The Philosophy And Prospects Of Fragment Contribution Estimations In Drug Discovery

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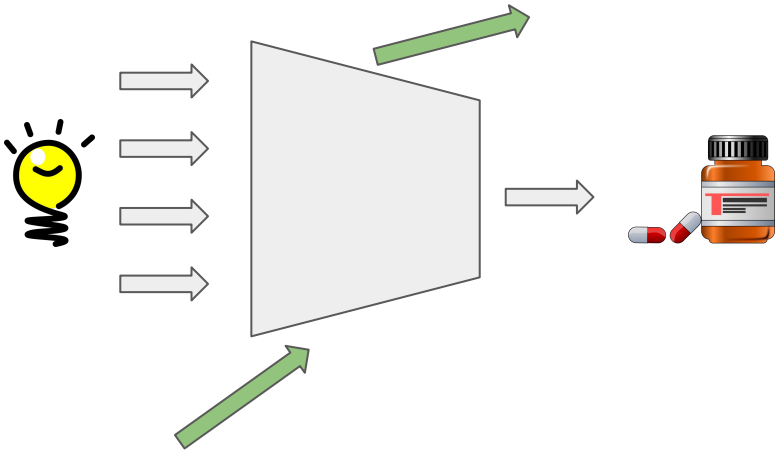
BCADD2022

current state and trends in DD

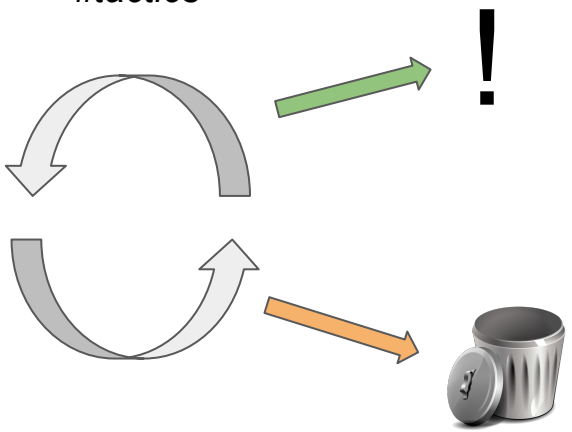
hard times - require versatile, lean and agile tools…

#strategy



Open Innovation

#tactics



Agile and lean hypotheses testing

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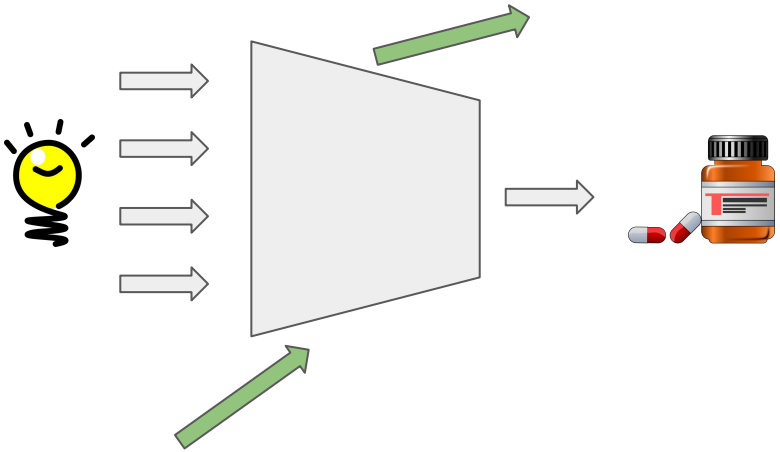

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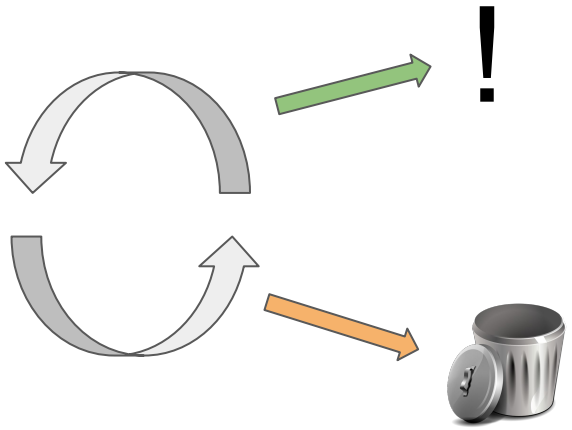

Agile and lean hypotheses testing

[theoretical part]

which conceptions and tools support agile and lean iterations?

here come fragments

what is ~logP of an organic molecule?

