Dynamic Undocking
a new tool for virtual ligand screening
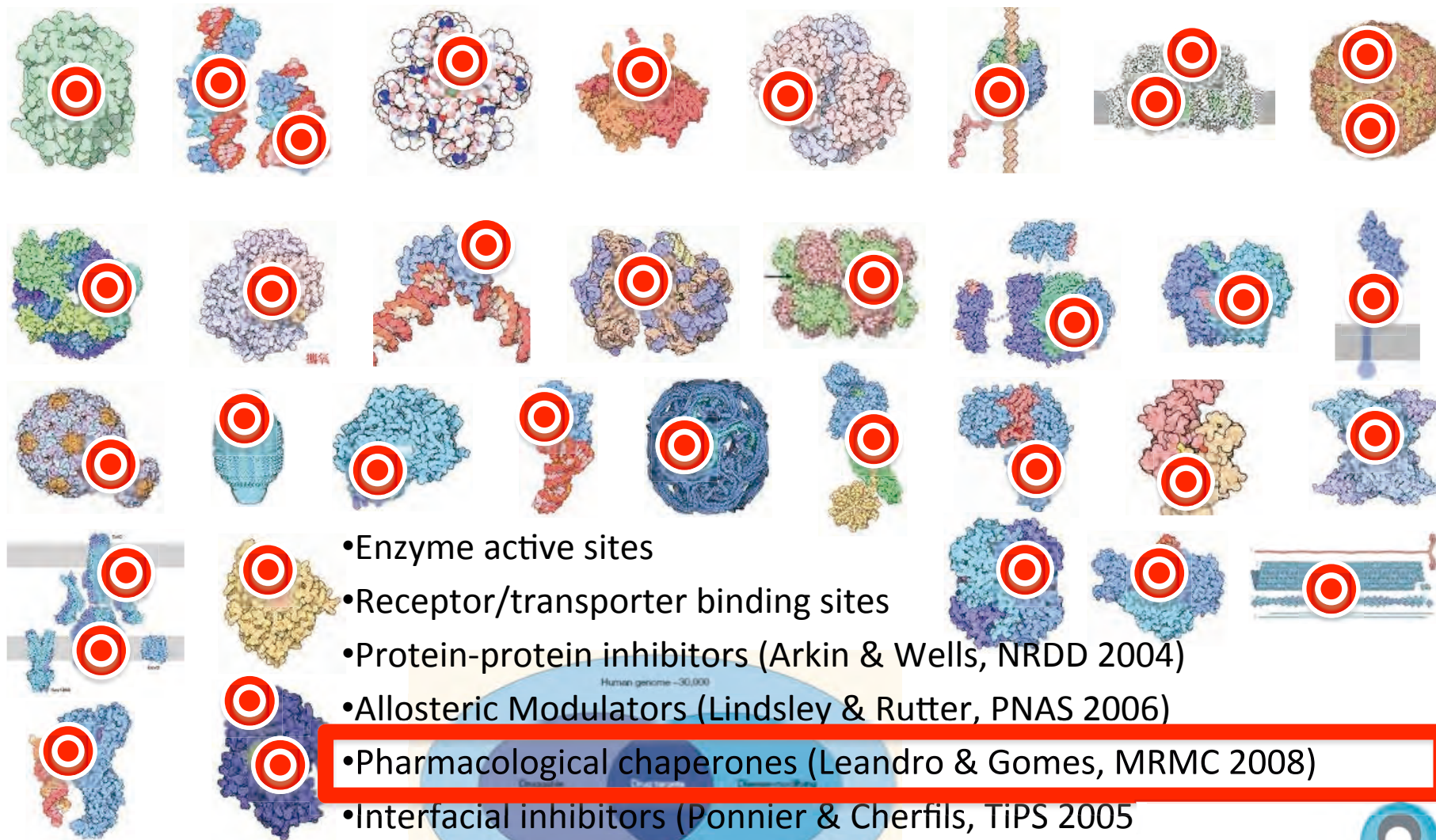
Xavier Barril

ICREA Research Professor at Barcelona University

10th RES Users'Conference

León, 20 de Septiembre de 2016

UNIVERSITAT DE BARCELONA

ICREA

Our Mission: Expanding the druggable genome

- Enzyme active sites
- Receptor/transporter binding sites
- Protein-protein inhibitors (Arkin & Wells, NRDD 2004)
- Allosteric Modulators (Lindsley & Rutter, PNAS 2006)
- Pharmacological chaperones (Leandro & Gomes, MRMC 2008)
- Interfacial inhibitors (Ponnier & Cherfils, TiPS 2005
- Transient binding drugs (Ohlson, DDT 2008)
- RNA (Guan & Disney, ACS Chem. Biol. 2012)

