ALiBERO

“hands-on” session

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ALiBERO: Evolving a team of complementary pockets rather than a single leader

J. Chem. Inf. Model., 2012, 52 (10), pp 2705–2714.
DOI: 10.1021/ci3001088

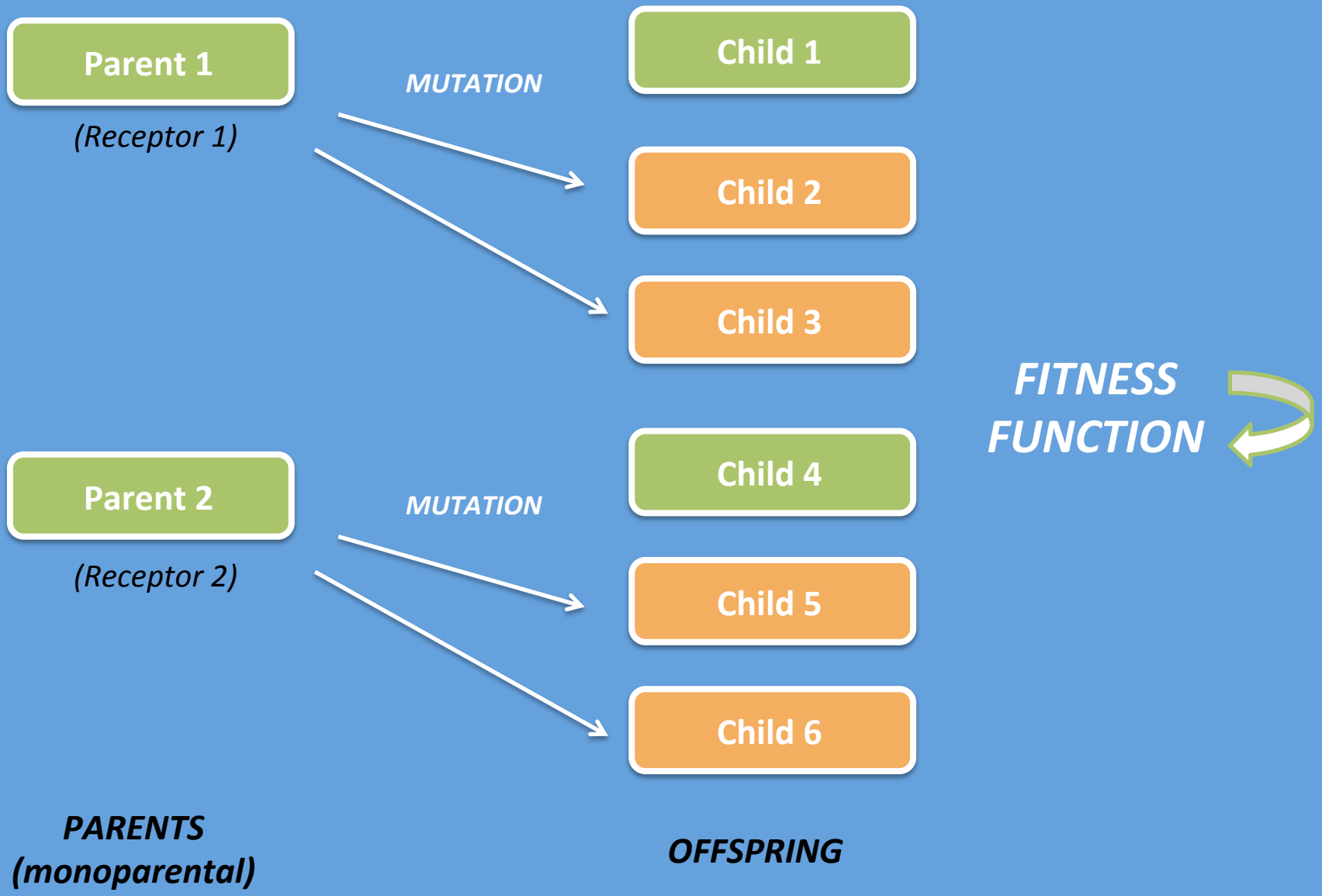
What is ALiBERO?