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functional group based estimation!

basis: intermolecular interactions

works almost perfect for predicting many physico-chemical properties…

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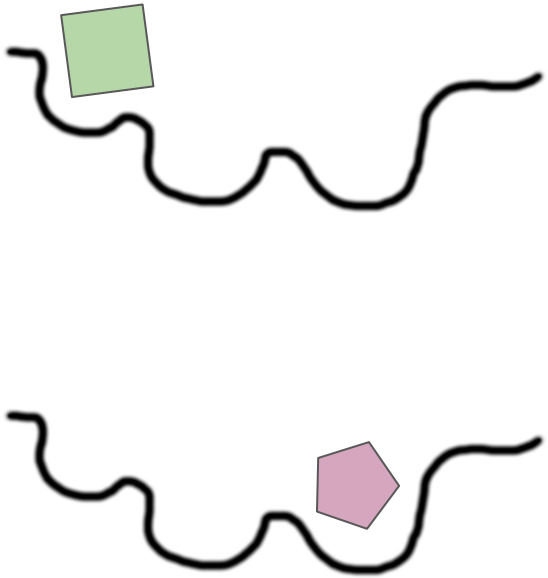
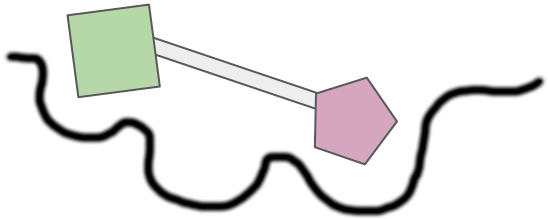
more broadly: module technology (LEGO-like) - convenient and efficient

fragment-based drug discovery (FBDD)

small molecules/fragment



drug like molecules



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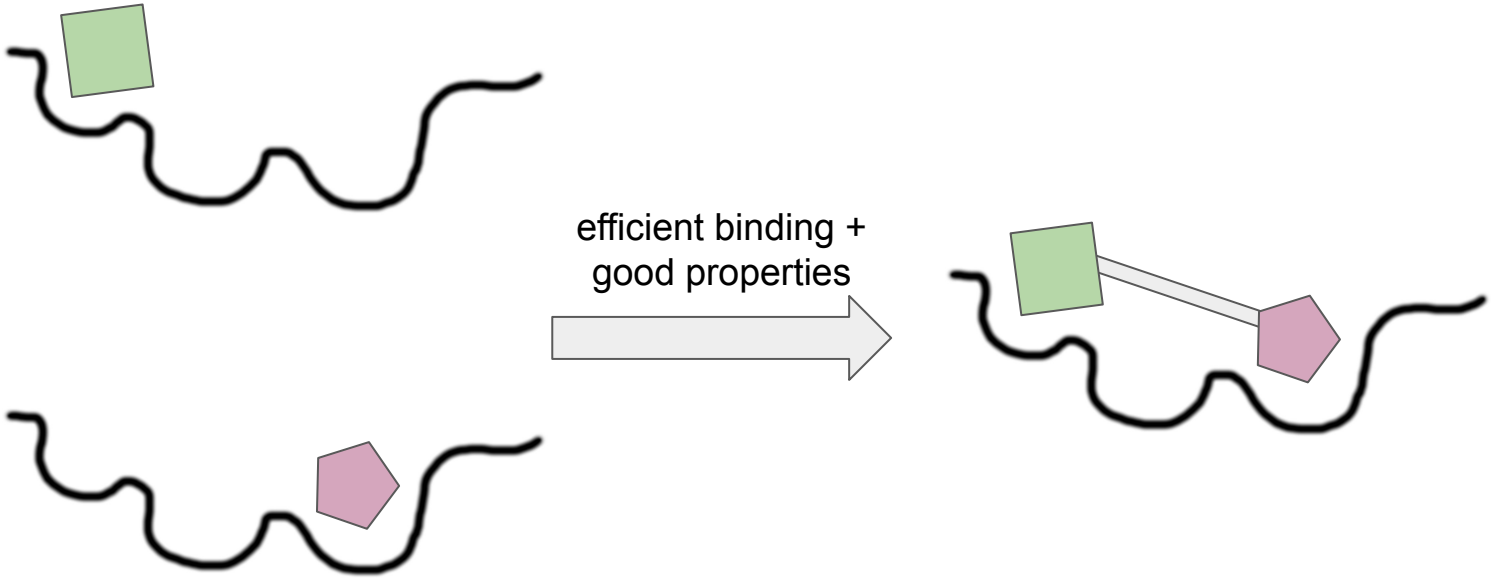

