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marvin: A Platform for Chemoinformatics Software Development

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Abstract: A strategy for a new type of platform for chemoinformatics software development and its first implementation are presented. The basic task of such a platform is to apply sequences of computational methods to high numbers of molecules. The implementation presented is based on four major components: (a) the application manager, responsible for running programs and for data management; (b) executable applications that supply limited pieces of functionality; (c) syntax definitions for data and control files and (d) the runtime library which comprises routines for data handling and user interface. This simple concept is implemented in the software package ***marvin***. Different computational methods are available within ***marvin***, including parts of commercial software packages (e.g. molecular modeling, bioinformatics, statistics, etc.) as well as newly developed and innovative algorithms. The basic layout of ***marvin*** is described and a simple example illustrates its application.

Keywords: chemoinformatics, software platform, chemical similarity assessment, data management, drug discovery

Introduction

Recent developments in automation of chemical synthesis and biochemical screening have resulted in a fundamental paradigm shift in the drug discovery process [1]. Today, pharmaceutical companies are searching for new lead structures by screening huge compound libraries, including hundreds of thousands or even millions of chemical compounds against an increasing number of biological targets. This new drug discovery workflow is designated as "new technologies" or NT [2, 3]. The NT approach outputs enormous amounts of experimental results, produced by high-throughput robotic systems. On the other hand new and innovative methods of data management and molecular modeling are required in order to handle the corresponding data and to reunite the experimental results with molecular structures and with predicted molecular properties [4, 5]. These new computational methods must be able to derive properties such as three-dimensional structures, structural indices, physicochemical properties and other molecular descriptors for huge numbers of compounds in order to increase efficiency of drug discovery [6, 7].

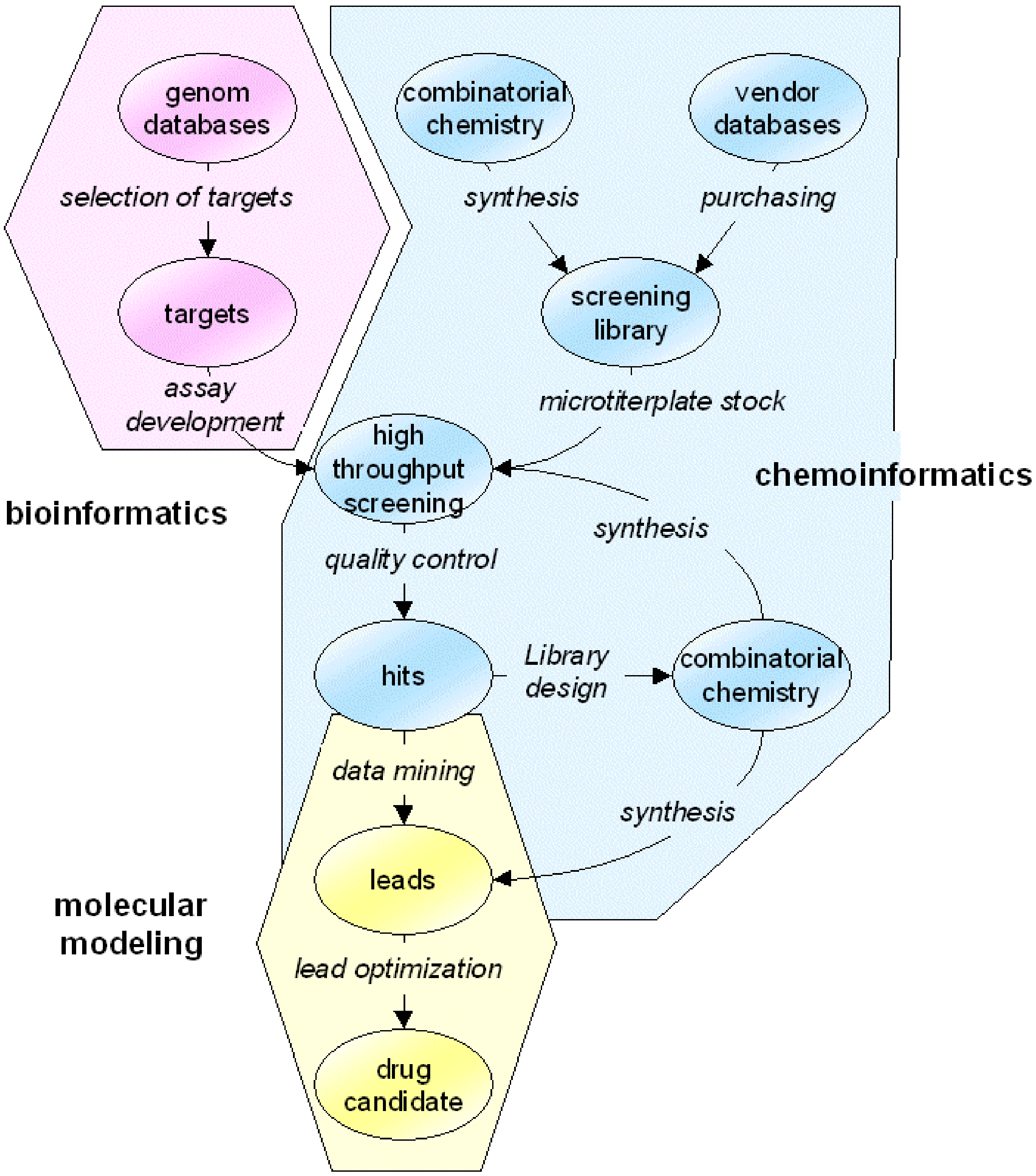
As a consequence of this development the new discipline chemoinformatics has been emerging [8-10]. Chemoinformatics combines the techniques of molecular modeling, computer aided drug design, data management and data mining and becomes an integrated part of the drug discovery process in the pharmaceutical companies today [11-13]. Major parts of the drug discovery process are supported by the new computational science (see Figure 1).

The new applications of chemoinformatics require rapid development of novel algorithms in order to solve arising problems. Typical aims addressed by upcoming chemoinformatics software involve huge numbers of screening data and huge numbers of molecular structures. The screening laboratories output more than 100,000 points of data every day [14]. The number of compounds in the compound stocks already exceeds the magic number of one million. Combinatorial libraries comprising more than 10,000 compounds are synthesized [15]. Virtual combinatorial libraries already contain more than 10 million compounds. Future computational algorithms must be able to apply molecular modeling methods to these compound libraries in order to find typical patterns in structural space, in pharmacological space or in property space [16]. Chemoinformatics software is set up to compute properties, such as physico-chemical properties [17], lipophilocity or drug-likeness [18] as well as molecular and structural descriptors [19, 20] for huge numbers of molecules. Data-mining techniques are applied to correlate descriptor similarity to chemical or biological similarity.

In the last few years the development in drug discovery was mainly driven by automation techniques - as a consequence the computational methods must now follow quickly. Major developers of commercial molecular modeling software are addressing the new problems by adding chemoinformatics modules to the software packages. However commercial solutions suffer from the limitation to proprietary computational methods and on complex data management systems.

In contrast, the concept implemented in the software package ***marvin*** [21, 22], is very simple and open. It represents a first example for a platform that allows very fast development of innovative chemoinformatics algorithms by combining the functionality of newly developed programs with modules from existing molecular modeling software packages. Beyond this, ***marvin*** provides completely automated setup and testing as well as automated application of the new methods to current data sets. Because of its very simple basic concept, the strategy can be implemented very fast on any computational platform. Because of its open interface, a multitude of modules and computational methods is available at once. Because of its modular concept, only small parts of any new chemoinformatics algorithms must be developed from scratch - most parts of the algorithm can be imported by interfacing software packages that already exists.

Figure 1: Simplified scheme of the preclinical drug discovery process. Every step in the workflow is accompanied by computational sciences. Bioinformatics is an important tool for target finding and target validation. Molecular modeling methods are used mainly in the lead optimization cycles. Chemoinformatics supports a major part of the process with property calculations, similarity assessment, data management and data mining.



Basic strategy

The basic idea of ***marvin*** is to automatically run a sequence of computer programs on a number of compounds. The functionality of the entire sequence is called *algorithm* in the context of ***marvin***. The single programs are addressed by the term *application*. Therefore, a ***marvin*** algorithm is built up by putting together applications and running them on molecules. ***marvin*** is only the integration platform that links together all pieces of data and software needed in a chemoinformatics project.

marvin *as a black box*

Because of the high level of automation, any ***marvin*** algorithm can be applied as a black box: Chemical structures are used as input and results of the entire study are presented as output. Usage as a black box is an important demand on an integrated chemoinformatics software solution, because applying a variety of computational methods, implemented in different software packages on different computational platforms, to millions of compounds would be a very time consuming job. High efficiency and fast application of computational methods however, is one of the major preconditions for chemoinformatics software within the strategy of NT drug discovery.

