Rapid Calculation of Polar Molecular Surface Area and its Application to the Prediction of Transport Phenomena

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Computer-Aided Drug Design

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Background/Rationale

- Andersen Consulting report* - 3 NCEs/year
- Reduce fall-out rate in development
- *Nature* of compounds, not just *number* of compounds is important
- “Fail fast” is the watchword
- *In vitro* ADME screening - synthesized compounds
- Computational screens - virtual compounds

* Banerjee, P. “Re-inventing Drug Discovery” (July 1997).

Overview

- Intestinal Absorption
  - Lipinski's rule-of-5
  - Polar Surface Area (PSA)
- Blood-Brain Barrier (BBB) Penetration
  - Introduction
  - Application of PSA calculations
- Applications in drug design

Note: passive absorption only!

Intestinal Absorption - Rule of 5

Compound flagged as having possible absorption problems if any <u>two</u> of the following rules apply to it:

- Molecular weight > 500.0
- ClogP > 5.0 (MlogP > 4.15)
- Number of H-bond acceptors (any N,O) > 10
- Number of H-bond donors (any N-H, O-H) > 5

Reference:

- Lipinski, C.A. *et al.* Experimental and Computational Approaches to Estimate Solubility and Permeability in Drug Discovery and Development Settings. *Adv. Drug Deliv. Rev.* 1997, 23, 3-25.

Intestinal Absorption - Rule of 5

Advantages:

- Widely adopted by industry
- Quick to calculate
- Should give few false negatives

Disadvantages:

- A crude prediction method
- Lots of false positives
- Not discriminating enough

Intestinal Absorption - PSA

Background:

- Polar surface: N, O; H attached to N or O
- Palm *et al.* correlated “dynamic” PSA with fractional absorption in humans for 20 carefully selected drugs
- Sigmoidal fit: r^2=0.94, RMSE=9.2% (but slow!)
- Using single conformation:
- Sigmoidal fit: r^2=0.94, RMSE=9.1%

Reference:

- Palm, K. *et al.* Polar Molecular Surface Properties Predict the Intestinal Absorption of Drugs in Humans. *Pharm. Res.* 1997, 14, 568-571.

