GadsCooperativityEstimateProgram

```
import numpy as np
```

```
from scipy.integrate import odeint, quad
```

```
from scipy import optimize
```

```
import matplotlib.pyplot as plt
```

```
%matplotlib inline
```

Import and Plot Experimental Data

In [2]:

```
# WT exp. data in uM
```

```
WT_raw_exp_y=np.array([0.294207761,0.26337707,0.23638426,0.214669316,0.179110633])
```

```
sd_WT=np.array([0.000117522,0.00033228,0.000167249,0.000169248,6.7524E-05])
```

```

```

```
# F92D exp. data in uM
```

```
F2D_raw_exp_y = np.array([0.271768565,0.213041181,0.184558209,0.172836008,0.15602546])
```

```
sd_F2D=np.array([0.000172372,0.000113375,0.000101194,0.000195189,0.000130786])
```

```

```

```
# 1pY-LAT exp. concentration in uM
```

```
L0_exp = np.array([0,5,10,15,20])
```

In [3]:

```
# Plot the Experimental Data
```

```
plt.figure(1)
```

```
plt.errorbar(L0_exp,F2D_raw_exp_y,yerr=sd_F2D,fmt='--o') # plot for F92D mutant
```

```
plt.errorbar(L0_exp,WT_raw_exp_y,yerr=sd_WT,fmt='--o') # plot for WT
```

```
plt.title('[Gads dimer] vs. [1Yp-LAT]')
```

```
plt.xlabel('[1Yp-LAT], uM')
```

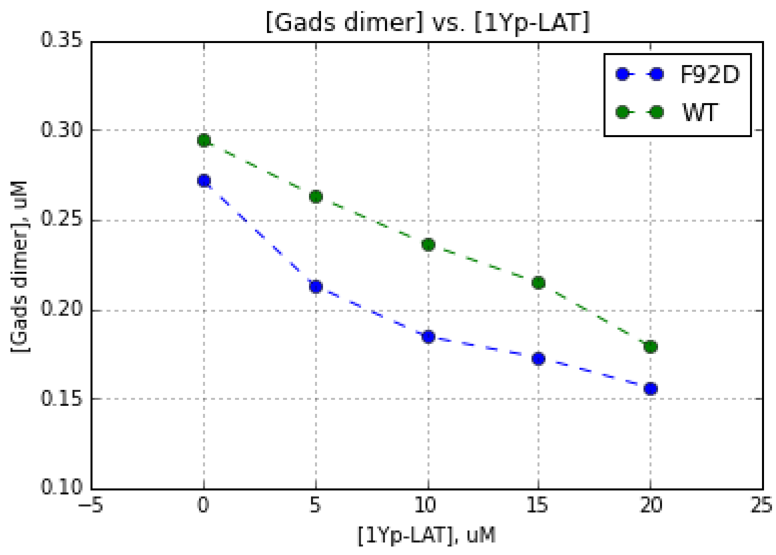
```
plt.ylabel('[Gads dimer], uM')
```

```
plt.legend(['F92D','WT'])
```

```
plt.axis([-5,25,0.10,0.35])
```

```
plt.grid(True)
```

```
plt.show()
```



```
# IMPORTANT: Set fitting till 20 uM
```

```
cut = 5 # 5 # equals 5 for fitting till 20 uM
```

```

```

```
# IMPORTANT: Select the Data Set Here
```

```
raw_exp_y = F2D_raw_exp_y # WT_raw_exp_y or F2D_raw_exp_y
```

```
raw_exp_y = raw_exp_y[0:cut]
```

```

```

```
# Exp. data converted from uM to computational units of number of molecules
```

```
exp_y=raw_exp_y*50/(0.7*0.5)
```

Parameters Used in Calculations in Computer Units

In [5]:

```
# Concentrations
```

```
G=35 # Gads = 0.7 uM
```

```
L=250 # 2pY-LAT = 5 uM
```

```
L0=L0_exp*50 # convert 1pY-LAT concentration to computer units
```

```
L0=L0[0:cut]
```

```

