Introduction to Ligand-Based Drug Design

SAPIENZA
UNIVERSITÀ DI ROMA

QSAR Building Procedure

Identification of Active Ligands

Identification of Suitable Descriptors (molecular fingerprint)

Establish Mathematical Expression Relating Descriptors to Activity

Construction and Validation of the QSAR model

QSAR Limitations

- Congeneric Series
- Same Binding Mode
- Lack of 3-D Structural Information
- Statistical Limitation

Statistical Tools for Model Development and Validation

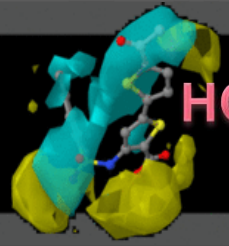
(i) Multivariable linear regression analysis (MLR)

(ii) Principal component analysis (PCA)

http://setosa.io/ev/principal-component-analysis/

(iii) Partial least square analysis (PLS)

least square applications



HOW TO EVALUATE THE QUALITY OF A MODEL

Squared Correlation Coefficient

R^2 or r^2

$$r^2 = 1 - \frac{\sum_{i=1}^{N} (Y_{\text{exp},\,i} - Y_{calc\,,i})^2}{\sum_{i=1}^{N} (Y_{\text{exp},\,i} - \overline{Y})^2}$$

Cross-Validated R^2

Q^2 or q^2

$$q^2 = 1 - \frac{\sum_{i=1}^{N} (Y_{\text{exp},\,i} - Y_{pred\,,i})^2}{\sum_{i=1}^{N} (Y_{\text{exp},\,i} - \overline{Y})^2}$$

Fitting

Squared Correlation Coefficient

R^2 or r^2

$$r^2 = 1 - \frac{\sum_{i=1}^{N} (Y_{exp,\,i} - Y_{calc\,,i})^2}{\sum_{i=1}^{N} (Y_{exp,\,i} - \overline{Y})^2}$$

$$0 \leq r^2 \leq 1$$

$$r^2 = 1 - \frac{\sum_{i=1}^{N} (Y_{exp,\,i} - Y_{calc\,,i})^2}{\sum_{i=1}^{N} (Y_{exp,\,i} - \overline{Y})^2}$$

CV (Cross-Validation) – Robustness of a model
Internal Predictivity Evaluation

Cross-validated R^2 Q^2 or q^2

$$r^2_{CV} = q^2 = 1 - \frac{\sum_{i=1}^{N} (Y_{\text{exp},\,i} - Y_{pred\,,i})^2}{\sum_{i=1}^{N} (Y_{\text{exp},\,i} - \overline{Y})^2}$$

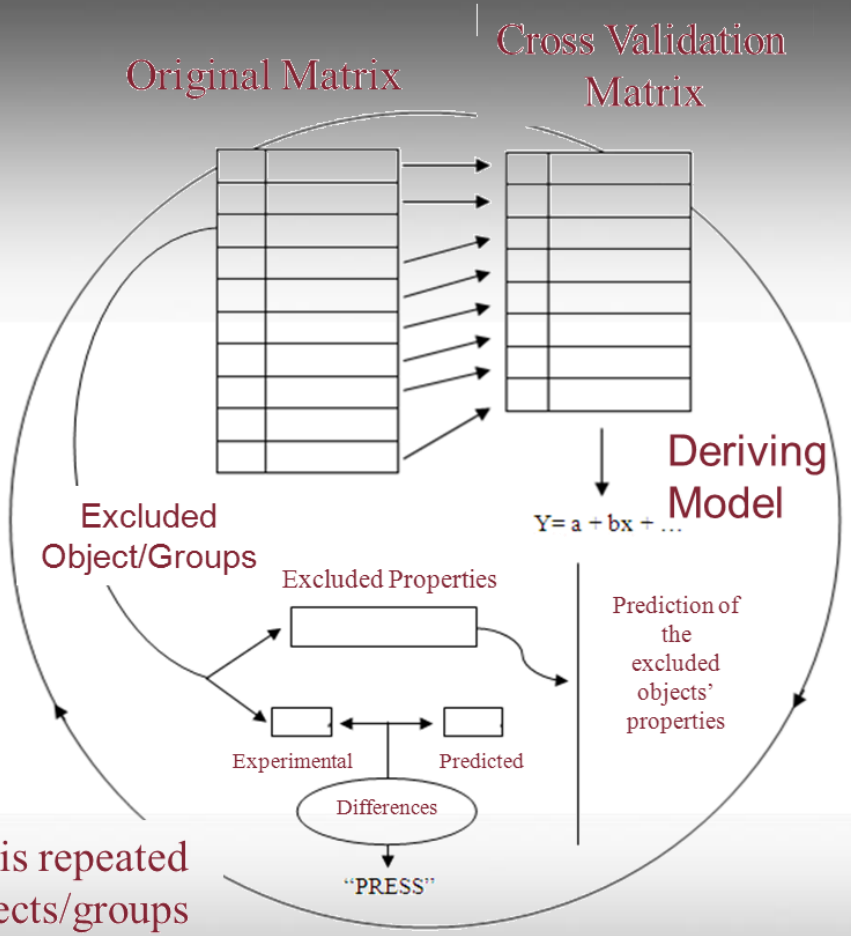
$$SDEP = \sqrt{\frac{\sum_{i=1}^{N} (Y_{\text{exp},\,i} - Y_{pred\,,i})^2}{N}}$$