The concept of ***marvin*** allows manual setup and flexible optimization of an algorithm. Once it is tested and validated, even a complex algorithm can be run at the touch of a button without any user interaction until the final result is presented.

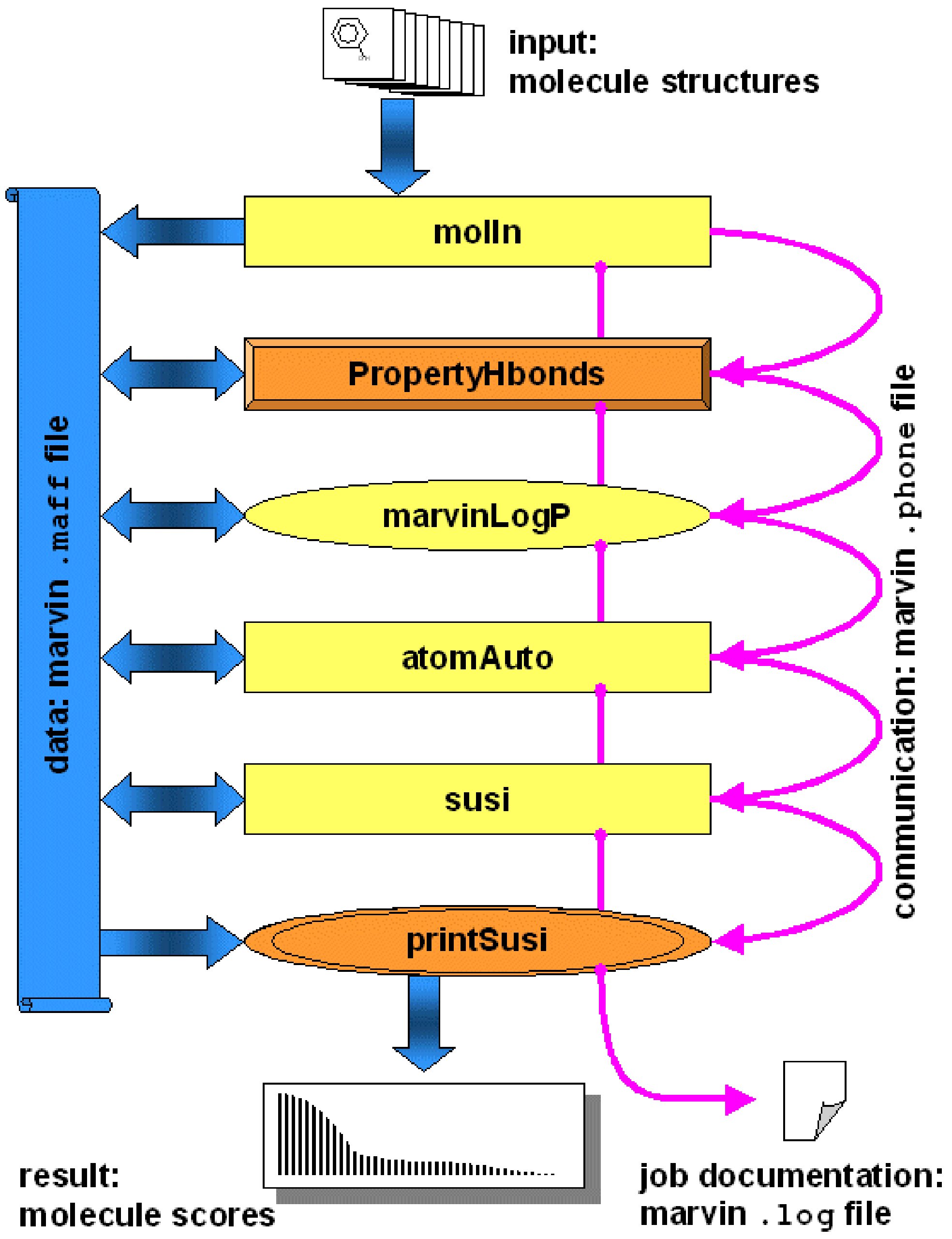
marvin *as a box of bricks*

Looking inside the black box, ***marvin*** presents itself as a box of bricks (see Figure 2). All applications - the modules of the algorithm - are built up based on a small number of precisely defined interfaces. These interfaces are data file formats and communication file formats, handled by ***marvin*** library functions. All communication between applications is performed via these files. This is why all applications can be designed individually and every application can be used together with any other one. There is no need to interface modules from different software suppliers - as long as integrating of the single modules into the integration platform is simple.

Before running an algorithm on this file based platform, the global setup file, that holds all runtime parameters for all applications of the algorithm, must be created. The library functions read this setup file and pass the parameters to the corresponding applications. Every application writes its output to data files which are readable by all other ***marvin*** applications. Additional inter-application communication is possible via the communication file, which is how error messages and warnings are passed from one application to another.

The status output (such as warnings and error messages) are written to a common output file that comprises a detailed documentation of the entire study. This status file is generated automatically.

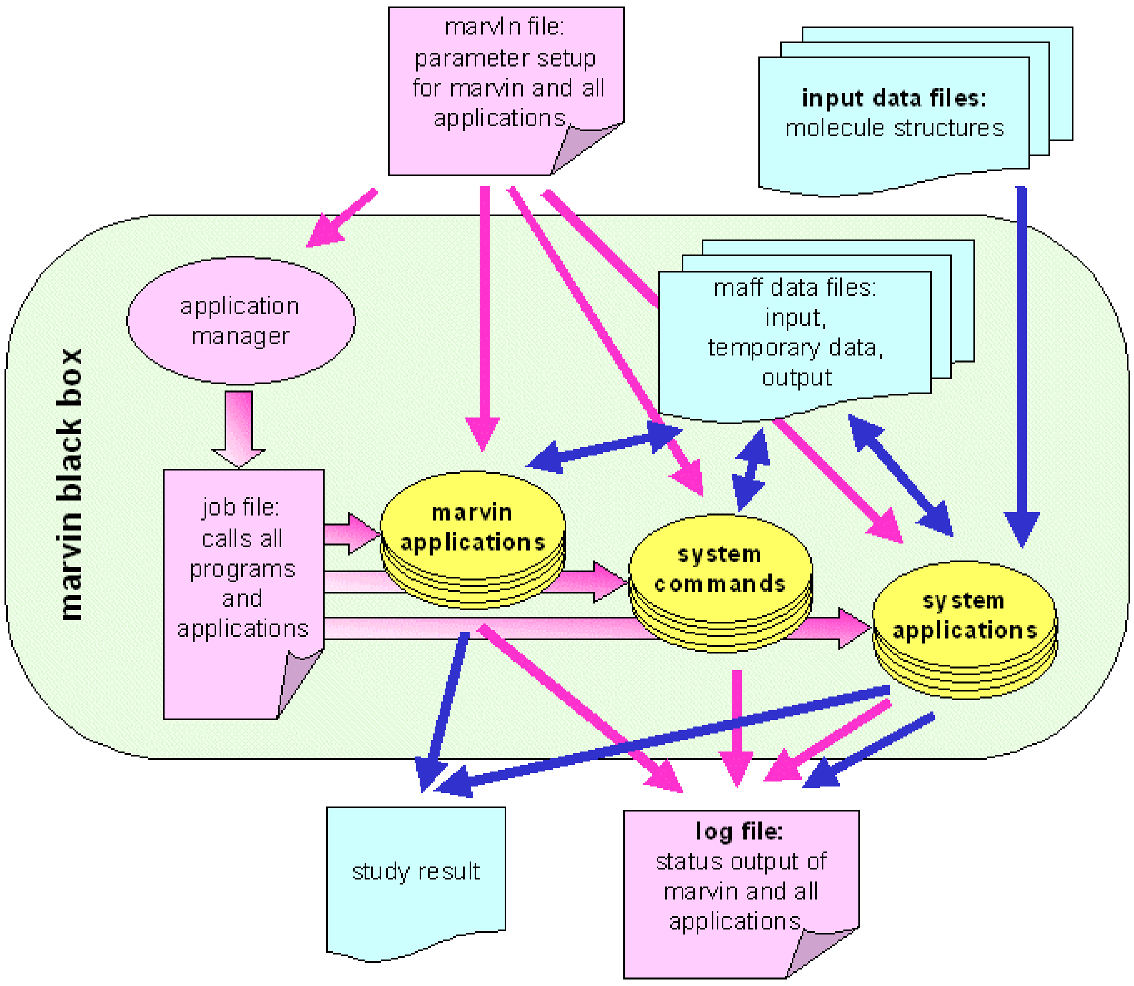
Figure 2: Visualization of the modular structure of a ***marvin*** algorithm (see Section 4 for the example study). Data sets are transferred between applications by so-called maff data files. Different types of applications, such as generic applications (displayed as yellow rectangles), interfaced applications (ovals) or high-level applications (in orange and 3D representation) are used seamlessly in order to include all functionality needed by the ***marvin*** algorithm. Blue arrows indicate data flow, magenta arrows indicate control flow.