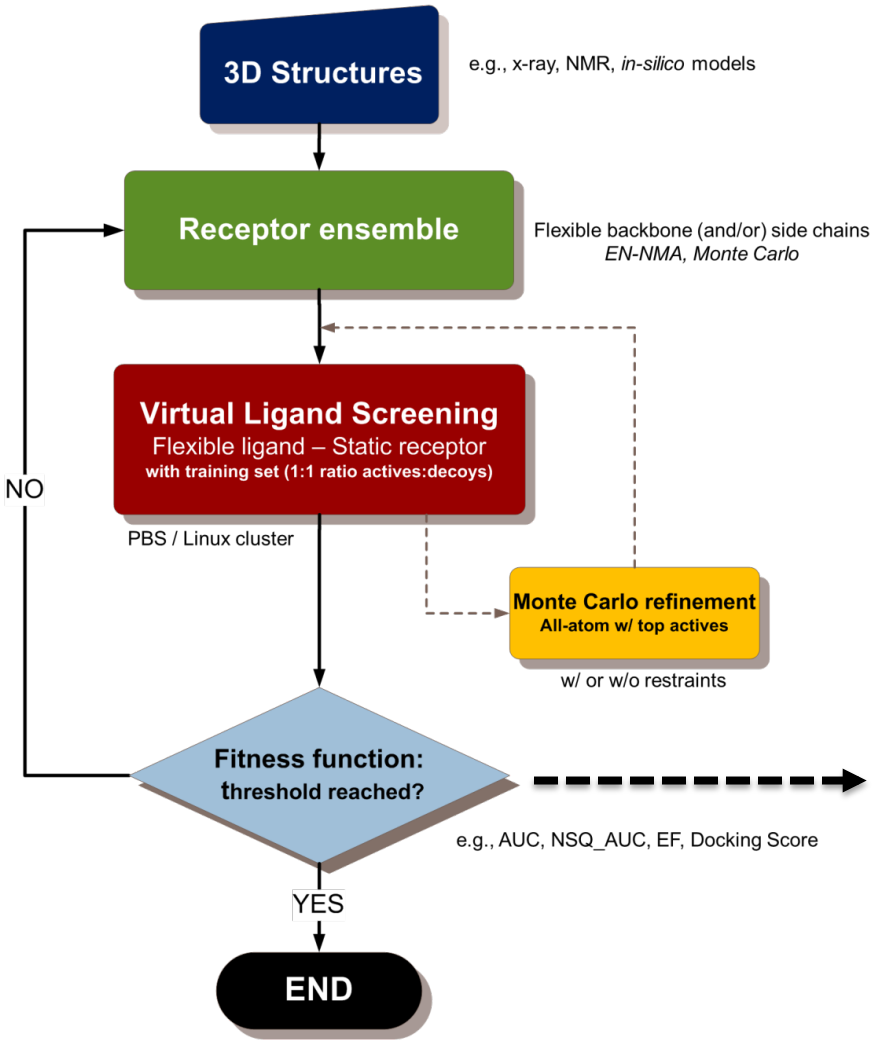
- A computational method that iteratively selects the **combination of pockets** that maximize a fitness function (e.g., AUC)
- **Perl script** (command line) + **ICM**-VS
  - Connected via icm scripts
  - Results come as graphical .icb

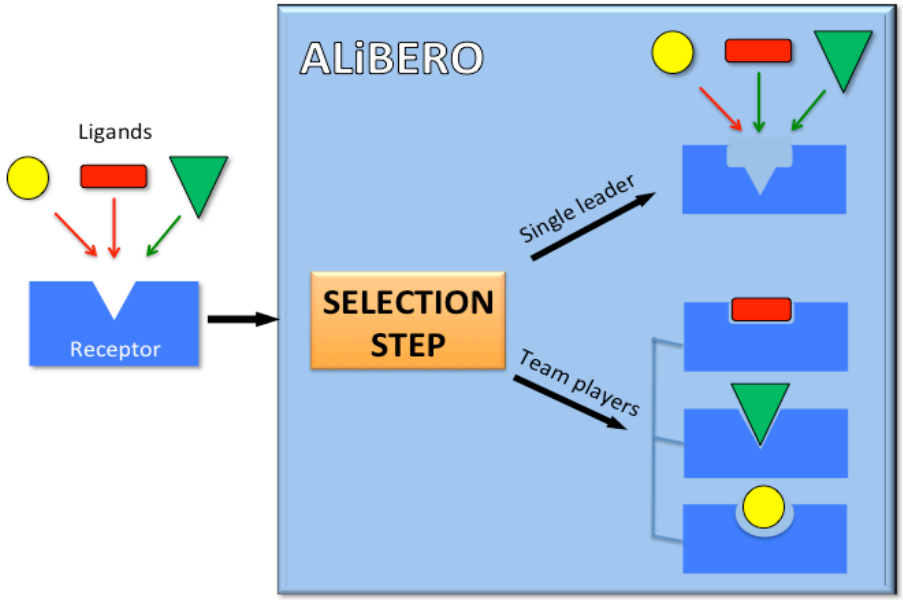
What do I need to run it?

