Tutorial on Generative Topographic Mapping

G. MARCOU, D. HORVATH, O. KLIMCHUK,
F. BONACHERA and A. VARNEK

Your materials

- **Materials are on your USB key**
  - ✔ CS3_2018/Tutos/Tuto1
- **Download URL (from the web site of the school):**
  - ✔ https://tinyurl.com/CS3-2018-Tuto1
- **Softwares**
  - ✔ Directories: Softs/Windows, Softs/Mac, Softs/Linux
    - **xGTMapTool, xGTMView, GTMmanifold**
    - **licence.dat**
- **Datasets**
  - ✔ Data/FDB
    - **Initial files**

      train _Freq_01.hdr, train _Freq_01.svm, train _Freq_01.arff
      test _Freq_01.hdr, test _Freq_01.svm, test _Freq_01.arff
    - **Precomputed files**

      Directories: Exo1, Exo2, Exo3, Exo4, Exo5
    - **Raw data**

      FLAVOR_DB_OK.sdf
      train.sdf, train.hdr, train.svm, train.arff
      test.sdf, test.hdr, test.svm, test.arff

License

- **The software are licensed by the University of Strasbourg.**
  - The license file is called `licence.dat` and is situated in the OS specific directories: Windows, Mac and Linux
- **Windows: create the directory at the root of your home directory**
  - `AppData\local\ISIDAGTM2018` directory
  - copy the file `license.dat` in it with read and write permissions.
    - `C:\Users\username\AppData\local\ISIDAGTM2018\licence.dat`
- **Mac: create the directory at the root of your home directory**
  - `.config/ISIDAGTM2018`
  - copy the file `license.dat`
    - `/Users/username/.config/ISIDAGTM2018/licence.dat`
- **Linux: create the directory at the root of your home directory**
  - `.config/ISIDAGTM2018`
  - copy the file `license.dat` in it
    - `/home/username/.config/ISIDAGTM2018/licence.dat`

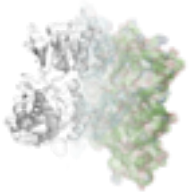
FlavorDB

- **FlavorDB is a database published in 2017**
  - ✔ **D1210–D1216** *Nucleic Acids Research*, 2018, Vol. 46, Database issue
    - **doi: 10.1093/nar/gkx957**
  - ✔ **URL:** http://cosylab.iiitd.edu.in/flavordb

An aggregation of existing sources

Flavornet: http://www.flavornet.org/
Arn,H., Acree,T.E. (1998), *Dev. Food Sci.*, **40**, 27

SuperSweet: http://bioinformatics.charite.de/sweet/
Ahmed,J., Preissner,S., Dunkel,M., Worth,C.L., Eckert,A., Preissner,R. (2011), *Nucleic Acids Res.*, 39.



BitterDB: http://bitterdb.agri.huji.ac.il/dbbitter.php
Wiener,A., Shudler,M., Levit,A. and Niv,M.Y. (2012), *Nucleic Acids Res.*, 40, 413–419, D377-82.

FooDB: http://foodb.ca/

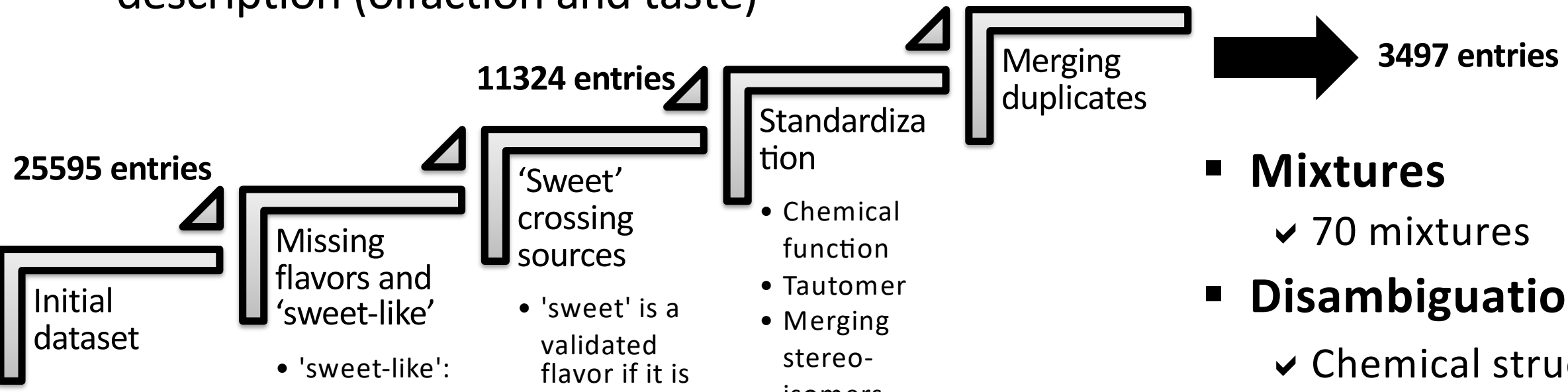
Université de Strasbourg

Bibliographic sources

- Burdock,G.A. (2010) *Fenaroli's handbook of flavor ingredients.*
- Ahn,Y.-Y., Ahnert,S.E., Bagrow,J.P. and Barabási,A.-L. (2011) Flavor network and the principles of food pairing. *Sci. Rep.*, 1, 196.
- Jain,A., Rakhi,N.K. and Bagler,G. (2015) Analysis of food pairing in regional cuisines of India. *PLoS One*, 10.
- Jain,A., Rakhi,N.K. and Bagler,G. (2015) Spices form the basis of food pairing in Indian cuisine. *arXiv:1502.03815*.

Data curation

- **Aim**
  - ✔ Collect a set of identified chemical substances with an organoleptic description (olfaction and taste)



- **Mixtures**
  - ✔ 70 mixtures
- **Disambiguations**
  - ✔ Chemical structures
  - ✔ Monomers

3438 entries

Additional source:

Rojas et al., *Front Chem.* 2017; 5: 53.

Dataset content

- **The Flavor dataset**
  - ✔ 3438 compounds
  - ✔ 713 flavors
    - **132 rules**

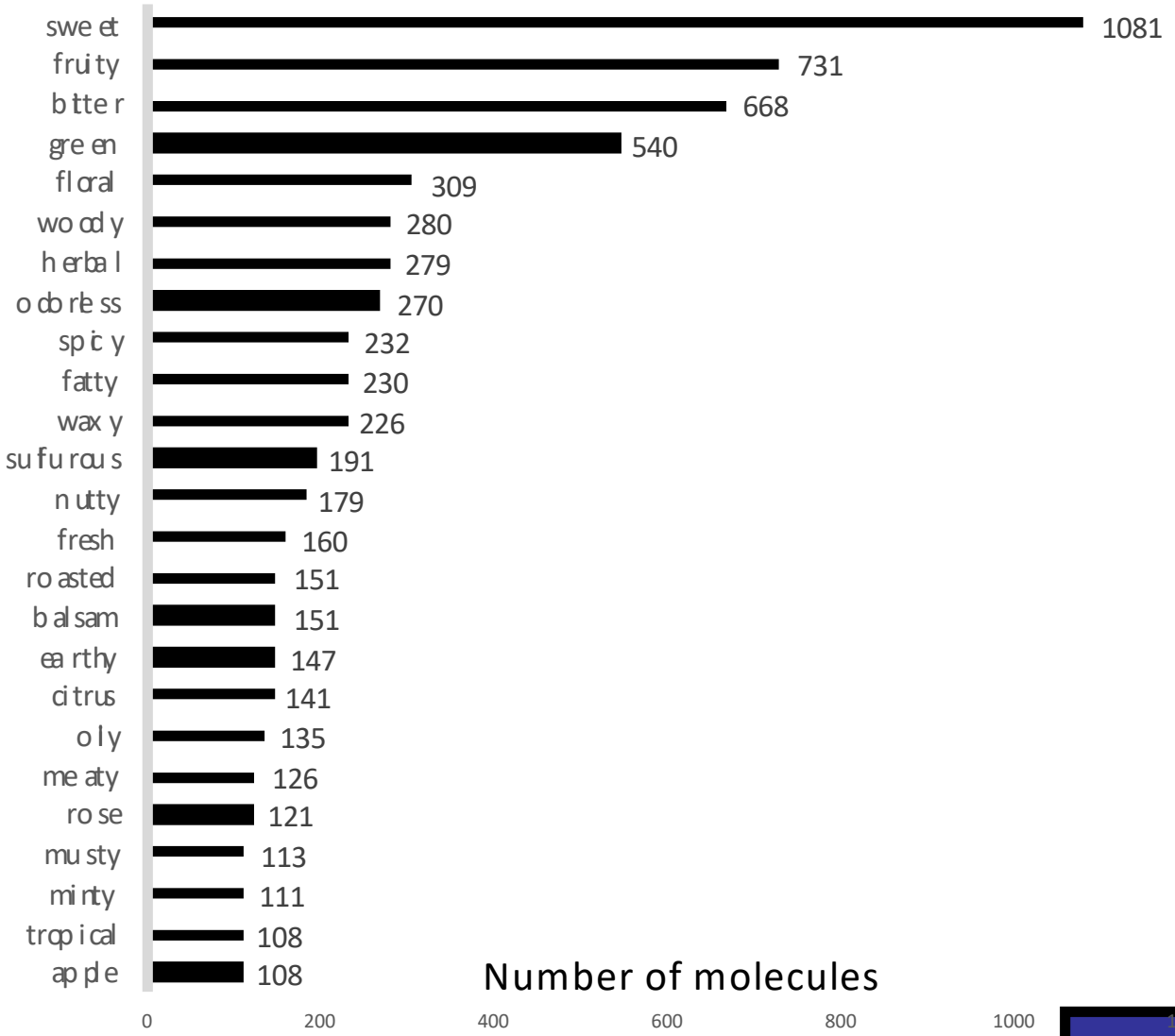
      ‘old wood’, ‘woody’, ’wood’ merged as ‘wood’
    - **4 main flavors:**

      Sweet

      Fruity

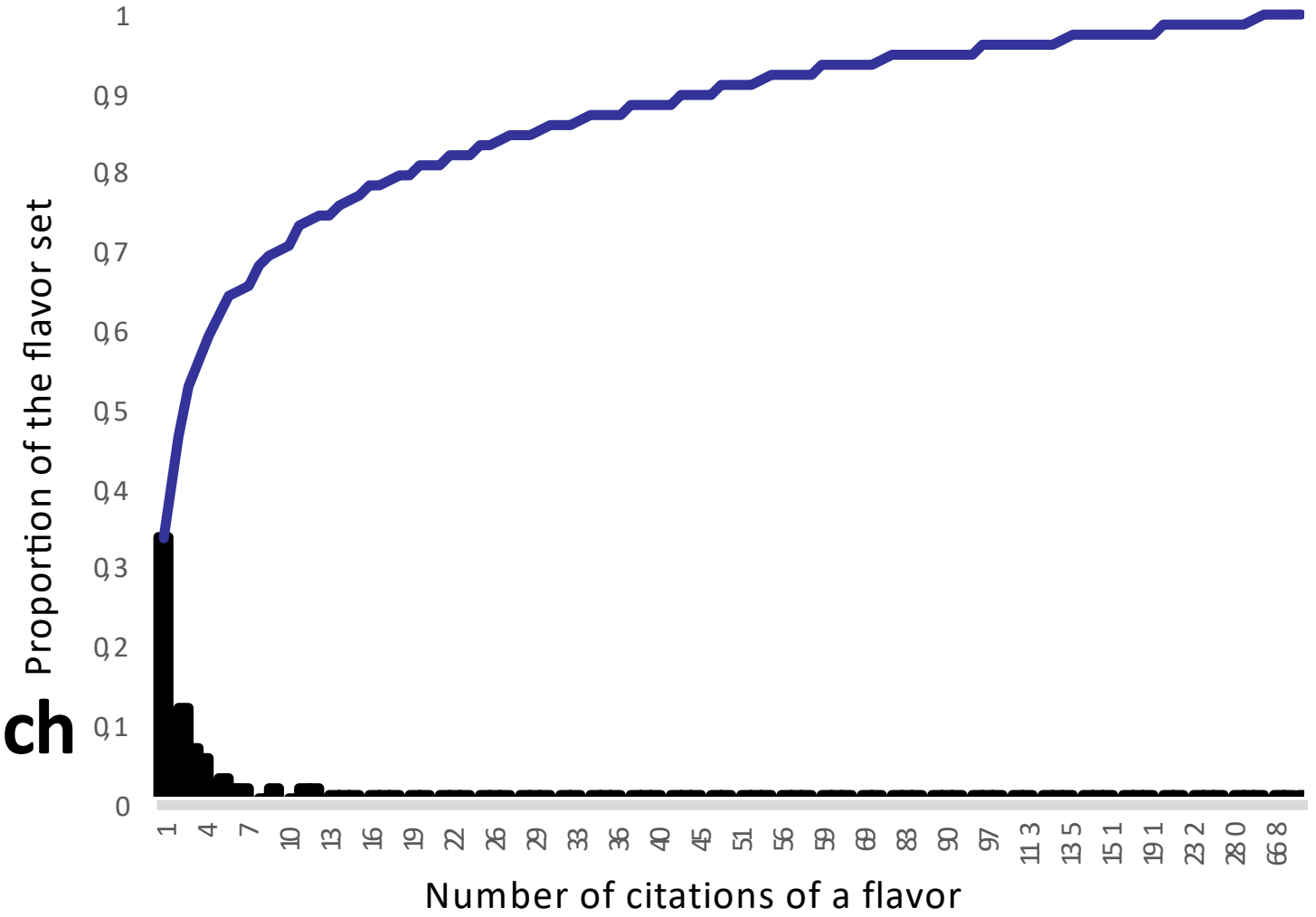
      Bitter

      Green



How many substances described by a flavor?

- **Most flavors are low populated**
  - ✔ 50% of flavors are in the description of less than 3 molecules
  - ✔ 90% of flavors are in the description of less than 50 molecules
- **Most flavors are out of reach for QSAR modeling…**

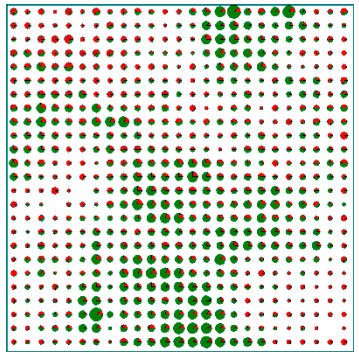


…But the chemical space of flavors can be depicted

Université de Strasbourg

GTM – a probabilistic extension of SOM

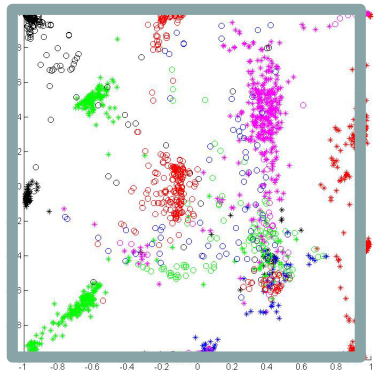
Self-Organizing Maps (SOM)



Teuvo Kohonen

Uniform distribution

Generative Topograhic Maps (GTM)



Christopher Bishop

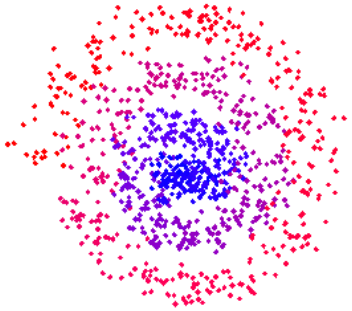
Normal distribution

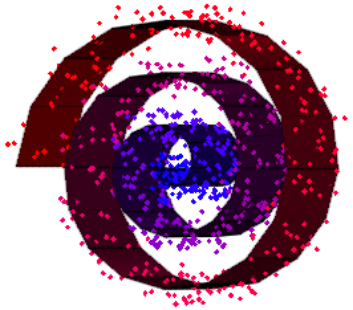
Limitations of SOMs

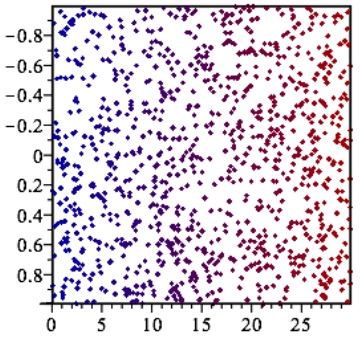
- the lack of a theoretical basis for choosing learning rate parameter schedules and neighborhood parameters to ensure topographic ordering;
- (Depending of implementation,) the absence of proofs of convergence;
- Mathematically complicated to compute a likelihood.

