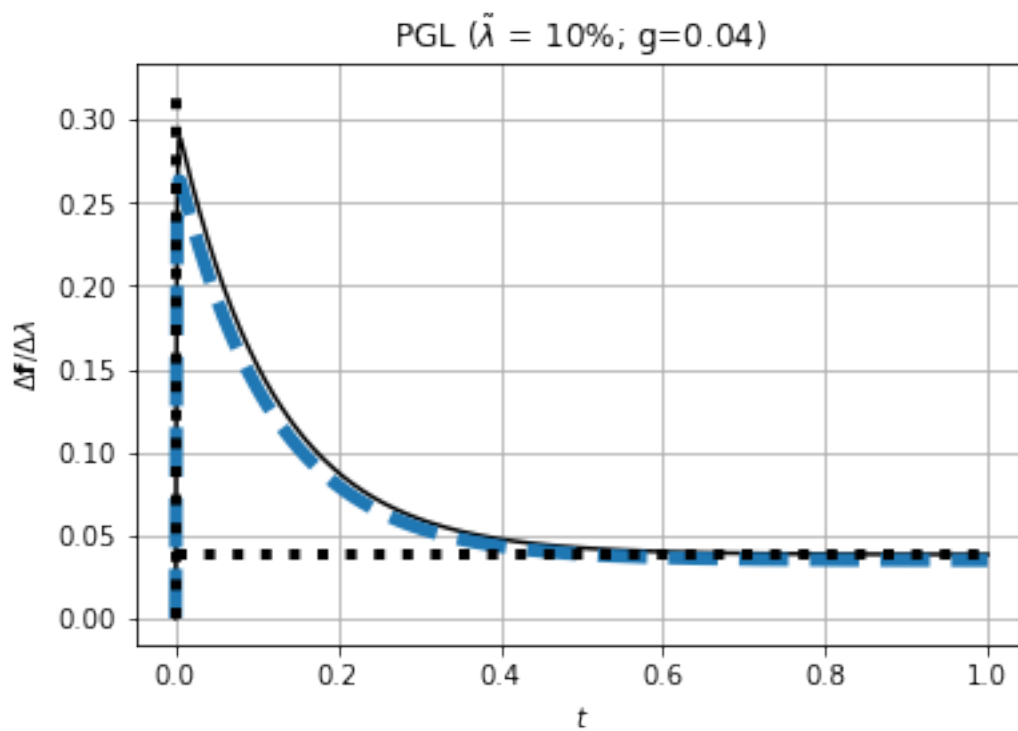
$g = 22.126061707076737$   $\tau = 0$

d $\lambda$  = 10

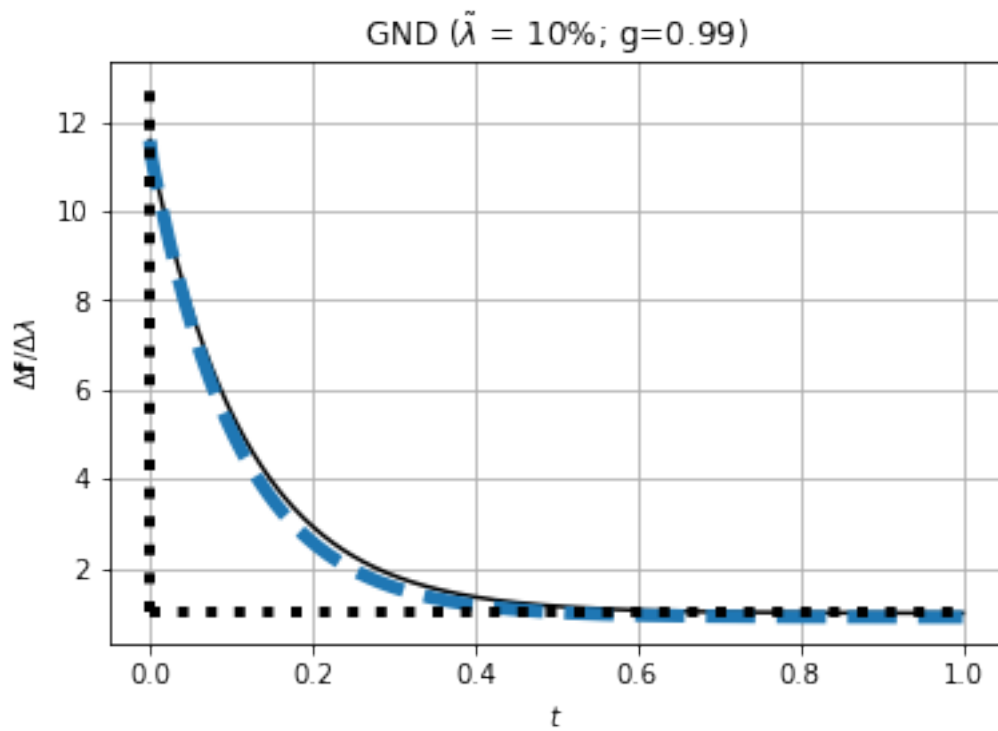
NADPH



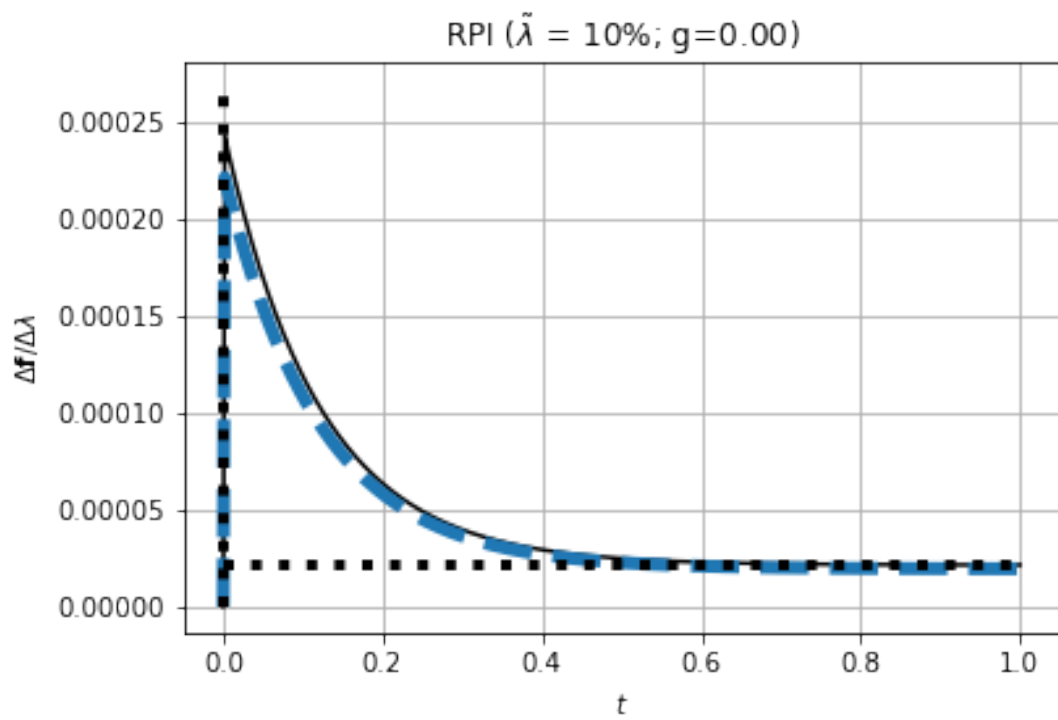
Doing: sPGL  
 kappa\_PGL  
 $g = 0.03835400588527368$   $\tau = 0.001025533527882495$   
 $d\lambda = 10$   
 NADPH



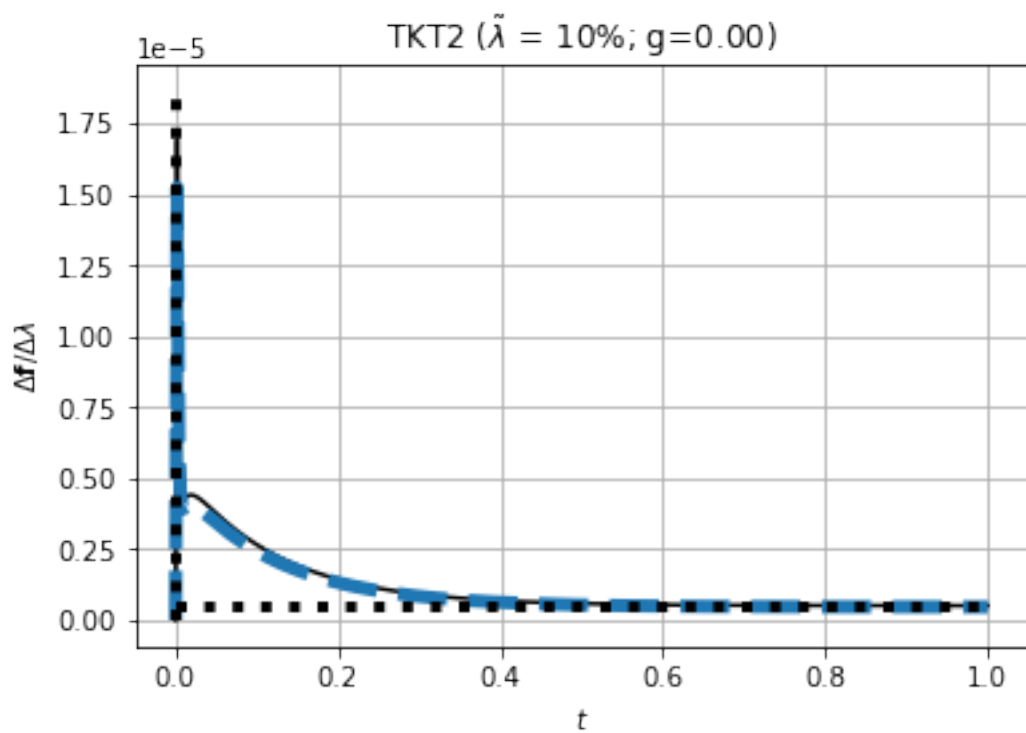
Doing: sGND  
kappa\_GND  
 $g = 0.9921612692650577$   $\tau = 0$   
dlam = 10  
NADPH



Doing: sRPI  
kappa\_RPI  
 $g = 2.1458155641420664\text{e-}05$   $\tau = 2.699186974424081\text{e-}06$   
dlam = 10  
NADPH



Doing: sTKT2  
 kappa\_TKT2  
 $g = 5.073036156607876e-07$   $\tau = 0.00016943022110076314$   
 $d\lambda = 10$   
 NADPH