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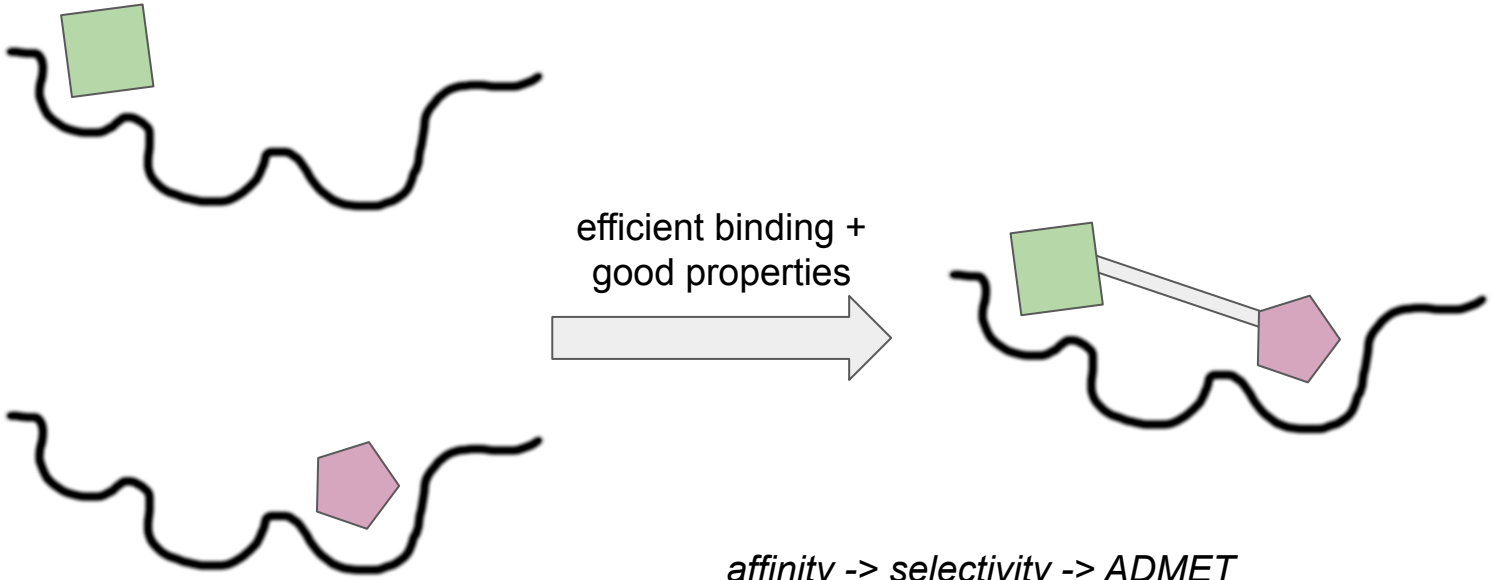
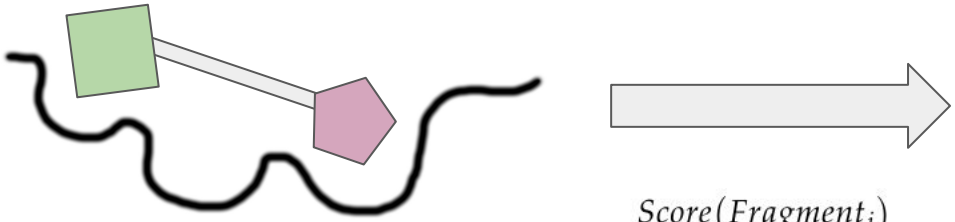


affinity -> selectivity -> ADMET

it’s the old story… where’s something new?