C.M.Bishop, M.Svensen, C.K.I.Williams, « The Generative Topographic Mapping», *Neural Computation*, 10, No. 1, 215-234 (1998)

Generative Topographic Map

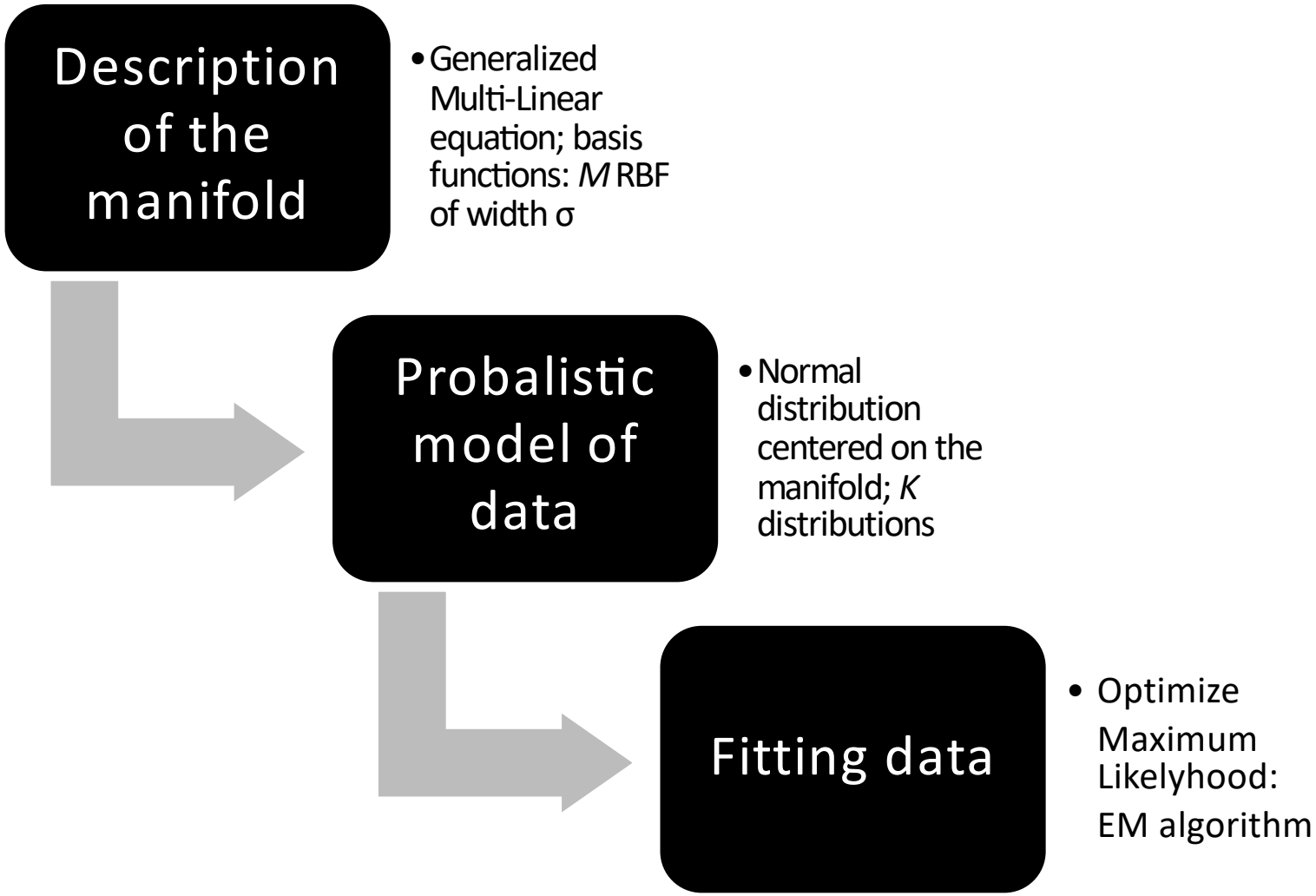




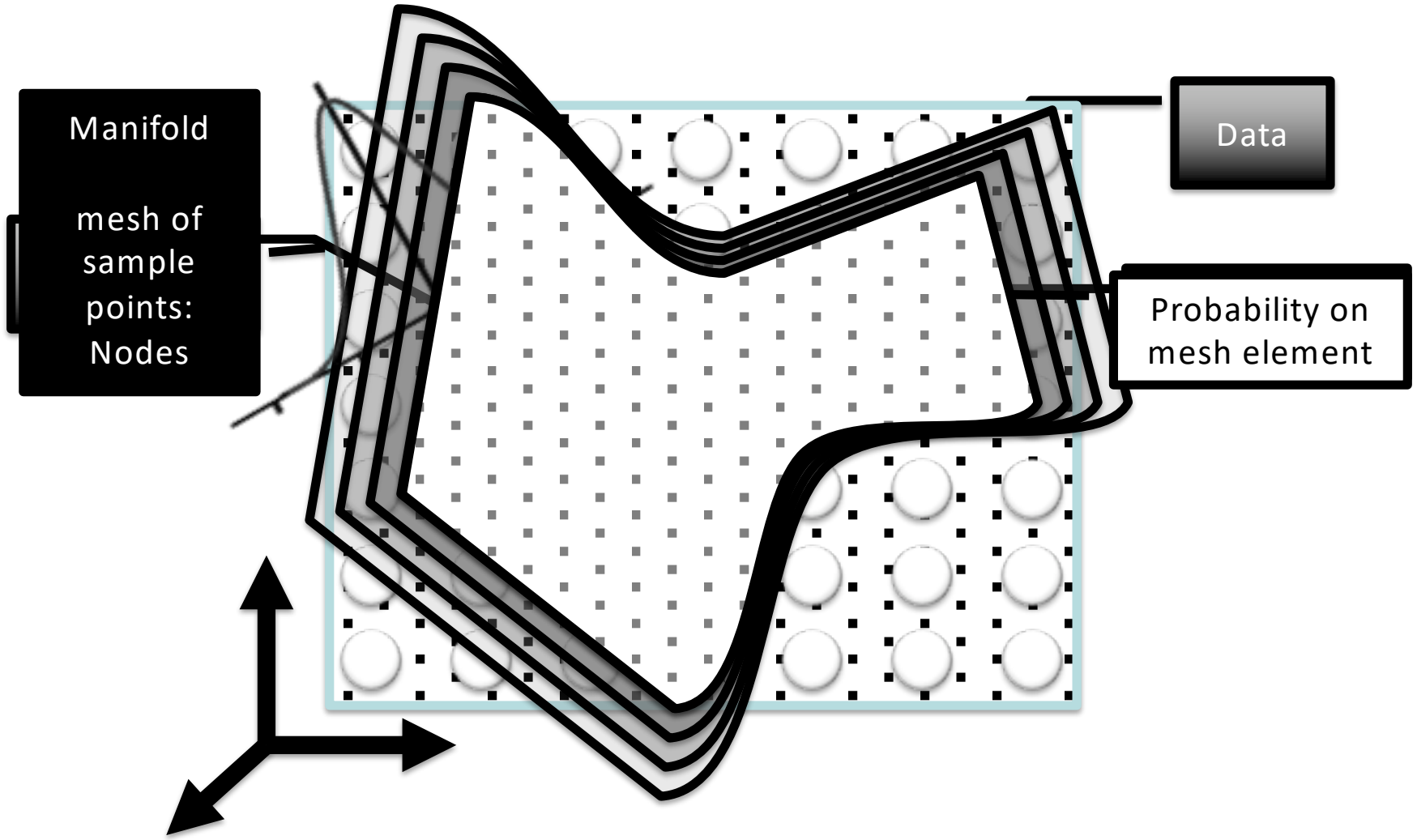


Initial space	Probability model	Fitting	Unfolding
• A dataset is distributed in the initial space	• Gaussian distribution centered in a 2D manifold	• The fitted manifold maximizes the dataset likelihood	• Projected data to the manifold are unfolded appear as 2D map

GTM logic


Description of the manifold
• Generalized Multi-Linear equation; basis functions: *M* RBF of width σ
Probalistic model of data
• Normal distribution centered on the manifold; *K* distributions
Fitting data
• Optimize Maximum Likelyhood:
EM algorithm

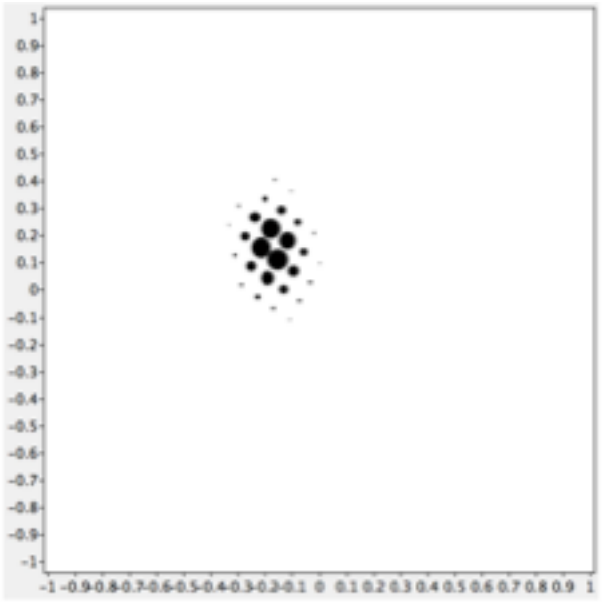
GTM building

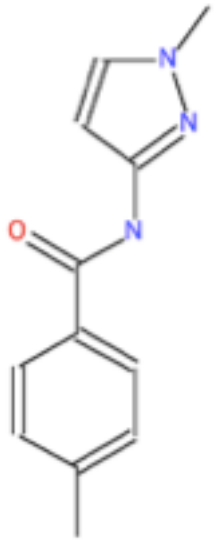


GTM responsibilities

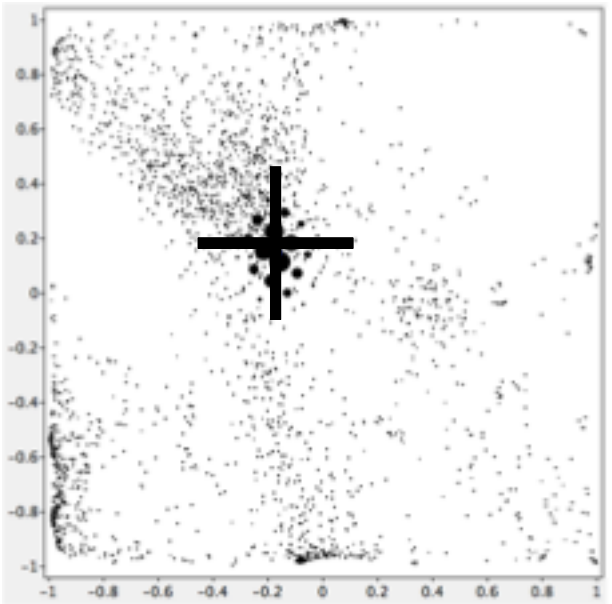
- **Responsibility:**
  - ✔ the probability that a node generated a data point.

A molecule appears on the manifold either as a responsibility pattern…



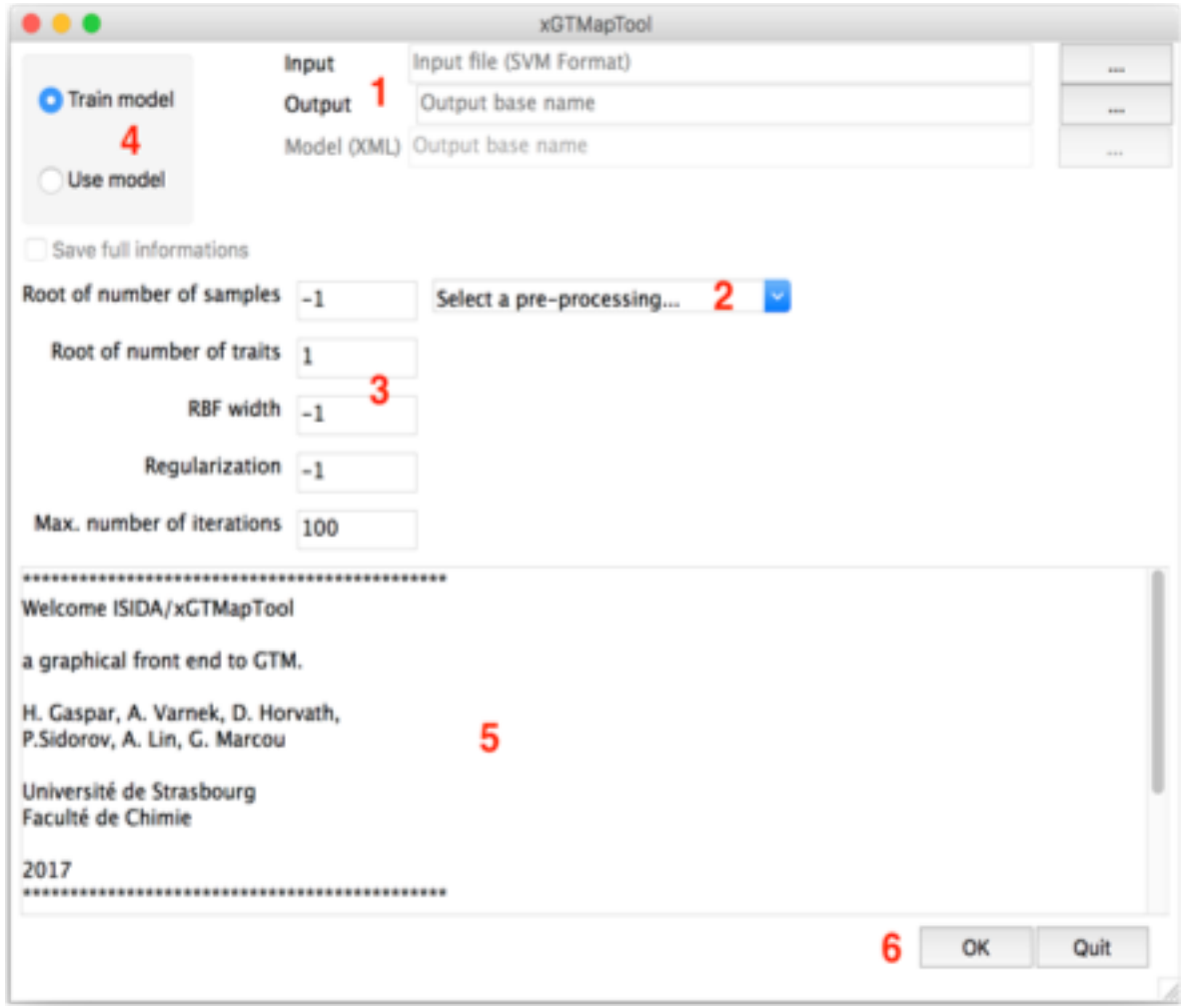


… or as an average coordinate on the manifold.



