

# MMPB

A little Physics is a dangerous thing

# Predicting Binding Energies-

## Oh how we try

1. QSAR
2. Correlation with a physics term
3. Mix the physics terms up -LIE (=QSAR)
4. Try dynamics-*lite* (MMPB)
5. Try dynamics

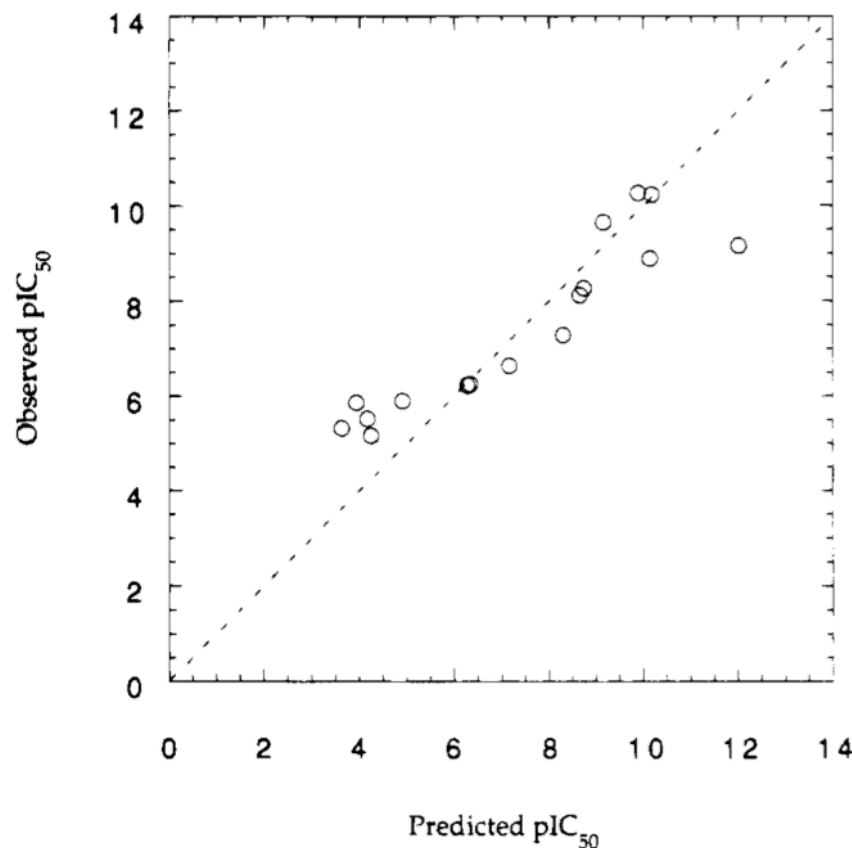
# The Holloway Slope

Train on 17 HIV-1 Protease Inhibitors

1) Minimization (MM2X)

2)  $\text{pIC}_{50} = -0.15 * E_{\text{inter}} - 8.1$

Prospectively used on 16 more

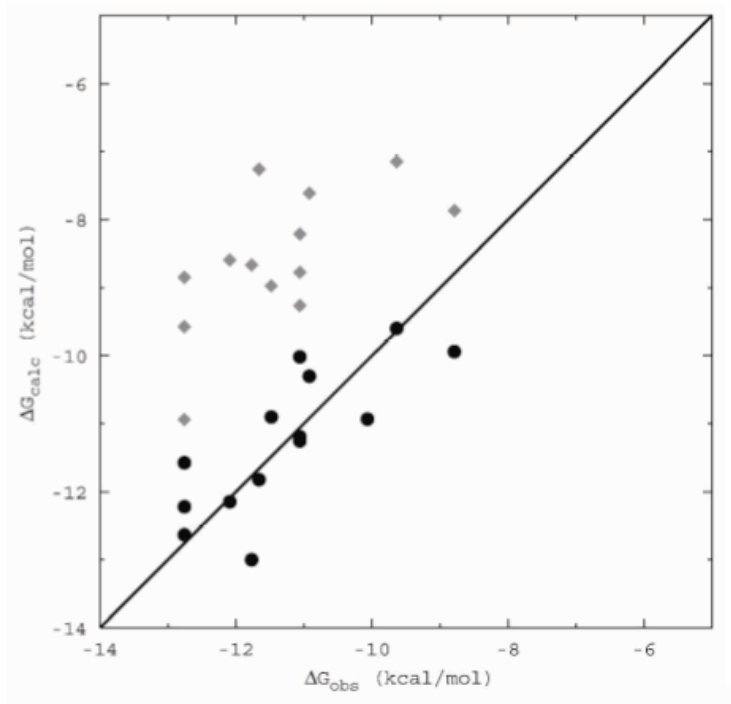
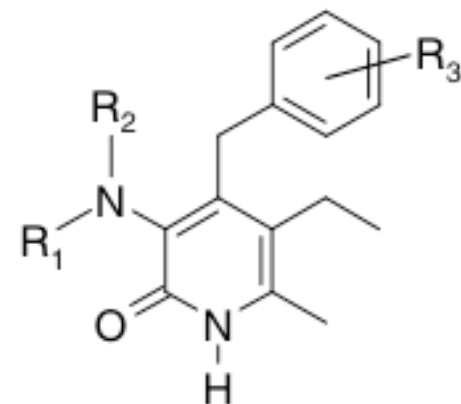


*J. Med. Chem.* 1995, 38, 305–317

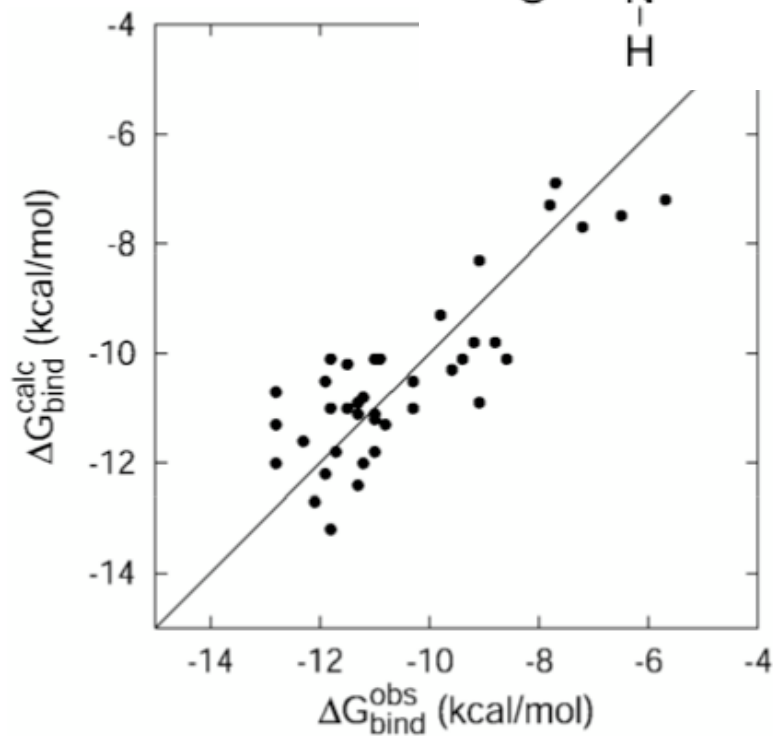
## ***A Priori* Prediction of Activity for HIV-1 Protease Inhibitors Employing Energy Minimization in the Active Site**

