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What Can We Learn from the Evolution of Protein-Ligand Interactions to Aid the Design of New Therapeutics?

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Overview

- Introduction
- Protein-protein interactions as drug targets
  - TIMBAL db
- Molecular recognition in structural databases
  - Comparison of different molecular subsets
  - Polarity of interactions
  - Interaction profile vs molecular properties
- Conclusions

Introduction

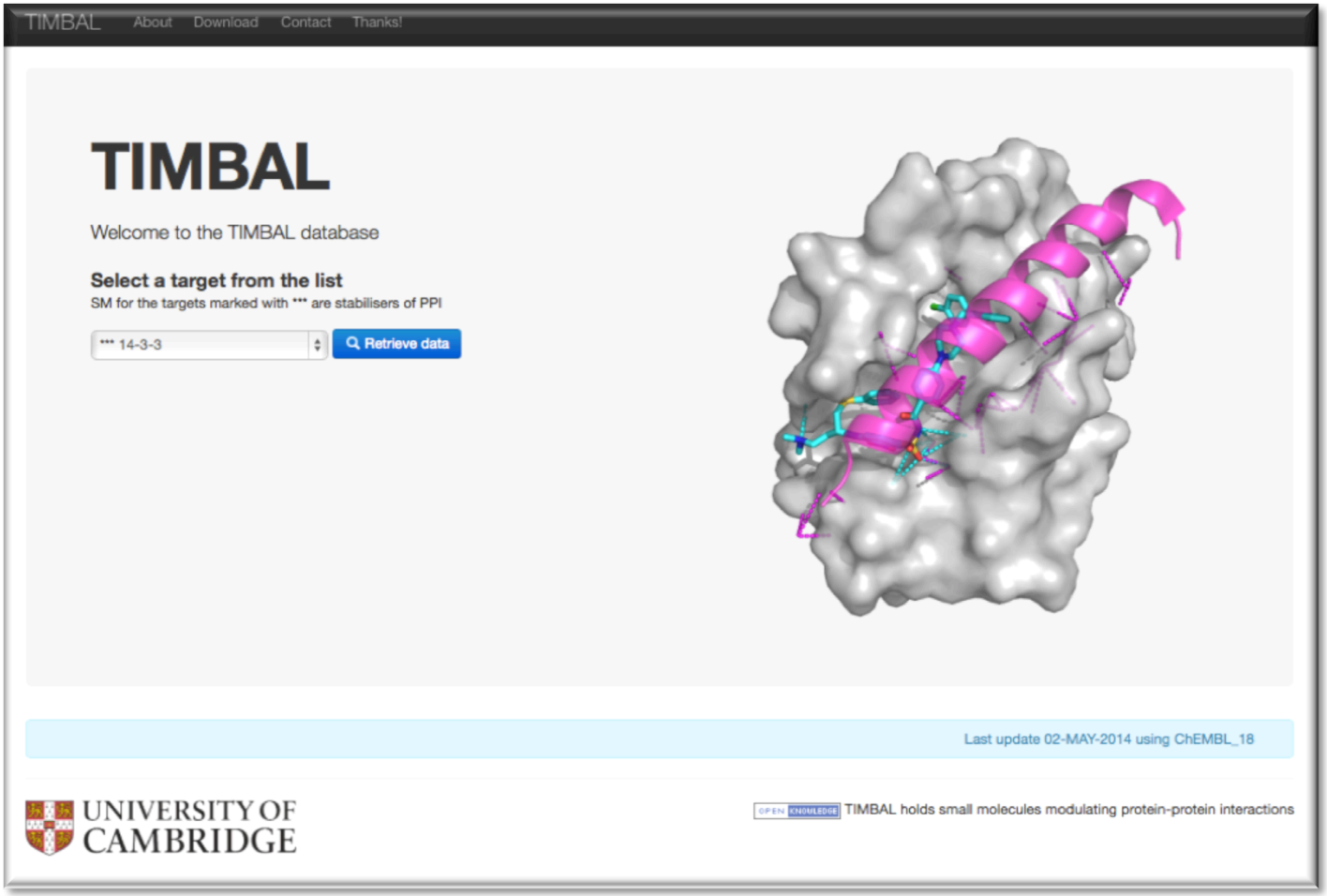
- The struggle of drug discovery to deliver drugs into the market is a many fold problem
  - From target selection to FDA regulations
- Focusing in the profile of drug candidates
  - Small molecules are far too lipophilic (*)
  - Correlation of logP with compound promiscuity (**)
  - Current opinion in DD is to try to keep logP low

* Molecular obesity, Hann 2011, MedChemComm 2:349
** Leeson & Springthorpe 2007, NatRevDD 6:881
** Gleeson et al 2011, NatRevDD 10:197

Introduction

- The struggle of drug discovery to deliver drugs into the market is a many fold problem
  - From target selection to FDA regulations
- Focusing in the profile of drug candidates
  - Small molecules are far too lipophilic
  - Correlation of logP with compound promiscuity
  - Current opinion in DD is to try to keep logP low
- Pursuing other targets
  - Protein-protein interactions

TIMBAL database – PPI modulators



www-cryst.bioc.cam.ac.uk/timbal

TIMBAL database - analyses

- In comparison with drugs and screening sets, small molecules disrupting protein-protein interfaces are
  - Bigger
  - More lipophilic
  - Less hydrogen bonding
- In correlation with the type of contacts these molecules made

Chem Biol Drug Des. 2009. 74(5):457-67

That's interesting

- Large, sticky, lipophilic molecules with few HB features are likely to be:
  - Promiscuous
  - Difficult to develop into a drug

Natural questions:

- Is this a requirement of the multi-protein interfaces?
- Or a short cut in Medicinal Chemistry?

Can we study molecular recognition?