minoryx
therapeutics

Exploring uncharted territory

Identification of druggable sites

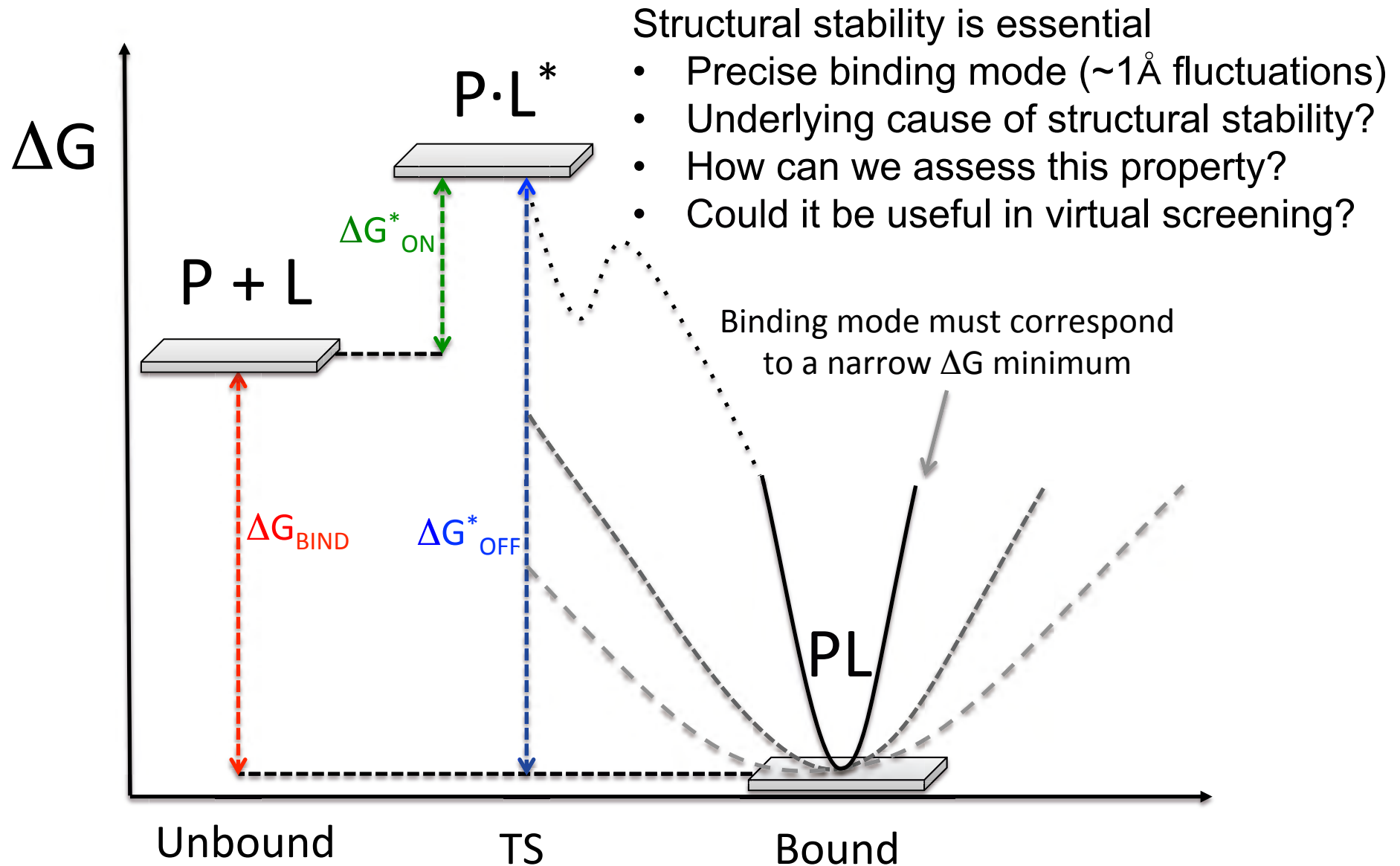## Improving success rates in hit ID

Virtual Library ~1.5M cpds → Hits

Discovery of chemical probes

Dynamic Undocking & the Quasi-Bound State

New concepts for Hit ID

Thermodynamics: is that all?

Structural stability is essential
- Precise binding mode (~1Å fluctuations)
- Underlying cause of structural stability?
- How can we assess this property?
- Could it be useful in virtual screening?

Binding mode must correspond to a narrow ΔG minimum

ΔG

$P \cdot L^*$

$P + L$

ΔG^*_{ON}

ΔG_{BIND}

ΔG^*_{OFF}
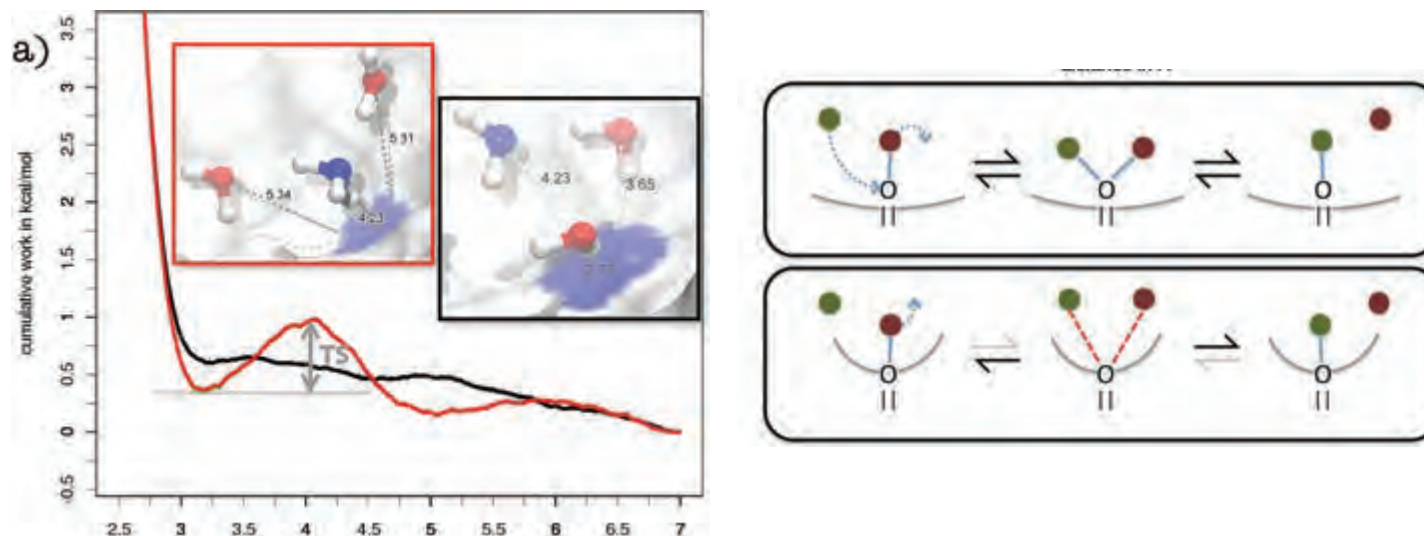
PL

Unbound

TS

Bound

H-bonds: Determinants of Structural Stability?