Information flow and control flow

Input of the ***marvin*** black box are molecule structures and parameter setup files. The information flow inside the black box is controlled by the application manager (APM, see Figure 3). At start time, the APM analyzes the setup, completes application parameter sets by looking up default values and writes a so-called job file. This job file is a script that runs the current study on the specified host computers. It holds all commands necessary to run applications as well as commands needed for data management and control flow. Additional functionality includes copying files, removing files, compressing and decompressing of files, transferring files to remote hosts, partitioning data sets for parallel processing, merging outputs from parallel processing, etc.

Figure 3: Control flow and data flow of a ***marvin*** study. The user can apply ***marvin*** as a black box. Only ***marvin*** input file and study results must be handled manually. The entire ***marvin*** study runs automatically and is controlled by the APM, which reads the setup from the input file. Blue arrows indicate data flow, magenta arrows indicate control flow.


marvin file: parameter setup for marvin and all applications
input data files: molecule structures
marvin black box
application manager
maff data files: input, temporary data, output
job file: calls all programs and applications
marvin applications
system commands
system applications
study result
log file: status output of marvin and all applications

marvin modules

mavin modules are the application manager (APM), applications, file format definitions and the ***marvin*** runtime library. The application manager reads basic parameters from the input files and sets up the entire marvin job.

Applications are computer programs, which address small functional parts of an algorithm (such as generation of 3-dimensional structure from molecular topology, calculate one molecular property, etc.).

The parameter input files contain all run-time parameters for all applications and the ***marvin*** specific setup.

The marvin run-time library is used to integrate new software into the ***marvin*** system. The library functions covers functionality concerning user interface, data input and output, protocol recording and documentation.

Application manager

The minimum requirement of an application manager is to apply a number of applications to a number of molecules. Beyond this, the ***marvin*** APM works as a data management and networking module by controlling host-to-host file transfers, batch job submission, inter-application communication etc. The ***marvin*** APM is controlled by keywords given in the input files (see Listing 2 for an example). The functionality of the ***marvin*** APM includes:

Multiple run modes (single, all, list): The application manager decides whether an application is to run with all molecules or just once for all molecules or only with a certain class of molecules (e.g. special handling of ionic compounds).

Network support: The APM finds applications in a local area network or the internet and starts them on the remote host. Data files are transferred if necessary, default settings are adapted and output files are concatenated automatically.

Integration of resources: Databases and other local or remote resources are included.

Commercial software packages: Functionality supported by commercial software packages is included. External packages can be run as interfaced applications as an integrated part of any ***marvin*** study.

Innovative applications: Novel and innovative applications can be implemented in c/c++ and seamlessly combined with the interfaced applications.

File format conversions: Necessary file-format conversions are recognized and performed automatically.

Runtime parameter organization: Every application is provided with the correct parameter input from the input file.

Checkpointing and restart of studies: Already calculated results are recognized and noticed (e.g. in order to restart stopped studies or rerun with only some of the application parameters changed).

Parallelisation: Time-consuming calculations are optimized by starting multiple instances of an application in parallel. This allows "cluster-like" parallelisation on multi-cpu computer servers.

Individual applications need not to be parallelized by compiling special versions for specific host computers. Even software modules of which no parallelized versions are available (e.g. commercial software packages) can be run in parallel using this concept.

Batch processing: If processes are submitted to a batch queue, the APM waits for the completion of the job. The ***marvin*** algorithm is continued as soon as all needed results are available.

Documentation and error log: The APM generates a detailed documentation for the run of all executed applications. Errors, warnings, status output and cpu-times are reported to the ***marvin*** output file.

Optimized data management: Data files are stored in a compressed format and temporary files are removed automatically.

Fail save concepts: The APM recognizes technical problems and tries to find work-arounds or notifies the user.

Applications

marvin applications are built up as generic, as high-level or as interfaced applications.

Generic applications are programs developed for usage within ***marvin*** algorithms by linking the ***marvin*** runtime library. The functions and data types of the ***marvin*** library can be used to handle all data and parameter input and output (see Section 3.4 for details on the runtime library). Generic applications are most commonly used for external data interfaces, such as reading external file formats, or for implementing innovative computational methods.

In addition, most of the ***marvin*** system functions (such as the application manager) are implemented as generic applications.

High-level applications are defined in one of the ***marvin*** input files. High-level applications run any other ***marvin*** applications with a different set of default parameters (see Listing 1 for an example).

Interfaced applications are external software packages, integrated by using the generic application cmdLine [24] or by implementing a generic ***marvin*** interface application.

Example applications are given in Table 1. All types of applications can be used to build up an algorithm, regardless of their type.

Table 1: Example applications for use within a ***marvin*** algorithm

Application	**Type**	**Description**
Add	Generic	Performs simple arithmetic operations on datasets
AutoAtom	Generic	Calculates autocorrelation coefficients based on 3-dimensional molecular structures and atomic properties (e.g. atomic point charges or extended properties)

Application	**Type**	**Description**
AutoScale	Generic	Scaling of all data sets in a study
AtomProperty	Generic	Calculates extended atom properies (e.g. lipophilicity, hydrogen bond acceptor/donor, etc.)
CmdLine	Generic	Interface to external command processor. cmdLine can be used to run external applications from within a ***marvin*** study
Derivat	Generic	Calculates the derivative of a multi-dimensional data set
ft2	Generic	Calculates the fast fourier transformation of a multi-dimensional data set (forward real to complex and backward)
GnuPlot2	Interfaced	Interface to gnuplot [30] program for plotting ***marvin*** data sets to a terminal, file or printer
MarvinBabel	Interfaced	Interface to the molecular structure file format translator babel [25] (babel reads and writes more than 60 file formats)
MarvinMOPAC	Interfaced	Interface to the quantum chemical program package MOPAC [23]
MarvinSybyl	Intefaced	Interface to the molecular modeling software package Sybyl
Mip	Generic	Calculates the molecular interaction potential as sum of the electrostatic potential and the 6-12-Lennard-Johnes potential in a rectangular box around a molecule
MkData	Generic	Generates a multidimensional dummy test-dataset (e.g. triangle, ramp, cube...) for software evaluation and testing
MolIn	Generic	Imports two- or three-dimensional molecular structures into ***marvin*** data files
MolOut2	Generic	Exports molecule structures
NLM	Generic	Performs non-linear mapping of high-dimensional data sets into one-, two-, or three-dimensional maps
PotSelect	Generic	Applies individual scaling factors to the points of a 3-dimensional potential depending on their distance to atoms of specified types. The application is used to select regions in space around atoms or groups in a molecule molecule for further calculation.
QSARtable	Generic	Organizes data from all molecules of a study in a pivot table

Application	**Type**	**Description**
Scale	Generic	Implements several different methods for linear and non-linear scaling of data sets
Smooth	Generic	Implements several different methods for smoothing (e.g. integral-smoothing, fourier-filtering, etc.) of data sets
Susi	Generic	Calculates the similarity between a molecular structure and a cluster of structures

marvin *files*

Communication between the different applications and between applications and APM is based on text files. Formats of these files are fixed and implemented in the ***marvin*** runtime library. Most important ***marvin*** files are input files (parameter setup), data files, phone files (communication between applications) and output files.

Input files

All run-time and control parameters of ***marvin*** are given in three hierarchically organized input files. The structure of all input files follows the same syntax. The file *local.defaults* holds the host dependent settings for the local computer, such as paths to local applications, the local ***marvin*** installation, etc. (see Listing 3 for an example).

The file *application.defaults* includes all default parameters for applications. When executing an application on a remote host, the application manager copies *application.defaults* to the remote system to guarantee usage of the same settings for the entire study. High-level applications are defined in this file preferably (see Listing 4).

The file *myname.marvIn* (= **marv**in **In**put) holds the setup for the current ***marvin*** study to be run. The setup section of this file contains the sequence of applications and the list of molecules of a study. All settings can be redefined in the marvIn file (see Listing 2).

