1. Miscellaneous
2. Case Studies
3. De novo Small Molecule Design

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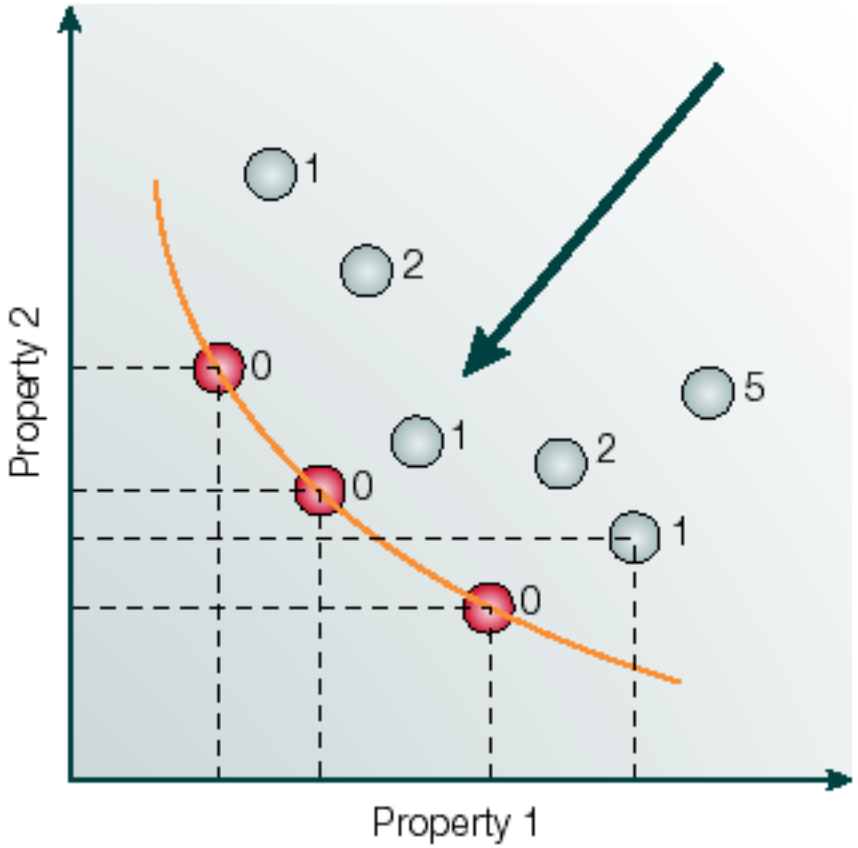
Pareto Optimality



From Schneider and Fechner (NRD 2005)

Case Studies

- Topic
  - Anything related to computational drug discovery (protease docking, example of focused libraries construction, new grid architectures, etc.)
  - Journal article fine. If white paper or something like that, just check with me.
  - Emphasize applications over methods
  - If you want to do something different (like research proposal), let me know

- Present what was done, what techniques were used, and what you think
  - Quick: 5 minute presentation (March 14)
  - More detailed: ~1 page written (due by March 23)

De novo Small Molecule Design

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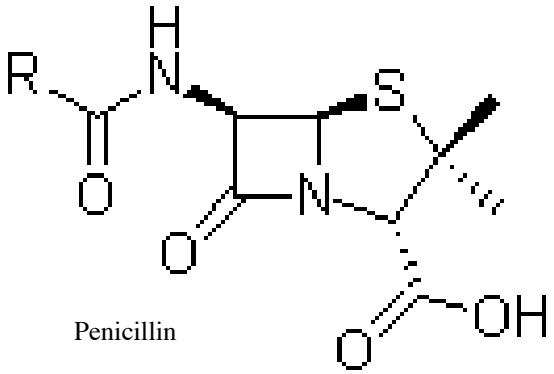
Paradigms

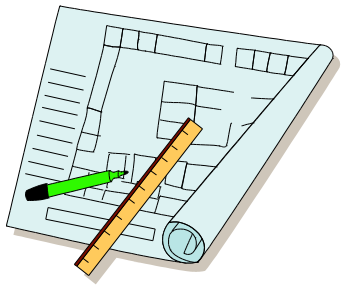
- Luck
  - Go out, collect samples, see if anything works
  - Asprin and penicillin examples



Penicillin

- Screening
  - Experimental vs. virtual
  - Various computational techniques
  - Can’t screen everything

