NAME

fwdsim − a tool for performing a forward simulation of an isotope labeling network.

SYNOPSIS

fwdsim [*options*]

DESCRIPTION

Fwdsim is a tool for simulating a FluxML specification of an isotope labeling network including all measurements.

For this purpose **fwdsim** reads the metabolic network and measurement configuration from a FluxML file, analyzes the network's stoichiometry and simulates the isotopic labeling distribution in order to provide synthetic measurement values. **fwdsim** allows to perform a (linearized) statistical analysis in order to assess the reliability and sensitivity of the current flux distribution.

The simulation results and the generated synthetic measurement values are written to a **fwdsim**(5) XML document. Apart from the XML output, **fwdsim** allows to export various data and symbolic equations to HDF5, MathML, and text documents.

COMMON OPTIONS

The following options are common to **fwdsim** and **fitfluxes**:

−h, −−help
Show a brief help for all command line options.

−i, −−in <FILE> [default: stdin]
The name of the FluxML (XML) input file. If omitted, the FluxML document is expected on standard input.

−o, −−out <FILE> [default: stdout]
The name of the FWDSIM (XML) output file. If omitted, the generated FWDSIM document is written to standard output.

−L, −−list
Specifying this option results in a list of allowed configuration names for the specified FluxML document. The program exits immediately after emitting the list.

−c, −−configure <CFG> [default: 'default']
Because FluxML documents may contain several **<configuration/>** elements this option allows to specify the configuration that should be used for the simulation. If this option is omitted it is assumed that the FluxML document contains a configuration with the name "default".

−l, −−log DEST
Specify the destination for the internal logging. In the most simple case **DEST** is a file name of a log file. In case the file exists new log messages are appended. Apart from log files it is possible to publish log messages to file descriptors, UNIX domain sockets, UDP and SCTP ports, and a small graphical user interface.

A file descriptor is specified by **fd:[num]**, where **[num]** is the number of the file descriptor.

A unix domain socket in the local file system is specified by **unix:[name]**, where **[name]** is the name of the socket file

A UDP or (connectionless) SCTP port is specified by **[proto]:[host]:[port]**, where **[proto]** is either "udp" or "sctp" and **[host]** is the name of the destination host and **[port]** is a UDP or SCTP port number on the destination host. Please note that the length of log messages is bounded by the minimum safe UDP packet size − log messages containing more than 548 characters will be truncated.

Finally, log messages can also be sent to a small GUI by specifying the destination **@gui@**. The GUI requires a working Perl/Tk installation and a running X server.

In order to capture all log messages concerning the command line processing this option should be specified in front of all other options.

−v, −−verbose 0..10 [default: 5]
Specify the verbosity 0, 1, ..., 10 of generated / emitted log messages. The meaning of the different log levels is as follows:

- **0 (QUIET)** do not emit log messages at all.
- **1 (ERROR)** only emit severe error messages.
- **2 (WARNING)** only report severe errors and warnings.
- **3 (NOTICE)** report all errors and warnings including important informal messages.
- **4 (INFO)** report all errors, warnings and all informal messages.
- **5 (THROW)** in case of an exception, try to give a diagnosis of the error; sometimes even gives a backtrace of the current function stack.
- **6 (DEBUG0)** emit the more important debugging messages.
- **7 (DEBUG1)** emit the less important debugging messages
- **8 (DEBUG2)** emit the superfluous debugging messages
- **9 (DEBUG3)** emit annoying debugging messages.
- **10 (DEBUG4)** don't dare to use it!

−t, −−tolerance <val> [default: 1e−9]
Specifies a constraint violation tolerance value. This parameter can be used to tolerate a certain constraint violation. Use with care.

SOLVER OPTIONS

There are three options affecting the behavior of the solver:

−a, −−apsolve
Solve the individual linear equation systems of the cumomer or EMU cascade using arbitrary precision arithmetic. Note that the results are converted to double precision immediately after solution. This option eliminates any round−off for the solution of the individual network levels.

−A, −−exact
In addition to option **−a** absolutely all computations are carried out using arbitrary precision arithmetic. If this option is used in conjunction with an analytical gradient (**−g analytic**) this results in exact derivatives. The results are converted to double precision just before writing them to the output file. This option is intended for debugging purposes. For large networks models the use of arbitrary precision arithmetic is probably to expensive.

−d, −−dbgsolve
When this option is used the network model is simulated in numerical debugging mode: for every equation system condition numbers are computed and the residual of the solution is checked.

−n, −−dry−run
Performs a dry−run, i.e. aborts the application after preprocessing of the input file and stoichiometry.

STATISTICS OPTIONS

fwdsim allows to evaluation linearized statistics.

−s, −−statistics
Compute linearized statistics for the current flux setting. This option is most beneficial if the flux setting is already optimized, i.e. results from an invocation of **fitfluxes**. Indeterminable fluxes will be reported. For all determinable fluxes standard deviations will be written to the output file (**−o**). If specified together with option **−H** (HDF5 export) the Jacobian of the measurements as well as the covariance matrix of the fluxes are exported into the HDF5 file.

−g, −−gradient <arg> [default: fd4]

The desired method for computaton of partial derivatives in case statistics are to be computed (option **−s**). Possible values are '**fd1**', '**fd2**', '**fd3**', '**fd4**' for finite difference approximations, and '**analytic**' for exact derivatives. The default value is '**fd4**', i.e. the gradient is approximated using an O(h^4) finite difference formula (which is slightly faster than using the exact derivatives).

