```
# This file runs in 8 hours using 5 cores at 2-3GhZ with 8GB RAM.
%config Completer.use_jedi = False # Disable jedi autocompleter to fix autocomplete issues. This may not be necessary with newer versions
```

In [1]:
```
# import libraries
import numpy as np
import os
import random as rand
import seaborn as sbn
from matplotlib import pyplot as plt
import pandas as pd
from multiprocess import Pool, cpu_count
from IPython.display import clear_output
# import a library with model associated functions
import modelfn

base_directory=os.getcwd()
```

Step0:

Input data and define Metric and Fit Objective Functions

```
# Uncomment this block to rerun simulation - this may consume 1-2 days of runtime
def fitmeta(ff):
    """Input fitflag options:'0','1','2','CA','NC','DP','DPNC','CADP','CANC'. Output is a best-fit parameters dataframe"""
    # -- Import Libraries --
    from fitdata import fitdata
    import pandas as pd
    # define a function to Normalize the data by loading control and by the drug-free readout
    # define a function to Normalize the data by loading control and by the drug-free readout
    def datanorm(data):
        """Inputs data for a list of drugs organized by [[pMEKdata],[pERKdata],[MEKdata]]. The pMEK and pERK data for each drug are normalized by MEK (loading control) and then each of the two rows==normalized by first element (drug=0)."""
        normdata0=[[row[0][iel]/row[-1][iel] for iel in range(len(row[0]))] for row in data]
        normdata=[[row[iel]/row[0] for iel in range(len(row)) if iel > 0] for row in normdata0]
        return normdata
    drugnames=['AZ','TAK','LY','SB','GDC','DAB','AZ-VEM','VEM','PB']
    drugvals=[0, 0.01, 0.03, 0.1, 0.3, 1, 3, 10] # micro-molar
    ## DATA==INPUT for a list of drugs arranged as [[pMEK],[pERK],[MEK]] data for each drug with each element corresponding to above concentrations.
```

```
    rawinpdata=[[[25, 55, 37, 40, 27, 17, 13, 10], [73, 119, 105, 92, 83, 50,37, 10], [34, 41, 29, 33, 32, 37, 37, 39]], [[22, 38, 49,   51, 45, 41, 25, 11], [90, 112, 139, 133, 150, 110, 58, 4], [27, 31,32, 33, 30, 31, 32, 35]], [[26, 41, 42, 39, 21, 12, 7,4], [105, 182, 159, 182, 97, 63, 13, 0.062], [59, 57, 51, 59, 53,   50, 50, 51]],[[17, 79, 83, 72, 49, 18, 5, 2], [89, 185, 182, 187, 166, 103,   15, 0.5], [32, 30, 33, 33, 32, 30, 30, 29]],[[7, 42, 63, 80, 73, 55, 23, 11], [71, 161, 176, 162, 176,   165, 118, 33], [43, 45, 40, 44, 44, 47, 47, 53]],[[25, 38, 64, 77, 84, 72, 72, 34], [110, 132, 158, 133, 161,   134, 160, 118], [51, 56, 61, 57, 55, 45, 51, 46]],[[14, 24, 31, 56, 59, 66, 73, 63], [76, 103, 124, 139, 146,   137, 153, 154], [61, 56, 55, 56, 52, 45, 55, 55]],[[26, 31, 37, 48, 48, 60, 71, 90], [113, 121, 127, 133, 133,   155, 156, 146], [68, 76, 91, 91, 91, 92, 91, 96]],[[38, 28, 34, 27, 33, 30, 35, 37], [100, 88, 79, 98, 102, 104,   98, 88], [44, 36, 42, 38, 38, 34, 36, 34]]]
    normMEK=datanorm(rawinpdata)
    drugvalsnorm=drugvals[1:]
    RAFval=0.04 #uM
    Kdimval=0.1 #uM
    KAval=0.0001 # Fixes CA mechanism. Ignored when CA is specified in fitflag and KA is therefore varied.
    normtyp=0 # normtype 0 results in l2 like norm which is far more efficient. normtype 1 measures mean proportional deviation across all data as the fitness measure.
    return fitdata(ydata=normMEK,drugvalues=drugvalsnorm,drugnames=drugnames,optionsinp={'fitflag':ff,'RAFval':RAFval,'Kdimval':Kdimval,'KA':KAval,'normtype':normtyp})
```

```
%%time # Uncomment this block to rerun simulation - this may consume 1-2 days of runtime
Nruns=1500 # Total number of runs
NeachRun=100 # store in file after this many runs
niter=int(Nruns/NeachRun)
# For the reasons of python importing system, restart the kernel each time a new fitflag is used - otherwise older libraries could remain in the memory.
ff='2' # set this to 0 for unrestricted fits and 2 to set KA and Kdim at values defined in the fitting function.
AlgoInit=[ff]*NeachRun
# Parallel process
resglobal=[]
ncores=cpu_count()-1 # replace this with 1 to run on a single core computer or simply run the command following the desired number of times: fitmeta(1)
for iter1 in range(niter):
    if __name__=='__main__':
        npool=min([len(AlgoInit),ncores])
        po=Pool(npool)
        resl=list(po.map(fitmeta,AlgoInit))
        po.close()
        po.join()
        resglobal=resglobal+resl
    print(iter1+1,'of',niter)
    # since the run keeps taking too much time, save intermeidate results so far in a file and keep updating.
    it1=0
    for idf in resglobal:
        idf['irun']=it1
        it1+=1
    dfres=pd.concat([elem for elem in resglobal if len(elem)>0])
    foutname='SKMEL2_Karoulia_'+ff+'.gz'
    dfres.to_csv(foutname,sep='\t',index=False)
```

In [2]:

```
# Homogeneous color scheme for the plots
colcycle={'AZ':'#1f77b4',
'TAK':'#ff7f0e',
 'LY':'#2ca02c',
 'SB':'#d62728',
 'GDC':'#9467bd',
 'DAB':'#8c564b',
 'AZ-VEM':'#e377c2',
 'VEM':'#7f7f7f',
 'PB':'#bcbd22'}
markercyc={'AZ':"o",'TAK':"s",'LY':"D",'SB':"^",'GDC':"v",'DAB':"P",'AZ-VEM':"*",'V


dic_inpfiles={'28pars':'SKMEL2_Karoulia_2_9Dec21.gz','30pars':'SKMEL2_Karoulia_0_9D
              '28pars_normtp1':'SKMEL2_Karoulia_ff2_normtp1_1Dec21.gz','30pars_norm
             'CADP':'SKMEL2_Karoulia_ffCADP_normtp1_1Dec21.gz','NC':'SKMEL2_Karouli
              'DP':'SKMEL2_Karoulia_ffDP_normtp1_1Dec21.gz','CA':'SKMEL2_Karoulia_f
              'CANC':'SKMEL2_Karoulia_ffCANC_normtp1_1Dec21.gz','DPNC':'SKMEL2_Karo
             }
modelfn.bdyglobal['rafr']=[modelfn.bdyglobal['RAF'][0]/modelfn.bdyglobal['Kdim'][1]

def datanorm(data):
    """Inputs data for a list of drugs organized by [[pMEKdata],[pERKdata],[MEKdata
    normdata0=[[row[0][iel]/row[-1][iel] for iel in range(len(row[0]))] for row in
    normdata=[[row[iel]/row[0] for iel in range(len(row)) if iel > 0] for row in no
    return normdata
drugnames=['AZ','TAK','LY','SB','GDC','DAB','AZ-VEM','VEM','PB']
drugvals=[0, 0.01, 0.03, 0.1, 0.3, 1, 3, 10] # micro-molar
## DATA==INPUT for a list of drugs arranged as [[pMEK],[pERK],[MEK]] data for each
rawinpdata=[[[25, 55, 37, 40, 27, 17, 13, 10], [73, 119, 105, 92, 83, 50,37, 10], [
normMEK=datanorm(rawinpdata)
drugvalsnorm=drugvals[1:]

cyc=[colcycle[dname] for dname in drugnames]
markr=[markercyc[dname] for dname in drugnames]

plt.rcParams['font.family'] = 'serif'
plt.rcParams['font.serif'] = ['Arial']
```