$$-\infty \leq q^2 \leq 1$$

The predictive ability of a model is estimated using a reduced set of structural data

Cross-Validation

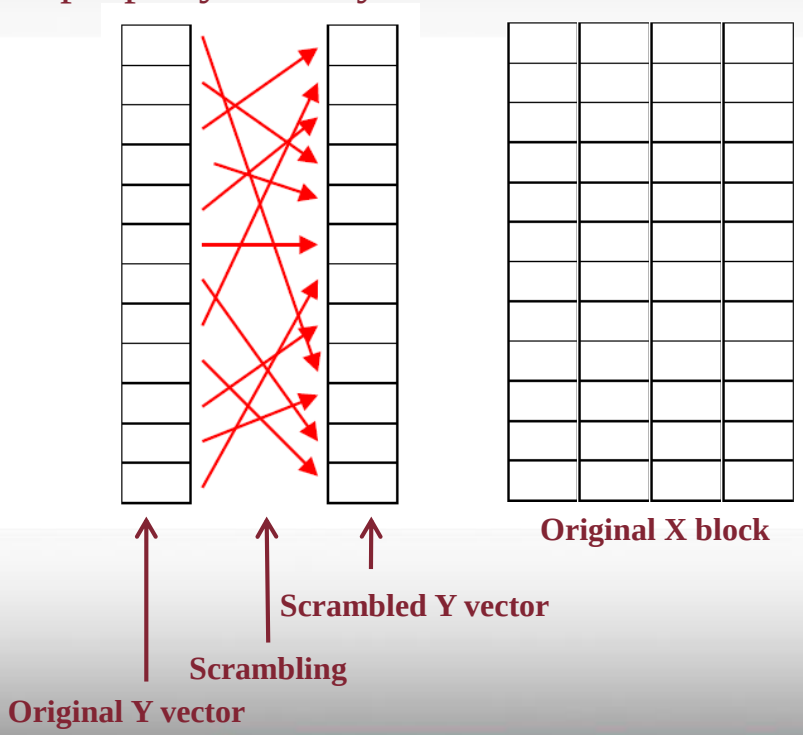
- *K*-fold cross-validation
- Repeated random sub-sampling validation
- Leave-one-out cross-validation



The process is repeated untill all objects/groups are predicted

Y-Scrambling

A statistical test of prediction tools, in which models are fitted for randomly reordered property/activity values and compared with the model obtained for the actual property/activity values.



A new model is obtained for such permuted data, R^2 and Q^2 are then recalculated.

This step is repeated for a sufficient number of times (iterations):

a good number being 50 to 100.

Values obtained in the above fashion are compared with the true values obtained for the model that was fitted on the real data.

External Test-Set

SDEP (Standard Deviation Error of Prediction)

$$SDEP = \sqrt{\frac{\sum_{i=1}^{N} (Y_{\exp,\ i} - Y_{pred\ ,i})^2}{N}}$$

N° of predicted compounds

1980: The Goodford's GRID

(Toward 3-D QSAR)

J. Med. Chem. 1985, 28, 849–857

Articles

A Computational Procedure for Determining Energetically Favorable Binding Sites on Biologically Important Macromolecules

P. J. Goodford

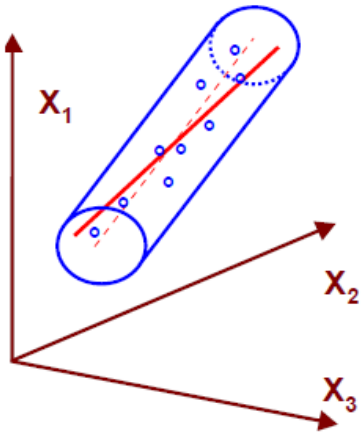
The Laboratory of Molecular Biophysics, The Rex Richards Building, University of Oxford, Oxford OX1 3QU, England.
Received August 3, 1984

The interaction of a probe group with a protein of known structure is computed at sample positions throughout and around the macromolecule, giving an array of energy values. The probes include water, the methyl group, amine nitrogen, carboxy oxygen, and hydroxyl. Contour surfaces at appropriate energy levels are calculated for each probe and displayed by computer graphics together with the protein structure. Contours at negative energy levels delineate regions of attraction between probe and protein and are found at known ligand binding clefts in particular. The contours also enable other regions of attraction to be identified and facilitate the interpretation of protein–ligand energetics. They may, therefore, be of value for drug design.