M. Katharine Holloway,<sup>\*,†</sup> Jenny M. Wai,<sup>†</sup> Thomas A. Halgren,<sup>\*,†</sup> Paula M. D. Fitzgerald,<sup>‡</sup> Joseph P. Vacca,<sup>§</sup> Bruce D. Dorsey,<sup>§</sup> Rhonda B. Levin,<sup>§</sup> Wayne J. Thompson,<sup>§</sup> L. Jenny Chen,<sup>§</sup> S. Jane deSolms,<sup>§</sup> Neil Gaffin,<sup>§</sup> Arun K. Ghosh,<sup>§</sup> Elizabeth A. Giuliani,<sup>§</sup> Samuel L. Graham,<sup>§</sup> James P. Guare,<sup>§</sup> Randall W. Hungate,<sup>§</sup> Terry A. Lyle,<sup>§</sup> William M. Sanders,<sup>§</sup> Thomas J. Tucker,<sup>§</sup> Mark Wiggins,<sup>§</sup> Catherine M. Wiscount,<sup>§</sup> Otto W. Woltersdorf,<sup>§</sup> Steven D. Young,<sup>§</sup> Paul L. Darke,<sup>⊥</sup> and Joan A. Zugay<sup>⊥</sup>

# Aqvist, HIV-1 RT

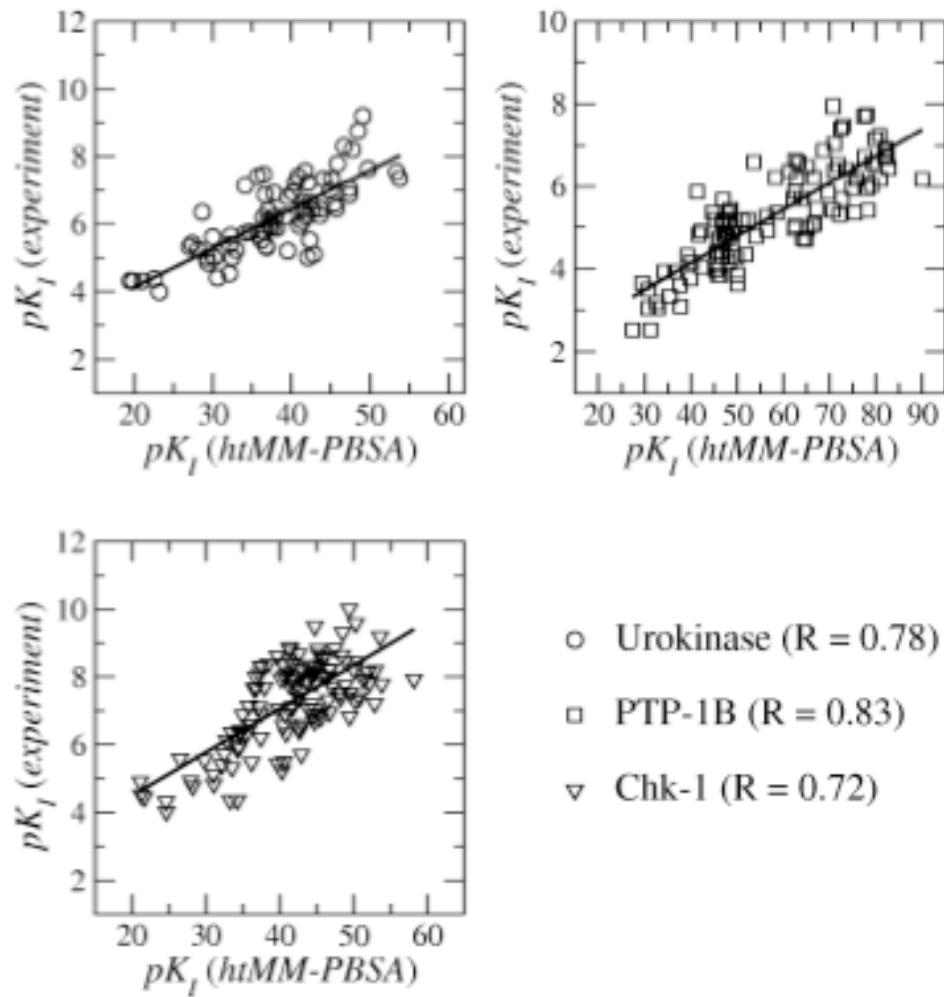


Some of the points



All of the points

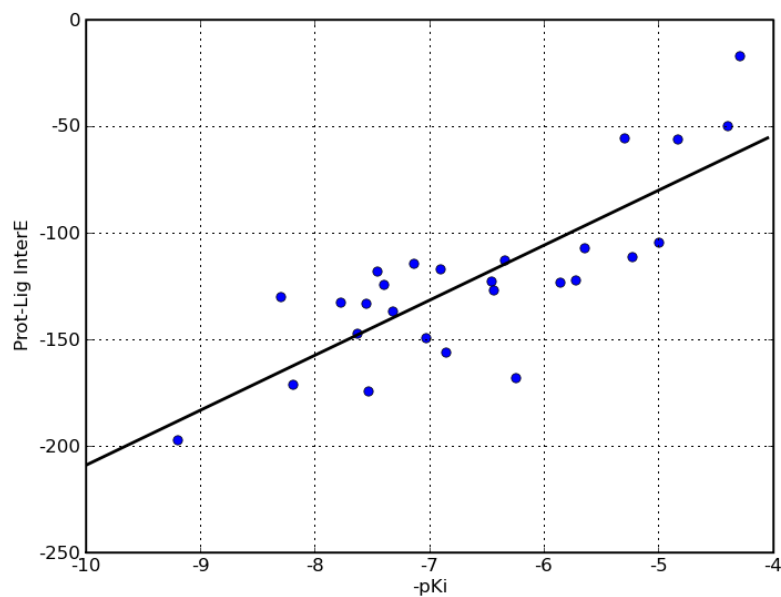
# MMPB



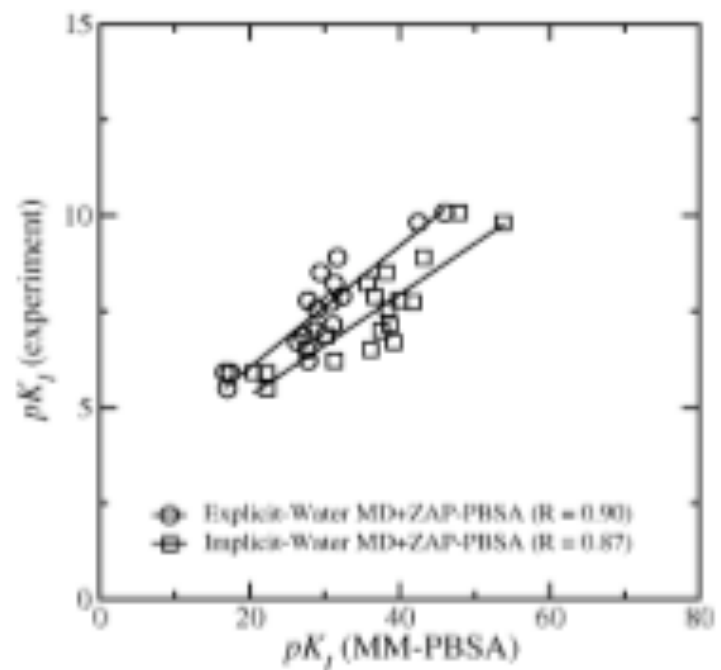
Brown & Muchmore, Abbott Labs, J. Med. Chem, 2009

# Not really

- Urokinase, SAMPL1



Coulombic Interaction



Brown & Muchmore, JCI, 2007, (47) 4

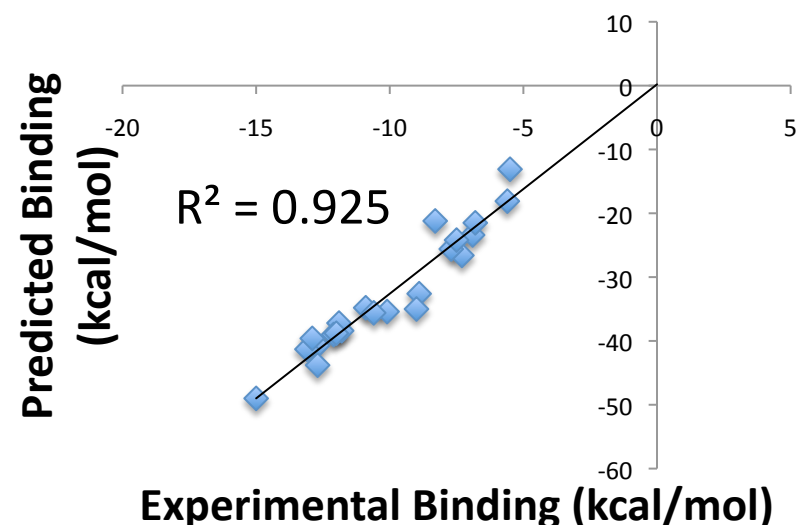
# Really, Not really.