All marvin input files are plain text files. A section is defined for each application. Beginning and end of an application section are marked by the keys `%%application` and `%%end of application`. Every application reads parameters from its personal section only. The application manager makes use of the section `%%setup`. Within the sections run-time parameters are characterized by their name (e.g. `number of data points:`). Several values of different data types can be given after the colon. The scope of a parameter definition can cover one or more lines. Different types of parameters are given in Table 2. Text outside a parameter definition and text outside a section are ignored by the parameter read functions of the ***marvin*** run-time library and thus can be used for user comments.

Table 2: List of runtime parameter types used in the input file

Type	**Description**
int	one integer value
float	one floating point value
string	one word
char	one character (i.e. first character of a word, such as yes or no)
list	list of words
line	one line (starting with the first visible character after the colon; continued lines are concatenated)
files list	list of filenames (including wildcards)

Data files

All ***marvin*** applications output molecular data into a standard data file for every molecule (molecule.*maff* = **ma**rvin **f**ile **f**ormat). Maff files are text-files that store molecule date and history information in a readable form. Therefore every data file includes a brief documentation displaying the applications, used to generate these data. Listing 6 shows an example maff data file from the example algorithm described in Section 4. For optimized data management ***marvin*** allows automatic compression and decompression of data files. Maff files may contain different types of information assigned to molecules, such as molecular topology (i.e. structural formula), three-dimensional structure, additional properties of the molecule or the atoms, tables of high-dimensional data (e.g. potentials, surfaces, etc.) and comments.

Communication file

The ***marvin*** communication file (study.*phone*) allows applications of a study to communicate to each other (e.g. an application can exclude some molecules from the data set at run-time, see Listing 9 for an example).

Output file

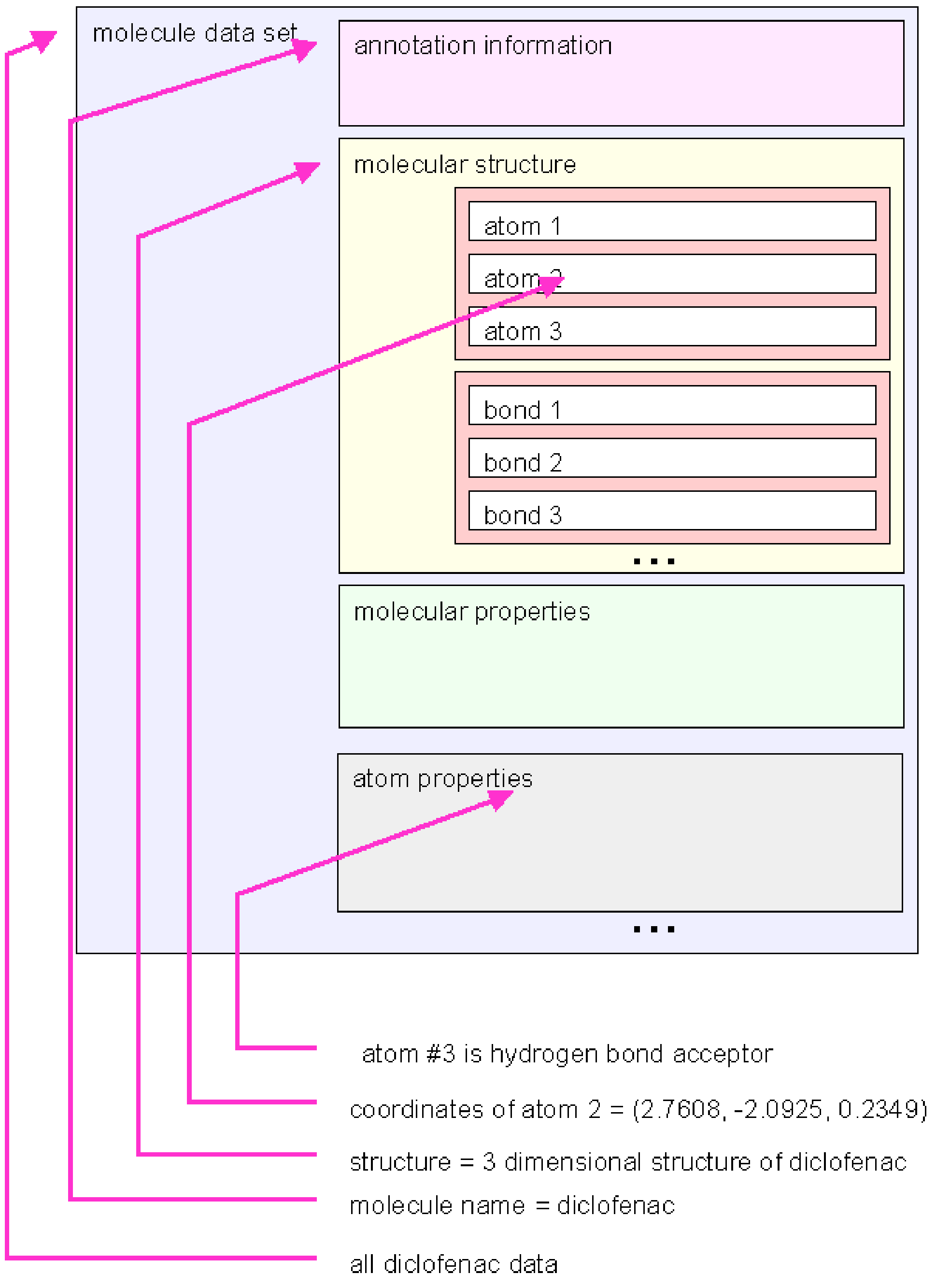
The ***marvin*** output file (study.*log*) comprises all status information from all applications, such as warnings, error messages, computation times, etc. The thoroughness of this information is adjusted by setting the `logfile size:` parameter in the `%%setup` section of the ***marvin*** input file (possible values are small, medium, big or debug, see Listings 7 and 8).

marvin *run-time library*

The ***marvin*** run-time library is a compilation of functions and data types that help software developers in implementing novel ***marvin*** applications. The library functions are designed to address problems of data handling, file handling, user interface and ***marvin*** system management.

Data structures: ***marvin*** library functions are used to accessing molecular data stored in predefined data structures. The data show the same modular structure as the data files (see Figure 4).

Figure 4: Schematic representation of a ***marvin*** dataset. The molecule data can be handled on different levels of graining. The ***marvin*** library function provide access to many types of grouped information.


molecule data set
annotation information
molecular structure
atom 1
atom 2
atom 3
bond 1
bond 2
bond 3
...
molecular properties
atom properties
...
atom #3 is hydrogen bond acceptor
coordinates of atom 2 = (2.7608, -2.0925, 0.2349)
structure = 3 dimensional structure of diclofenac
molecule name = diclofenac
all diclofenac data

Different nesting levels of variables are used to address different levels of detail of information. In the highest hierarchical level entire sets of information about one molecule are handled as one object. But the interface gives handles to more fine-grained information, such as molecular structure, molecular properties or even properties of single atoms.

Functions for data handling: The data-handling library includes functions for writing and reading data from maff data files into predefined data structures and functions for managing these data. ***marvin*** data structures include molecular data (e.g. atom coordinates, atom properties, topologies, molecular properties, etc) and high-dimensional vectors (e.g. potential fields, description vectors, etc). The functions allow accessing data in different ways, such as addressing values by index or by coordinates (see Table 3 for example functions).

User interface functions: The user interface library includes functions to read run time parameters from one of the input files. The parameters must be specified by section name, parameter name and parameter element number in the parameter list. The routines are searching all ***marvin*** input files for the demanded parameter hierarchically: If the parameter is not found in the setup of the current job (i.e. the *marvIn* file), the file applications.defaults and – if necessary – the file local.defaults are searched. This way parameters are set to default settings automatically (see Table 4 for example functions).

marvin **system management:** The ***marvin*** system management library includes functions for setting and accessing information in the ***marvin*** environment (see Table 5 for example functions).

Table 3: ***marvin*** runtime library: Example functions for data handling

Function	**Description**
ReadData(*Name*)	reads a molecular data set from maff file *Name*
MarvinWriteData(*Name*)	writes a molecular data set into maff file *Name*
MarvinGridPoint(*Index*)	returns the value referenced by index vector *Index*
MarvinGridInterp(*Coors*)	returns the value of a n-dimensional vector at the point given by the coordinates *Coors* by interpolating the grid
MarvinGridNumber(*Coors*)	returns a pointer to the data point next to the point defined by the coordinates *Coors* in a n-dimensional vector
MarvinAtomProperty(*Num*)	returns the properties of atom number *Num*
…	…

Table 4: ***marvin*** runtime library: Example user interface functions.