- Design



Uses of Design

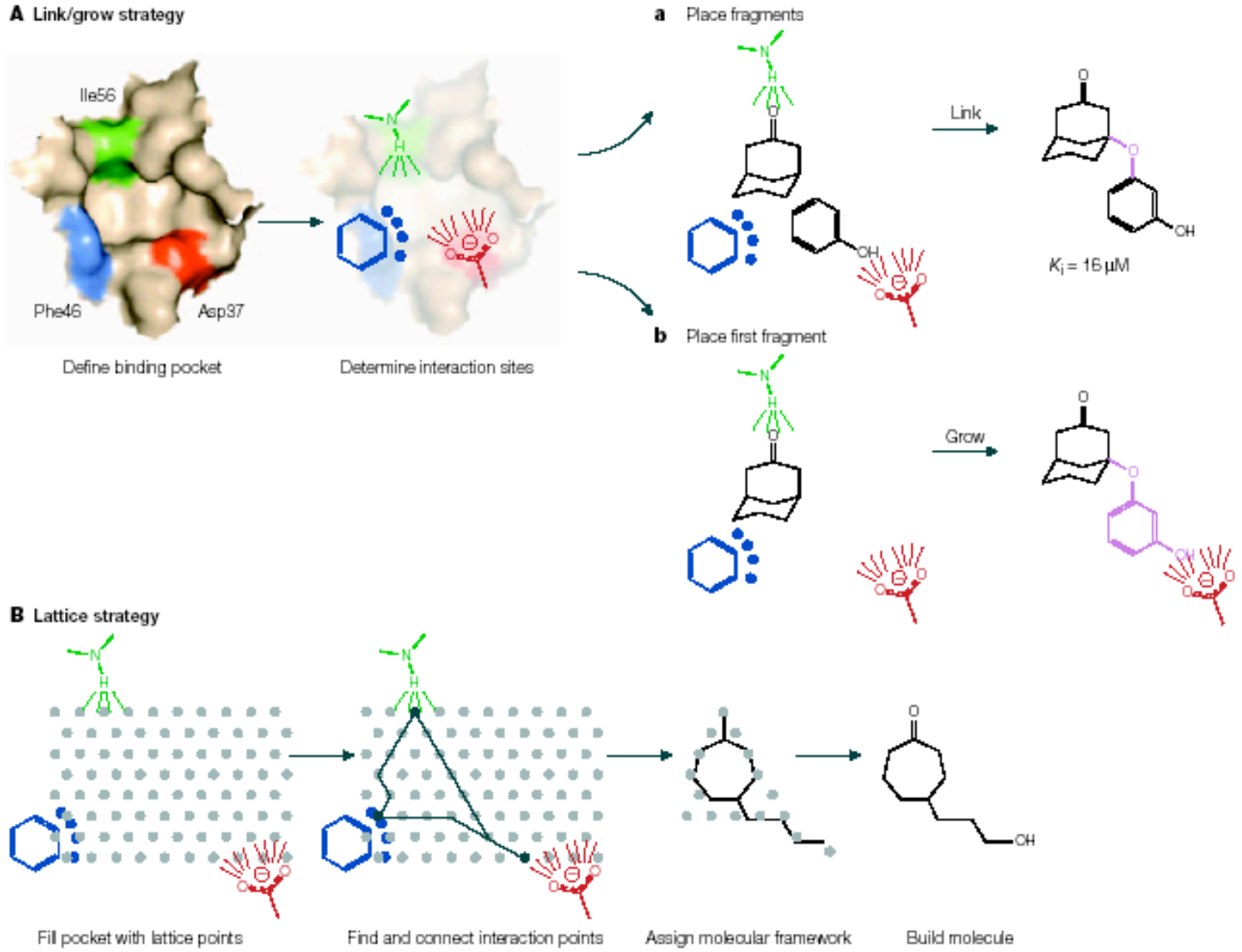
- Goal
  - Ligand that binds to receptor and can be synthesized (synthetic accessibility has been a big challenge)
  - Maybe other goals like ADME (so multidimensional optimization)

- Motivation
  - Lead generation for screening
  - Novel compounds and scaffold hopping
  - Give new ideas to chemists