PSA Calculation Method

1) SMILES representation of compound

2) CONCORD generates approximate 3-D structure

3) Structure optimized using Maximin2 in SYBYL

4) Van der Waals surface calculated by MOLVOL

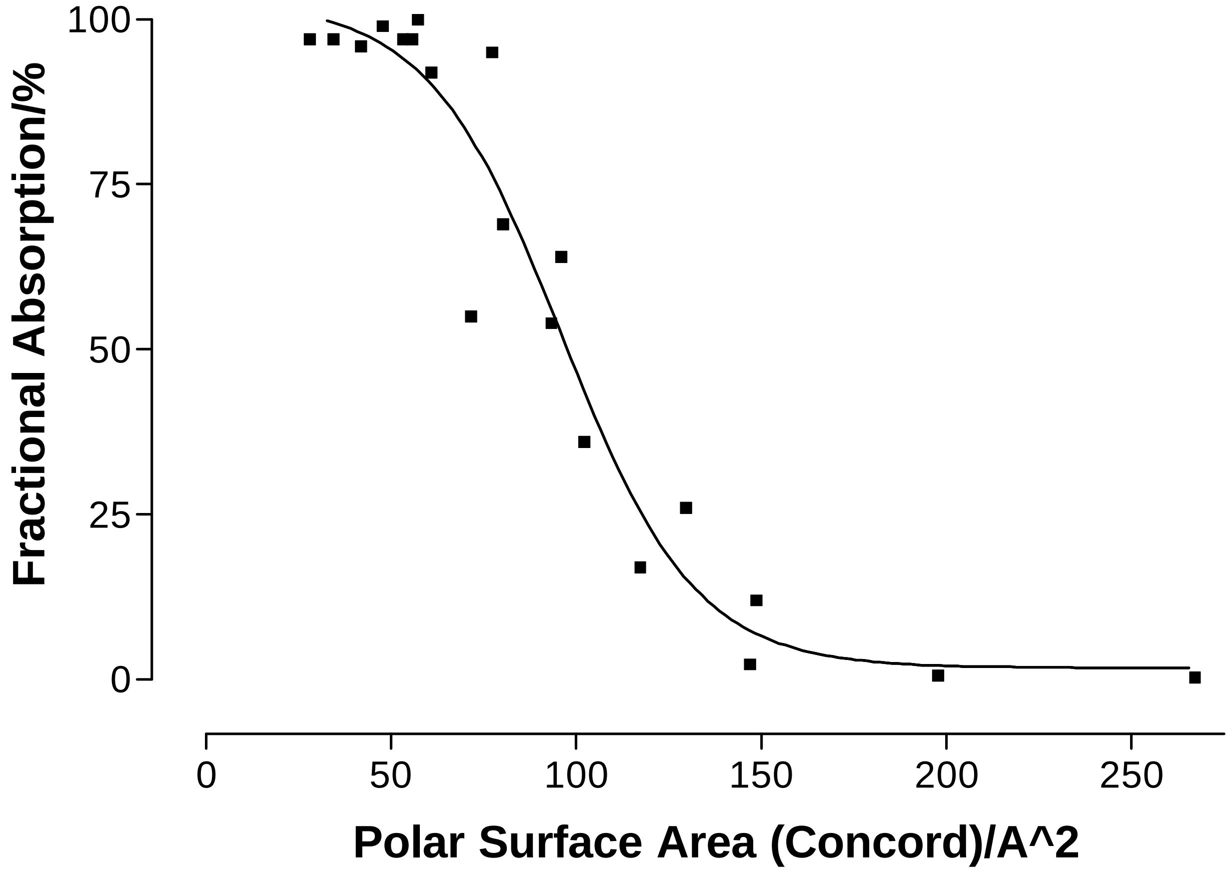
5) Inhouse program determines PSA

CPU time: ~10 secs/structure (SGI R10000)

Fully automated: intranet interface/batch scripts

Intestinal Absorption - PSA

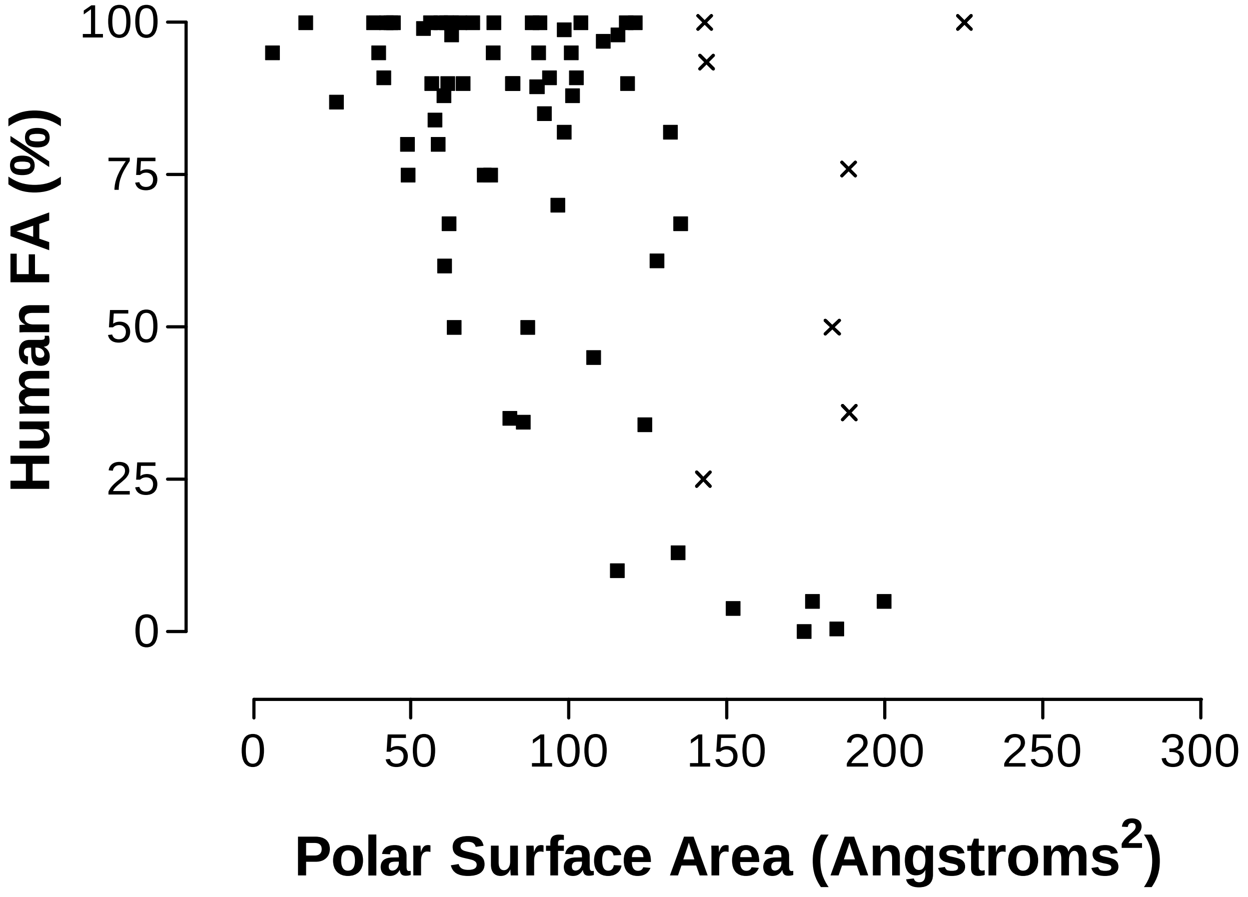
PSA > 140 A^2 => possible absorption problems