“Fast and Accurate Predictions of Binding Free Energies using MM-PBSA and MM-GBSA”

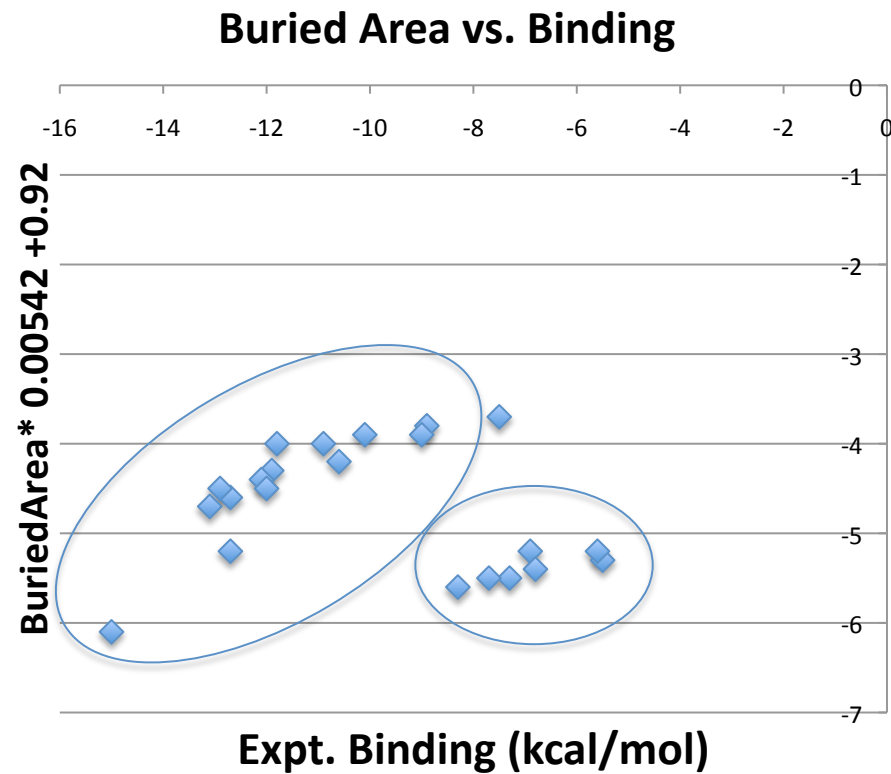
– Rastelli, G., Del Rio, A., Degliesposti, G., Sgobba, M.  
J. Comp. Chem. Vol 31, #4, pg

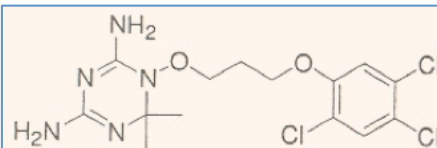
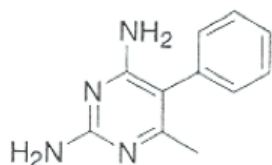
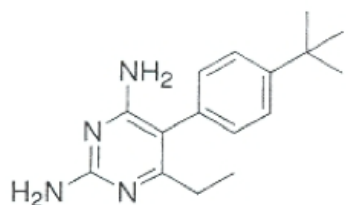
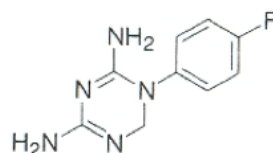
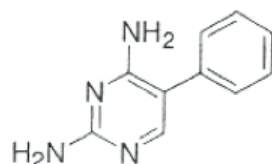
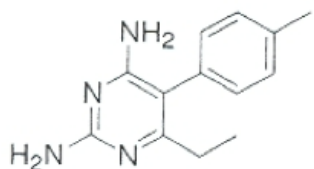
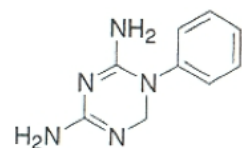
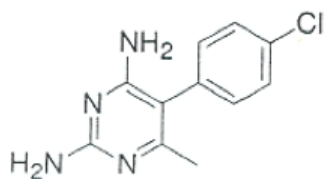
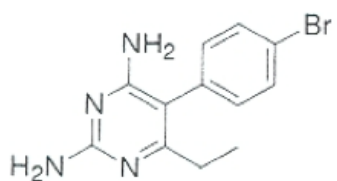
797-810

- *Pf* DHFR
- 2ns simulations
- 22 inhibitors
- 7 orders of magnitude of activity
- Single snapshot and ensembles

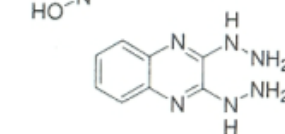
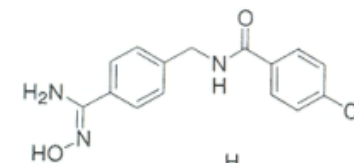
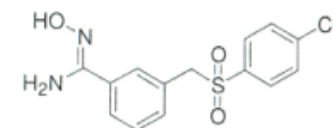
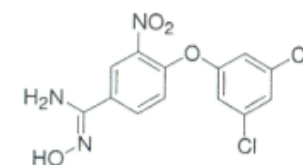
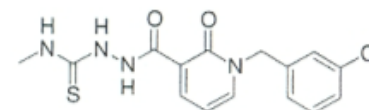
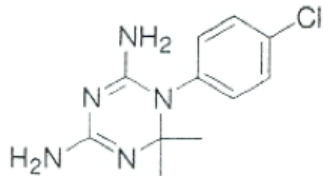
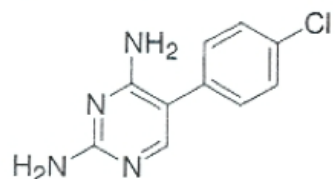


# Deconstructionism

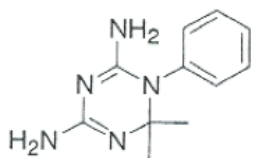
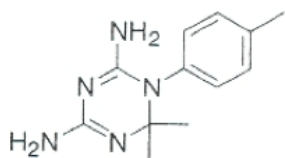




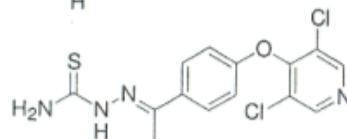
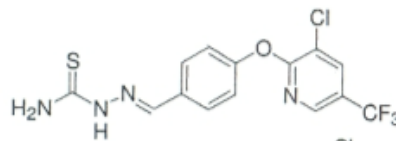
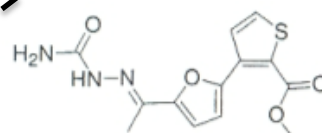
WR99210  
PDB1J31  
Charged  
11pm