let’s reverse the direction

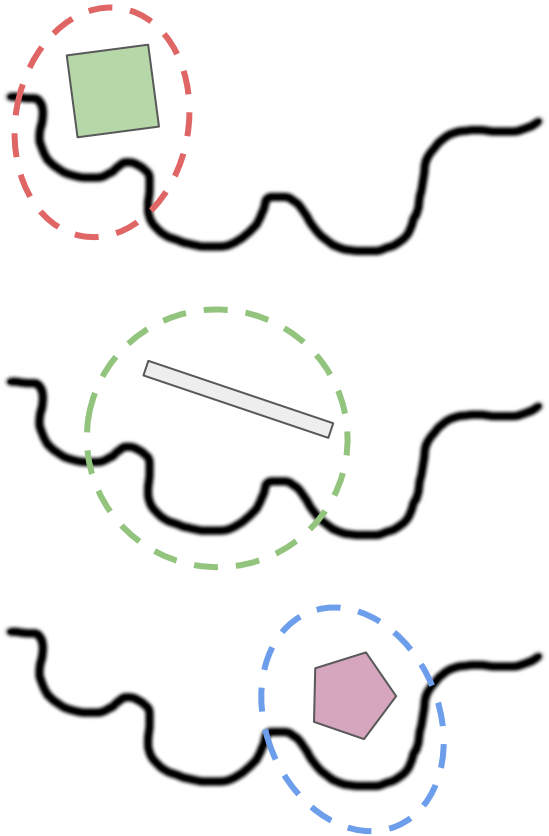
Reverse Fragment-Based Drug Discovery



$$\omega_j = \frac{Score(Fragment_j)}{\sum_{i=1}^{N} Score(Fragment_i)}$$

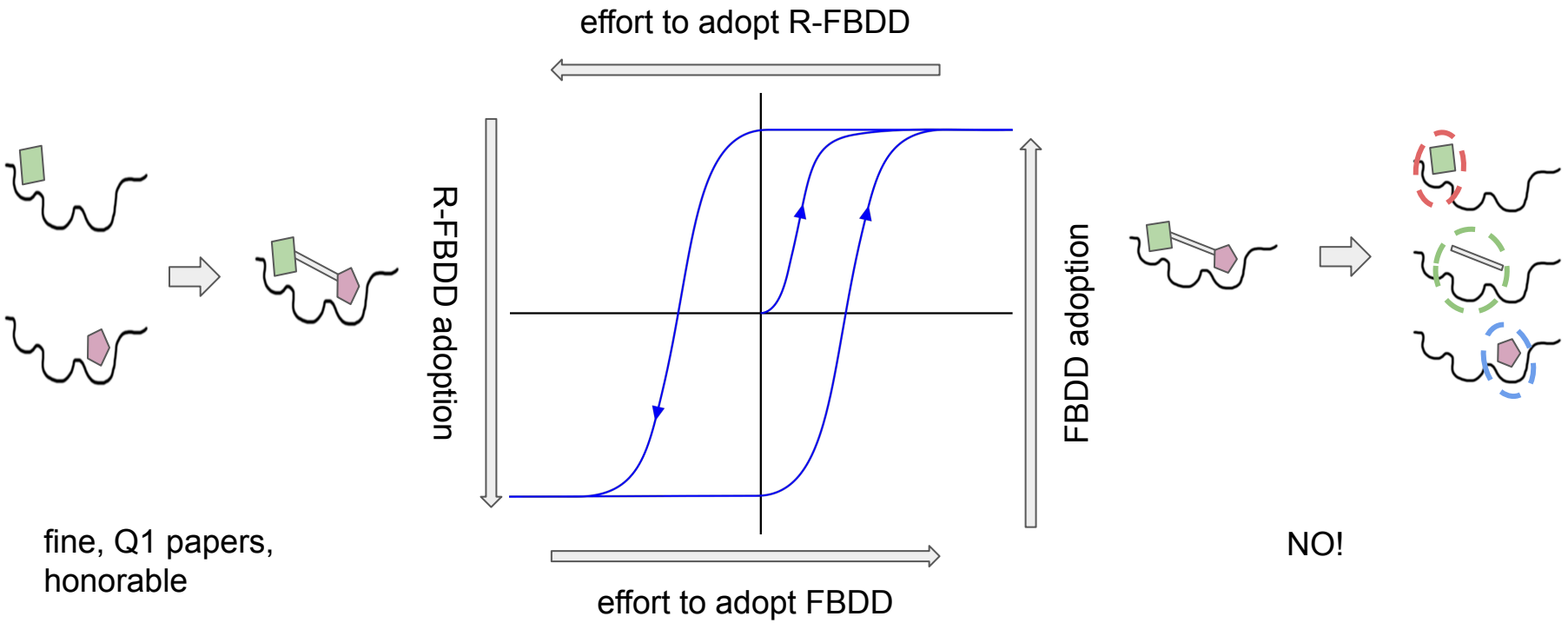
$$E_j^{Scaled} = \omega_j \cdot \Delta E_{mol}$$

