Tutorial:
From chemical structures to outlier analysis

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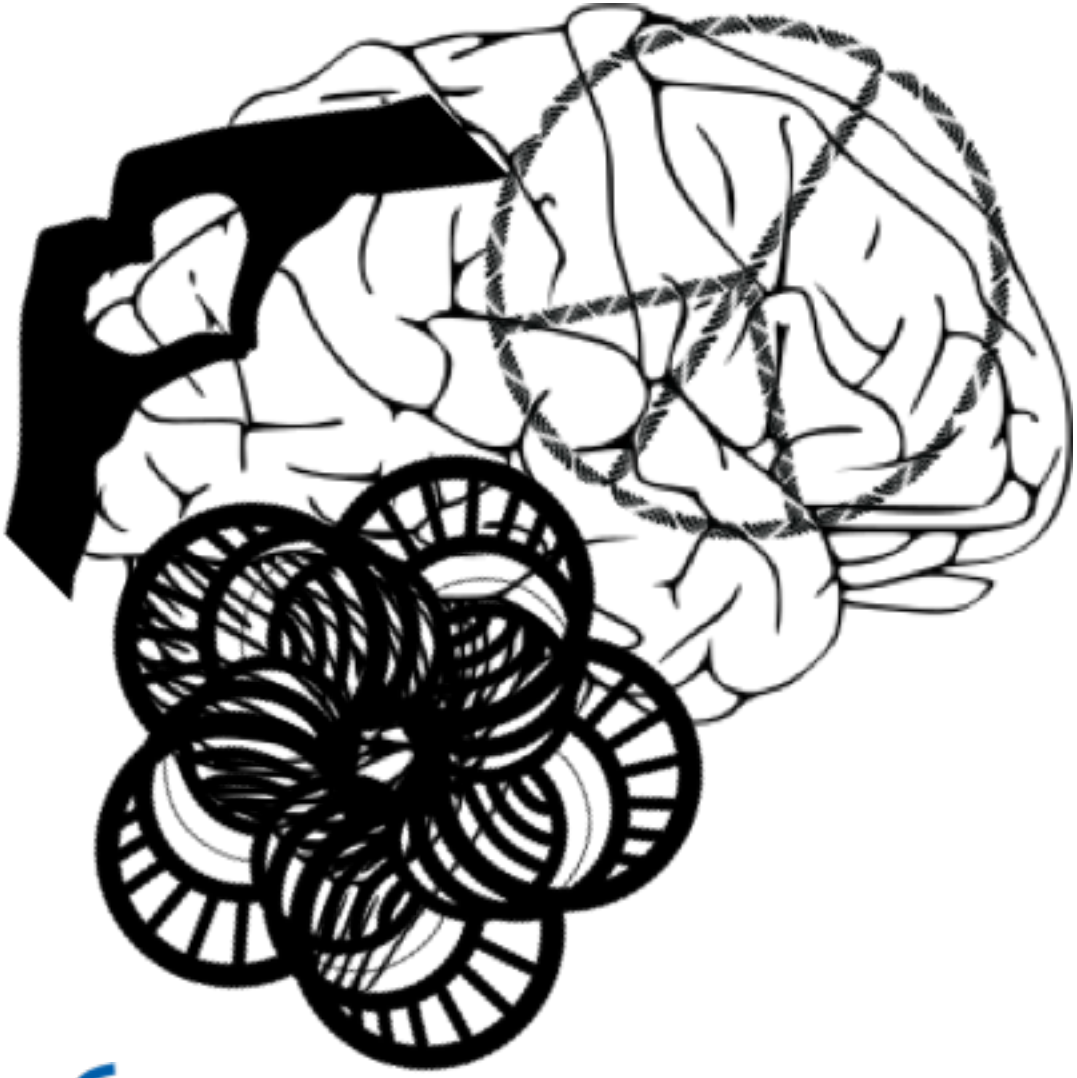
Download your materials

- **Download URL (tinyURL to Renater FileSender repository):**
  - ✔ https://tinyurl.com/y99km3nd
- **Content (<150Mo when unziped)**
  - ✔ Softwares
    - **ExtCV.exe, xFragmentor.exe, xModelAnalyzerR.exe**
  - ✔ Datasets
    - **Datamining**
      - 5-HT2B (a database)
      - Iter0 (tutorial directory)
      - Iter1 (result after the tutorial)
    - **Pubmed**
      - Relevant articles

Introduction

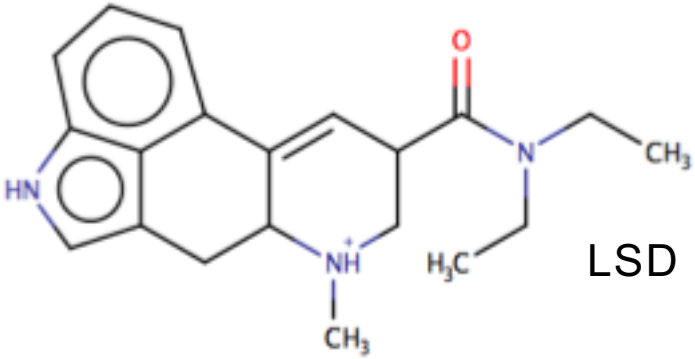
- **The IUPHAR 5-HT2B dataset**
  - ✔ 88 compounds
  - ✔ Affinity values
    - **pKi, pKd**
    - **Mostly human**
  - ✔ Type
    - **Agonist**
    - **Antagonist**
  - ✔ Bibliography
    - **PubMed Ids**

5-HT2A



Expressed in forebrain cerebral cortex

Famous 5-HT2A agonist



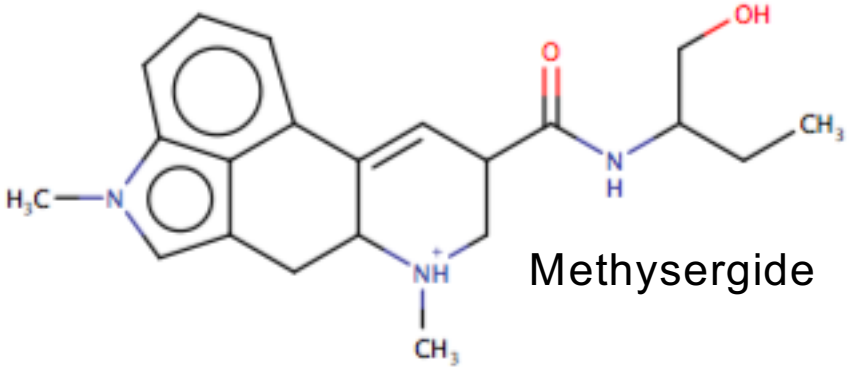
LSD

IMPLICATED IN FLOWER POWER

5-HT2C

Expressed in CNS

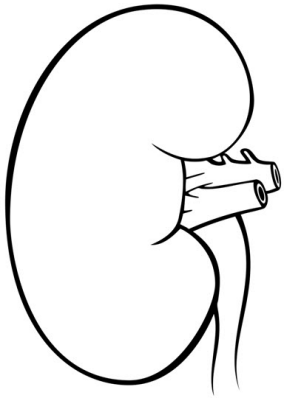
Example 5-HT2C antagonist

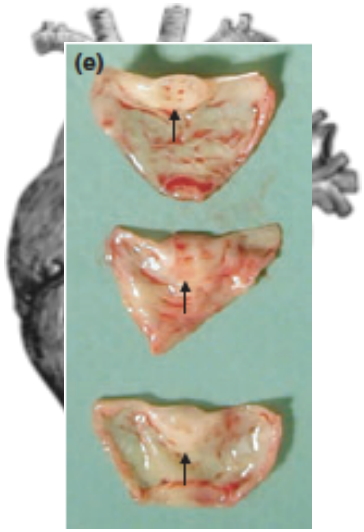


Methysergide

Implicated into:
obesity, seizure, psychotic disorder

5-HT2B, the anti-target

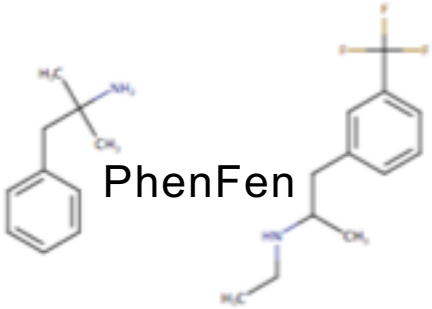


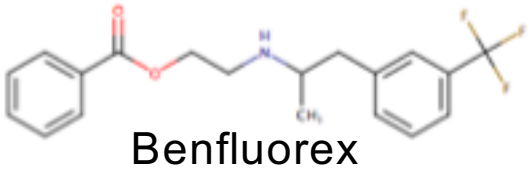


Expressed into

- Liver
- Kidney
- Heart

Example ligands:





Drug induced valvular heart disease

Exercise 1

- **Goal:**
  - ✔ Create a database of 5-HT2B ligand
- **Software:**
  - ✔ InstantJChem
- **File**
  - ✔ IUPHAR_5HT2B.sdf
- **Output**
  - ✔ Directory 5-HT2B

Create a local database

1. **Choose Project**
2. ...

Instant JChem

Categories:

General

Projects:

- IJC Project (empty)
- IJC Project (with local database)
- IJC Project (local database with demo data

Description:

New Instant JChem project with local database

Configure local database

Steps

1. Choose Project
2. **IJC Project Name**

Instant JChem

IJC Project Name

Project Name: 5-HT2B

Project Location: /Users/marcou/Desktop/Tutorial Browse...

Project Folder: /Users/marcou/Desktop/Tutorial/5-HT2B

☑ Close Already Opened Projects

Help < Back Next > Finish Cancel

Load an SDF into the database

Steps

1. Select schema
2. **File and new table details**
3. Field details
4. Monitor import

File and new table details

Database: localdb

File to import: /Users/marcou/Desktop/Tutorial/IUPHAR_5HT2B.sdf

File type: Structure file – SDF

Table details: New structure entity (using JChemBase table)

Summary: IUPHAR_5HT2B [APP.IUPHAR_5HT2B] Type: Molecules

10 fields found:

Structure [Text,Structure,List (Text)]
CdId [Text,List (Text),Boolean,Decimal,Integer]
Mol Weight [Text,List (Text),Decimal]
Formula [Text,List (Text)]
target_species [Text,List (Text)]
ligand [Text,List (Text)]
type [Text,List (Text)]
affinity_units [Text,List (Text)]
affinity [Text,List (Text),Decimal]
pubmed_id [Text,List (Text)]

Records read: 88

Read more 100

Instant JChem

SDF field management

Steps

1. Select schema
2. File and new table details
3. **Field details**
4. Monitor import

Instant JChem

Field details

Fields in file

Structure
CdId
Mol Weight
Formula
target_species
ligand
type
affinity_units
affinity
pubmed_id

Add >
< Merge >
< Map >
< Remove
Move up
Move down

Fields in database

CdId
Structure [Structure]
Mol Weight
Formula
target_species
ligand
type
affinity_units
affinity
pubmed_id
Original CdId [CdId]

New field type: 123 Integer Field

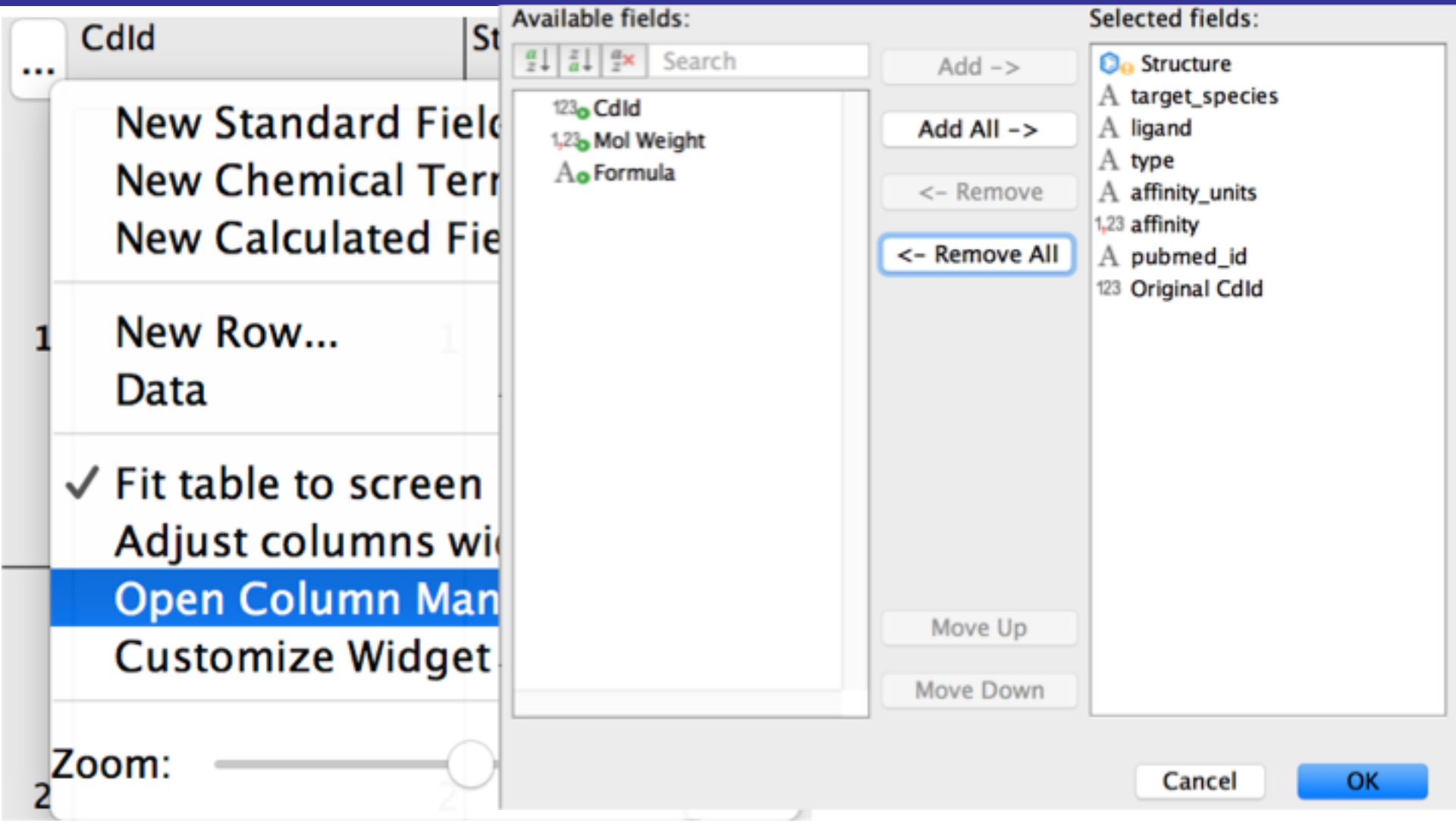
Display name: Original CdId

Required: FALSE

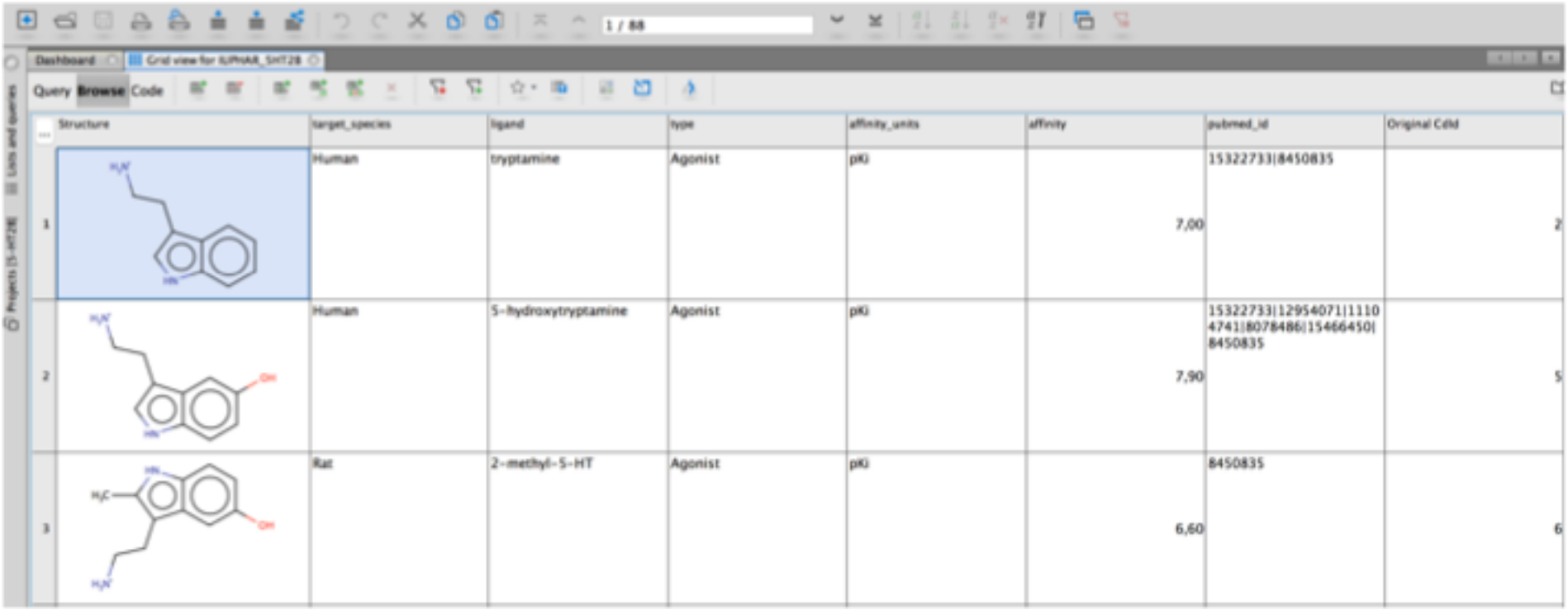
Default value:

DB Column Name: Original_CdId

Grid view column management



Final state of the interface



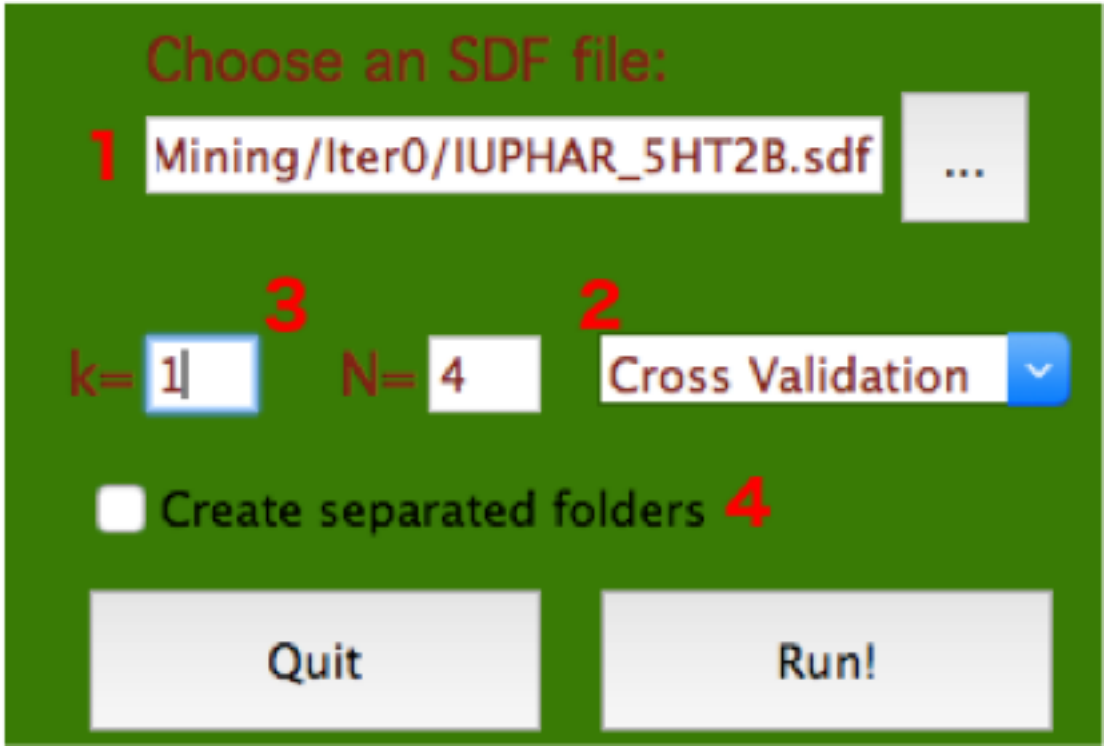
	Structure	target_species	ligand	type	affinity_units	affinity	pubmed_id	Original CdId
1		Human	tryptamine	Agonist	pKi	7,00	15322733|8450835	2
2		Human	5-hydroxytryptamine	Agonist	pKi	7,90	15322733|12954071|11104741|8078486|15466450|8450835	5
3		Rat	2-methyl-5-HT	Agonist	pKi	6,60	8450835	6

- A database of 5-HT2B ligands
- Access to chemical structures, affinity, type, identifier, bibliographic references
- Possibility to edit the dataset: structures, instances and values

Exercise 2

- **Goal:**
  - Set up an External Cross-Validation procedure
- **Software:**
  - ExtCrossValidate
  - xFragmentor
- **File**
  - IUPHAR_5HT2B.sdf
- **Output**
  - Directories CVIter*i*Fold*j*, files train.sdf and test.sdf
  - ISIDA Substructural Molecular Fragments, files *.hdr, *.svm, *.arff

Software: ExtCrossValidate



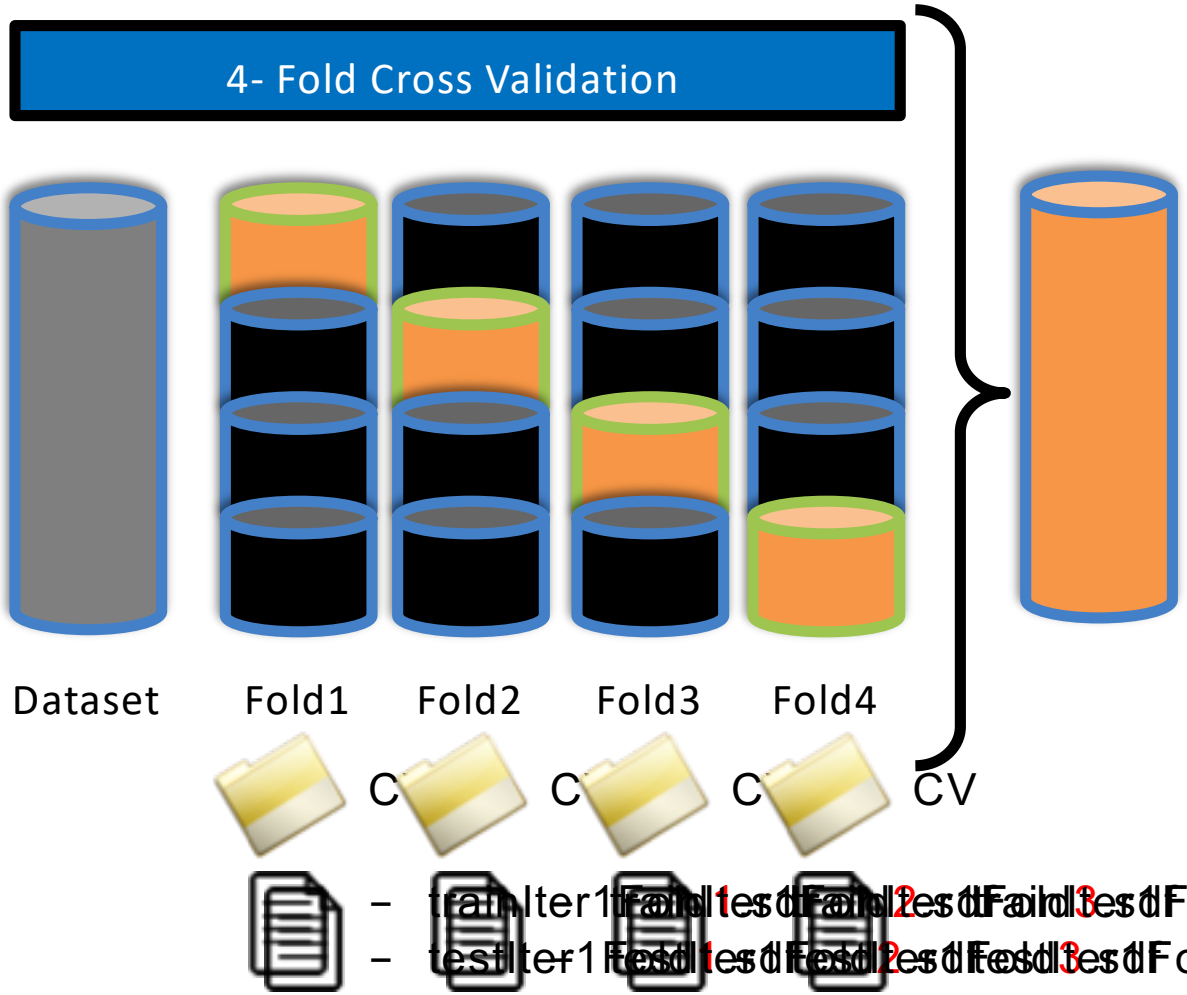
1 Select the **IUPHAR_5HT2B.sdf** file

2 Choose **Cross Validation**

3 Set 1 iteration to 1: **k=1** and 4 folds: **N=4**

4 **Uncheck** the tick-box. Store all train and test sets into a folder named CV

External Cross-Validation



Each compound is used once in a test set.

Training and test sets are structural files.

Each fold produces a dedicated training and test files in a directory named CV.

Software: xFragmentor

List of SDF files to process:

ktop/Tutorial/CVIter1Fold1/train.se
ktop/Tutorial/CVIter1Fold2/train.se
ktop/Tutorial/CVIter1Fold3/train.se
ktop/Tutorial/CVIter1Fold4/train.se
ktop/Tutorial/IUPHAR_5HT2B.sdf

1

Add SDF

Remove SDF

SDF field of interest:

affinity

Select a topology:

IIR (Atom centered, homogeneous path s

Add Fragment

Delete Fragment

Min length 2

Max length 4

2

Select a coloration scheme for atoms:

A Atom type

Read XML

Save XML

Select a coloration scheme for bonds

B Bond type

Atom Pairs

Do All Ways

Use Formal Charges

0 Do not use marked atom

Use predifined fragments

Base name of header files...

Check

Use only those fragments

Get atom contribution to fragment

3

E
IIAB_R(2-4)_FC

%%
ISIDA/xFragmentor

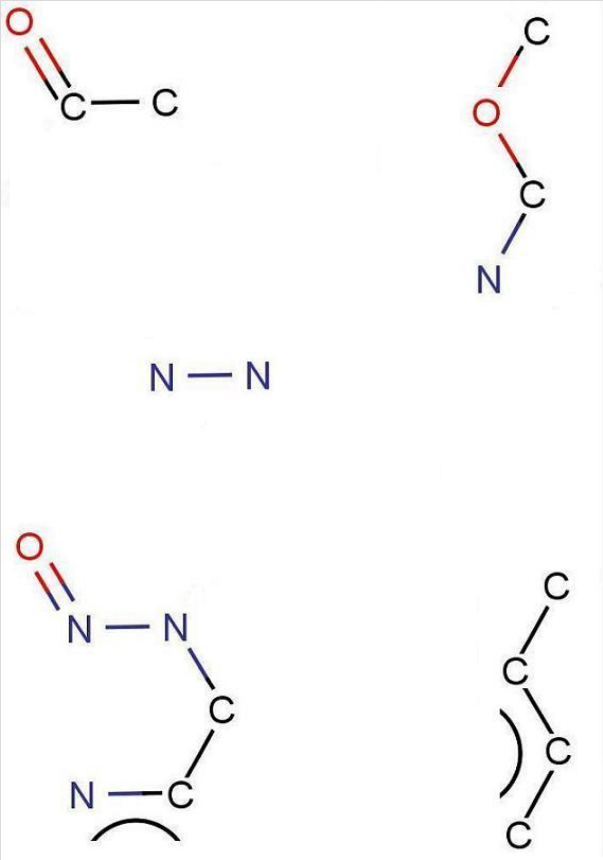
Université de Strasbourg, 2016
%%

Quit Reset Run!

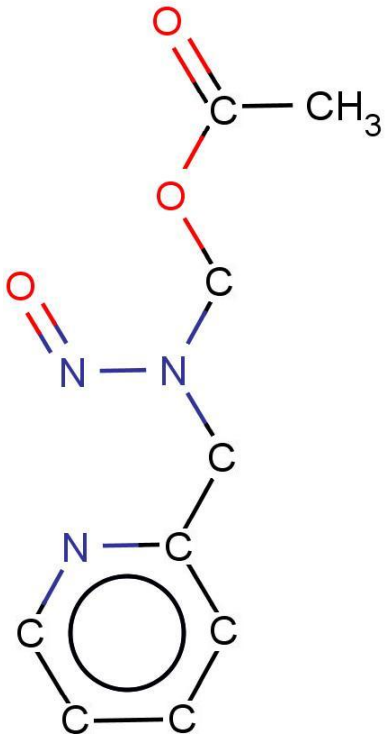
ISIDA fragments

Sequences of atoms and bonds containing

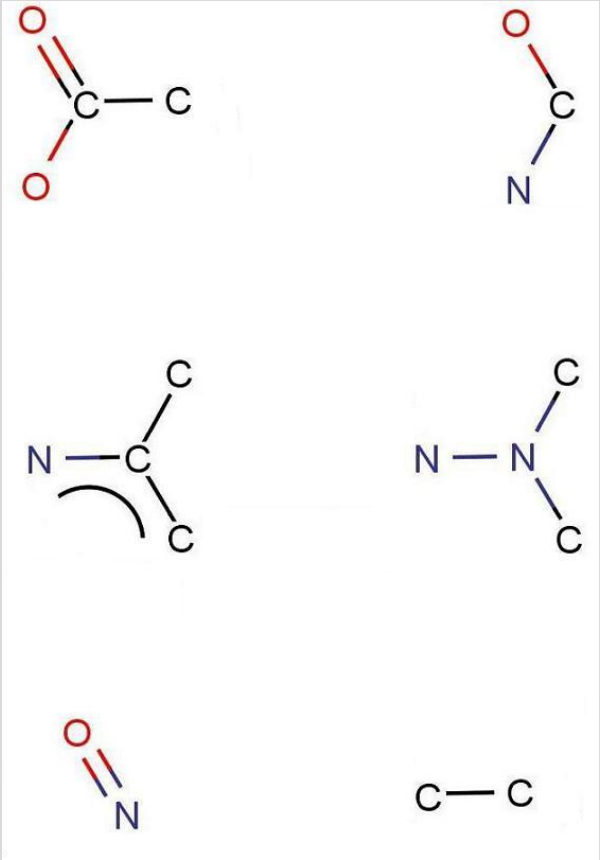
N_{min} > 2 to N_{max} < 15 atoms



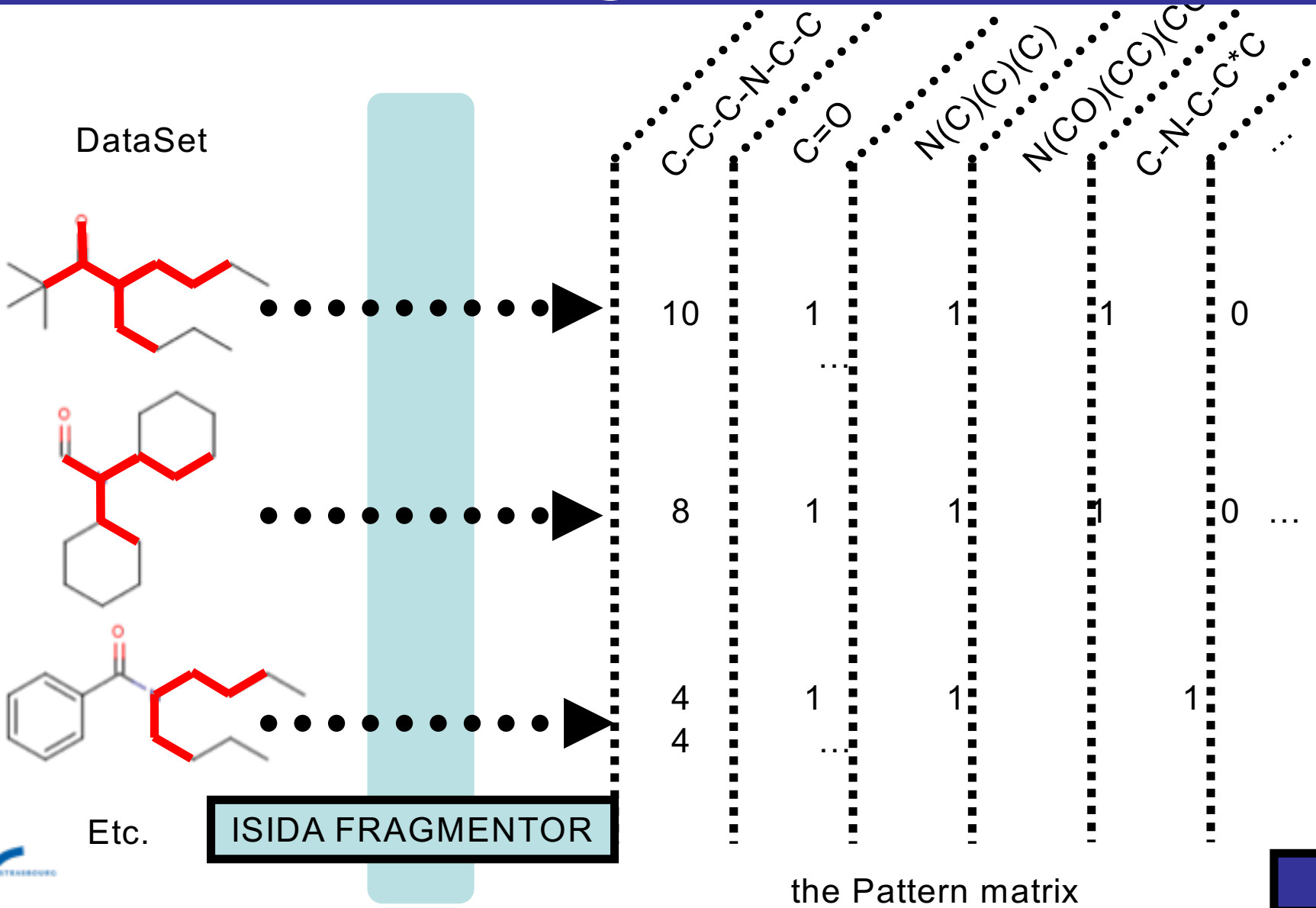
atoms and bonds



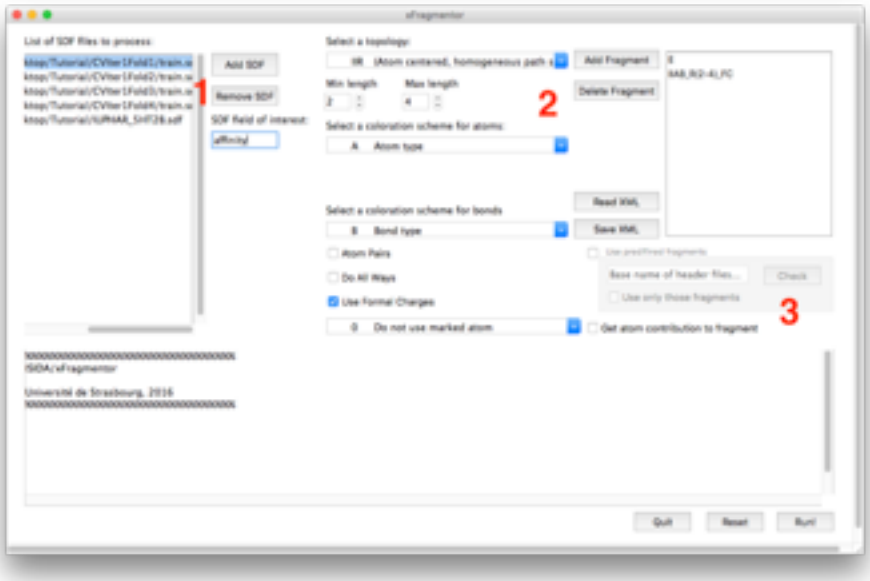
Augmented atoms (a central atom and his direct neighbours)