```

```
# Monomeric Rate Constants
```

```
# for WT: kon = 4.52 1/(uM*s) = 0.09 1/(molec*s)
```

```
# for F92D: kon = 1.70 1/(uM*s) = 0.03 1/(molec*s)
# koff = 0.8 1/s
```

```
kon = 0.03 # IMPORTANT: Select the Corresponding System Here !!!
```

```
koff = 0.8
```

```
kon_m = kon
```

```
koff_m = koff
```

```
kon_m2 = kon
```

```
koff_m2 = koff
```

```
kon_d = kon
```

```
koff_d = koff
```

```
k1 = kon_m # kon of 2pY-LAT: G + L -> L01
```

```
k2 = kon_m # kon of 2pY-LAT: G + L -> L10
```

```
k3 = koff_m # koff of 2pY-LAT: G + L <- L01
```

```
k4 = koff_m # koff of 2pY-LAT: G + L <- L10
```

```
k5 = kon # kon of 1pY-LAT: G + L0 -> L0_10
```

```
k6 = koff # koff of 1pY-LAT: G + L0 <- L0_10
```

```

```

```
# Unknown Rate Constants
```

```
# 1) Dimer Formation from Gads-bound LAT Monomers
```

```
k7 = kon_m2 # kon of 2pY-LAT: G + L01 -> L11
```

```
k8 = kon_m2 # kon of 2pY-LAT: G + L10 -> L11
```

```
k9 = koff_m2 # koff of 2pY-LAT: G + L01 <- L11
```

```
k10 = koff_m2 # koff_m2 # koff of 2pY-LAT: G + L10 <- L11
```

```

```

```
# 2) Dimer Formation Overall
```

```
k11 = kon_d # kon of 2G + L -> L11
```

```
k12 = koff_d # koff of 2G + L <- L11
```

```

```

```
# Set up Time for Calculations
```

```
t_graph = np.arange(0, 600, 0.1)
```

```
P=[] # initialize array for RSS = COST function
```

```
X=[]
```

```python

def func(param,i):
    p0 = [G,L,0,0,0,L0[i],0]
    soln=odeint(calc,p0,t_graph,args=(param,),mxstep=10000)
    R3 = soln[:,3]
    diff = R3[-1]-exp_y[i]
    return diff

def obj_fun(x):
    return np.sum((func(x,j)**2 for j in range(0,len(L0))),axis=0)

# specify initial condition
num=1e-4 # for a full model: WT and F92D num = 1e-4
         # for a simplified model: WT and F92D num = 1e-6
x0=[num,num,num] # intial parameter guess
bounds=[(num,None)]*3 # boundaries for parameter optimization

x,f,d = optimize.fmin_l_bfgs_b(obj_fun, x0=x0, approx_grad=True,bounds=bounds)
```

```
```

```
k9,k10,k12 = x # for a full model
```

```
print k9,k10,k12
```

```
```

```
#k11,k12 = x # for simplified model
```

```
#print k11,k12
```

```
```

```
print f
```

```
print d
```

```
0.00199529511967 0.00199629181168 0.0445917853694
8.88481096268
{'warnflag': 0, 'task': 'CONVERGENCE: REL_REDUCTION_OF_F_<=_FACTR*EPSMCH', 'grad':
array([ -4.65927918,  17.25476846,  61.88377721]), 'nit': 15, 'funcalls': 172}
```

Results: Fitting the Experimental Data Using the Optimized Parameter

In [8]:

```
param = [k9,k10,k12] # optimized parameters
```

```
#param = [k11,k12]
```

```
result=[] # initialize the result array
```

```
for i in range(0,len(L0)):
```

```
    p0 = [G,L,0,0,0,L0[i],0]
    soln=odeint(calc,p0,t_graph,args=(param,))
```

```
    R3 = soln[:,3]
```

```
    result.append(R3[-1])
```

```
# Compare the experimenal and calculated results using the oprimized parameter
```

```
result=np.array(result)
```

```
print "Calculated Gads dimer in uM"
```

```
print result*0.7*0.5/50 # convert the results from computer to experimental units
```

```
print "Experimental Gads dimer in uM"
```

```
print raw_exp_y
```

```