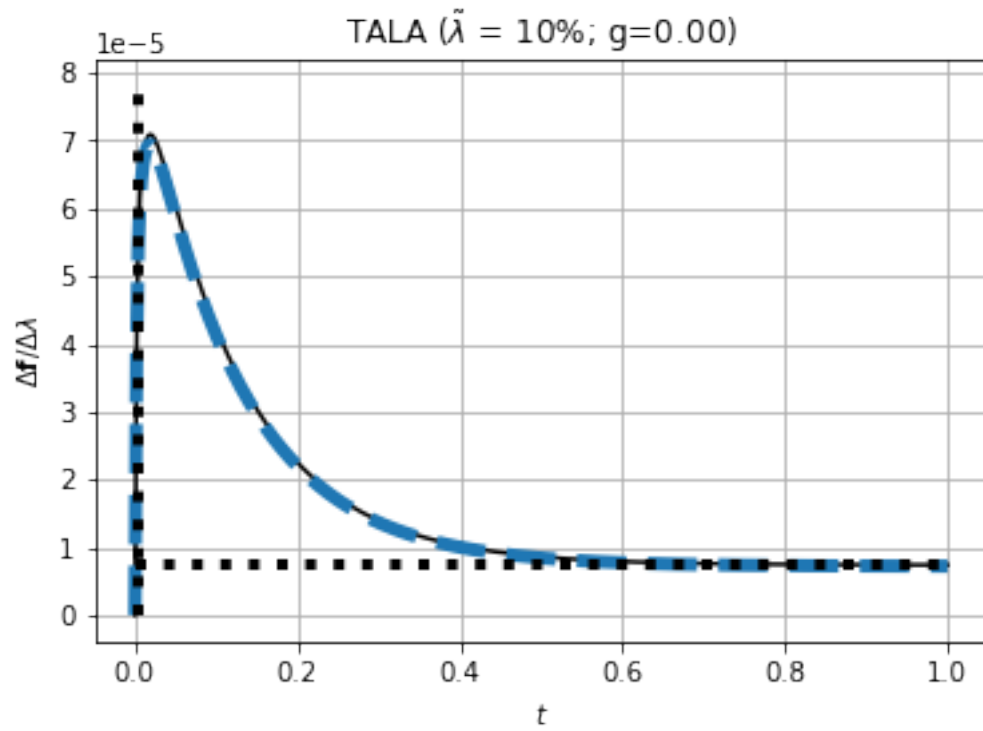
Doing: sTALA

kappa\_TALA

$g = 7.373994570839489\text{e-}06$   $\tau = 0.0028552247467929955$

d $\lambda$  = 10

NADPH



Doing: sTKT1

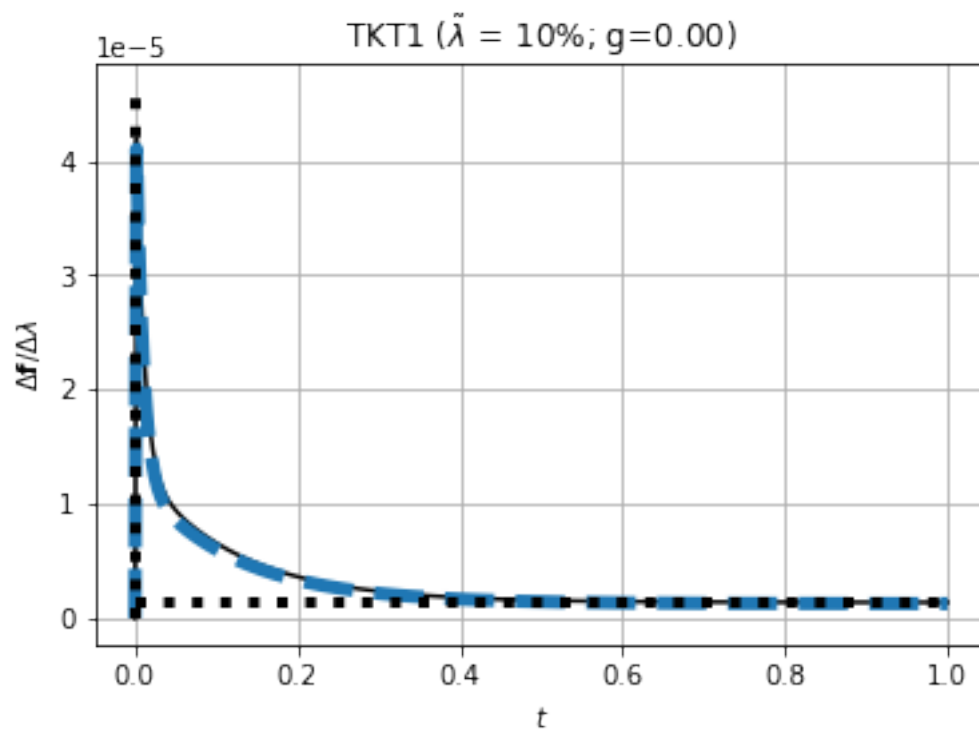
kappa\_TKT1

$g = 1.3847735970665945\text{e-}06$   $\tau = 0.00018475667332612674$

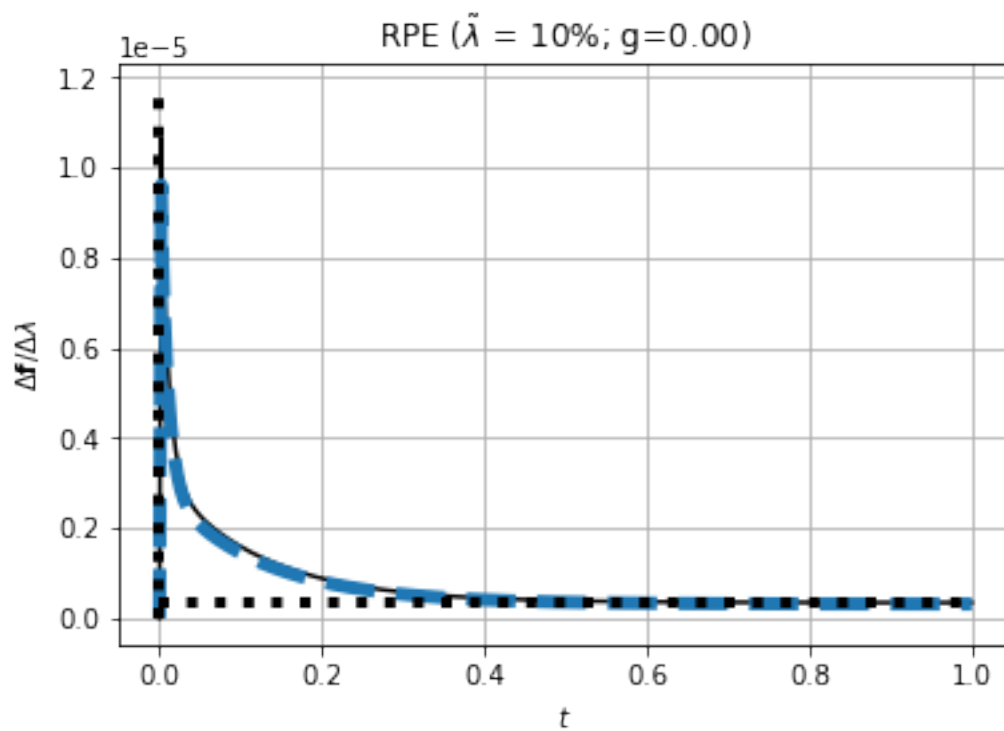
d $\lambda$  = 10

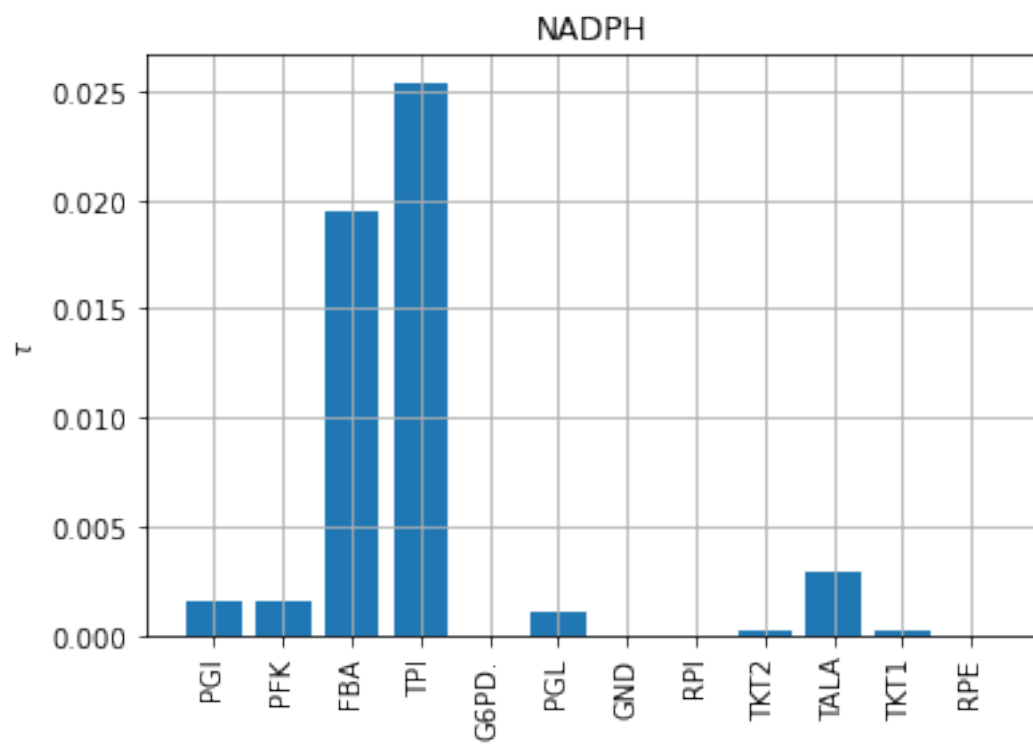
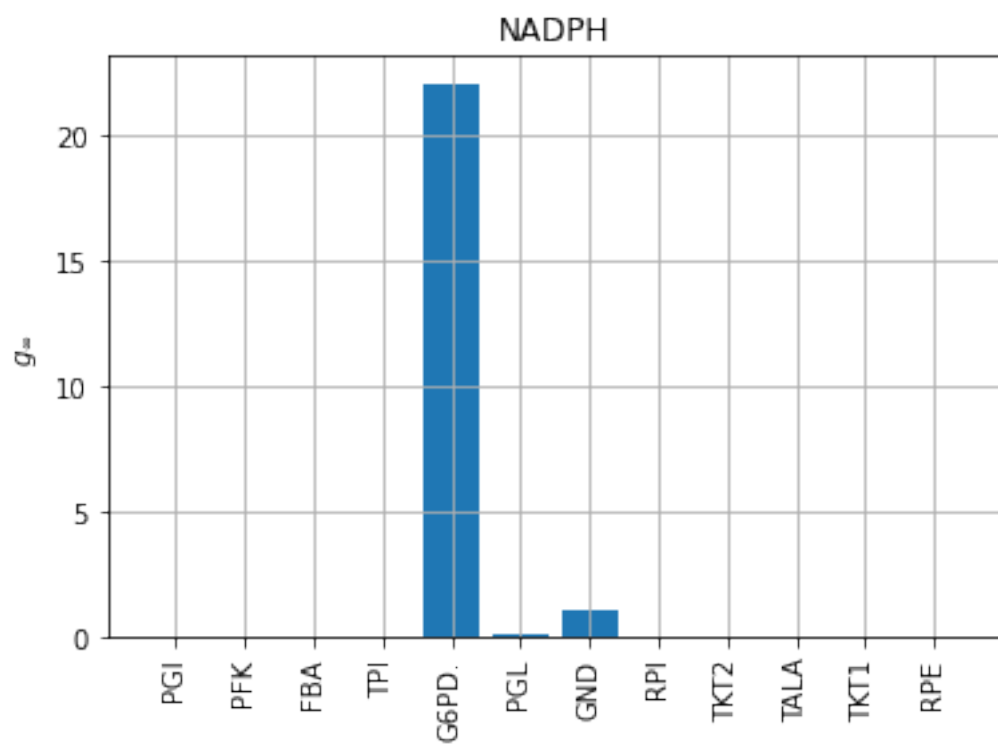
NADPH



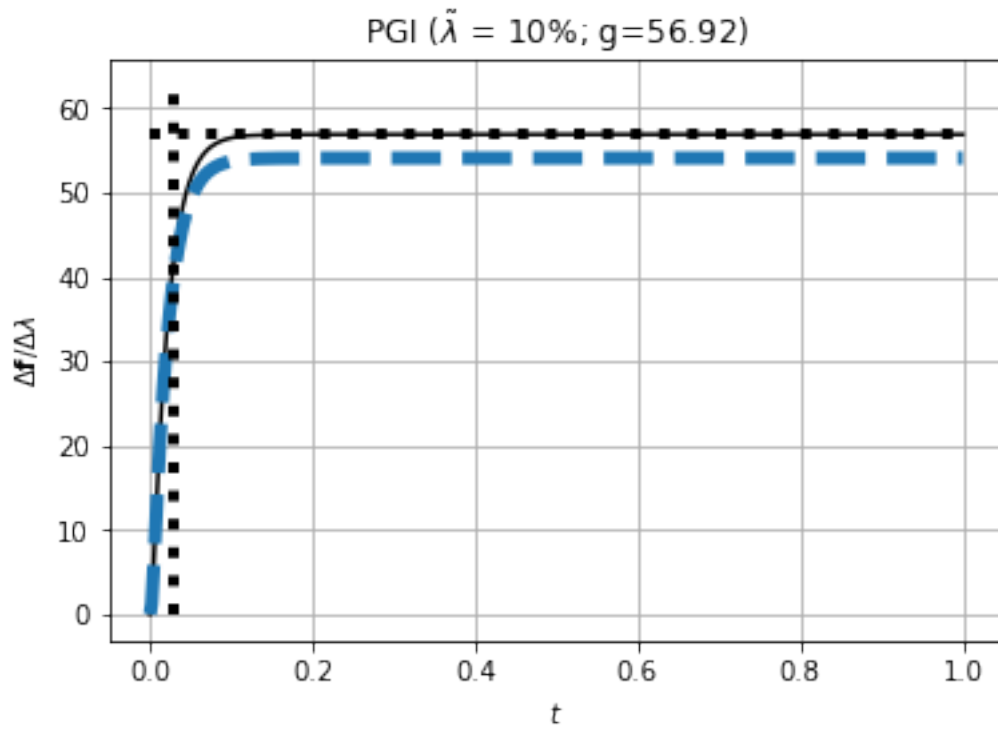


Doing: sRPE  
 kappa\_RPE  
 $g = 3.457667861388965e-07$   $\tau = 2.6565945344600007e-06$   
 $d\lambda = 10$   
 NADPH