Description of Molecules with Molecular Interaction Fields (MIF)

197x-198x: The Wold's PLS
(Toward 3-D QSAR)

PLS (Partial Least Squares) Analysis

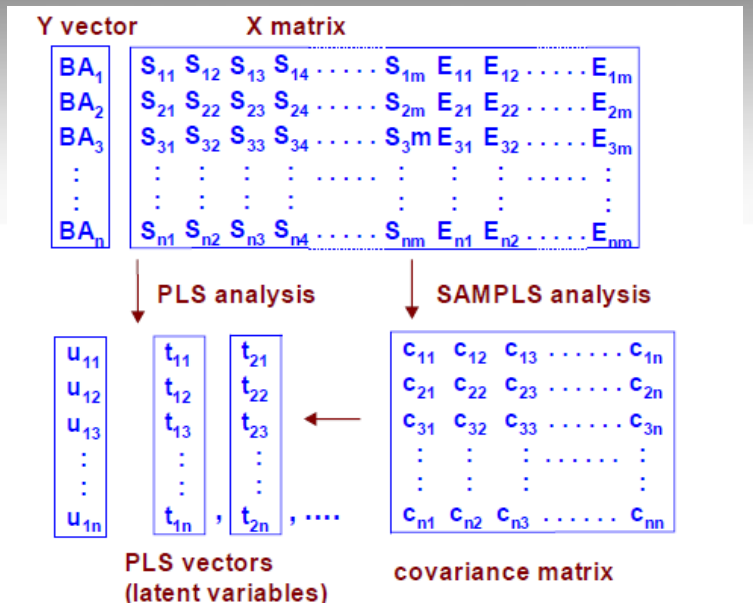


From u = kt

(k = constants k_1, k_2 ... k_j;
j = number of PLS vektors)

follows:

$$BA_i = a_1S_{i1} + a_2S_{i2} + a_3S_{i3} + \ldots + a_mS_{im} + b_1E_{i1} + b_2E_{i2} + b_3E_{i3} + \ldots + b_mE_{im}$$

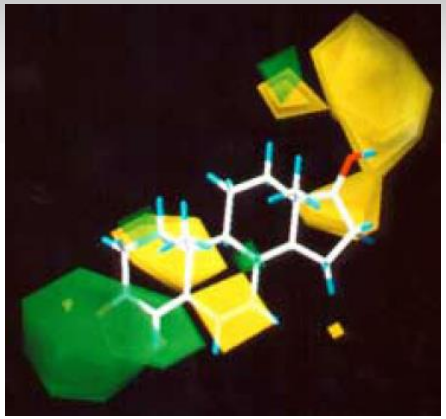


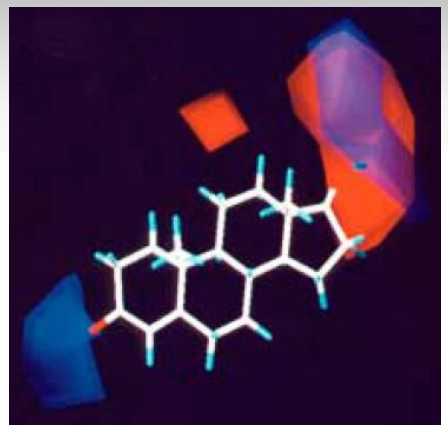
Reduction of Dimensionality into Few New Highly Informative Entities

----- Principal Components -----

1988: The First 3-D QSAR

PLS + MIF → CoMFA!



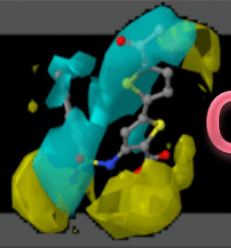


J. Am. Chem. Soc. **1988**, *110*, 5959–5967

Comparative Molecular Field Analysis (CoMFA). 1. Effect of Shape on Binding of Steroids to Carrier Proteins

Richard D. Cramer, III,* David E. Patterson, and Jeffrey D. Bunce

Contribution from Tripos Associates, 1699 South Hanley Road, St. Louis, Missouri 63144. *Received January 5, 1988*

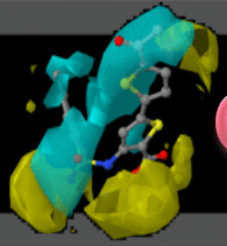


CoMFA/3-D QSAR Procedure

- Physical properties are measured for the molecule as a whole
- Properties are calculated using computer software
- No experimental constants or measurements are involved
- Properties are known as ‘Fields’
- Steric field - defines the size and shape of the molecule
- Electrostatic field - defines electron rich/poor regions of molecule
- Hydrophobic properties are relatively unimportant