Intestinal Absorption - PSA

Validation Study 1:

- 74 compounds taken from Wessel *et al.*



Intestinal Absorption - PSA

Seven apparent “false negatives” (shown as crosses)

- 6/7 shown to be actively transported:
  - methotrexate: folate carrier, AZT: rCNT
  - lisinopril, amino-beta-lactams: dipeptide carrier
- Etoposide - erratic bioavailability, active transport?
- Remaining 67 compounds are classified correctly by PSA >140 criterion
- Rule-of-5 only generates warnings for 2 out of the 5 poorly absorbed compounds (%FA < 10)

Reference:

- Wessel, M.D. *et al*. Prediction of Human Intestinal Absorption of Drug Compounds from Molecular Structure. *J. Chem. Inf. Comput. Sci.* 1998, 38, 726-735.

Intestinal Absorption - PSA

Validation Study 2:

• Kansy set - 24 compounds with % absorption data

Classified experimentally (human fractional absorption):

• High (abs. > 70%): 19

• Moderate (< 30% abs. < 70%): 2

• Low (abs. < 30%): 3

Reference:

• Kansy, M. *et al*. Physicochemical High Throughput Screening: Parallel Artificial Membrane Permeation Assay in the Description of Passive Absorption Processes. *J. Med. Chem.* 1998, 41, 1007-1010.

Intestinal Absorption - PSA

Kansy experimental PAMPA classification:

- High: 13. (Correct)
- Moderate: 8. (6 errors)
- Low: 3. (Correct)

PSA classification:

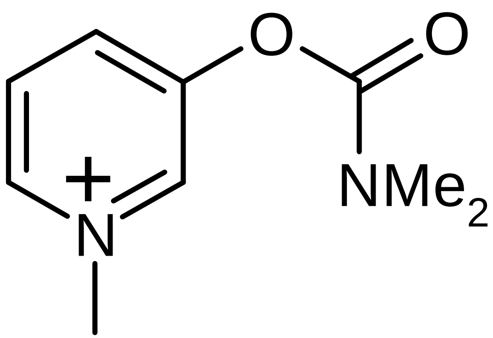
- High (PSA < 83): 16. (Correct)
- Moderate ($83 < \text{PSA} < 113$): 4. (2 errors)
- Low (PSA > 113): 4. (1 error)

Applying PSA > 140 cutoff predicts low absorption compounds correctly

Intestinal Absorption - PSA

Conclusions:

- Slower to calculate than rule-of-5
- But more accurate at prediction
- PSA >140 criterion for poor absorption seems robust
- Why does PSA seem to work?
- False positives indicate other criteria are necessary for more accurate prediction of absorption, e.g. pKa, logD



BBB Penetration - QSARs

Introduction - QSARs for logBB ($BB=C_{brain}/C_{blood}$):

