Comprehensive Descriptors

For Structural and

Statistical Analysis

CODESSA PRO

User’s manual

by

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**INTRODUCTION**

CODESSA PRO is an entirely new software package, which performs tasks similar to CODESSA, but with many distinct advantages over the previous software package. In particular, its add-in mechanism makes CODESSA PRO expandable, its calculation engine has been optimized at the assembly language level for Pentium, Pentium Pro, Pentium II, Pentium III and Pentium IV processors, and finally, it has been designed to run in 32-bit Windows environments. CODESSA (Comprehensive Descriptors for Structural and Statistical Analysis) PRO is a comprehensive program for developing quantitative structure/property relationships (QSPR), integrating all necessary mathematical and computational tools to (i) calculate a large variety of molecular descriptors on the basis of the 3D geometrical and/or quantum-chemical structural input of chemical compounds; (ii) develop (multi)linear and non-linear QSPR models of the chemical, physical or biological properties of individual compounds (non-linear QSPR models are still in preparation); (iii) perform cluster analyses of the experimental data and molecular descriptors; (iv) interpret the developed models, and (v) predict properties for compounds previously unknown or unavailable.

This manual presents the guidelines for the successful development of a QSAR/QSPR models using the CODESSA PRO program. The execution of each step of the program normally requires knowledge of the proceeding steps, and the steps are therefore discussed in the sequence in which they would be accomplished. This manual also provides further information concerning the features and methods available in the CODESSA PRO program, their purpose, and the interpretation of the results. For a more detailed description of the program and the techniques employed, please refer to the CODESSA PRO Reference Manual.

The CODESSA PRO program is designed to operate in the following Microsoft Windows environments: Windows 2000, Windows XP, Windows NT and Windows 9x. To start CODESSA PRO, double click on its icon shown above. When the program starts, the CODESSA PRO Visual Interface (CVI) window will open. Click **Calculate** on the menu-bar to open a pull-down menu, next click on the **Load storage** option to refresh the current snapshot, which is then displayed on the screen. Alternatively, the single keystroke **F5** will refresh the snapshot. Before attempting to use CODESSA PRO, it is necessary to understand some of the concepts and terminology used within the program.
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Chapter 1 Installing CODESSA PRO

1.1 System requirements:

Hardware:
---------

Processor: Pentium class systems - minimum. All processors developed hereafter by Intel Corp. are supported on the assembly level optimization. All AMD current processors work as old Pentium with higher clock frequency (no special optimization).

Memory: 128MB minimum, 256MB default tuning.

CD-ROM: A CD-ROM or a compatible DVD device is required to install CODESSA PRO software.

Other: A 3D graphics accelerator is highly recommended because of extensive use of OpenGL for presentation of molecules. 2-button mouse is required.

Software:
---------


On Windows ME, Windows 98 and Windows 95, the program works with many limitations and is tested not very well.

Operation system extensions: Internet Explorer 4.0 SP2 or newer version.
1.2 Installation instructions.

1. Place the CODESSA PRO CD in your CD-ROM drive.
2. If the windows Autorun feature is turned on, the installation options will be displayed automatically. If the installation options do not appear, open the Windows Start Menu and choose Run. The RUN dialog box opens.
3. Enter the following command in the open text box (assuming D is your CD-ROM):

   D:\setup.exe

4. Choose OK. The CODESSA PRO setup program initializes and the CODESSA PRO setup dialog box opens.
5. Follow the on screen instructions for product choice and installation.

The CODESSA PRO setup program will detect an existing CODESSA PRO installation and offer you the choice of uninstalling or keeping the older version of the program.
Chapter 2 Description of CODESSA PRO

2.1 Concepts and definitions

The use of CODESSA PRO requires an understanding of the following concepts:

Artifacts:

These are the individual files or items used by CODESSA PRO. There are four types of artifacts: structures, descriptors, properties, and models. Using the CODESSA PRO program will frequently require manipulation of single artifacts or lists of artifacts. CODESSA PRO names explicitly most artifacts (e.g. descriptors and models).