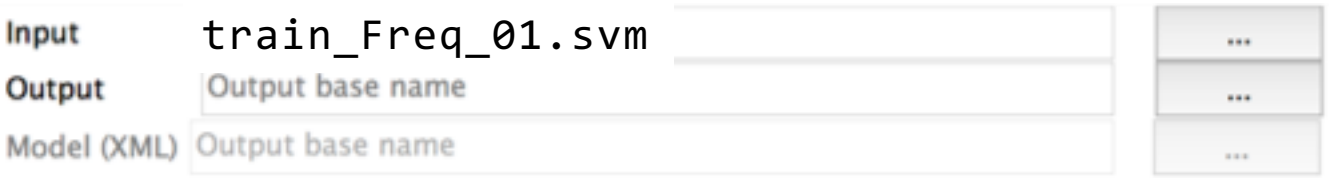
Exercise I

- **Open xGTMapTool**
  1. *File management*
  2. *Preprocessing*
  3. *Parameterization of the model*
  4. *interface to train or apply a GTM model log of the calculations*
  5. *launching the calculations*

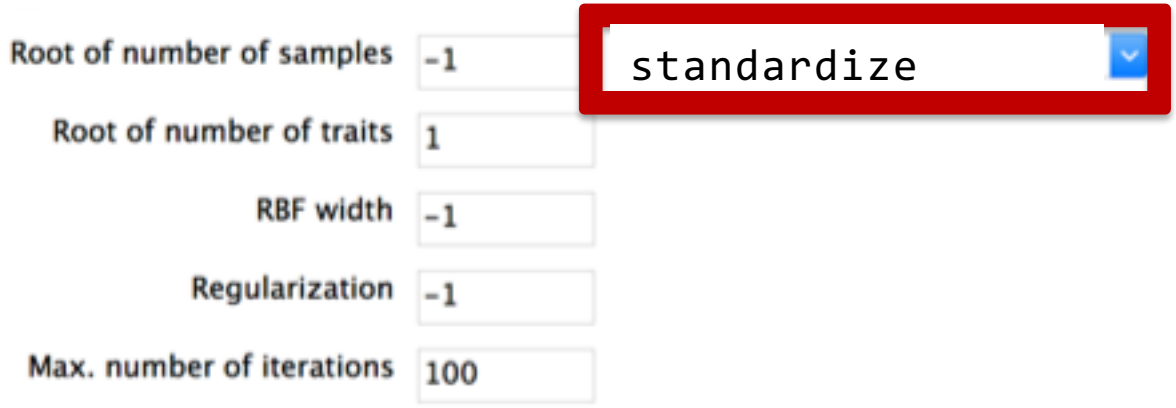


Exercise I

- **Click the button to the right of the Input label and select the file** `train_Freq_01.svm`



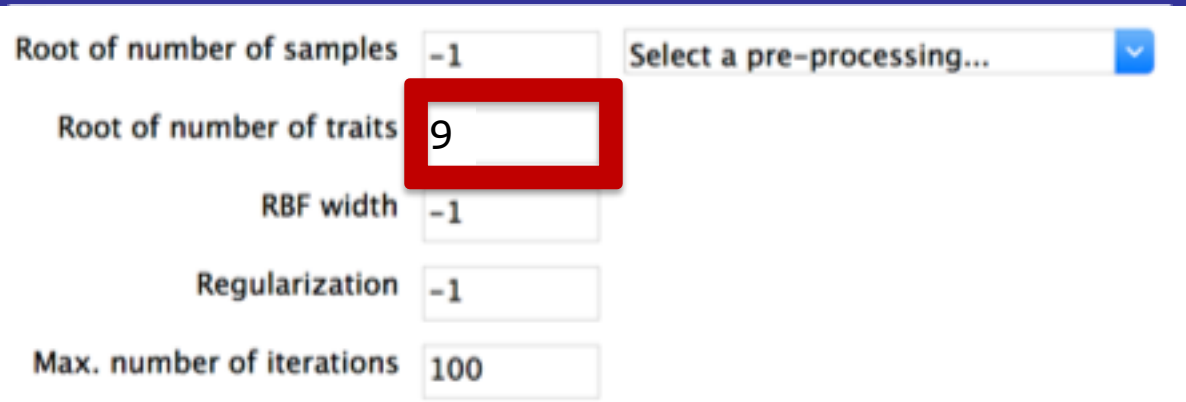
- **As a preprocessing option use the** `standardize` **option.**



GTM manifold is initialized on 2 first PCA:
PCA calculation requires data to be standardized

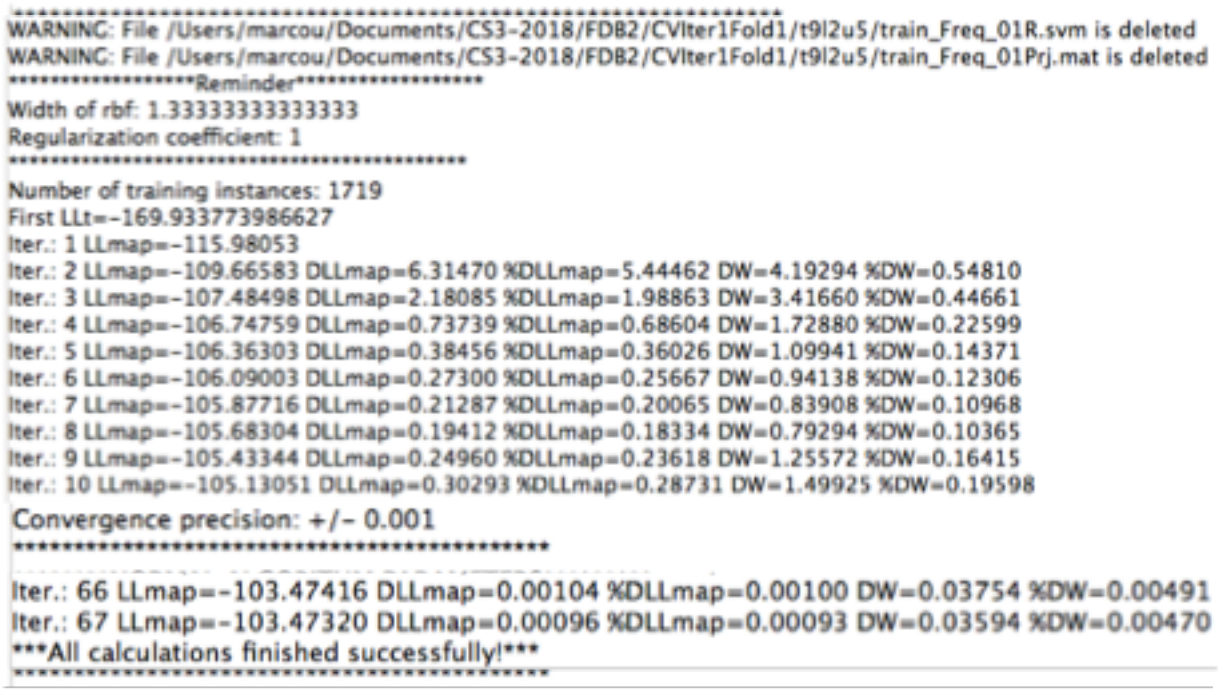
Exercise I

- **Set the Number of traits value to 9 then click on the button OK**



- **The log resume the calculation parameters**

- **The log monitor the calculation progress**



Exercise I

- **The GTM models is stored in an XML file:**
  - ✔ <Mean> and <SD> fields are the shift and scale of the preprocessing
  - ✔ <PC123> are the first 3 PCA components
  - ✔ <Manifold> store the weights defining the GTM manifold
  - ✔ <LatentSamples> are the latent space coordinates of the nodes
  - ✔ <LatentTraits> are the latent space coordinates of the RBF centers

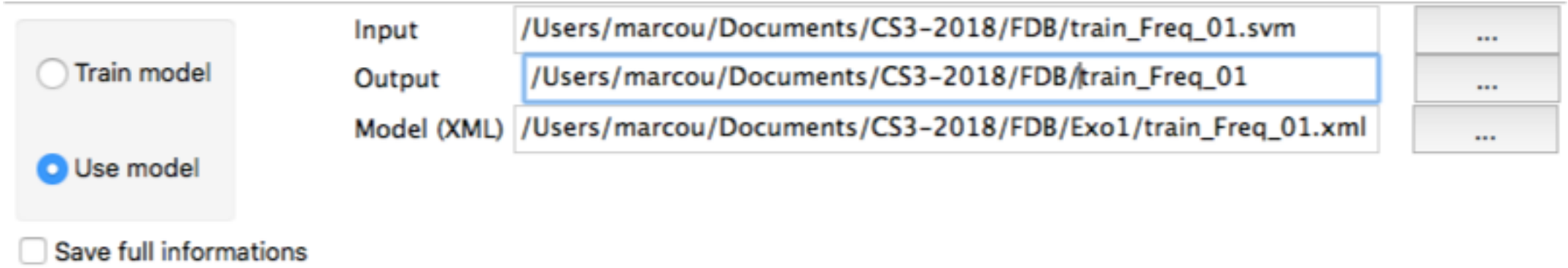
```
1   <?xml version="1.0" encoding="utf-8"?>
2   <GTM D="85" N="1719" Type="BISHOP" nIter="67" Preprocess="1">
3     <Mean D="85"> ... </Mean>
5     <SD D="85"> ... </SD>
7     <PC123 D="85"> ... </PC123>
93    <Manifold D="85" K="225" M="9" beta="1.62922" alpha="1.00000" sigma="1.33333"> ... </Manifold>
179   <LatentSamples> ... </LatentSamples>
405   <LatentTraits> ... </LatentTraits>
415 </GTM>
```

Exercise I: conclusion

- **A GTM model of the flavor dataset is build.**
- **The model is store into an XML file**
- **The following exercises will concentrate on the following questions**
  - ✔ How to use the GTM model?
  - ✔ What the model looks like?
  - ✔ Did the model trained long enough?
  - ✔ Are there better parameter choices?

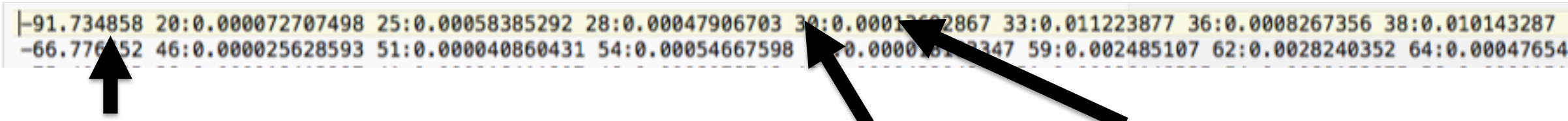
Exercise 2

- **Chose the use model option**
- **Set up the input for the training set**
  - ✔ Choose as input the file `train_Freq_01.svm`
  - ✔ Choose as Model (XML) the file `train_Freq_01.xml`
- **Check if the `Save full information` box is not ticked**
  - ✔ Untick if needed
- **Click the OK button**



Exercise 2

- **Two files are created**
  - ✔ `train_Freq_01R.svm` and `train_Freq_01Prj.svm`
- **File `R.svm` contains responsibilities at each node for each molecule**



Likelihood of the molecule

At a give **node** the **responsibility** of the molecule

- **File `Prj.mat` contains latent coordinates of each molecule**

```
*.*.*.*.*/ Proj \*.*.*.*.*
-0.48869,-0.24423
-0.22177,-0.22772
-0.28950,-0.19545
```

Top of the file

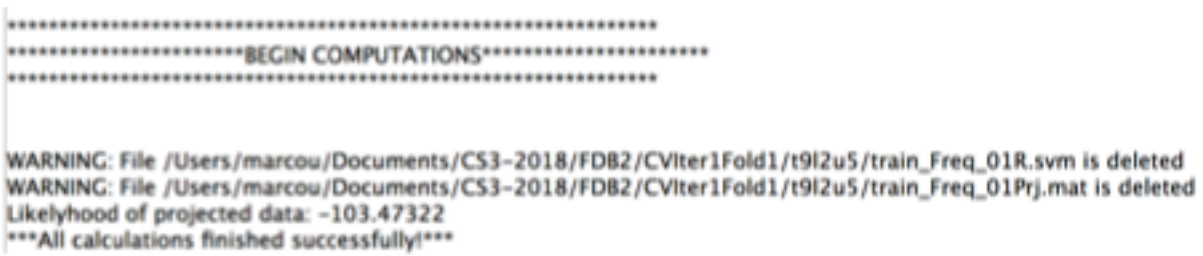
x coordinate y coordinate

```
-0.45712,0.16268
-0.18552,-0.11347
0.36441,-0.69162
.*.*.*.*.\ Proj /.*.*.*.*.
```

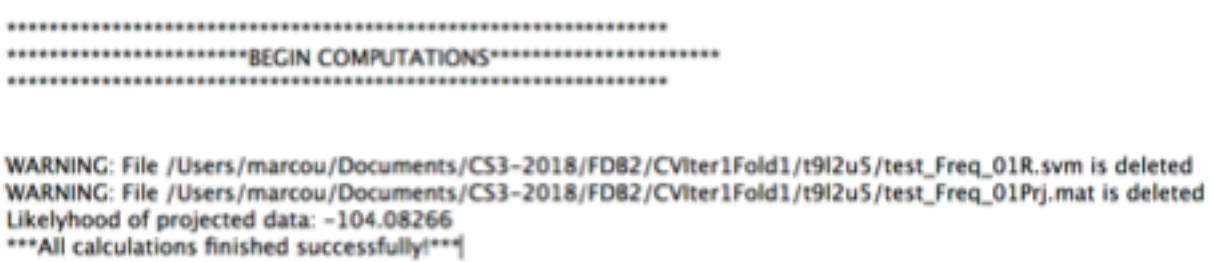
Bottom of the file

Exercise 2

- **Chose the use model option**
- **Set up the input for the training set**
  - ✔ Choose as input the file `test_Freq_01.svm`
  - ✔ Choose as Model (XML) the file `train_Freq_01.xml`
- **Check if the `Save full information` box is not ticked**
  - ✔ Untick if needed
- **Click the OK button**



Training set likelihood: -103.5



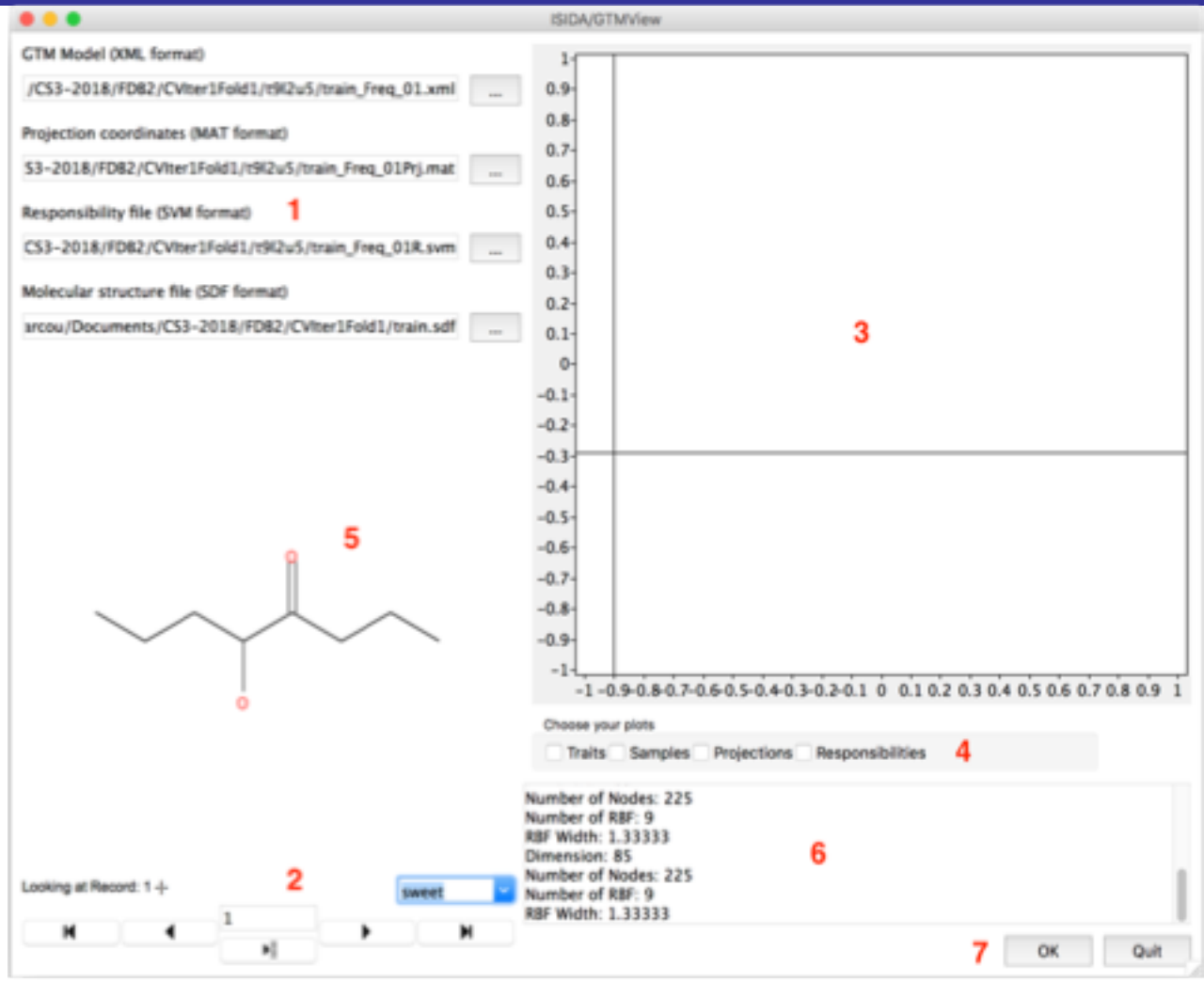
Test set likelihood: -104.1

Exercise 2

- **The GTM model is used on the training dataset and on an independent test dataset**
  - ✔ The likelihood are comparable
    - **The model explains as well the training data as the test date**
- **The output are sufficient to analyze with your favorite plotting tools (Datawarrior, spotfire, etc).**
  - ✔ In the next exercise, we will use xGTMView: a dedicated plotting interface.