Advantages over classical QSAR

- No reliance on experimental values (*i.e.* logP)
- Can be applied to molecules with unusual substituents
- Not restricted to molecules of the same structural class
- Improved predictive capability



CoMFA/3-D QSAR Procedure

Training Set

Molecular Alignment

Molecular Interaction Fields (MIF)

Model Generation

Internal and External Validation

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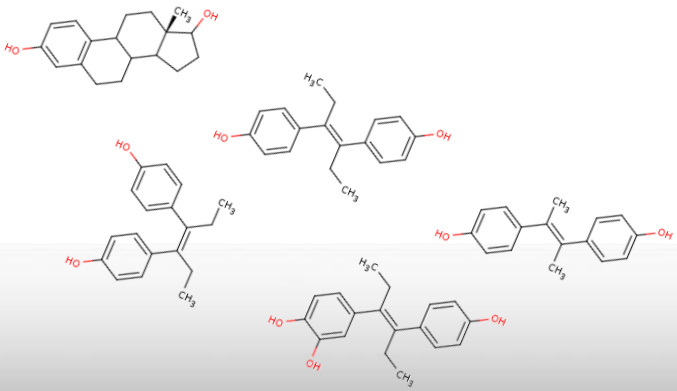

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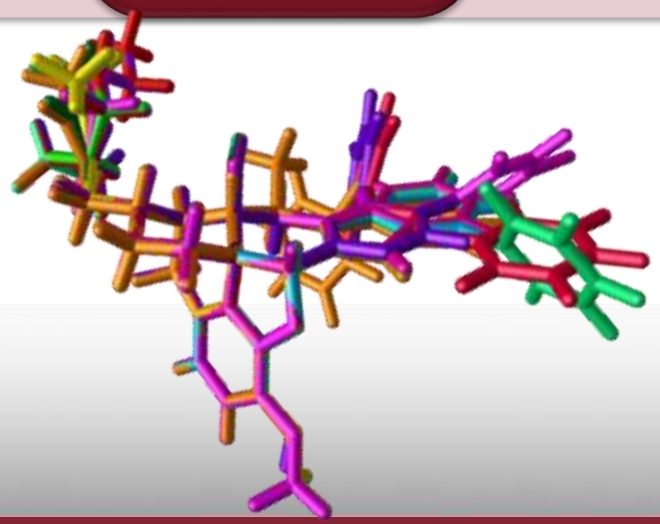

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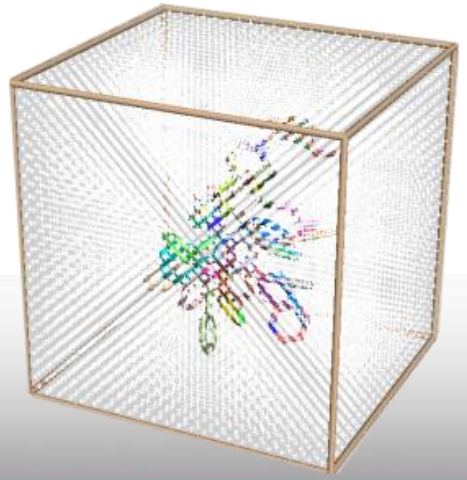

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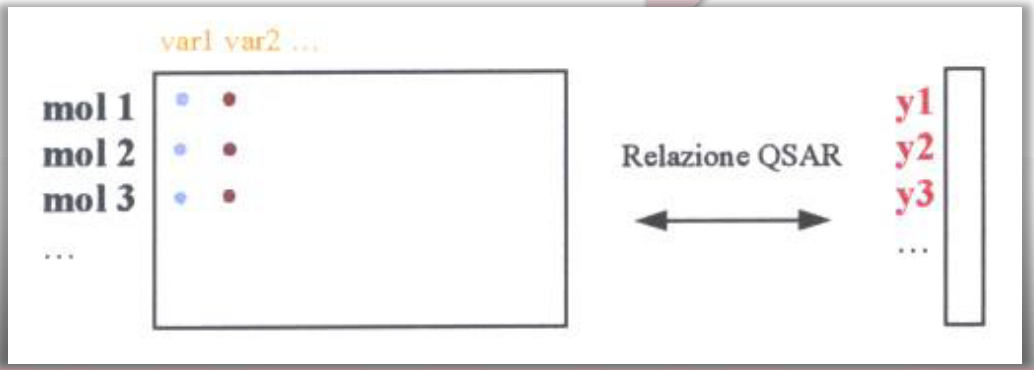


CoMFA/3-D QSAR Procedure

Training Set

Molecular Alignment

Molecular Interaction Fields (MIF)

