LNA++

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# Introduction

LNA++ is a tool designed to efficiently compute the linear noise approximation to a chemical reaction network, along with the first two sensitivities of the mean and temporal cross-covariance matrix, using a fast C++ implementation. LNA++ can be either be integrated into a C++ project, or used in conjunction with Matlab or Python for parameter inference in chemical reaction networks.

This document describes the library requirements, installation and usage of LNA++.

# Installation

The contents of the LNA++ distribution zip file should be placed into a separate folder, such as in a folder within the home directory. The archive contains all the necessary scripts and source code for building LNA++ Python modules or Matlab executable files. No further building or installation is necessary until the creation of the model executables, as described below.

# Requirements

LNA++ uses the standard C++ libraries, the CVODES Sundials library for numerical integration of ODEs and forward sensitivities, and the Blitz++ library for fast, templatized tensor operations.

### Compiler

Compilation of C++ source code for use as a standalone executable, or with Matlab or Python requires the use of a suitable compiler such as gcc/g++ on Linux-based systems, or clang on mac OS.

### Blitz++

Blitz++ version 0.9 or greater is required. It can be obtained via the included source code in the ‘libraries’ folder, or from <http://sourceforge.net>. It is also available via macports on mac OS, and the apt repository on Ubuntu.

### CVODES

Numerical integration is computed using the CVODES Sundials package. Source code is included in the ‘libraries’ folder, and is also available for download from <http://computation.llnl.gov/casc/sundials/main.html>.

**Note: CVODES should be compiled using the -fPIC flag to ensure cross-platform compatibility. This can be enabled by specifying --with-pic to the configure script.**

## Python

In order to use LNA++ with Python, you must first install the necessary scientific computing modules, listed below. Python libraries can be installed using package managers such as apt on Ubuntu, or macports/homebrew on Mac OS, or using the Pip3 Python package manager.

**LNA++ is currently only compatible with Python 3.0 or greater. All libraries must thus be the Python3-compatible version.**

**Note for Ubuntu Users:** the necessary Python packages can be installed using the command “sudo apt-get install libblitz0-dev libblitz0ldbl libblitz-doc python-sympy libsbml5-python

”

### Numpy

Numpy is a widely used mathematics and numerical library.

### Sympy

Sympy provides a framework for symbolic/algebraic computations, and is necessary for computing the linear noise approximation for arbitrary models.

### Libsbml

Libsbml is required for translating SBML models for use with LNA++.

### (optional) pylab

Pylab provides functions for plotting vectors and matrices, and might thus be useful.

## Matlab

In order to use LNA++ with Matlab, the Matlab Symbolic Toolbox is required in order to compute the analytic components of the LNA and its sensitivities. If the Symbolic Toolbox is not available, LNA++ can still be used in two ways:

1. **Python only**. Use the Python implementation (no Matlab) as described in the remainder of this document.
2. **Mixed Matlab/Python**.Both the Python and Matlab implementations of LNA++ generate C code for the analytical components of the LNA and its sensitivities. It is therefore possible to generate the C code using the Python scripts, through the generateLNAComponentsstep, as described below. The Matlab executable is then generated in the normal way, resuming with the compileLNA step.

# Usage

In this section we describe how to use LNA++ to create Matlab executable models and Python modules.

## Overview

LNA++ converts a user specified model, provided as an SBML model configuration file, into a set of symbolic functions for the time derivatives of means, temporal cross-covariances, and their sensitivities. These functions are converted to C code which is then compiled together with the core computation engine to generate either Matlab or Python executable files/modules. The system can then be simulated using these executables and user-specified initial conditions and model parameters.

The stoichiometric matrix and reaction propensity functions are extracted from a user-supplied SBML model file, e.g. see [http://sbml.org/SBML\_Software\_Guide/SBML\_Software\_Summary - cat\_7](http://sbml.org/SBML_Software_Guide/SBML_Software_Summary#cat_7).

## Matlab

To generate the Matlab executable simply call the function generateLNA specifying the path to the SBML input file, the model name and an optional argument indicating whether to attempt to compute the steady state of the system, see below.