Storage:

All items that are connected with a project are stored in a single location within the file system - in the storage. To change a storage location, click Option on the main menu-bar and select Storage. The box that opens allows the user to control the storage location of structure files, correlations, descriptors, lists etc.

Snapshot (Cache File):

The snapshot (CODESSA PRO cache file) is a binary (compressed) representation of all items in storage. This file is located in the memory whenever work is being performed on the CVI module. The cache file reloads each time the CVI detects a change in the storage contents. The snapshot can be reloaded manually at anytime by opening the pull-down menu Calculate on the menu-bar, then selecting Load storage, or by using F5 keyboard shortcut.

Workspace:

The workspace is a window within the CVI that represents the snapshot, it is located in the workspace area on the top left side of the CVI frame.

Folder:

A folder is used to store lists and is similar to a directory. CODESSA PRO uses four types of folders: structure, descriptor, property, and model (correlation). Each of the first three folders has a system-generated list named All. This list will contain “ALL” of the structures, descriptors or properties for the corresponding folder. The Descriptors folder also includes system-defined descriptor lists according to group and type. A particular descriptor item may be contained in several lists. The Correlations folder contains lists for each property item in the property folder. The list is generated automatically by the system when a property item is created. When correlations are
calculated, 50 correlation items (by default) will be stored in the list that corresponds to the property.

**Structure:**

A **structure** is a representation of an individual chemical object with a precise chemical constitution. Examples of structures include a single molecule, a monomeric unit of a polymer, or a molecular complex with a definite composition. The minimum information that a structure must include is the types of atoms involved and their connectivity. Each structure must be linked with three files containing: 3-D structure, SCF, and Force information. Before a 3-dimensional structure can be input into CODESSA PRO, it must be converted to MDL *molfile* format and be optimized. The *molfile* structures are stored in the **3D MOL(MOPAC) Subfolder**, SCF output files are stored in the **SCF Subfolder**, and Force output files are stored in the **THERMO Subfolder**. SCF and Force structures will be created and properly stored automatically by the CMol3D module. See **Starting a New Project** for instructions to create each file type. It is vital that the name for a particular structure be exactly the same in each directory. Structure names must be in the form Sdddddddd.xxx and should be added in sequential order (e.g. S0000001.xxx, S0000002.xxx…), which will be produced automatically by CODESSA PRO.

**Descriptors:**

Descriptors are defined as numerical characteristics associated with chemical structures. They are derived from the structures’ chemical constitution, topology, geometry, inherent wavefunction, potential energy surface or some combination of these items. The values of a particular descriptor can be provided by the user or calculated by the CODESSA PRO program. Each descriptor value must be associated with a previously defined structure. Descriptors calculated by the CODESSA PRO program are named automatically; renaming descriptors is not recommended.

**Property:**

Property is a physical or chemical characteristic, biological activity, or other characteristic of interest. Each property value must be associated with a structure located in the Structure folder.

**Descriptor/Property Matrix:**

The descriptor/property matrix consists of descriptor (all columns except the last) and property (the last column) values. The horizontal dimension of the matrix is the descriptor/property ID sequence and the vertical dimension is the structure ID sequence. The matrix has two presentations: binary and text. The binary presentation is used for internal use, while the text presentation is optimized for import into the STATISTICA and other software package at present in the CSV format.
Current Analysis Dimensions:

The dimensions used for an analysis by CODESSA PRO are the property, the list of descriptors, and the list of the structures. All the dimensions are selected by right clicking the dimension desired; this will open a context pop-up menu, from which should be chosen make current; the one chosen will be in boldface font to indicate that it is the currently selected dimension. The default dimensions for a new snapshot file are:

<table>
<thead>
<tr>
<th>Dimension</th>
<th>Default value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Property</td>
<td>First selected</td>
</tr>
<tr>
<td>List of descriptors</td>
<td>All group</td>
</tr>
<tr>
<td>List of structures</td>
<td>All group</td>
</tr>
</tbody>
</table>

The selected dimensions are used in the formation of the descriptor/property matrix.