- Kansy/van de Waterbeemd:
  - *Chimia* 1992, 46, 299-303.
  - PSA, molecular volume
    - n=20, r=0.84, s=0.45, F=19.5
  - training set too small, not general enough

- Abraham *et al.* (AB):
  - *J. Pharm. Sci.* 1994, 83, 1257-1268.
  - 5 empirical solute descriptors
    - n=57, r=0.95, s=0.20, F=99.2
  - not yet automated, missing fragments

BBB Penetration - QSARs

- Lombardo *et al*. (LO):
  - *J. Med. Chem*. 1996, 39, 4750-4755.
  - Free-energy of solvation (AMSOL)
    - n=55, r=0.82, s=0.41, F=108.3
  - Computationally expensive

- Norinder *et al*. (NO):
  - *J. Pharm. Sci.* 1998, 87, 952-959.
  - MolSurf parameters, PLS analysis (3 comps.)
    - n=56, r=0.91, s=0.31, F=87.0
  - Computationally expensive

BBB Penetration - QSARs

- Luco (LU):
  - JCICS 1999, 39, 396-404.
  - Topological descriptors, PLS model (3 comps.)
    - n=58, r=0.92, s=0.32, F=102.0
  - Interpretability?

- In-house equation (RPR):

  logBB = -0.0148 PSA + 0.152 ClogP + 0.139

  n=55, r=0.89, s=0.35, F=95.8

  - Large training set, automatic, fast
  - Can also use MlogP with good results

BBB Penetration - Test Sets

Prediction set 1:

logBB values

Compound	Expt	AB	LU	RPR
Y-G14	-0.30	-0.31	-0.14	-0.30
Y-G15	-0.06	-0.01	0.02	-0.09
Y-G16	-0.42	-0.41	-0.51	-0.59
Y-G19	-1.30	-0.14	-0.04	-0.24
Y-G20	-1.40	-0.57	-0.29	-0.53
SKF89124	-0.43	-0.44	-0.26	-0.56
SKF101468	0.25	0.24	0.17	-0.11
Mean abs. error:		0.30	0.42	0.37

Ref: Abraham, M.H. *et al*. *Drug Des. Discov.* 1995, 13, 123-131.

BBB Penetration - Test Sets

Prediction set 2:

		logBB values			
Cmpd	Expt	LO	NO	LU	RPR
31	0.00	-0.14	-0.58	-0.01	-0.25
32	-0.34	-0.28	-1.11	0.01	-0.75
33	-0.30	-0.46	-0.75	-0.45	-0.70
34	-1.34	-0.64	-0.99	-0.93	-1.26
35	-1.82	-0.82	-1.35	-1.31	-1.77
Mean abs. error:		0.41	0.52	0.29	0.24

Refs: Lombardo, F. *et al. J. Med. Chem.* 1996, 39, 4750-4755.
Norinder, U. *et al. J. Pharm. Sci.* 1998, 87, 952-959.
Luco, J.M. *J. Chem. Inf. Comput. Sci.* 1999, 39, in press.

BBB Penetration - Test Sets

Prediction set 3

- Most stringent test
- 25 diverse drug compounds from Luco (1999)
- Luco results:
  - mean abs. error = 0.43
  - RMSE = 0.54
- RPR results:
  - mean abs. error = 0.50
  - RMSE = 0.59

BBB Penetration

Conclusions:

- Predictive capability of RPR equation comparable to other methods
- Fully automated, properties are quick to calculate
- Easy to interpret
- Physically sensible:

  $$\log BB = -0.0148\ PSA + 0.152\ ClogP + 0.139$$

- PSA reflects H-bonding capacity (desolvation)
- ClogP indicates lipophilicity
- Brain is more lipophilic than blood

Applications in Drug Design

- (Virtual) compound assessment
  - Intranet interface for medicinal chemists
  - Batch processing for large sets
- Combinatorial library design
  - Product-based reagent selection
- Database for analysis
  - Graphical viewing of trends/patterns
  - Validation against inhouse experimental data
  - Example: Caco-2 %abs vs. PSA