From our structural databases

CREDO
- protein – small molecules
- protein – small peptides

PICCOLO
- protein – protein

Contact definitions

- Hydrogen-bonds calculation are not trivial
  - Proteins have a finite number of atom types
  - Small molecules are too diverse

- Homogenous definition of contacts for cross-comparison
  - Simple distance cut-off and atom type

Polar and apolar contacts

Can we study molecular recognition?

trends of

atomic interactions (polar *vs* apolar)

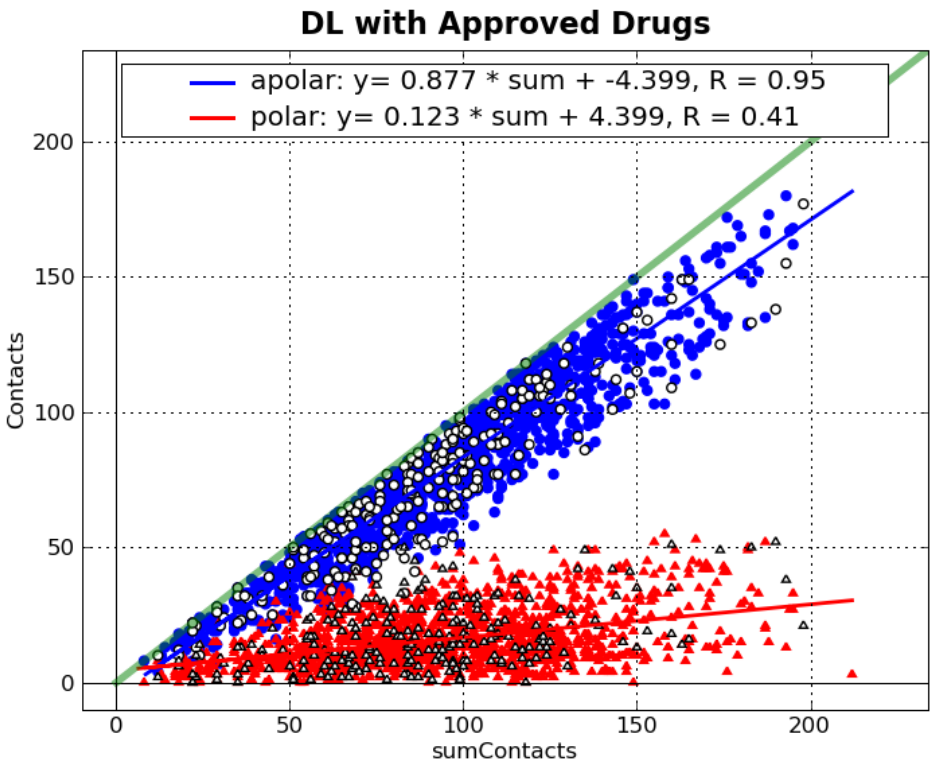
for

meaningful **subsets of molecules**

Subsets from CREDO and PICCOLO

	Subset	Annotation source
Small molecules	Synthetic small molecules	Chemical filters
	Approved and oral drugs	DrugBank, ChEMBL
	Natural Molecules	KEGG, HMDB, ChEMBL
	Small Peptides	CREDO
	PPI Inhibitors	TIMBAL
Proteins	Obligate / transient dimers	Mintseris, NOXClass
	Quaternary interfaces	PICCOLO, PISA

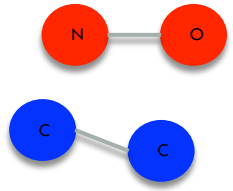
Scissors plots

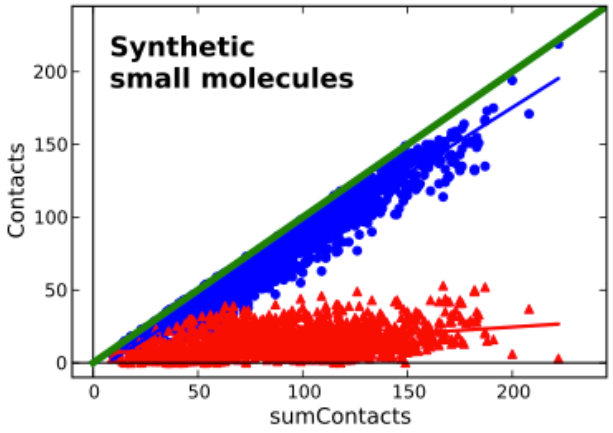


- Plot polar and apolar contacts versus sum of contacts
- Openness of the trend lines gives the ratio of polar contacts versus apolar

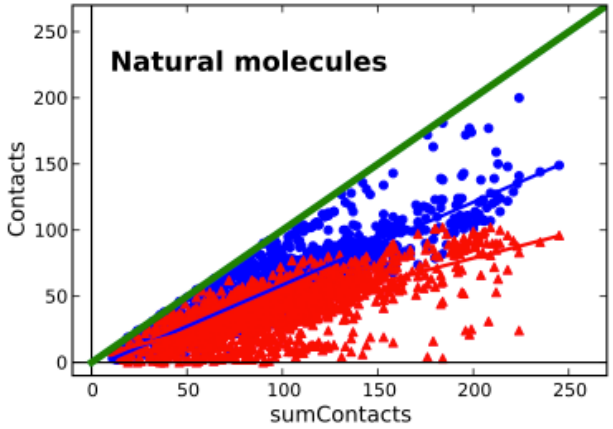
Olsson et al. J Mol Biol. 2008. 384(4):1002-17