Correlation:

A correlation represents the results of a (multi)linear regression between a property of interest \( y \) and one or more selected descriptors \( x_i \).

\[
y = a_0 + \sum a_i x_i
\]

Correlations are composed of regression coefficients \( a_i \), a correlation coefficient \( R^2 \), a squared standard deviation \( s^2 \) and a Fisher criterion \( F \) value for the set of structures used in the derivation of the correlation. By default, each correlation is named by its number of structures \( N \), correlation coefficient \( R^2 \), crossvalidated correlation \( R^2_{CV} \) and Fisher criterion value \( F \), and squared standard deviation \( s^2 \).

List:

A list is collection of the chemical structures, descriptors, physical and chemical or other property of interest, or models (correlations). Lists can be either system type or user type. System lists cannot be deleted by the user. To select the items that it is desired to include in a new list, right click to show a context pop-up menu, and then choose create list to make a new list. To delete a list, click the list that you want to delete, right click to show a context pop-up menu, and then choose delete list.
2.2 CODESSA PRO Visual Interface

**Workspace:** An on-screen presentation of the current cache file.

**Work Area:** The screen space for various view windows.

**Property Window:** The property window depicts information about properties of the selected object and is available for almost all objects.

**Log Window:** The window’s purpose is protocol all operation on the storage.

**Tool Bar:** Shortcuts to commonly performed tasks. The task will be displayed when the pointer is positioned over the icon.
2.2.1 Workspace

The workspace area contains an on-screen presentation of the current cache file which is essentially a directory tree. Clicking on the minus will collapse a folder (branch of the tree) and clicking on a plus will expand a folder. When a folder is expanded (note the structures folder) it will show the lists (note **All** list) contained in the folder. The same icon is used to represent lists as folders because they are also used to contain files. If a list is empty then there will be no plus or minus beside it.

The **Structures** folder is expanded to show the list **All**. The list **All** is also expanded to show the structure artifacts. Notice the icon beside the structure artifact. Each type of artifact will have a different icon. The name that is listed will be the same as the name given on the first line of the molfile. The last structure artifact gives the filename of the molfile because the name was not entered on the first line of the molfile. Double clicking on an artifact launches a **structure view** window in the **work area**.

The **descriptors** folder is expanded to show the **All, External, and Constitutional** lists as well as several other descriptor artifacts. The **All** list is in boldface font because it is the currently selected analysis dimension for descriptors. Notice the descriptor icon is different from the structure icons pictured above. If an artifact is selected, its color will change from black to blue.
The **Properties** folder is expanded to show the **All** list and several property artifacts. Notice that the fifth property is in boldface font, which indicates that it is the property dimension currently selected. Notice the icon used to represent property artifacts. The name of the property artifact is the same name given on the first line of the property (P0000005.prp) file. As you can see in the picture, the first four property files are named “<insert name of property here>”. This is because all these four property files are presently empty, therefore the first line of these property files is now “<insert name of property here>”. You can alter the property files’ name by double click the current name and then changing it.

The **models** folder has been expanded to display several lists and artifacts. A list is created automatically for each property artifact. If the pointer is held over a correlation artifact, the details of the artifact are displayed. Double clicking on an artifact launches **correlation view**.
2.2.2 Work Area

2.2.2.1 Structure View Window

Double clicking on a structure artifact in the structures folder opens a structure view window in the work area. Structures are 3-dimensional and can be viewed as wire-frame, ball and stick, CPK surface, solvent accessible surface (SASA), Zefirov’s charges on SASA (solvent accessible surface area) and MOPAC charges on SASA(solvent accessible surface). Right clicking inside the window opens the view and label context pop-up menu. Selecting view provides the six options mentioned above, and the label identifies the number or the type of each atom. When the pointer is positioned over the view window, it changes to a 4-sided arrow that can be dragged to rotate the structure.
2.2.2.2 Correlation View Window

Double clicking on a correlation artifact opens the correlation view window. The graph shows the observed (experimental) values versus the predicted values of the property in question. When the window is first opened, all the points for outliers will be blue rather than yellow. The color of the points will change to blue to indicate they have been selected. Clicking once on a point will display its properties and their associated values in the properties window. Double clicking on a point will open in the work area a structure view window, for the structure that corresponds to that point. Right clicking the window will open a context pop-up menu that will give the opportunity to show structures, show descriptors, create Sublists, mark outliers and mark non-outliers as desired.