$$\sum_{i=1}^{N} E_i^{Scaled} = \Delta E_{mol} \cdot \sum_{i=1}^{N} \omega_i = \Delta E_{mol}$$



Mend.Comm., 2021, 31(3), 291, doi: 10.1016/j.mencom.2021.04.004

fragment perception hysteresis



confusion… in terms of probability

$\Delta G \sim \ln P$

R-FBDD **FBDD**

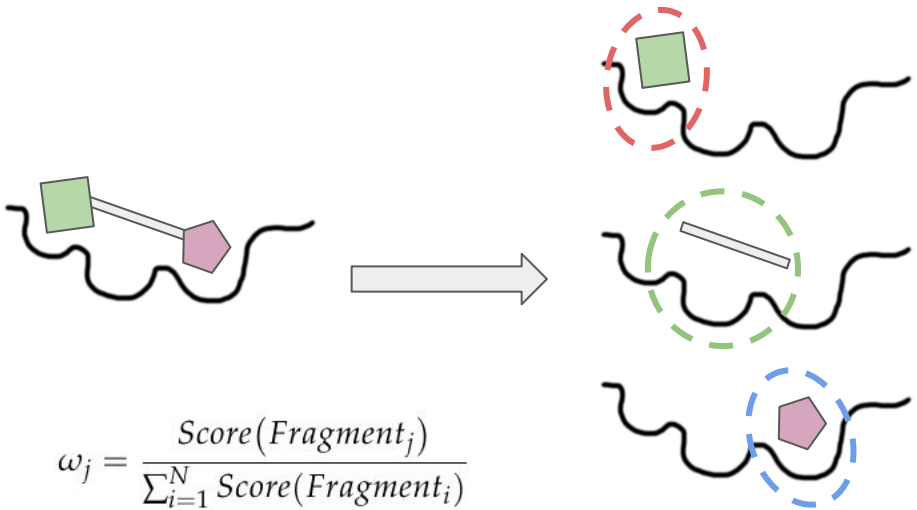
P(bind|rec, position) != P(bind|rec)

P(binding| position, receptor) = **P(position| binding, receptor)** * **P(binding| receptor)** / P(position| receptor)

NB: in (in silico) R-FBDD fragments are estimated in their position in the molecule under question

[practical aspects of the R-FBDD approach]