Nature does more polar





open



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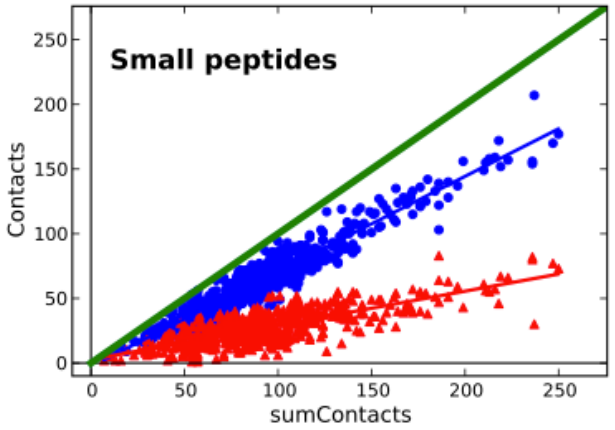
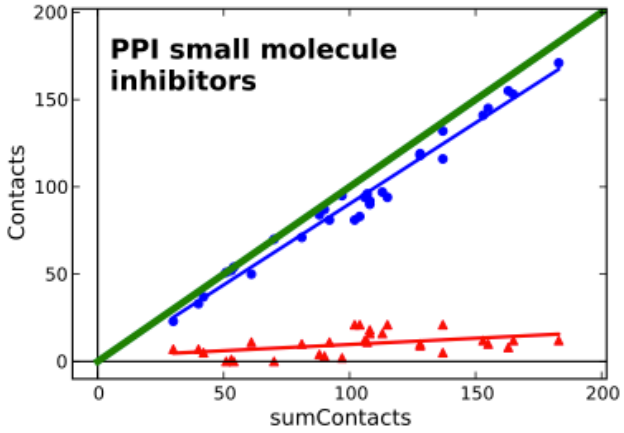
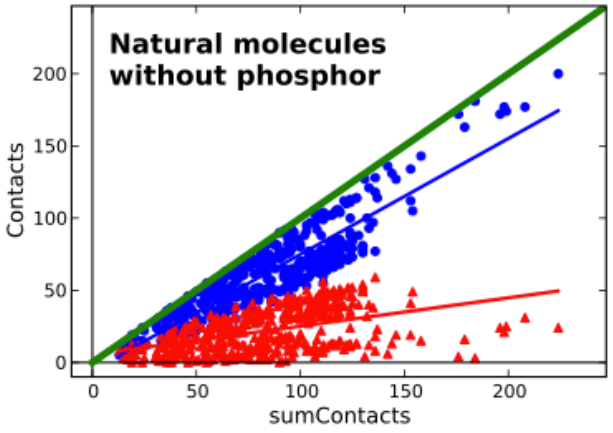
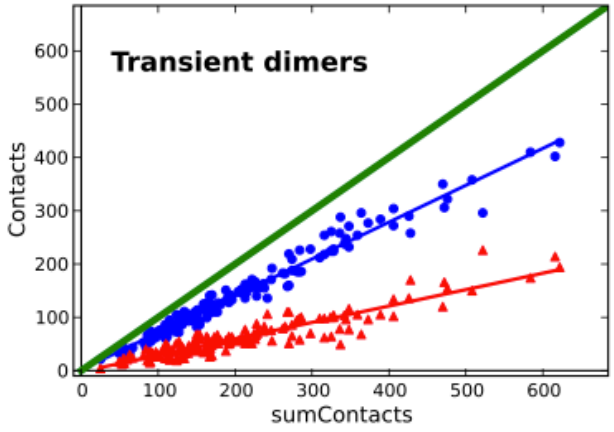