Choices

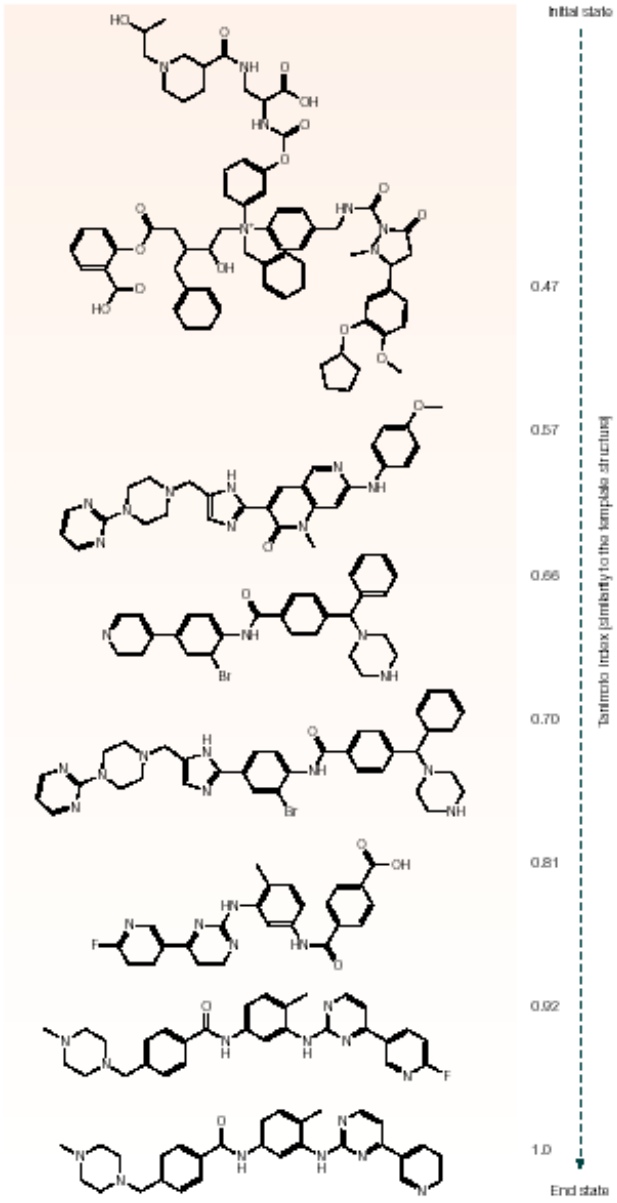
- Information input
  - Receptor based (need structure of receptor) or ligand based (use known ligands)
- Scoring function
  - Force field, knowledge based, empirical, similarity
- Structure assembly method
- Structure search algorithm

Example Construction Methods



From Schneider and Fechner (NRD 2005)

TOPAS Remaking Imanitib



Substitute fragments (so synthetically accessible)

50 generations to Gleevec

From Schneider and Fechner (NRD 2005)

Synthetic Accessibility

- Has been big problem in de novo design
  - A virtually ligand isn't very useful if it can't be made real
- One approach: build in what reactions are possible
- Use parts of known ligands (like in BREED)

Example Programs

Name (year)	Building blocks		Primary target constraints		Search strategy					Structure sampling					
	At	Fr	Rc	Li	DFS	BFS	Rnd	MC	EA	Gr	Lk	Lat	MD	Sto	Scoring function
HSITE/2D Skeletons[12,31,95] (1989)		X	X			X				Fitting and clipping of planar skeletons					Steric constraints and hydrogen bonds
3D Skeletons[32] (1990)		X	X		X					X					Steric constraints and hydrogen bonds
Diamond Lattice[33] (1990)	X		X		X							X			Steric constraints and hydrogen bonds
BUILDER v1[28] (1992)		X	X		X	X						X			Steric constraints and key interaction sites
LEGEND[20] (1991)	X		X				X			X					Force field
LUDI[13,14,96–98] (1992)		X	X			X				X	X				Empirical scoring function (SCORE1; revised version SCORE2 in 1998)
NEWLEAD[30] (1993)	X	X	X			X					X				Steric constraints
SPLICE[60] (1993)		X	X		X						X				Pharmacophore and steric constraints
GenStar[34] (1993)	X		X		X					X					Steric constraints and ligand–enzyme contact
GroupBuild[18] (1993)		X	X		X					X					Force field
CONCEPTS[39] (1993)	X		X					X					X		Empirical scoring function
SPROUT[17,57–59] (1993)		X	X		X	X				X	X				Solvent accesible surface, hydrogen bonds, electrostatic and hydrophobic interactions
MCSS & HOOK[25,27] (1994)		X	X			X					X				Simplified van der Waals potential of non-polar interactions
GrowMol[21] (1994)	X	X	X					X		X					Simple empirical scoring function
MCDNLG[61] (1995)	X		X					X						X	Potential energy

At, atoms; BFS, breadth-first search; DFS, depth-first-search; EA, evolutionary algorithms; Fr, fragments; Gr, grow; Lat, lattice; Li, ligand; Lk, link; MC, Monte Carlo sampling with Metropolis criterion; MD, molecular dynamics; QSAR, quantitative structure–activity relationship; Rc, receptor; Rnd, random; Sto, stochastic.

Readings

- Combinatorial computational method gives new picomolar ligands for a known enzyme (Grzybowski, et. al.)
- BREED: Generating Novel Inhibitors through Hybridization of Known Ligands. Application to CDK2, P38, and HIV Protease (Pierce, Road, and Bemis)
- CONCERTS: Dynamic Connection of Fragments as an Approach to de Novo Ligand Design (Pearlman and Murcko)
- A genetic algorithm for structure-based de novo design (Pegg, Haresco, and Kuntz)