what we get out of R-FBDD



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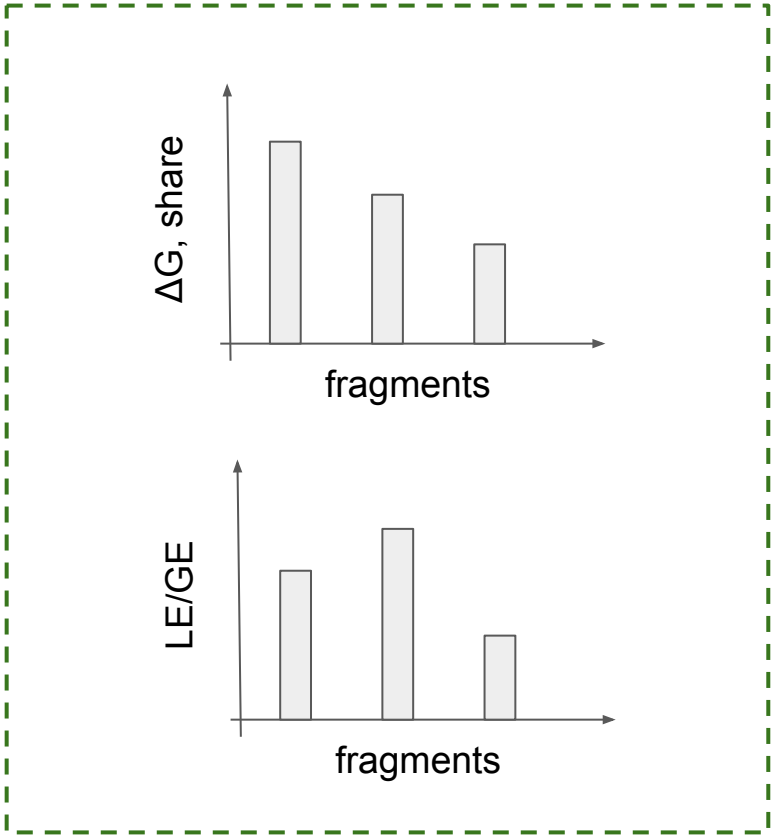
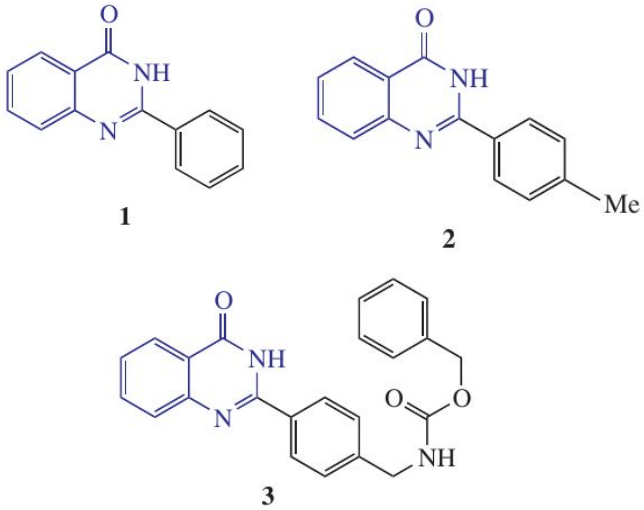


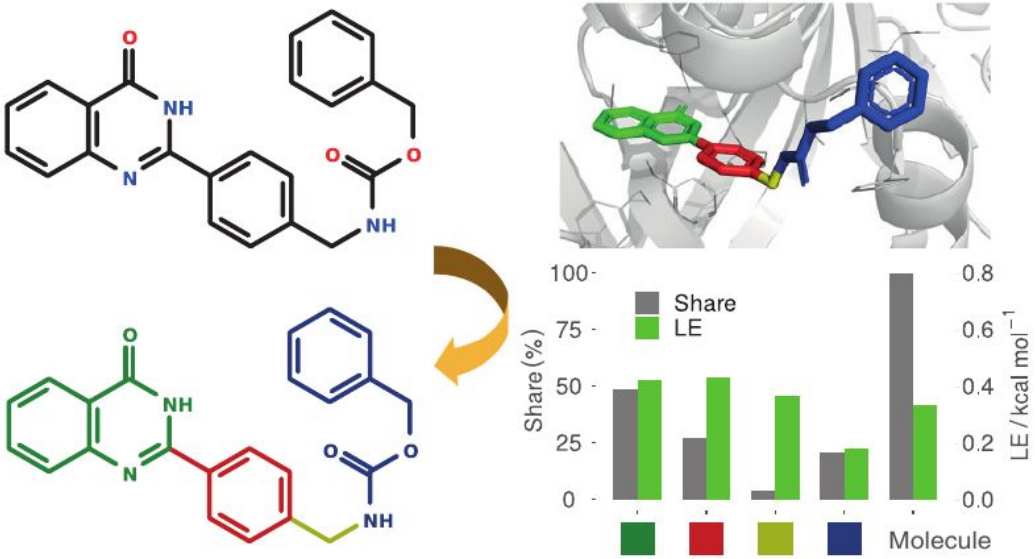
two main use cases

1. rational growth
2. ligand trimming (for subsequent growth)

use case I: ligand growth

Tankyrase 2 inhibitors case
- retrospective analysis





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use case II: ligand trimming