In [3]:

```
dic_res10p=dict()
for ChooseModel in dic_inpfiles.keys(): #='CA' # CHOOSE MODEL - from the keys of th

    dfres=pd.read_csv(os.path.join(base_directory,dic_inpfiles[ChooseModel]),sep='\
    dfres['rafr']=dfres['RAF']/dfres['Kdim']

    setlen=lambda x:len(set(x))
    minerr=min(dfres['fitmetric'])
    max10p=minerr*1.1
    dfres10p=dfres[dfres['fitmetric']<max10p]

    print('10% of min error cutoff, number of qualifying datapoints:',minerr,max10p

#     dfres10describe=dfres.groupby('drug').describe()
#     dfres10describe['KA'].iloc[[0]].round(2)

    dfres10p.sort_values(by='drug',inplace=True)
    dic_res10p[ChooseModel]=dfres10p

    plt.rc('axes', labelsize=35)    # fontsize of the x and y labels
    plt.rc('xtick', labelsize=25)    # fontsize of the tick labels
    plt.rc('ytick', labelsize=25)    # fontsize of the tick labels
    plt.rc('legend', fontsize=25)    # legend fontsize
    fig1,ax1=plt.subplots(figsize=(12,12),nrows=3,sharex=True,sharey=False)
    i=-1
    for ylabel in ['Kd','f','g']:
        i+=1
        sbn.boxplot(ax=ax1[i],x='drug',whis=[2.5,97.5],y=ylabel,data=dfres10p,palet
        ax1[i].set_xlabel(None)
        ax1[i].set_yscale('log')
        ax1[i].set_ylim(modelfn.bdyglobal[ylabel][0]/10,modelfn.bdyglobal[ylabel][1
    ax1[i].set_xticklabels(ax1[i].get_xticklabels(), rotation=90, horizontalalignme
    plt.savefig(os.path.join(base_directory,'subModel_plots',ChooseModel+'_paramete
    plt.close()

    plt.figure(figsize=(2,4))
    sbn.boxplot(y='KA',data=dfres10p.drop_duplicates(subset=['irun']),whis=[2.5,97.
    plt.yscale('log')
    plt.ylim(modelfn.bdyglobal['KA'])
    plt.savefig(os.path.join(base_directory,'subModel_plots',ChooseModel+'_paramete
    plt.close()

    plt.rc('axes', labelsize=50)    # fontsize of the x and y labels
    plt.rc('xtick', labelsize=50)    # fontsize of the tick labels
    plt.rc('ytick', labelsize=50)    # fontsize of the tick labels
    plt.rc('legend', fontsize=20)    # legend fontsize
    def plt2(xcol,ycol):
        plt.figure(figsize=[8,8])
        for i in range(len(drugnames)):
            dataplot=dfres10p[dfres10p['drug']==drugnames[i]]
            sbn.scatterplot(x=xcol,y=ycol,data=dataplot,color=cyc[i],s=205,marker=m
        plt.xscale('log')
        plt.yscale('log')
        if xcol in modelfn.bdyglobal.keys():
            plt.xlim(modelfn.bdyglobal[xcol])
            plt.xticks(np.geomspace(modelfn.bdyglobal[xcol][0],modelfn.bdyglobal[xc
        if ycol in modelfn.bdyglobal.keys():
            plt.ylim(modelfn.bdyglobal[ycol])
            plt.yticks(np.geomspace(modelfn.bdyglobal[ycol][0],modelfn.bdyglobal[yc
        plt.legend(drugnames,loc='center left',bbox_to_anchor=(1., 0.5))#,ncol=len(
    #     for i in range(len(drugnames)):
    #         dfres2_best=dfres2[dfres2.irun==dfres2.iloc[0].irun]
```

```
    #         sbn.scatterplot(x=xcol,y=ycol,data=dfres2_best[dfres2_best.drug==drug
        plt.title('Top 10% Total fit error (<'+str(max10p)+'%)')
        if ycol=='f':
            plt.plot(modelfn.bdyglobal[xcol],[1,1],linestyle='dashed',color='k')
        plt.savefig(os.path.join(base_directory,'subModel_plots',ChooseModel+'_'+xc
        return plt.close()
    plt2('Kd','f')
clear_output()
```

Tabulate results

In [4]:
```
dic_res10p.keys()
```

Out[4]:
```
dict_keys(['28pars', '30pars', '28pars_normtp1', '30pars_normtp1', 'CADP', 'NC', 'DP',
'CA', 'CANC', 'DPNC'])
```

In [109]:
```
imodel='DPNC'
fround=2
Kdround=1
df_mean=(dic_res10p[imodel][['KA','f','g','Kd','drug']]).groupby(by='drug').mean()
df_mean.g=df_mean.g.round(0).astype(int).astype(str)
df_mean.f=df_mean.f.round(fround).astype(str)
df_mean.Kd=df_mean.Kd.round(Kdround).astype(str)
df_mean.KA=df_mean.KA.round(3).astype(str)

df_std=(dic_res10p[imodel][['KA','f','g','Kd','drug']]).groupby(by='drug').std()
df_std.g=df_std.g.round(0).astype(int).astype(str)
df_std.f=df_std.f.round(fround).astype(str)
df_std.Kd=df_std.Kd.round(Kdround).astype(str)
df_std.KA=df_std.KA.round(3).astype(str)
df_tab=(df_mean+'+-'+df_std).transpose()
df_tab.to_excel(os.path.join(base_directory,'subModel_plots/',imodel+'.xlsx'))
df_tab
```

Out[109]:

drug	AZ	AZ-VEM	DAB	GDC	LY	PB	SB	TAK	VEM
KA	0.0+-0.0	0.0+-0.0	0.0+-0.0	0.0+-0.0	0.0+-0.0	0.0+-0.0	0.0+-0.0	0.0+-0.0	0.0+-0.0
f	1.18+-2.65	0.68+-1.19	0.01+-0.14	0.01+-0.24	1.29+-1.01	0.05+-0.26	2.91+-2.24	4.17+-2.89	0.01+-0.03
g	8+-42	11+-64	10+-31	12+-50	8+-38	12+-61	7+-46	5+-26	9+-36
Kd	2.6+-1.0	7.6+-8.6	9.1+-4.3	9.1+-7.2	1.1+-0.3	11.4+-5.3	1.8+-0.4	8.7+-4.3	11.9+-33.3

Dose response and fit plot

In [4]:

```
def datanorm(data):
    """Inputs data for a list of drugs organized by [[pMEKdata],[pERKdata],[MEKdata
    normdata0=[[row[0][iel]/row[-1][iel] for iel in range(len(row[0]))] for row in
    normdata=[[row[iel]/row[0] for iel in range(len(row)) if iel > 0] for row in no
    return normdata
drugnames=['AZ','TAK','LY','SB','GDC','DAB','AZ-VEM','VEM','PB']
drugvals=[0, 0.01, 0.03, 0.1, 0.3, 1, 3, 10] # micro-molar
## DATA==INPUT for a list of drugs arranged as [[pMEK],[pERK],[MEK]] data for each
rawinpdata=[[[25, 55, 37, 40, 27, 17, 13, 10], [73, 119, 105, 92, 83, 50,37, 10], [
normMEK=datanorm(rawinpdata)
drugvalsnorm=drugvals[1:]

clear_output()
```

In [5]:

```
%%time
# This block takes half an hour to run on a single core 2GhZ, 16 GB RAM machine
drugnames=['AZ','TAK','LY','SB','GDC','DAB','AZ-VEM','VEM','PB']
dvals=drugvalsnorm
dvals=[dvals[0]/100]+dvals
dvalsplot=np.geomspace(dvals[0],dvals[-1]*10,100)

dic_linplt=dict()
for ChooseModel in dic_inpfiles.keys():
    dfres10pp=dic_res10p[ChooseModel]
    dfres10p['paramsdic']=[dict(dfres10p[['Kdim','RAF','KA','f','g','Kd']].iloc[it1
    dflinplt=pd.DataFrame(columns=['DrugConc','pMEK/MEK','drug','irun'])
    for idx1 in range(len(dfres10p)):
        irun1=dfres10p.irun.iloc[idx1]
        idrug1=dfres10p.drug.iloc[idx1]

        dflinplt_idx=pd.DataFrame(columns=['DrugConc','pMEK/MEK','drug','irun'])
        idic=dfres10p.paramsdic.iloc[idx1]

        dflinplt_idx['DrugConc']=dvalsplot
        dflinplt_idx['pMEK/MEK']=dflinplt_idx['DrugConc'].apply(lambda iconc:modelf

        dflinplt_idx.irun=irun1
        dflinplt_idx.drug=idrug1
        dflinplt=pd.concat([dflinplt,dflinplt_idx])
        del dflinplt_idx
    clear_output()
    dic_linplt[ChooseModel]=dflinplt
```

```
Wall time: 28min 57s
```