- H-bonds interaction potentials have deep and narrow minima

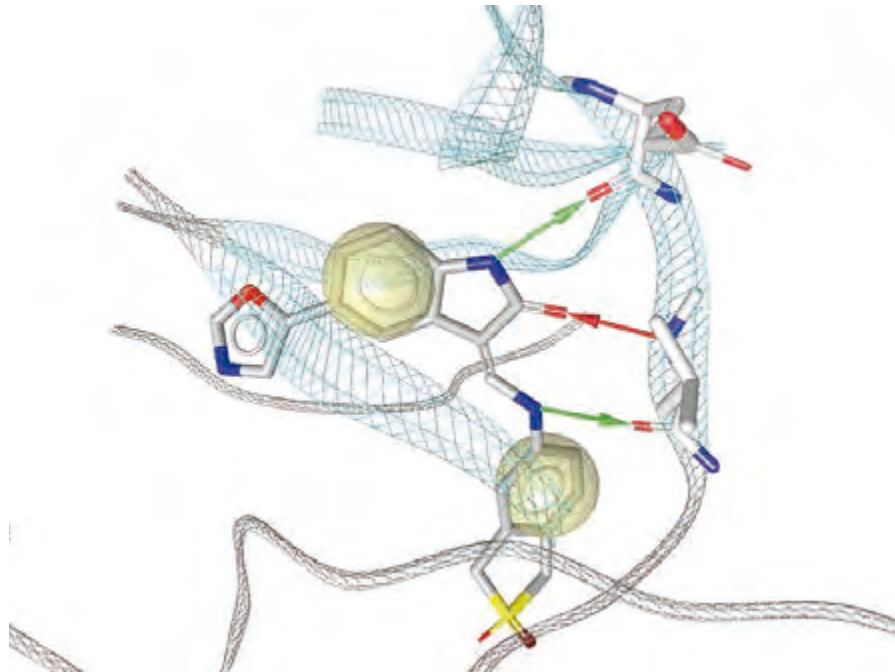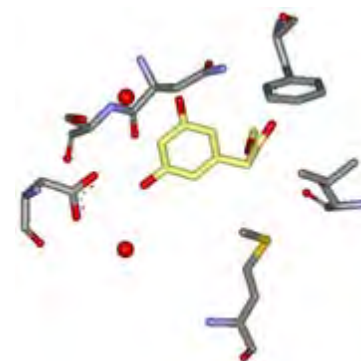# H-bonds: Determinants of Structural Stability?

- H-bonds interaction potentials have deep and narrow minima
- Water-shielded H-bonds present steep barriers (i.e. strong resistance to being broken)

Shielded Hydrogen Bonds as Structural Determinants of Binding Kinetics. Application in Drug Design.
Schmidtke P, Luque FJ, Murray JB, **Barril X**.
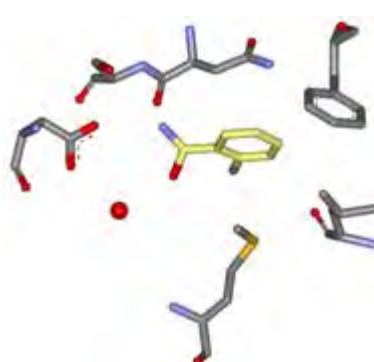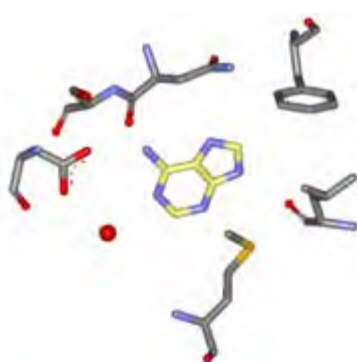Journal of the American Chemical Society, **2011;** 133(46):18903-18910

H-bonds: Determinants of Structural Stability?