```

```
# Calculate R^2
```

```
from sklearn.metrics import r2_score
```

```
y_true = raw_exp_y
```

```
y_pred = result*0.7*0.5/50
```

```

```

```
print "R^2 value:"
```

```
print 'R^2 =', round(r2_score(y_true, y_pred),2)
```

```
Calculated Gads dimer in uM
[ 0.26080334  0.22482422  0.19477616  0.16953087  0.14821846]
```

```
Experimental Gads dimer in uM
[ 0.27176857  0.21304118  0.18455821  0.17283601  0.15602546]
R^2 value:
R^2 = 0.95
```

In [10]:

```
# Plot the calculated and experimental results
```

```
plt.figure(1)
```

```
plt.plot(L0/50,raw_exp_y,'ko')
```

```
plt.plot(L0/50,result*0.7*0.5/50,'bo')
```

```
plt.title('[F92D Gads dimer] vs. [1Yp-LAT]')
```

```
plt.xlabel('[1Yp-LAT], uM')
```

```
plt.ylabel('[Gads dimer], uM')
```

```
plt.legend(['Experiment','Calculations'])
```

```
plt.axis([-5,25,0.10,0.35])
```

```
plt.grid(True)
```

```
plt.show()
```

```

```

```
plt.figure(2)
```

```
plt.plot(raw_exp_y,raw_exp_y,'ko',raw_exp_y,result*0.7*0.5/50,'bo')
```

```
plt.title('Calc. vs. Exp. Data')
```

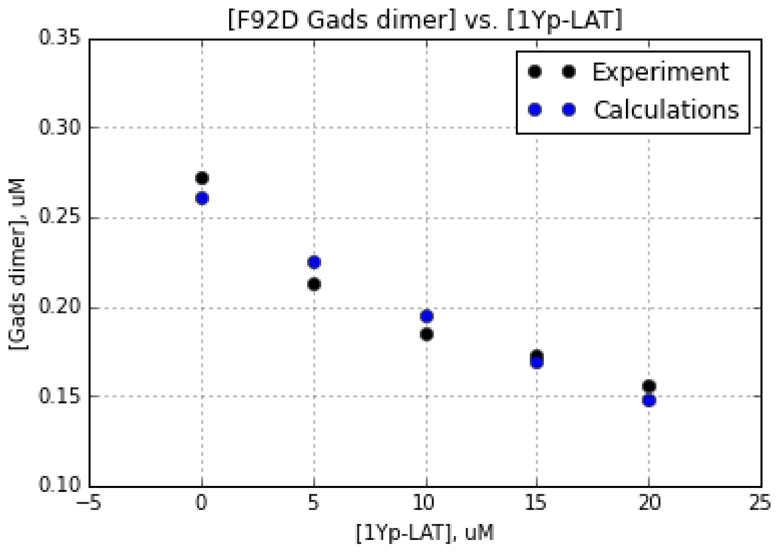
```
plt.xlabel('Exp. Data, uM')
plt.ylabel('Calc. Data, uM')
```