It is recommended to run this command using the ‘models’ subdirectory of the LNA++ root directory as the working directory. This ensures the correct relative path for the subsequent build steps.

See **BirthDeath.m** in ‘models’ and the **Tutorial** for an example of how this is done.

### Paths

After running the functions for generating the mex file, the resulting C code, executable file, and wrapper function are placed in a subdirectory with the name of the model as specified. Make sure that the wrapper function and executable are on the Matlab path, e.g. by changing to the directory of the model or by adding them to the path using addpath*.*

### Building the model

To build the model call generateLNA(sbmlPath, model, computeSS)

1. *sbmlPath*: the path to the SBML model specification file
2. *model:* the desired name of the model
3. *computeSS:* this argument is optional and can have only one of the values “Y0”, “V0”, “BOTH”, or “NONE”.
   1. *Y0*: LNA++ will attempt to calculate the steady state value of the MRE of the stochastic system specified. If Y0 is not explicitly provided when invoking the model, the computed value will be automatically substituted.
   2. *V0*: LNA++ will attempt to calculate the steady state value of the variance of the stochastic system specified. If V0 is not explicitly provided when invoking the model, the computed value will be automatically substituted.
   3. *BOTH*:LNA++will compute both V0 and Y0 if possible. If Y0 or V0 is not explicitly provided when invoking the model, the computed values will be automatically substituted.
   4. *NONE*: LNA++ will not compute any steady state values. Invocation of the model without explicitly specifying the initial conditions for Y0 and V0 will result in an error message being generated.

**Note for custom library paths and custom linker or compiler flags:**

It is also possible to specify custom flags to the linker or compiler, for example if CVODES or Blitz are not installed in a standard location. Linker and compiler flags can be specified using *Name, Value* argument pairs where *Name* is either Linker\_Flags, or Cpp\_Flags.

For example, generateLNA(sbmlPath, model, computeSS, ‘Linker\_Flags’, FLAGS) or generateLNA(modelName, S, Npar, ‘Cpp\_flags’, FLAGS).

Linker flags and compiler flags can both be specified, by providing both pairs of arguments.

#### Matlab executable

generateLNA generates a mex file and a Matlab wrapper, which provides help messages and removes singleton dimensions for more convenient output. These are placed in the model subdirectory corresponding to the *model* specified. To execute them, copy them to the desired final folder, or add them to the Matlab path. Usage of the generated function is specified in the help for that function.

See BirthDeath in ‘models’, and the generated *BirthDeath\_LNA.m* for an example of the generated wrapper function and its invocation.

### Using the generated mex wrapper

The mex wrapper corresponding to a particular model can be invoked with between 2 and 6 arguments, which must occur in the correct order:

#### Inputs

In the following, N is the number of observed variables (**obsVar**), T is the number of time points specified by **Time,** andd is the number of model parameters + the number of species.

1. **Theta:** the vector of model parameters, with the same dimension as specified during the model construction
2. **Time**: a vector of times at which the result of the model simulation is to be outputted. The first time is always zero.
3. **obsVar (optional)**: a vector of indices corresponding to the species which should be outputted. The numbering of species matches the numbering of species in the stoichiometric matrix. If omitted, all species are outputted.
4. **Merr (optional):** a vector of numbers (possibly of length 1) corresponding to estimated measurement error of each species, specified as a variance. The measurement error is added to diagonal of the temporal cross-covariance matrix. If only one number is specified, this number is used for all species. If multiple numbers are specified, the number specified must equal the number of observed variables. If omitted, measurement error is assumed to be zero for all species.
5. **Y0 (optional):** a vector of initial conditions for each of the species. The length must be the same as the number of species. If omitted, the steady-state initial conditions are assumed, if they were computed when the model was created; otherwise an error is generated requesting the initial conditions to be specified.
6. **V0 (optional):** a vector of initial conditions for the (co-)variances between all species. They are specified in column-major order, i.e. for a 3x3 matrix [[V\_11, V\_12, V\_13]; [V\_21, V\_22, V\_23]; [V\_31, V\_32, V\_33]], the initial conditions V0 would be specified in the order [V\_11, V\_12, V\_22, V\_13, V\_23, V\_33]. Only the upper triangular portion of the initial covariance matrix is specified due to symmetry. If omitted, the steady-state values are substituted, if they were computed when the model was created; otherwise an error is generated.