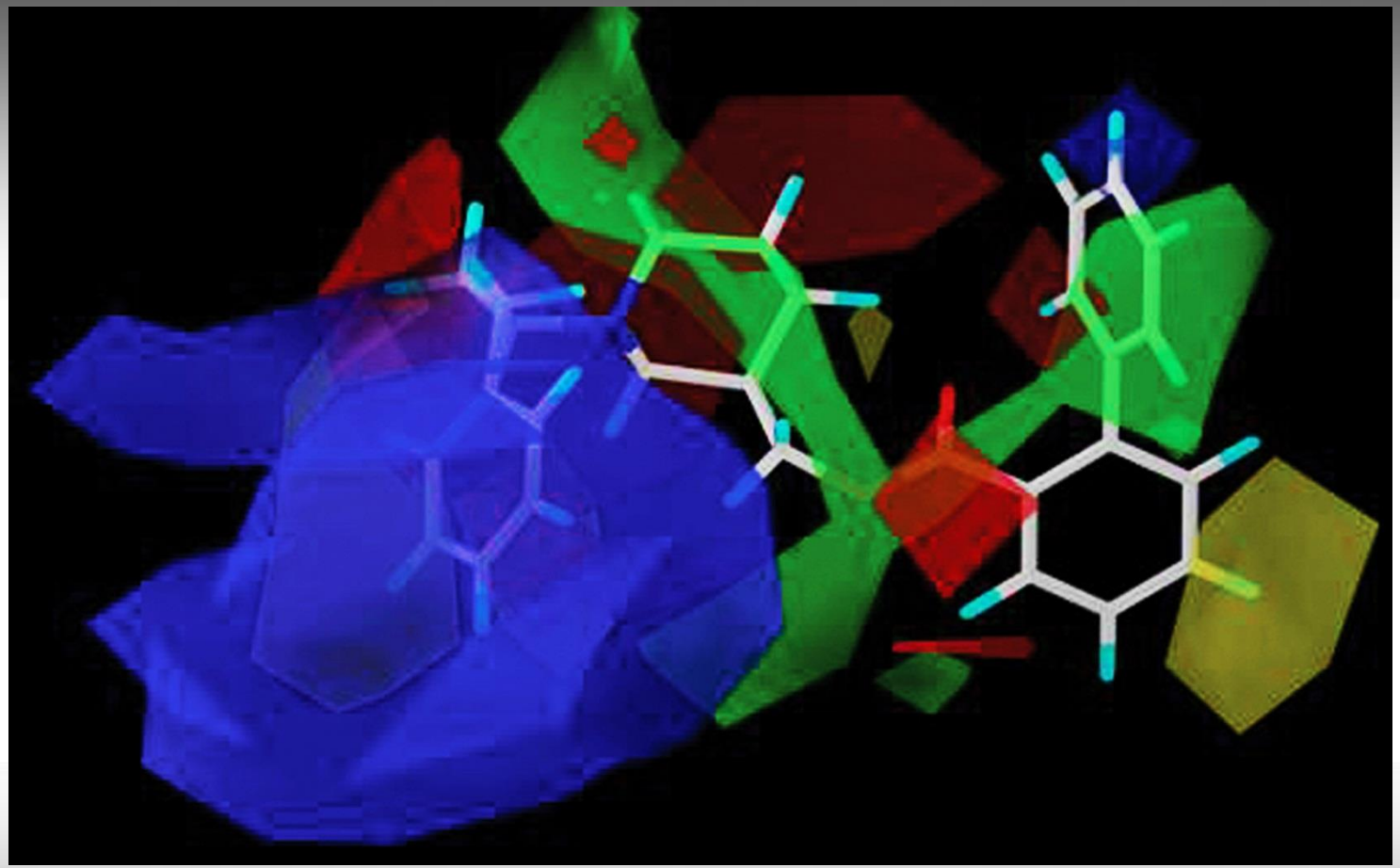
Model Generation

Internal and External Validation

$$SDEP = \sqrt{\sum \left(y_{\exp} - y_{pred} \right)^2 / n - 1}$$

$$q^2 = 1 - \sum \left(y_{\exp} - y_{pred} \right)^2 / \sum \left(y_{\exp} - y \right)^2$$

CoMFA/3-D QSAR Procedure



CoMFA Limits

CRUCIAL POINTS!

- Conformation of the training set molecules
- Superimposition of the training set molecules (molecular alignment rules)

Original CoMFA Tricks:

- Very rigid molecules: steroid scaffold!!!!
- Directed superimposed atom by atom!!!!

CoMFA Limits

CRUCIAL POINTS!