ISIDA Substructural Molecular Fragments

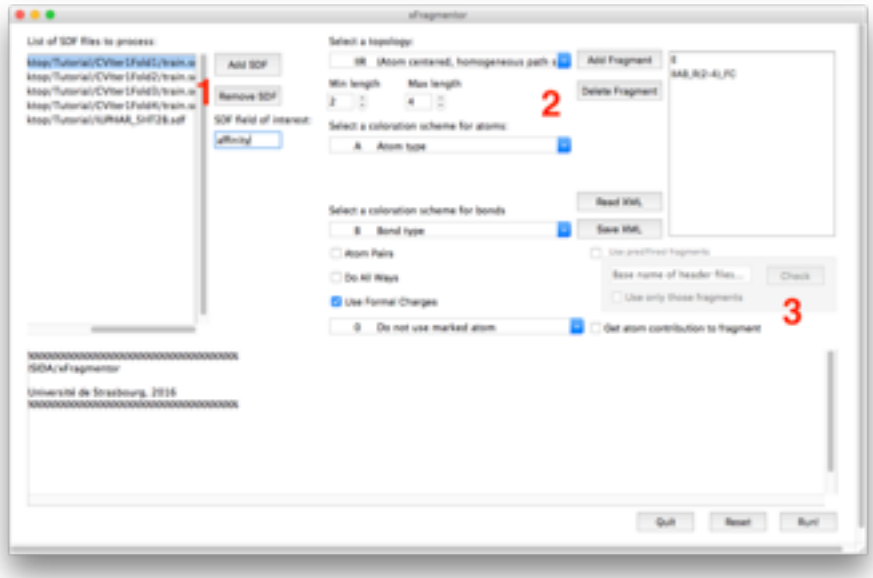


Compute training set descriptors



- **Add SDF files (area 1)**
  - ✔ IUPHAR_5-HT2B.sdf
  - ✔ CV/trainIter*i*Fold*j*.sdf
- **Add Fragmentations (area 2)**
  - ✔ Atom count: E
  - ✔ Atom centered of length 2 to 4: IIAB(2-4)
  - ✔ Use formal charge: FC
- **Save configuration**
  - ✔ Click the *Save XML* button
  - ✔ Name the file train_E_IIAB_R(2-4)_FC.xml
- **Click the *Run* button**

Compute test set descriptors



- **Remove all SDF files and add test SDF files (area 1)**
  - ✔ Remove IUPHAR_5-HT2B.sdf
  - ✔ Remove CV/trainIter*i*Fold*j*.sdf
  - ✔ Add CV/testIter*i*Fold*j*.sdf
- **Check the tickbox Use Predefined Fragments (area 3)**
  - ✔ Leave Basis name to default value or empty
- **Use the Check button (optional)**
  - ✔ You should receive the message *All hear files were found*.
- **Save configuration**
  - ✔ Click the *Save XML* button
  - ✔ Name the file test_E_IIAB_R(2-4)_FC.xml
- **Click the *Run* button**

Files created by xFragmentor

- XML:
  Configuration file.

```
<?xml version="1.0" encoding="u
<Fragmentation Max="2" Min="2" Atom
AtomFrg="False" Extended="NoFX" Mar
```

- HDF
  Lis

```
1.
2.
3.
4.
5.
6.
7.
8.
9.
10.
11.
12.
13.
14.
15.
16.
17.
18.
19.
20.
<SDFile>/Users/marcou/Desktop/Tutor
> <SDFile>/Users/marcou/Desktop/Tut
</SDFiles> </Fragmentations>
```

- SVM:
  Molecular descriptors (attributes)/ Property value (value) files in sparse format.

  Each molecule correspond to one line, in order of appearance in the SDF file.

- ARFF:
  Molecular descriptors (attributes)/ Property value (value) files in sparse format, compatible with the Weka software.

  Concatenate information from HDR and SVM

```
@RELATION "/Users/marcou/Desktop/Tutorial/CVIter1Fold1/test.sdf"

@ATTRIBUTE "C" NUMERIC
@ATTRIBUTE "N" NUMERIC
@ATTRIBUTE "O" NUMERIC
@ATTRIBUTE "(C-C),xC" NUMERIC
@ATTRIBUTE "(C-C-N),xC" NUMERIC
@ATTRIBUTE "(C-C-N-C),(C-C-N-C),xC" NUMERIC
@ATTRIBUTE "(C-C),(C-N),xC" NUMERIC
@ATTRIBUTE "(C-N-C),(C-N-C),xC" NUMERIC
@ATTRIBUTE "(C-N-C-C),(C-N-C-N),(C-N-C=O),xC" NUMERIC
@ATTRIBUTE "(N-C),(N-C),(N-C),xN" NUMERIC
@ATTRIBUTE "(N-C-C),(N-C-C),(N-C-N),(N-C=O),xN" NUMERIC
@ATTRIBUTE "(N-C-N-C),xN" NUMERIC
@ATTRIBUTE "(C-N),(C-N),(C=O),xC" NUMERIC
{ 8.05 1:22 2:3 3:2 7:1 10:1 13:1 14:1 16:1 17:1 18:1 19:1 39:1 42:4 45:7 46:1 48:1 62:2 63:
{ 6.6 1:24 2:1 3:6 16:2 24:1 27:1 30:2 31:2 39:4 42:2 45:8 46:2 48:3 108:2 114:1 115:2 117:2
{ 6.9 1:14 2:4 3:1 4:1 8:1 13:1 16:1 17:1 19:2 45:5 50:2 52:1 55:1 62:1 66:1 78:1 86:1 88:1
{ 8.0 1:11 2:2 3:1 24:1 39:1 42:1 45:3 50:1 52:1 53:1 55:1 58:1 62:1 63:1 64:1 65:1 66:1 67:
{ 8.65 1:20 2:3 3:1 4:2 5:2 6:2 7:2 8:2 10:1 16:1 24:1 27:1 28:1 30:1 31:1 32:1 33:1 36:1 39
{ 8.2 1:19 2:2 4:1 24:2 27:1 32:1 33:1 34:1 36:2 37:1 39:3 42:2 43:1 44:1 45:3 46:1 47:1 48:
{ 7.0 1:22 2:4 3:2 4:2 7:1 10:1 13:1 14:1 16:1 17:1 18:1 19:1 39:1 42:3 45:6 46:1 62:2 65:2
{ 6.45 1:22 2:3 3:2 4:1 7:2 16:1 19:1 24:3 27:1 28:1 36:1 39:5 42:1 45:4 48:2 50:1 52:1 55:1
{ 7.48 1:32 2:5 3:5 4:4 7:1 10:2 16:3 19:1 21:2 24:1 27:1 28:1 30:1 31:1 32:1 33:1 34:1 35:1
{ 7.4 1:25 2:2 3:1 7:2 10:1 24:3 27:1 28:1 36:1 42:2 45:14 46:4 48:8 74:1 88:1 91:1 108:4 11
{ 8.95 1:23 2:2 3:3 4:4 16:1 21:1 24:1 27:1 28:1 30:1 31:1 32:1 33:1 34:1 35:1 36:2 37:1 39:
{ 7.5 1:23 2:2 3:1 24:3 27:1 28:1 39:4 42:2 45:8 46:2 48:4 50:1 52:1 53:1 55:1 58:1 62:1 63:
{ 9.0 1:18 2:4 3:2 4:1 7:2 10:1 24:3 27:1 28:1 42:2 45:7 46:3 48:3 88:2 91:1 108:2 110:1 149
{ 6.0 1:22 2:1 3:3 24:3 27:1 28:1 36:1 39:3 42:2 45:7 46:3 48:2 68:1 74:2 107:2 108:2 109:1
{ 6.9 1:17 2:1 3:2 24:1 27:1 28:1 30:1 31:1 32:1 33:1 39:2 42:5 45:5 46:3 48:1 54:1 60:1 108
{ 7.1 1:19 2:5 3:1 7:4 10:2 13:1 16:1 17:1 24:2 27:1 39:1 45:4 48:2 110:1 166:1 232:1 237:1 1,
{ 8.1 1:11 2:2 3:1 4:1 33:1 39:1 42:1 45:3 48:1 50:1 52:1 53:1 55:1 58:1 60:1 62:1 63:1 64:1
{ 6.9 1:14 2:2 3:1 24:2 39:1 42:1 45:3 50:1 52:1 53:1 55:1 62:1 63:1 65:1 66:1 67:1 70:1 84:
{ 5.3 1:16 2:1 3:1 24:1 39:1 42:2 45:9 46:4 48:3 68:3 108:2 110:2 111:3 115:2 117:1 118:1 12
{ 6.6 1:15 2:1 3:2 4:1 7:1 16:1 19:1 39:1 42:1 45:6 46:1 48:1 55:2 99:1 102:1 115:1 117:1 11
{ 8.95 1:27 2:3 3:1 4:1 16:1 24:3 27:1 28:1 39:3 42:3 45:8 46:4 48:2 62:1 63:1 65:1 68:2 78:
{0 22, 1 3, 2 2, 3 1, 6 2, 15 1, 18 1, 23 3, 26 1, 27 1, 35 1, 38 5, 41 1, 44 4, 47 2, 49
{0 32, 1 5, 2 5, 3 4, 6 1, 9 2, 15 3, 18 1, 20 2, 23 1, 26 1, 27 1, 29 1, 30 1, 31 1, 32 1
{0 25, 1 2, 2 1, 6 2, 9 1, 23 3, 26 1, 27 1, 35 1, 41 2, 44 14, 45 4, 47 8, 73 1, 87 1, 90
{0 23, 1 2, 2 3, 3 4, 15 1, 20 1, 23 1, 26 1, 27 1, 29 1, 30 1, 31 1, 32 1, 33 1, 34 1, 35
{0 23, 1 2, 2 1, 23 3, 26 1, 27 1, 38 4, 41 2, 44 8, 45 2, 47 4, 49 1, 51 1, 52 1, 54 1, 5
{0 18, 1 4, 2 2, 3 1, 6 2, 9 1, 23 3, 26 1, 27 1, 41 2, 44 7, 45 3, 47 3, 87 2, 90 1, 107
{0 22, 1 1, 2 3, 23 3, 26 1, 27 1, 35 1, 38 3, 41 2, 44 7, 45 3, 47 2, 67 1, 73 2, 106 2,
{0 17, 1 1, 2 2, 23 1, 26 1, 27 1, 29 1, 30 1, 31 1, 32 1, 38 2, 41 5, 44 5, 45 3, 47 1, 5
{0 19, 1 5, 2 1, 6 4, 9 2, 12 1, 15 1, 16 1, 23 2, 26 1, 38 1, 44 4, 47 2, 109 1, 165 1, 2
{0 11, 1 2, 2 1, 3 1, 32 1, 38 1, 41 1, 44 3, 47 1, 49 1, 51 1, 52 1, 54 1, 57 1, 59 1, 61
{0 14, 1 2, 2 1, 23 2, 38 1, 41 1, 44 3, 49 1, 51 1, 52 1, 54 1, 61 1, 62 1, 64 1, 65 1, 6
{0 16, 1 1, 2 1, 23 1, 38 1, 41 2, 44 9, 45 4, 47 3, 67 3, 107 2, 109 2, 110 3, 114 2, 116
{0 15, 1 1, 2 2, 3 1, 6 1, 15 1, 18 1, 38 1, 41 1, 44 6, 45 1, 47 1, 54 2, 98 1, 101 1, 11
{0 27, 1 3, 2 1, 3 1, 15 1, 23 3, 26 1, 27 1, 38 3, 41 3, 44 8, 45 4, 47 2, 61 1, 62 1, 64
```

Summary

- **Division of the dataset into 4 sets of training and test structural files**
- **Calculation of the ISIDA Substructural Molecular Fragments descriptors**
  - ✔ Atom Count
  - ✔ Atom Centered fragment including from 2 to 4 atoms
  - ✔ Atoms and bonds standard annotation
  - ✔ Formal Charge

Exercise 3

- **Goal:**
  - ✔ Setup Gaussian Processes models using only the training sets.
- **Software:**
  - ✔ Weka/Experimenter
- **File**
  - ✔ CV/trainIter*i*Fold*j*.sdf and CV/train_Iter*i*Fold*j*_ *.arff
- **Output**
  - ✔ ExtCVtrain.arff
  - ✔ ExtCVtrain.exp

Introduction to Gaussian Processes

- **Goal:**
  - ✔ Model a probability distribution of the property.
    - Y^{train}, Y^{test} **are random vectors representing properties**
    - X^{train}, X^{test} **are the molecular descriptors matrices**

$$\begin{bmatrix} Y^{train} \\ Y^{test} \end{bmatrix} = N\left(0, \begin{bmatrix} K(X^{train}, X^{train}) + \mathbf{1}\sigma^2 & K(X^{train}, X^{test}) \\ K(X^{test}, X^{train}) & K(X^{test}, X^{test}) \end{bmatrix}\right)$$

- **Parameters of the method**
  - ✔ $K(.,.)$ the kernel. In this tutorial, the linear kernel is used.
  - ✔ σ^2 the noise level. Closely related to the experimental noise on the property.