Double clicking on a descriptor artifact will also open a correlation view window. The window will show the relationship between the descriptor and the property dimension selected. The value predicted according to any model chosen maybe viewed by selecting that model, clicking the view pull-down menu, and then choosing predicted properties. This will display the observed property values, predicted property value and errors.
2.2.3 Property Window

The item selected determines the contents of the property window. If a folder or list is selected in the workspace, the number of artifacts contained is displayed. If an artifact is selected, the property window will provide varying information, depending on the type of artifact.

The picture on the left shows the information given in the property window when a structure artifact is selected. It will also show the experimental value and calculated value of the property of the current structure, which are not shown in the picture now.

The picture shows the information provided when a descriptor artifact is selected in the workspace.

When a property artifact is selected, information from the prp file is displayed. This includes name, comments and the number of structures.

The property window for correlation artifacts lists the details of the correlation. Details displayed include the properties used in the correlation.
2.2.4 Log Window

The log window describes each operation that has been performed on the storage. Double clicking on a correlation in the workspace will give a full description of the correlation (as pictured below). The text is in RTF format and can be cut and pasted directly into a word processing program.

The edit pull-down menu has options to select all log, copy from log, paste to log and clear all log. Transferring the information for several correlations to a word processing program can be accomplished by clearing all log, double clicking on each of the correlations, then clicking select all log, finally copy from log.
Chapter 3 Using CODESSA PRO to start a new project

3.1 Creating a new folder for the new project

You can select the drive on which it is desired to save the data, and then make a new folder which can be named either by project number or any other way of your choosing.

3.2 Creating a storage list

You have two choices for creating a storage list, either one for many projects or just for one individual project. If you decide to use a single storage list for many projects, you must keep an index of the structure and molecule names. Although a general storage for many projects allows a research group to avoid repeating the calculations of structures and descriptors as well as to minimize the amount of storage space used, we strongly recommended the use of separate storage list for each project.

To create storage for a new project, click the option pull-down menu, click storage, and browse to find the folder that has just been created for your storage. Then, click OK to close the window. Now, in the project folder you will find a subfolder list, an example of which appears in the following picture. You can name each folder in many desired manner or use the default names which shown in the shaded area.
All the storage subfolders should be empty before starting any optimization or calculation. First, you need to prepare .mol files of your structures and save them either in the MOL subfolder or in a location of your choosing. Keep in mind, no matter how you name your .mol files, whenever you run CODESSA PRO, the program will automatically name the files as Sddddddd.mol.

### 3.3 Preparing storage

Compared with old CODESSA, a major enhancement achieved by CODESSA PRO is that CODESSA PRO is highly automatic, and this obviates manual storage preparation.

Since you already have all the .mol files of all the structures, if you save your .mol files in the MOL Subfolder, pressing F5 keyboard shortcut automatically prepares all the data which are necessary for doing correlation. If the location of your .mol files is different, then select the edit pull-down menu, choose add structure, browse for the folder where your .mol files are located and click ok.

The process through which CODESSA PRO prepares all the data, except property files, is divided into 11 stages. Each of these 11 stages is performed automatically in sequence by CODESSA PRO.

#### Stage 1

This is the first model building stage. The program applies simple molecular mechanics preoptimization and transfers the 2-dimensional structures from the MOL subfolder to the 3-dimensional structures that will be stored in the 3D MOL (Molecular Mechanic) subfolder. Missing hydrogen atoms are added according to the formal valence rules. The model building is done deterministically for the first iteration and stochastically for subsequent iterations.
Stage 2
This stage is concerned with the conversion of the file from MDL MOL format in the 3D MOL (Molecular Mechanic) subfolder into the MOPAC input file format for preliminary geometry optimization in the MOPAC Optimization (step1) subfolder.