MT3/QR2 example

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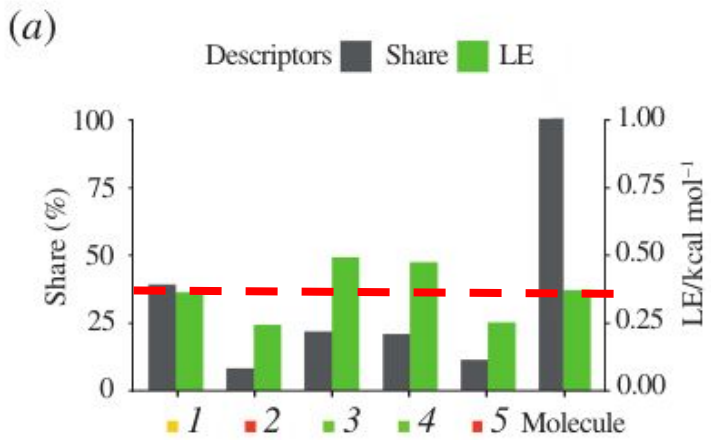

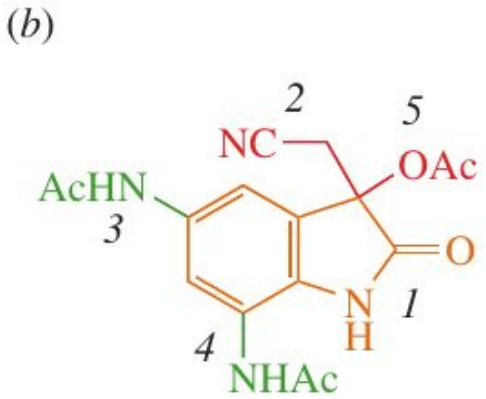

get rid of fragments 2 and 5

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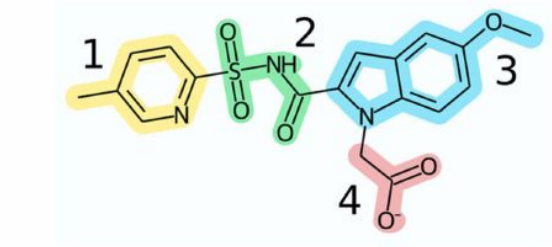
use case II: ligand trimming - using LE

Mycobacterium tuberculosis pantothenate synthetase

Experimental energy/structure fragment based optimization: Hung, A. W. et. al, 2016. Optimization of inhibitors of Mycobacterium tuberculosis pantothenate synthetase based on group efficiency analysis. *ChemMedChem*, *11*(1), 38-42. https://doi.org/10.1002/cmdc.201500414



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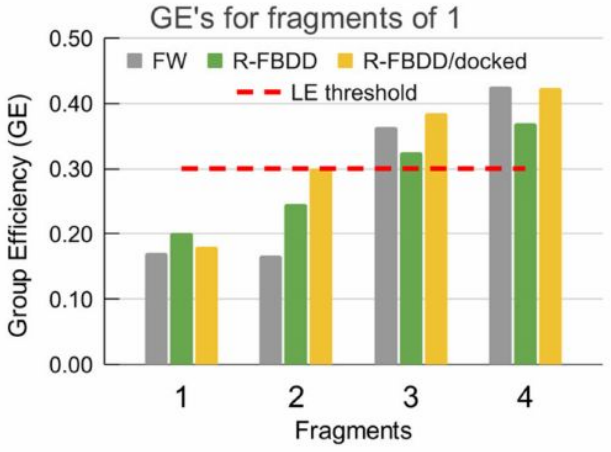


In silico R-FBDD results in the same conclusions!