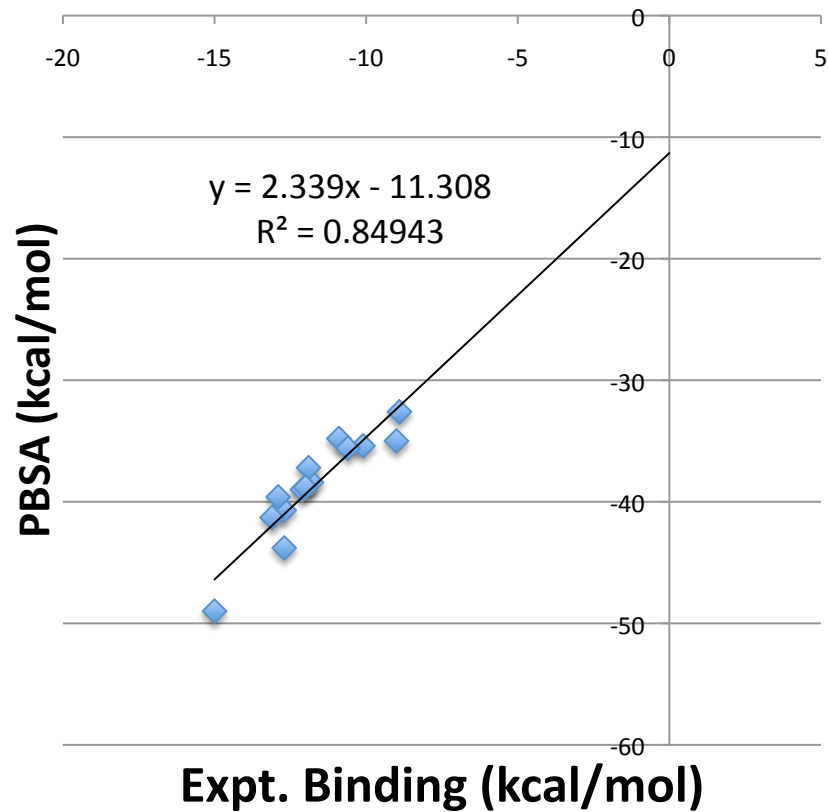
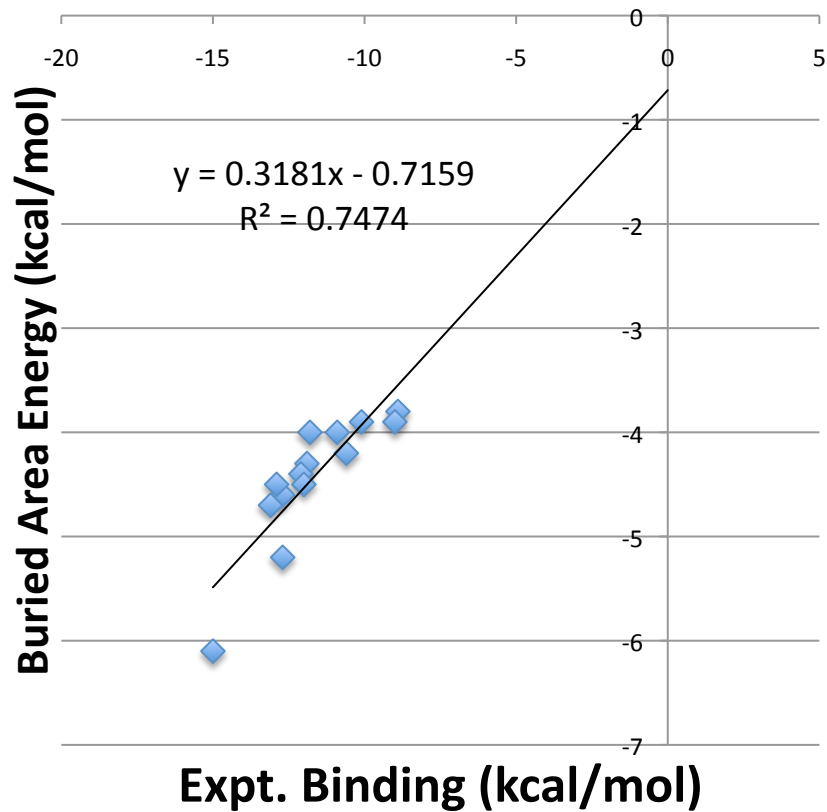
Variants of  
WR99210  
Charged  
<330nm



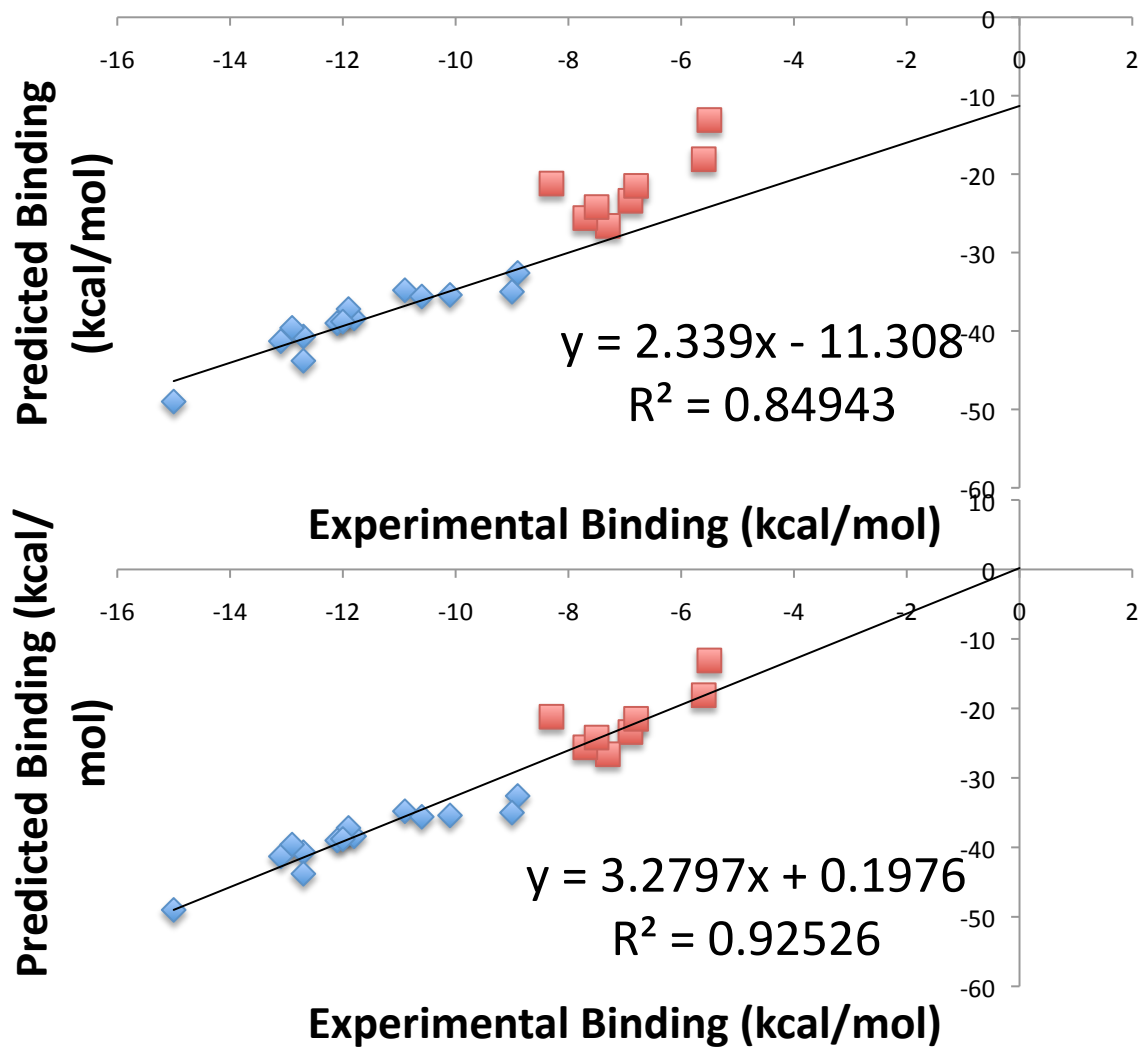
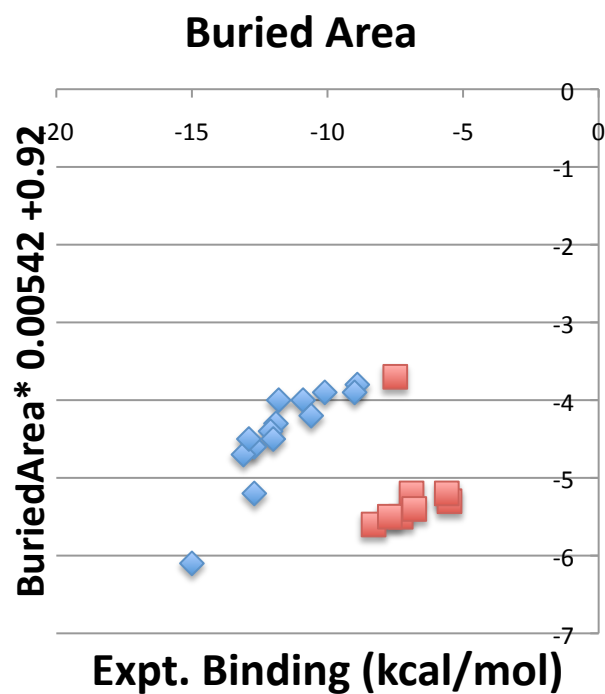
'Others'  
Neutral  
>330nm