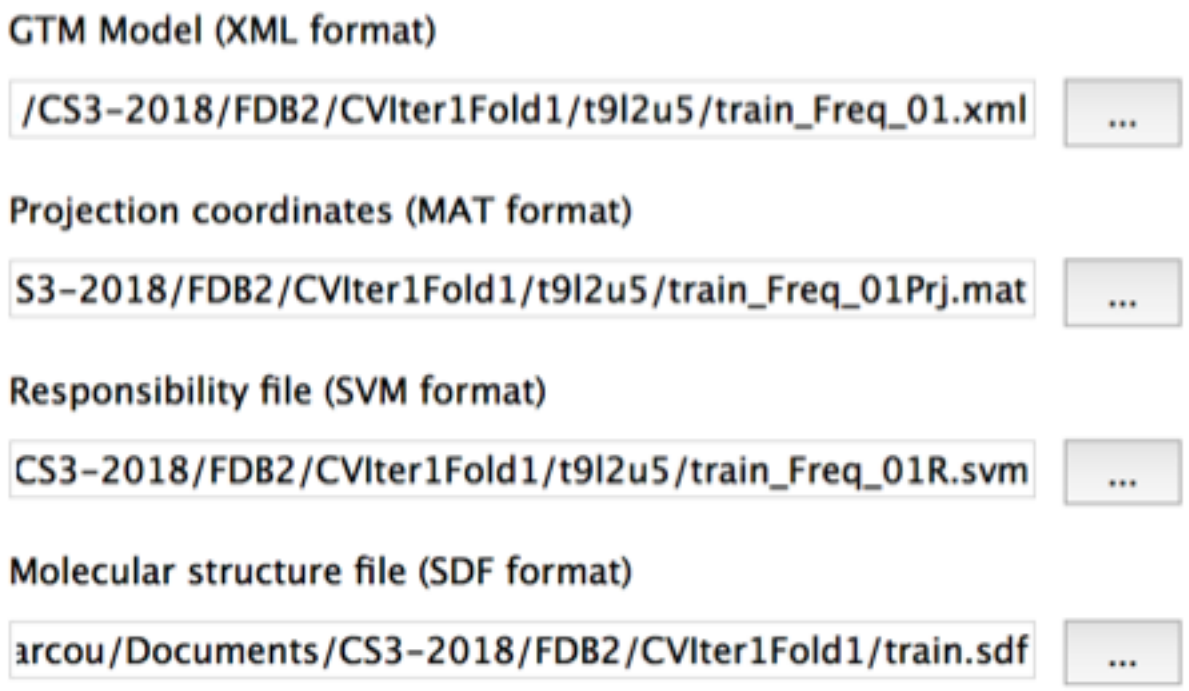
Exercise 3

- **Open the application** `xGTMView`
  1. Input management
  2. Navigation in the chemical structure file
  3. Chemical structures
  4. GTM data plotting area
  5. Plot selection
  6. Log output
  7. Start processing



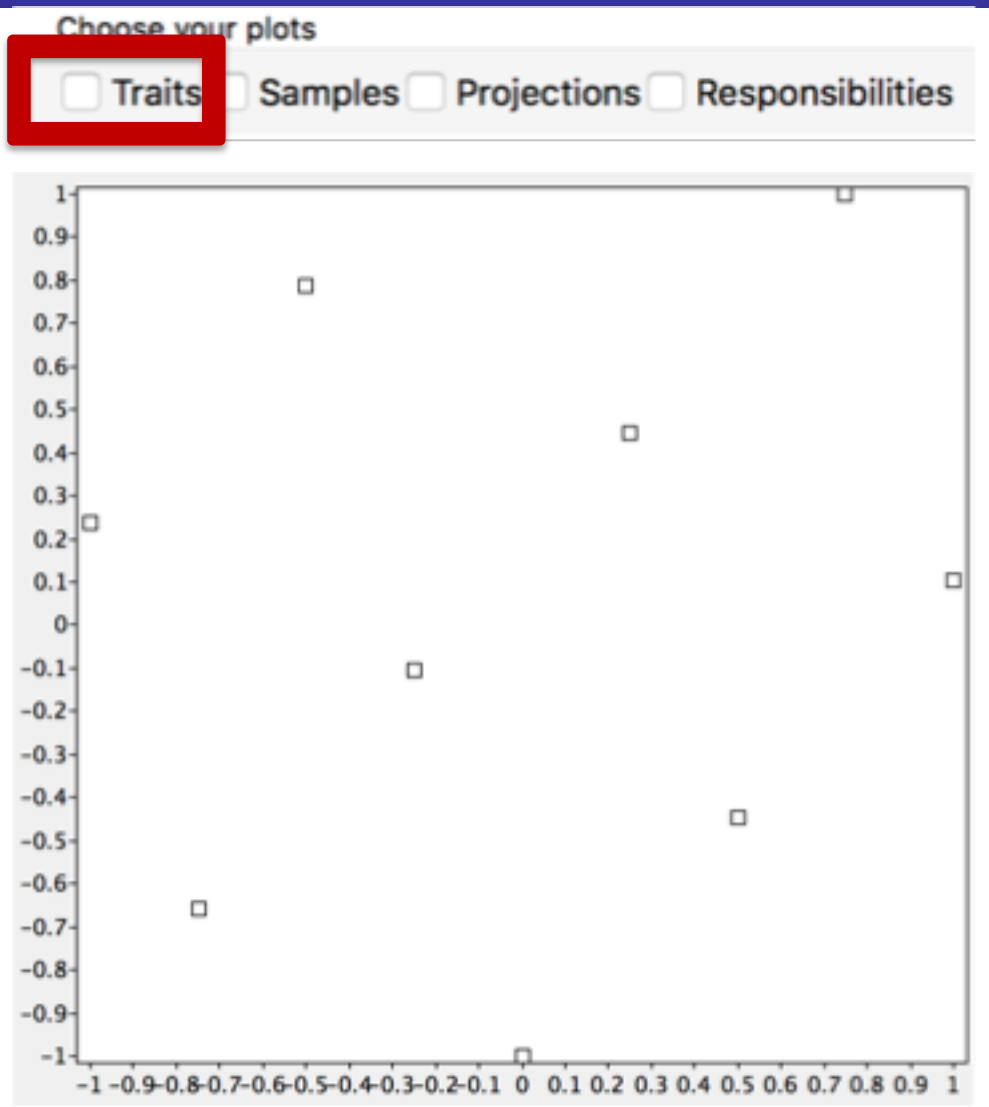
Exercise 3

- **Setup the input files to process**
  - ✔ Click the **GTM Model (XML format)** button, chose the file `train_Freq_01.xml`
  - ✔ Click the **Projection coordinates (MAT format)** button, chose the file `train_Freq_01Prj.mat`
  - ✔ Check that the `train_Freq_01R.svm` file is selected as the **Responsibility file (SVM format)**
  - ✔ Set **Molecular structure file (SDF format)** to the file `train.sdf`
- **Click the** OK **button.**



Exercise 3

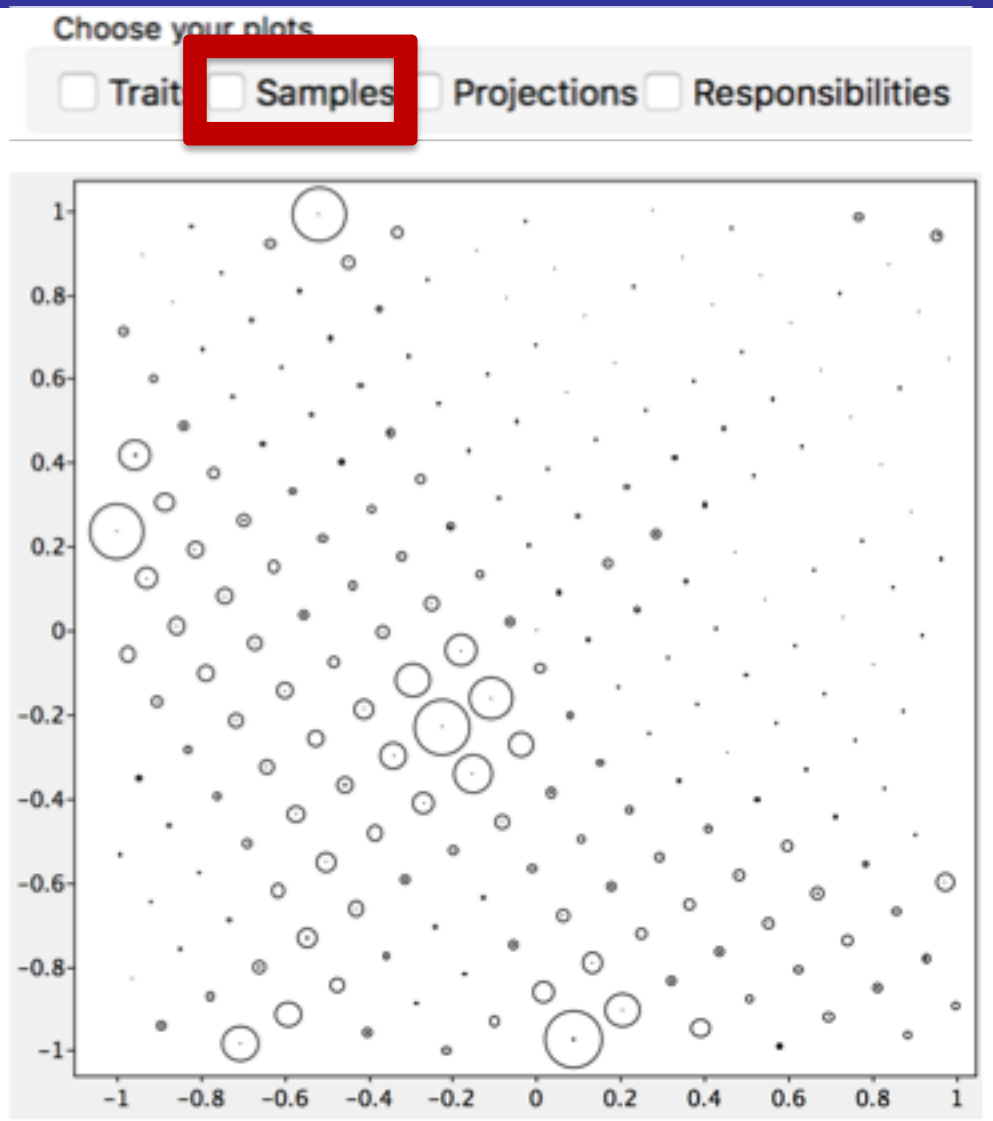
- **Tick the `Traits` box**



It displays the location of the RBF centers on the latent space

Exercise 3

- **Untick the `Traits` box**
- **Tick the `Samples` box**



It displays the location of the Nodes on the latent space.

Circles' size monitor the population of the chemical space portion associated to nodes

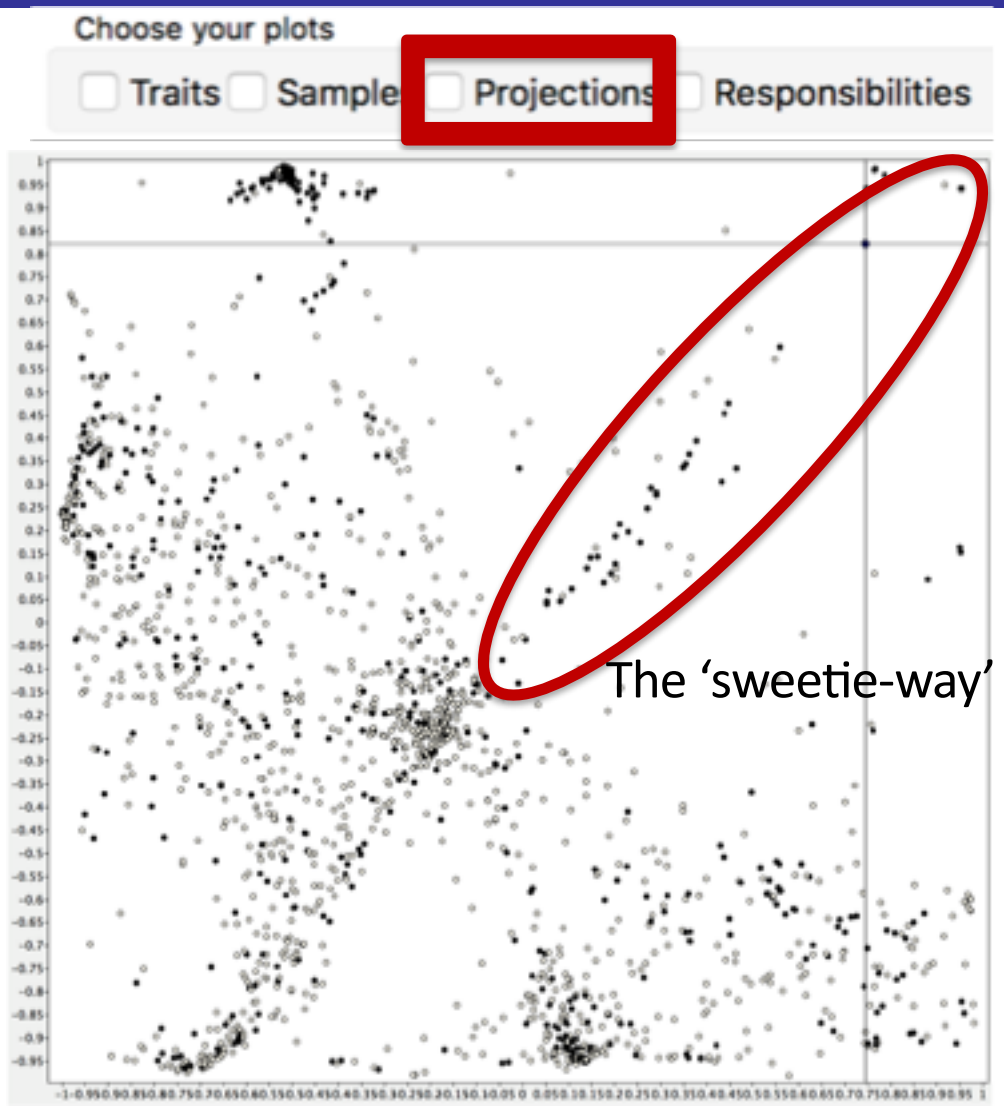
Exercise 3

- **Untick the `Samples` box**
- **Tick the `Projections` box**

Select from the list of available SDF fields, the '*sweet*' key.