Stage 3
This stage performs the preliminary geometry optimization using CMOPAC (MOPAC Version 7 clone). If the gradient is less than 5.0, the program automatically proceeds to Stage 4. If the gradient is more than 5.0, then the program automatically goes back to Stage 1 and starts model building again, stochastically. This process is continued up to 10 times until the optimization stage passes on the criteria of the gradient value being less than 5.0. If success is not achieved after 10 iterations, then program stops.

Stage 4
During this stage, the program converts the MOPAC output files in the MOPAC Optimization (step1) subfolder into a MOPAC input file for precise geometry optimization, and stores them in the MOPAC Optimization (step2) subfolder.

Stage 5
CODESSA PRO is performing precise geometry optimization at this stage. If the gradient value can be reduced to less than 0.5, then the program proceeds automatically to Stage 6. If the gradient is more than 0.5, then CODESSA PRO goes back to Stage 1 and does model building again, stochastically. This process is continued up to 10 iterations until the gradient value test for the precise optimization is satisfied. If 10 iterations are unsuccessful, the calculations are stopped.

Stage 6
At this stage, the CODESSA PRO program converts the MOPAC output files in the MOPAC Optimization (step2) Subfolder into MOPAC input files for calculation of molecular properties. It is possible to do this without calculation of the Hessian matrix. The resulting MOPAC input file is stored in SCF Subfolder.

Stage 7
Next, at stage 7, the CODESSA PRO program produces a set of molecular properties calculated using CMOPAC. MOPAC input files. The resulting output files are stored in the SCF Subfolder.

Stage 8
Next, CODESSA PRO program takes the molecular geometries in the MOPAC Optimization (step2) Subfolder, prepares MOPAC input files for force calculations, and stores them in the THERMO Subfolder. At this stage keyword ROT=1 is added, which is valid for C1, CI, and CS groups of symmetry (This applies to almost all organic molecules). However, If molecular symmetry is different from point groups C1, CI, and CS mentioned above, the keywords need to be edited manually. To achieve manual
editing, open the .mni files in MOPAC Optimization (step1) Subfolder or MOPAC Optimization (step2) Subfolder with Notepad or Wordpad, and then add the desired keywords.

Stage 9

At this stage, CODESSA PRO program calculates the molecular properties using the Hessian matrix ("force" calculation). The state of the molecule is determined using the signs of eigenvalues of the Hessian matrix. If the molecule are in a transition state, than the program goes back to Stage 1 and restarts by using stochastic addition again. If the molecule is in its ground state, then go to Stage 10. If 10 iterations are unsuccessful, stop calculation.

Stage 10

This stage will be reached only in situations when all mentioned the geometry tests above are satisfied. At this stage, the MDL MOL file in the 3D MOL (MOPAC) Subfolder is formed, based on formal connectivity information from the MDL MOL file in the MOL Subfolder, and atomic coordinates from the MOPAC output file in the MOPAC Optimization (step2) Subfolder.

Stage 11

CODESSA PRO takes all MDL MOL files in the 3D MOL (MOPAC) Subfolder, the MOPAC output file in the SCF Subfolder and the MOPAC output file in the THERMO Subfolder to do descriptor value calculations. The resulting text file with descriptor values is stored in the Descriptor’s Subfolder. All intermediate files are deleted from storage at this stage. Only MDL MOL files in the MOL Subfolder and the 3D MOL (MOPAC) Subfolder, and MOPAC input and output files in the SCF Subfolder and THERMO Subfolder remains.