Inference of Gaussian Processes

- **Two quantities are inferred for a test set**
  - ✔ The mean vector

$$\left\langle Y^{test} \right\rangle = K(X^{test}, X^{train})\left[K(X^{train}, X^{train}) + \mathbf{1}\sigma^2\right]^{-1} Y^{train}$$

  - ✔ The covariance

$$\sigma^2_{Y^{test}} = K(X^{test}, X^{test}) -$$

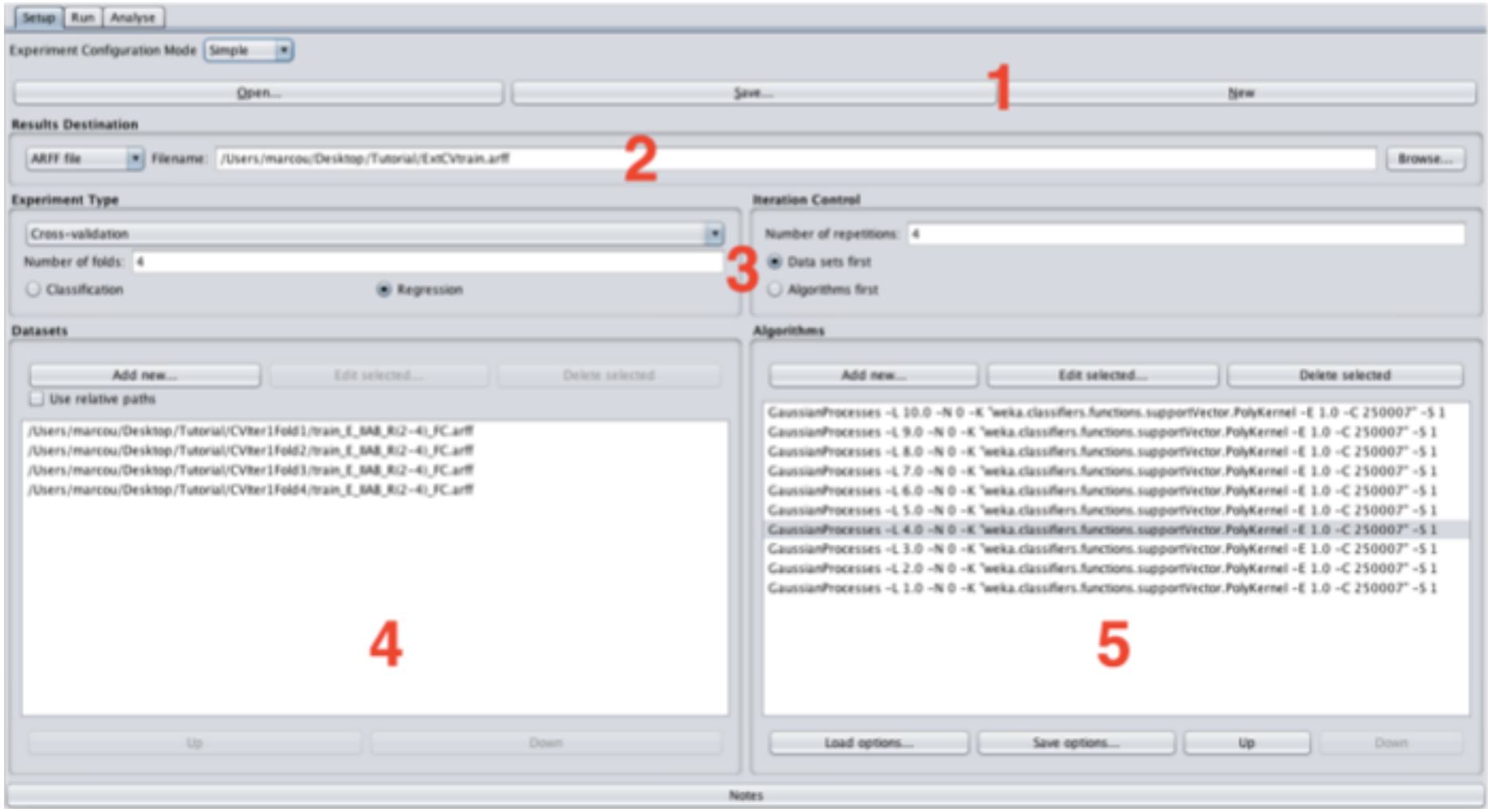
$$K(X^{test}, X^{train})\left[K(X^{train}, X^{train}) + \mathbf{1}\sigma^2\right]^{-1} K(X^{train}, X^{test})$$

(•) Data points

(——) Mean vector

(——) +/- two variances

Weka/Experimenter

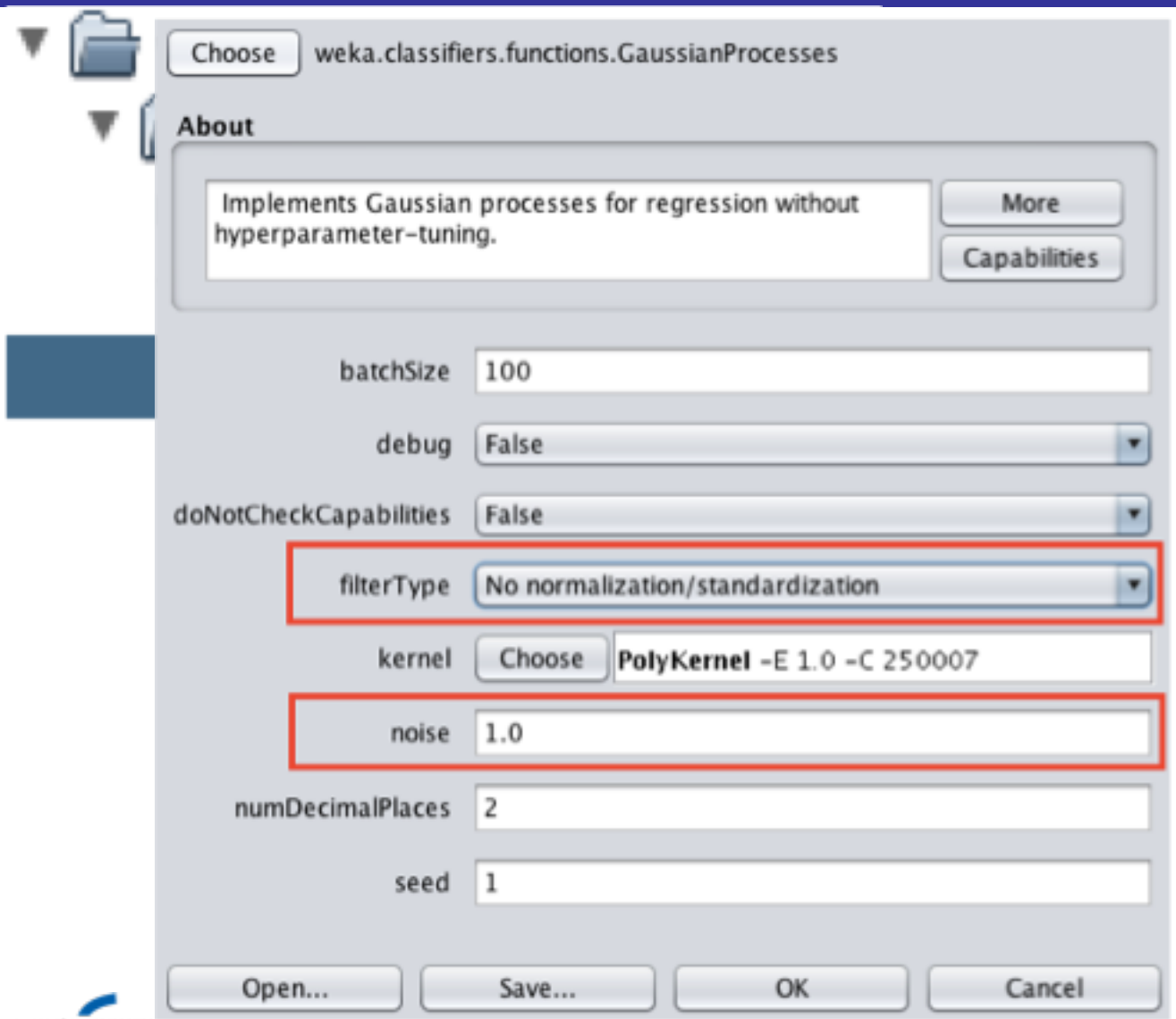


Weka/Experimenter

- ✔ Click New.
- ✔ Results destination: “ExtCVtrain.arff”

- ✔ 4-fold cross validation repeated 4 times.
- ✔ Experiment type: Regression
- ✔ Add the training files to the Datasets
- ✔ Add the ZeroR method to the Algorithms
- ✔ Add Gaussian Processes method to the Algorithms

Setup Gaussian Processes



Add Gaussian Processes:

- no data transformations
- Noise level in the range [1..10]

Finalize the experiment

- **Click the button *Save…***
  - ✔ Save you setup as *ExtCVtrain.exp*
- **Click the *Run* tab, then *Start***

- **Click the *Analyse* tab**

Analyze the experiment on training data

- Click the *Experiment* button
- Set the *Comparison field* to *Relative Absolute Error*
- Click the *Perform test* button

Dataset	(1) rules.Zer	(2) funct	(3) funct	(4) funct	(5) funct	(6) funct	(7) funct	(8) funct	(9) funct	(10) func	(11) func
CVIter1Fold1_affinity	(16) 100.00	86.58 *	85.92 *	85.26 *	84.60 *	83.99 *	83.53 *	83.22 *	83.02 *	83.41 *	85.01
CVIter1Fold2_affinity	(16) 100.00	89.82 *	89.31 *	88.77	88.24	87.90	87.60	87.33	87.15	87.16	87.55
CVIter1Fold3_affinity	(16) 100.00	90.35	89.75	89.16	88.62	88.11	87.65	87.28	87.50	88.88	91.09
CVIter1Fold4_affinity	(16) 100.00	85.02 *	84.17 *	83.41 *	82.64 *	81.89 *	81.28 *	80.96 *	81.17 *	81.90 *	83.23 *
	(v/ /*)	(0/1/3)	(0/1/3)	(0/2/2)	(0/2/2)	(0/2/2)	(0/2/2)	(0/2/2)	(0/2/2)	(0/2/2)	(0/3/1)

```
Key:
(1) rules.ZeroR '' 48055541465867954
(2) functions.GaussianProcesses '-L 10.0 -N 2 -K \"functions.supportVector.PolyKernel -E 1.0 -C 250007\" -S 1' -8620066949967678545
(3) functions.GaussianProcesses '-L 9.0 -N 2 -K \"functions.supportVector.PolyKernel -E 1.0 -C 250007\" -S 1' -8620066949967678545
(4) functions.GaussianProcesses '-L 8.0 -N 2 -K \"functions.supportVector.PolyKernel -E 1.0 -C 250007\" -S 1' -8620066949967678545
(5) functions.GaussianProcesses '-L 7.0 -N 2 -K \"functions.supportVector.PolyKernel -E 1.0 -C 250007\" -S 1' -8620066949967678545
(6) functions.GaussianProcesses '-L 6.0 -N 2 -K \"functions.supportVector.PolyKernel -E 1.0 -C 250007\" -S 1' -8620066949967678545
(7) functions.GaussianProcesses '-L 5.0 -N 2 -K \"functions.supportVector.PolyKernel -E 1.0 -C 250007\" -S 1' -8620066949967678545
(8) functions.GaussianProcesses '-L 4.0 -N 2 -K \"functions.supportVector.PolyKernel -E 1.0 -C 250007\" -S 1' -8620066949967678545
(9) functions.GaussianProcesses '-L 3.0 -N 2 -K \"functions.supportVector.PolyKernel -E 1.0 -C 250007\" -S 1' -8620066949967678545
(10) functions.GaussianProcesses '-L 2.0 -N 2 -K \"functions.supportVector.PolyKernel -E 1.0 -C 250007\" -S 1' -8620066949967678545
(11) functions.GaussianProcesses '-L 1.0 -N 2 -K \"functions.supportVector.PolyKernel -E 1.0 -C 250007\" -S 1' -8620066949967678545
```

Summary

- **The optimum noise level is deduced only from the internal cross-validation on training sets.**
  - ✔ Optimal value about 4
- **Different performances on different training sets**
  - ✔ Must be statistically demonstrated
- **The test sets are fully independent.**
  - ✔ The setup of the model building is complete without the help of the test sets

Exercise 4

- **Goal:**
  - ✔ External validation of Gaussian Processes models.
- **Software:**
  - ✔ Weka/Experimenter
- **File**
  - ✔ CV/trainIter*i*Fold*j*.sdf and CV/trainIter*i*Fold*j*_*.arff
  - ✔ CV/testIter*i*Fold*j*.sdf and CV/testIter*i*Fold*j*_*.arff
- **Output**
  - ✔ ExtCVtrain.arff
  - ✔ ExtCVtrain.exp

Weka/Experimenter Advanced mode

Setup | Run | Analyse

Experiment Configuration Mode: Advanced

Open... | Save... | New

1

Destination

Choose: InstancesResultListener -O ExpCVtest.arff

2

Result generator

Choose: ExplicitTestsetResultProducer -R -O splitEvalutorOut.zip -dir /Users/marcou/Desktop/Tutorial/testsets -suffix _test.arff -W weka.experiment.RegressionSplitEvaluator -- -

3

Runs

From: 1 To: 1

Distribute experiment

Hosts

By data set | By run | By property

Generator properties

Disabled | Select property...

Can't edit

Iteration control

Data sets first | Custom generator first

Datasets

Add new... | Edit selected... | Delete selected

Use relative paths

/Users/marcou/Desktop/Tutorial/CVIter1Fold1/train_E_IIAB_R(2-4)_FC.arff
/Users/marcou/Desktop/Tutorial/CVIter1Fold2/train_E_IIAB_R(2-4)_FC.arff
/Users/marcou/Desktop/Tutorial/CVIter1Fold3/train_E_IIAB_R(2-4)_FC.arff
/Users/marcou/Desktop/Tutorial/CVIter1Fold4/train_E_IIAB_R(2-4)_FC.arff

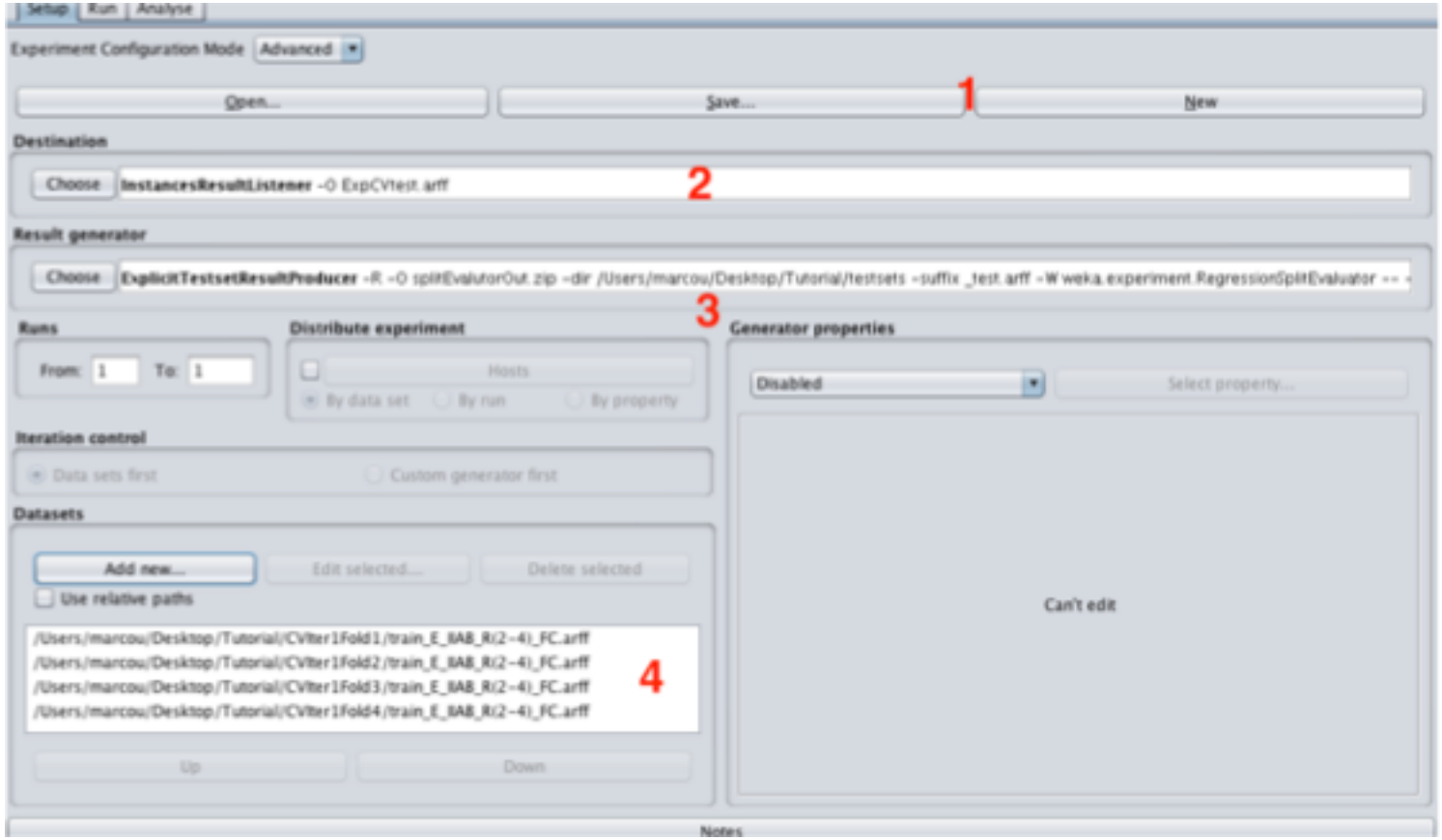
4

Up | Down

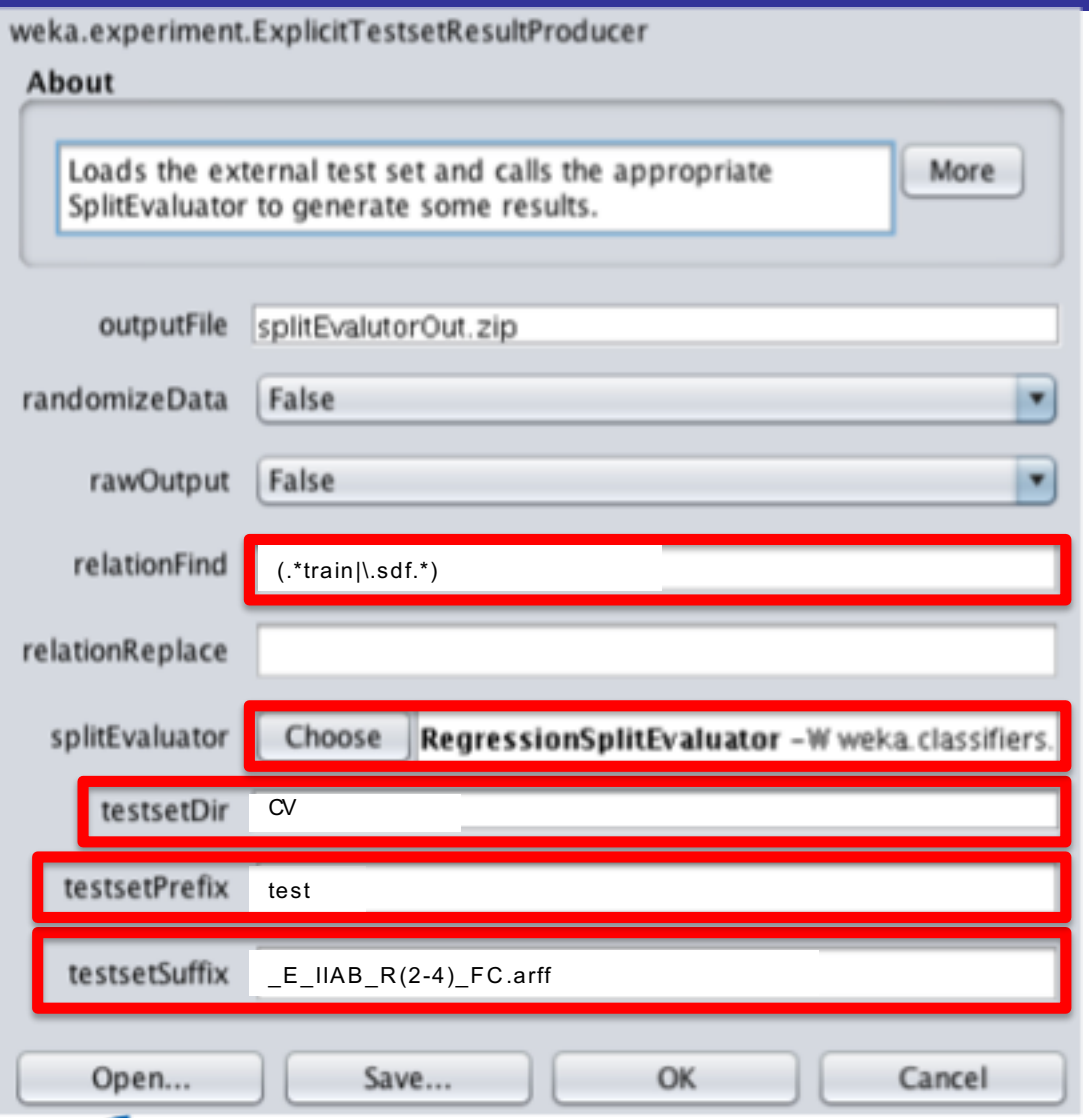
Notes

Weka/Experimenter Advanced mode

- Set the *Destination* to *ExpCVtest.arff*
- Set the *Runs* from 1 to 1
- Check or set the *Datasets*