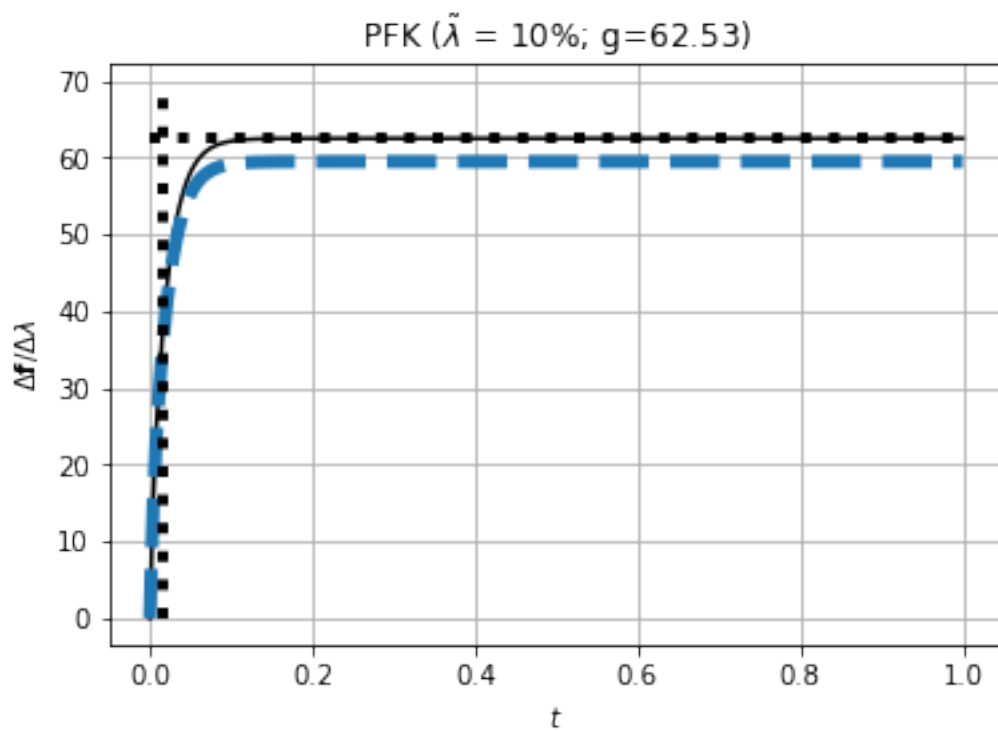




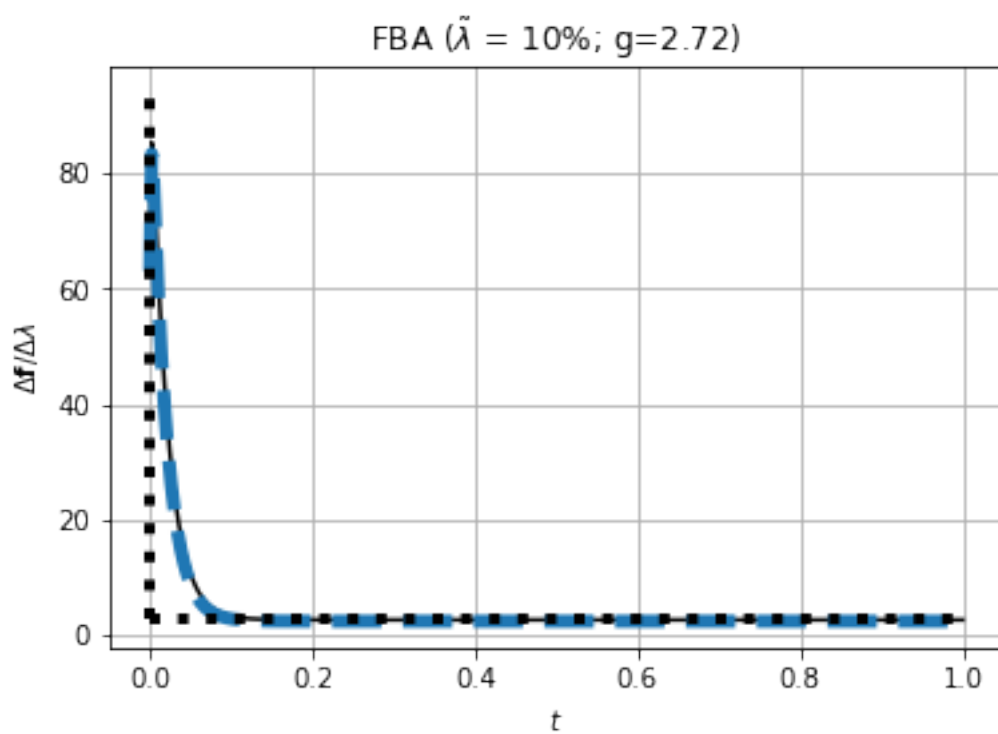
Doing: sPGI  
kappa\_PGI  
 $g = 56.91833245076208$   $\tau = 0.030041038107083886$   
 $d\lambda = 10$   
G3P



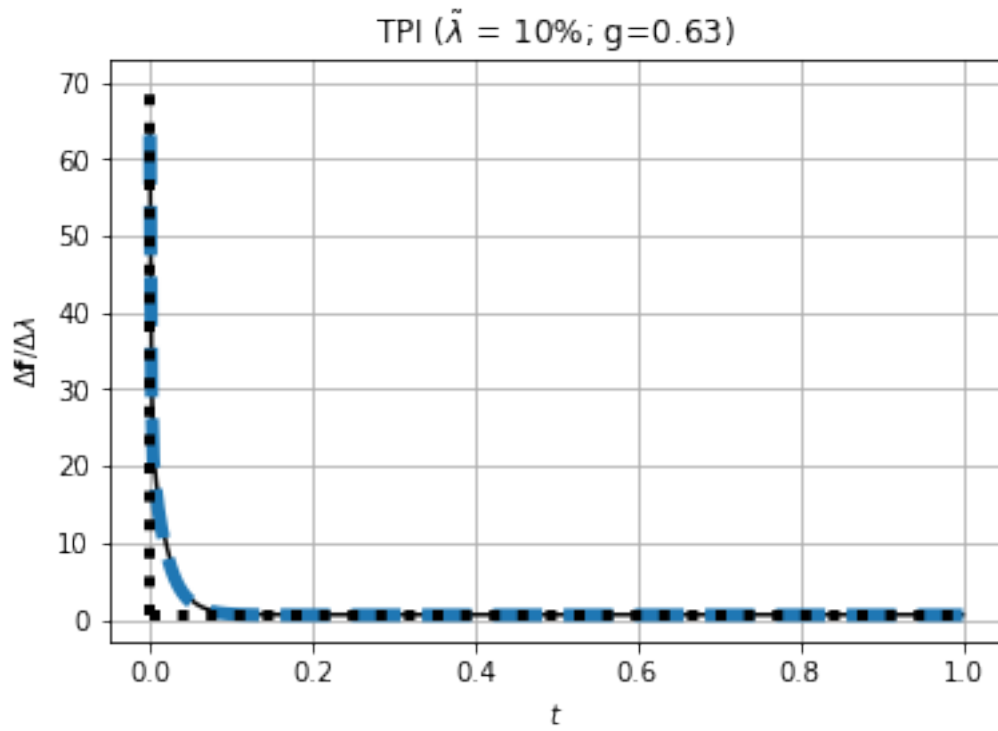
Doing: sPFK  
kappa\_PFK  
 $g = 62.533290299526094$   $\tau = 0.014866156765752257$   
 $d\lambda = 10$   
G3P



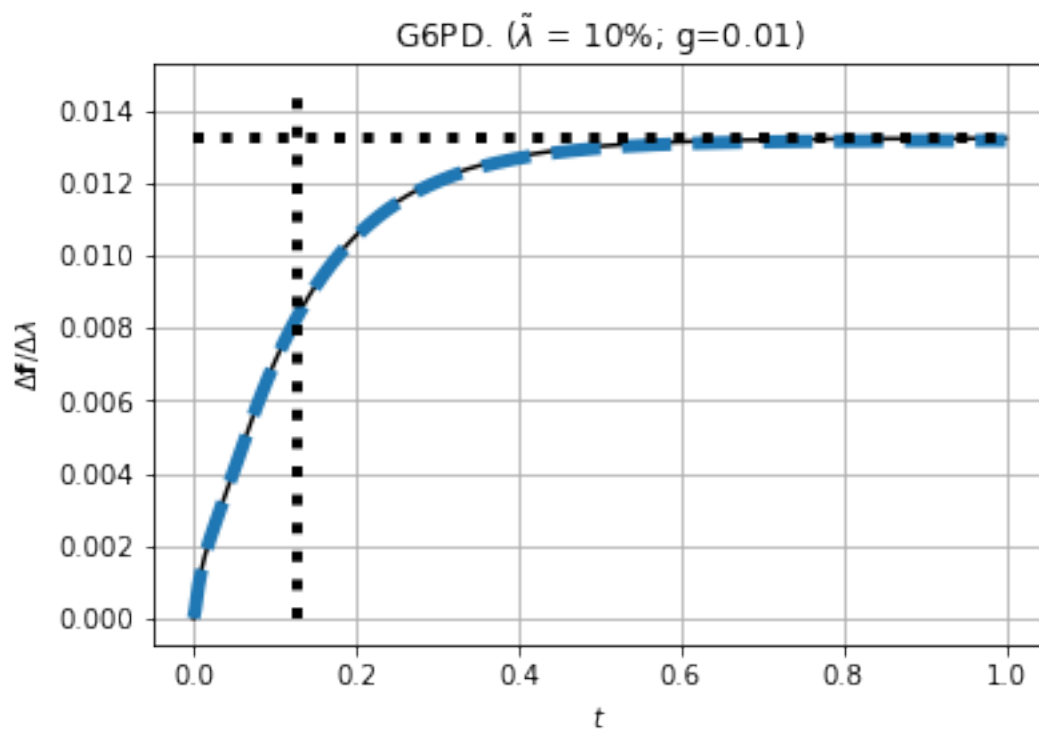
Doing: sFBA  
 kappa\_FBA  
 $g = 2.7162306181456373$   $\tau = 0$   
 $d\lambda = 10$   
 G3P



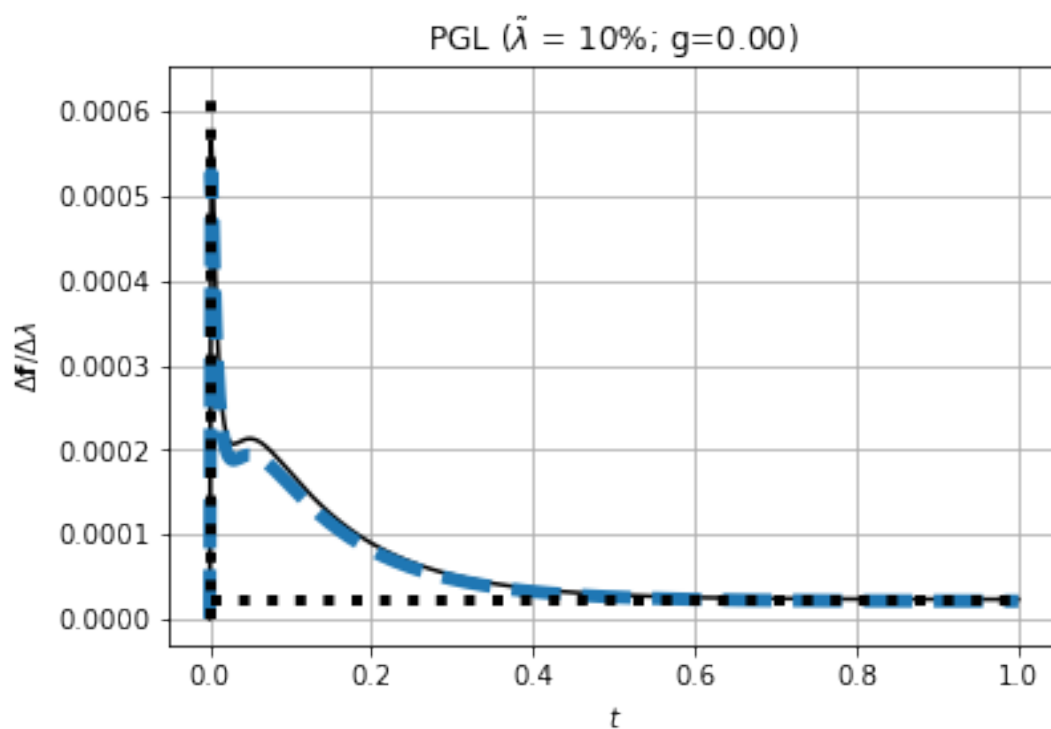
Doing: sTPI  
kappa\_TPI  
 $g = 0.6295989394585817$   $\tau = 0$   
 $d\lambda = 10$   
G3P



Doing: sG6PDH2R  
kappa\_G6PDH2R  
 $g = 0.01322349914204985$   $\tau = 0.12800864302389323$   
 $d\lambda = 10$   
G3P



Doing: sPGL  
 kappa\_PGL  
 $g = 2.2922026197106206e-05$   $\tau = 0.0014045237898896985$   
 $d\lambda = 10$   
 G3P