In [27]:

```
# Plot data with along with a fit curve.

# plt.rcParams['font.family'] = 'serif'
plt.rcParams['font.family'] = ['Arial']
plt.rc('axes', labelsize=35)    # fontsize of the x and y labels
plt.rc('xtick', labelsize=35)    # fontsize of the tick labels
plt.rc('ytick', labelsize=35)    # fontsize of the tick labels
plt.rc('legend', fontsize=20)    # legend fontsize

for ChooseModel in dic_inpfiles.keys():
    dflinplt=dic_linplt[ChooseModel]
    ax1=plt.figure(figsize=[8,8])
    daty=normMEK
    daty=[[1.]+irow for irow in daty]
    cyc=[colcycle[dname] for dname in drugnames]
    markr=[markercyc[dname] for dname in drugnames]
    for i in range(len(daty)):
        ax1=plt.scatter(dvals,daty[i],color=cyc[i],label=drugnames[i],marker=markr[
    plt.legend(drugnames,bbox_to_anchor=(1,1))
    for idrug in drugnames:
        pldf=dflinplt[dflinplt.drug==idrug]
        ax1=sbn.lineplot(data=pldf,x='DrugConc',y='pMEK/MEK',ci='sd',color=colcycle

    ax1.set_xscale('log')
    ax1.set_yscale('log')
    ax1.set_xlabel(r'Drug $(\mu$M)')
    ax1.set_ylabel('%pMEK norm to no-drug')
    plt.savefig(os.path.join(base_directory,'subModel_plots',ChooseModel+'_DoseResp
    plt.close()
```

Supplementary Figure 2f

In [5]:

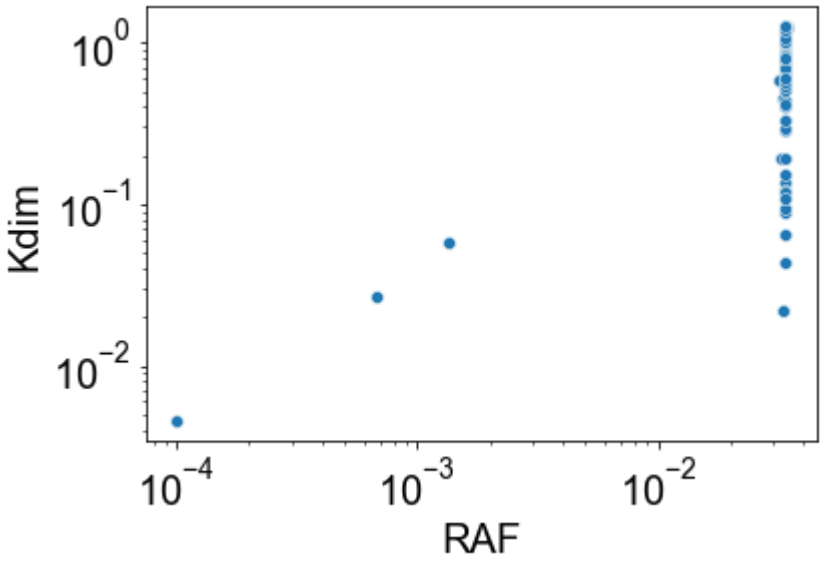
```
dic_res10p['30pars'].columns
```

Out[5]:

```
Index(['Kdim', 'RAF', 'KA', 'f', 'g', 'Kd', 'drug', 'fitmetric', 'algorithm',
       'init', 'irun', 'rafr'],
      dtype='object')
```

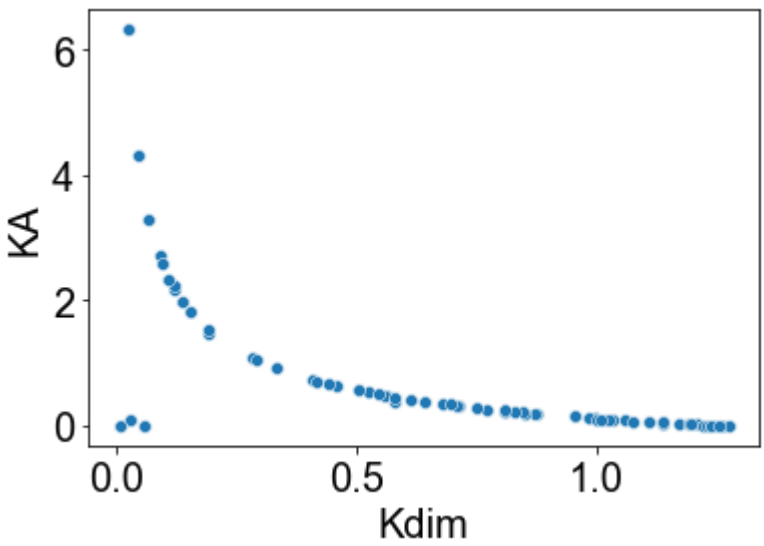
In [6]:

```
# Run this block ONLY when data is from the file "SKMEL2_Karoulia_0_9Dec21.gz" is i
plt.rc('axes', labelsize=20)
plt.rc('xtick', labelsize=20)    # fontsize of the tick labels
plt.rc('ytick', labelsize=20)    # fontsize of the tick labels
ChooseModel='30pars'
dfplt=dic_res10p[ChooseModel]
sbn.scatterplot(data=dfplt,x='RAF',y='Kdim')
plt.xscale('log')
plt.yscale('log')
plt.show()
```



In [8]:

```
# Run this block ONLY when data is from the file "SKMEL2_Karoulia_0_9Dec21.gz" is i
ChooseModel='30pars'
dfplt=dic_res10p[ChooseModel]
sbn.scatterplot(data=dfplt,x='Kdim',y='KA')
# plt.xscale('log')
# plt.yscale('log')
plt.show()
```



Best-Fit (10p) parameter correlations in the unified model

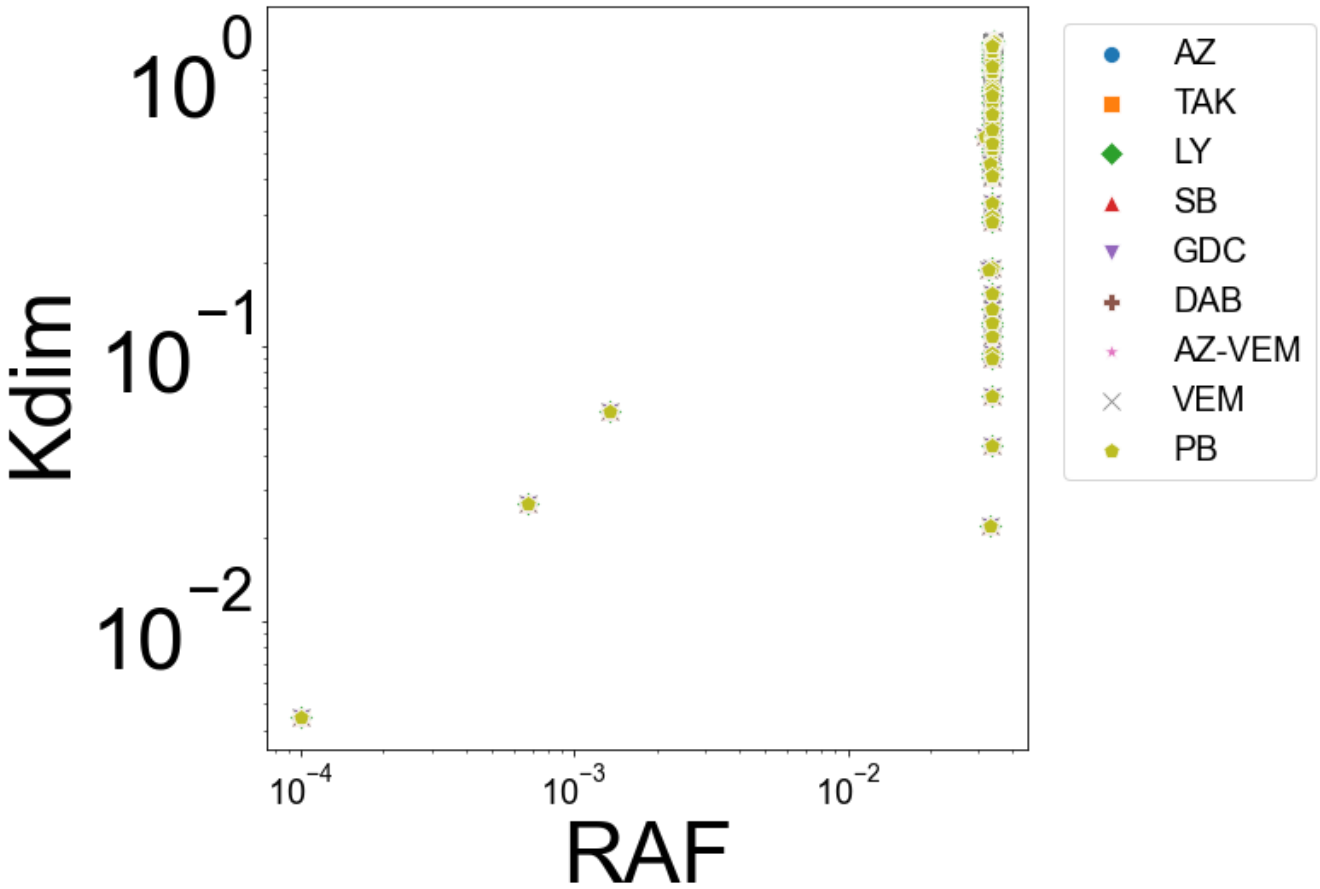
In [10]:
```
1 dic_res10p['28pars'].columns
```