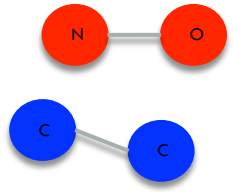
medium

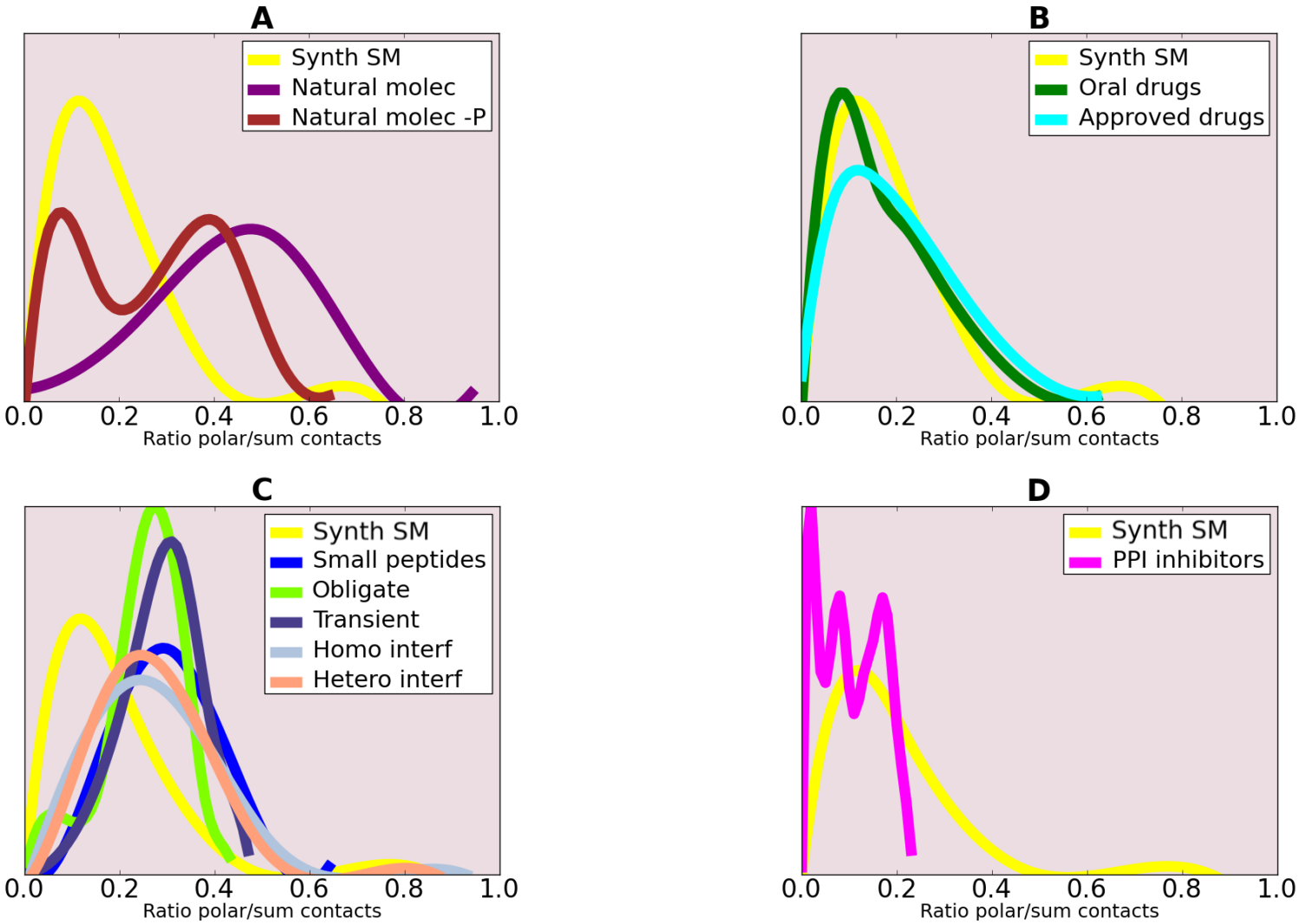






Nature does more polar





How can we explain this?

Atomic composition

heteroatoms ratio

Flexibility

rotatable bonds ratio

Flexibility small molecules

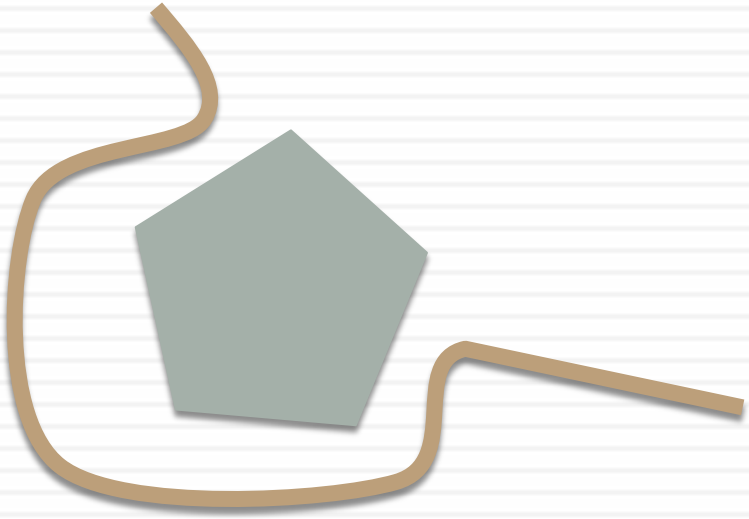
- Count of rotatable bonds and heteroatoms

	Profile	RotBonds / N_at	Hetatms / N_at
Synthetic SM	**Apolar**	Rigid	Low
Natural molecules	**Polar**	Rigid	High
Small Peptides	**Polar**	Flexible	Low

- Natural molecules have higher content in heteroatoms placed in the right conformation
- Peptides compensate the lower heteroatom content with more flexibility

Matched and unmatched atoms

From this molecular composition, how many atoms are successfully interacting with the protein target?