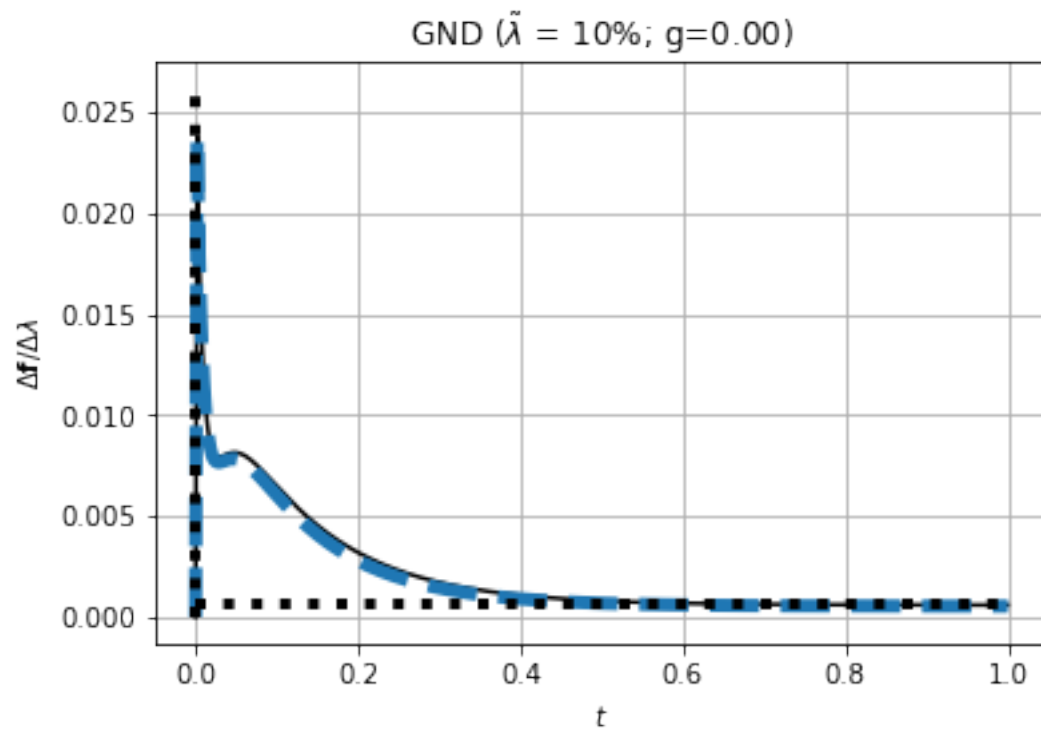
Doing: sGND

kappa\_GND

$g = 0.0005929588339176166$   $\tau = 0.00017684665624202348$

d $\lambda = 10$

G3P



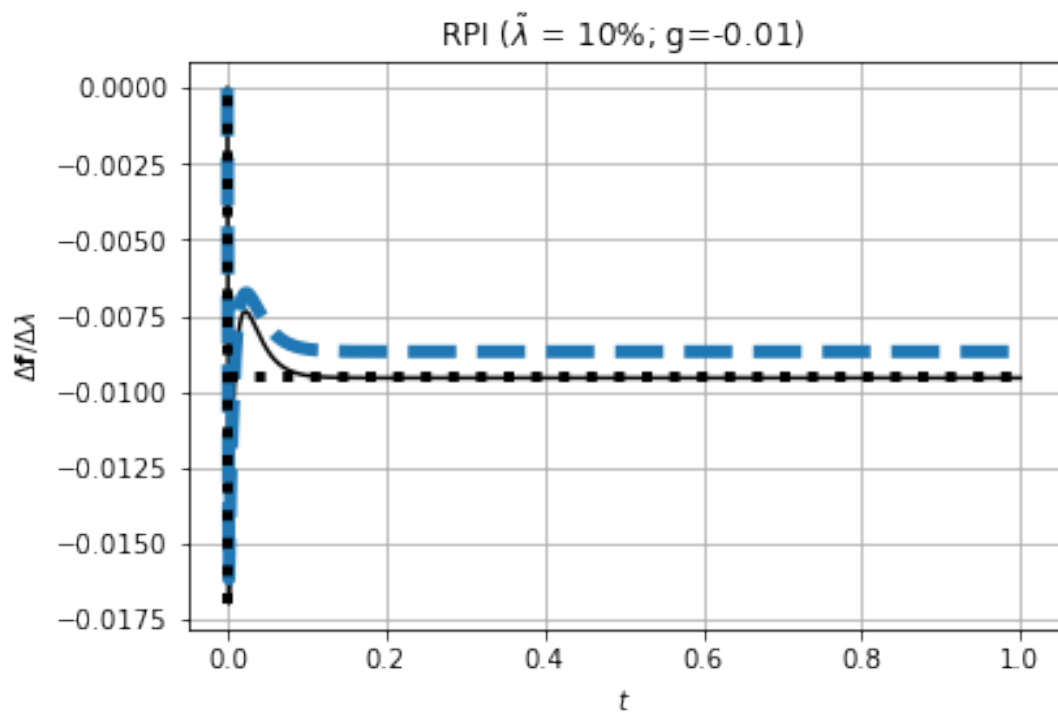
Doing: sRPI

kappa\_RPI

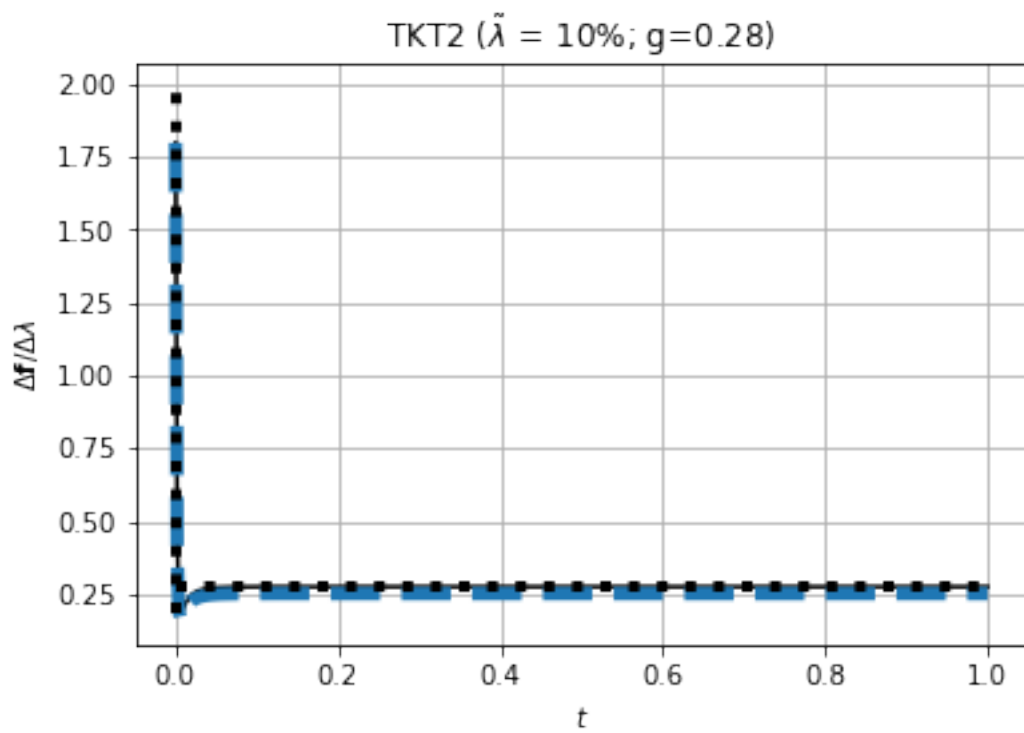
$g = -0.009544022155095424$   $\tau = 0.00017769464683751047$

d $\lambda = 10$

G3P

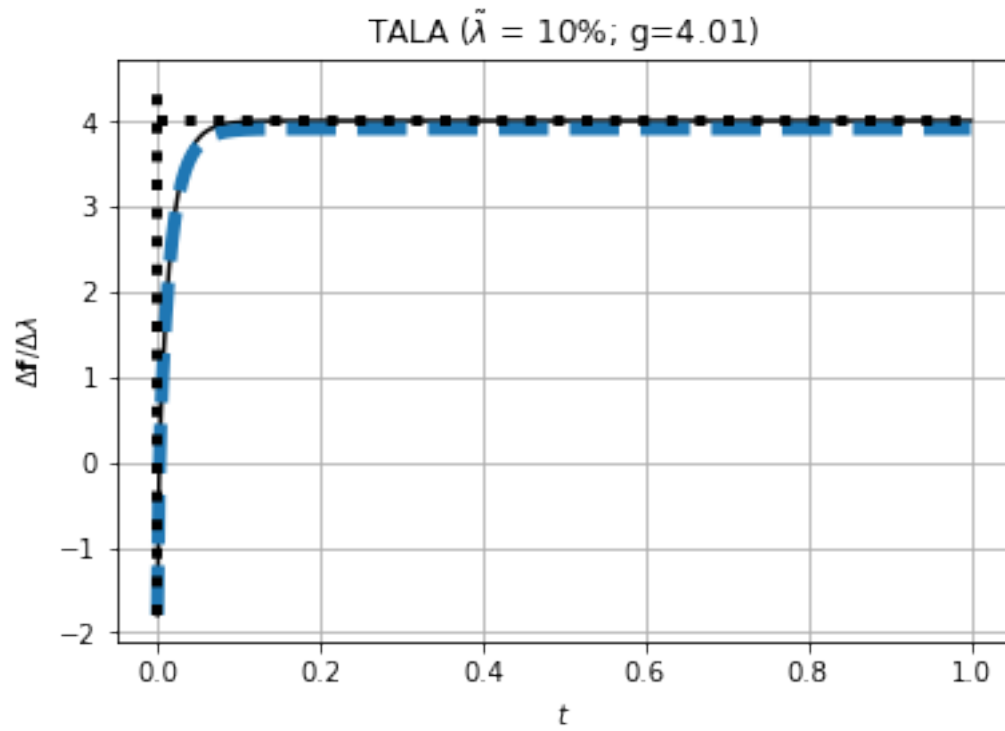


Doing: sTKT2  
kappa\_TKT2  
 $g = 0.2759715745850926$   $\tau = 0$   
 $d\lambda = 10$   
G3P

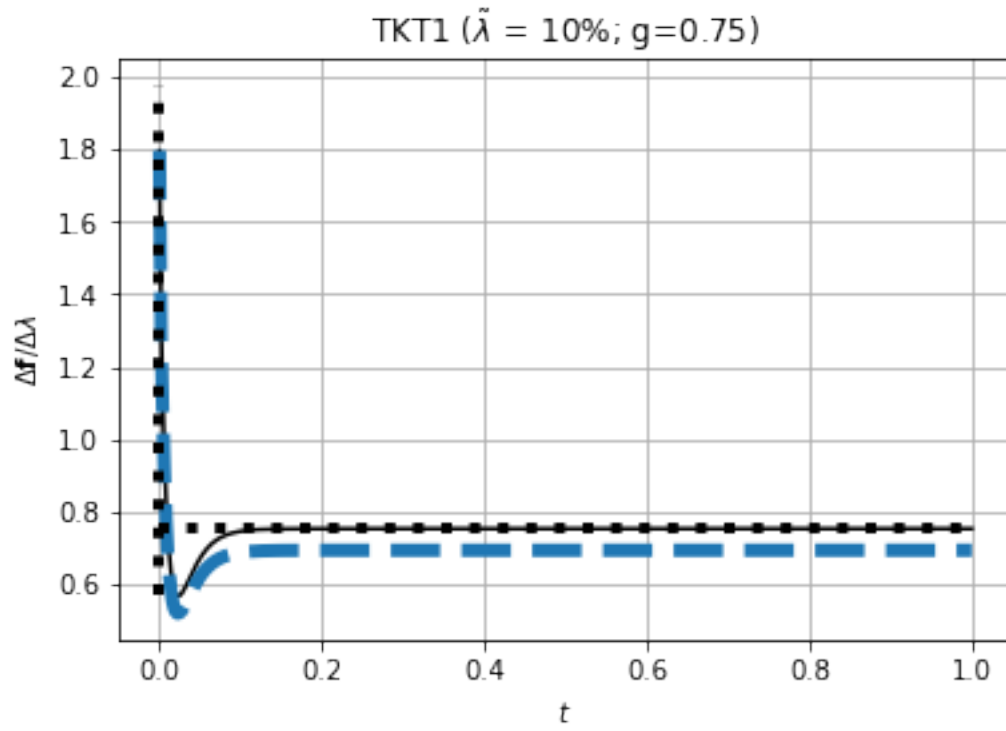




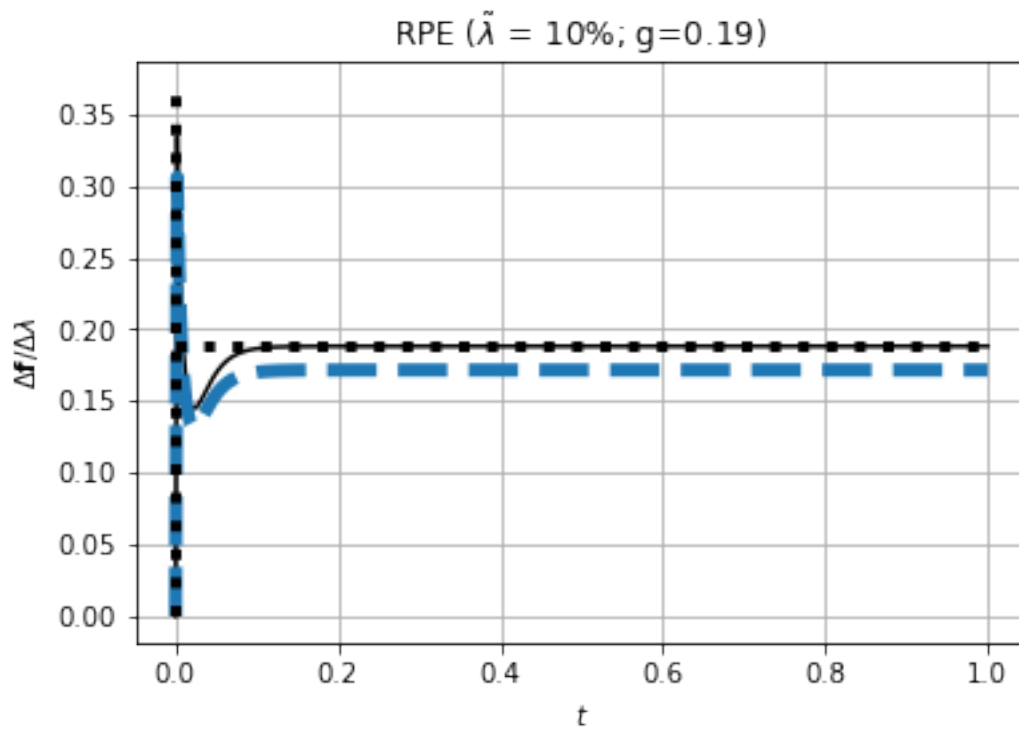
Doing: sTALA  
kappa\_TALA  
 $g = 4.011429900742118$   $\tau = 0$   
 $d\lambda = 10$   
G3P