It displays the location of the projections of molecules on the latent space

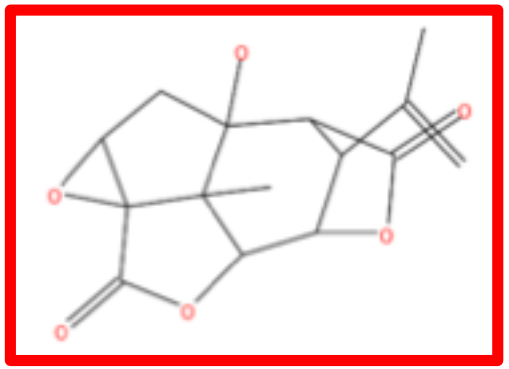
Sweet compounds are black colored

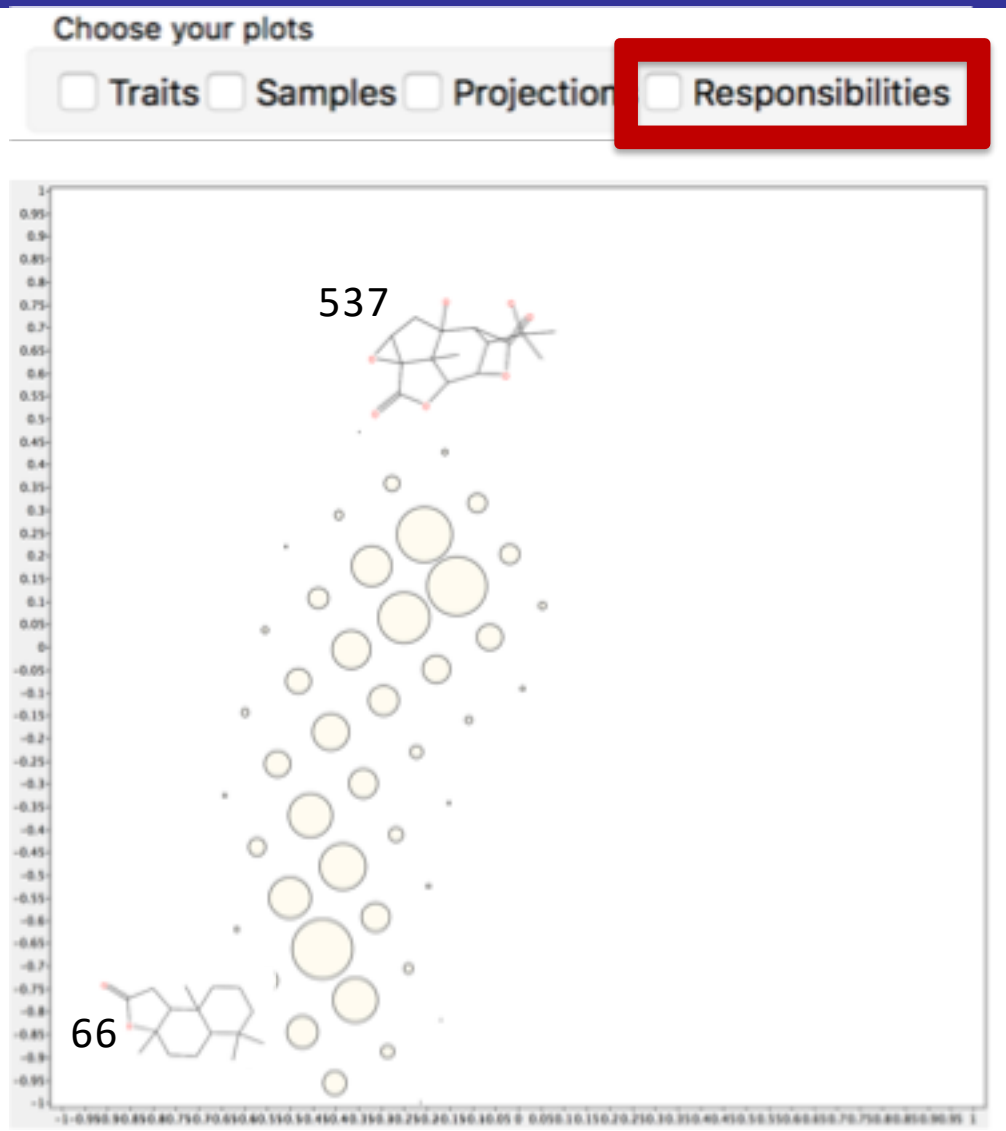


Université de Strasbourg

Exercise 3

- **Untick the** `Projections` **box**
- **Tick the** `Responsibilities` **box**
- **Display compound 118**





It displays the Responsibilities of the selected compound.

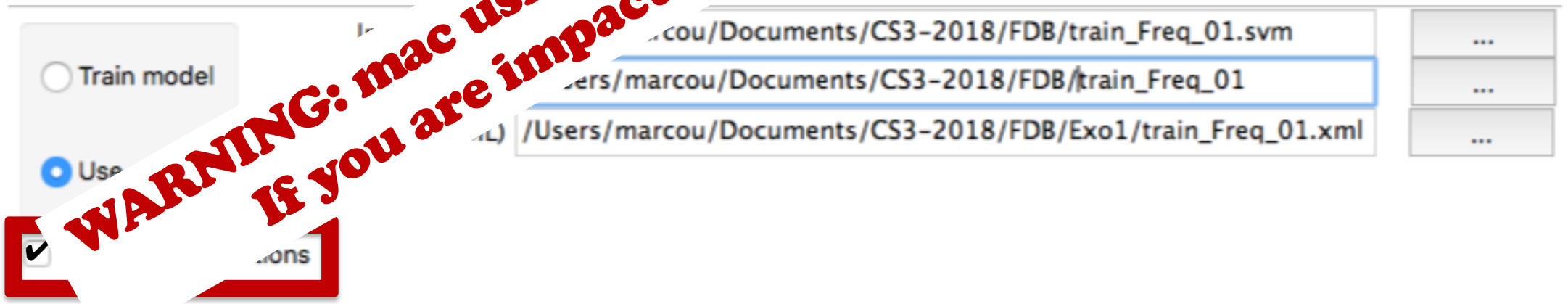
Circles are proportional to the responsibility values

Exercise 3: Conclusion

- **Try to load the test files:**
  - ✔ Click the **GTM Model (XML format)** button, chose the file `test_Freq_01.xml`
  - ✔ Click the **Projection coordinates (MAT format)** button, chose the file `test_Freq_01Prj.mat`
  - ✔ Check that the `test_Freq_01R.svm` file is selected as the **Responsibility file (SVM format)**
  - ✔ Set **Molecular structure file (SDF format)** to the file `test.sdf`
- **Test data share the same chemical space with the train data**
- **Next questions:**
  - ✔ What the manifold looks like?
  - ✔ Did the model building converged?

Exercise 4

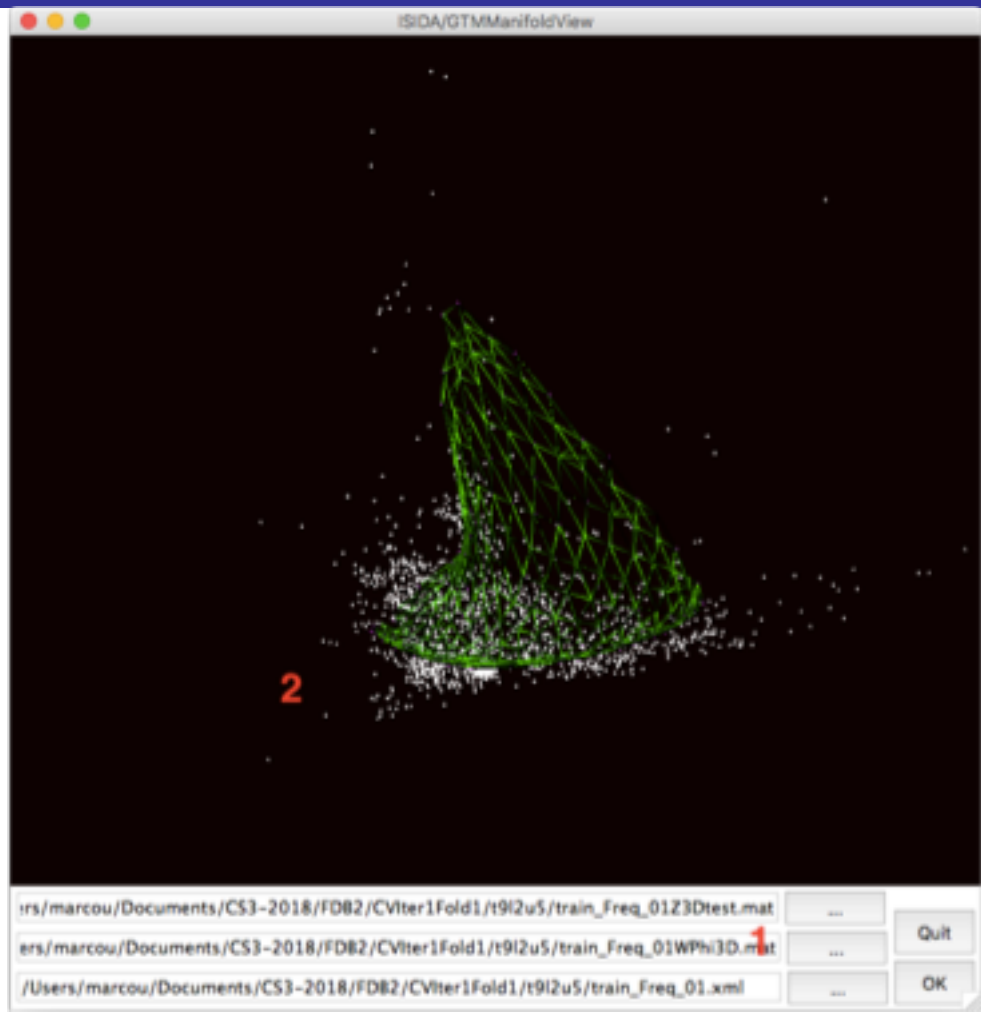
- **Use the** `xGTMapTool` **application**
- **Choose the** `use model` **option**
- **Set up the input for the training set**
  - ✔ Choose as input the file `train_Freq_01.sv`
  - ✔ Choose as Model (XML) the file `train_`
- **Tick the** `Save full informa`
- **Click the** `OK` **button.**



WARNING: mac using Nvidia GPU have an OpenGL bug.
If you are impacted, you will be logged out

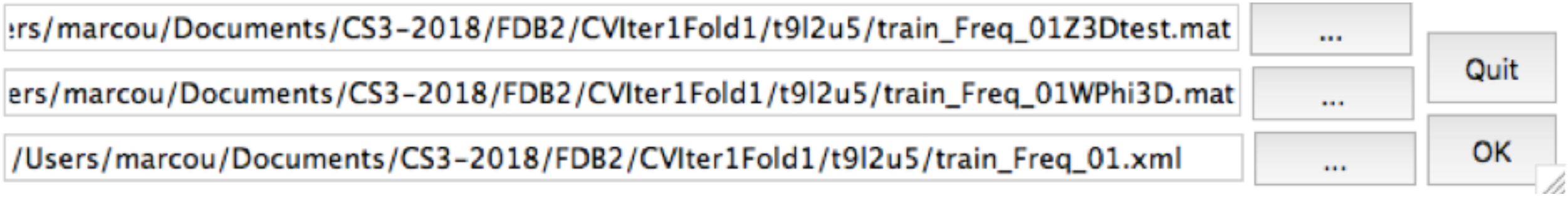
Exercise 4

- **Open the `GTMmanifold` software**
  1. Load 3D coordinates files
  2. Plotting area



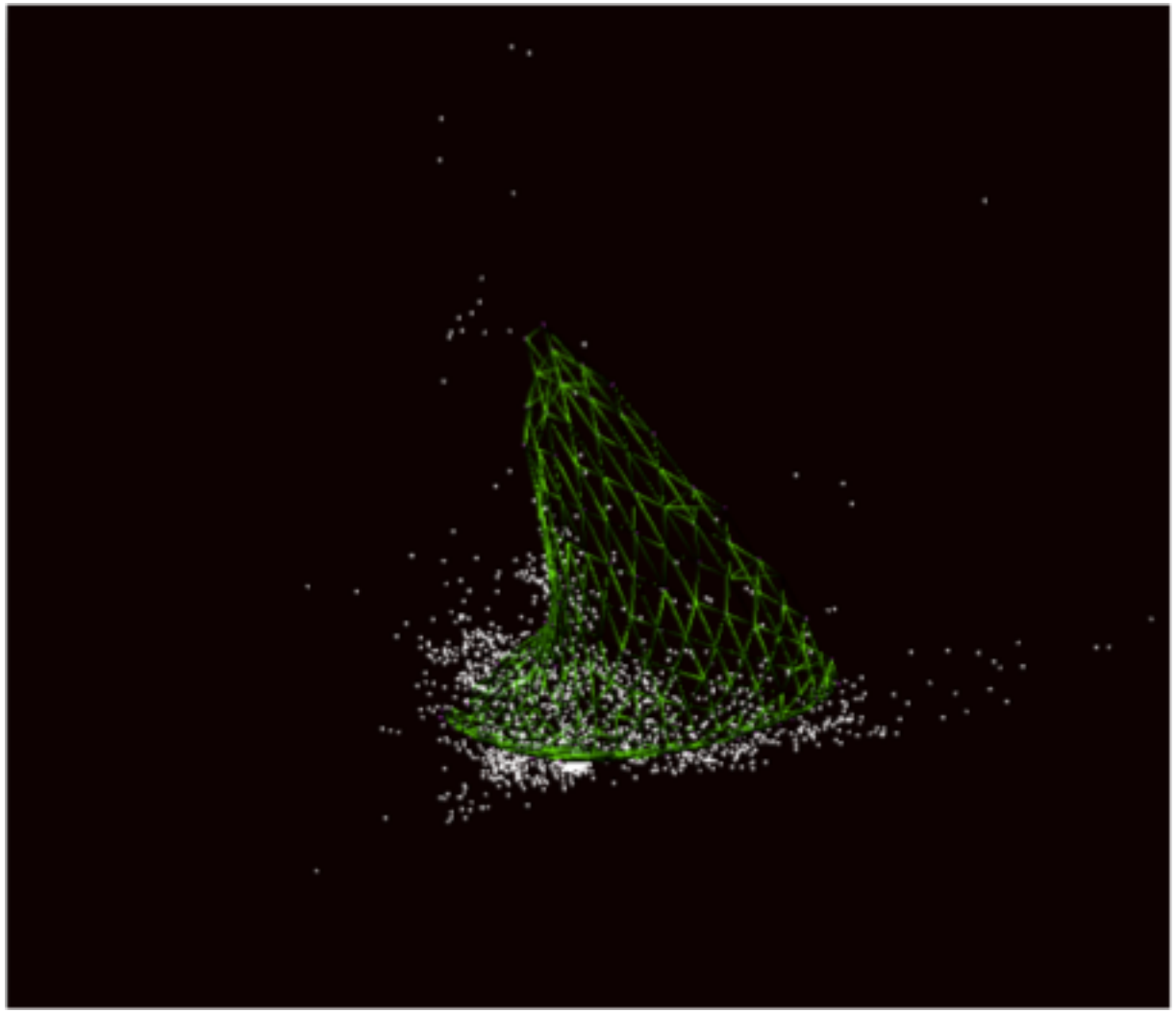
Exercise 4

- **Load the file** `train_Freq_01Z3D.mat` **in the top text box**
- **Load the file** `train_Freq_01WPhi3D.mat` **in the middle text box**
- **Load the file** `train_Freq_01.xml` **in the bottom text box**
- **Click the** `OK` **button.**



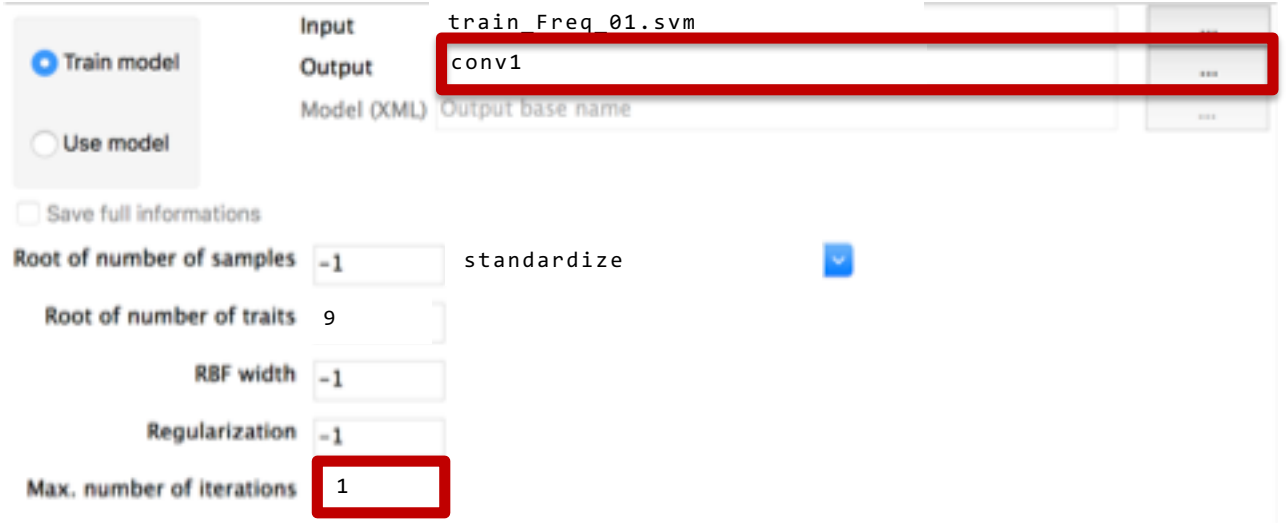
Exercise 4

- **Molecules as white dots**
- **Manifold as green wire-frame shape**
- **The 3 first PCA represent 40% of variance**
  - ✔ The picture illustrate a necessary condition but not sufficient proof of convergence