For convenience, the function toLinear is provided as a Matlab script, which converts a symmetric covariance matrix into a column-major-ordered vector.

#### Outputs

If only 2 output arguments are specified, the computation engine does not compute sensitivities, which can be substantially faster. If 3 or 4 outputs are specified, first order sensitivities are computed. If 5 or 6 outputs are specified, first and second order sensitivities are computed which can take longer. In the following N is the number of observed variables (**obsVar**), T is the number of time points specified by **Time,** andd is the number of model parameters + the number of species. Note that LNA++ computes sensitivities with respect to model parameters and the initial conditions of the MRE, but not currently with respect to the initial variances.

1. **MRE:** a NxT matrix corresponding to the solution of the macroscopic rate equation for all observed variables.
2. **Sigma:** a NxNxT array corresponding to the temporal cross-covariance of all observed species at all time points.
3. **dMRE (optional):** a NxTxd array corresponding to the first order sensitivities of the MRE to each of the model parameters over all time points. The sensitivities are ordered such that the first sensitivities are of the MRE with respect to the model parameters, followed by sensitivities with respect to the initial conditions of each species.
4. **dSigma (optional):** a NxNxTxd array corresponding to the first order sensitivities of the temporal cross-covariance matrix at all timepoints for the observed species. The sensitivities are ordered such that the first sensitivities are of the MRE with respect to the model parameters, followed by sensitivities with respect to the initial conditions of each species.
5. **d2MRE (optional):** a NxTxdxd array corresponding to the second order sensitivities of the MRE at all timepoints for the observed species. The sensitivities are ordered such that the first sensitivities are of the MRE with respect to the model parameters, followed by sensitivities with respect to the initial conditions of each species.
6. **d2Sigma (optional):** a NxNxTxdxd array corresponding to the second order sensitivities of the temporal cross-covariance matrix at all timepoints for the observed species. The sensitivities are ordered such that the first sensitivities are of the MRE with respect to the model parameters, followed by sensitivities with respect to the initial conditions of each species.

## Python

To use LNA++ with Python, call the function generateLNA of the LNA module, with the following arguments:

1. *sbmlPath*: the path to the SBML model specification file
2. *model:* the desired name of the model
3. *computeSS:* this argument is optional and can have only one of the values “Y0”, “V0”, “BOTH”, or “NONE”.
   1. *Y0*: LNA++ will attempt to calculate the steady state value of the MRE of the stochastic system specified. If Y0 is not explicitly provided when invoking the model, the computed value will be automatically substituted.
   2. *V0*: LNA++ will attempt to calculate the steady state value of the variance of the stochastic system specified. If V0 is not explicitly provided when invoking the model, the computed value will be automatically substituted.
   3. *BOTH*:LNA++will compute both V0 and Y0 if possible. If Y0 or V0 is not explicitly provided when invoking the model, the computed values will be automatically substituted.
   4. *NONE*: LNA++ will not compute any steady state values. Invocation of the model without explicitly specifying the initial conditions for Y0 and V0 will result in an error message being generated.

**Note:** It is recommended to save the model as a script in the ‘models’ subdirectory of the LNA++ root directory. This ensures the correct relative path for the subsequent build steps.

### Creating the Python module

After running generateLNA, a Python module is created and placed in the *modules* subdirectory. The module is named *modelLNA,* where model is replaced by the name of the model specified. The module can be imported using *import*, as long as the module is on the Python module path. To add this directory to the module path either modify the value of sys.path or add the modules directory to the PYTHONPATH environmental variable.

**Note for non-standard library or include paths:**

If CVODES or Blitz++ are not installed in a standard location (e.g. due to lack of administrator permissions), then custom include and/or library paths can be provided by specifying two additional arguments to generateLNA:

* include\_dirs: a Python list of directories to be searched for header files, specified as a list of strings.
* lib\_dirs: a Python list of directories to be searched for libraries, specified as a list of strings.