Function	**Description**
MarvinGetFloat(*Sect, Para, Num, Val*)	Reads the value at position *Num* from the input parameter *Par* in the section *Sect* into the variable addressed by *Val*.
MarvinGetChar(*Sect, Para, Num, Val*)	Reads the first character of the word at position *Num* from the input parameter *Par* in the section *Sect* into the variable addressed by *Val* (e.g. **y**es or **n**o)
MarvinGetInt(), MarvinGetString(), MarvinGetNum(), MarvinGetList(), MarvinGetLList(), MarvinGetLine(), …	Different types of run time parameters in the input files are accessible directly from within an application (e.g. words, lines, lists (as vectors), lists (as linked lists), etc.
MarvinLog(*size, string*)	writes a message into the status output file if size matches the global setting of the current output detail level (one of small, medium, big, debug). E.g. the command MarvinLog(“d”, “The value of Errorlevel is -1”) will write the message into the log file only if the output detail level is set to debug.
MarvinError(*Num, Mssg*)	The function reports the error message corresponding to the error number *Num*. The correct error message is assigned to *Num* and the string *Mssg* is printed as an additional explanation.
MarvinPercent(*Actual, Total*)	Reports the progress of a computation in percent.
...	...

Table 5: ***marvin*** runtime library: Example functions for ***marvin*** system management.

Function	**Description**
MarvinStart()	Initializes all ***marvin*** related settings. The marvin library functions can be used after call of MarvinStart().
MarvinEnd()	Cleans up all data structures previously used by ***marvin***.
MarvinStop(*Error*)	Stops the execution of the current application or of the entire ***marvin*** job, depending on the error level.
MarvinPhone(*Recipient, Message, Signal*)	Transmits a message to another application.
MarvinReadPhone()	Reads messages from other applications.
…	…

Example algorithm

Example problem

The ***marvin*** platform allows building up complete chemoinformatics algorithms by simply combining generic, high-level and interfaced applications. In the following example, a ***marvin*** algorithm is set up to address the problem of mining a chemical database for compounds which are similar to a set of well known drug molecules.

The database comprises 5000 synthetically available compounds designed as a virtual combinatorial library. The reference set consists of the 15 non-steroidal antiinflamatory drugs (NSAIDs) Diclofenac, Flufenamic Acid, Flurbiprofen, Ibuprofen, Indometacin, Ketoprofen, Meclofenamic Acid, Mefenamic Acid, Naproxen, 6-MNA (active metabolite of Napxoxen), Nabumeton, Piroxicam, Sulindac Sulfide (active metabolite of Sulindac), Tenoxicam and Meloxicam.

As a first step in the algorithm, different molecular properties are calculated for all molecules in the reference set and in the database. These calculated properties are called molecular descriptors in this context. As next, pairs of descriptors are compared and the similarities are computed as Euclidean distances between the descriptor pairs (i.e. similarity is not assessed in space of chemical structures but in descriptor space).

Obviously, the choice of descriptors is crucial – different descriptors will result in different similarities of the molecules. Therefore, the algorithm used for the virtual screening of the database must allow high flexibility in choice of computational methods for descriptor calculations.

Applications

Several high-level, interfaced and generic marvin applications are needed to perform all calculations of the example study. Application setup and a detailed listing of parameter definition are given in the listings.

Applications used within this algorithm are molIn (generic), PropertyHbonds (high-level), marvinLogP (interfaced), atomAutoCharge (high-level), atomAutoHbond (high-level), susi (generic) and printSusi (high-level). In the following, these ***marvin*** applications are described briefly. The description is focused on technical aspects – the theoretical background of the implemented methods is discussed in more detail in [22].

molIn reads the topology of all molecules and writes an initial maff-file for each molecule. molIn is a generic application that generates the ***marvin*** specific molecule format. It accepts more than 50 different input formats by accessing the external program babel [25]. Maff files, written by molIn, hold the topology information of the molecules only. Following applications will add data fields to the files and after finishing the ***marvin*** run, every file contains a variety of molecular information such as descriptors, properties and the results of filtering operations.

PropertyHbonds is a high-level application that runs the generic application atomProperty with the parameters needed to scan the molecules for hydrogen bond acceptors and hydrogen bond donors. All hydrogen bond acceptors are marked by a –1 and all donors by a +1 flag. The markers are stored as extended atom properties in the maff files.

marvinLogP is an interfaced application that uses the clogP program [26] for calculation of octanole/water partition coefficients (logP values). The clogP values are stored in table type data sets, that consist of one row and one column.

atomAutoCharge is a high-level application that uses the generic application atomAuto to compute autocorrelation coefficients based on the atom charges.

atomAuto derives spatial autocorrelation coefficients [22, 27, 28] from three-dimensional molecular structures. Autocorrelation coefficient describe properties of atom pairs for given distances (e.g. The coefficient A_{CH}(10-11) indicates patterns of charges in distance between 10Å and 11Å). Usage of autocorrelation coefficients is widespread in automated comparison of molecules, because comparison of the autocorrelation coefficients is possible without the necessity of superimposing the molecules [29].

atomAutoHbond is the corresponding high-level application that uses the same generic application atomAuto to compute autocorrelation coefficients based on the extended atom property hydrogen bond, previously calculated by propertyHbonds.

susi is a generic application that computes similarity of one molecule compared to a reference set. First, Euclidean distances between the sample descriptors and all reference descriptors are calculated. Non-linear scaling of the Euclidean distances leads to similarity scores that are in a range between 0.0 and 1.0. A similarity score of 1.0 denotes exact similarity (respectively a small distance between the descriptors). A similarity score of 0.0 indicates no similarity (i.e. the distance between the descriptors is higher than the predefined maximum distance).

All similarity scores for the sample molecule and reference set are summed up to and gives the so-called susi (**su**m of **si**milarity scores). Small values of the susi characterizes molecules that are similar to the reference set [22].

In the example study the description vector for each molecule is built up from two sets of autocorrelation coefficients and the computed cLogP value (41 values in total, see Listing 6).

printSusi is a high-level application that parameterizes the interfaced application GnuPlot in order to give a graphical output of the study result.

The application GnuPlot uses the external GnuPlot [30] program to plot data to a printer or file. Most of the GnuPlot parameters are accessible from within the marvIn setup. The GnuGlot application provides suitable default settings for plotting ***marvin*** datasets of different types and is used mainly to output study results. Default plot styles, defined as high-level applications, hide most of the GnuPlot parameters.

Run modes

The applications molIn, PropertyHbonds, marvinLogP, atomAutoCharge and atomAutoHbond are configured to run with all molecules so that all molecule data files contain the descriptors needed for the comparison. The applications susi and printSusi are called only once to calculate the sum of similarity scores for all molecules in the database. Susi lists molecule names and corresponding susi values into the status output file. Compounds with high scores can be selected from the list for synthesis.

Listings

Application setup and a detailed listing of parameter definitions are given in Listing 2. Run-time parameters for ***marvin*** are defined in the section %%setup, parameters for the applications in the subsequent sections. Comments are included for better readability. The syntax for parameter definitions is the same in all input files and for generic, high-level or interfaced applications.

Listings 3 and 4 display parts of the files local.defaults and application.defaults, used in the example study.

Example application manager output is shown in Listing 5. This file is an unix shell script and runs all applications and helper programs of the study.

An example data file is given in Listing 6. The header of every data file includes a history section with messages from all programs, worked on the molecule or the data. This history section is generated automatically every time a data set is written by the MarvinWriteData() functions that are part of the ***marvin*** run-time library.

Listing 7 and Listing 8 show clippings from the status output file, printed with the log file detail setting small and medium. The settings big and debug generate a more detailed status output.

Optimization of the algorithm

The success of any similarity assessment of molecule databases depends on the descriptors used. This is because every similarity or diversity assessment is based on descriptors instead on molecular structures. Strictly speaking, not the similarity of molecules, but the similarity of descriptors is calculated and diplayed.

Therefore a platform for chemoinformatics algorithm development must allow very high flexibility in parameter setup and in usage of descriptor calculation programs [31]. The platform must be able to rerun a study with minimum expenditure of time in order to optimize the parameter setup for descriptor calculation and comparison.