LOKI Menu

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View List

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Data Analysis

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Feedback

Logout

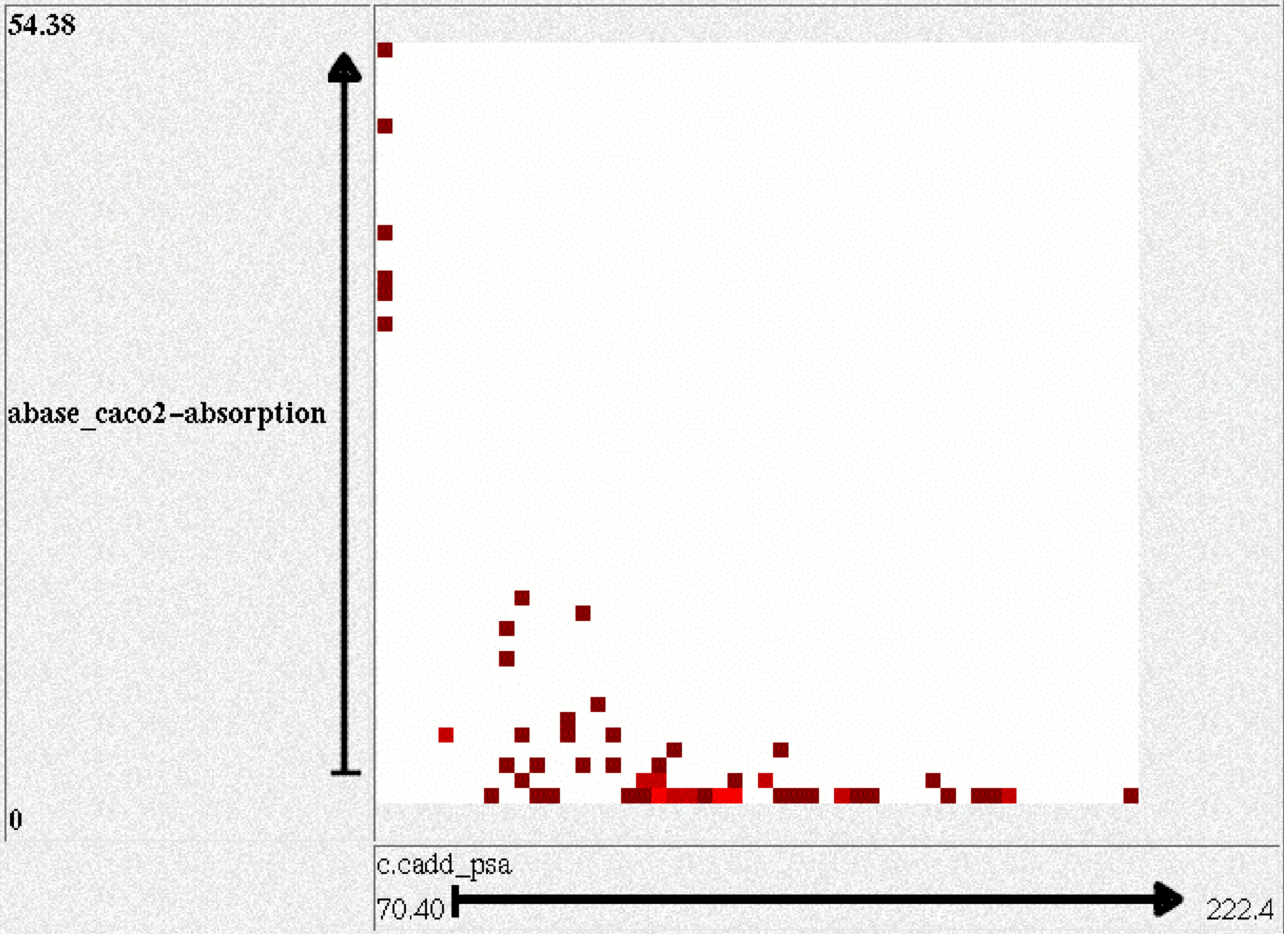
1-,2- and 3-D Charts

Histograms by List

List used : decacs99

List Viewer

This may take a little while please be patient



Conclusions

- Intestinal Absorption
  - Lipinski's rule-of-5: fast but crude
  - Polar Surface Area: slower but more accurate. PSA > 140 for poor absorption
- Blood-Brain Barrier (BBB) Penetration
  - Fast and relatively accurate predictions using PSA/ClogP-based QSAR
- Widely applied to inhouse drug discovery programs

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