- H-bonds interaction potentials have deep and narrow minima
- Water-shielded H-bonds present steep barriers (i.e. strong resistance to being broken)
- Most proteins contain an essential H-bond, fulfilled by all ligands (e.g. kinases, proteases, nuclear receptors...)
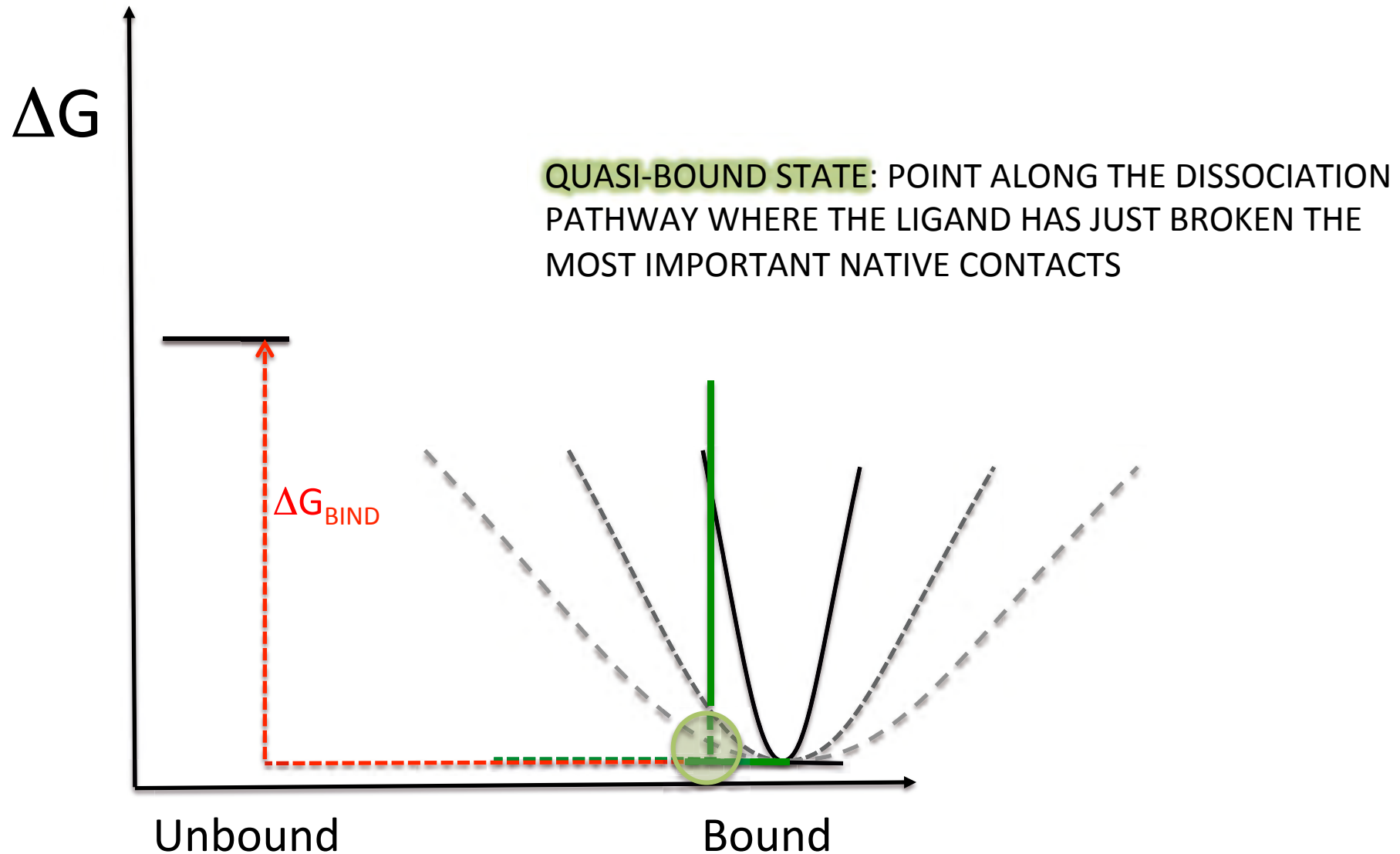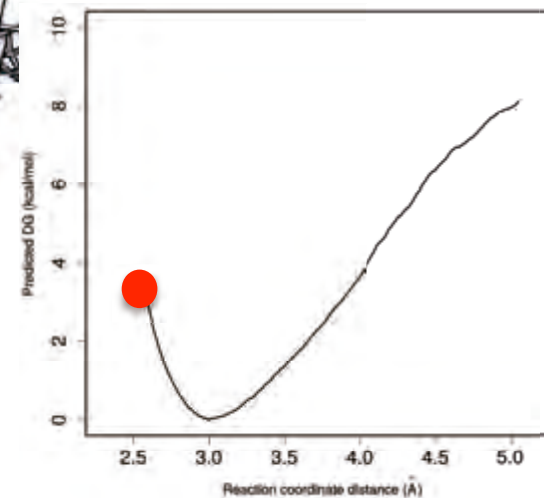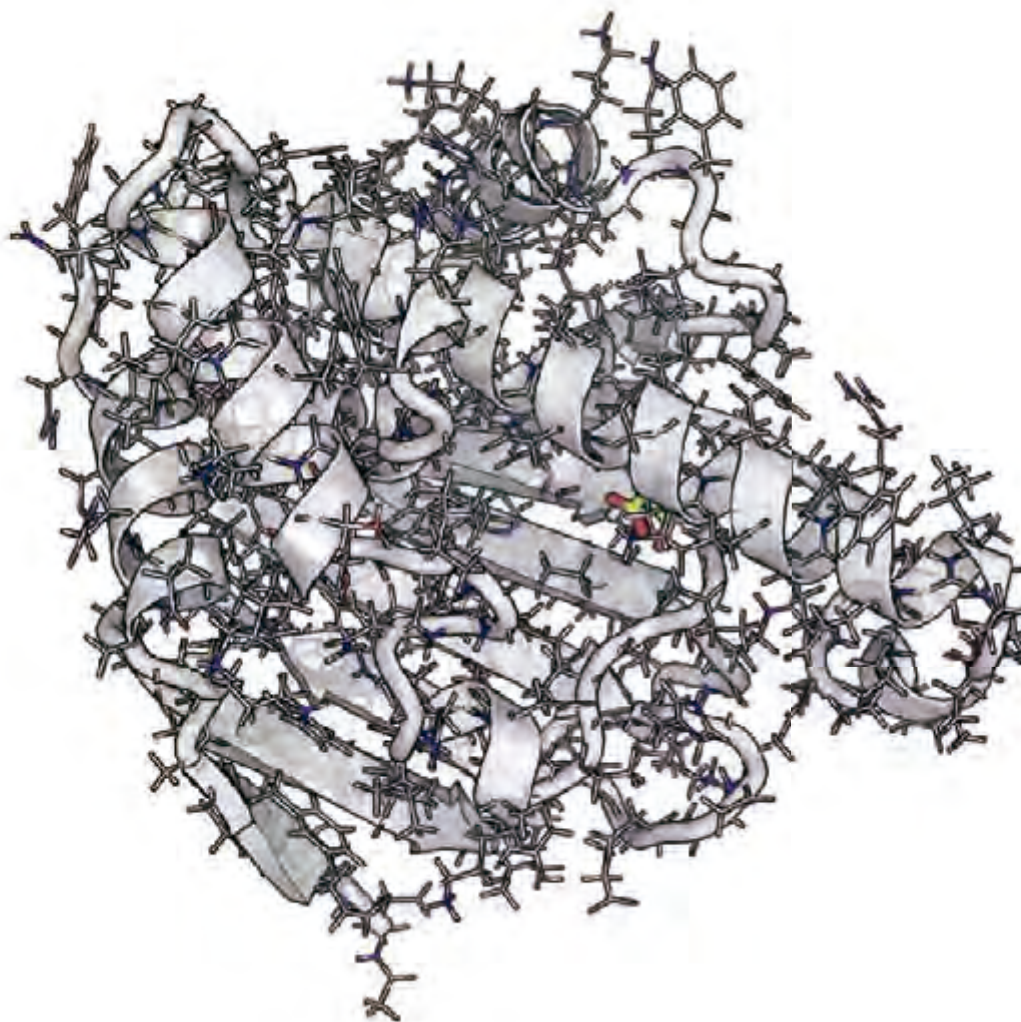
H-bonds: Determinants of Structural Stability?