In a study that runs under the ***marvin*** platform all parameters for every single application can be modified easily and any application can be replaced by another one. It is possible to rerun the entire study with modified setup. The job setup and all parameter settings are documented automatically in the marvin status output file for every single run. The studies run without further user interaction so that optimization of the algorithm by variation of parameters and methods is only limited by cpu time available.

Summary and outlook

The modular chemoinformatics platform ***marvin*** allows flexible setup of algorithms such as the similarity screening outlined in the example. Multiple runs of the same study are possible with different parameterization or with different methods used. Interactive work on the algorithm is reduced to a minimum. All runs are documented automatically. Data management tasks, such as removal, copying or compression and decompression of files as well as network file transfers are handled and controlled by marvin. All applications, the algorithm and the ***marvin*** components are controlled by the same input file using an uniform and easy to use syntax.

Most of the requirements of a platform for chemoinformatics algorithm development are met by a simple modular system like ***marvin***. The combination of the basic components application manager, runtime library and interface to external software packages has proven to be flexible and strong enough to work as a chemoinformatics software platform. Chemoinformatics algorithms can be developed and optimized easily. The basic strategy of marvin is very simple and can be implemented quickly.

However, the layout of ***marvin*** shows major disadvantages, mainly in handling huge data sets: The application manager executes all applications internal and external to ***marvin*** in a simple way from the unix command line. All data is stored in compressed plain text files. Both characteristics cause a limitation of the number of molecules examined in a study. No considerable problems occur with data sets between 1000 and 10 000 molecules. Applied to a higher number of molecules the script files become too big and the number of data files too high.

Therefore the platform is appropriate for development of new applications and algorithms. Further developments are necessary in order to apply the new algorithms to data sets of more than 10 000 molecules.

Tomorrow chemoinformatics platforms should be implemented in a different way. For example, using completely object-oriented concepts, CORBA-interfaces for communications tasks and object-relational databases for storage of huge data sets. But this first implementation demonstrates the proof-of-priciple: A simple concept is able (or necessary) to meet the needs to a future chemoinformatics platform.

Listings

The listings illustrate the way parameters are set in a ***marvin*** algorithm. All listings are clippings from the control files and data files of the example study.

Listing 1

Example definitions for nested high-level applications (file: application.defaults): The high-level application “mopacAM1” runs the external program mopac [23] with the AM1 hamiltonian. The second high-level application “mopac-on-Sun” runs mopac with the same parameters on a remote host named bigsun. Both high-level applications refer to the interfaced application marvinMOPAC.

```
mopac high-level applications:
%%mopacAM1
default keys:       AM1 PRECISE NOINTER \
                MMOK GEOOK
geo opt:            all
time:              3600 sec
default:            marvinMOPAC
%%end of mopacAM1

%%mopac-on-Sun
machine:                bigsun          target host name
launch:                 run QUEUE       run on normal queue
arguments:              no
wait:                   yes             wait for all mopac output files output
default:                mopacAM1
%%end of mopac-on-Sun

        the mopac interface application:
%%marvinMOPAC
run mode:               files
remove:                 *  .dat

        MOPAC execution parameters:
mopac execute:          $MARVIN_DIR/bin/mopac
batch queue:            normal
wait interval:          1 48 h    ask for mopac results every hour,
                           maximum wait time: 48 hours
mopac id:               _mopac    suffix of all temporary mopac files
result file name:       arc

        MOPAC default keywords:
hamilton:               AM1
time:                   172000    maximum mopac run time in seconds
geo opt:                yes
default keys:           NOINTER XYZ
mopac keys:
mopac comment line:     mopac job from marvinMOPAC version 3.1

        retrieve options:
retrieve:               energy geo charges

%%end of marvinMOPAC
```

Listing 2

marvin input file for the example algorithm. Text outside a section or outside parameter definitions is ignored by the ReadParameter() routines of the ***marvin*** runtime library. Section %%setup contains marvin settings. Other sections (e.g. %%molIn, %%PropertyHbonds, %%marvinLogP, etc.) are used to define application specific setup.

```
selection of similar compounds from a database

%%setup
owner name:           dominik
project:              similarity selection

hold temp files:      no
compress:             yes
handle existing files:  new
```

```
logfile size:          small
system logfile:         no
echo to stdout:         yes


   molecules = reference and
             database (in separate file db.list)

molecules:                      diclofenac        \
          flufenamic_acid         flurbiprofen      \
          ibuprofen              indometacin       \
          ketoprofen             meclofenamic_acid \
          mefenamic_acid          naproxen          \
          nabumeton              piroxicam         \
          sulindac_sulfide        tenoxicam         \
          meloxicam              6-mna
inline:    db.list

program sequenz:      molIn PropertyHbonds marvinLogP    \
                    atomAutoCharge atomAutoHbond susi printSusi
%%end of setup

***** import molecules           *****
%%molIn
paralell:            1
input type:           mol       (mdl mol file)
comment:              molecule from db.list
%%end of molIn

***** h-bond property              *****
%%PropertyHbonds
default:             atomProperty
parallel:            8
machine:              local
property:             h-bond           property to compute
%%end of PropertyHbonds

***** log P                        *****
%%marvinLogP
parallel:            8
machine:              local
%%end of marvinLogP

***** autocorrelation              *****
%%atomAutoCharge
default:             atomAutoAll
property:             charges     use atom charges
%%end of autoAtomCharge

%%atomAutoHond
default:             atomAutoAll
property:             h-bond     use extended property h-bond
%%end of autoAtomHbond

%%atomAutoAll
parallel:            1
machine:              computeServerSGI
range:               5  20  20  calculate 20 autocorrelation coefficients
                              for distances between 5 and 20 angstroems)
%%end of autoAtomAll

***** susi                       *****
%%susi
```

```
machine:            local
dataset number:       3     (use the 3. data set in maff file)

                 use the first 15 molecules as reference:
reference:          1  2  3  4  5  6  7  8  9  10 \
                 11 12 13 14 15
scaling:            0.5
score function:       linear
%%end of susi

***** print susi results            *****
%%printSusi
machine:            computeServerSGI
default:            GnuPlot
title string:        susi of similarity dataset
set title:          yes setname owner name date
printer:            ps001
%%end of printSusi
end of marvin input file
ADo.
```

Listing 3

marvin setup file local.defaults. Pathnames and specific settings of the local ***marvin*** installation and remote host information are given in this file.

```
*************************************************************************
*                    marvin.defaults                           *
*************************************************************************

%%local
local host:          myWorkstation
marvin dir:           /usr1/local/Soft/marvin
tables dir:          /usr1/local/Soft/marvin/tables
compress:             compress -f
uncompress:            uncompress -f
remove:              rm -rf
remote execute:       rsh
remote copy:          rcp

jobfile shell:        /sbin/csh

system applications:  setup  cpuTime  wait

maff version:         maff by ADo: Version 4.20
read maff versions:   maff by ADo: Version 4.x
%%end of local


%%setup
machine:            local
execute:            $MARVIN_DIR/bin/setup
launch:
arguments:
parallel:           1

maff status line:     marvin application manager
maff history line:    setup: marvin application manager, 0.1v4.0
%%end of setup
```

```
%%computeServerSGI
work dir:          $MARVIN_DIR/tmp/NetWork
login script:      .login
network log:         computeServerSGI.netlog
login name:          sgi1 -l dominik -n
rcp adress:        dominik@sgi1
remove:            rm -rf
%%end of computeServerSGI

%%molIn
machine:           local
execute:           $MARVIN_DIR/bin/molIn
launch:
arguments:
parallel:        1

table for Sybyl atom types: $MARVIN_DIR/tables/molIn/AtomTypesSybyl.table
table for Sybyl bond types: $MARVIN_DIR/tables/molIn/BondTypesSybyl.table

maff status line:    molecular dataset imported
maff history line:   molIn: marvin input interface, 0.11v3.1
%%end of molIn

%%autoAtom
machine:           local
execute:           $MARVIN_DIR/bin/autoAtom
launch:
arguments:
parallel:        1

maff status line:    atom based autocorrelation function
maff history line:   autoAtom: autocorrelation, 0.31v1.2
%%end of autoAtom

%%marvinMOPAC
machine:           computeServerSGI
execute:           $MARVIN_DIR/bin/marvinMOPAC
launch:            queue
arguments:           -q long
parallel:        8

maff status line:    MOPAC V6.0 interface
maff history line:   marvinMOPAC: interface to MOPAC V6.0, 0.12v4.1
%%end of marvinMOPAC

  ...
```

