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Link, Merge & Grow Fragments Interactively
ReCore’s Initial Task

Very fast, interactive replacement of undesired cores:
Searching with Vectors

define “Exit Vectors”

search 3D fragment library

Development by Maass, Rarey (ZBH, Hamburg)
in cooperation with Hoffmann-La Roche AG (Basel, Switzerland)

Maass, P.; Schulz-Gasch, T.; Stahl, M.; Rarey, M.: 
Recore: A Fast and Versatile Method for Scaffold Hopping Based on Small Molecule Crystal Structure Conformations 

Pictures courtesy of Tanja Schulz-Gasch & Martin Stahl, Hoffmann-La Roche AG
ReCore: Indexed Searching

- ReCore has an “index” to search extremely fast: instead of looking at every single possibility, you jump to the answer in seconds:

- The Index needs a pre-generated “descriptor”:

  - Telephone book: the alphabet
  - ReCore: Vector relationships
ReCore Ranking

- The ranking is purely geometric (CAVEAT-like)

- Sorting according to Euclidean distance in 4D:
  - distance $d$
  - torsion $\theta$
  - $2x$ angles $a_1$ and $a_2$ formed with connecting path

In other words: The better the geometric fit, the better the rank
By design the best fitting replacements are found first.
The ranking is according to deviation from perfect vector overlap.
Enumeration of Fragments

Advantages:
- more possibilities
- bridging larger gaps
- still respect conformation seen in root structure
  (ideally: experiment/bioactive)

trivial fragmentation

"partial enumeration"
ReCore Needs at least 2 Vectors

- Vectors = EVs and Pharm Features (non-spherical pharmacophores):

⇒ Sensible Query Scenarios:
  - 2 EV + opt’l: any Pharm Features or EVs
  - 1 EV + 1 directed Pharm Feature + opt’l: any Pharm Features
Three Levels of Synthetic Acc’y Checks

1. Fragment creation
   Retrosynthetic shredding rules = more reasonable fragments!

2. Query definition
   Interactivity: Cut where chemist can synthesize!

3. Linking
   Forbid unwanted bond formation!
1. Torsions within the fragment (typically from expt., or from Corina or the like)

```
\begin{center}
\includegraphics[width=0.5\textwidth]{fragment_diagram}
\end{center}

‘observed’ prior to indexing
```

2. Torsions upon forming new single bonds: Link Constraints

```
\begin{center}
\includegraphics[width=0.5\textwidth]{link_diagram}
\end{center}

torsions controllable by user, connections can even be forbidden
Automatic Postprocessing: Filters, Shape

Mimick pocket (pocket spheres, = “allowed area“)

Forbid areas (exclusion spheres, opt‘l: SMARTS)

Refine definitions (inclusion w/ optional SMARTS)
A Striking Analogy

Core Replacement

Merging & Linking

Growing

Essentially, this required dealing with multiple input molecules.
Linking / Merging: Examples
How close do we get to Howard et al.’s JMC success with Thrombin?

Howard et al., JMC 49 1346 (2006)
Fragment Linking - A First, Simple Example

ReCore Queries with alignment of ligand PDBs 2c93 and 2c90:

This is too easy! Roche do not have simple –CH\textsubscript{n} – as linkers, so we don’t either…
Fragment Linking - A First, Simple Example

Can we ‘carve out’ the amine? And still link to the chlorophenyl?
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Fragment Linking - A First, Simple Example

Yes, that’s possible:

Found first (= Rank 1):

IC$_{50}$: ??

published structure:

IC$_{50}$: 1.4nM
... and: Fragment Merging

The idea: Connect multiple known fragment binders where they overlap.

P. Hajduk: “Fragment-Based Drug Design at Abbott“ (Talk at the FBLD’2008, San Diego) and many, many others nowadays.
A Tough Merging Example

Thymidylate Synthase Inhibition à la Sunesis (Erlanson et al., PNAS 2000 97 9367)

mTHF
Kₘ: 14mM

PDB: 1F4E
Kᵢ: 1.1mM

“...tosyl group is in roughly the same position and orientation as the benzamide moiety of methylenetetrahydrofolate...”

24μM, further opt’d to 330nM
A Tough Merging Example

Thymidylate Synthase Inhibition à la Sunesis (Erlanson et al., PNAS 2000 97 9367)

“...tosyl group is in roughly the same position and orientation as the benzamide moiety of methylenetetrahydrofolate...”
A Tough Merging Example

Thymidylate Synthase Inhibition à la Sunesis (Erlanson et al., PNAS 2000 97 9367)

To ensure the result accommodates in the pocket the input ligand envelope shapes were used.
A Tough Merging Example
A Growing Example
Growing into a $\pi-\pi$ Interaction Pattern


Let us try to get the $\pi$-stacking right as in the original finding in ABT-737

2 vectors are needed for the Query:
   a) Exit Vector
   b) $\pi$-interaction ‘Pharm. Feature’
Growing into a $\pi-\pi$ Interaction Pattern

Here it is in 3D:
Growing into a $\pi-\pi$ Interaction Pattern

The Result in 2D:

ABT-737

ReCore Solution No.11:
Growing into a $\pi-\pi$ Interaction Pattern

Solution No. 11 in comparison to ABT-737 (green):
Almost identical positions obtained!
Wrap-Up

Today, ReCore is an indexed (= interactively fast) machinery

- for fragment linking and merging
- for growing/evolving from experimental fragment binders
- to replace unwanted cores

You can only find what you put in, but put in whatever you want.

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