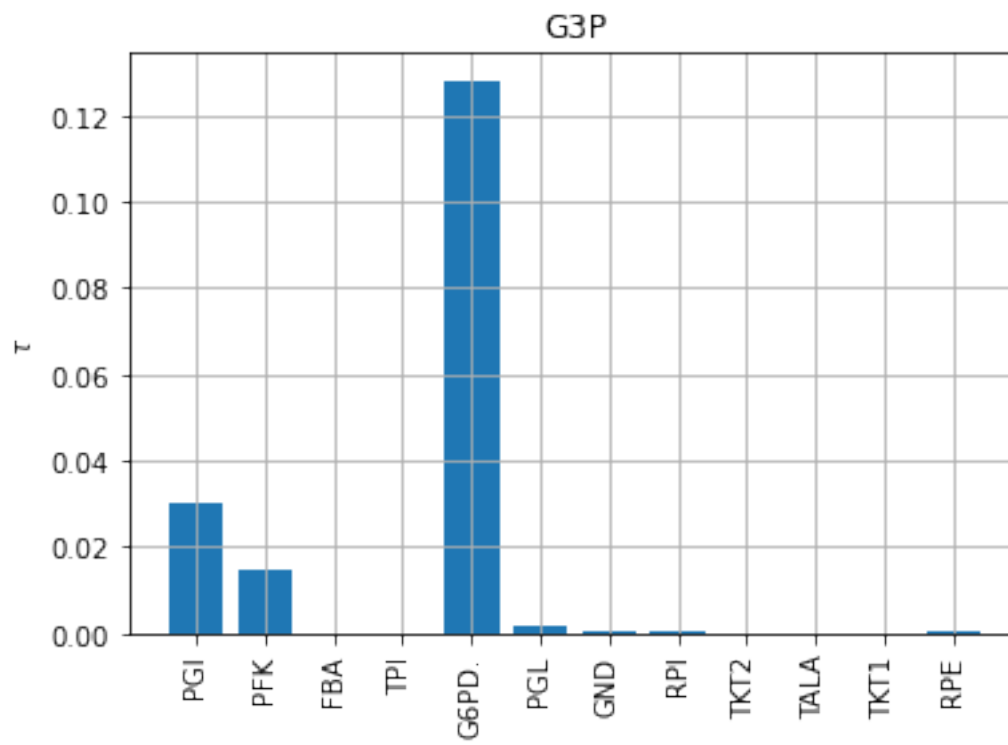
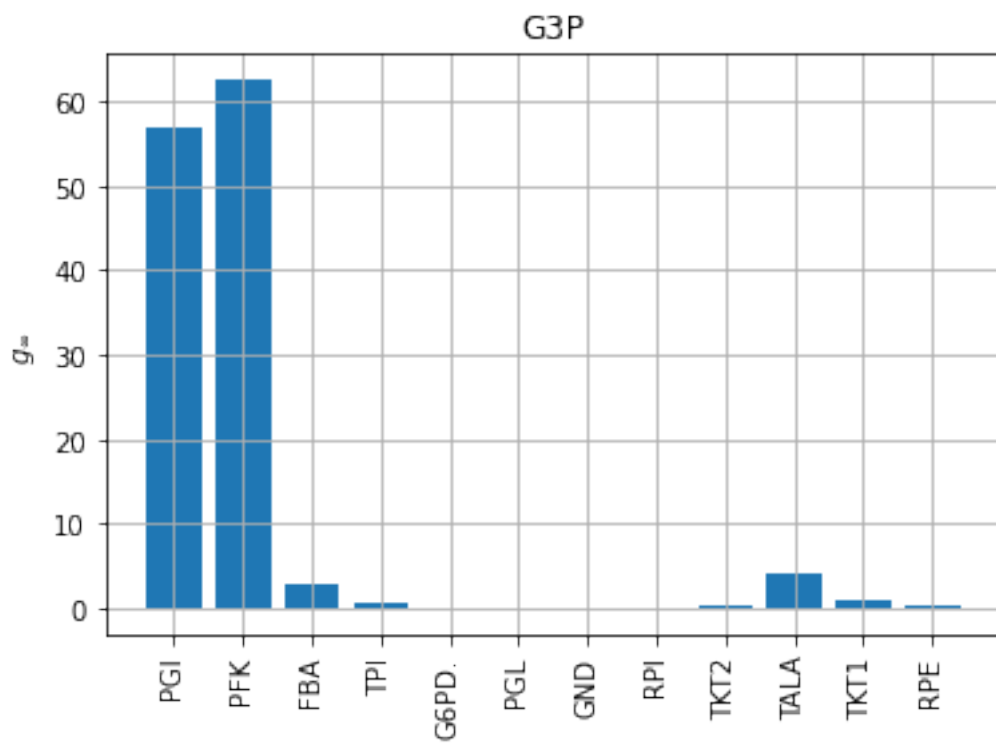


Doing: sTKT1  
kappa\_TKT1  
 $g = 0.7533124901897006$   $\tau = 0$   
 $d\lambda = 10$   
G3P



Doing: sRPE  
 kappa\_RPE  
 $g = 0.18809604636010738$   $\tau = 0.00016682574714716445$   
 $d\lambda = 10$   
 G3P





## 6.5 Vary Lambda

```
[34]: ## Vary Lambda

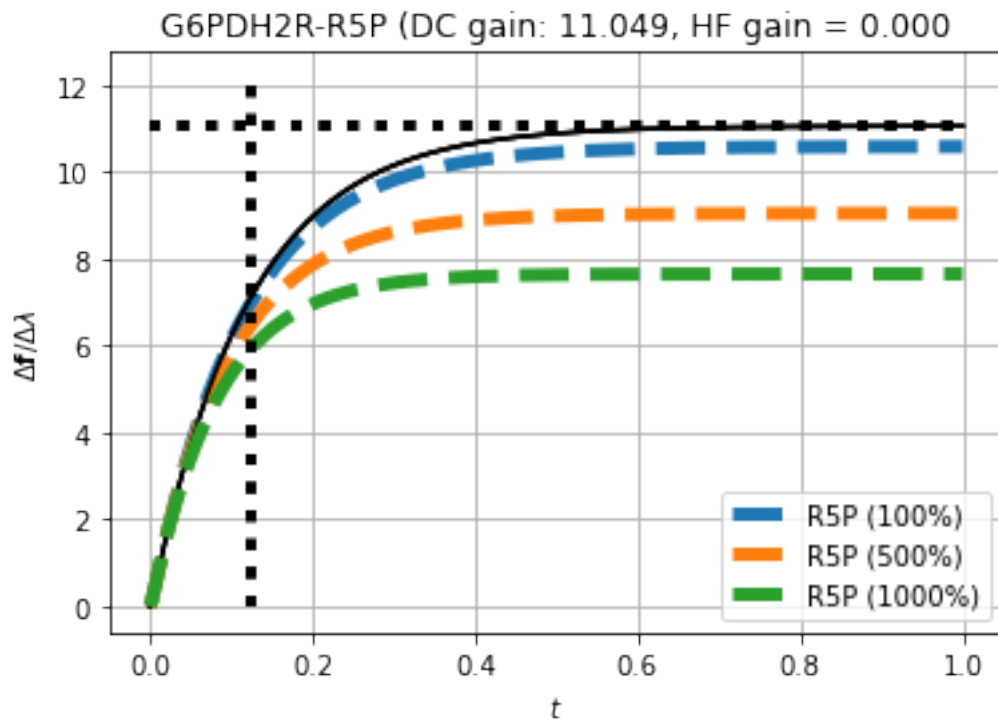
# inp = 'sG6PDH2R'
# outp = ['R5P']
Lin = {}
Nlin = {}
Lam = [1.1,2,6,11]
species = s['species']
for inp in ['sG6PDH2R','sG6P']:
    for outp in ['R5P','NADPH']:
        lin = []
        nlin = []
        for lam in Lam:
            dat,y_step,t,sys = simSensitivity(s,sc,sf,sys,X_ss,V_ss,dX_ss,
            parameter=parameter,inp=[inp],outp=[outp],lam=lam,t_last=t_last)
#             g = con.dcgain(sys)
            g,tau = tfProps(sys)
            g_hf = hfgain(sys)

            lin.append(g)
            i = species.index(outp)
            dX = dat['dX'][-1,i]
            ng = (dX-dX_ss[i])/(lam-1)
            nlin.append(ng)

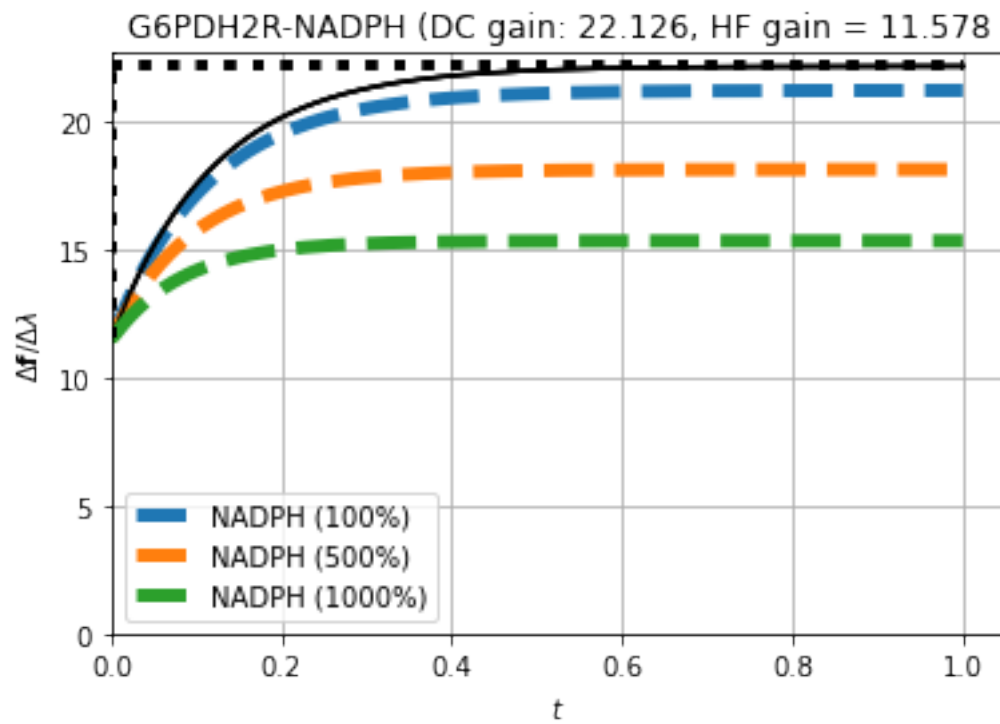
            name = inp[1:]
            Name = f'{name}-{outp}'
            print(f'{Name} (DC gain: {g:.3f}, HF gain = {g_hf:.3f}')
            if Titles:
                plt.title(f'{Name} (DC gain: {g:.3f}, HF gain = {g_hf:.3f}')
            if lam>1.5:
                setZero = outp in ['NADPH']
                plotSensitivitydX(dat,species=[outp],setZero=setZero)
                plotLines()
            Lin[Name] = lin
            Nlin[Name] = nlin
            Savefig(f'PPPdX_{name}_{outp}_lambda')
            plt.show()
# print(Lin)
# print(Nlin)
```

```
kappa_G6PDH2R
G6PDH2R-R5P (DC gain: 11.049, HF gain = 0.000
kappa_G6PDH2R
G6PDH2R-R5P (DC gain: 11.049, HF gain = 0.000
R5P
kappa_G6PDH2R
G6PDH2R-R5P (DC gain: 11.049, HF gain = 0.000
```

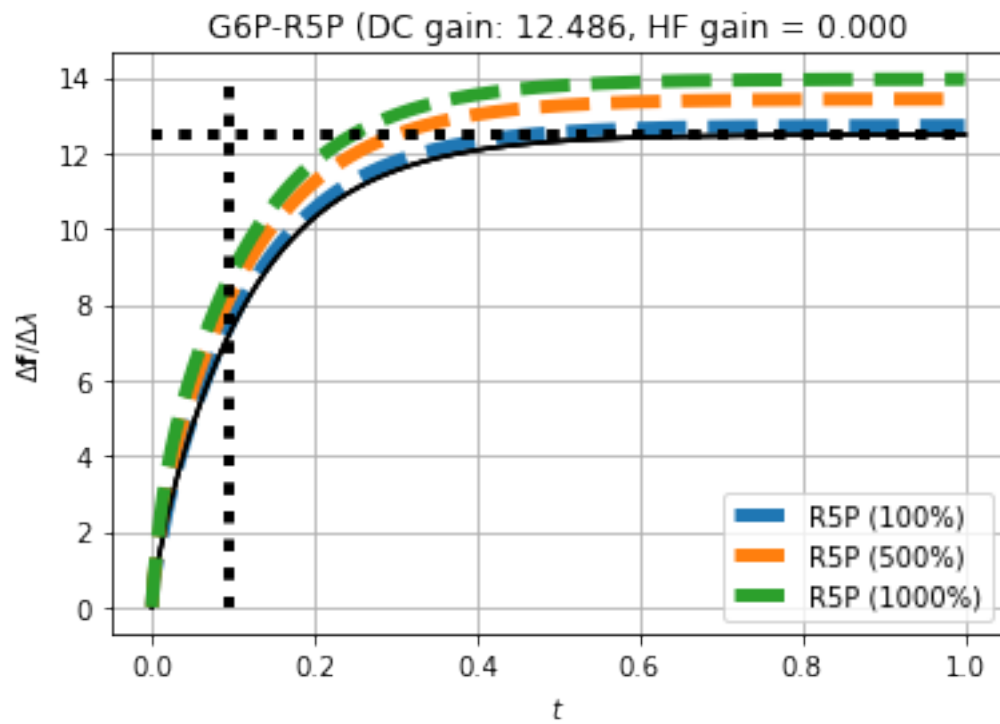
R5P  
kappa\_G6PDH2R  
G6PDH2R-R5P (DC gain: 11.049, HF gain = 0.000  
R5P