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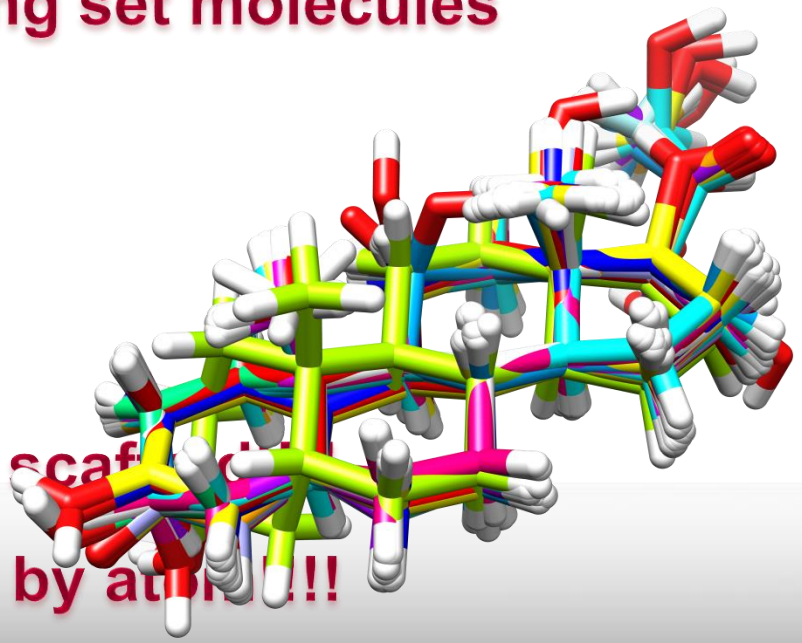

Original CoMFA Tricks:

- Very rigid molecules: steroid scaf[illegible]
- Directed superimposed atom by at[illegible]!!!

1991: The WO CoMFA Patent and 3-D QSAR Development

The Lattice Model: A General Paradigm for Shape-Related Structure/Activity Correlation
Cramer, R.D., and Milne, M., *Abstracts ACS Meeting*, Honolulu, 1979, COMP 44.

SIAM J. Sci. and Stat. Comput. / *Volume 5* / *Issue 3*

The Collinearity Problem in Linear Regression. The Partial Least Squares (PLS) Approach to Generalized Inverses
S. Wold, A. Ruhe, H. Wold, and W. J. Dunn, III
SIAM J. Sci. and Stat. Comput. Volume 5, Issue 3, pp. 735-743

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Baroni, M.; Costantino, G.; Cruciani, G.; Riganelli, D.; Valigi, R.; Clementi, S.,
Generating Optimal Linear Pls Estimations (Golpe) - an Advanced Chemometric Tool for Handling 3D-QSAR Problems.
Quant Struct-Act Rel 1993, 12, (1), 9-20.

J. Med. Chem. **1994**, *37*, 2589–2601 2589

Comparative Molecular Field Analysis Using GRID Force-Field and GOLPE Variable Selection Methods in a Study of Inhibitors of Glycogen Phosphorylase *b*

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Department of Chemistry, University of Perugia, Via Elce di Sotto, 8, 06100 Perugia, Italy, and Laboratory of Molecular Biophysics, University of Oxford, South Parks Road, OX1 3QU, Oxford, England

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(21) International Application Number: PCT/US91/04292
(22) International Filing Date: 17 June 1991 (17.06.91)

Published
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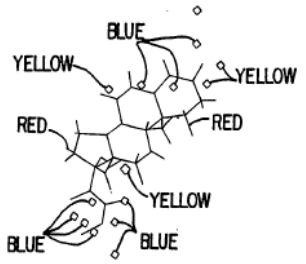
(74) Agent: LIPTON, Robert, S.; Lipton & Famiglio, 201 N. Jackson Street, P.O. Box 546, Media, PA 19063 (US).

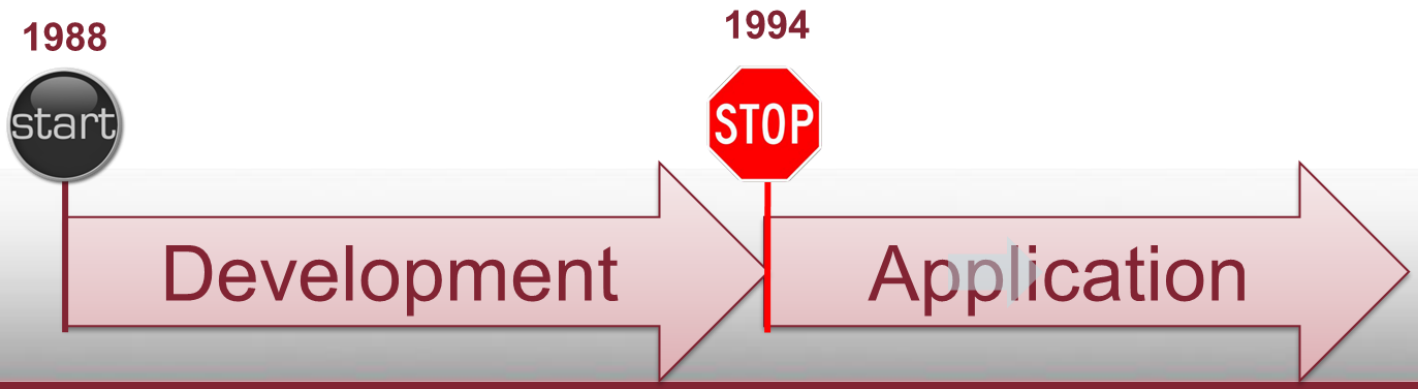
(81) Designated States: AT (European patent), BE (European patent), CH (European patent), DE, DE (European patent), DK (European patent), ES (European patent), FR (European patent), GB, GB (European patent), GR (European patent), IT (European patent), JP, LU (European patent), NL (European patent), SE (European patent).