# Just the 'Charged' Molecules



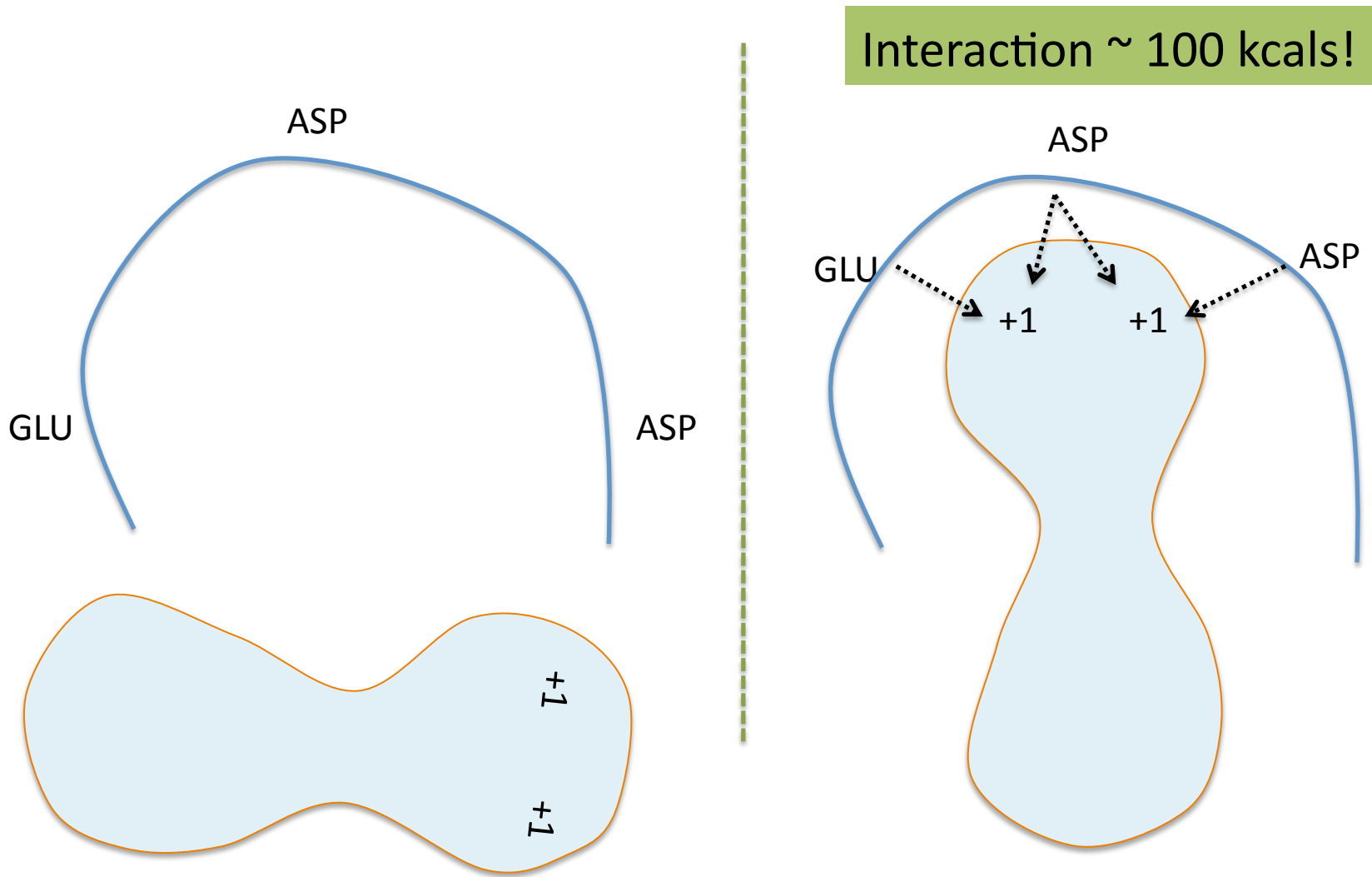
# How to make a Great Fit



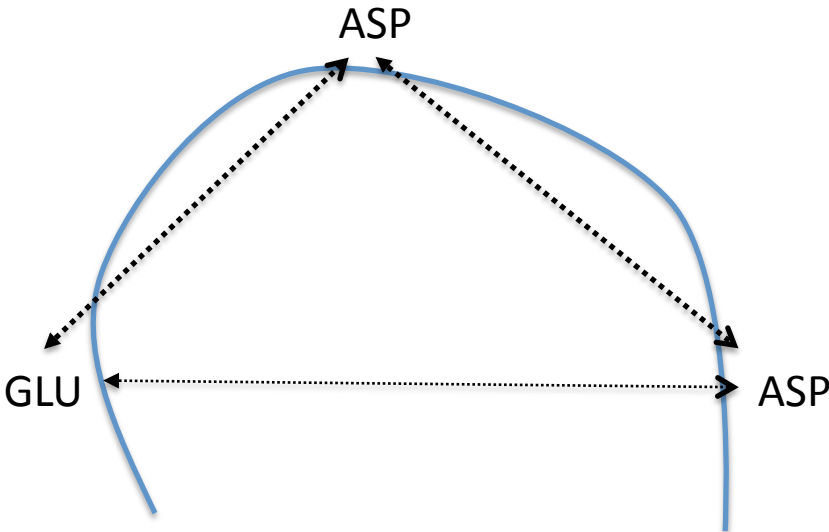
# So what's wrong with MM/PBSA?

- Proper conformational averaging
- Proper Entropy estimation
- Polarization
- Ionization states
- Reorganization energy of the protein