Listing 4

The ***marvin*** setup file application.defaults. Default settings for all ***marvin*** applications are defined in this file.

```
**************************************************************************
*                       application.defaults                        *
**************************************************************************

%%setup
echo to stdout:         yes
logfile size:         big
system logfile:         none
hold temp files:         yes
```

```
compress:               yes
handle existing files:    new
owner name:              Andreas Dominik
project:                unknown
%%end of setup

%%wait
interval:               1 sec
%%end of wait

%%molIn
run mode:               files
remove:
format:                 detect
need all molecules:       yes
comment:                 imported molecule!
%%end of molIn

%%atomAtuo
run mode:                files
remove:
range:                   5    15    20     range and grid spacing of
                                           autocorrelation (20 coefficients in a
                                           distance of 5 – 20 A)
dataset:                 1                 number of data set in data file
autocorrelation function:  product
%%end of autoAtom

   ...
```

Listing 5

marvin job file for the example algorithm. This shell script is automatically gerenated by the application manager. It runs all applications for the molecules of the study. In the example the application molIn is executed on a single CPU of the local host. The application PropertyHbonds runs on eight molecules in parallel and the example application atomAuto is executed on the remote host “sgi1” that is configured as computeServerSGI (see file local.defaults, Listing 3).

```
#!/sbin/csh
#*****************************************************************
#                                              *
#                                              *
#        marvin  -  job  -  file                     *
#                                              *
#                                              *
#*****************************************************************
#
#
# run molIn:
#
uncompress -f diclofenac.mol2.Z
$MARVIN_DIR/bin/molIn molIn diclofenac similarity 1
compress -f diclofenac.mol2
compress -f diclofenac.molecule
#
# run molIn:
#
uncompress -f flufenamic_acid.mol2.Z
```

```
$MARVIN_DIR/bin/molIn molIn flufenamic_acid similarity 1
compress -f flufenamic_acid.mol2
compress -f flufenamic_acid.molecule
#
# run molIn:
#
uncompress -f flurbibrofen.mol2.Z
$MARVIN_DIR/bin/molIn molIn flurbibrofen similarity 1
compress -f flurbibrofen.mol2
compress -f flurbibrofen.molecule
#

   ...

#
# run PropertyHbonds:
#
uncompress -f diclofenac.molecule.Z
$MARVIN_DIR/bin/atomProperty PropertyHbonds diclofenac similarity 1 &
#
uncompress -f flufenamic_acid.molecule.Z
$MARVIN_DIR/bin/atomProperty PropertyHbonds flufenamic_acid similarity 2 &
#
uncompress -f flurbibrofen.molecule.Z
$MARVIN_DIR/bin/atomProperty PropertyHbonds flurbibrofen similarity 3 &
#
uncompress -f ibuprofen.molecule.Z
$MARVIN_DIR/bin/atomProperty PropertyHbonds ibuprofen similarity 4 &
#
uncompress -f indometacin.molecule.Z
$MARVIN_DIR/bin/atomProperty PropertyHbonds indometacin similarity 5 &
#
uncompress -f ketoprofen.molecule.Z
$MARVIN_DIR/bin/atomProperty PropertyHbonds ketoprofen similarity 6 &
#
uncompress -f meclofenamic_acid.molecule.Z
$MARVIN_DIR/bin/atomProperty PropertyHbonds meclofenamic_acid similarity 7 &
#
uncompress -f mefenamic_acid.molecule.Z
$MARVIN_DIR/bin/atomProperty PropertyHbonds mefenamic_acid similarity 8 &
#
$MARVIN_DIR/bin/wait wait similarity similarity diclofenac.hb
compress -f diclofenac.hb
rm -f diclofenac.molecule
$MARVIN_DIR/bin/wait wait similarity similarity flufenamic_acid.hb
compress -f flufenamic_acid.hb
rm -f flufenamic_acid.molecule
$MARVIN_DIR/bin/wait wait similarity similarity flurbibrofen.hb
compress -f flurbibrofen.hb
rm -f flurbibrofen.molecule
$MARVIN_DIR/bin/wait wait similarity similarity ibuprofen.hb
compress -f ibuprofen.hb
rm -f ibuprofen.molecule
$MARVIN_DIR/bin/wait wait similarity similarity indometacin.hb
compress -f indometacin.hb
rm -f indometacin.molecule
$MARVIN_DIR/bin/wait wait similarity similarity ketoprofen.hb
compress -f ketoprofen.hb
rm -f ketoprofen.molecule
$MARVIN_DIR/bin/wait wait similarity similarity meclofenamic_acid.hb
compress -f meclofenamic_acid.hb
rm -f meclofenamic_acid.molecule
$MARVIN_DIR/bin/wait wait similarity similarity mefenamic_acid.hb
```

```
compress -f mefenamic_acid.hb
rm -f mefenamic_acid.molecule
#
cat similarity.log similarity.log.1 similarity.log.2 similarity.log.3 similarity.log.4 similarity.log.5 similarity.log.6 similarity.log.7
similarity.log.8 > marvin_tmp_logfile.log
#
mv marvin_tmp_logfile.log similarity.log
rm -f similarity.log.1 similarity.log.2 similarity.log.3 similarity.log.4 similarity.log.5 similarity.log.6 similarity.log.7 similarity.log.8
#

  ...

# run atomAutoCharge:
#
uncompress -f diclofenac.logp.Z

rsh sgi1 -l dominik -n 'source .login ; mkdir $MARVIN_DIR/tmp/NetWork' >>& computeServerSGI.netlog

rsh sgi1 -l dominik -n 'source .login ; rm –rf $MARVIN_DIR/tmp/NetWork/similarity' >>& computServerSGI.netlog

rsh sgi1 -l dominik -n 'source .login ; mkdir $MARVIN_DIR/tmp/NetWork/similarity ' >>& computeServerSGI.netlog

rcp 'diclofenac.logp' 'dominik@sgi1:$MARVIN_DIR/tmp/NetWork/similarity/'

rcp 'similarity.marvIn' 'dominik@sgi1:$MARVIN_DIR/tmp/NetWork/similarity/'

rcp 'similarity.log' 'dominik@sgi1:$MARVIN_DIR/tmp/NetWork/similarity/'

rcp 'similarity.phone' 'dominik@sgi1:$MARVIN_DIR/tmp/NetWork/similarity/'

rcp '$MARVIN_DIR/tables/marvin/application.defaults' 'dominik@sgi1:$MARVIN_DIR/tmp/NetWork/similarity/home.defaults'

echo "application is running on remote host computeServerSGI " >> similarity.log

rsh sgi1 -l dominik -n 'source .login ; cd $MARVIN_DIR/tmp/NetWork/similarity;  $MARVIN_DIR/bin/atomAuto atomAutoCharge
diclofenac similarity 1 ' >>& computeServerSGI.netlog

rsh sgi1 -l dominik -n 'source .login ; cd $MARVIN_DIR/tmp/NetWork/similarity; $MARVIN_DIR/bin/wait wait similarity similarity
diclofenac.aac >>& computeServerSGI.netlog

rcp 'dominik@sgi1:$MARVIN_DIR/tmp/NetWork/similarity/ diclofenac.aac' '.'
rcp 'dominik@sgi1:$MARVIN_DIR/tmp/NetWork/similarity/similarity.log_1' '.'
rcp 'dominik@sgi1:$MARVIN_DIR/tmp/NetWork/similarity/similarity.phone' '.'
compress -f diclofenac.aac
rm -rf diclofenac.logp
cat similarity.log similarity.log.1  > marvin_tmp_logfile.log
mv marvin_tmp_logfile.log similarity.log
rm -f similarity.log.1
#

  ...

#
# write end logfile
#
$MARVIN_DIR/bin/cpuTime cpuTime similarity similarity

echo "marvin job similarity finished on host local" |
      mail -s "similarity.marvIn" $USER
```