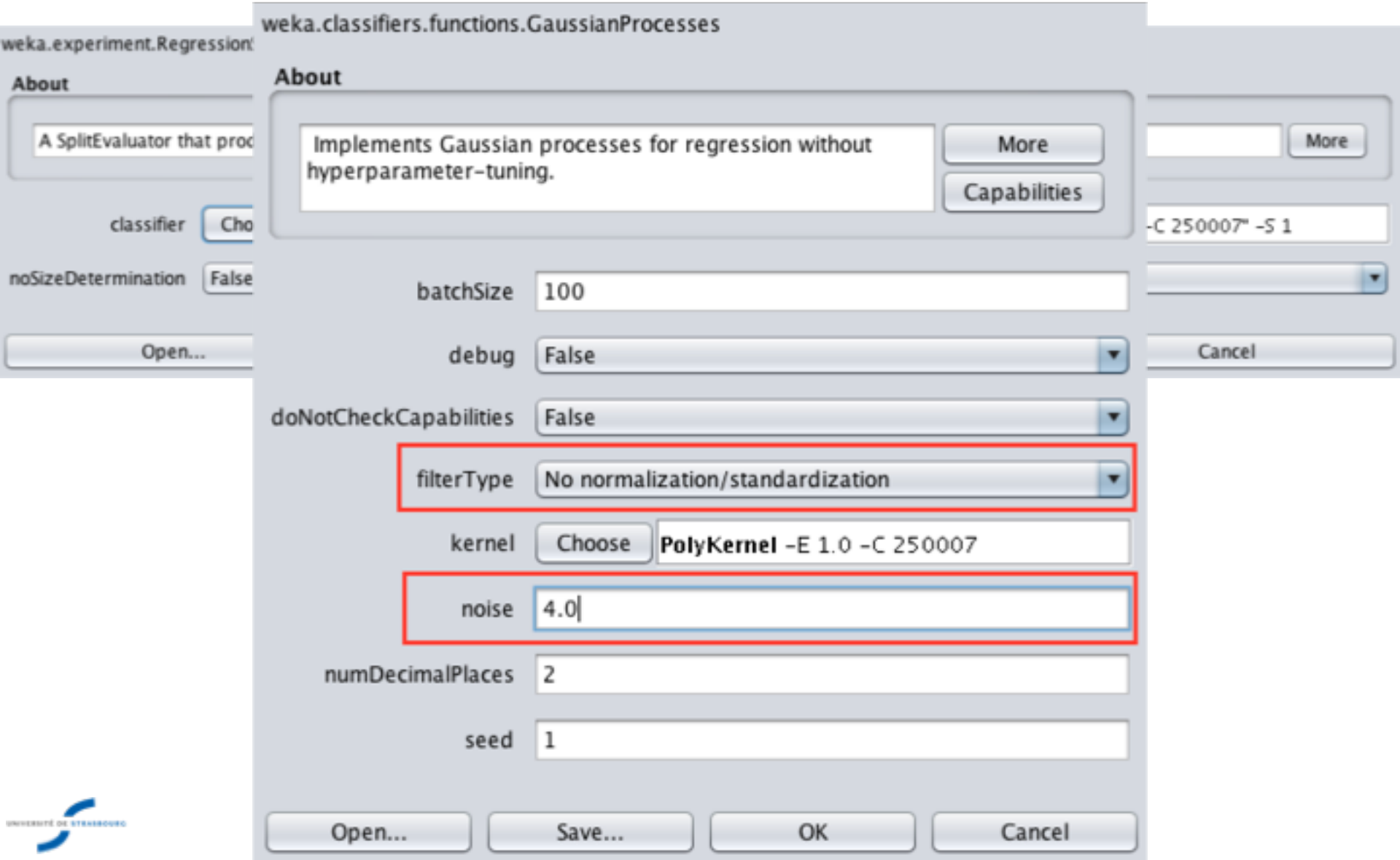


Setup the Results Generator



- Set the value of *RelationFind* to *(.*train|\.sdf.*)*
- Set the value of *testsetPrefix* to *test*
- Set the value of *testsetSuffix* to *_E_IIAB(2-4)_FC.arff*
- Set the *testsetDir* to *CV*
- Click the *RegressionSplitEvaluator*

RegressionSplitEvaluator: GP with optimum noise level



Finalize the experiment

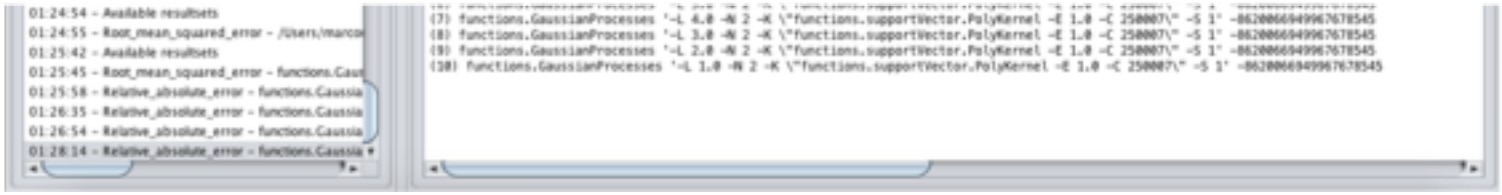
- **Click the button *Save…***
  - ✔ Save you setup as *ExtCVtrain.exp*
- **Click the *Run* tab, then *Start***

- **Click the *Analyse* tab**

Analyze the experiment on training data

- Click the *Experiment* button
- Set the *Comparison field* to *Relative Absolute Error*
- Click the *Perform test* button

```
Datasets:   4
Resultsets: 1
Confidence: 0.05 (two tailed)
Sorted by:  -
Date:       10/06/16 15:22


Dataset                    (1) functions.
----------------------------------------
CVIter1Fold1_affinity      (1)   80.30 |
CVIter1Fold2_affinity      (1)   74.91 |
CVIter1Fold3_affinity      (1)   73.11 |
CVIter1Fold4_affinity      (1)   84.02 |
----------------------------------------
(v/ /*)                                |


Key:
(1) functions.GaussianProcesses '-L 4.0 -N 2 -K \"functions.supportVector.PolyKernel -E 1.0 -C 250007\" -S 1' -8620066949967678545
```



Summary

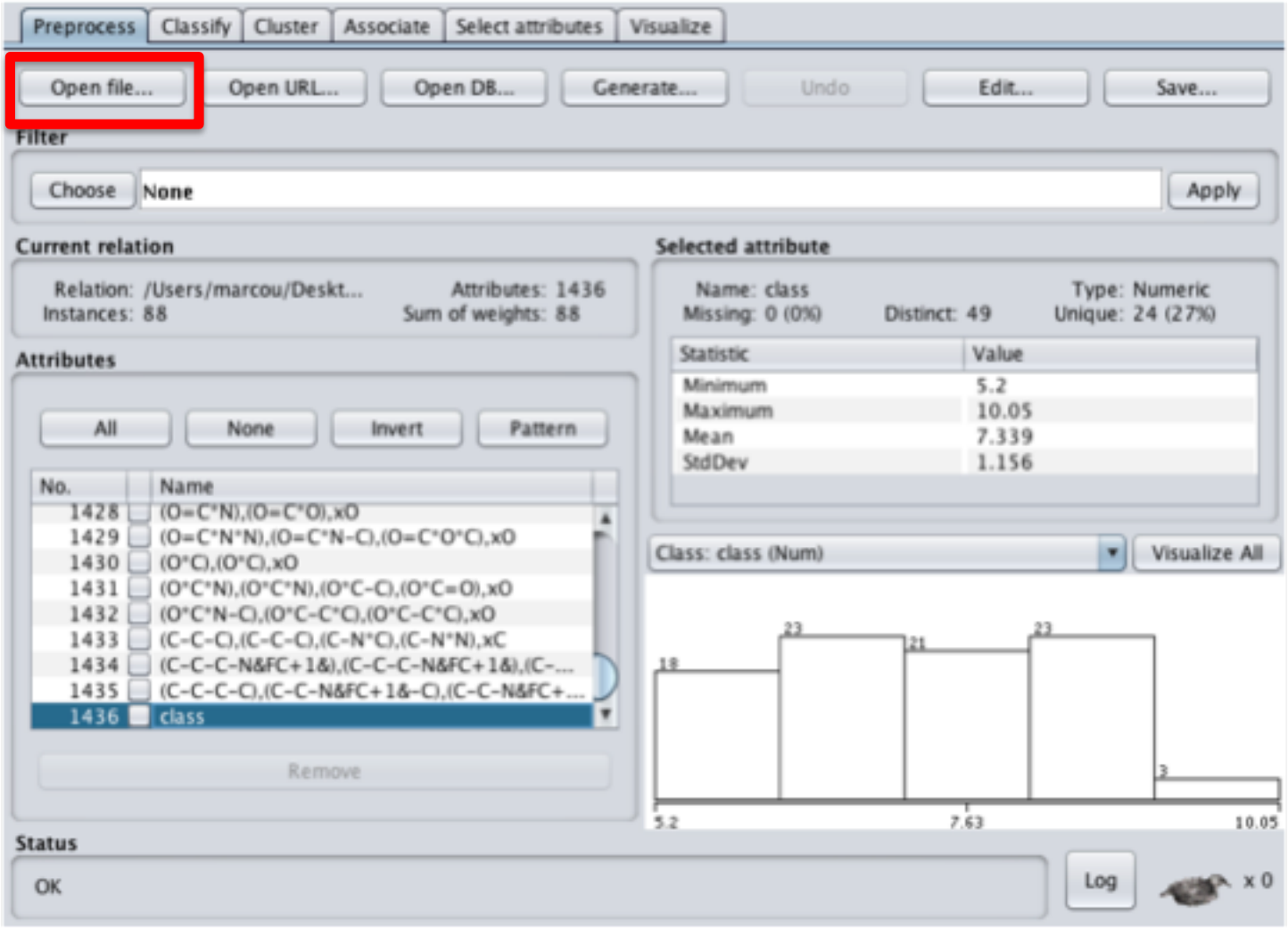
- **The optimum noise level is deduced only from the internal cross-validation on training sets.**
  - ✔ Optimal value about 4
- **The configuration is used to validate the models on the test sets**
  - ✔ Relative absolute error about 80%
- **Performances are dependent of the cross-validation fold**
  - ✔ Are there outliers?

Exercise 4

- **Goal:**
  - ✔ Outlier identification
- **Software:**
  - ✔ Weka/Explorer
  - ✔ xModelAnalyzerR
  - ✔ InstantJChem
- **Files**
  - ✔ ARFF files
- **Output**
  - ✔ Log files of Weka/Explorer
  - ✔ New SDF without an outlier.

Weka/Explorer

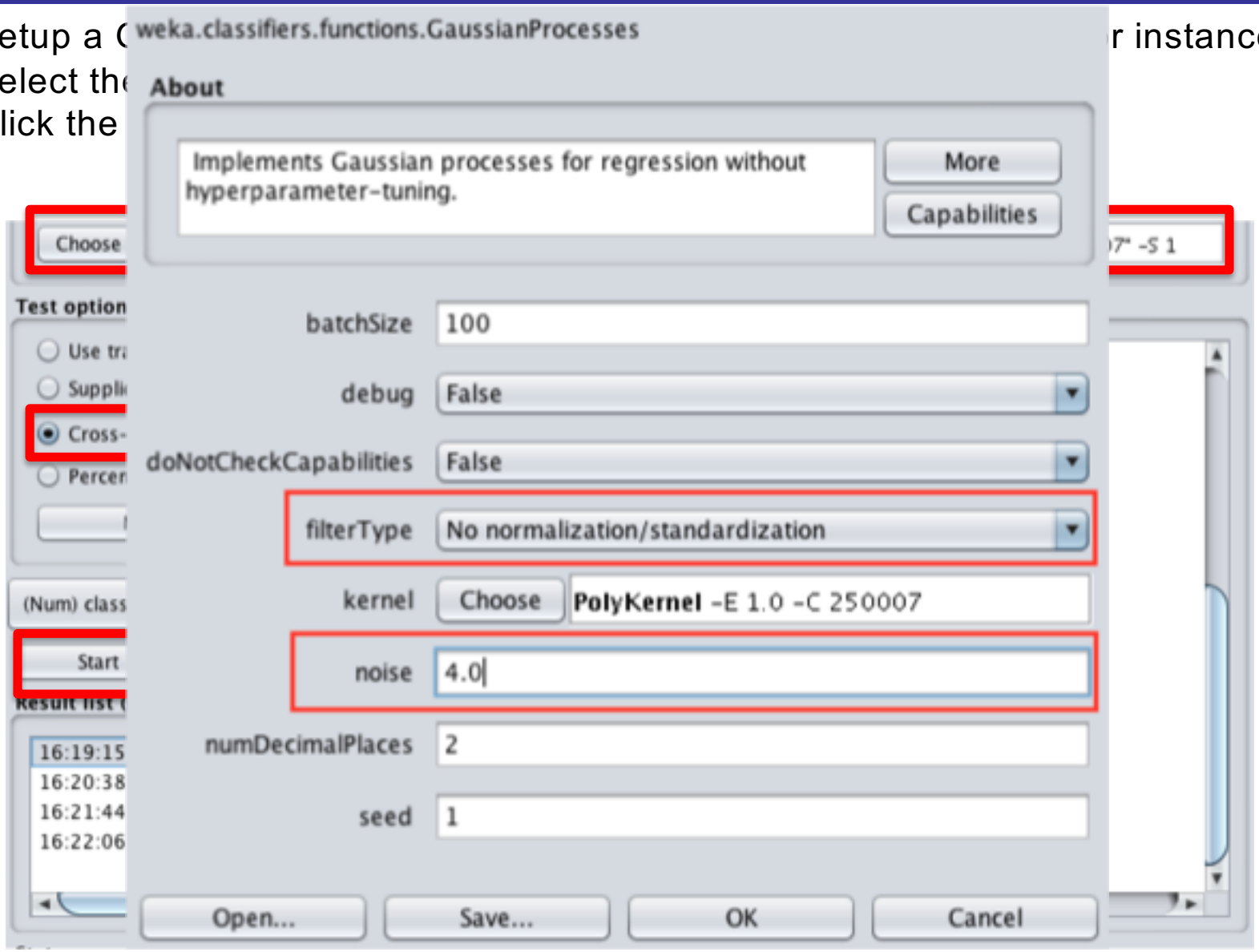
Load the file IUPHAR_5HT2B_E_IIAB_R(2-4)_FC.arff



Setup a Gaussian Processes model

- Setup a G
- Select the
- Click the

r instance 4)



Weka/Explorer Gaussian Processes Cross-Validation results

```
Attributes:   1436
              [list of attributes omitted]
Test mode:    4-fold cross-validation
```