Out[10]:
```
Index(['Kdim', 'RAF', 'KA', 'f', 'g', 'Kd', 'drug', 'fitmetric', 'algorithm',
       'init', 'irun', 'rafr'],
      dtype='object')
```

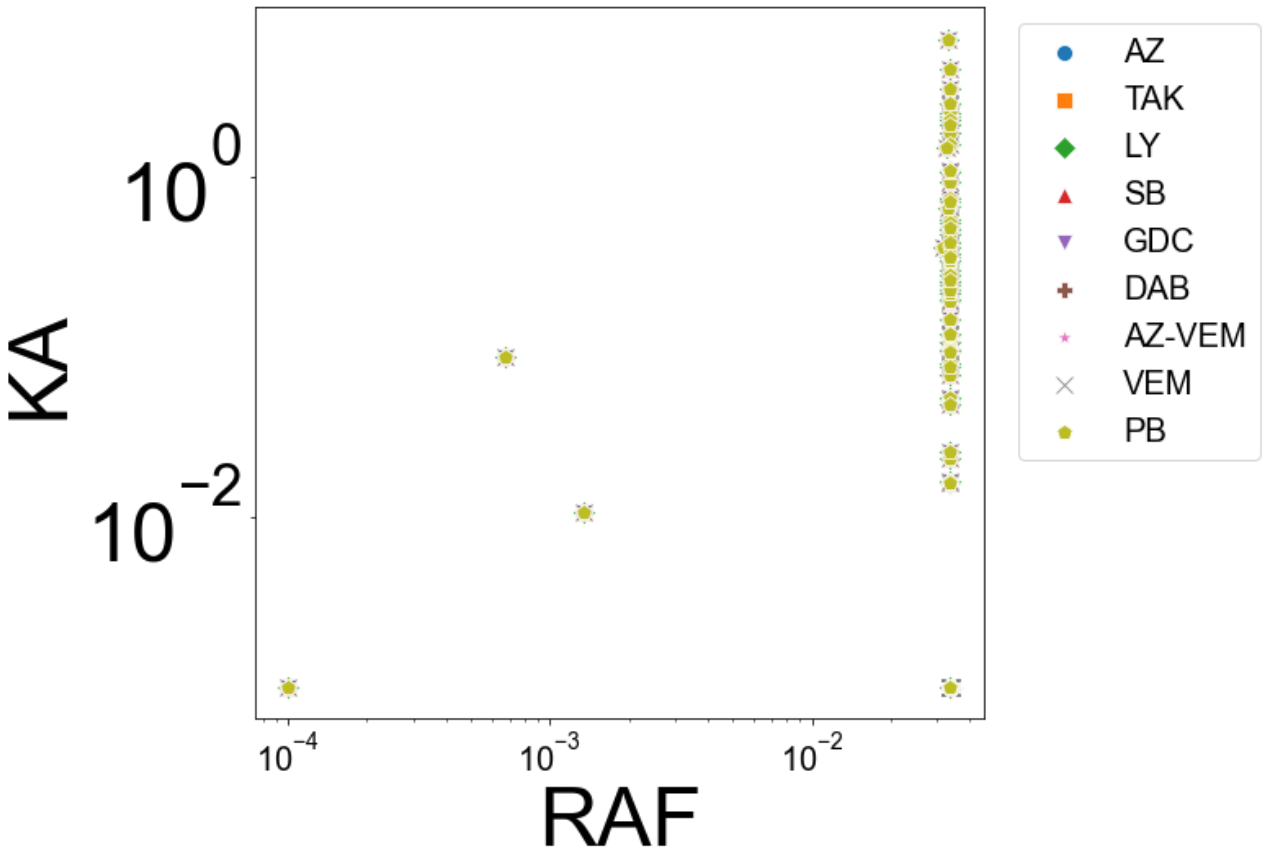
In [53]:

```
labelslist=['RAF','Kdim','KA', 'f', 'g', 'Kd']
pltdf=dic_res10p['30pars']
it1=0
for xlabel in labelslist:
    it1+=1
    for ylabel in labelslist[it1:]:

        ax1=plt.figure(figsize=[8,8])
        for idrug in drugnames:
            pldf=pltdf[pltdf.drug==idrug]
            ax1=sbn.scatterplot(data=pldf,x=xlabel,y=ylabel,color=colcycle[idrug],m

        if xlabel != 'KA':
            ax1.set_xscale('log')
        ax1.set_yscale('log')
        ax1.set_xlabel(xlabel)
        ax1.set_ylabel(ylabel)
        plt.legend(bbox_to_anchor=(1.4,1))
        plt.show()
```

```
C:\Users\GM\anaconda3\lib\site-packages\seaborn\relational.py:651: UserWarning: You pa
ssed a edgecolor/edgecolors ('w') for an unfilled marker ('x').  Matplotlib is ignorin
g the edgecolor in favor of the facecolor.  This behavior may change in the future.
  points = ax.scatter(*args, **kws)
```




```
C:\Users\GM\anaconda3\lib\site-packages\seaborn\relational.py:651: UserWarning: You pa
ssed a edgecolor/edgecolors ('w') for an unfilled marker ('x').  Matplotlib is ignorin
g the edgecolor in favor of the facecolor.  This behavior may change in the future.
  points = ax.scatter(*args, **kws)
```




```
C:\Users\GM\anaconda3\lib\site-packages\seaborn\relational.py:651: UserWarning: You pa
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  points = ax.scatter(*args, **kws)
```