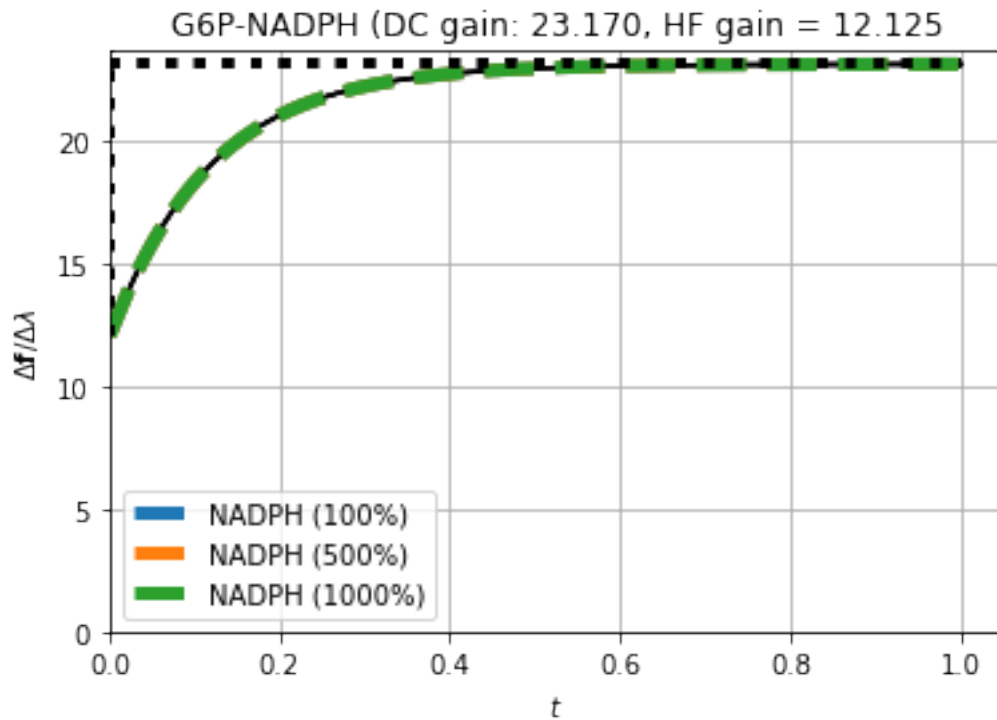
kappa\_G6PDH2R  
G6PDH2R-NADPH (DC gain: 22.126, HF gain = 11.578  
kappa\_G6PDH2R  
G6PDH2R-NADPH (DC gain: 22.126, HF gain = 11.578  
NADPH  
kappa\_G6PDH2R  
G6PDH2R-NADPH (DC gain: 22.126, HF gain = 11.578  
NADPH  
kappa\_G6PDH2R  
G6PDH2R-NADPH (DC gain: 22.126, HF gain = 11.578  
NADPH



K\_G6P  
G6P-R5P (DC gain: 12.486, HF gain = 0.000  
K\_G6P  
G6P-R5P (DC gain: 12.486, HF gain = 0.000  
R5P  
K\_G6P  
G6P-R5P (DC gain: 12.486, HF gain = 0.000  
R5P  
K\_G6P  
G6P-R5P (DC gain: 12.486, HF gain = 0.000  
R5P



K\_G6P  
 G6P-NADPH (DC gain: 23.170, HF gain = 12.125  
 K\_G6P  
 G6P-NADPH (DC gain: 23.170, HF gain = 12.125  
 NADPH  
 K\_G6P  
 G6P-NADPH (DC gain: 23.170, HF gain = 12.125  
 NADPH  
 K\_G6P  
 G6P-NADPH (DC gain: 23.170, HF gain = 12.125  
 NADPH



```
[35]: ## Plot error curves
name = ['a', 'b', 'c', 'd']
lw = [10, 4, 4, 4]
for i, Name in enumerate(Nlin):
    print(Name)
    G = np.array(Lin[Name])
    NG = np.array(Nlin[Name])
    Err = (NG - G) / G
    ErrPC = 100 * Err
    LamPC = (Lam - np.ones(len(Lam))) * 100

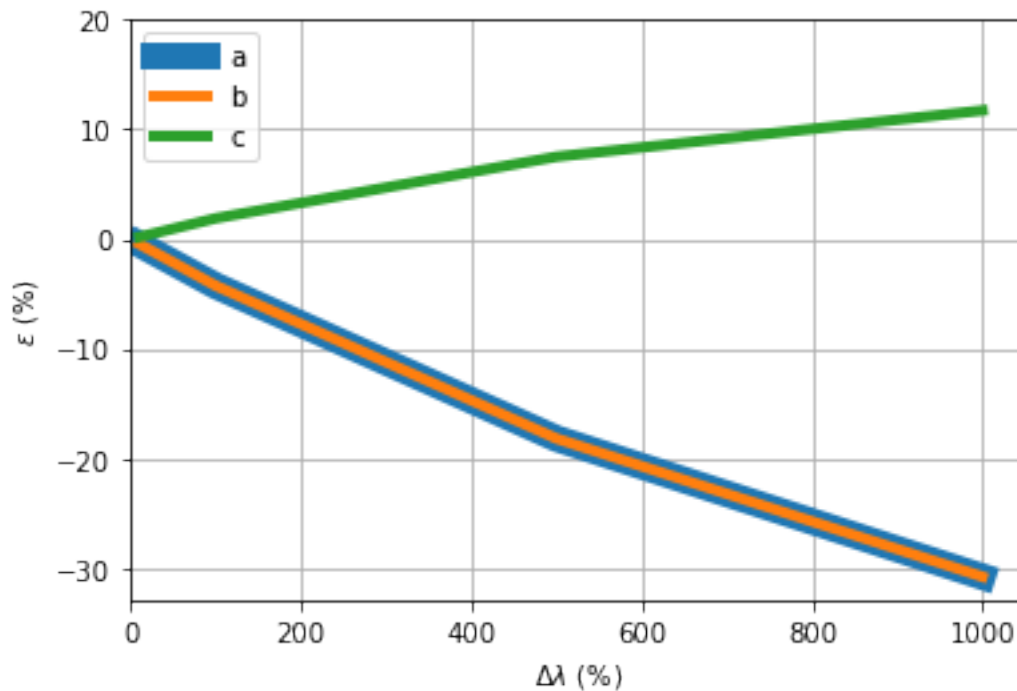
    ## Just plot the first 3
    if i < 3:
        plt.plot(LamPC, ErrPC, label=name[i], lw=lw[i])

plt.legend()
plt.grid()
plt.ylim(top=20)
plt.xlim(left=0)
plt.xlabel(r'$\Delta \lambda$ (%)')
# plt.ylabel(r'$\tilde{\dot{x}} / \tilde{\lambda} - g$ (%)')
plt.ylabel(r'$\epsilon$ (%)')
Savefig(f'PPdX_lambda')
plt.show()
```

G6PDH2R-R5P  
G6PDH2R-NADPH



G6P-R5P  
G6P-NADPH



## 7 Sloppy parameter analysis

```
[36]: imp.reload(slp)
def sloppy(Sys,inp,oup,t=None):

    sys = extractSubsystem(Sys,sc,sf,inp,oup)
    #print(sys)
    H,eig,eigv,t = slp.Sloppy(sys,t=t)
    cond = np.linalg.cond(H)
    print(f'Log10 condition number: {np.log10(cond):.1f}')
    slp.SloppyPrint(eig,eigv,inp)
    slp.SloppyPlot(eig,eigv,inp,square=False)
    #slp.SloppyPlotData(t,y,inp,oup)

def sloppyBoth(Sys,inp,oup,t=None):

    sys = extractSubsystem(Sys,sc,sf,inp,oup)
    #SysName = sc['name']
    blurb = '\n*****\n'
    print(blurb,SysName,blurb)
    if t is None:
        name = f'{SysName}_sloppy_{inp[0]}'
    else:
```

```

        name = f'{SysName}_sloppy_{inp[0]}_long'

        #print(sys)
        H,eig,eigv,t = slp.Sloppy(sys,t=t,GainOnly=False)
        print('H:\n',H)
        slp.SloppyPrint(eig,eigv,inp,min_eig=0)
        H,Eig,Eigv,t = slp.Sloppy(sys,t=t,GainOnly=True)
        print('H_ss:\n',H)
        slp.SloppyPrint(Eig,Eigv,inp,min_eig=0)
        slp.SloppyPlot(eig,eigv,inp,Eig=Eig,Eigv=Eigv)

        Savefig(name)
        plt.show()

for t_last in [0,1e1]:
    if t_last==0:
        t = None
    else:
        t = np.linspace(0,t_last,100)

    SysName = 'GlyPPP_PFK_2'
    inp = ['sG6PDH2R','sPFK']
    outp = ['NADPH','R5P']
    sloppyBoth(Sys,inp,outp,t=t)

    SysName = 'GlyPPP_PFK_all'
    Outp = []
    for chemo in sc['chemostats']:
        if not chemo[0] in ['s']:
            Outp.append(chemo)
    print(Outp)
    sloppyBoth(Sys,inp,Outp,t=t)

    SysName = 'GlyPPP_PGI_all'
    inp = ['sG6PDH2R','sPGI']
    sloppyBoth(Sys,inp,Outp,t=t)

```

```

*****
GlyPPP_PFK_2
*****

```

```

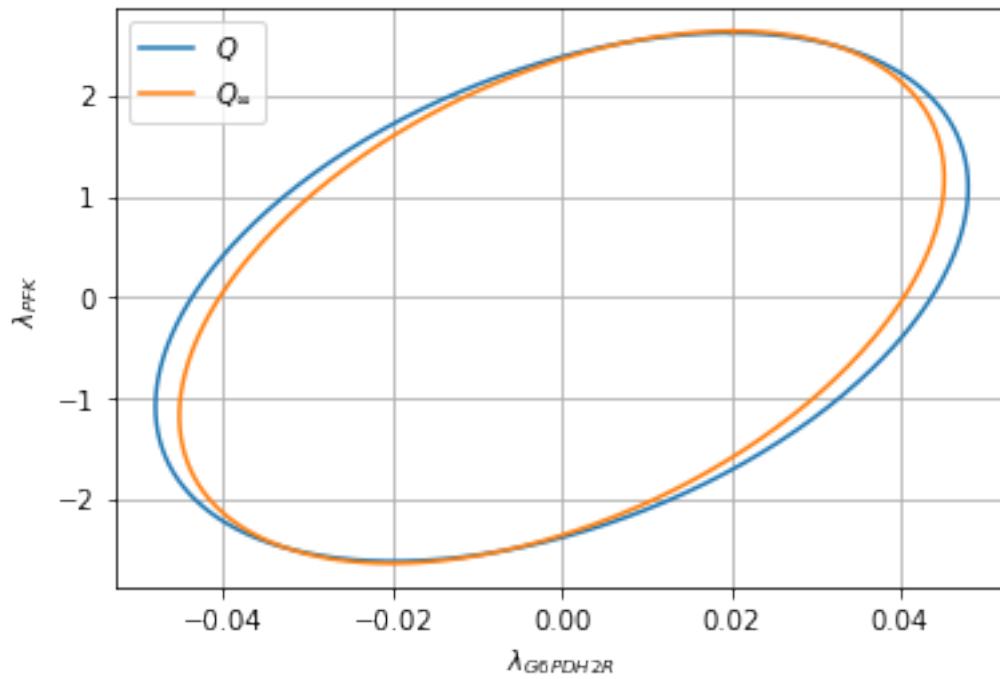
H:
[[ 5.23558279e+02 -3.97898795e+00]
 [-3.97898795e+00  1.76090966e-01]]
\sqrt{\sigma_1} &= 23 & V_1\Lambda &= + 1.00 \lambda_{G6PDH2R} - 0.01
\lambda_{PFK}
\sqrt{\sigma_2} &= 0.38 & V_2\Lambda &= + 1.00 \lambda_{PFK} + 0.01
\lambda_{G6PDH2R}
H_ss:

```

```

[[ 6.12e+02 -4.68e+00]
[-4.68e+00  1.79e-01]]
\sqrt{\sigma_1} \&= 25 \& V_1\Lambda \&= + 1.00 \lambda_{\{G6PDH2R\}} - 0.01
\lambda_{\{PFK\}}
\sqrt{\sigma_2} \&= 0.38 \& V_2\Lambda \&= + 1.00 \lambda_{\{PFK\}} + 0.01
\lambda_{\{G6PDH2R\}}

```



```

['ADP', 'ATP', 'CO2', 'G6P', 'H', 'H2O', 'NADP', 'NADPH', 'R5P', 'G3P']