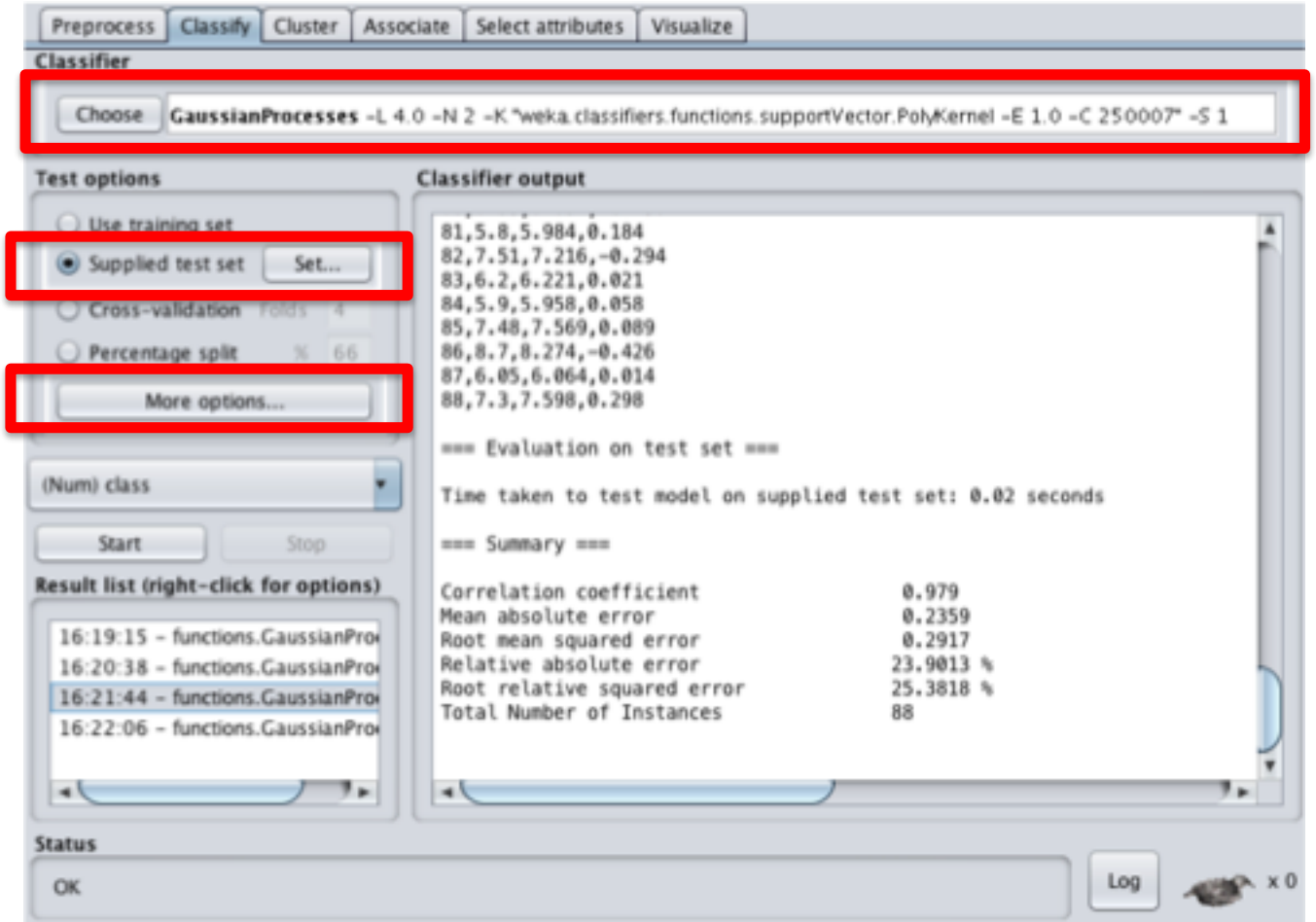
```
=== Classifier model (full training set) ===

Gaussian Processes

Kernel used:
  Linear Kernel: K(x,y) = <x,y>

All values shown based on: No normalization/standardization

Average Target Value : 7.3390909090909044
Inverted Covariance Matrix:
    Lowest Value = -0.01993988339279234
    Highest Value = 0.04610399059836405
Inverted Covariance Matrix * Target-value Vector:
    Lowest Value = -0.06391563323426866
    Highest Value = 0.04158533375446235



Time taken to build model: 0 seconds
```

```
=== Cross-validation ===
=== Summary ===

Correlation coefficient                  0.5175
Mean absolute error                      0.7924
Root mean squared error                  0.9886
Relative absolute error                 79.8931 %
Root relative squared error             85.4517 %
Total Number of Instances               88
```

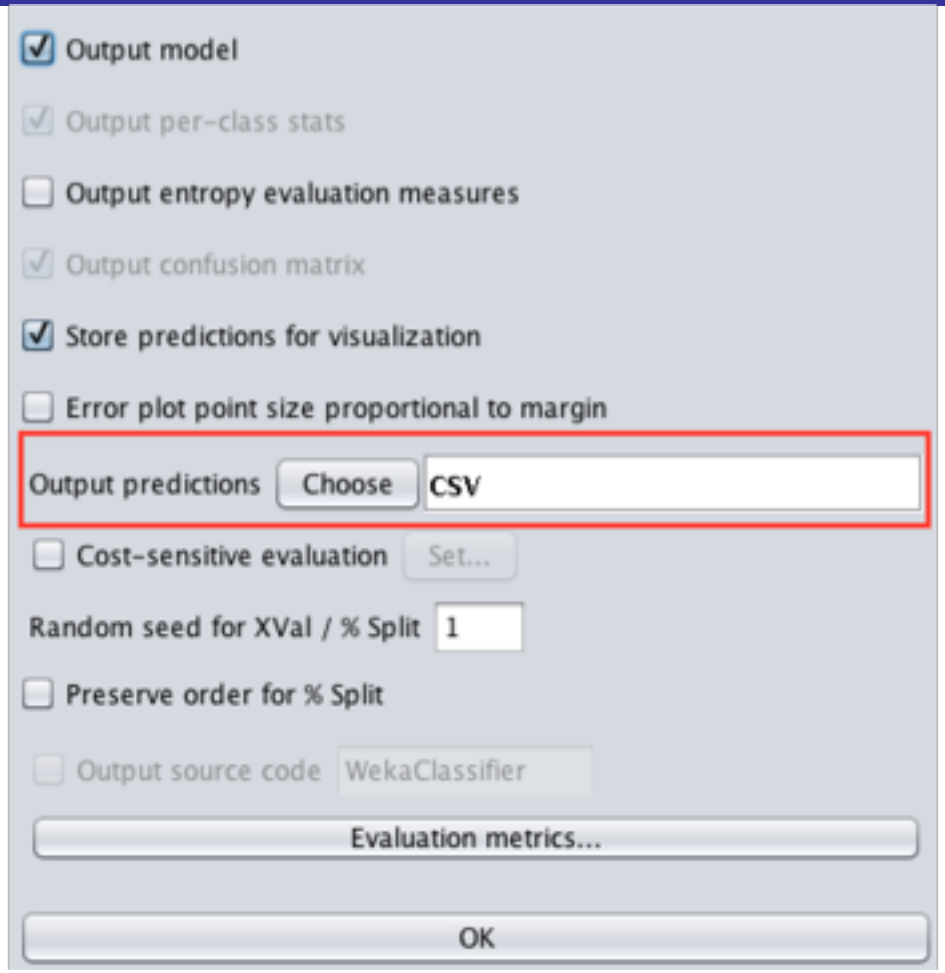
- Experiment summary
- Description of the model
- Cross-validation statistics

Setup a Gaussian Processes model

- Setup a Gaussian Processes model if needed
- Select the *Supplied test set* option and set the training file as test. This produces fitting results.
- Click the *More options…* button.



Weka/Explorer classifier options



- Set the *Output predictions* to *CSV*.
- Click *OK* then click the button *Start.*

Weka/Explorer Gaussian Processes Fitting results

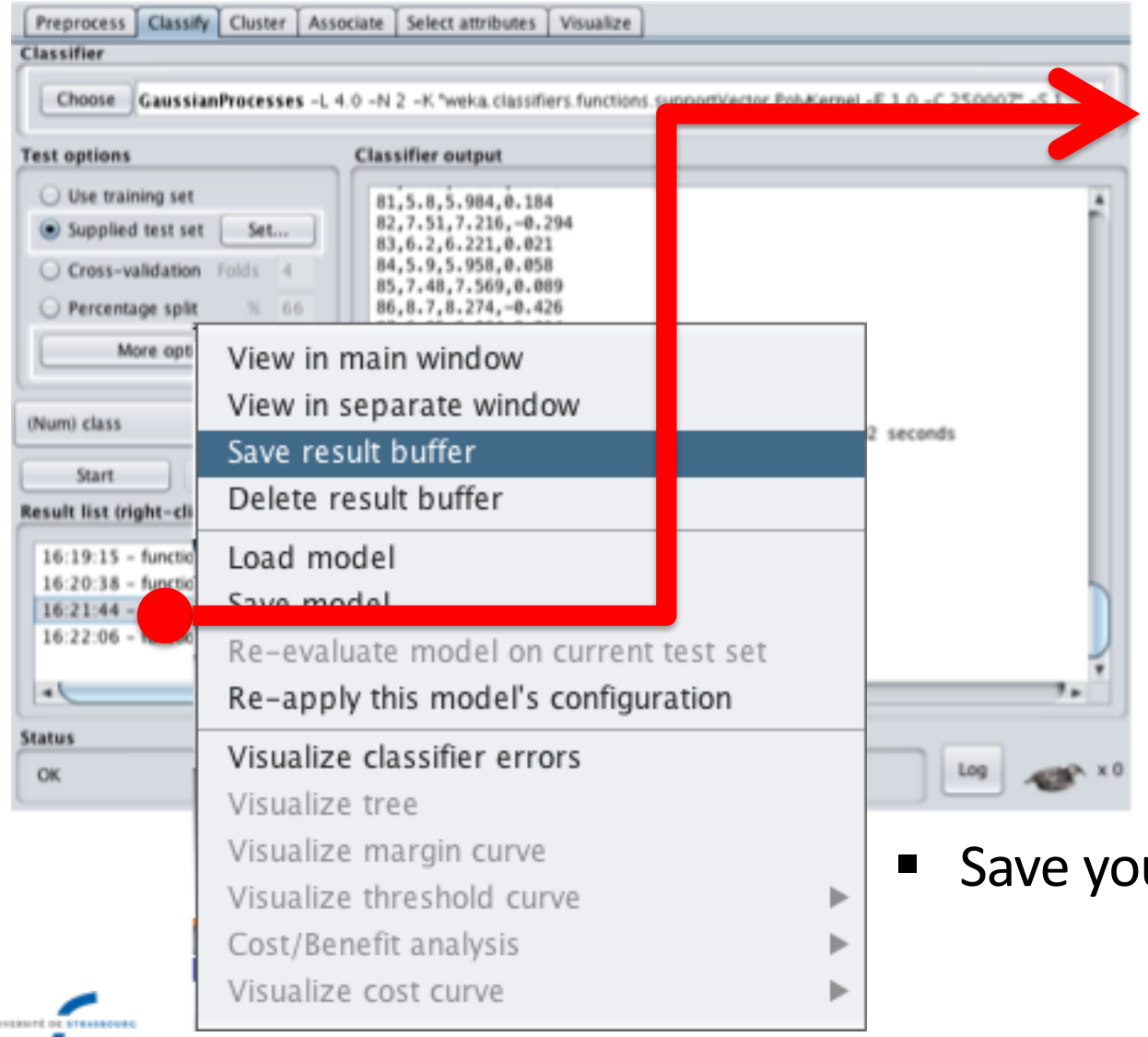
```
75,8.05,8.003,-0.047
76,5.9,6.059,0.159
77,6.8,6.677,-0.123
78,8.9,8.504,-0.396
79,5.8,6.114,0.314
80,8.95,8.692,-0.258
81,5.8,5.984,0.184
82,7.51,7.216,-0.294
83,6.2,6.221,0.021
84,5.9,5.958,0.058
85,7.48,7.569,0.089
86,8.7,8.274,-0.426
87,6.05,6.064,0.014
88,7.3,7.598,0.298
```

```
=== Evaluation on test set ===

Time taken to test model on supplied test set: 0.02 seconds
```

```
=== Summary ===

Correlation coefficient                  0.979
Mean absolute error                      0.2359
Root mean squared error                  0.2917
Relative absolute error                 23.9013 %
Root relative squared error             25.3818 %
Total Number of Instances               88
```

- **Estimation for each instance**
  - ✔ Weka/Explorer does not provide the covariance matrix.
- **Fit performances.**
  - ✔ As they are excellent, the outliers become visible
  - ✔ Outliers *do not* fit.

Save Weka result buffer

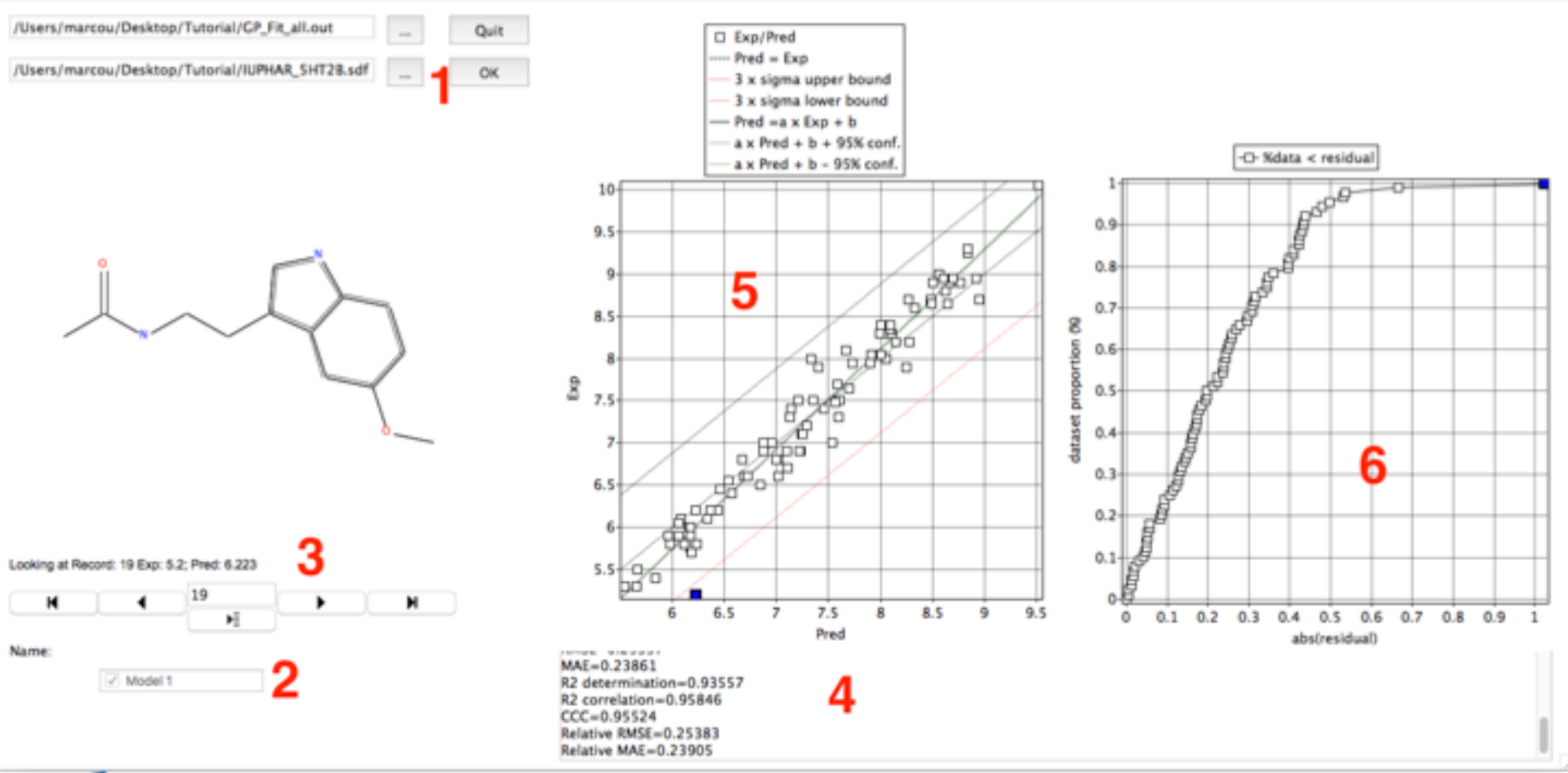


- Right click on the model's line

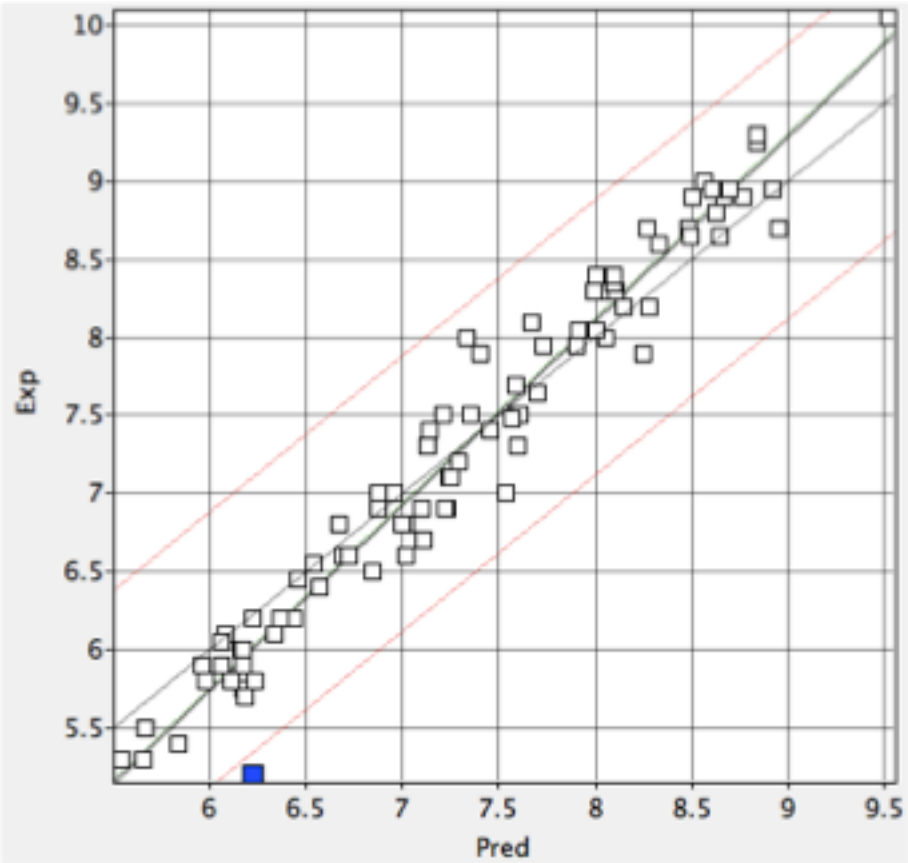
- Save your file as *GP_Fit_all.out*

xMoldelAnalyzerR

- Open the file GP_Fit_all.out and the file IUPHAR_5HT2B.sdf.
- Click the *OK* button.