- H-bonds interaction potentials have deep and narrow minima
- Water-shielded H-bonds present steep barriers (i.e. strong resistance to being broken)
- Most proteins contain an essential H-bond, fulfilled by all ligands (e.g. kinases, proteases, nuclear receptors…)
- Even the smallest ligands (i.e. fragments) form at least one H-bond Ferenczy & Keserű. Thermodynamics of fragment binding. *J. Chem. Inf. Model.* **52,** 1039–45 (2012).
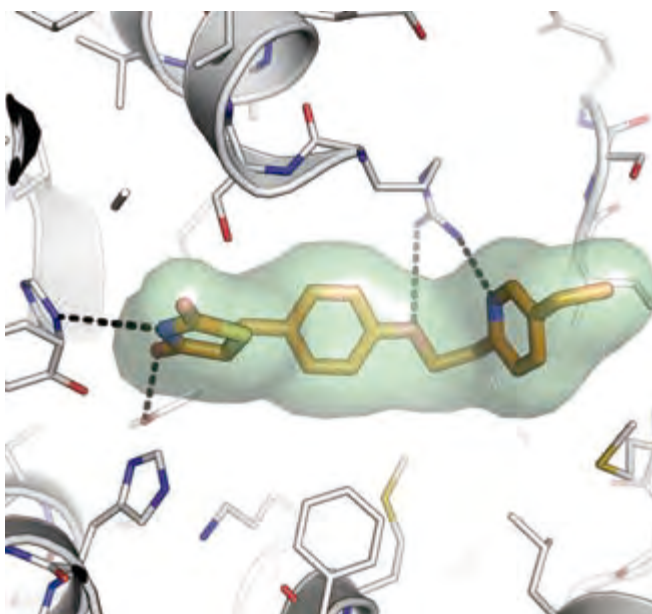
Assessing Structural Stability:
The Quasi-Bound State

QUASI-BOUND STATE: POINT ALONG THE DISSOCIATION PATHWAY WHERE THE LIGAND HAS JUST BROKEN THE MOST IMPORTANT NATIVE CONTACTS
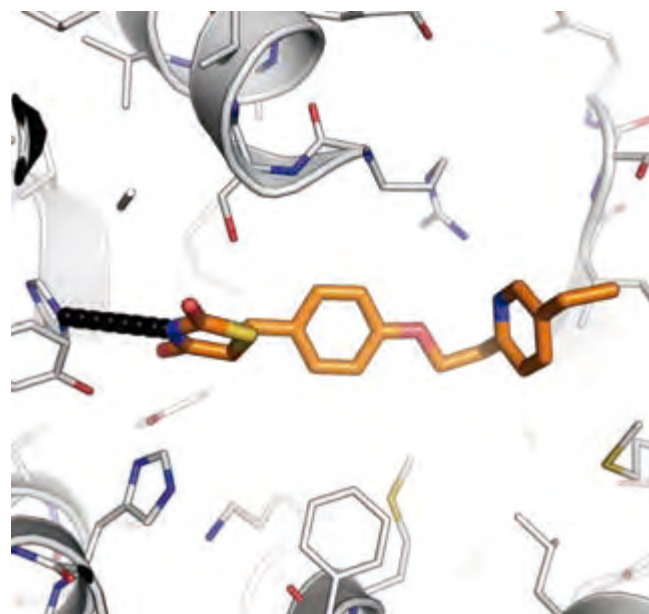
How we do it in practice?

Docking and DUck are complementary
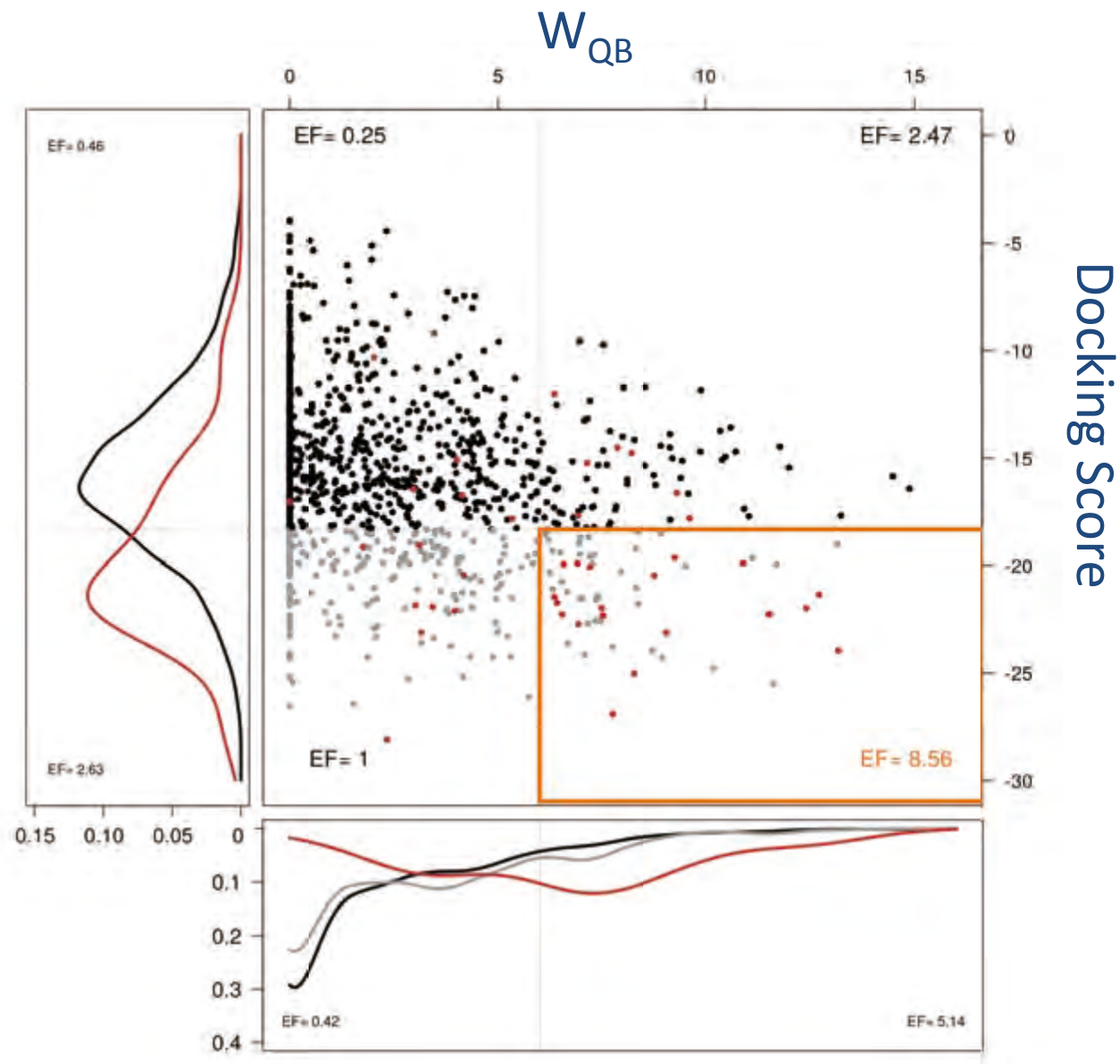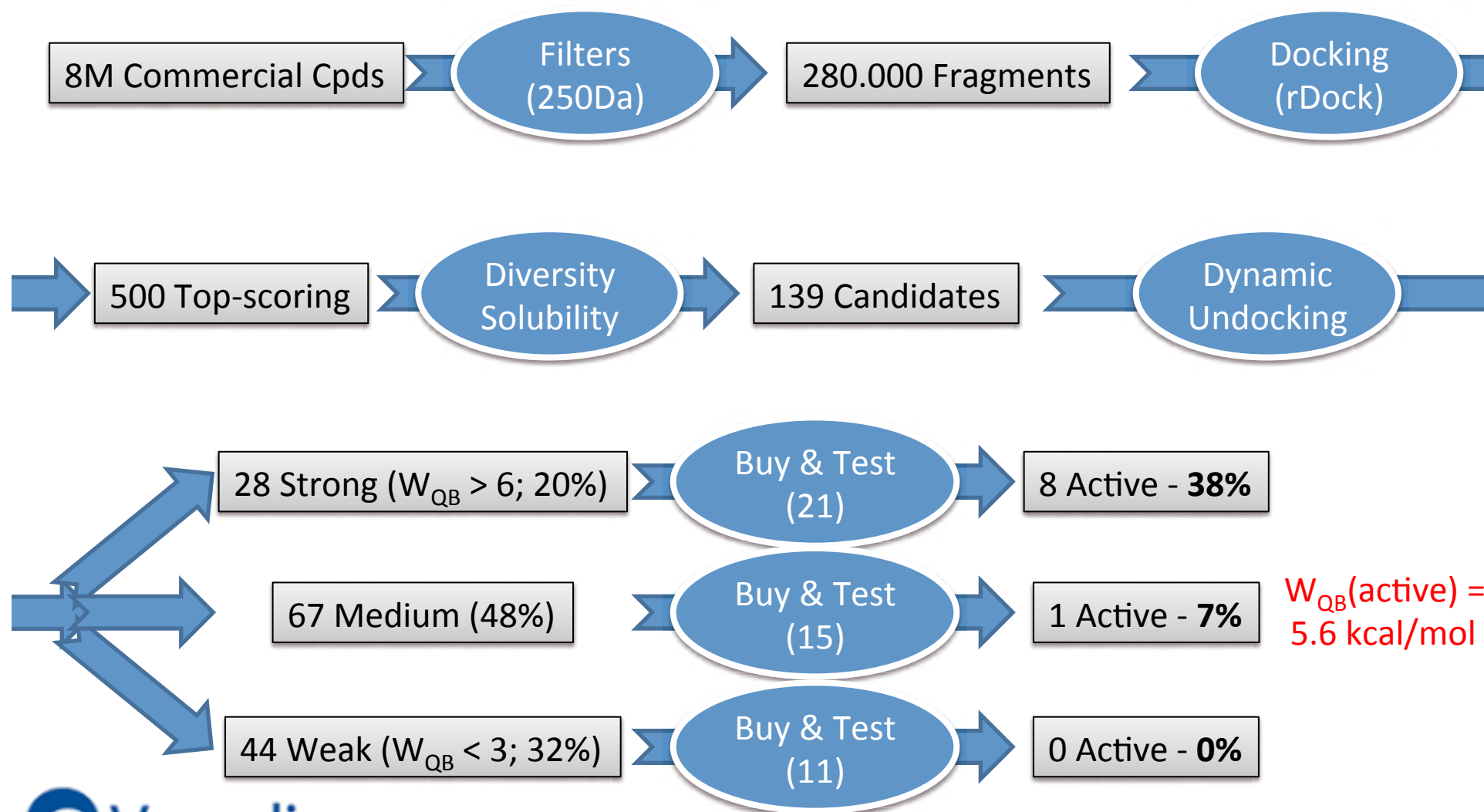

Docking

All interactions

Equilibrium

Dynamic Undocking

A single interaction

Out of equilibrium

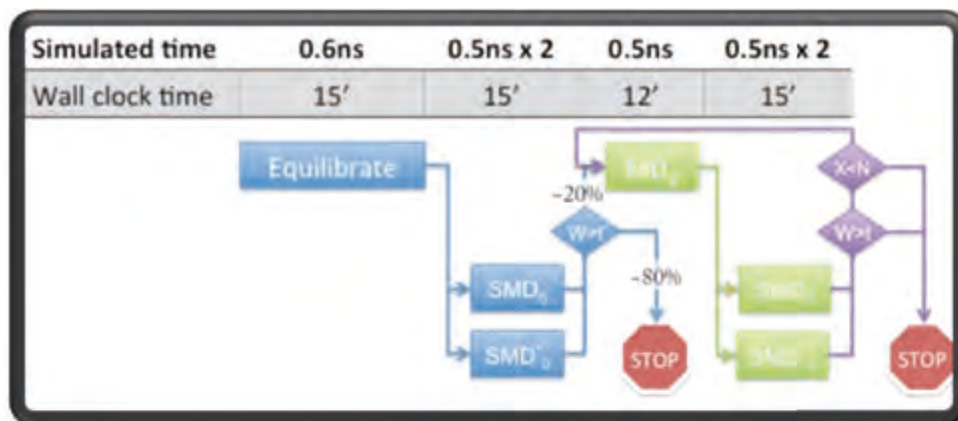# Dock, then Undock!

Prospective Application to Virtual Fragment Screening – Hsp90

8M Commercial Cpds → Filters (250Da) → 280.000 Fragments → Docking (rDock) →

500 Top-scoring → Diversity Solubility → 139 Candidates → Dynamic Undocking →

28 Strong ($W_{QB} > 6$; 20%) → Buy & Test (21) → 8 Active - **38%**

67 Medium (48%) → Buy & Test (15) → 1 Active - **7%**

44 Weak ($W_{QB} < 3$; 32%) → Buy & Test (11) → 0 Active - **0%**

W_{QB}(active) = 5.6 kcal/mol

Vernalis

Computational performance

Simulated time	0.6ns	0.5ns x 2	0.5ns	0.5ns x 2
Wall clock time	15'	15'	12'	15'

MINOTAURO (BSC)
61 blades x 2 M2090 NVIDIA GPU Cards
39 x 2 K80 NVIDIA GPU Cards

2500 ligands assessed in ~1.5 days (clock time)
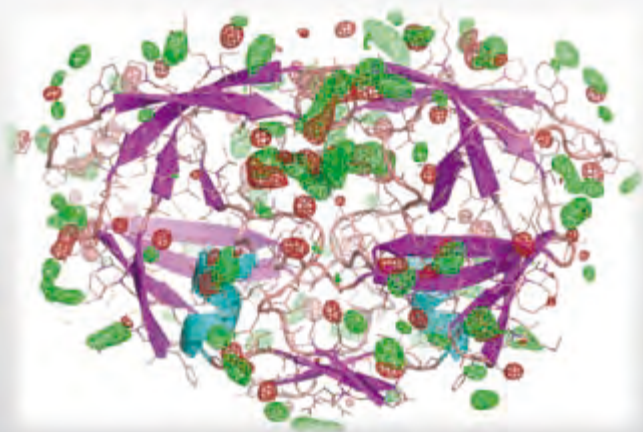Discard ~75% of ligands
Increased hit rate:
- Less compounds tested: €€ savings
    - Cost per compound: 50-100€ (10mg)
    - 50 cpds purchased: savings >10K€
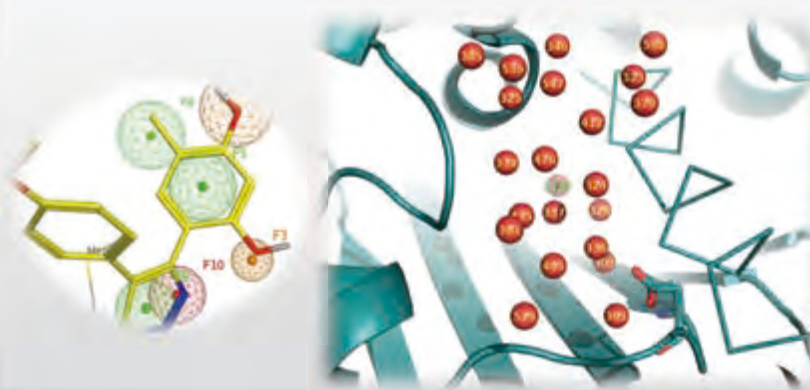   - Assay: time & cost savings
- Better outcomes

Tackling New Sites with Confidence

DISCOVERY OF DRUGGABLE SITES

J. Med. Chem. 2009, 52, 2363–2371

BINDING SITE CHARACTERIZATION
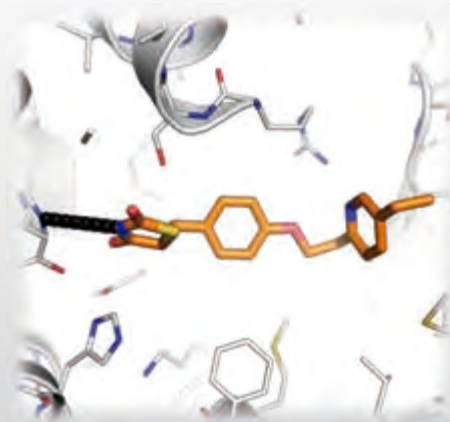

J. Med. Chem. 2014, 57, 8530–8539

J. Chem. Theory Comput. 2014, 10, 2608

HT VIRTUAL LIGAND SCREENING

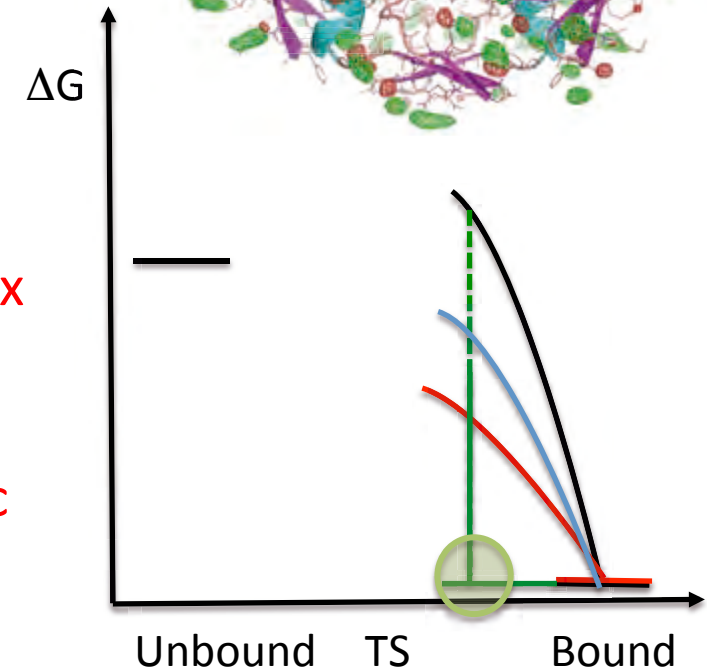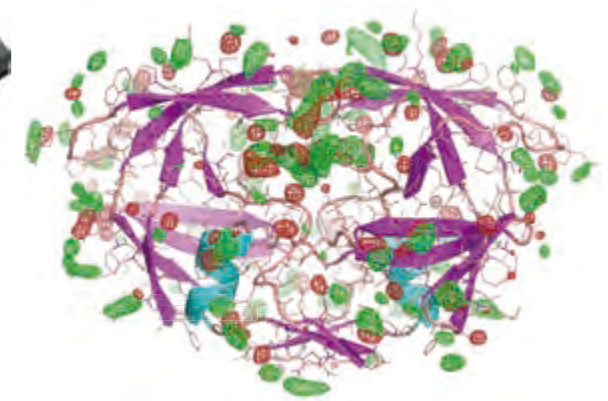PLoS Comput. Biol. 2014, 10(4):31003571

INCREASED HIT RATES POST-VS

Ruiz-Carmona et al. 2016, accepted

Conclusions

- New techniques are pushing SBDD forward
- Proteins do not behave as "ideal" receptors. This can actually work to our advantage:
  - Anisotropic distribution of ΔG_{bind} => Hot spots can be reliably predicted with MDmix
  - Theoretically "irrelevant" states actually matter => The Quasi-Bound (QB) state informs about structural stability. Dynamic Undocking (DUck) is useful for VS and orthogonal to docking
- Effective VS against novel sites

ΔG

Unbound   TS   Bound

Rod Hubbard   Lisa Baker
Ben Davis   Natalia Matassova
James Murray   Stephen Roughley

Sergio Ruiz

Peter Schmidtke, F. Javier Luque

Barcelona Supercomputing Center
Centro Nacional de Supercomputación

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