### Using the created Python module

The Python module for a given model must first be imported as described above. The model is simulated using the *LNA* function in the module. For example if the model is called ‘myModel’ then the generated module is called ‘myModelLNA’ and the *LNA* function can be imported using the statement:

from myModelLNA import LNA

### Input

The LNA function requires 2-8 input arguments, as follows. Arguments 3-8 are optional, and can be specified either by position or as formal (named) arguments.

1. **Theta:** a list of model parameters
2. **Time:** a list of time points for outputting the simulation results
3. **obsVar (optional):** a list of observed variables to be output. The default is to output all species.
4. **merr (optional):** either a single number specifying the measurement error (variance) to be added to the covariance of all observed species, or a list of numbers of the same length as the number of observed variables, specifying each measurement error individually. The default is zero observation error.
5. **Y0 (optional):** the initial conditions for the MRE. If initial conditions are not specified, but were computed using the *computeSS* flag at the time of the module creation, then the steady state values are implicitly used. If the initial conditions were not computed when generating the module, then an error occurs if no initial conditions are specified.
6. **V0 (optional):** a vector of initial conditions for the (co-)variances between all species. They are specified in column-major order, i.e. for a 3x3 matrix [[V\_11, V\_12, V\_13]; [V\_21, V\_22, V\_23]; [V\_31, V\_32, V\_33]], the initial conditions V0 would be specified in the order [V\_11, V\_12, V\_22, V\_13, V\_23, V\_33]. Only the upper triangular portion of the initial covariance matrix is specified due to symmetry. For convenience, the function toLinear is provided in the LNA module, which converts a symmetric covariance matrix into a column-major-ordered vector.

If initial conditions are not specified, but were computed using the computeSS flag at the time of the module creation, then the steady state values are automatically used. If the initial conditions were not computed when generating the module, then an error occurs if no initial conditions are specified.

1. **computeSens (optional):** a Boolean variable indicating whether the first order sensitivities should be computed. By default no first order sensitivities are computed.
2. **computeSens2**: a Boolean variable indicating whether the second order sensitivities should be computed. By default no second order sensitivities are computed.

### Output

The LNAfunction returns between 2 and 6 output arguments. In the following N is the number of observed variables (**obsVar**), T is the number of time points specified by **Time,** andd is the number of model parameters + the number of species. Note that LNA++ computes sensitivities with respect to model parameters and the initial conditions of the MRE, but not currently with respect to the initial variances.

1. **MRE:** an NxT matrix corresponding to the solution of the macroscopic rate equation for all observed variables.
2. **Sigma:** an NxNxT array corresponding to the temporal cross-covariance of all observed species at all time points.
3. **dMRE (if computeSens):** an NxTxd array corresponding to the first order sensitivities of the MRE to each of the model parameters over all time points. The sensitivities are ordered such that the first sensitivities are of the MRE with respect to the model parameters, followed by sensitivities with respect to the initial conditions of each species.
4. **dSigma (if computeSens):** an NxNxTxd array corresponding to the first order sensitivities of the temporal cross-covariance matrix at all timepoints for the observed species. The sensitivities are ordered such that the first sensitivities are of the MRE with respect to the model parameters, followed by sensitivities with respect to the initial conditions of each species.
5. **d2MRE (if computeSens2):** an NxTxdxd array corresponding to the second order sensitivities of the MRE at all timepoints for the observed species. The sensitivities are ordered such that the first sensitivities are of the MRE with respect to the model parameters, followed by sensitivities with respect to the initial conditions of each species.
6. **d2Sigma (if computeSens2):** an NxNxTxdxd array corresponding to the second order sensitivities of the temporal cross-covariance matrix at all timepoints for the observed species. The sensitivities are ordered such that the first sensitivities are of the MRE with respect to the model parameters, followed by sensitivities with respect to the initial conditions of each species.

**Note:** if computeSens2 is True, the first order sensitivities are always also computed and outputted.

# Examples

## Birth-death model

One example is provided with LNA++. It is the case of a simple birth death model with two species: mRNA and protein. The model is described in detail in the supplementary materials of the LNA++ paper (see references).