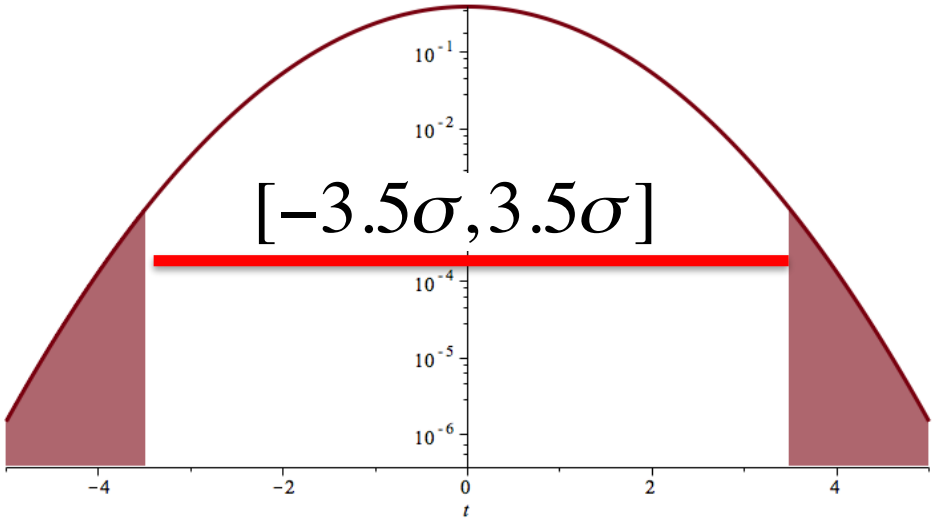


Outlier detection
Example of a single step procedure



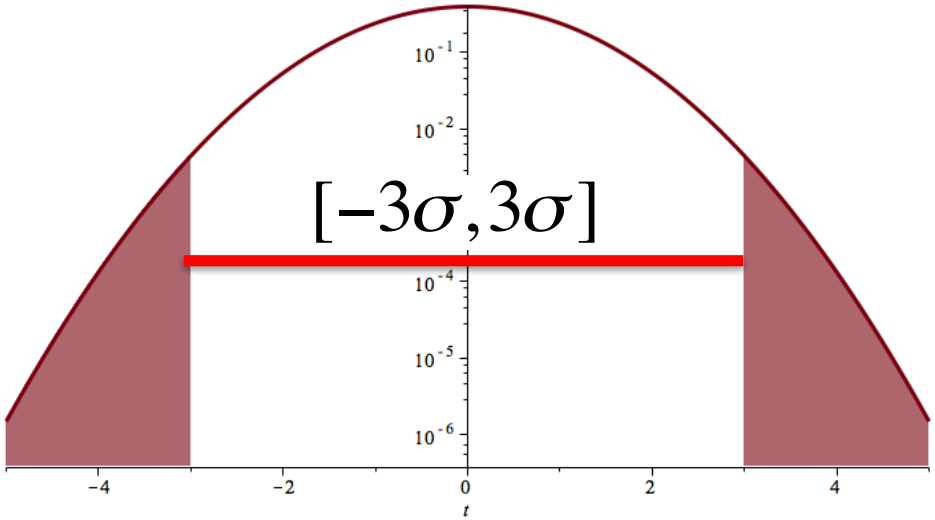
- **All points outside the [-3σ, 3σ] range.**
  - ✔ Assumption: data follow a normal distribution.
  - ✔ High impact of outliers on the mean (μ) and standard deviation (σ) values.

Interval width and risk in outlier detection



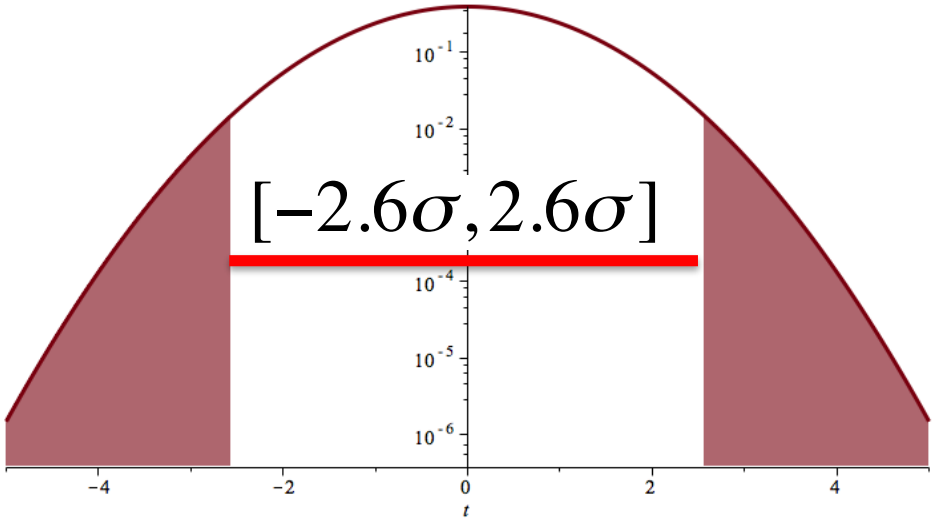
Risk(%)	u (sigma)
0.05	3.5

Interval width and risk in outlier detection



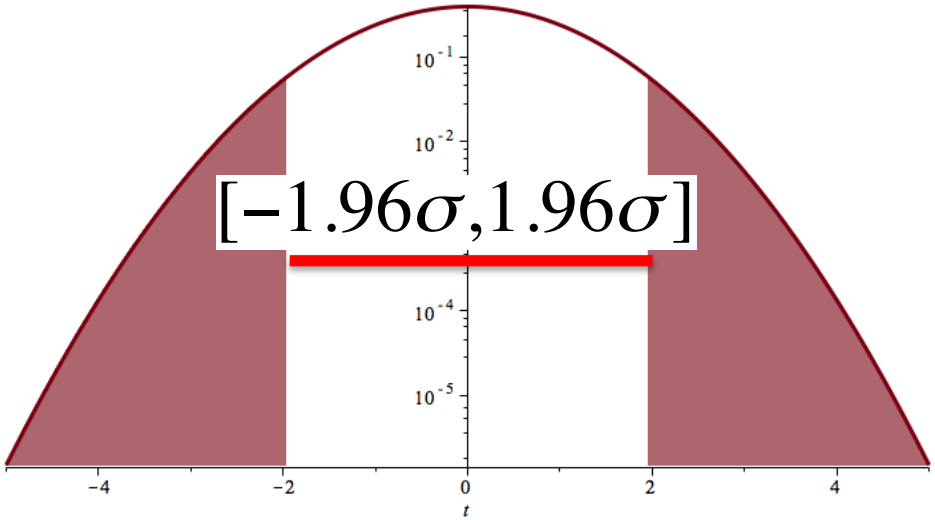
Risk(%)	u (sigma)
0.05	3.5
0.25	**3**

Interval width and risk in outlier detection



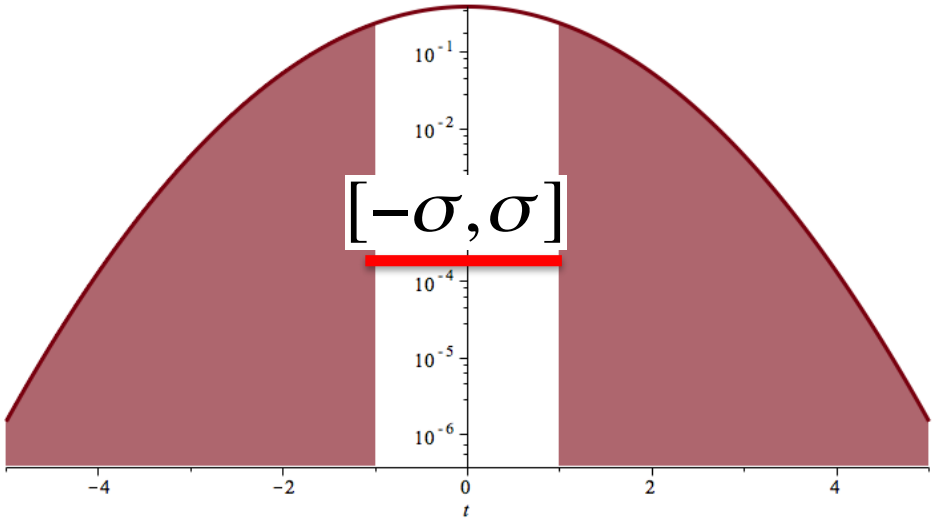
Risk(%)	u (sigma)
0.05	3.5
0.25	3
1.00	**2.6**

Interval width and risk in outlier detection



Risk(%)	u (sigma)
0.05	3.5
0.25	3
1.00	2.6
5.00	**1.96**

Interval width and risk in outlier detection

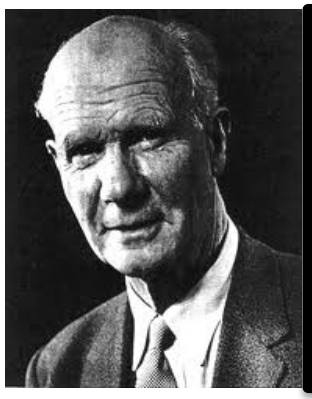


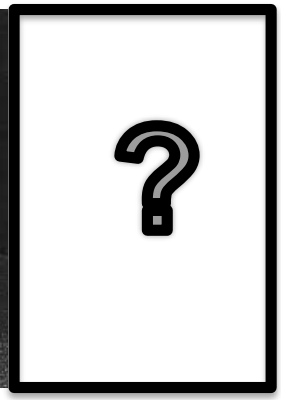
Risk(%)	u (sigma)
0.05	3.5
0.25	3
1.00	2.6
5.00	1.96
32.00	**1.00**

Outlier detection
Example of sequential procedure

WR Thompson (?)

Formulation of the test in 1935





ES Pearson
C Chandra Sekar

Domain of validity of the test, 1936

FE Grubbs

Tables of critical values, 1950

- **The Grubbs test.**
  - ✔ Compute decision variables:

$$G_1 = \frac{\langle r \rangle - r_1}{s}$$

$$G_N = \frac{r_N - \langle r \rangle}{s}$$

  - ✔ Compute critical value:

$$G_c = \frac{N-1}{N}\sqrt{\frac{t^2}{N-2+t^2}}$$

t, α/2N fractile of student distribution with N-2 degrees of freedom

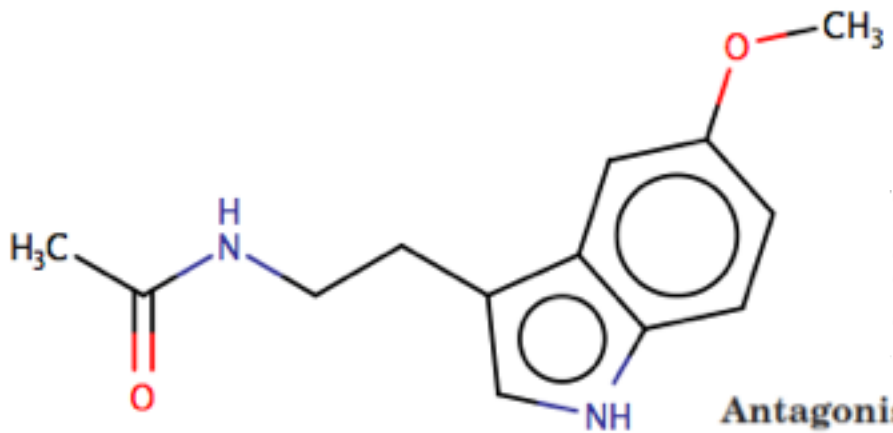
  - ✔ Take a decision:

$$G_1 > G_c \Rightarrow r_1, \quad \text{outlier}$$

$$G_N > G_c \Rightarrow r_N, \text{outlier}$$

Outlier identification

- **Outlier, compound 33**
  - ✔ Melatonin
  - ✔ PubID 12750432



0022-3565/03/3063-954–964$7.00
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The Novel Melatonin Agonist Agomelatine (S20098) Is an Antagonist at 5-Hydroxytryptamine$_{2C}$ Receptors, Blockade of Which Enhances the Activity of Frontocortical Dopaminergic and Adrenergic Pathways

M. J. MILLAN, A. GOBERT, F. LEJEUNE, A. DEKEYNE, A. NEWMAN-TANCREDI, V. PASTEAU, J.-M. RIVET, and D. CUSSAC

Department of Psychopharmacology, Institut de Recherches Servier, Croissy/Seine, France

Received March 18, 2003; accepted April 30, 2003

TABLE 1
Binding affinities of agomelatine compared to melatonin at 5-HT$_2$ receptor subtypes
Data are means ± S.E.M. of pK_i values derived from at least three independent determinations, each of which was performed in triplicate.

Drug	h5-HT$_{2C}$	h5-HT$_{2B}$	h5-HT$_{2A}$	r5-HT$_{2A}$	p5-HT$_{2C}$
Agomelatine	6.15 ± 0.04	6.59 ± 0.07	5.35 ± 0.08	<5.0	6.39 ± 0.02
Melatonin	<5.0	5.24 ± 0.09	<5.0	<5.0	<5.0

h, human; r, rat; p, porcine.

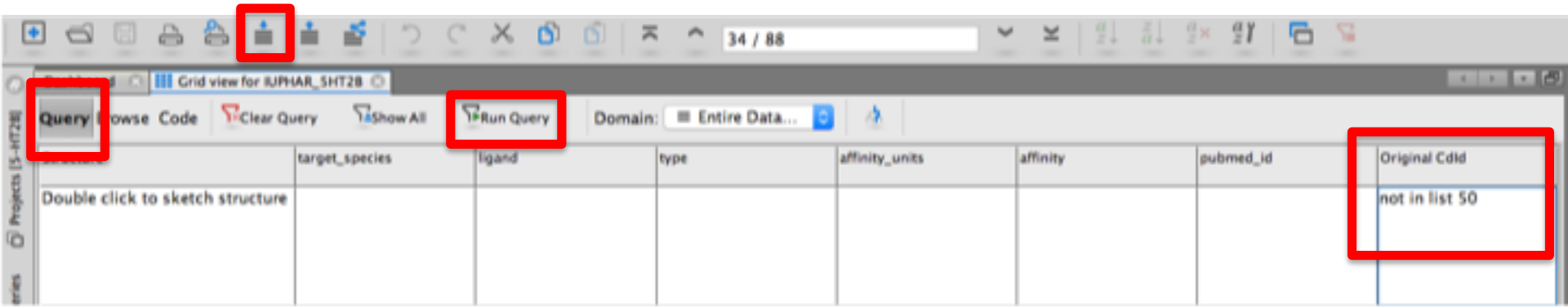
Antagonist Properties of Agomelatine and Melatonin at h5-HT$_{2B}$ Receptors: [^{3}H]PI Depletion (Fig. 4; Table 2). Agomelatine failed to elicit [^{3}H]PI depletion alone and concentration dependently blocked the action of 5-HT with a pK_B value of 6.6 corresponding well to its pK_i value (6.6) at these sites. Melatonin likewise did not enhance [^{3}H]PI depletion and partially attenuated the action of 5-HT, although only ~50% of inhibition was acquired even at a concentration of 100 μM. It was not possible, for reasons of solubility, to evaluate higher concentrations of melatonin.

Exercise 5

- **Goal:**
  - ✔ Outlier identification
- **Software:**
  - ✔ Weka/Explorer
  - ✔ xModelAnalyzerR
  - ✔ InstantJChem
- **Files**
  - ✔ ARFF files
- **Output**
  - ✔ Log files of Weka/Explorer
  - ✔ New SDF without an outlier.