# Reorganization

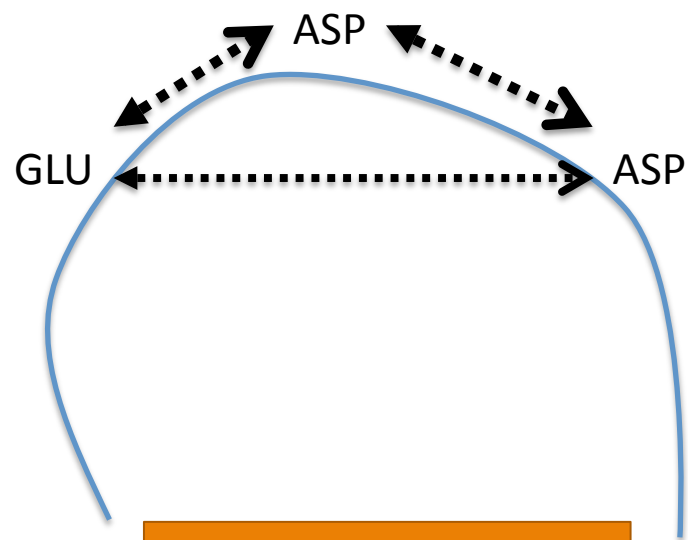


# Reality



Strain ~ 20 kcals

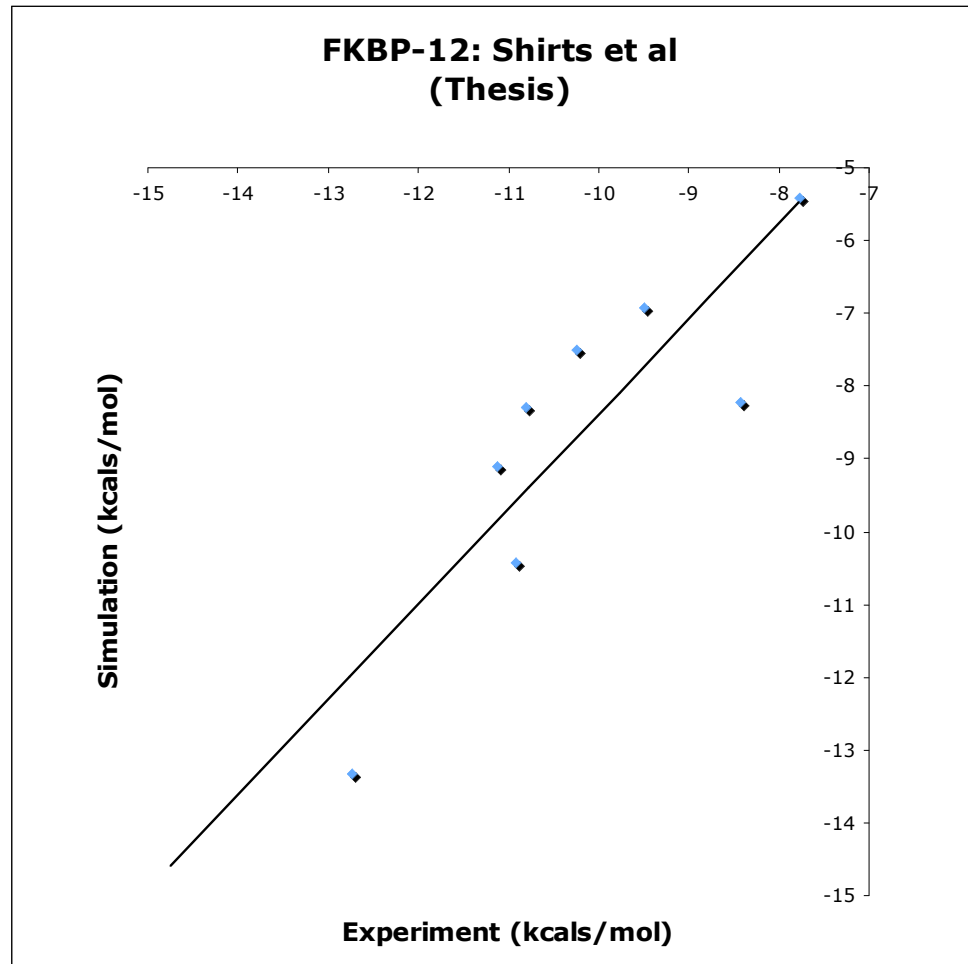
Interaction ~ 100 kcals!