The stoichiometric matrix is given by:

**S** = [[1 -1 0 0]; [0 0 1 -1]]

The reaction flux vector is given by:

**F** = [k\_m, g\_m\*m, k\_p\*m, g\_p\*p]

with model parameters

**k\_m**: production rate of mRNA

**k\_p**: production rate of protein

**g\_m**: degradation rate of mRNA

**g\_p**: degradation rate of protein

A Matlab implementation of this model, along with code to perform simulations and generate plots for the output is included in the script ‘models/BirthDeath.m’, and a Python implementation of the same in ‘models/BirthDeath.py’.

# Advanced Notes

## Specifying custom propensity functions

It is possible to manually specify the components necessary for the computation of the linear noise approximation instead of deriving them from a supplied SBML file. For both Matlab and Python, the following components need to specified:

### State variables

These are the species in the chemical reaction network, e.g. mRNA or proteins.

### Stoichiometric matrix

This is the N by M matrix of stoichiometric coefficients describing the chemical reaction network, where N is the number of species and M is the number of reactions. Thus entry *(i,j)* corresponds to the net change in the number of molecules of species *i*, due to the firing of reaction *j*.

### Reaction fluxes

This is a vector function of length M, describing the rate of each reaction as a function of the current state of the system, the kinetic constants, and potentially with explicit time dependence. By entering the reaction fluxes manually (i.e. not from SBML), custom propensity functions can be specified.

### Model parameters

The model parameters are the set of model-specific constants that influence the reaction rates. Sensitivities of the mean and temporal cross-covariance matrices are computed with respect to the model parameters.

Below we show how to specify the model components manually, in both Matlab and Python, using the Birth-death example from above.

## Matlab

1. **Define the stoichiometry matrix (S) for the model:**

S = [1 -1 0 0; % change to mRNA

0 0 1 -1]; % change to protein

1. **Define the state variables and model parameters as symbols:**

syms k\_m k\_p g\_m g\_p real

syms m p real

phi = [m,p]; % state vector

Theta = [k\_m, k\_p, g\_m, g\_p]; % parameter vector

npar = length(Theta); % 4 parameters

1. **Define the reaction fluxes as a function of phi, t and Theta:**

f = @(phi,t,Theta) ...

[ Theta(1), Theta(3)\*phi(1), Theta(2)\*phi(1), Theta(4)\*phi(2)];

1. **Generate the symbolic C code:**

addpath('../matlab')

model = 'BirthDeath';

generateLNAComponents(model, S, f, phi, Theta, 'BOTH')

1. **Compile the code and generate the Mex file:**

compileLNA(model);

## Python

1. **Setup**

from sympy import Matrix

from LNA import \*

1. **Define the stoichiometry matrix (S) for the model:**

S = Matrix([[1, -1, 0, 0], [0, 0, -1, 1]])

1. **Define the state variables and model parameters as symbols:**

# mRNA(m) and protein(p)

phi = symbols('m,p', real=True)

# reaction constants

Theta = symbols('k\_m,k\_p,g\_m,g\_p', real=True)

1. **Define the reaction fluxes as a function of phi, t and Theta:**

f = lambda phi,t,Theta: \

[Theta[0], Theta[2]\*phi[0], Theta[1]\*phi[0], Theta[3]\*phi[1]]

1. **Generate the symbolic C code:**

tups = generateLNAComponents(model, S, fHandle, species, parameters, computeSS)

npar = len(parameters) # number of parameters

1. **Compile the code and generate the Python module:**

compileLNA(model, S, tups, npar)

## Using LNA++ in Matlab without the Symbolic Toolbox

To compute the solution to the LNA, LNA++ must solve several algebraic expressions symbolically and use the result to create C code. The result is compiled together to create the final executable files. Doing this in Matlab usually requires the Symbolic Toolbox. If this is not available, it is possible to solve the equations and generate the C code using Python (see instructions above). After generating the Python module, run compileLNA in Matlab using the same model name specified in Python– see the instructions for **Specifying custom propensity functions** above**.**