```

```

*****
GlyPPP_PFK_all
*****

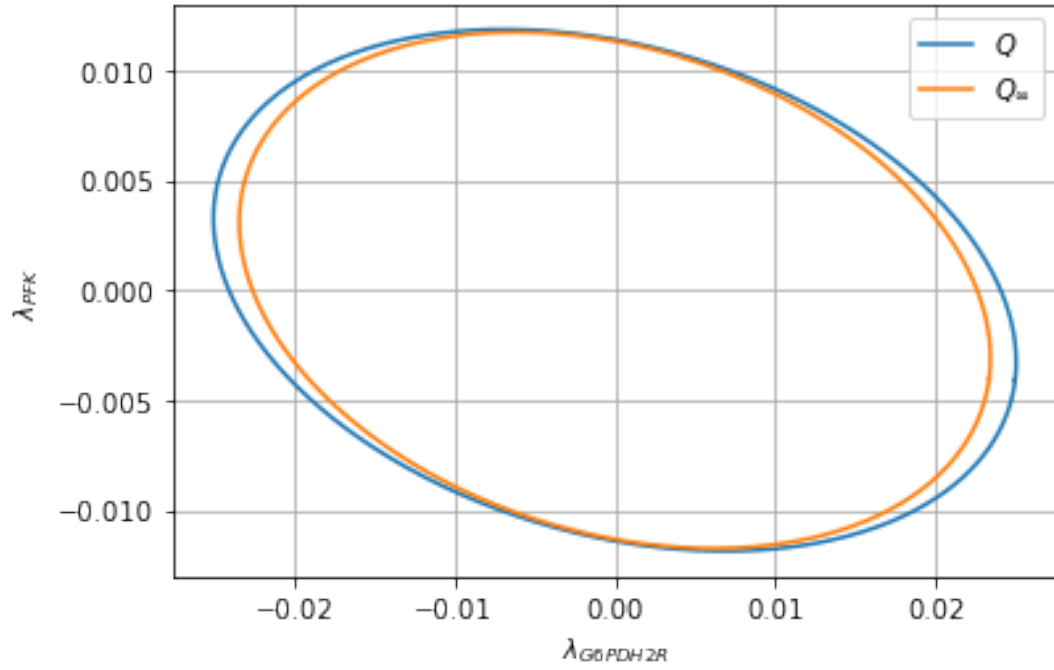
```

H:

```

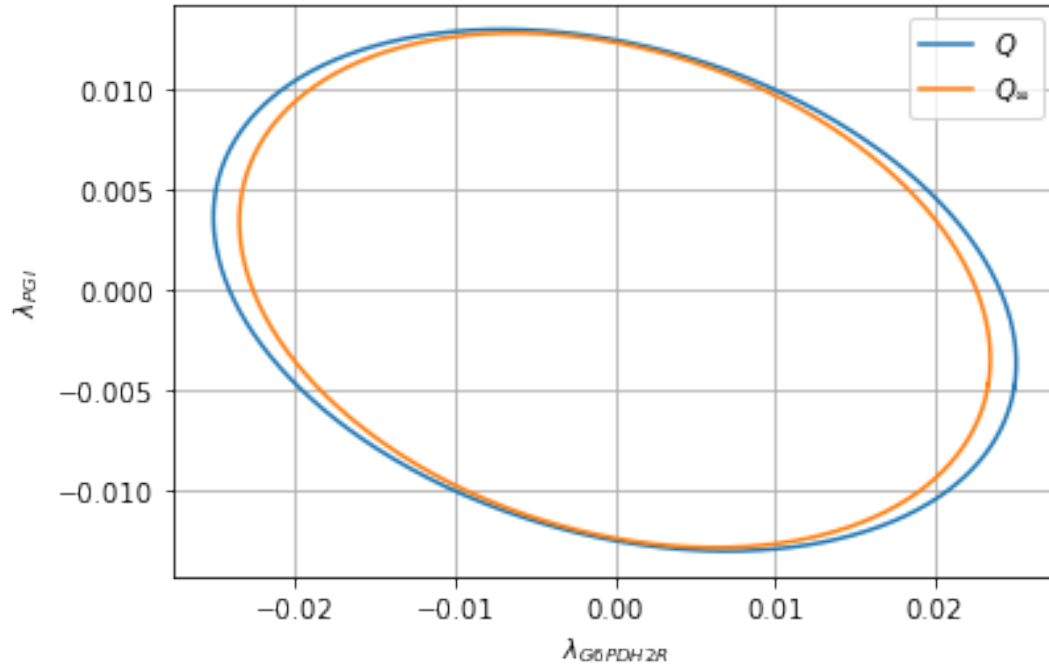
[[1726.16 1001.12]
[1001.12 7677.69]]
\sqrt{\sigma_1} \&= 89 \& V_1\Lambda \&= + 0.99 \lambda_{\{PFK\}} + 0.16
\lambda_{\{G6PDH2R\}}
\sqrt{\sigma_2} \&= 40 \& V_2\Lambda \&= + 0.99 \lambda_{\{G6PDH2R\}} - 0.16
\lambda_{\{PFK\}}
H_ss:
[[1958.04 1028.65]
[1028.65 7785.82]]
\sqrt{\sigma_1} \&= 89 \& V_1\Lambda \&= + 0.99 \lambda_{\{PFK\}} + 0.17
\lambda_{\{G6PDH2R\}}
\sqrt{\sigma_2} \&= 42 \& V_2\Lambda \&= + 0.99 \lambda_{\{G6PDH2R\}} - 0.17
\lambda_{\{PFK\}}

```



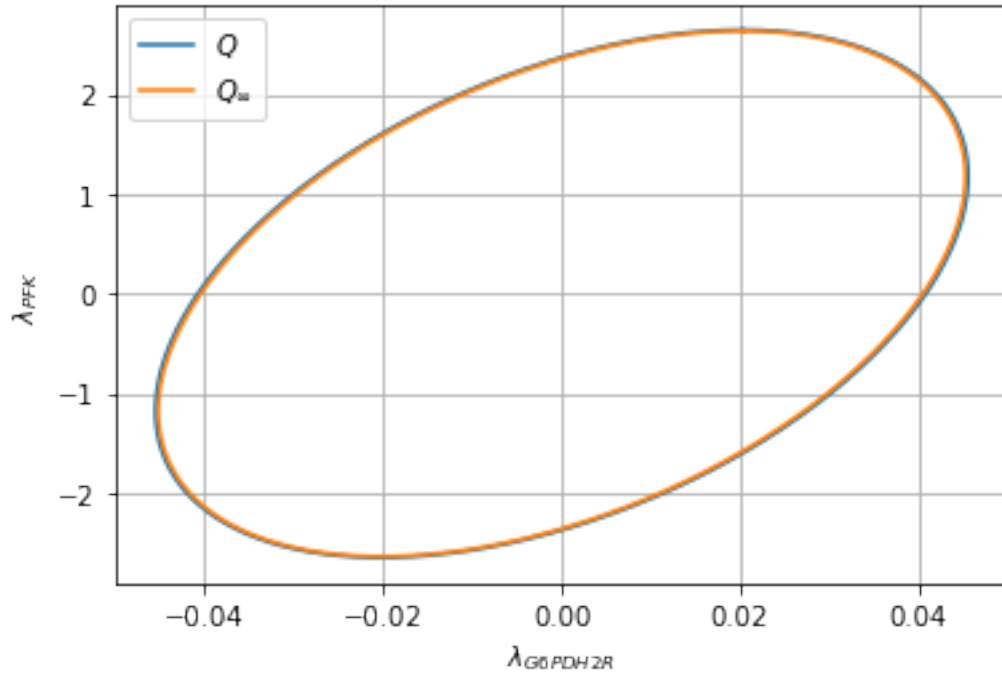
```
*****
GlyPPP_PGI_all
*****
```

```
H:
[[1726.16  928.88]
 [ 928.88 6383.28]]
\sqrt{\sigma_1} &= 81 & V_1\Lambda &= + 0.98 \lambda_{PGI} + 0.19
\lambda_{G6PDH2R}
\sqrt{\sigma_2} &= 39 & V_2\Lambda &= + 0.98 \lambda_{G6PDH2R} - 0.19
\lambda_{PGI}
H_ss:
[[1958.04  955.61]
 [ 955.61 6511.65]]
\sqrt{\sigma_1} &= 82 & V_1\Lambda &= + 0.98 \lambda_{PGI} + 0.20
\lambda_{G6PDH2R}
\sqrt{\sigma_2} &= 42 & V_2\Lambda &= + 0.98 \lambda_{G6PDH2R} - 0.20
\lambda_{PGI}
```



```
*****
GlyPPP_PFK_2
*****
```

```
H:
[[ 6.02e+02 -4.60e+00]
 [-4.60e+00  1.78e-01]]
\sqrt{\sigma_1} &= 25 & V_1\Lambda &= + 1.00 \lambda_{G6PDH2R} - 0.01
\lambda_{PFK}
\sqrt{\sigma_2} &= 0.38 & V_2\Lambda &= + 1.00 \lambda_{PFK} + 0.01
\lambda_{G6PDH2R}
H_ss:
[[ 6.12e+02 -4.68e+00]
 [-4.68e+00  1.79e-01]]
\sqrt{\sigma_1} &= 25 & V_1\Lambda &= + 1.00 \lambda_{G6PDH2R} - 0.01
\lambda_{PFK}
\sqrt{\sigma_2} &= 0.38 & V_2\Lambda &= + 1.00 \lambda_{PFK} + 0.01
\lambda_{G6PDH2R}
```



['ADP', 'ATP', 'CO2', 'G6P', 'H', 'H2O', 'NADP', 'NADPH', 'R5P', 'G3P']

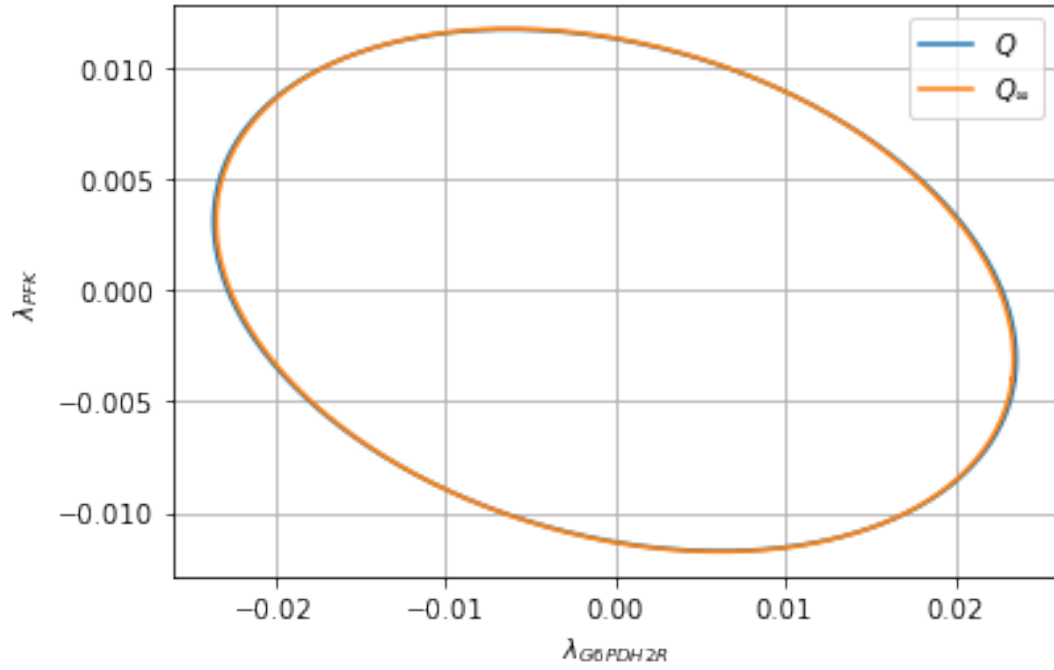
\*\*\*\*\*  
 GlyPPP\_PFK\_all  
 \*\*\*\*\*

H:

```
[[1930.92 1024.22]
 [1024.22 7827.07]]
\sqrt{\sigma_1} &= 89 & V_1\Lambda &= + 0.99 \lambda_{PFK} + 0.17
\lambda_{G6PDH2R}
\sqrt{\sigma_2} &= 42 & V_2\Lambda &= + 0.99 \lambda_{G6PDH2R} - 0.17
\lambda_{PFK}
```