Listing 6

marvin data file from the example study. The file header includes a brief documentation of status and history of the data. Header information (%%comment and %%history sections) is generated automatically by the library functions. The file holds four data sets in total, including molecular structure (data type mol), clogP value (data type table, one row and one column only) and the autocorrelation coefficients (data type grid) from hydrogen bond properties and atomic charges.

```
%%maff by ADo: Version 3.x
%%diclofenac.aac2
%%autocorrelation coefficients calculated
%%begin of comment
molecule from db.list
reference molecule for susi similarity scores
%%end of comment
%%begin of history
diclofenac.molecule: molIn: import molecule: 0.11v2.1
   Mon May 31 15:00:22 1999
diclofenac.hb: atomProperty: calculate extended atom property: 0.33v1.0
   Mon May 31 15:04:13 1999
diclofenac.logp: marvinLogP: calculate clogP value: 0.34v0.9
   Mon May 31 15:48:34 1999
diclofenac.aac: atomAuto: atom based autocorrelation: 0.32v1.6
   Mon May 31 16:03:41 1999
diclofenac.aac2: atomAuto: atom based autocorrelation: 0.32v1.6
   Mon May 31 17:35:13 1999
%%end of history
dataset type:          mxgg
number of datasets:    4
%%begin of dataset
dataset number:        1
dataset type:          m
dataset name:          diclofenac with extended properties
energy type:           none
energy:                0
charges type:          GASTEIGER
extended properties:   1
number of atoms:       30
number of bonds:       31
%%begin of atoms:
num type    X        Y         Z        charge    name
1   604   4.0891   -2.4130   0.5652    0.0636    C1
2   604   2.7608   -2.0925   0.2349    0.0002    C2
3   706   5.0994   -1.5224   0.3778   -0.2766    N1
4   604   4.3840   -3.6761   1.0970   -0.0456    C3
5   604   1.7701   -3.0763   0.3662   -0.0678    C4
6   601   2.3982   -0.6806  -0.2673    0.0791    C5
7   604   6.3556   -1.9372   0.0813    0.0852    C6
8   604   3.3920   -4.6493   1.2238   -0.0789    C7
9   604   2.0830   -4.3516   0.8417   -0.0804    C8
10  602   0.9569   -0.5015  -0.6750    0.2409    C9
11  604   7.4428   -1.4508   0.8180    0.0613    C10
...
%%end of atoms
%%begin of bonds
number    from    to    type
1         1       2     16
2         1       3     10
3         1       4     16
```

```
4        2        5        16
5        2        6        10
6        3        7        10
7        4        8        16
8        5        9        16
9        6        10       10
10       7        11       16
11       7        12       16
12       10       13       10
13       10       14       20
14       11       15       16
...
%%end of bonds
%%begin of property:
property type:        h-bond
property name:        h-bond
0
0
-1
0
0
0
0
0
0
0
0
0
-1
-1
0
0
0
0
0
0
0
0
0
0
0
1
0
0
0
%%end of property
%%end of dataset
%%begin of dataset
dataset number:       2
dataset type:         x
dataset name:         clogP
number of columns:    1
%%X1
min:                  4.711
max:                  4.711
number of points:     1
%%begin of data
4.711
%%end of data
%%end of dataset
%%begin of dataset
dataset number:       3
dataset type:         g
dataset name:           autocorrelation coefficients
number of axis:          2
%%X1:
min:                    5
max:                    20
grid points:            20
%%X2 (values):
min values:             -0.350815
max values:             0.837681
number of points:           20
%%begin of data
0.837681
0.767013
0.599279
0.34065
-0.0288451
-0.280594
-0.350815
-0.33142
-0.277938
-0.21335
-0.149994
-0.0906098
-0.0420099
-0.0112209
0.00534179
0.0108576
0.0108935
0.00837755
0.00577135
0.00371506
%%end of data
%%end of dataset
%%begin of dataset
dataset number:          4
dataset type:           g
dataset name:           autocorrelation coefficients
number of axis:          2
%%X1:
min:                    5
max:                    20
grid points:            20
%%X2 (values):
min values:             -0.0833
max values:             1.0000
number of points:           20
%%begin of data
0.7083
1.0000
0.7500
0.4166
-0.1667
-0.0833
-0.0833
-0.0416
0.0000
0.0000
0.0000
0.0000
0.0000
0.0000
0.0000
0.0000
```

```
0.0000
0.0000
0.0000
0.0000
%%end of data
%%end of dataset
%%end of file
```

Listing 7

Clippings from the ***marvin*** status output file of the example study recorded with log mode small. Log mode small is the default for running studies with a validated and tested algorithm.

```
filename:  similarity.log
*****************************************************************
*                                              *
*                    marvin - logfile                  *
*                                              *
*****************************************************************
*  job:      similarity
*  owner:    dominik
*  project:  similarity selection
*****************************************************************
*  files in fileset:
*          diclofenac
*          flufenamic_acid
...
*  programs of the job:
*          molIn
*          PropertyHbonds
*          marvinLogP
*          atomAutoCharge
*          atomAutoHbond
*          susi
*          printSusi
*****************************************************************
   application: molIn
   host:        myWorkstation
   file:        diclofenac
   at:          Mon May 31 15:00:21 1999
molecule diclofenac imported!
CPU-time used by Marvin:  0.01  sec

   application: molIn
   host:        myWorkstation
   file:        flufenamic_acid
   at:          Mon May 31 15:00:21 1999
molecule flufenamic_acid imported!
CPU-time used by Marvin:  0.01  sec

...

   application: PropertyHbonds
   host:        myWorkstation
   file:        diclofenac
   at:          Mon May 31 15:04:13 1999
extended property hb calculated for molecule diclofenac!
CPU-time used by Marvin:  0.04  sec

...
```

```
application: susi
   host:       myWorkstation
   file:       similarity
   at:         Mon May 31 18:09:23 1999
susis calculated for 5015 structures:

rank       name                     susi
         1 flufenamic_acid            1.0000 (ref)
         2 ibuprofen                1.0000 (ref)
         3 naproxen                 1.0000 (ref)
         4 nabumeton                  1.0000 (ref)
         5 piroxicam                1.0000 (ref)
         6 tenoxicam                 1.0000 (ref)
         7 meloxicam                  1.0000 (ref)
         8 6-mna                   1.0000 (ref)
         9 flurbiprofen             0.9986 (ref)
        10 ketoprofen                0.9865 (ref)
        11 diclofenac               0.9855 (ref)
        12 meclofenamic_acid          0.9531 (ref)
        13 mefenamic_acid             0.9145 (ref)
        14 indometacin              0.8722 (ref)
        15 sulindac_sulfide          0.8548 (ref)
        16 db567                  1.0000
        17 db571                  1.0000
        18 db572                  1.0000
        19 db573                  1.0000
        20 db586                  1.0000
...
      5013 db4998                    0.0000
      5014 db4999                    0.0000
      5015 db5000                    0.0000
CPU-time used by Marvin:  32.40  sec

...

**
* Total CPU time used by marvin:  10713.36  sec
* no error in marvin job!
* marvin done.
```

Listing 8

Clippings from the ***marvin*** status output file of the example study recorded with log mode medium. Log mode medium and log mode large are used for validating an algorithm or a single application. All parameters read by the ***marvin*** library functions are echoed to the log file.

```
   application: molIn
   host:       myWorkstation
   file:       diclofenac
   at:         Mon May 31 20:10:01 1999
read: input(2) = .mol2
read: output(2) = .molecule
read: format(1) = detect
read: table for Sybyl atom types(1) = $MARVIN_DIR/tables/molIn/AtomTypesSybyl.table
read: table for Sybyl bond types(1) = $MARVIN_DIRmarvin/tables/molIn/BondTypesSybyl.table
Reading molecule from Sybyl-.mol2 file: diclofenac.mol2
writing maff-file diclofenac.molecule
```

```
Molecule imported: diclofenac.molecule
CPU-time used by Marvin:  0.090000  sec

...

   application: PropertyHbonds
   host:        myWorkstation
   file:        diclofenac
   at:          Mon May 31 20:34:35 1999
read: input(2) = .lipo
read: output(2) = .hbond
read: molecule(1) = 1
read: property(1) = h-bonds
reading maff-file diclofenac.lipo

Property calculated for molecule diclofenac

writing maff-file diclofenac.hbond
CPU-time used by Marvin:  0.080000  sec

...

   application: autoAtomHbond
   host:        computeServerSGI
   file:        diclofenac
   at:          Thu Apr 20 16:01:16 2000
read: input(2) = .hbond
read: output(2) = .aac
read: dataset(1) = 1
read: replace(1) = n
read: range(1) = 5
read: range(2) = 20
read: range(3) = 20
read: autocorrelation function(1) = product
read: property(1) = 1
read: scaling(1) = y
read: scaling(2) = 1.0
reading maff-file diclofenac.hbond
Calculate autokorrelation
  input name: diclofenac, (30 atoms) based on property hbond profile
  output: 5.000000 A - 20.000000 A, (20 points, 20 total)
Default autokorrelation
...
```

Listing 9

Example ***marvin*** phone file for communication between individual applications.

```
filename:  similarity.phone
*******************************************************************
*
*                    marvin - phone-file
*
*******************************************************************
%%signal
from: marvinInput
to:   all
signal: exclude tenoxicam
%%end of signal
%%signal
...
```

References and Notes

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Source code and data availability: Available from the authors.