DATA EXPORT OPTIONS

fwdsim allows to export the preprocessed stoichiometry, the generated system matrices, the symbolic system equations, the Jacobian of measurements, and covariance matrices into HDF5 and text files. A fully−fledged simulator−code for Octave/MATLAB can be exported into a .m file.

−H, −−hdf5 <FILE>

Export the stoichiometry and the left and right hand sides of the Cumomer / EMU equation systems into a HDF5 file. If, in addition, the computation of linearized statistics is requested (by option **−s**) the Jacobian of the measurements and the covariance matrix of the fluxes are exported, as well.

The exported data in the HDF5 files is intended to be used in MATLAB, but may also be used in other scientific software, such as Octave. The data in HDF5 files is organized in a directory−like structure. For example, in order to load the stoichiometric matrix out of the generated HDF5 file in MATLAB, the following command may be used:

```
S = hdf5read('file.h5','/stoichiometry/matrix');
```

Currently the following data is exported:

- '/stoichiometry/matrix': The stoichiometric matrix
- '/stoichiometry/r': The row labels of the stoichiometric matrix, i.e. string values. Assuming the row labels are imported into a MATLAB array 'rows' the proper way to access the k'th label is 'rows(k).Data'.
- '/stoichiometry/c': The column labels of the stoichiometric matrix.
- '/stoichiometry/fluxes': The flux distribution in net / exchange coordinates including the flux types. Possible flux types are:
  - FREE (free): the flux value may be chosen freely. In **fitfluxes**, these fluxes are adjusted by the optimization algorithm.
  - CONS (constraint): the flux value has a constant value. In **fitfluxes**, these fluxes must not be adjusted by the optimization algorithm.
  - DEPD (dependent): the flux value is determined by a number of constraint and free fluxes.
  - QCON (quasi−constraint): the flux value is completely determined by constraint fluxes.

  The first two columns in '/stoichiometry/fluxes' contain the values of the net and exchange fluxes. The remaining columns are boolean flags indicating the type of the type of the net and exchange flux.
- '/stoichiometry/r_fluxes': The row labels of the matrix '/stoichiometry/fluxes', i.e. the flux names.
- '/stoichiometry/c_fluxes': The column labels of the matrix '/stoichiometry/fluxes'. If the column label has the suffix '.n', it refers the net flux (e.g. FREE.n). The suffix '.x' flags the exchange flux (e.g. QCON.x).
- '/stoichiometry/kernel/matrix_net' and '/stoichiometry/kernel/matrix_xch': The kernel matrices for net and exchange fluxes. Given the values of the free net and exchange fluxes the kernel matrices are used for recomputing the values of the dependent fluxes. For a kernel matrix K, this is achieved by evaluating v = K*[1; v_f];, where v_f contains the values of the free fluxes.

Because 13CFLUX 2 determines kernel matrices using arbitrary precision arithmetic, the kernel matrices are the exact solutions of the stoichiometric system.

- '/stoichiometry/kernel/r_net' and '/stoichiometry/kernel/r_xch': The row labels of the kernel matrices for net and exchange fluxes, i.e. all flux values.
- '/stoichiometry/kernel/c_net' and '/stoichiometry/kernel/c_xch': The column labels of the kernel matrices for net and exchange fluxes, i.e. the names of the free net and free exchange fluxes. The label of the first column always contains the label '1', flagging that the first column of the kernel matrices contain the particular solution.

In case option **−s** is passed additional statistical data is written to the HDF5 files:

- '/cov_free/matrix': The covariance matrix of the free fluxes.
- '/cov_free/r' and '/cov_free/c': The row and column labels of the covariance matrix, i.e. the names of the free fluxes. Net and exchange fluxes are distinguished by the suffix '.n' or '.x'.
- '/cov/matrix': The full covariance matrix of all fluxes.
- '/cov/r' and '/cov/c': The row and column labels of the full covariance matrix.
- '/jacobian/matrix': The Jacobian of the measurements, i.e. partial derivatives of the measurement values with respect to the free fluxes.
- '/jacobian/r': The row labels of the Jacobian, i.e. names of the measurement values. The names of the measurement values are given in short notation (see bibliography).
- '/jacobian/c': The column labels of the Jacobian, i.e. the names of the free fluxes. Net and exchange fluxes are distinguished by the suffix '.n' or '.x'.

−M, −−mathml <FILE>
Export the cascade's symbolic systems into a MathML file. The resulting Content−MathML file may be imported in computer algebra systems like Maple and Mathematica.

−T, −−text <FILE>
Exports the cumomer / EMU cascade's symbolic equation system into the specified text file.

−m, −−matlab <FILE>
Generate an Octave/MATLAB simulator function for the current network in the specified text file. The function name will match the name of the text file. The external function cumulate is contained in the 13CFLUX 2 installation.

EXAMPLES

Simulate an isotope labeling network and safe the XML output to file network.fwd (most simple case):

fwdsim −i network.fml −o network.fwd

Convert an old FTBL to FluxML, simulate and filter out the simulated measurement values (**fwdsim** reads from stdin and writes to stdout):

ftbl2fml −i network.ftbl | fwdsim | fwdsimflt −m

Simulate an isotope labeling network and generate all possible output; send the XML output to /dev/null:

fwdsim −i net.fml −o /dev/null −M m.mml −T t.txt −m f.m −H net.h5

Simulate an isotope labeling network and and compute linearized statistics. In addition to the simulation results, write estimated standard deviations to the output file. Save the stoichiometry, the cascaded equation systems, the Jacobian of measurements, and the covariance matrices to a HDF5 file:

fwdsim −s −i network.fml −o network.fwd −H network.h5

SEE ALSO

fitfluxes(1), fwdsimflt(1), ftbl2fml(1), simreport(1)

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