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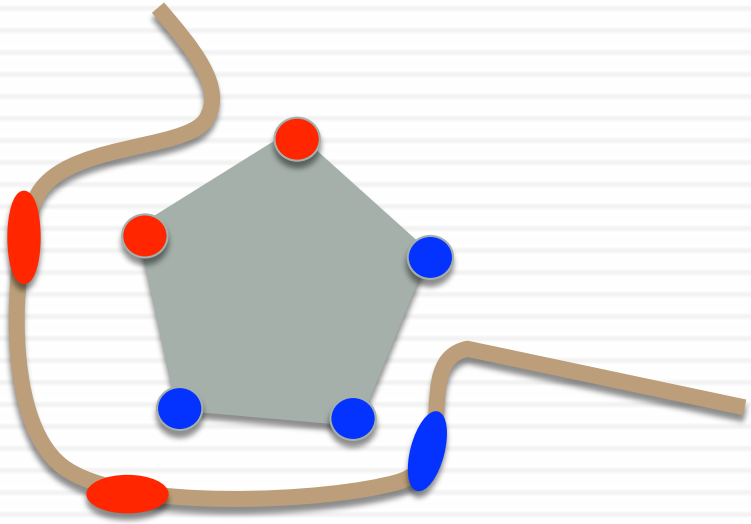
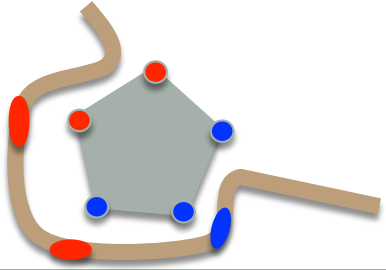
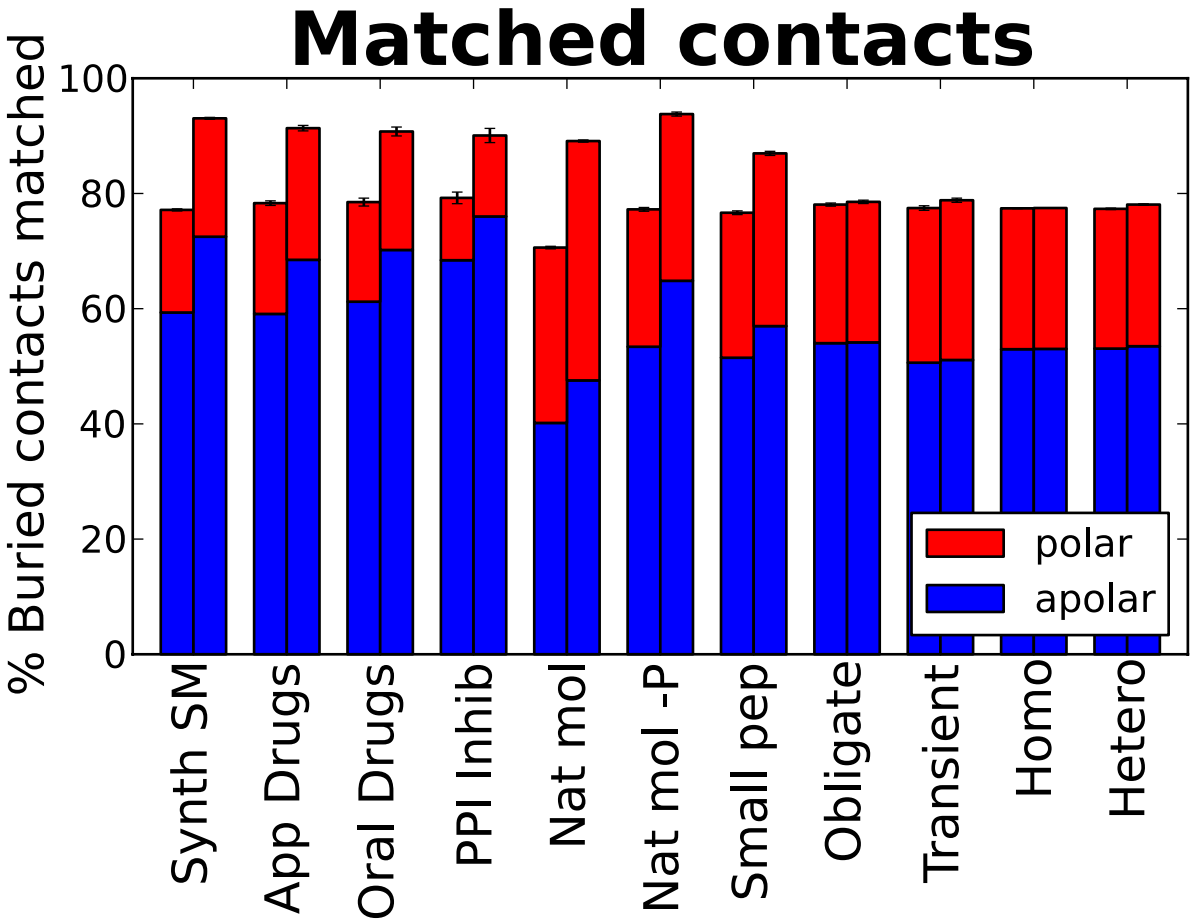