Exercise 4

- **Use the** `xGTMapTool` **application**
- **Choose the** `train model` **mode**
- **Set up the input for the training set**
  - ✔ Choose as input the file `train_Freq_01.svm`
  - ✔ Choose as output the name `conv1`
  - ✔ Set the **Preprocessing** to `standardize`
  - ✔ Set the value **Number of traits** to 9
- **Set the** `Max. Number of Iterations` **to** `1`
- **Click the** `OK` **button.**

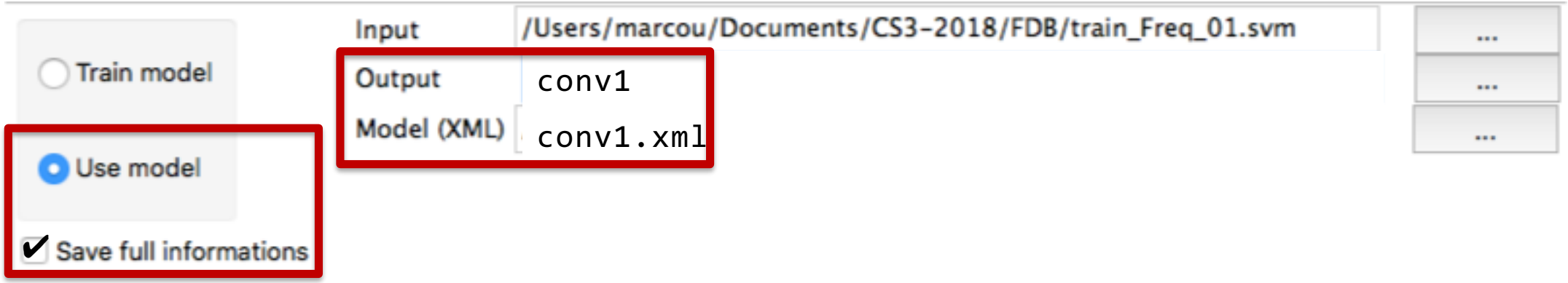


Repeat:

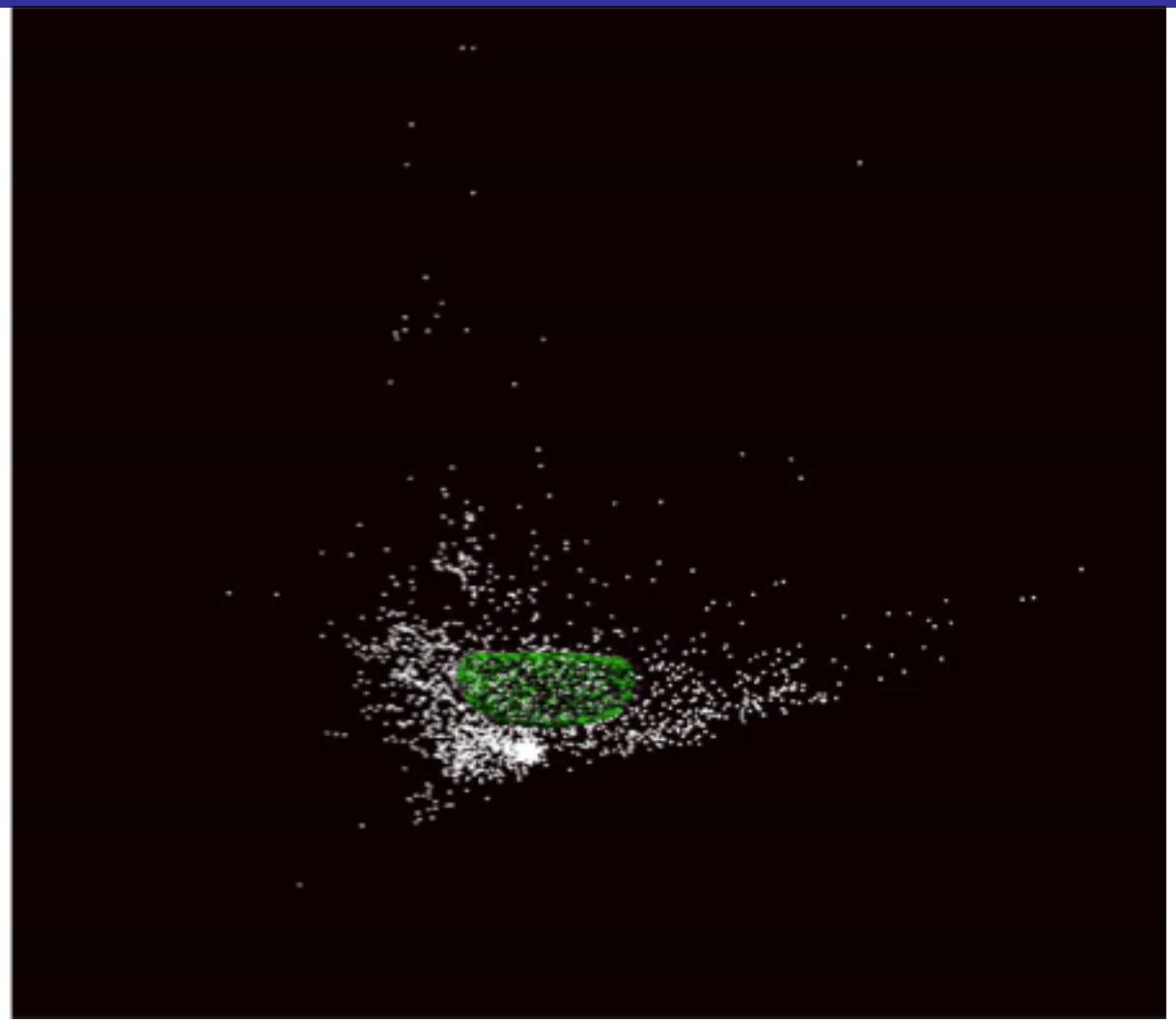
- **Set the** `Max. Number of Iterations` **to** `10, 20, 30, 40` **and** `50`
- **Set output to** `conv10, conv20, conv30, conv40, conv50`

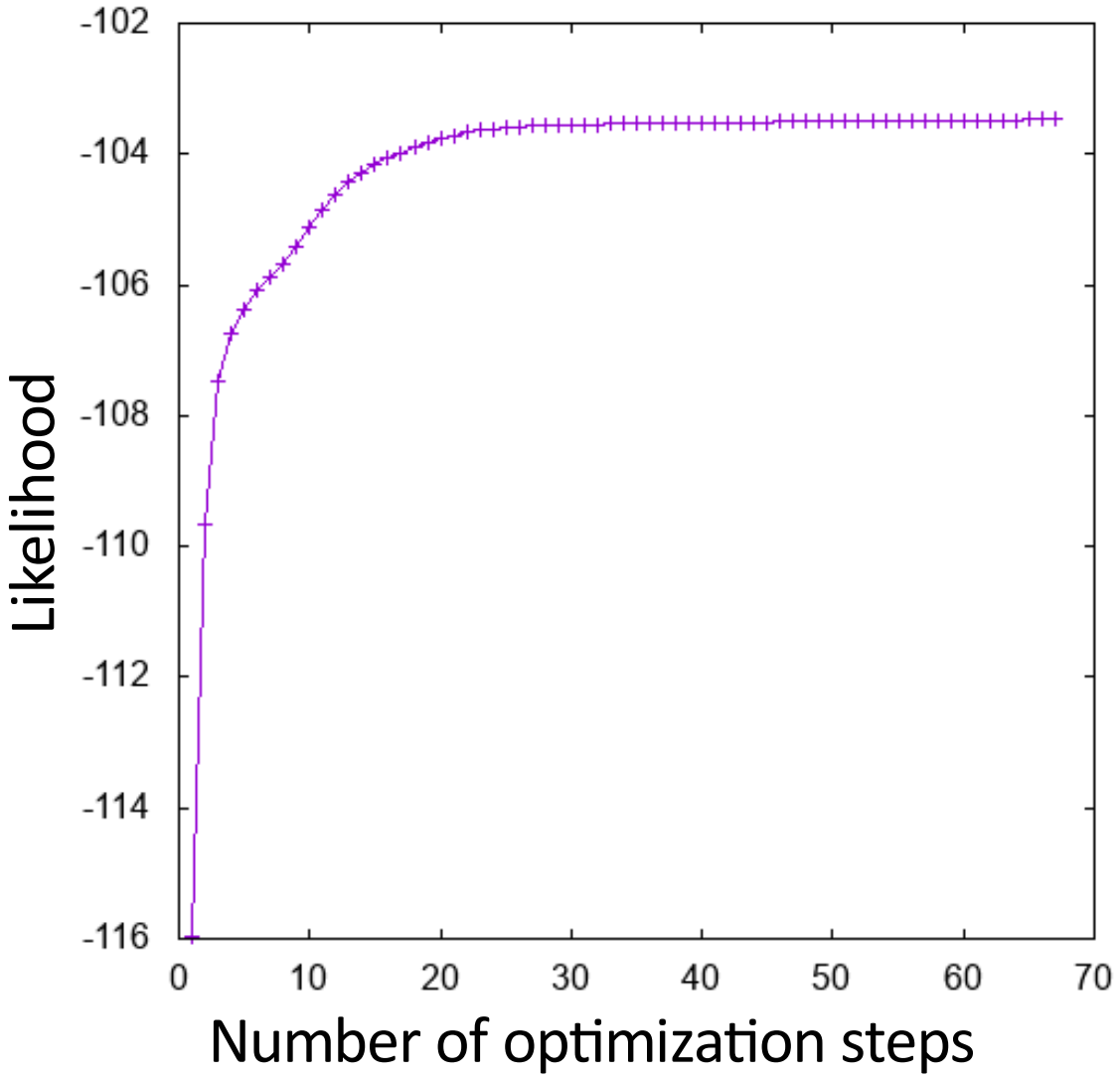
Exercise 4

- **Choose the use model option**
- **Tick the** `Save full information` **box (if you want to plot the manifold)**
- **Choose as input the file** `train_Freq_01.svm`
- **Repeat with** `<name>` **equal to** `conv1`, `conv10`, `conv20`, `conv30`, `conv40` **and** `conv50`:
  - ✔ Choose as output `<name>`
  - ✔ Choose as Model (XML) the file `<name>.xml`
  - ✔ Click the OK button
- **Report the likelihood with varying number of steps.**



Exercise 4



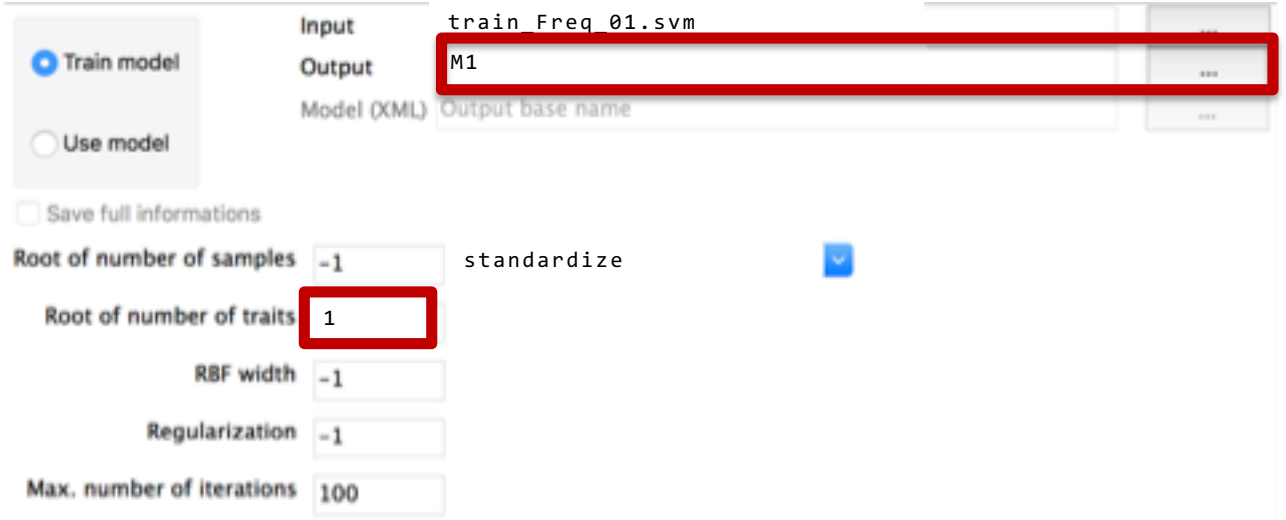

-102
-104
-106
-108
-110
-112
-114
-116
Likelihood
0
10
20
30
40
50
60
70
Number of optimization steps

Exercise 4: Conclusion

- **Convergence of the manifold monitored on the likelihood gain**
  - ✔ The likelihood difference between two consecutive steps logged as DLLmap
  - ✔ The manifold max weight difference between two consecutive steps logged as DW
- **The manifold converges faster than the likelihood**
  - ✔ Although the shape of the manifold has converged, the width of the normal distribution continue to change.
- **Next question:**
  - ✔ Are there better parameters to train the GTM?

Exercise 5

- **Create a folder named** `M`
- **Copy to this folder the file** `train_Freq_01.svm` **and** `test_Freq_01.svm`
- **Use the** `xGTMapTool` **application as** `train model`
- **Set up the input for the training set**
  - ✔ Choose as input the file `train_Freq_01.svm`
  - ✔ Choose as output the name `M1`
  - ✔ Set the **Preprocessing** to `standardize`
  - ✔ Set the value **Number of traits** to `1`
  - ✔ Set the **Max. Number of Iterations** to `100`
  - ✔ Click the OK button.