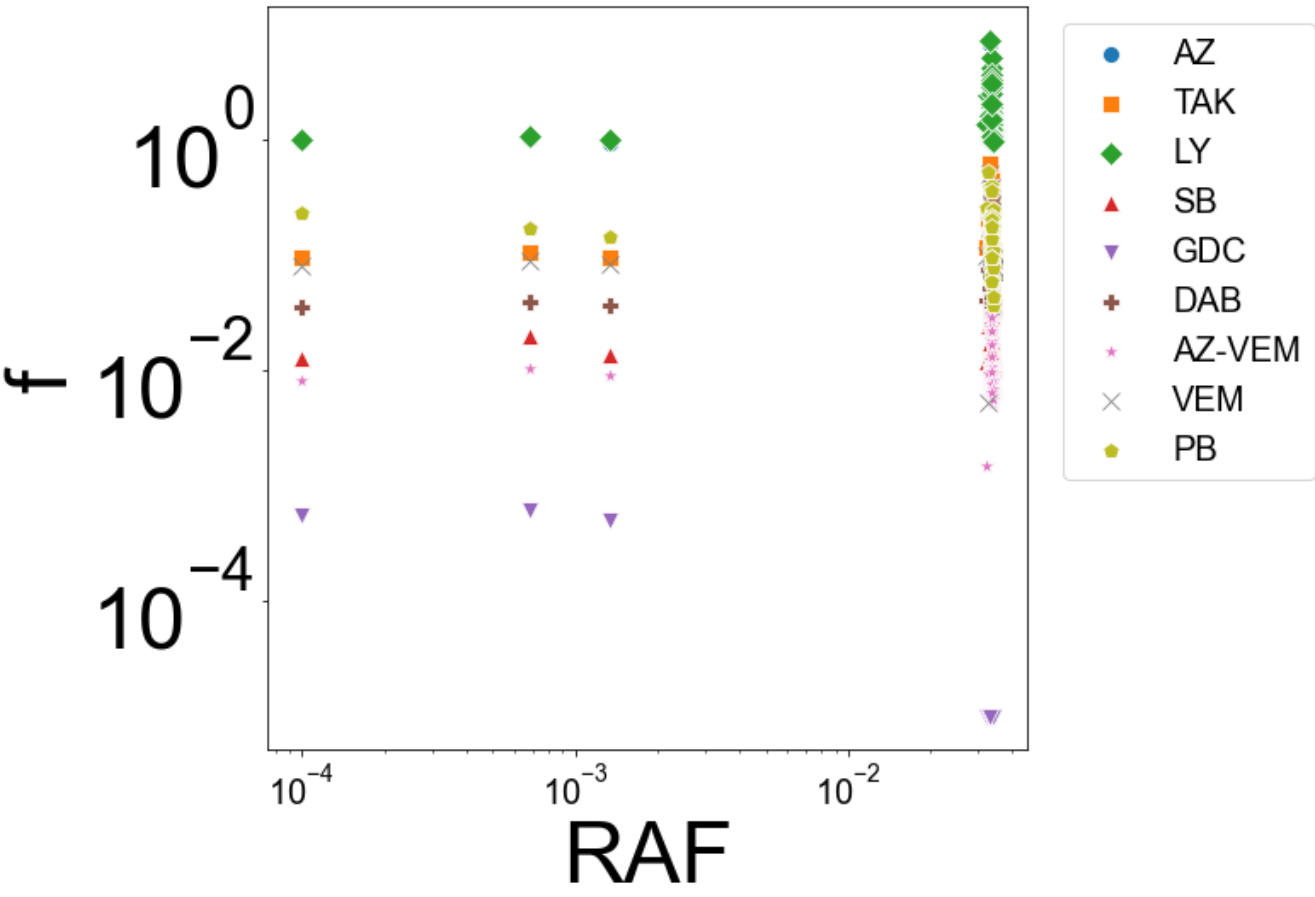


```
C:\Users\GM\anaconda3\lib\site-packages\seaborn\relational.py:651: UserWarning: You pa
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  points = ax.scatter(*args, **kws)
```

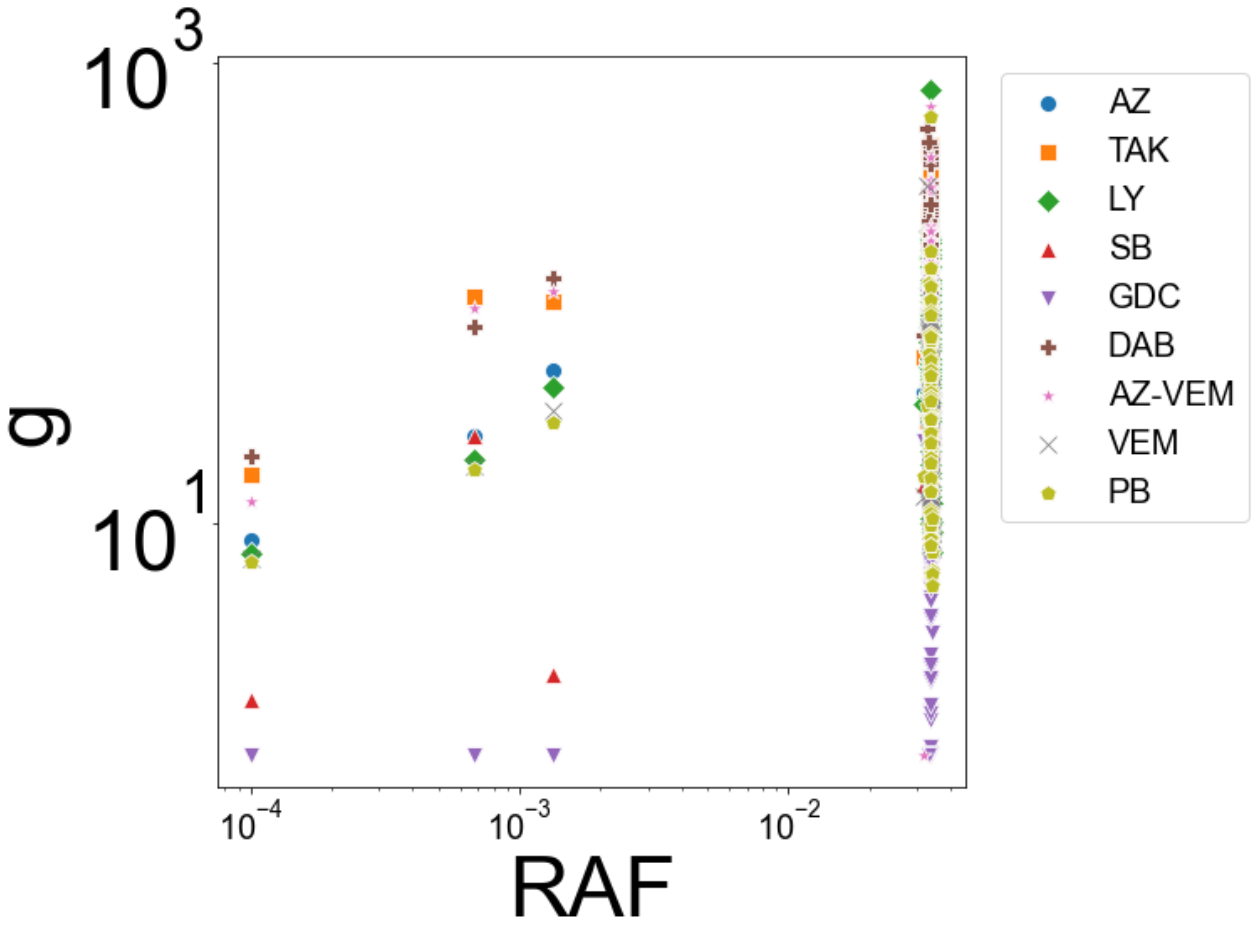


```
C:\Users\GM\anaconda3\lib\site-packages\seaborn\relational.py:651: UserWarning: You pa
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g the edgecolor in favor of the facecolor.  This behavior may change in the future.
  points = ax.scatter(*args, **kws)
```

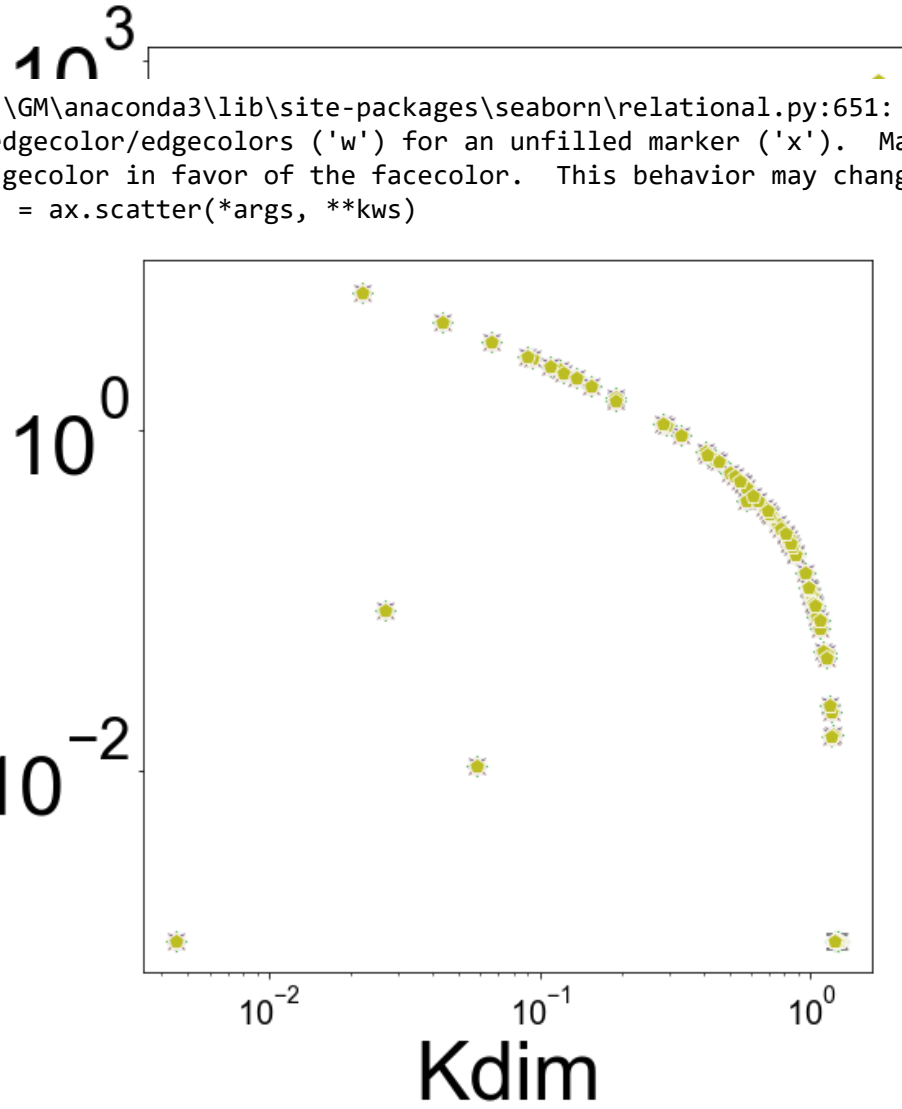


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C:\Users\GM\anaconda3\lib\site-packages\seaborn\relational.py:651: UserWarning: You pa
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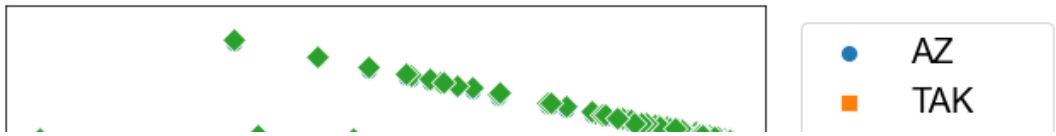


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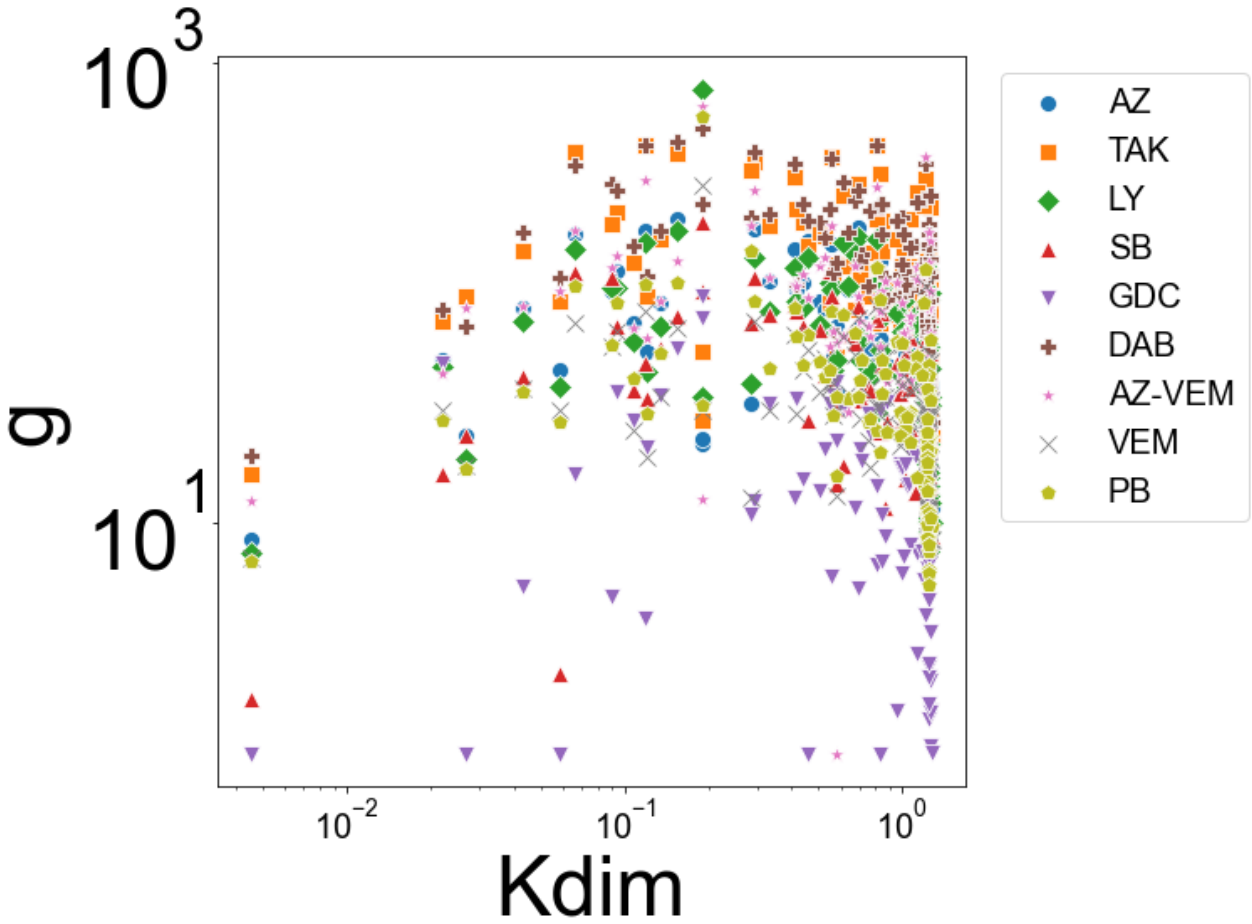

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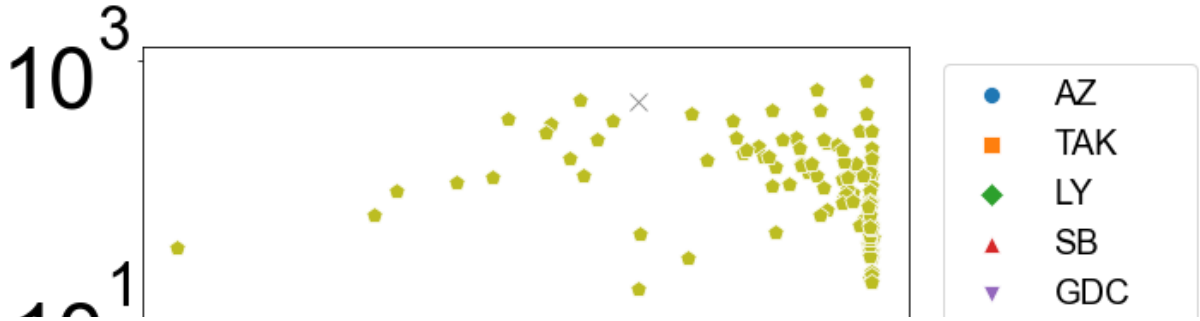


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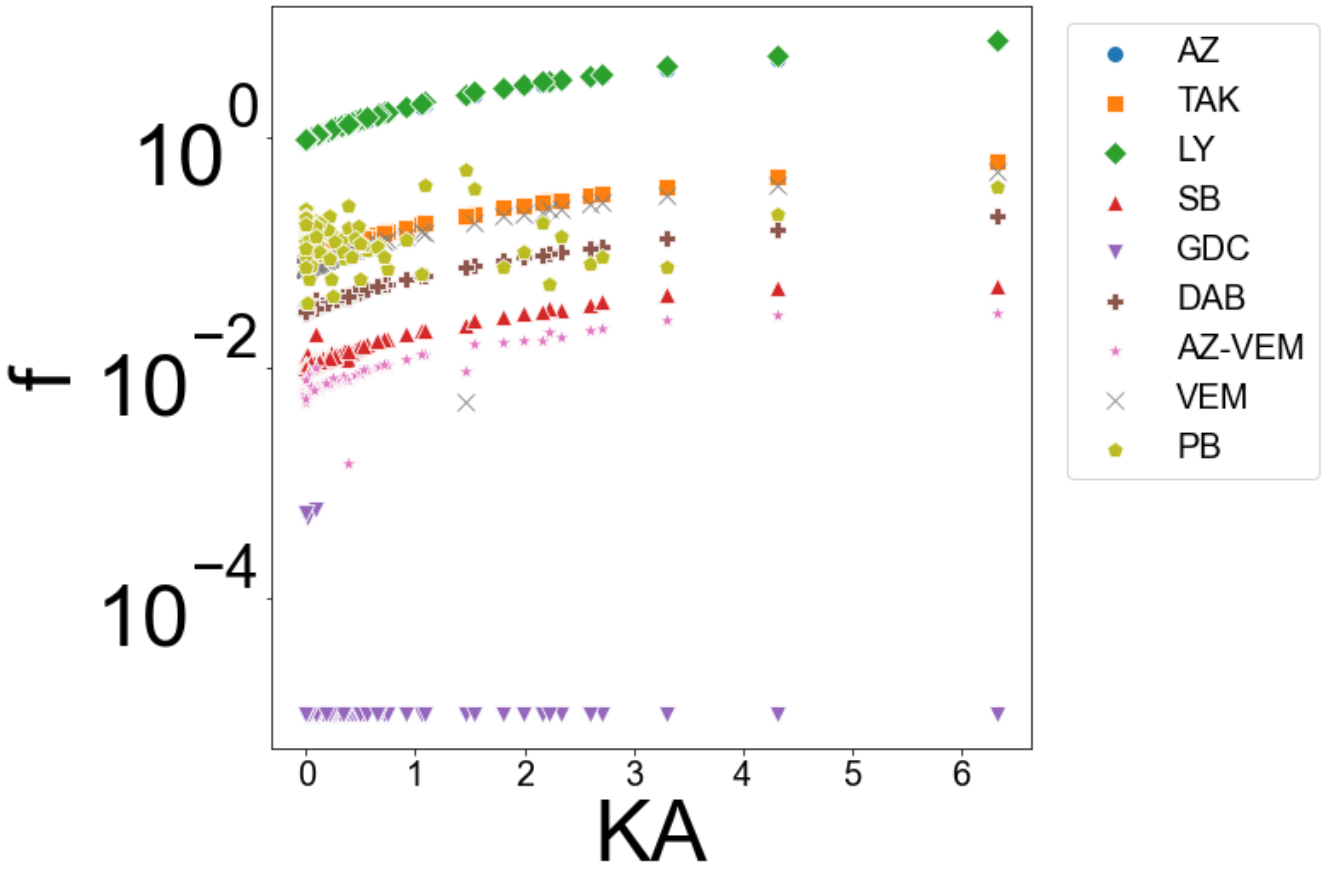


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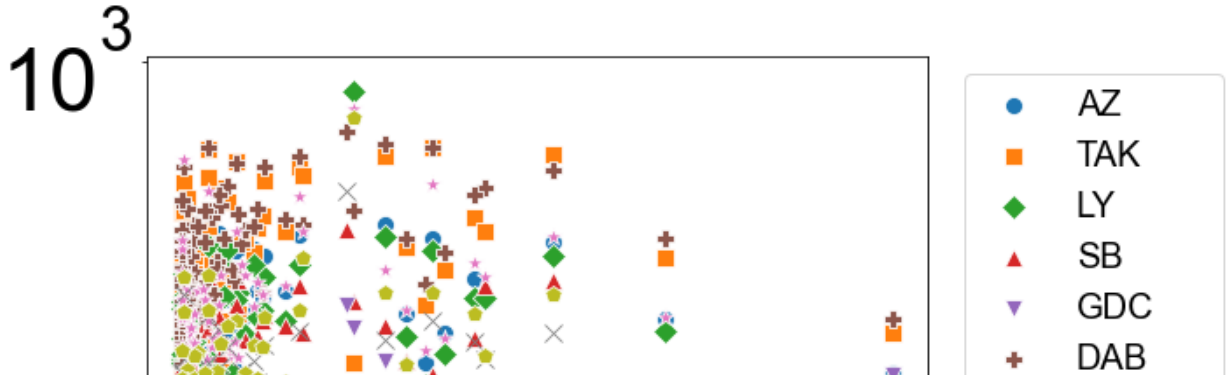


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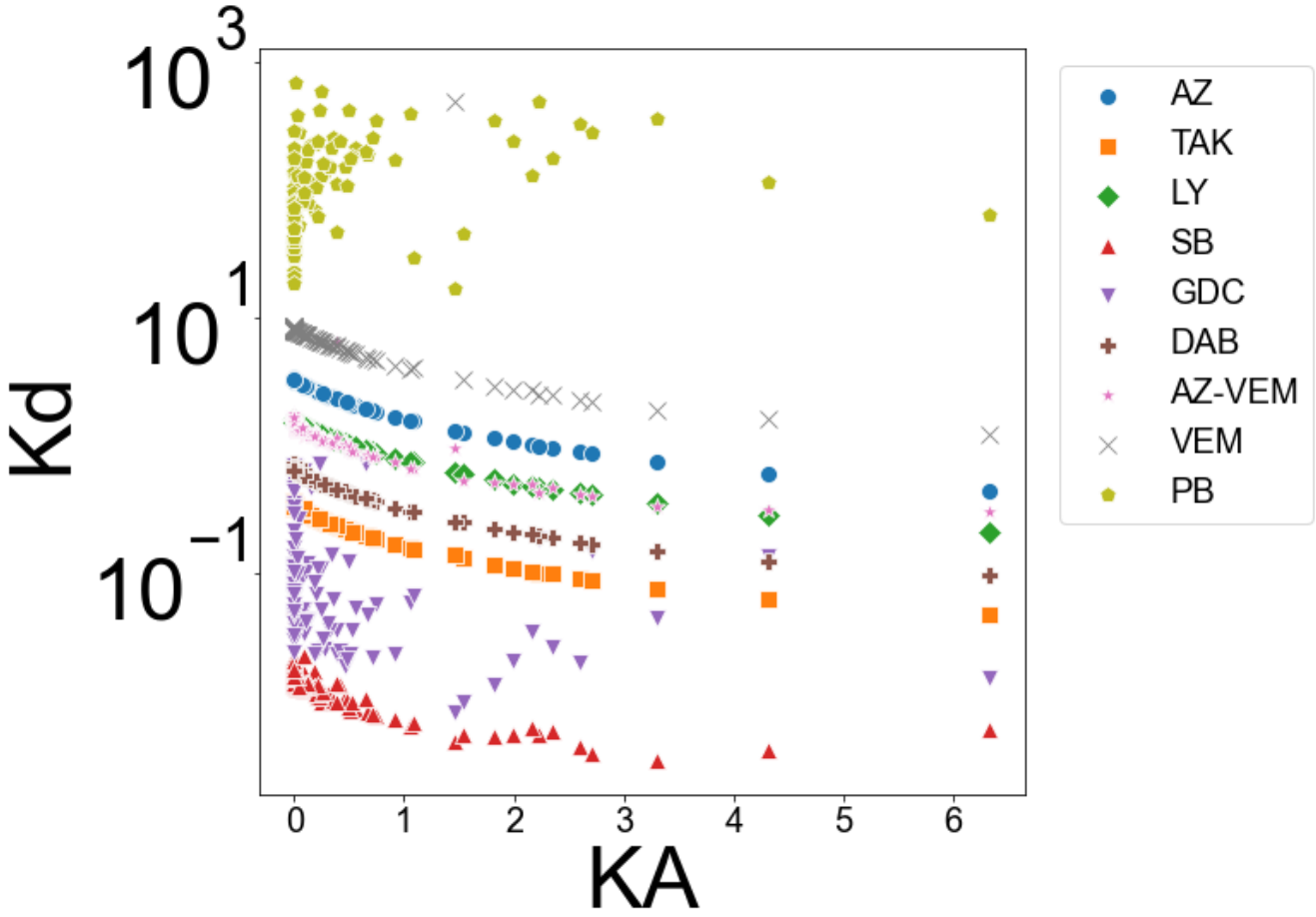