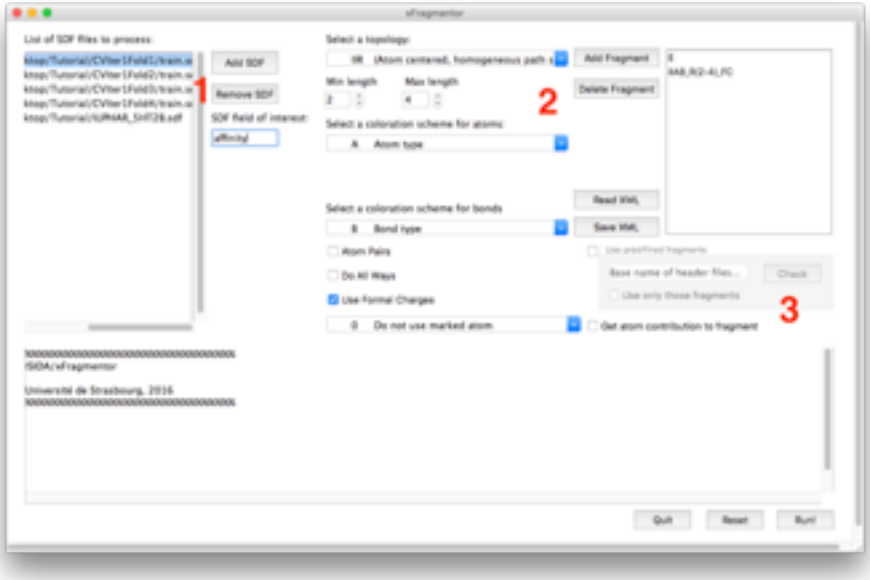
Remove Melatonin from the training set

- In *InstantJChem* software, click the *Query* button.
- Set the query field Origninal CdId to « not in list 50 » - the Original CdId of Melatonin.
- Click the *Run Query* button.



- Click the export button.
- Save the exported SDF file as IUPHAR_5HT2B-33.sdf.

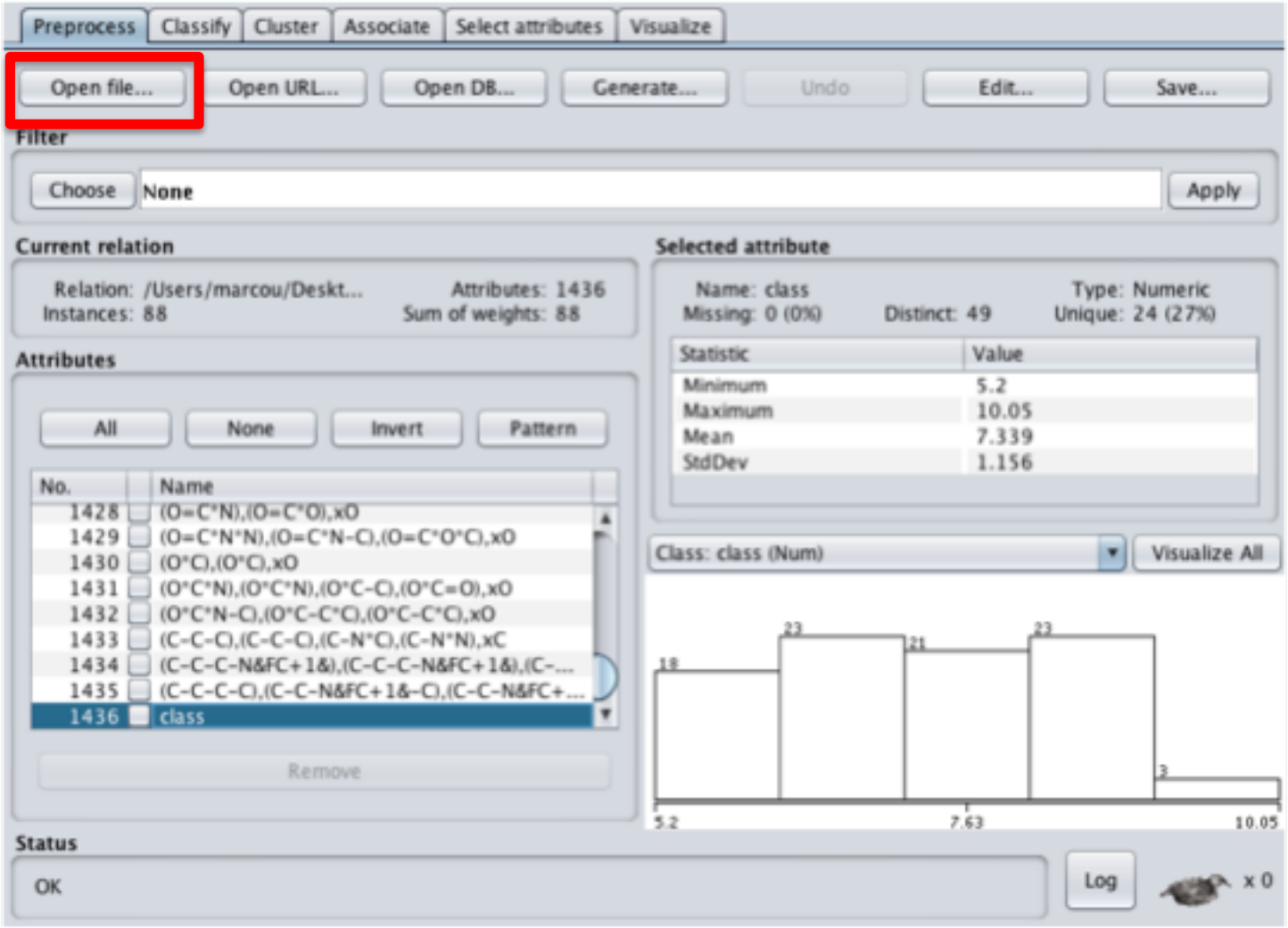
Fragment the curated dataset



- **In the *xFragmentor* interface**
  - ✔ If needed, click the Read XML button and read the file *train_E_IIAB_R(2-4)_FC.xml*
  - ✔ Remove all SDF files
  - ✔ Add the file IUPHA_5-HT2B-33.sdf
  - ✔ Click the button *Run*.

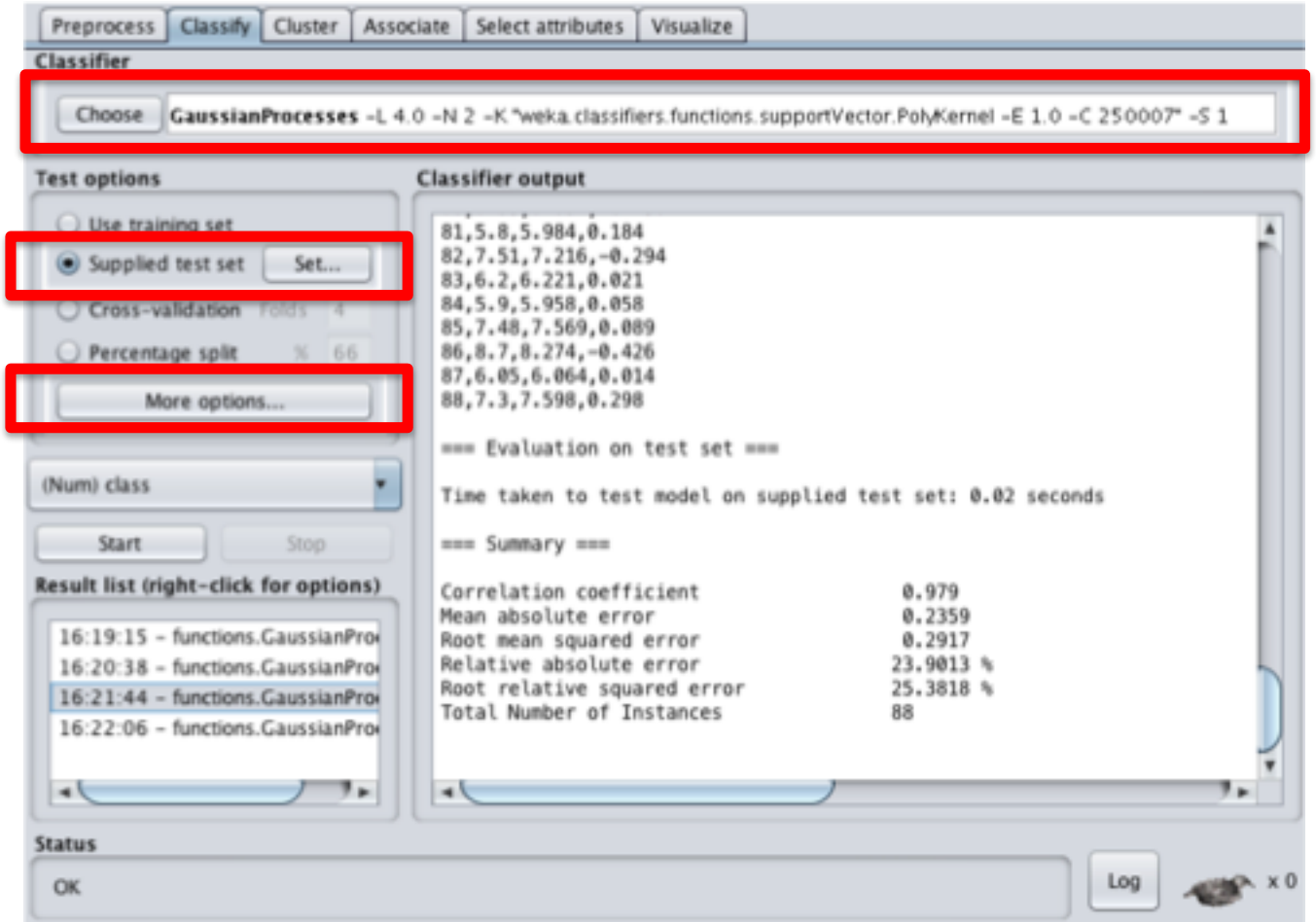
Load the curated dataset into the Weka/Explorer software

Load the file IUPHAR_5HT2B-33_E_IIAB_R(2-4)_FC.arff



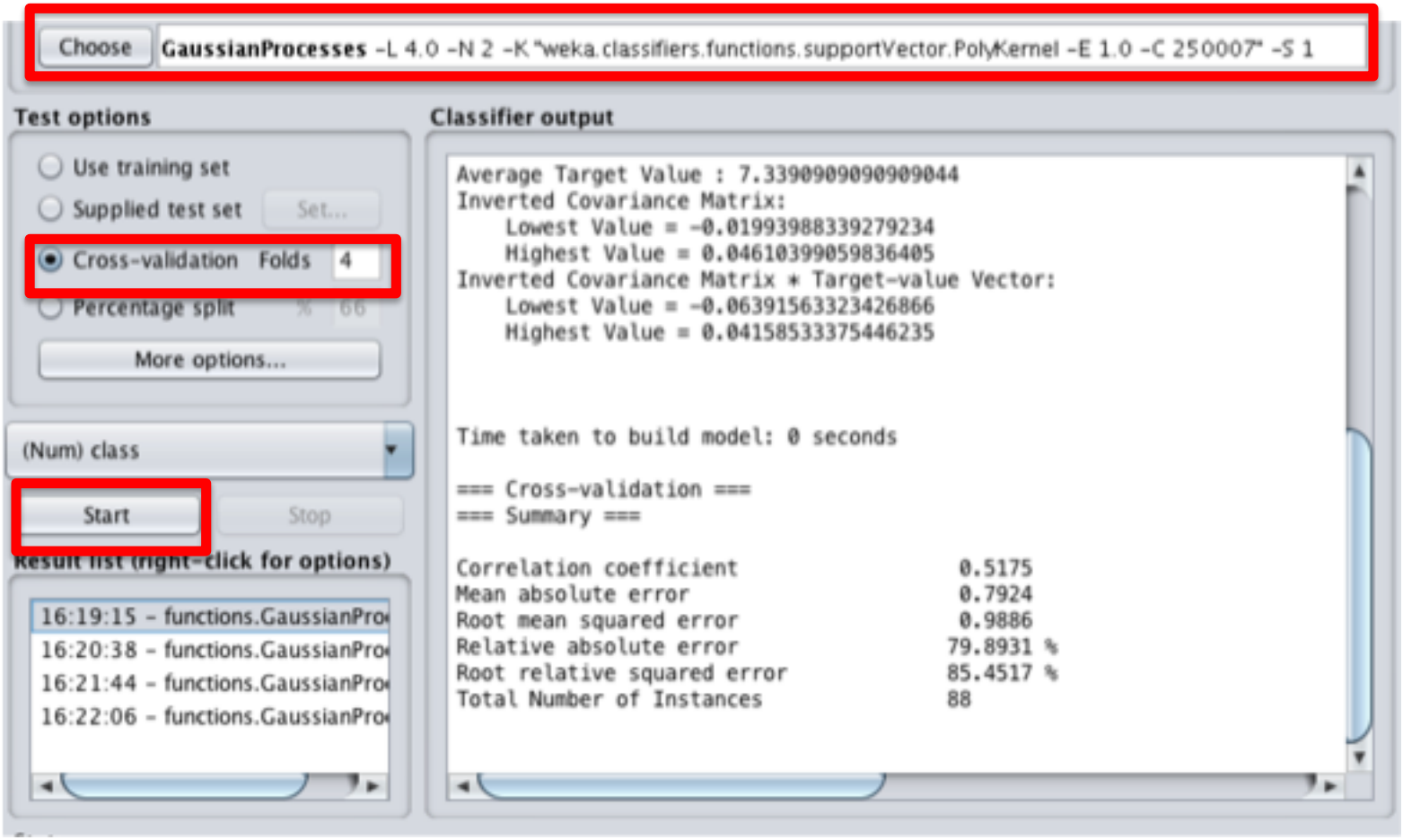
Re-fit the Gaussian Processes model

- Setup a Gaussian Processes model if needed
- Select the *Supplied test set* option and set the training file as test. This produces fitting results.
- Click the *More options…* button.



Re-evaluate the Gaussian Processes model

- Setup a Gaussian Processes model with an optimal noise value (for instance 4)
- Select the *Cross-validation* option and set the *Folds* value to 4.
- Click the *Start* button



Gaussian Processes model on currated dataset

Fit

```
=== Summary ===

Correlation coefficient                  0.9818
Mean absolute error                      0.2299
Root mean squared error                  0.2705
Relative absolute error                 23.6221 %
Root relative squared error             23.881  %
Total Number of Instances               87
```

Cross-validation

```
=== Cross-validation ===
=== Summary ===

Correlation coefficient                  0.5157
Mean absolute error                      0.7881
Root mean squared error                  0.9771
Relative absolute error                 78.6143 %
Root relative squared error             83.9261 %
Total Number of Instances               87
```

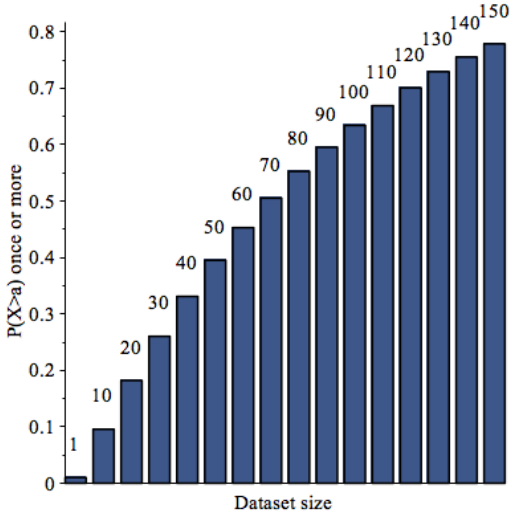
Performances are (slightly) improved

Summary

- **Single step procedure**
  - ✔ Fast and simple
  - ✔ False estimation of risk in outlier detection:
    - **Distribution parameters are distorted by outliers**
    - **The risk estimation is valid for only one point.**
  - ✔ The bigger the dataset is, the greater the chances to interpret a standard instance as outlier (false positive)

$$P(X > a) = p$$

$$P(\{x_i \mid x_i > a\} \subset \text{Sample}) = \text{Binomial}(N, p)$$



Summary

- **Sequential procedure**
  - ✔ Fastidious
    - **the whole procedure repeats after each identified outlier.**
  - ✔ Distribution parameters are distorted by the outlier
    - **Use robust statistics**

      resampling by the half-means method or by the smallest half-volume method

      Egon WJ, Morgan SL, *Anal. Chem.*, 1998, **70**(11), pages 2372-2379
- **Identify multiple outliers**
  - ✔ Rank instances by outlier likeliness

    Higher rank to instances that are consistently not fitted in consensus modeling

Conclusion

- **Outlier detection may depend on data modeling**
  - ✔ Molecular Descriptors, Machine Learning method,…
  - ✔ Therefore, a consensus model-based approach may help (pick the outliers that are common to the several distinct models)
- **Use internal and external cross-validation to avoid overfitting.**
- **Exploit the fitted values (rather than cross-validated predictions) for outlier detection**
- **An "outlier" not confirmed as anomalous cannot be discarded**
  - ✔ but it may help understand the limitations of your model
  - ✔ It might be a "discovery"!

Thanks

Thank you