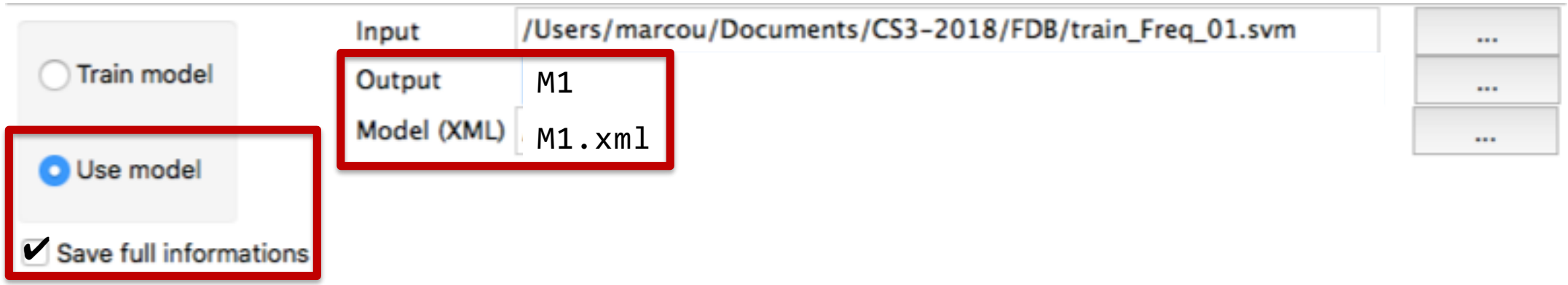
Repeat:

- **Set the** `Number of traits` **to** `5, 7, 9, 11, 13` **and** `15`
- **Set output to** `M5, M7, M9, M11, M13, M15`

Record the last step likelihood value

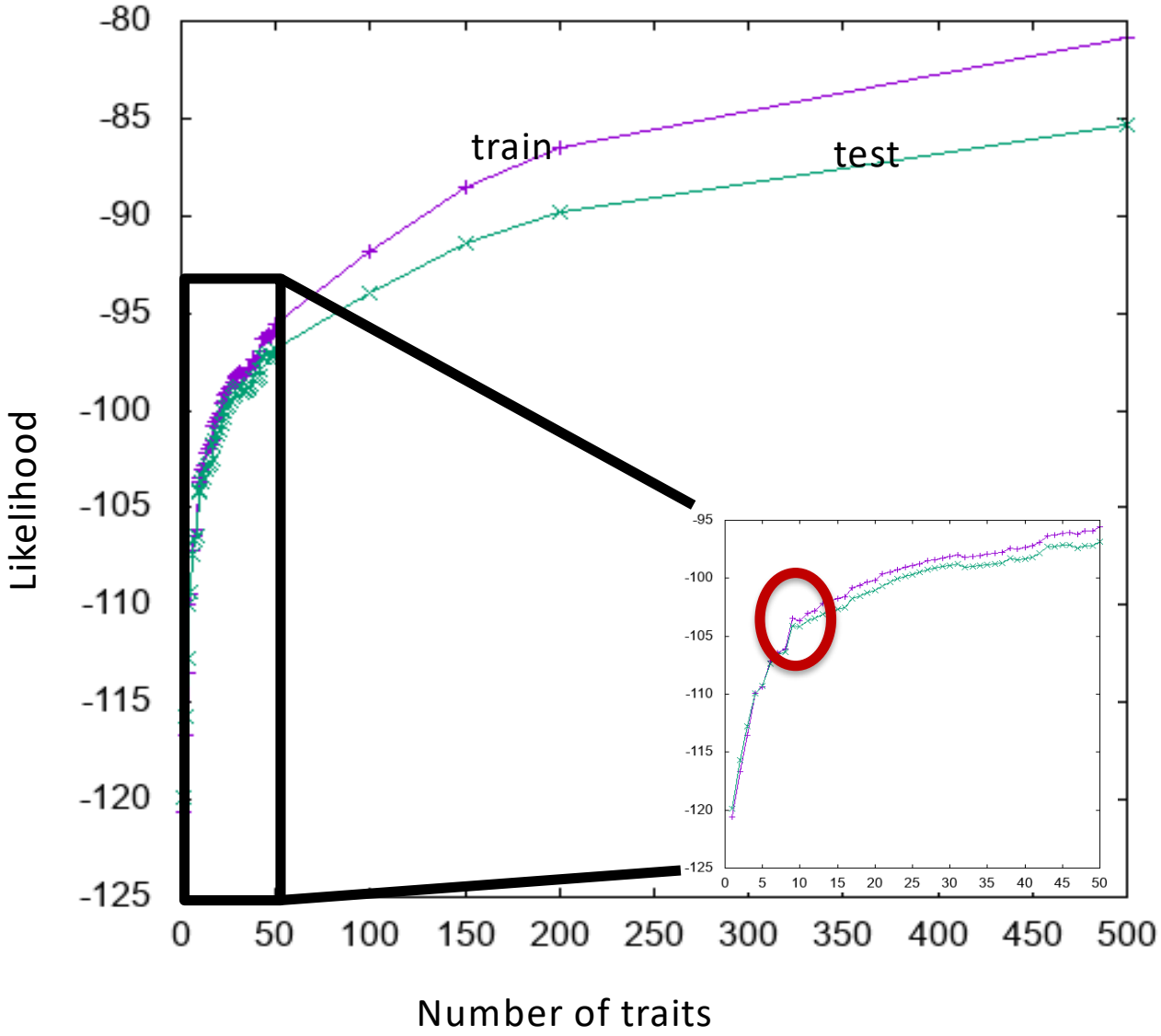
Exercise 5

- **Switch to `use model` mode**
- **Tick the `Save full information` box (if you want to plot the manifold)**
- **Choose as input the file `test_Freq_01.svm`**
- **Repeat with `<name>` equal to `M1`, `M5`, `M7`, `M9`, `M11`, `M13` and `M15`:**
  - ✔ Choose as output `<name>`
  - ✔ Choose as Model (XML) the file `<name>.xml`
  - ✔ Click the OK button
- **Report the test likelihood with varying number of traits.**



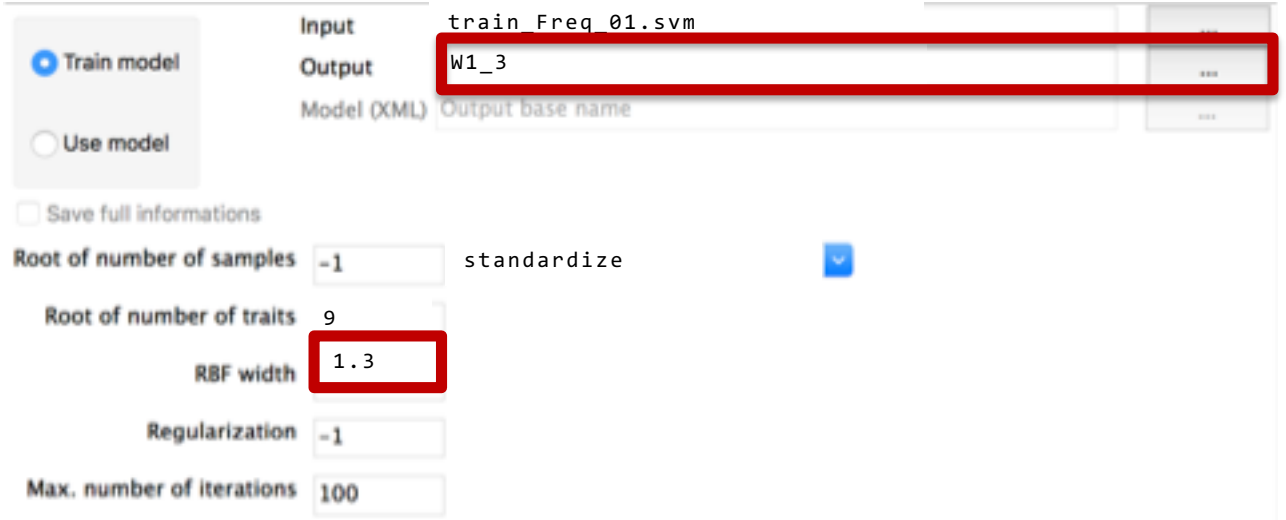
Exercise 5

- **The likelihood increases with the number of traits.**
- **Overfitting is observable as the likelihood difference between the training and the test set increases.**
- **The choice of 9 traits was motivated to prevent overfitting**
  - ✔ It is small enough for the calculation to stay reasonnable
  - ✔ But it is likely to be a bit underfitted



Exercise 5

- **Create a folder named** `W`
- **Copy to this folder the file** `train_Freq_01.svm` **and** `test_Freq_01.svm`
- **Use the** `xGTMapTool` **application as** `train model`
- **Set** `Number of traits` **to** `9`
- **Set up the input for the training set**
  - ✔ Choose as input the file `train_Freq_01.svm`
  - ✔ Choose as output the name `W1_3`
  - ✔ Set the **Preprocessing** to `standardize`
  - ✔ Set the value **RBF width** to `1.3`
  - ✔ Click the OK button.



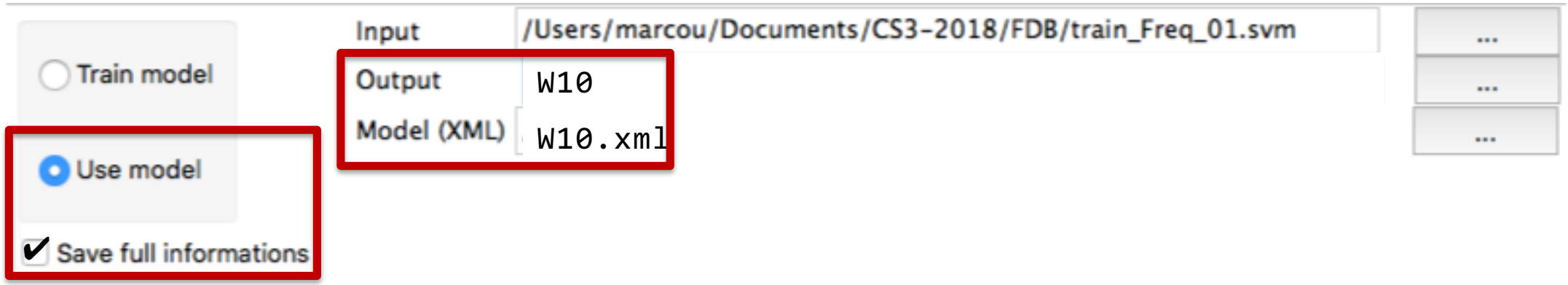
Repeat:

- **Set the** `RBF width` **to** `10, 1, 0.1, 0.01` **and** `0.001`
- **Set output to** `W10, W1, W0_1, W0_01, W0_001`

Record the last step likelihood value

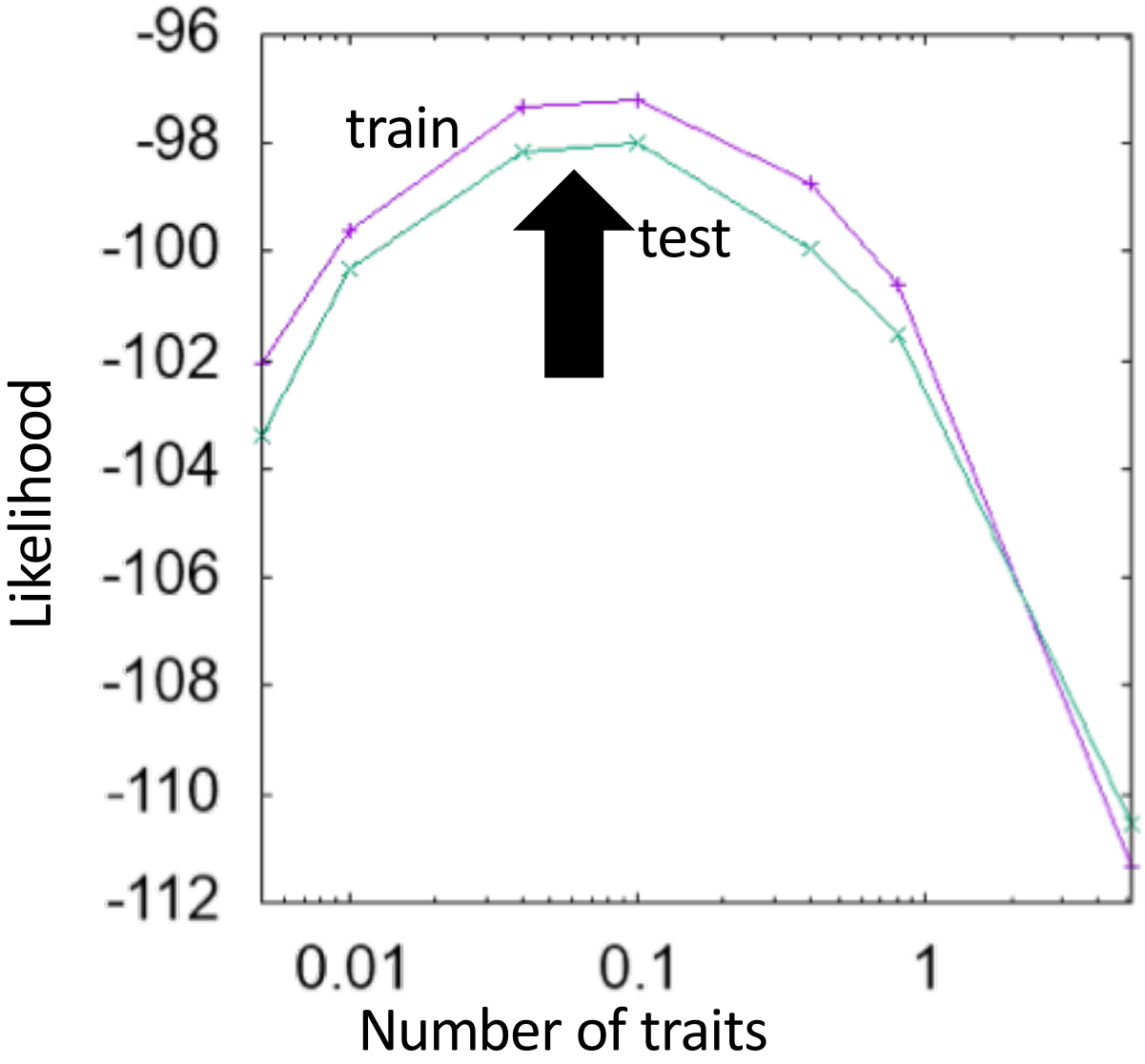
Exercise 5

- **Switch to `use model` mode**
- **Tick the `Save full information` box (if you want to plot the manifold)**
- **Choose as input the file `test_Freq_01.svm`**
- **Repeat with `<name>` equal to `W10`, `W1`, `W0_1`, `W0_01` and `W0_001`:**
  - ✔ Choose as output `<name>`
  - ✔ Choose as Model (XML) the file `<name>.xml`
  - ✔ Click the OK button
- **Report the test likelihood with varying number of traits.**



Exercise 5

- **The likelihood reaches an optimum for a width value equal `0.1`.**
- **RBF width controls the coupling of the components of the manifold**
  - ✔ Small value: manifold changes are local
  - ✔ Large value: local changes affect the manifold globally
- **Default value is set to 2 times the RBF distance on the 2D latent space.**



Exercise 5

- **Create a folder named** `L`
- **Copy to this folder the file** `train_Freq_01.svm` **and** `test_Freq_01.svm`
- **Use the** `xGTMapTool` **application as** `train model`
- **Set** `Number of traits` **to** `9` **and** `RBF width` **to** `0.1`
- **Set up the input for the training set**
  - ✔ Choose as input the file `train_Freq_01.svm`
  - ✔ Choose as output the name `L100`
  - ✔ Set the **Preprocessing** to `standardize`
  - ✔ Set the value **Regularization** to `100`
  - ✔ Click the OK button.

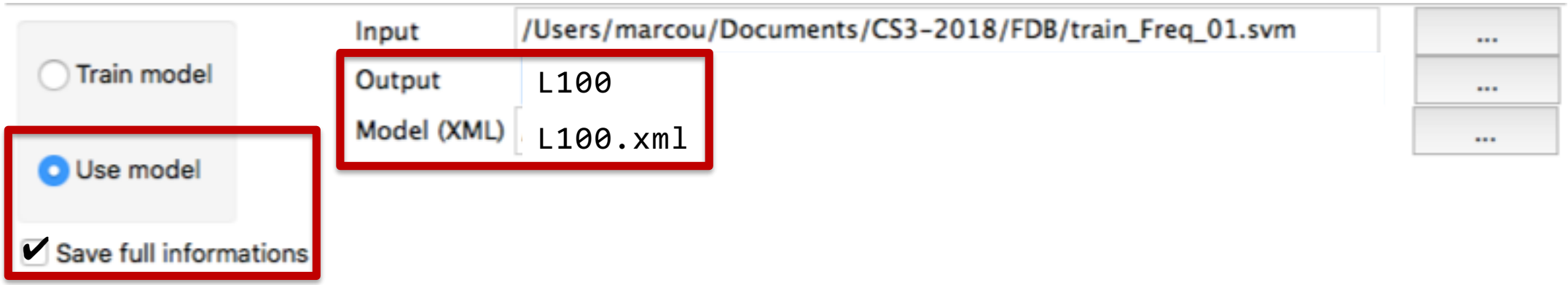
Repeat:

- **Set the** `Regularization` **to** `10, 1, 0.1, 0.01` **and** `0.001`
- **Set output to** `L10, L1, L0_1, L0_01, L0_001`