Molecules **2022**, *27*(6), 1985; **https://doi.org/10.3390/molecules27061985**

take care, but use!

1. the choice of position for P(bind|rec, position) depends on the Researcher
2. rapid testing of binding hypotheses
3. (re-)introduce the focus on ligand/group efficiency (LE/GE)
4. reasonable hit-to-lead and lead structure series -> Agile style iterations

thank you!

- we see prospects for the R-FBDD approach application in practice
- looking for the fruitful collaborations!

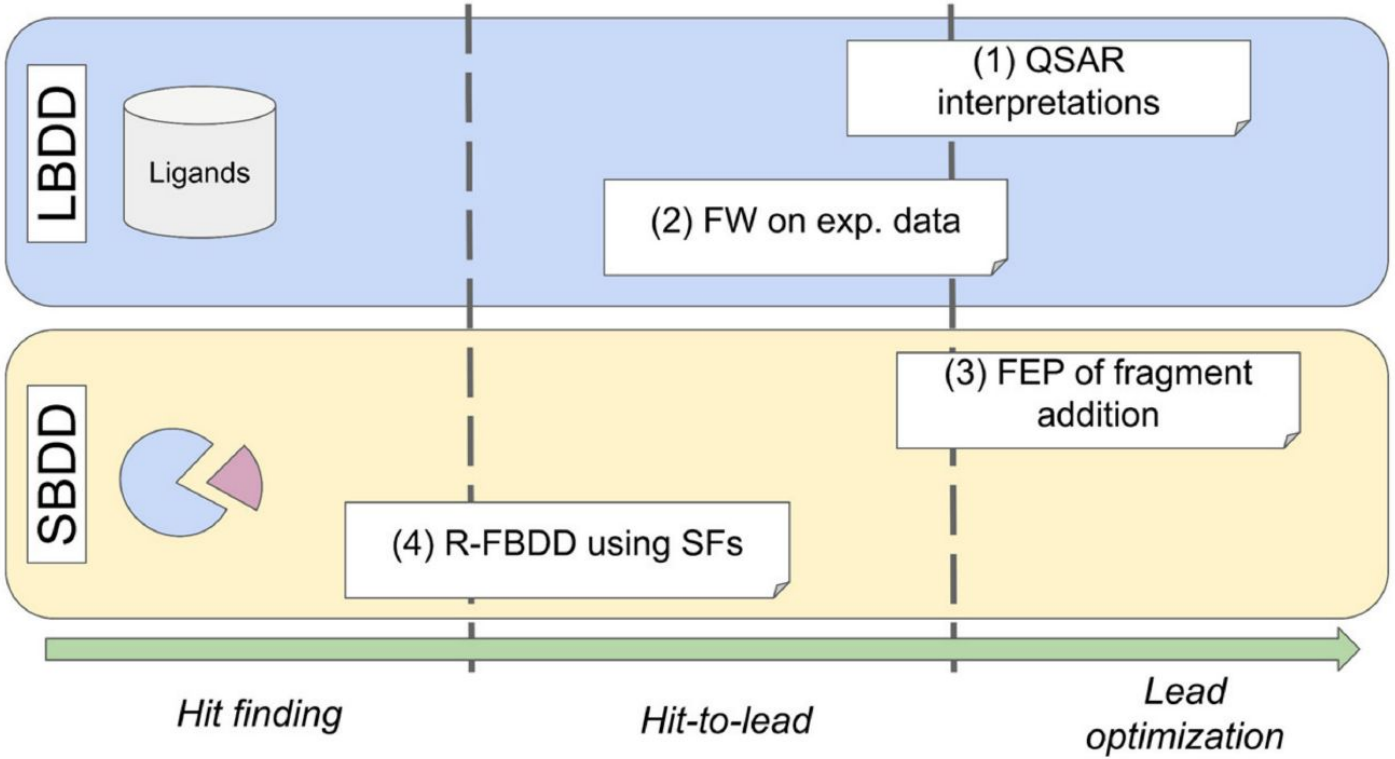
contacts

Dmitry Shulga, PhD, MBA

[academic version]

[contract research/consultancy version]

alternative fragment contribution approaches



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