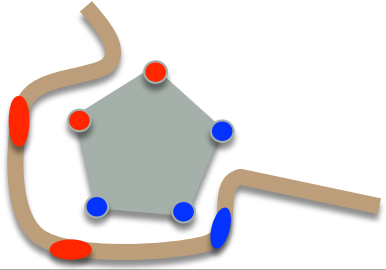
Matched atoms

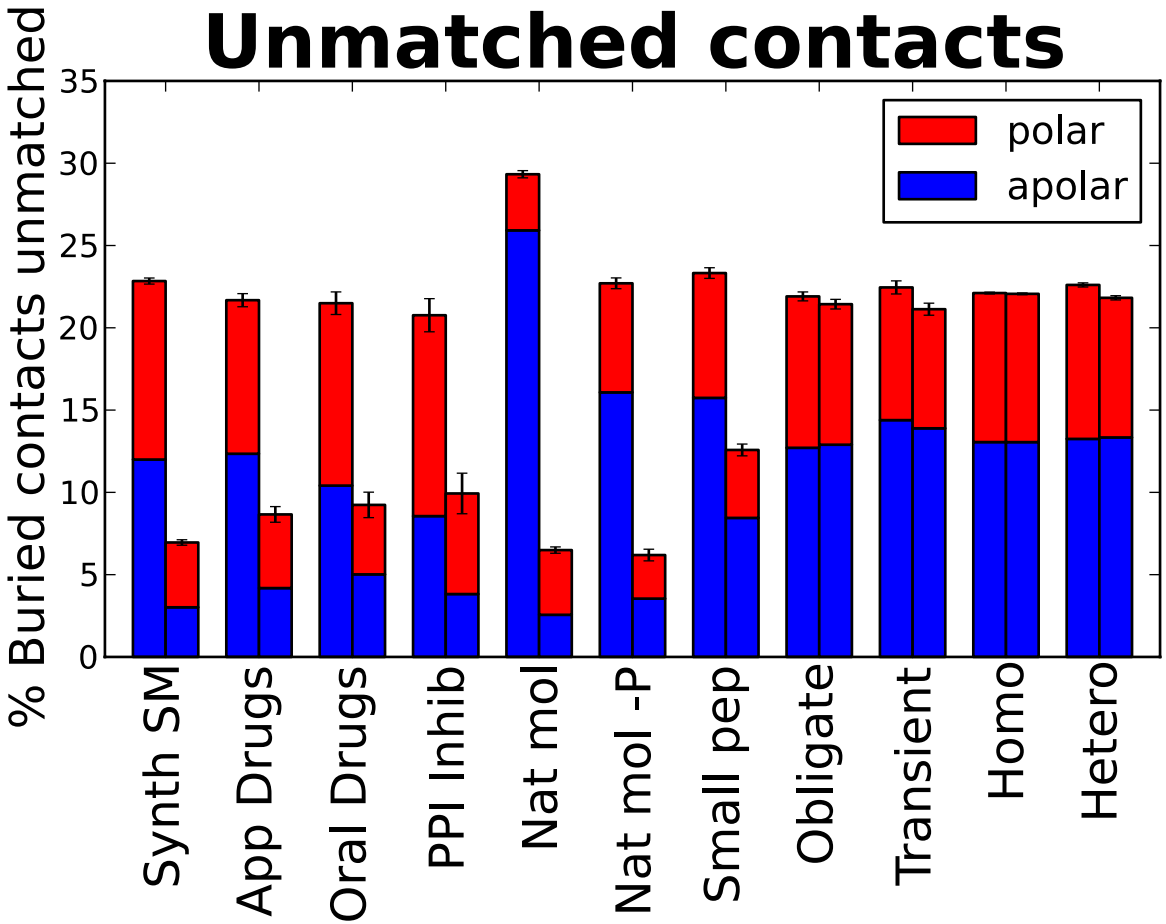




- Small molecules more contact efficient than proteins
- Mainly small molecules are wrapped by the protein

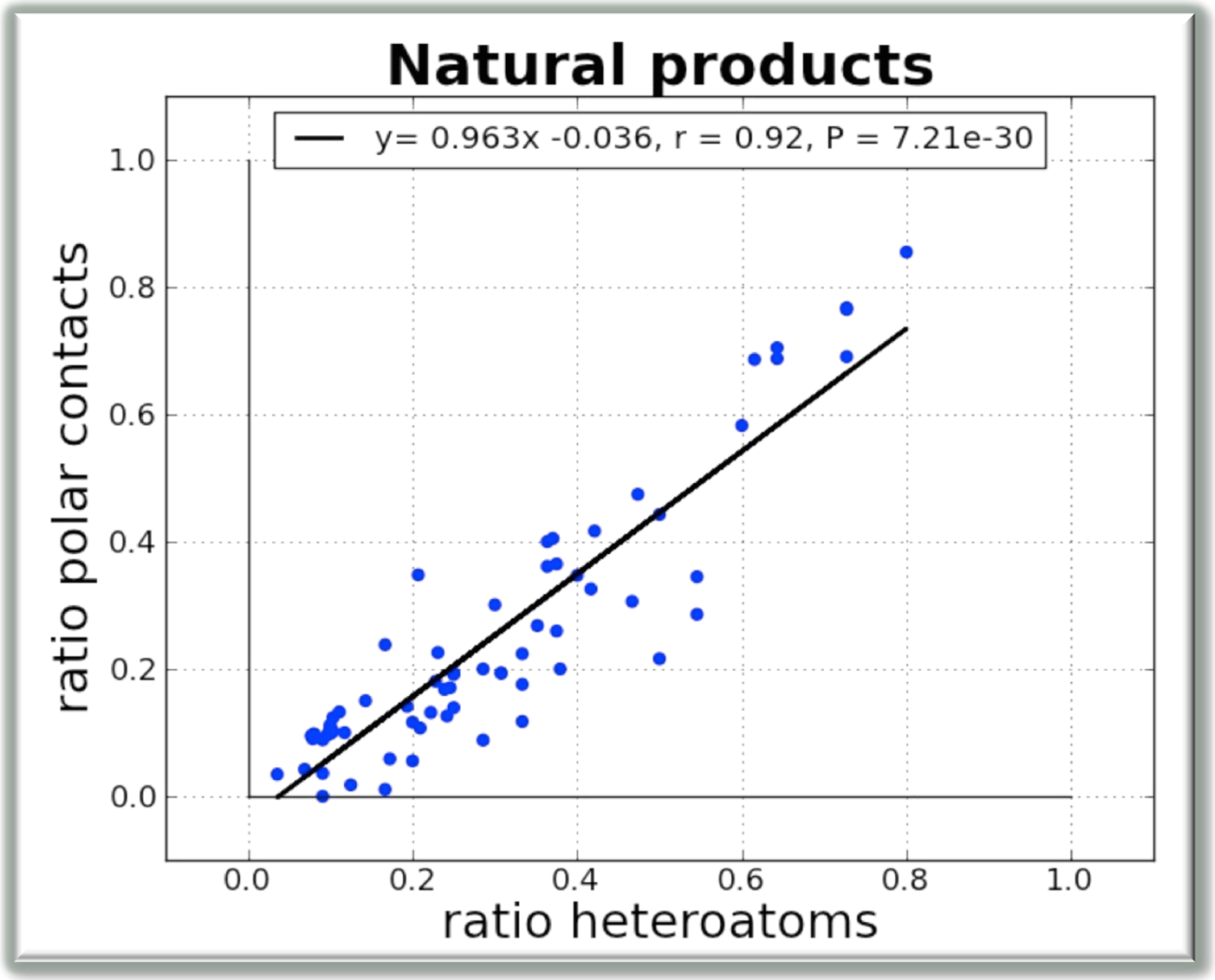
Unmatched atoms





- Synthetic molecules have higher proportion of unmatched polar atoms
- Drugs **are not making the most** of their polar composition

Making the most of your atomic composition



Molecular properties for Drugs

- Natural molecules:
  - Are synthetised in-situ
  - Do not need to be absorbed and distributed

- Maybe what it takes to be a drug constrains the polar specific contacts that a drug-like molecule can make?