- Linux workstation
- Alibero script (from github)
- ICM-VS license
- Optional
  - Linux cluster

ALiBERO is Implemented as an *Evolutionary Algorithm*







- Rueda. M, et al. ALiBERO: evolving a team of complementary pocket conformations rather than a single leader. *J Chem Inf Model*. 2012 Oct 22;52(10):2705-14.


SAMPLING ROUTE
("mutations")
NON-SAMPLING ROUTE

When should I try it?

- You have experimental data for a few *actives* (2D is fine) and…

⟶ ***Sampling route***: your pocket(s) display bad recognition (AUC, scores) of known actives

  - *Non-sampling route*: you have multiple pockets and want to select the optimum ensemble for VS
  - both

*via Normal Mode Analysis and Monte Carlo side chain refinement

What is the expected performance?

Training Set
AUC: 80-90%
NSQ_AUC: ≥60%
Homology model

Test Set
NSQ_AUC
15-20%

Great for predicting binding modes

OK, now the bad news…

Overfitting happens

Prospective VS sensitive to false positive team players ≤ 5

What files do I need?

- One or multiple **converted** receptors embedded as objects in an .icb file
  - Unless there exist sampling reasons, I recommend to delete residues not involved in the pocket
- ICM scripts (provided)
- An *.sdf* file with the ligands to be docked
  - The file must contain a column named "Active" with 1=actives and 0=decoys

Where is ALiBERO exe?

/pro/alibero/alibero

(latest version)

How do I run ALiBERO?

- $path/alibero –i *config_file* –n *MRCs* [–options]

  -v

  -help

  -man

  -verbose

  -debug

What is the flag –n?

- Number of “children”
  - Two modes:
    - Desktop (slow when –n > ncpu)
    - Cluster (recommended when –n 100)
      - Note that PBS.pm must be updated if outside Abagyan’s lab
      - You’ll need passwordless communication with the cluster

What is the flag –i?

- Configuration file

```
pbs          bluefish
inputicb     INPUT/RECEPTORS/aliberoMicro.icb
projdir      ESR1_HUMAN_test
cfsdir       /cfs/mrueda/CFS_TEST_ALiBERO
temperature   300  # 1A->300, 1.5A ->600, 2A->1100, 2.5A->1600
function      nsa   # NSQ_AUC
nligands      41
sdf          INPUT/LIGANDS/v10actives_w31Decoys.sdf
macrodir      INPUT/MACROS
refinement    off  # Check the restraints in macro
mrc          5
ntop         3
repeat       1    #
laziness     10   # %
```

ALiBERO has 5 fitness functions

- AUC (auc)
- NSQ_AUC (nsa)
- Average Score for ½ actives (score)
- NSQ_AUC+ (nsaplus)←recommended
- Consistency of binding mode for actives (con)

What do I need to modify?

- Configuration file (parameters)
- *asel* for pocket definition
  - @ MakeDock.icm
- Drestraints (if any)
  - @Refine_Hitlist.icm

A few notes about ALiBERO runs

- Remember: It does not modify your input files
- “Parents” & “offspring” compete on each generation. Each parent breeds equal offspring
- Docking *answers* are kept (huge)
- Everything is stored inside project_dir
  - Project_dir/GEN_1
  - Results will appear as Gen_1.icb or Gen_Ref_1.icb (if MC refinement)
  - Gen*icb are browsable

Is there any test I can run?

- Yes, just copy this folder:

  /pro/alibero/test/

  locally, then modify the paths inside the *in file and you are good to go.

  Please, be gentle with the cluster!

Addendum: How do I select the best combination of pockets from a X-ray ensemble, say, from Pocketome?

- alibero –i *config_file* –n *equal_to_your_npockets_in_ensemble*
- Make sure that you have these parameters on the input file

maxgen 1

refinement off