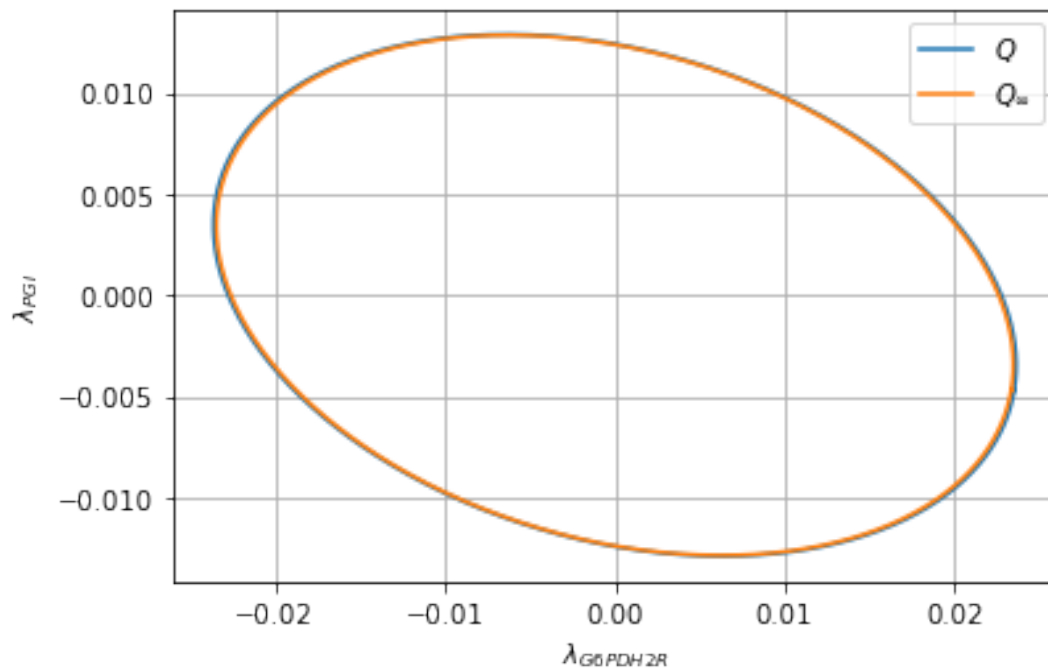
H\_ss:

```
[[1958.04 1028.65]
 [1028.65 7785.82]]
\sqrt{\sigma_1} &= 89 & V_1\Lambda &= + 0.99 \lambda_{PFK} + 0.17
\lambda_{G6PDH2R}
\sqrt{\sigma_2} &= 42 & V_2\Lambda &= + 0.99 \lambda_{G6PDH2R} - 0.17
\lambda_{PFK}
```



```
*****
GlyPPP_PGI_all
*****
```

```
H:
[[1930.92  951.55]
 [ 951.55 6481.53]]
\sqrt{\sigma_1} &= 82 & V_1\Lambda &= + 0.98 \lambda_{PGI} + 0.20
\lambda_{G6PDH2R}
\sqrt{\sigma_2} &= 42 & V_2\Lambda &= + 0.98 \lambda_{G6PDH2R} - 0.20
\lambda_{PGI}
H_ss:
[[1958.04  955.61]
 [ 955.61 6511.65]]
\sqrt{\sigma_1} &= 82 & V_1\Lambda &= + 0.98 \lambda_{PGI} + 0.20
\lambda_{G6PDH2R}
\sqrt{\sigma_2} &= 42 & V_2\Lambda &= + 0.98 \lambda_{G6PDH2R} - 0.20
\lambda_{PGI}
```



```
[37]: imp.reload(slp)
      Outp = ['R5P', 'NADPH', 'G3P']
      # Outp = ['R5P']
      def PrintSloppy(Inp, Outp, GainOnly=True):
          blurb = '\n*****\n'
          for outp in Outp:
              print(blurb, outp, blurb)
              sys = extractSubsystem(Sys, sc, sf, Inp, [outp])
              # print(con.dcgain(sys))
              gain = con.dcgain(sys)[0]
              norm = np.sum(gain*gain)
              ngain = gain/np.sqrt(norm)
              # print(norm, gain/np.sqrt(norm))
              H, eig, eigv, t = slp.Sloppy(sys, GainOnly=GainOnly, small=1e-10)
              slp.SloppyPrint(eig, eigv, Inp, min_eig=0.01, min_eigv=0.1, max_eigs=5)
              if GainOnly:
                  print('Direct')
                  slp.SloppyPrint([norm], np.array([ngain]).T, Inp, min_eig=0.
→01, min_eigv=0.1, max_eigs=5)
              # print(eigv[:,0])
              # print(ngain)

      ## Reactions
      for GainOnly in [True, False]:
          print('\nGainOnly =', GainOnly)
          PrintSloppy(Inp_reac, Outp, GainOnly=GainOnly)
```

GainOnly = True



\*\*\*\*\*

R5P

\*\*\*\*\*

$\sqrt{\sigma_1} = 12 \cdot V_1 \cdot \lambda + 0.93 \cdot \lambda_{\text{G6PDH2R}} - 0.35$

$\lambda_{\text{TALA}}$

Direct

$\sqrt{\sigma_1} = 12 \cdot V_1 \cdot \lambda + 0.93 \cdot \lambda_{\text{G6PDH2R}} - 0.35$

$\lambda_{\text{TALA}}$

\*\*\*\*\*

NADPH

\*\*\*\*\*

$\sqrt{\sigma_1} = 22 \cdot V_1 \cdot \lambda + 1.00 \cdot \lambda_{\text{G6PDH2R}}$

Direct

$\sqrt{\sigma_1} = 22 \cdot V_1 \cdot \lambda + 1.00 \cdot \lambda_{\text{G6PDH2R}}$

\*\*\*\*\*

G3P

\*\*\*\*\*

$\sqrt{\sigma_1} = 85 \cdot V_1 \cdot \lambda + 0.74 \cdot \lambda_{\text{PFK}} + 0.67 \cdot \lambda_{\text{PGI}}$

Direct

$\sqrt{\sigma_1} = 85 \cdot V_1 \cdot \lambda + 0.74 \cdot \lambda_{\text{PFK}} + 0.67 \cdot \lambda_{\text{PGI}}$

GainOnly = False

\*\*\*\*\*

R5P

\*\*\*\*\*

$\sqrt{\sigma_1} = 11 \cdot V_1 \cdot \lambda + 0.91 \cdot \lambda_{\text{G6PDH2R}} - 0.38$

$\lambda_{\text{TALA}} + 0.15 \cdot \lambda_{\text{GND}}$

$\sqrt{\sigma_2} = 3 \cdot V_2 \cdot \lambda + 0.94 \cdot \lambda_{\text{GND}} - 0.25 \cdot \lambda_{\text{G6PDH2R}}$

$- 0.21 \cdot \lambda_{\text{TALA}}$

\*\*\*\*\*

NADPH

\*\*\*\*\*

$\sqrt{\sigma_1} = 21 \cdot V_1 \cdot \lambda + 0.99 \cdot \lambda_{\text{G6PDH2R}} + 0.11$

$\lambda_{\text{GND}}$

$\sqrt{\sigma_2} = 2.7 \cdot V_2 \cdot \lambda + 0.99 \cdot \lambda_{\text{GND}} - 0.11$

$\lambda_{\text{G6PDH2R}}$

\*\*\*\*\*

G3P

\*\*\*\*\*

```
\sqrt{\sigma_1} \&= 76 \& V_1 \backslash \Lambda \&= + 0.74 \backslash \lambda_{\text{PFK}} + 0.65 \backslash \lambda_{\text{PGI}} +
0.16 \backslash \lambda_{\text{FBA}}
\sqrt{\sigma_2} \&= 26 \& V_2 \backslash \Lambda \&= + 0.94 \backslash \lambda_{\text{FBA}} + 0.29 \backslash \lambda_{\text{TPI}} -
0.17 \backslash \lambda_{\text{PGI}}
```

```
[38]: ## Chemostats
for GainOnly in [True,False]:
    print('\nGainOnly =',GainOnly)
    PrintSloppy(Inp_chemo,Outp,GainOnly=GainOnly)
```

GainOnly = True

\*\*\*\*\*

R5P

\*\*\*\*\*

```
\sqrt{\sigma_1} \&= 21 \& V_1 \backslash \Lambda \&= + 0.59 \backslash \lambda_{\text{G6P}} + 0.57 \backslash \lambda_{\text{NADP}} -
0.56 \backslash \lambda_{\text{R5P}}
```

Direct

```
\sqrt{\sigma_1} \&= 21 \& V_1 \backslash \Lambda \&= + 0.59 \backslash \lambda_{\text{G6P}} + 0.57 \backslash \lambda_{\text{NADP}} -
0.56 \backslash \lambda_{\text{R5P}}
```

\*\*\*\*\*

NADPH

\*\*\*\*\*

```
\sqrt{\sigma_1} \&= 34 \& V_1 \backslash \Lambda \&= + 0.72 \backslash \lambda_{\text{NADP}} + 0.69 \backslash \lambda_{\text{G6P}}
```

Direct

```
\sqrt{\sigma_1} \&= 34 \& V_1 \backslash \Lambda \&= + 0.72 \backslash \lambda_{\text{NADP}} + 0.69 \backslash \lambda_{\text{G6P}}
```

\*\*\*\*\*

G3P

\*\*\*\*\*

```
\sqrt{\sigma_1} \&= 1.4e+02 \& V_1 \backslash \Lambda \&= + 0.87 \backslash \lambda_{\text{G6P}} + 0.48
\backslash \lambda_{\text{ATP}}
```

Direct

```
\sqrt{\sigma_1} \&= 1.4e+02 \& V_1 \backslash \Lambda \&= + 0.87 \backslash \lambda_{\text{G6P}} + 0.48
\backslash \lambda_{\text{ATP}}
```

GainOnly = False

\*\*\*\*\*

R5P

\*\*\*\*\*

```
\sqrt{\sigma_1} \&= 1.5e+03 \& V_1 \backslash \Lambda \&= + 1.00 \backslash \lambda_{\text{R5P}}
```

\*\*\*\*\*

NADPH

\*\*\*\*\*

\sqrt{\sigma\_1} \&= 32 \& V\_1 \backslash \text{Lambda} \&= + 0.74 \backslash \lambda\_{\text{NADP}} + 0.67 \backslash \lambda\_{\text{G6P}}

\*\*\*\*\*

G3P

\*\*\*\*\*

\sqrt{\sigma\_1} \&= 1.3e+02 \& V\_1 \backslash \text{Lambda} \&= + 0.86 \backslash \lambda\_{\text{G6P}} + 0.48

\lambda\_{\text{ATP}} - 0.16 \backslash \lambda\_{\text{G3P}}

\sqrt{\sigma\_2} \&= 48 \& V\_2 \backslash \text{Lambda} \&= + 0.98 \backslash \lambda\_{\text{G3P}} + 0.17 \backslash \lambda\_{\text{G6P}}

[39]: *## Three outputs*

```
Outp = ['R5P', 'NADPH', 'G3P']
sys = extractSubsystem(Sys, sc, sf, Inp, Outp)
for GainOnly in [True, False]:
    print('\nGainOnly =', GainOnly)
    H, eig, eigv, t = slp.Sloppy(sys, GainOnly=GainOnly, small=1e-10)
    slp.SloppyPrint(eig, eigv, Inp, min_eig=1e-3, min_eigv=0.1, max_eigs=4)
```

GainOnly = True

\sqrt{\sigma\_1} \&= 85 \& V\_1 \backslash \text{Lambda} \&= + 0.74 \backslash \lambda\_{\text{PFK}} + 0.67 \backslash \lambda\_{\text{PGI}}

\sqrt{\sigma\_2} \&= 25 \& V\_2 \backslash \text{Lambda} \&= + 1.00 \backslash \lambda\_{\text{G6PDH2R}}

\sqrt{\sigma\_3} \&= 3.8 \& V\_3 \backslash \text{Lambda} \&= + 0.97 \backslash \lambda\_{\text{TALA}} + 0.18 \backslash \lambda\_{\text{TKT1}} - 0.14 \backslash \lambda\_{\text{PGI}}

GainOnly = False

\sqrt{\sigma\_1} \&= 83 \& V\_1 \backslash \text{Lambda} \&= + 0.74 \backslash \lambda\_{\text{PFK}} + 0.67 \backslash \lambda\_{\text{PGI}}

\sqrt{\sigma\_2} \&= 23 \& V\_2 \backslash \text{Lambda} \&= + 0.99 \backslash \lambda\_{\text{G6PDH2R}} + 0.12

\lambda\_{\text{GND}}

\sqrt{\sigma\_3} \&= 11 \& V\_3 \backslash \text{Lambda} \&= + 0.95 \backslash \lambda\_{\text{FBA}} + 0.29 \backslash \lambda\_{\text{TPI}}

\sqrt{\sigma\_4} \&= 4.3 \& V\_4 \backslash \text{Lambda} \&= + 0.73 \backslash \lambda\_{\text{GND}} - 0.64 \backslash \lambda\_{\text{TALA}}

- 0.14 \backslash \lambda\_{\text{G6PDH2R}} - 0.14 \backslash \lambda\_{\text{TKT1}}

[40]: *## All outputs*

```
for chemo in sc['chemostats']:
    if not chemo[0] in ['s']:
        Outp.append(chemo)
print(Outp)
sys = extractSubsystem(Sys, sc, sf, Inp, Outp)

for GainOnly in [True, False]:
    print('\nGainOnly =', GainOnly)
    H, eig, eigv, t = slp.Sloppy(sys, GainOnly=GainOnly, small=1e-10)
    slp.SloppyPrint(eig, eigv, Inp, min_eig=0.001, min_eigv=0.1, max_eigs=4)
```

['R5P', 'NADPH', 'G3P', 'ADP', 'ATP', 'CO2', 'G6P', 'H', 'H2O', 'NADP', 'NADPH', 'R5P', 'G3P']

GainOnly = True

\sqrt{\sigma\_1} \&= 1.5e+02 \& V\_1 \backslash \text{Lambda} \&= + 0.74 \backslash \lambda\_{\text{PFK}} + 0.67

```

\lambda_{PGI}
\sqrt{\sigma_2} \&= 50 \& V_2\Lambda \&= + 0.99 \lambda_{G6PDH2R}
\sqrt{\sigma_3} \&= 6.3 \& V_3\Lambda \&= + 0.97 \lambda_{TALA} + 0.18 \lambda_{TKT1}
- 0.13 \lambda_{PGI}

```

```

GainOnly = False
\sqrt{\sigma_1} \&= 1.5e+02 \& V_1\Lambda \&= + 0.74 \lambda_{PFK} + 0.67
\lambda_{PGI}
\sqrt{\sigma_2} \&= 47 \& V_2\Lambda \&= + 0.99 \lambda_{G6PDH2R} + 0.11
\lambda_{GND}
\sqrt{\sigma_3} \&= 16 \& V_3\Lambda \&= + 0.95 \lambda_{FBA} + 0.29 \lambda_{TPI}
\sqrt{\sigma_4} \&= 7.4 \& V_4\Lambda \&= + 0.92 \lambda_{GND} - 0.35 \lambda_{TALA}
- 0.12 \lambda_{G6PDH2R}

```

[ ]: