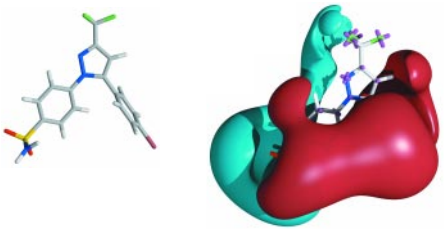
Molecular Fields as Structureless Pharmacophores for Virtual Screening

T J Cheeseright, M D Mackey & J G Vinter

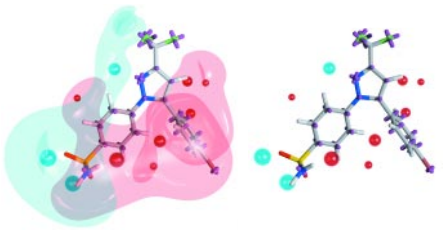
Cresset BioMolecular Discovery Ltd

Field Generation

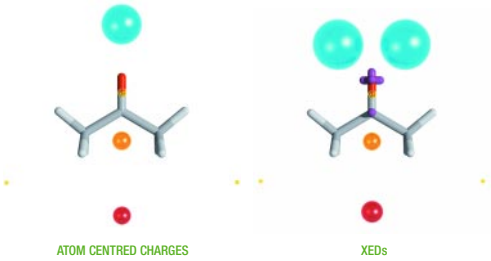
Proteins respond to the **electron cloud** round a molecule rather than to the 3D arrangement of its individual atoms.



For ease of analysis, the electron clouds can be distilled to **3D 'field' points** around the molecule, the sizes of which depict their relative strengths.

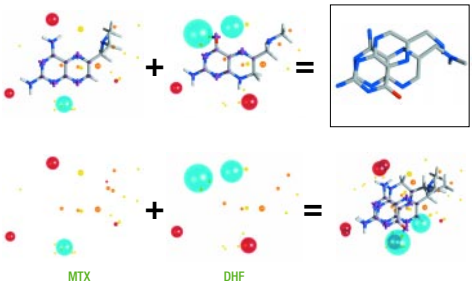


Without a good description of electrostatics, the field points are incorrect. Cresset's **XED** force field explicitly models the electron distribution around atoms rather than placing charge at the centre of atoms. This significantly increases the accuracy of the Molecular Electrostatic Potential.



The carbonyl group on acetone should show two field points from the oxygen lone pairs.

Field Overlay



As is well known, the DHFR inhibitor Methotrexate (MTX) binds upside down relative to the natural substrate dihydrofolate (DHF) in the enzyme.

If the two **structures** are naïvely superimposed, this fact is not apparent.

However, the overlay of **fields** - positive with positive and negative with negative (bottom) reproduced the experimental results (boxed stucture).

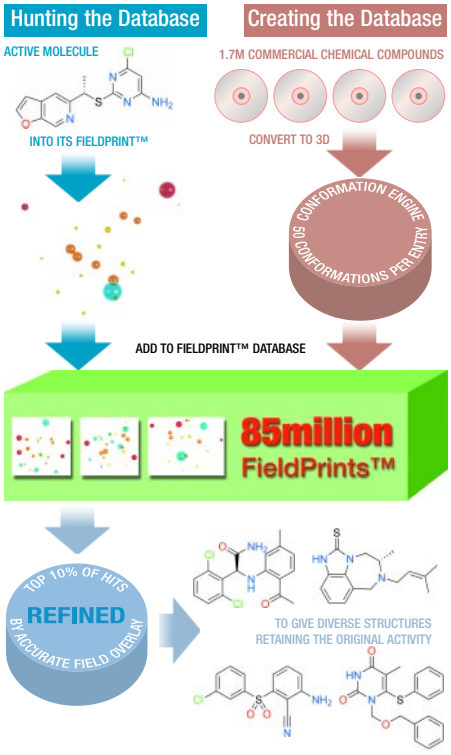
If field points are describing the 'binding properties' of molecules, can they be used for virtual screening?

We need a fast & accurate way of asking
'Is this molecule active?'

Virtual Screening with Fields

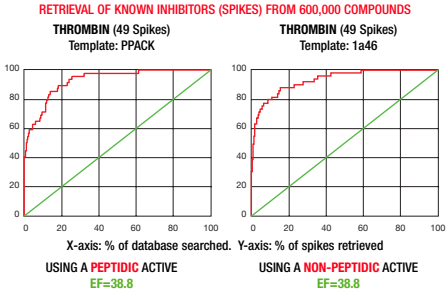
The storage and retrieval of structureless field patterns as patented FieldPrints™ are at the heart of our FieldPrint™ Database Technology.

The database is fed from standard commercial chemical collections and is searched using the field pattern template of an active compound.



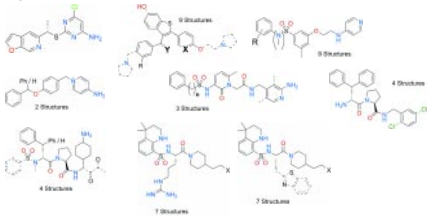
Spike Retrieval

A number of known active molecules from literature sources are '**spiked**' or added into the main database. The four examples below, show how efficiently these spikes are retrieved using the **FieldPrint**™ of a known active in its active conformation as the search **template**.



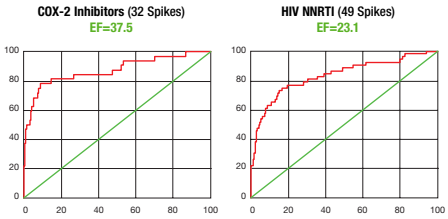
The enrichment factor measures the efficiency of the search; an EF of 10 means that we find 10 times more actives than expected by chance. The EFs reported are at 1% of the database.

Both searches retrieved a significant number of non-peptide drug-like actives.



Virtual Screening with fields is therefore shown to be **structure-independent**.

We can go from a peptide active to a drug-like lead.



The final 20% of spikes, which were retrieved poorly, turned out to be binding at a different site on **COX-2** from the active used to hunt the database.

The fields of **HIV NNRTI** inhibitors are poorly defined. These molecules are fatty lumps with little electrostatic character. Our search performed well even in this difficult case.

Validation

A **validation exercise** was performed in collaboration with the James Black Foundation (supported by Johnson & Johnson).

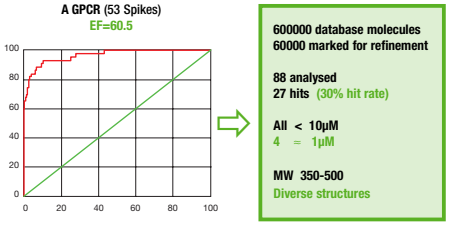
A library of >600,000 commercially available compounds was screened for a GPCR target (for which no structural information is available).

The best 10% of the database as ranked with FieldPrints™ was optimised by performing full 3D field overlays.

100 compounds were chosen for purchase. Of these, 88 were available.

Testing revealed that 27 (30%) of these were hits (pK_b>5, 1-10μM).

Most of the hits had **no structural similarity** to any known actives at the GPCR target.



Benefits

Rapid Solutions for Finding Leads, Jumping Series & Diverging Scaffolds

Cresset offers a completely novel *in silico* lead-finding service for medicinal chemistry programs

Using proprietary science, we describe molecules from the protein's viewpoint rather than its 'bare bones' structure. We can take any ligand and identify different structural types predicted to show similar activity. Information on the protein target is not a pre-requisite. The result is compounds with unprecedented structural diversity that are ideal starting points for medicinal chemistry programs.

The advantages to you are:

A HEAD START:
- Rapid entry into medicinal chemistry programs
- Increased speed of lead optimisation

NEW DIRECTIONS:
- Hit finding on new programs
- Lead switching inside existing programs

SUPPORT:
- Overcoming patent issues.
- Reducing ADMET problems
- Identifying novel back-up series

COST BENEFITS:
- Lower attrition rate
- Fewer compounds from Hit to Candidate Drug

Cresset Biomolecular Discovery Ltd, Letchworth, Herts SG6 4ET, United Kingdom