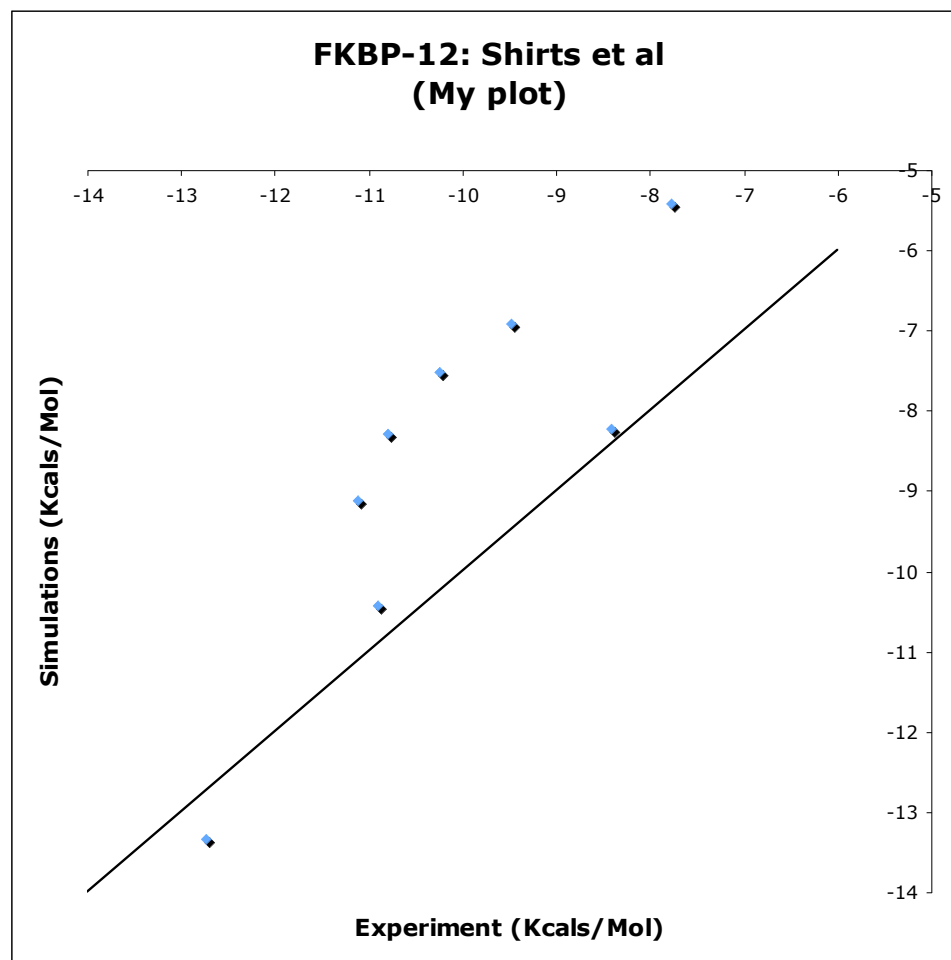
Strain ~ 120 kcals

Total ~ 0 kcals

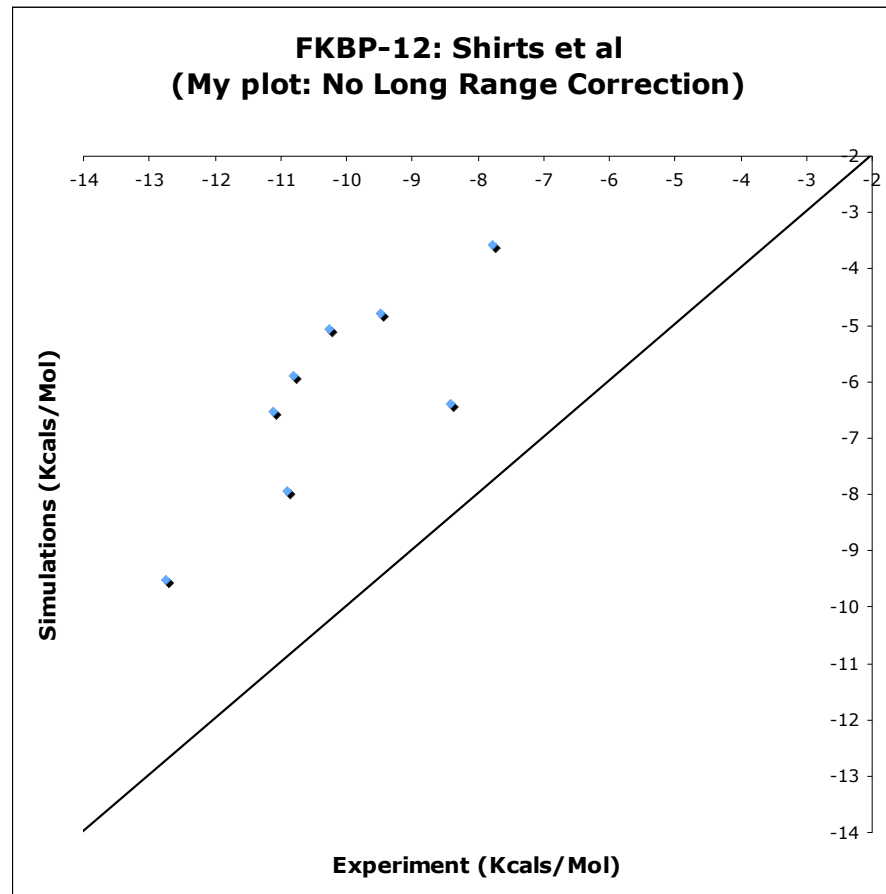
# FKBP-12



# FKBP-12 Again



# FKBP-12 Yet Again



# Fujitsu: Same Data

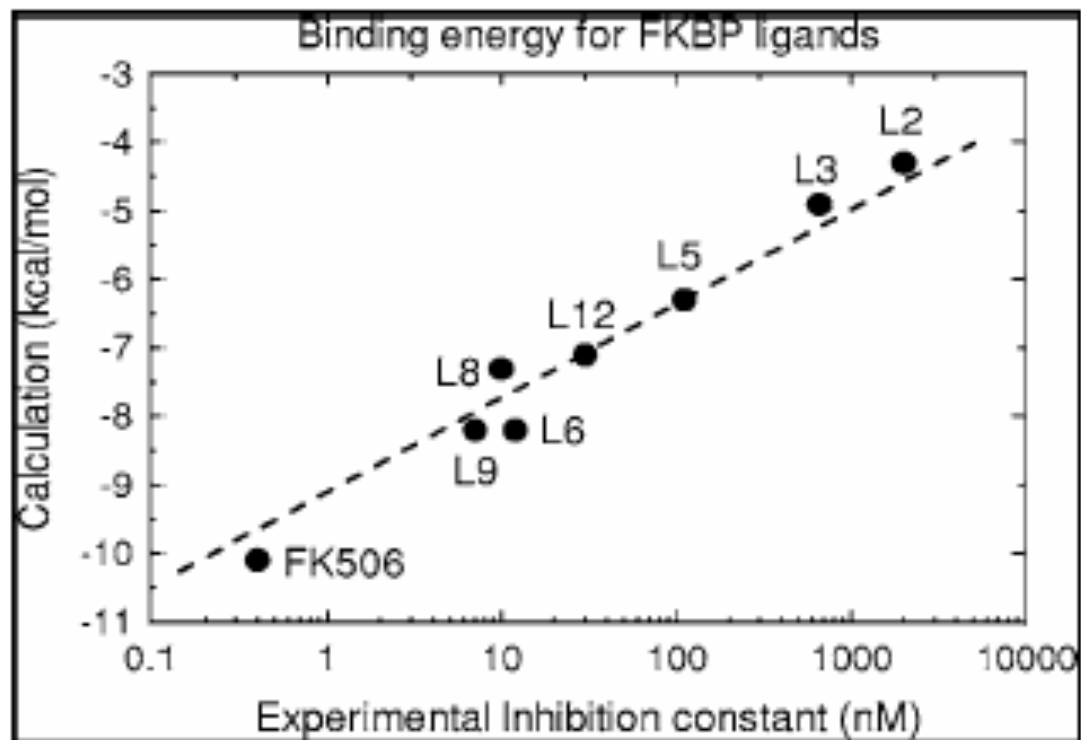


Fig2: Comparison between computed values and experimental values (FKBP-8ligands).<sup>2</sup>

# My observation over 20 years

- For congeneric series of molecules, something basic usually correlates, sometime well
- For random sets of molecules, on some targets sometimes have some correlation
- For random sets on random targets, nothing works

# The Big Four

Contribution	Abb.	Proportional To:	Notes
VdW	V	Contact Area	
Coulombic	C	VdW	For good binders
Desolvation	D	-Coulombic	For good binders
Buried Area	B	Contact Area	

(S)Talking Points:	Polarization	proportional to Coulombic
	Discrete Waters	proportional to Buried Volume
	Entropy	proportional to Total Energy

“Cancellation of errors is proportional to chemical similarity”

## Example: Doing worse by adding PB

$$\text{Actual } C = 2 * V + \{-2, 2\}$$

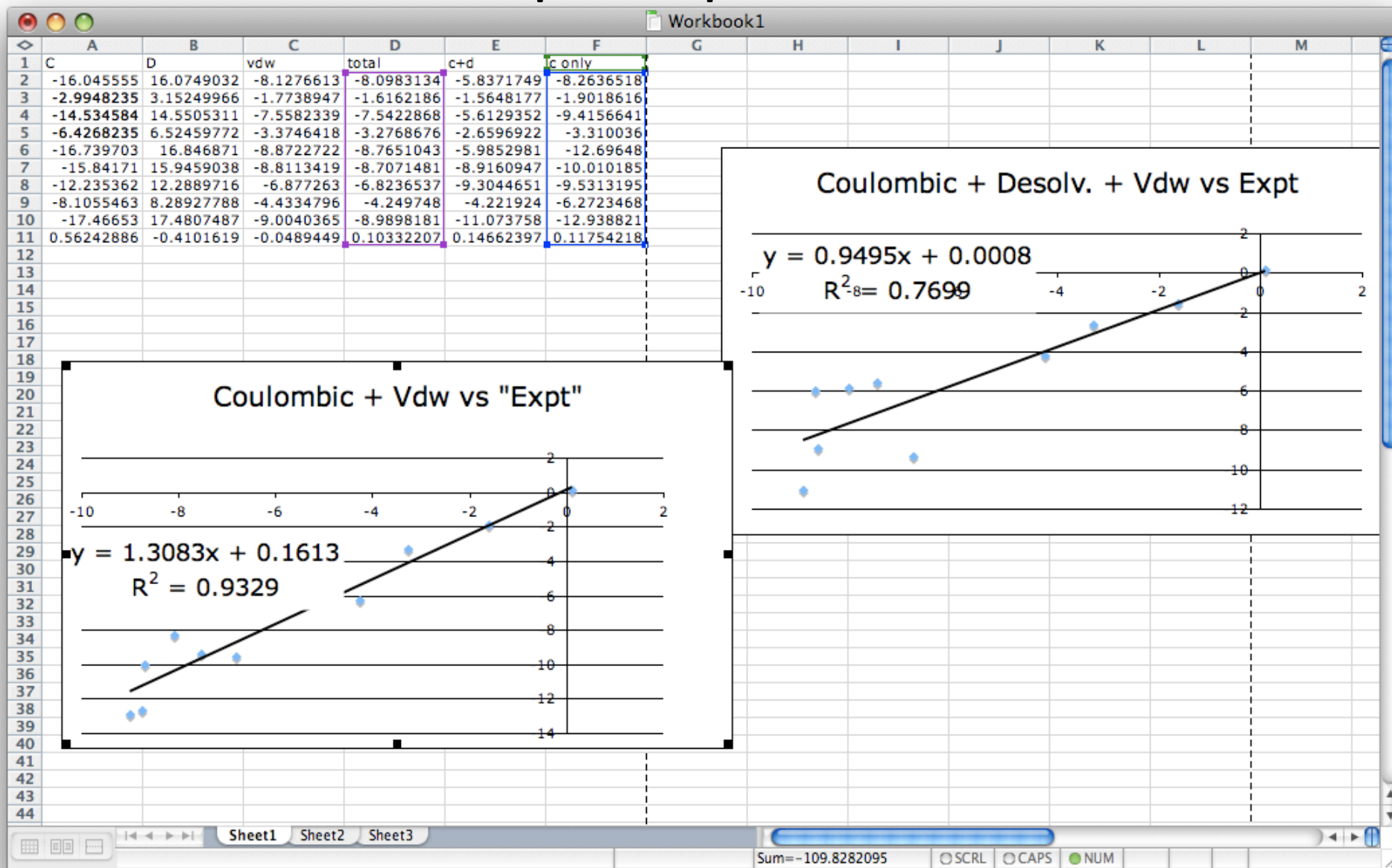
$$\text{Actual } D = -C + \{-0.25, 0.25\}$$

$$\text{Binding} = V + C + D$$

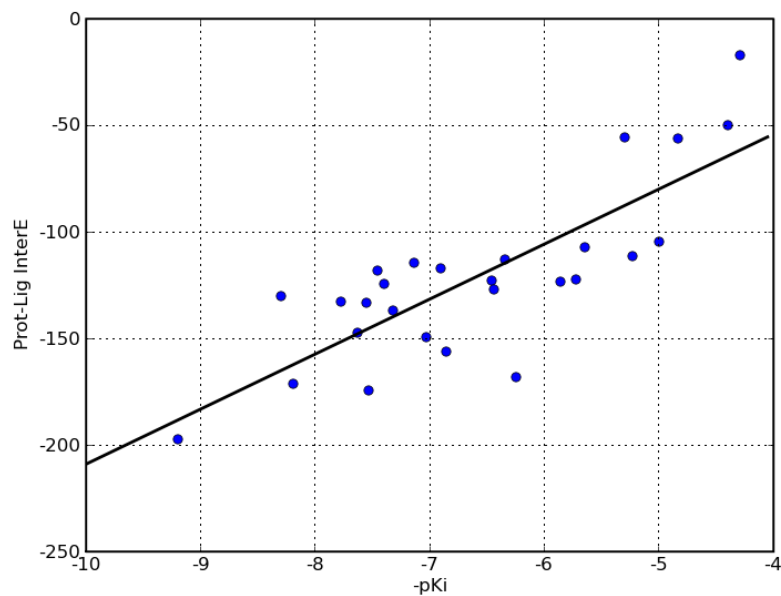
$$\text{Calculated } C = \text{Actual } C * \{0.75, 1.25\}$$

$$\text{Calculated } D = \text{Actual } D * \{0.75, 1.25\}$$

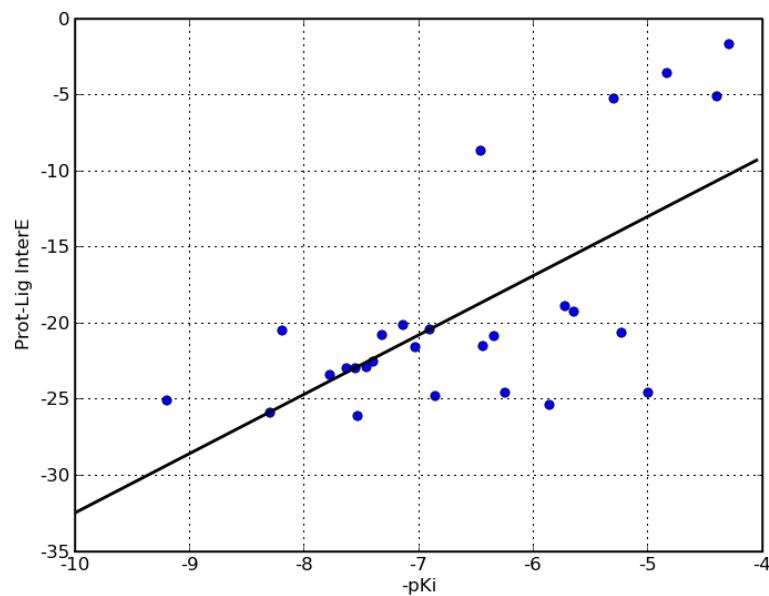
# Example Experiment



# Worse with PB: Urokinase, SAMPL1

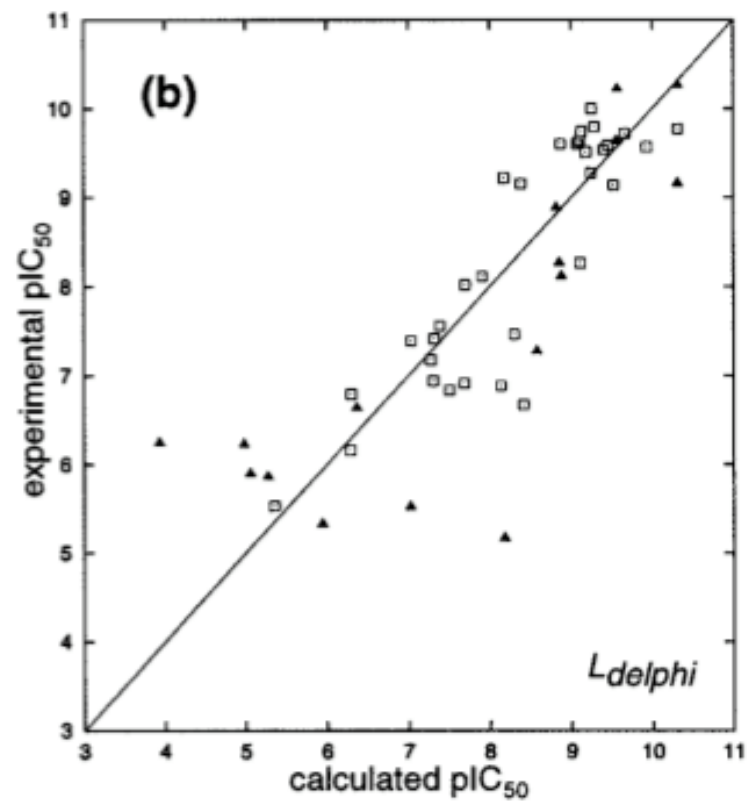
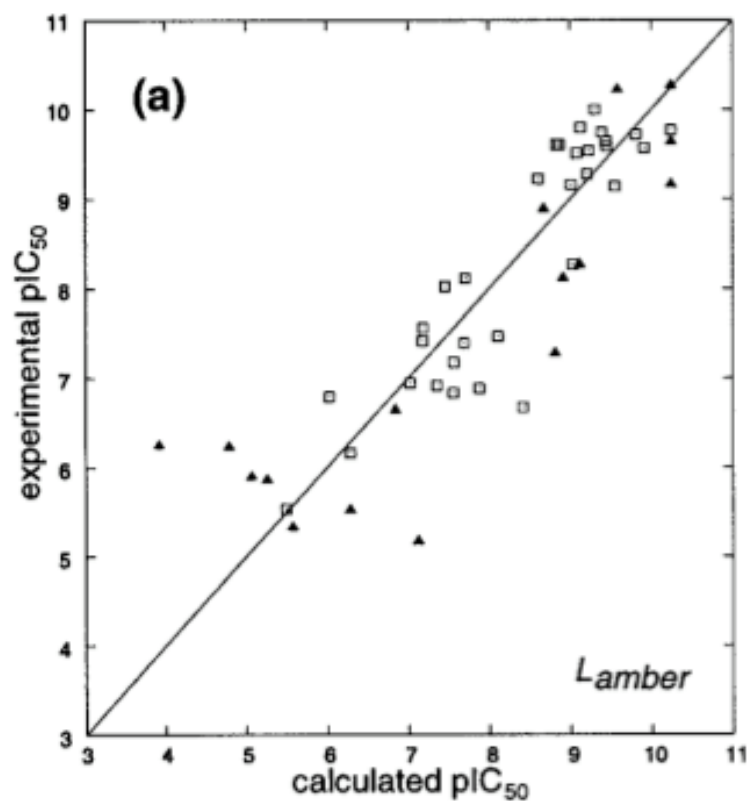


Coulombic Interaction



PB Interaction

# Worse with PB: HIV Protease



Comparative Binding Energy Analysis of HIV-1 Protease Inhibitors:  
Incorporation of Solvent Effects and Validation as a Powerful Tool in  
Receptor-Based Drug Design

Carlos Pérez, Manuel Pastor, Angel R. Ortiz,<sup>†</sup> and Federico Gago\*

# My Beliefs

- All methods with some physics do well on some systems
  - Correlation of components, errors cancel
- No method without all physics can do well on all systems
  - But not always
- How do you know when you have all the physics?
  - Binding slope is 1.0