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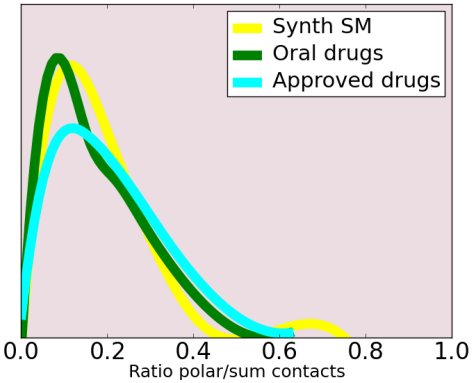
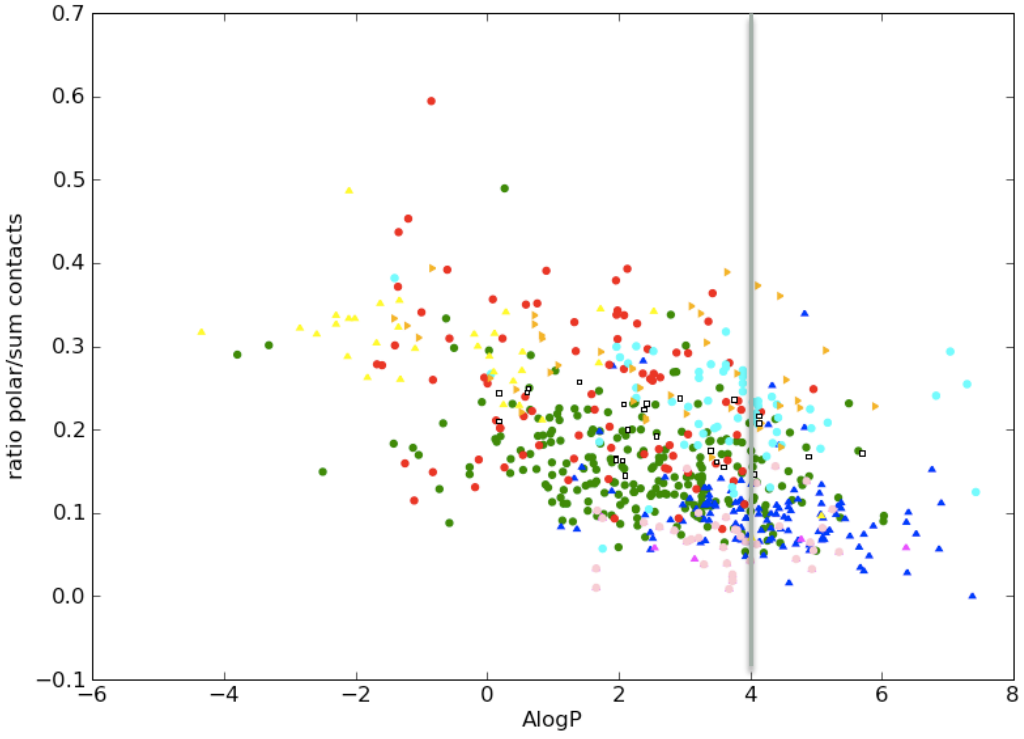


Properties *vs* interaction profile

For synthetic small molecules

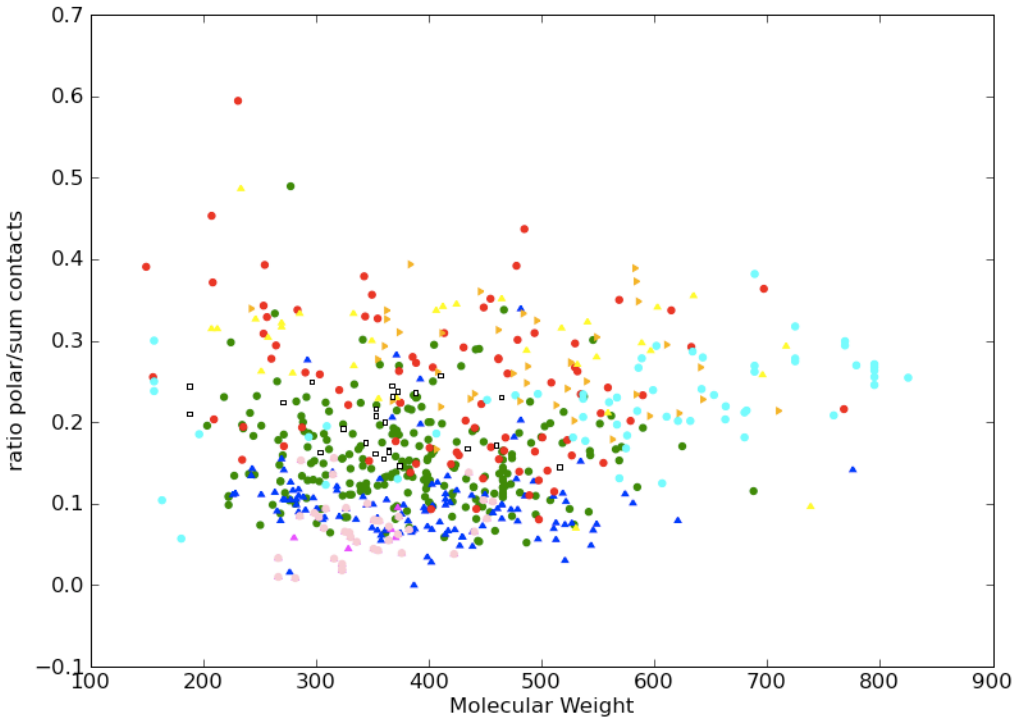
Synthetic small molecules: properties and interaction profile