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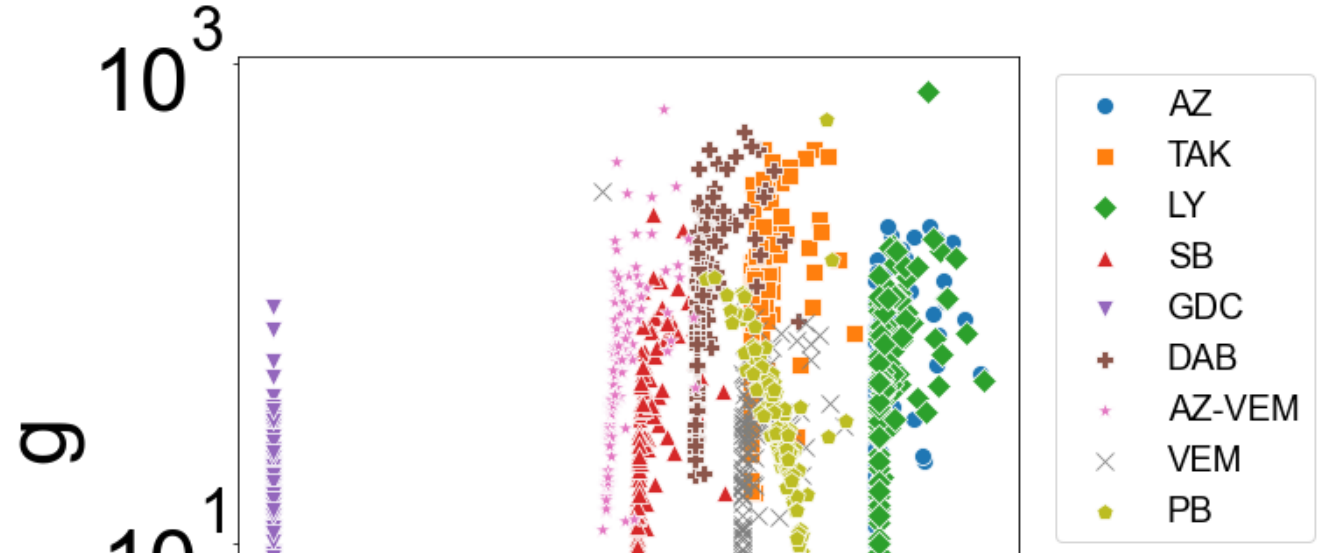


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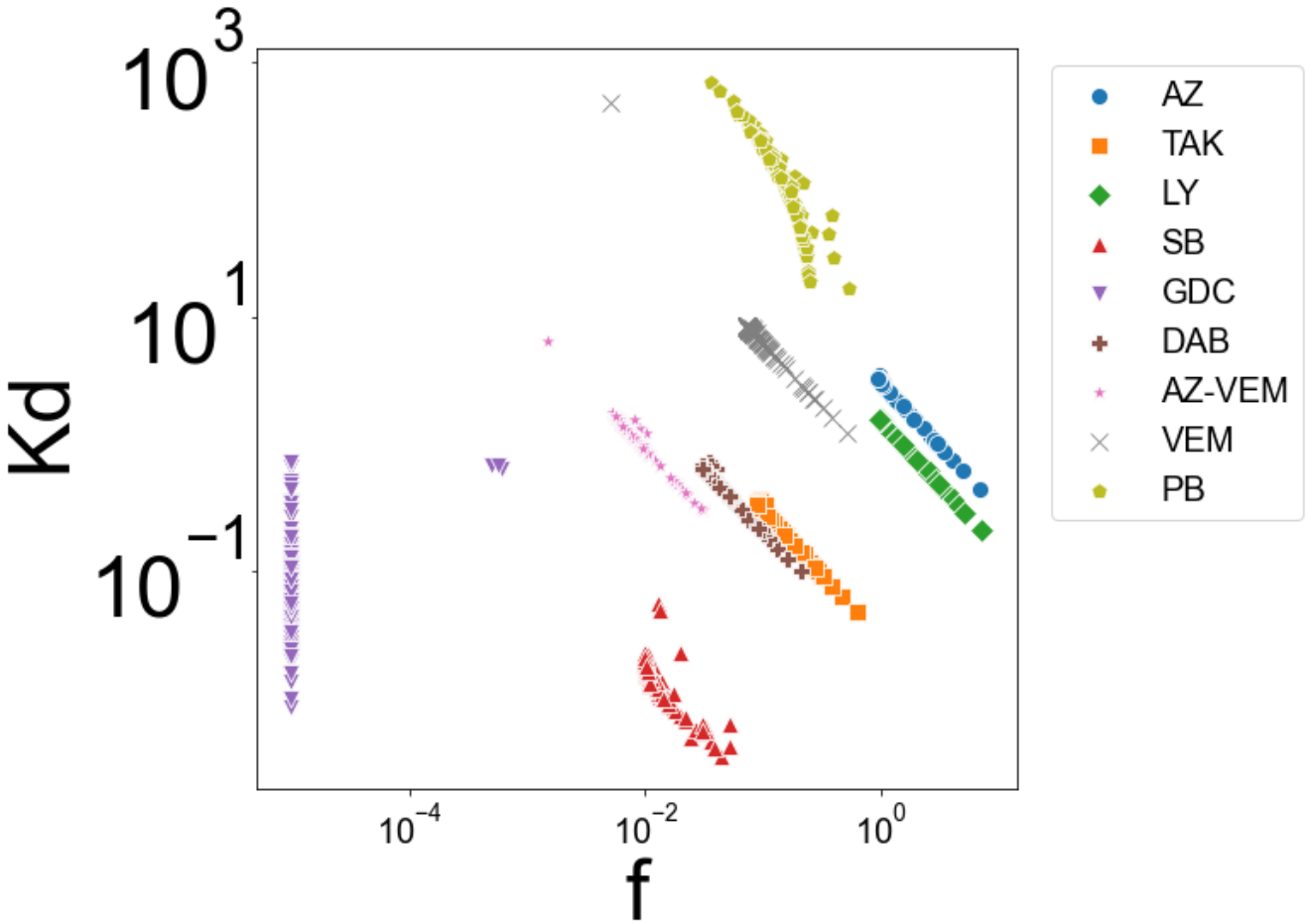


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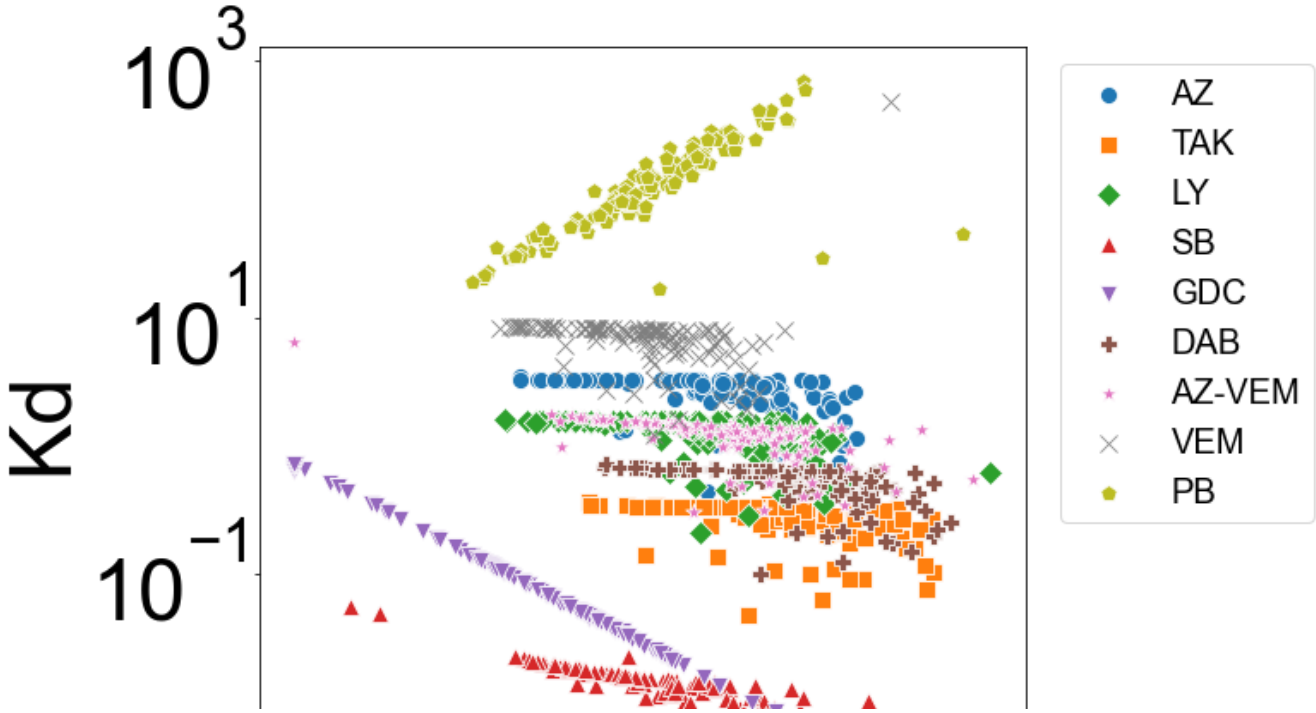
Kd
10^{3}
10^{1}
10^{-1}
AZ
TAK
LY
SB
GDC
DAB
AZ-VEM
VEM
PB

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