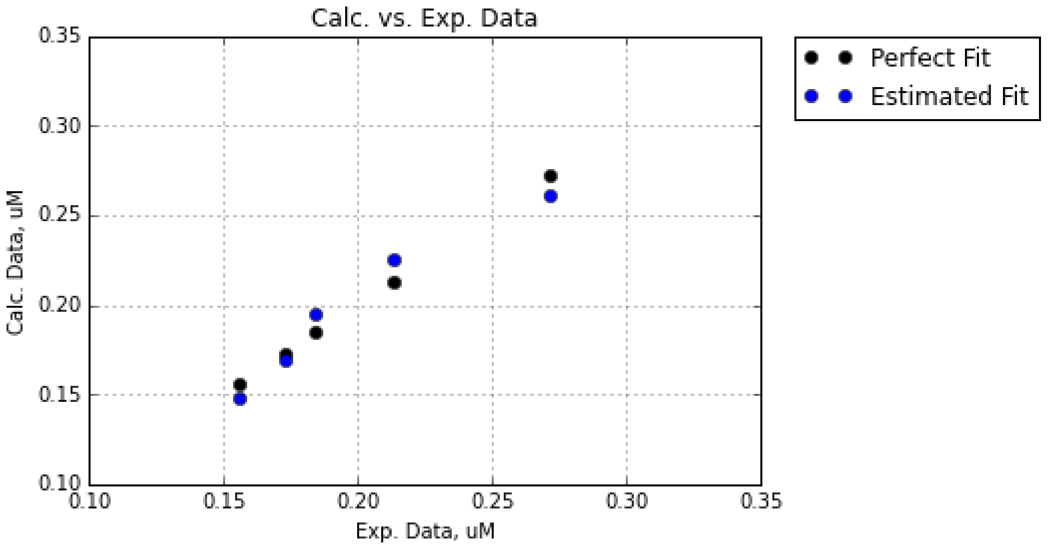
```
plt.legend(['Perfect Fit','Estimated Fit'],bbox_to_anchor=
(1.05,1),loc=2,borderaxespad=0.)
```

```
plt.axis([0.10,0.35,0.10,0.35])
```

```
plt.grid(True)
```

```
plt.show()
```





Calculations of Cooperativity and Binding Constants

In [11]:

```
# convert kon rates from computer to exp. units
```

```
k11 = k11 * 2.31 * 1e+3 * 1e+12 # in 1/(s*M**2)
```

```
k7 = k7 * 50 * 1e+6 # in 1/(M*s)
```

```
k8 = k8 * 50 * 1e+6 # in 1/(M*s)
```

```

```

```
# Experimental Values for KA1 for WT and F92D
```

```
WT_KA1 = 5.65 * 1e+6 # in 1/M
```

```
F2D_KA1 = 2.12 * 1e+6 # in 1/M
```

```

```

```
# IMPORTANT: Select the Corresponding System Here
```

```
KA1= F2D_KA1 # WT_KA1 or F2D_KA1
```

```

```

```
# Calculated Constants
```

```
KA = k11 / k12
```

```
KA2 = k7 / k9 # from optimized k9
```

```
#KA2 = beta2 / KA1 # from optimized k12
```

```
KD2 = 1 / KA2
```

```
rho_1= KA2 / KA1 # from optimized k9
```

```
rho_2 = KA / (KA1)**2 # from optimized k12
```

```

```

```
print "Calc. Const.\t Values\t\tUnits \t\tConv. Values\tConv. Units"
```

```
np.set_printoptions(precision=2)
```

```
print "simultaneous constants"
```

```
print "KA\t\t %.3g \t1/M**2 \t\t%.3g \t1/uM**2" % (KA,KA*1e-12)
```

```
print "KD\t\t %.3g \tM**2 \t\t%.3g \t\tnM**2" % (1/KA,1e+18/KA)
```

```
print "sequential constants"
```

```
print "KA2 \t\t %.3g \t1/M \t\t%.3g \t1/uM" % (KA2,KA2*1e-6)
```

```
print "KD2 \t\t %.3g \tM \t\t%.3g \t\tnM" % (KD2,KD2*1e+9)
```

```
print "cooperativity for sequantial mechanism"
```

```
print "rho_1\t\t %.3g" % rho_1
```

```
print "cooperativity for simultaneous mechanism"
```

```
print "rho_2\t\t %.3g" % rho_2
```

```
Calc. Const.     Values         Units           Conv. Values    Conv. Units
simultaneous constants
KA               1.55e+15       1/M**2          1.55e+03        1/uM**2
KD               6.43e-16       M**2            643             nM**2
sequential constants
KA2              7.52e+08       1/M             752     1/uM
KD2              1.33e-09       M               1.33            nM
cooperativity for sequantial mechanism
rho_1            355
```

```
cooperativity for simultaneous mechanism
rho_2            346
```

In [12]:

```
print 'k9 =', round(k9,3)
```

```
print 'k10 =', round(k10,3)
```

```
print 'k11 =', round(k11,3)
```

```
print 'k12 =', round(k12,3)
```

```
k9 = 0.002
k10 = 0.002
k11 = 6.93e+13
k12 = 0.045
```