Synthetic small molecules bound to different SCOP fam

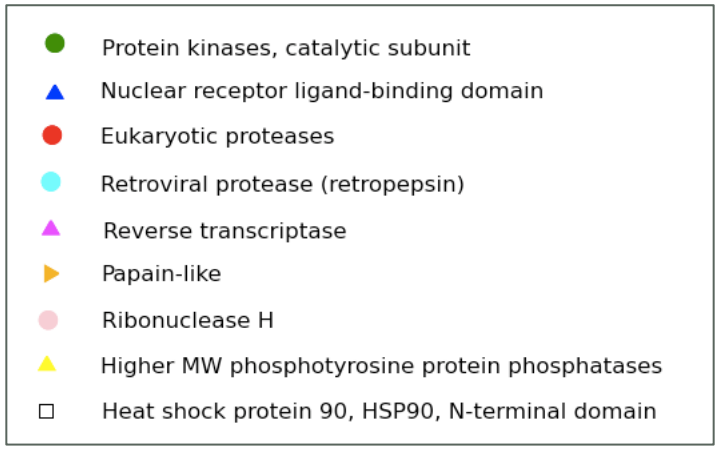
- Trends depending on their targets
- **No correlation** between lipophilicity or MW and polar interactions
- ex:
  - logP 4 presents a range of 4-37% polar contacts

Synthetic small molecules: properties and interaction profile



Synthetic small molecules bound to different SCOP fam

- But
  - higher polar ratio happens for smaller molecules (fragments)



Going back to the initial question…

- Large, sticky, lipophilic molecules with few HB features are likely to be:
  - Promiscuous
  - Difficult to develop into a drug

Natural questions:

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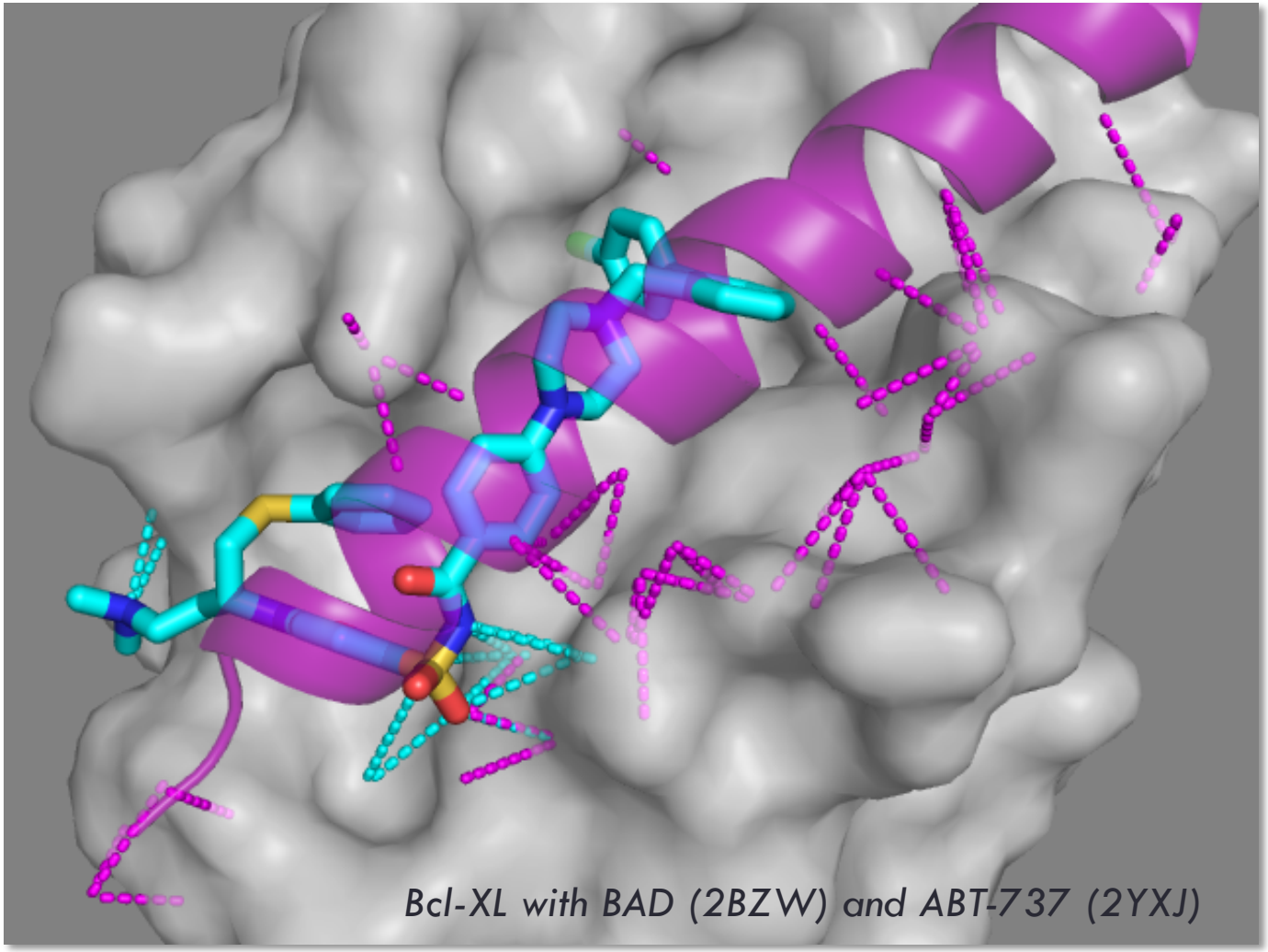
- Or a short cut in Medicinal Chemistry?

Protein-protein inhibitors



Conclusions I

- Natural complexes typically engage more polar interactions than synthetic molecules
- Synthetic small molecules have higher proportion of unmatched heteroatoms
- For synthetic small molecules in general, but for PPI in particular we conclude that early efforts should be invested to increase polar contacts
  - better resemble the interaction patterns of natural molecules
  - minimise promiscuity and poor ADMET profile

Conclusions II

- Synthetic small molecules show no correlation between logP and ratio of polar contacts
  - suggesting the improvement of specific interactions should not change drastically the molecular properties
- Ratio of polar contacts is higher for smaller molecules
  - Fragments anchor with higher proportion of specific contacts
- Current viewpoints in the field advocate to improve affinity of fragments *before* adding MW to maximise interactions with the original hot spot

Thank you!

- Tom Blundell
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