If the calculation cycle is not finished at Stage 1, changes can be made to the files at the last successful stage manually (usually it is editing of MOPAC keywords) and the calculations restarted. If four files (MDL MOL files in the MOL Subfolder and the 3D MOL (MOPAC) Subfolder, and the MOPAC output files in the SCF Subfolder and the THERMO Subfolder) are present and up-to-date, no further calculation will be done. The up-to-date state is defined using the modification time of the files. In case it is not, the calculations will be processed starting from the most recently corrected file. To invoke the recalculation, select from the menu Calculate/Load Storage (F5) or Calculate/Descriptors (F6). In the last case, only problematic structures which show in MOPAC Optimization (step1) Subfolder and MOPAC Optimization (step2) Subfolder will be recalculated. If the problems arise as a result of a structure’s improper format, you must redraw the structure in the MOL Subfolder.

Note:

Before a correlation is run, you should check if everything in the storage is ready. All subfolders in the storage should be empty except the following:

1. **MOL Subfolder**- this subfolder should contain all .mol files of all structures.
2. **SCF Subfolder** - this subfolder should contain only .mni and .mno files of all structures.

3. **THERMO Subfolder** - this subfolder should contain only .mni and .mno files of all structures.

4. **3D MOL (MOPAC) Subfolder** - this subfolder should contain only .mol files of all structures which are different .mol files from the mol files present in the **MOL Subfolder**.

**Preparing property files**

If the above is accomplished satisfactorily, the final requirement prior to correlation is to prepare the property files. On the CODESSA PRO window, click the **edit** pull-down menu and choose **add property**. Then you input the name, comment, and property value according to the format which is indicated in the notepad, and finally, use the **F5** keyboard shortcut for CODESSA PRO to load the data.

**3.4 Calculating the correlation.**

Ensure that structures, descriptors, and properties of interest are selected (they should all appear in boldface font). If not, right click the name of structures, descriptors or property to show a context pop-up menu, then select **make current** to highlight them. Click on the **calculate** pull-down menu and choose HMPRO, or just press the **F9** keyboard shortcut instead. The correlation will be finished automatically by CODESSA PRO. If you just want to calculate descriptors, then click on the **calculate** pull-down menu and choose **descriptors**, or press the **F7** keyboard shortcut instead. You can also choose **form matrix** which in addition to descriptor calculation will also form a matrix. You can limit the maximum number of descriptors for your model by clicking on the **option** pull-down menu, choosing HMPRO, clicking **expanding**, then inputting the maximum number of descriptors you permit in your model.

**3.5 Viewing correlations**

When the correlations are finished, you just double click **model** and all the models respond to each property file will show up. Then you double click the model that you want to take a look to open the **correlation view window** (see page 17).

**3.6 Printing your results.**
Use **print** from the **file** menu bar to print the correlation plot from the **work area**. To print information from the **log area**, follow the instructions given on page 19 and then print from the corresponding word processing program.

### 3.7 Manipulating lists

CODESSA PRO automatically produce one or more lists in each folder, but when analyzing a property or correlation, it is sometimes helpful to create a user-defined list, e.g. a list of structures containing phenyl rings. The simplest method for creating a list in CODESSA PRO is to select several artifacts from one or more existing lists (i.e. all), right click to open the context pop-up menu and left click on **create list**. A list can also be formed from a group of artifacts that are linked to a **common** artifact. If a descriptor is chosen to be the **common** artifact, then all the structures that are defined for that descriptor could be selected for a list. To create the list from a **common** artifact, open the context pop-up menu, click on **Select Linked**, and then select the type of artifacts that you want to add to the list. To create a list from multiple **common** artifacts, select the list that is created corresponding to each **common** artifact, then perform the **AND** operation (see below).
The List Logic module in CODESSA PRO compares the artifacts contained in two lists and can be opened by clicking any artifact, right clicking to show the context pop-up menu, and choosing lists logic, or just using the F4 keyboard shortcut instead. Choose the type of artifact that will be contained by the list by clicking on the appropriate button in the Sub-List Type box (descriptors is selected in the example above). Choose the desired lists for comparison and the appropriate Operation. The artifacts from the two lists that meet the criteria of the operation will be displayed in the Results box. The results can then be copied to a new list (Create) or be selected (Select) for further comparison. When comparing three or more lists, first compare two of the lists, click on Select, restart List Logic, select Current Selection in The First List box, then select the remaining list in The Second List box.