(54) Title: COMPARATIVE MOLECULAR FIELD ANALYSIS (CoMFA)

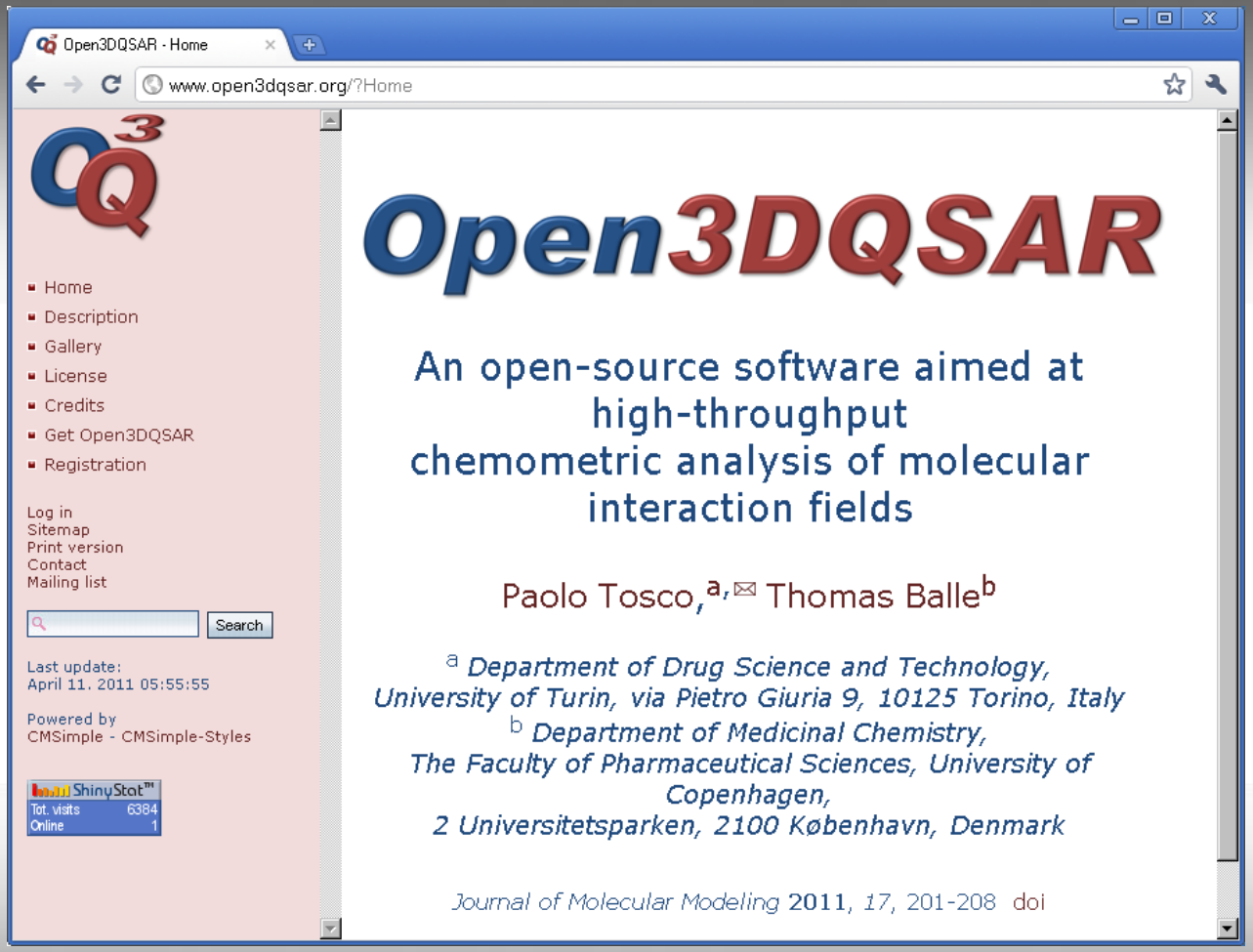


3-D QSAR Development

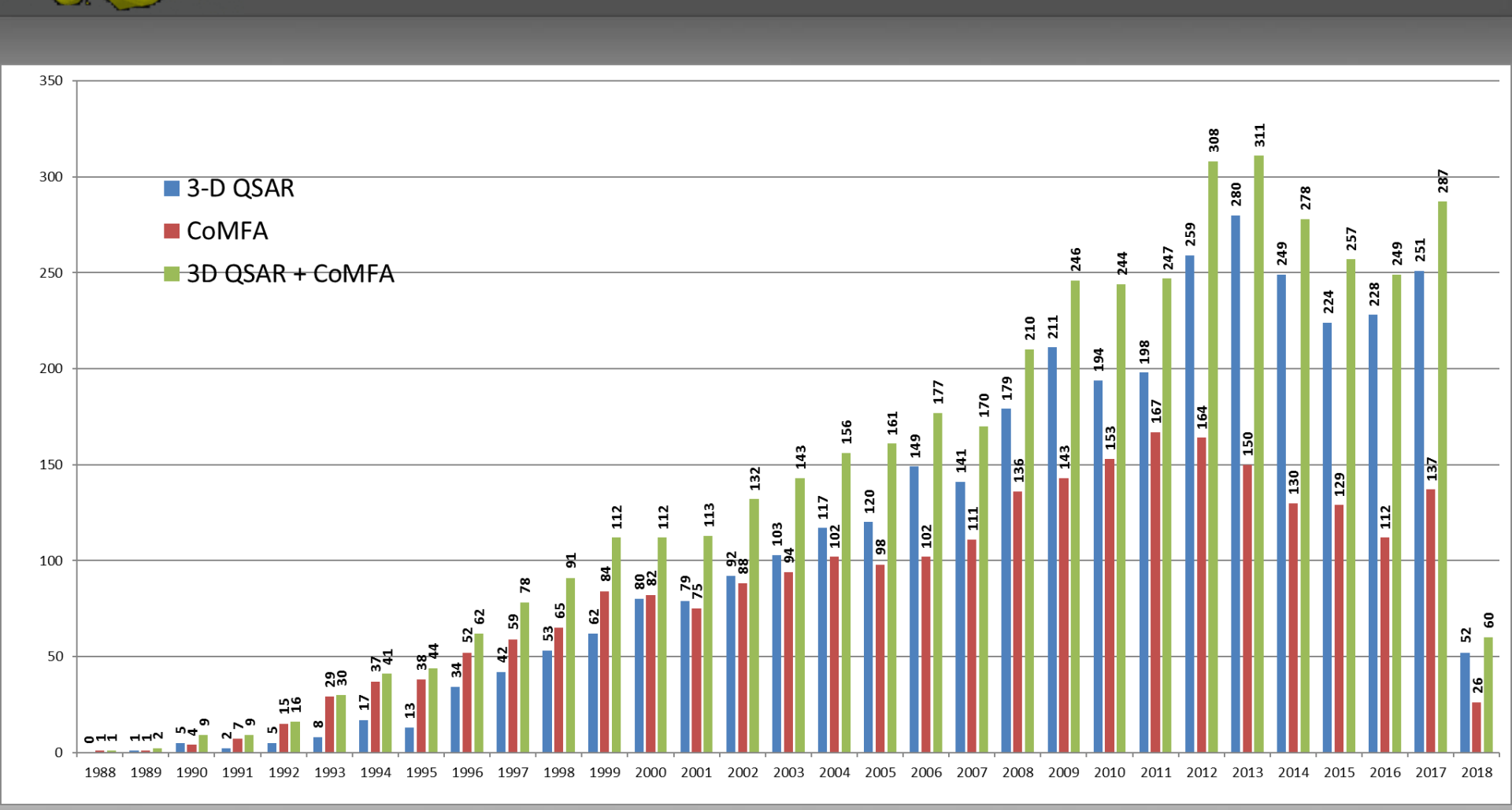
- 4-D QSAR, each molecule is represented by an ensemble of conformations, orientations, and protonation states
- 5-D QSAR, inclusion of the induced fit
- 6-D QSAR, the simultaneous evaluation of different solvation models
- CoMSIA
- VolSurf
- .....



2009: First Free 3D-QSARs



3D-QSAR is Alive!



2011: The First 3D-QSAR Server

On 17 June 2011 the patent PLS+MIF restriction dropped and now a new 3-D QSAR explosion is expected.

In view of this event, at RCMD, we started an ambitious project aimed to build a 3-D QSAR web server using just open source or free software

www.3D-QSAR.com
Three-Dimensional Quantitative Structure-Activity Relationships Server

Sapienza Università di Roma