Record the last step likelihood value

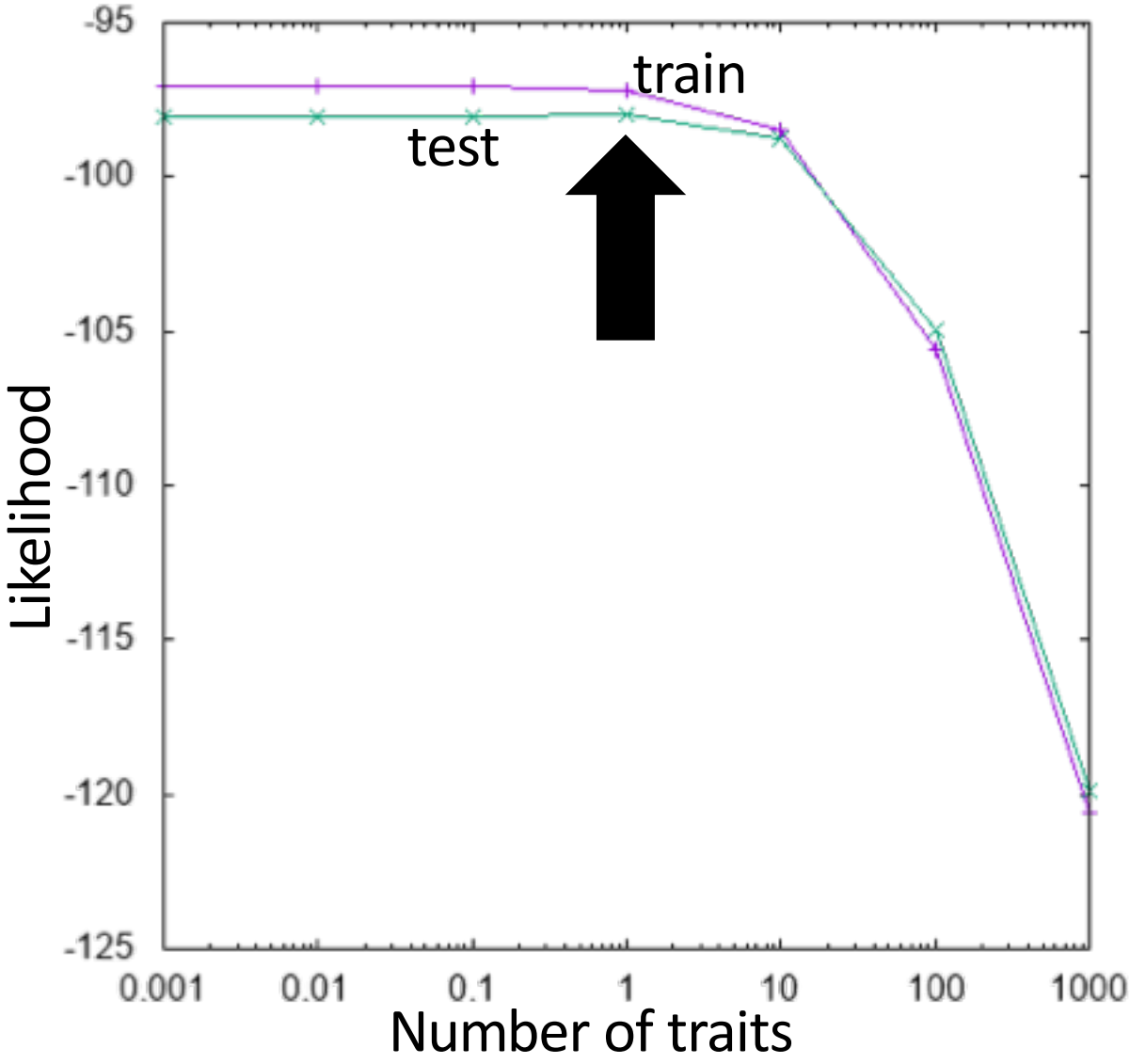
Exercise 5

- **Switch to `use model` mode**
- **Tick the `Save full information` box (if you want to plot the manifold)**
- **Choose as input the file `test_Freq_01.svm`**
- **Repeat with `<name>` equal to `L100`, `L10`, `L1`, `L0_1`, `L0_01` and `L0_001`:**
  - ✔ Choose as output `<name>`
  - ✔ Choose as Model (XML) the file `<name>.xml`
  - ✔ Click the OK button
- **Report the test likelihood with varying number of traits.**



Exercise 5

- **The likelihood reaches an ‘flat’ optimum for a regularization value equal to `1.0`**
- **Regularization controls the magnitude of the weights defining the manifod**
  - ✔ Small value: the manifold can be rugged
  - ✔ Large value: the manifold is smooth
- **Default value is set to 1.**
  - ✔ This value is connected to the most neutral assumption about weights distribution.



Exercise 5

- **Create a folder named** K
- **Copy to this folder the file** `train_Freq_01.svm` **and** `test_Freq_01.svm`
- **Use the** `xGTMapTool` **application as** `train model`
- **Set** `Number of traits` **to** `9` **and** `RBF width` **to** `0.1` **and** `Regularization` **to** `1`
- **Set up the input for the training set**
  - ✔ Choose as input the file `train_Freq_01.svm`
  - ✔ Choose as output the name `K200`
  - ✔ Set the **Preprocessing** to `standardize`
  - ✔ Set the value **Number of samples** to `200`
  - ✔ Click the OK button.

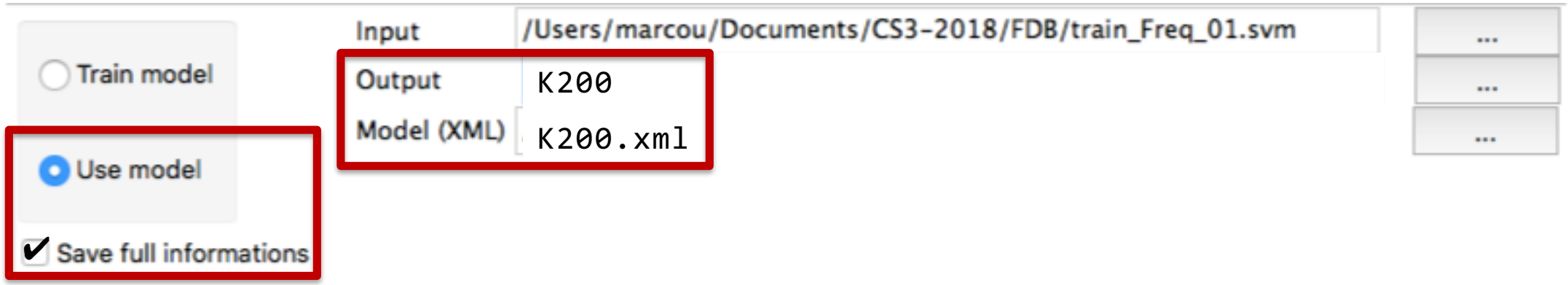
Repeat:

- **Set the** `Number of samples` **to** `200`, `300`, `400` **and** `500`
- **Set output to** `K200`, `K300`, `K400`, `K500`

Record the last step likelihood value

Exercise 5

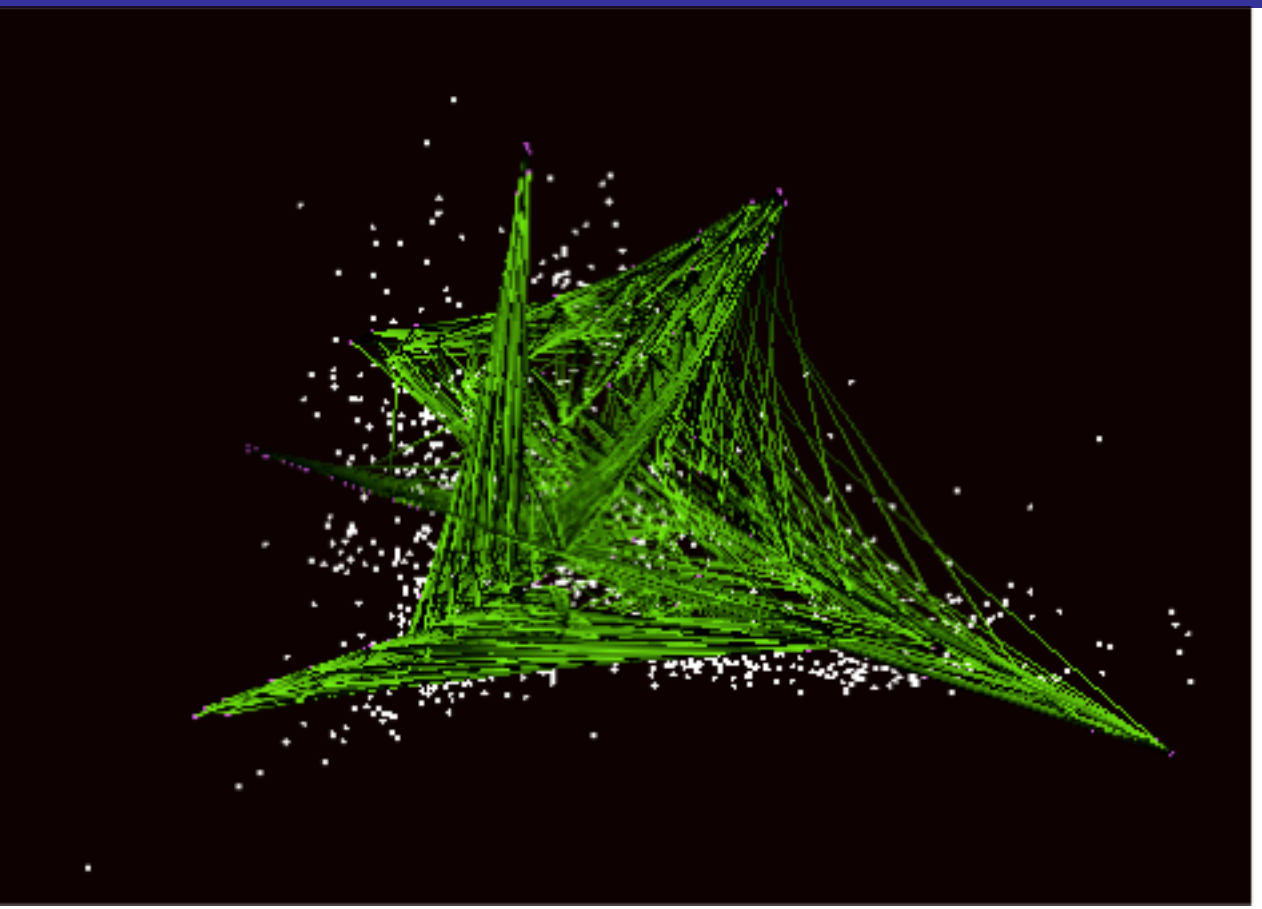
- **Switch to `use model` mode**
- **Tick the `Save full information` box (if you want to plot the manifold)**
- **Choose as input the file `test_Freq_01.svm`**
- **Repeat with `<name>` equal to `K200`, `K300`, `K400`, and `K500`:**
  - ✔ Choose as output `<name>`
  - ✔ Choose as Model (XML) the file `<name>.xml`
  - ✔ Click the OK button
- **Report the test likelihood with varying number of traits.**

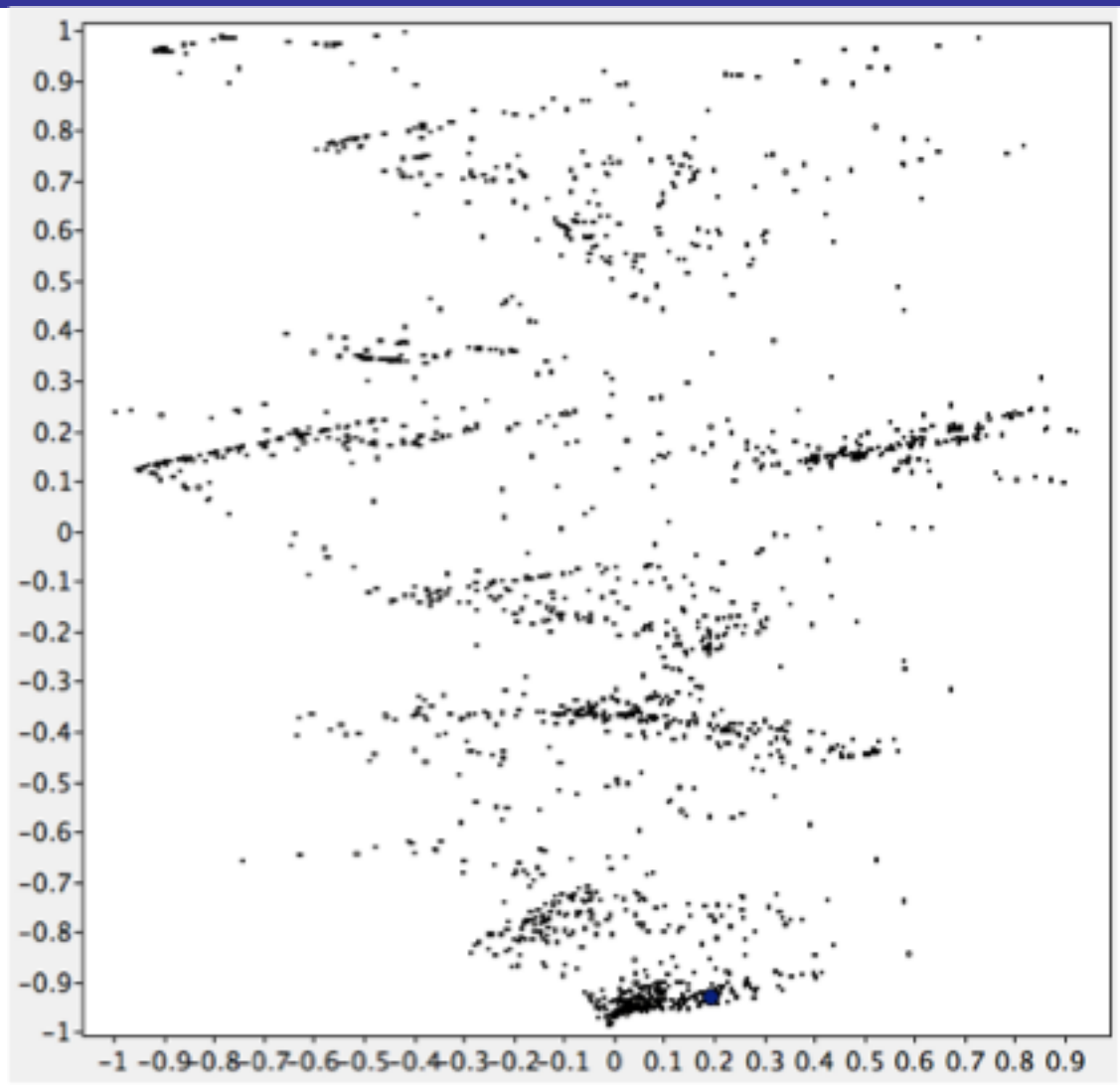


Exercise 5

- **The likelihood is independent of the number of nodes.**
  - ✔ The value oscillates between **-97.5 and -99.5**
- **The number of nodes controls the resolution of the GTM**
  - ✔ Small value: Fast to compute but few details
  - ✔ Large value: Slow to compute but more detailed map
- **Default value is set to 25 times the number of RBF.**
  - ✔ The number of nodes cannot be less than the number of RBF
  - ✔ A minimum number of nodes is needed to ensure a correct estimation of the Likelihood

Exercise 5





GTM parameters:
Number of RBFs=9
Number of nodes=500
RBF width=0.1
Regularization=1.0

Exercise 5: Conclusion

- **Modification of the parameters deeply impact the GTM**
  - ✔ The main parameter is the number of traits (RBFs)
  - ✔ The number of traits reflects the number of chemotypes to resolve
- **Default parameters use efficient heuristics**
  - ✔ They lead to underfitted models
  - ✔ Change of these parameter can induce overfitting
- **In terms of likelihood, optimum of the parameters are shallow**
  - ✔ No need of intensive optimization procedure

Conclusion

- **This tutorial presented the Generative Topographic Mapping approach**
- **One main parameter to set: the number of traits (RBFs)**
  - ✔ In this sense it is more simple than many dimensionality reduction algorithm, including SOM
- **The GTM is easily interpretable**
  - ✔ Visualization of the manifold
  - ✔ Coloration of the projected molecules
  - ✔ Property landscapes (not treated in this tutorial)
    - **And QSAR modeling…**

Perspectives

- **Analysis of a Chemical Libraries depends on**
  - ✔ Chemical Descriptors
  - ✔ Similarity measures
- **Why do you need to analyze your Chemical Library**
  - ✔ Looking for outliers – unusual data?
  - ✔ Sampling a Chemical Space region of interest?
  - ✔ Need to explore as many hypothesis as possible?
  - ✔ "To boldly go where no chemist has gone before?"
- **Chemical Library analysis is easier with visualization tools**
  - ✔ Self-Organizing Maps
  - ✔ Generative Topographic Maps
    - **PCA, Sammon mapping, Molecule Cloud, Scaffold Keys, Scaffold Trees**

Thanks

Université de Strasbourg