ODE-constrained mixture modeling

1.0

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Contents

1 ODEMM Documentation

1.1 Introduction

Cellular heterogeneity occurs at multiple levels. To cover these levels, ODEMM combines mixuture modeling with mechanistic models for the individual subpopulations.

ODEMM offers

- models that are able to include mechanistic descriptions of the **means** of individual subpopulations, e.g., by reaction rate equations (RRE) (Hasenauer et al., PloS CB (2014), Loos et al., CMSB (2016)). For more details see below.
- Hierarchical population models that incorporate **means and covariances** of the individual subpopulations, e.g., provided by the sigma-point approximation or the moment-closure approximation. For more details see below.

1.2 Availability

ODEMM is a freely available MATLAB (MathWorks) toolbox available at https://github.com/ICB-DCM/ODEMM/. It can be retrieved by downloading the zip archive at https://github.com/ICB-DCM/ODEMM/archive/master.zip or cloning the `git` repository.

1.3 Installation

If the repository was cloned, install_ODEMM.m needs to be run to add the folders to the MATLAB search path. If the zip archive was downloaded the archive needs to be unzipped before executing install_ODEMM.m.

Toolboxes required for the examples

In principle, every simulation that provides means (and covariances) can be incorporated into ODEMM. For our examples, we used the simulations obtained by AMICI and calibrated the models using the parameter estimation toolbox PESTO.

- AMICI (simulation): https://github.com/ICB-DCM/AMICI
- PESTO (parameter estimation): https://github.com/ICB-DCM/PESTO
- SPToolbox (sigma-point approximation): https://github.com/ICB-DCM/SPToolbox (required for the examples incorporating means and covariances)

1.4 Licensing

See `LICENSE` file in the ODEMM source directory.

1.5 Models

ODEMM implements different kinds of ODE constrained mixture models.

1.5.1 Incorporation of mechanistic description of the mean

If the mean of a subpopulation is described by, e.g., RRE, the variances of the measurements are treated as additional parameters. An example for setting up RRE constrained mixture models is given in models_RRE() which can be found in `examples/conversion_reaction/`.

1.5.2 Incorporation of mechanistic description of the mean and covariance

When not only a mechanistic description of the mean, but also of the covariance is provided by the simulation function for the individual subpopulations, a hierarchical population model can be created. In our examples, we assessed two approximations for obtaining the statistical moments of the subpopulations:

- Sigma-point approximation (`/examples/conversion_reaction/models_SP`)
- Moment-closure approximation (`/examples/two_stage_intrinsic`)

1.6 Distributions

For the mixture distribution, ODEMM implements

- multivariate normal distributions and
- multivariate log-normal distributions.

The density functions and corresponding functions required for the models can be found in `/distributions`.

2 Examples

The following examples are included:

- Conversion reaction (`examples/conversion_reaction`)
- Differential protein expression (`examples/differential_protein_expression`)
- Intrinsic noise for a two stage model of gene expression (`examples/two_stage_intrinsic`)
- Subpopulation differences in NGF-induced Erk1/2 signaling (`examples/subpopulation_differences`)
- Differences mediated by extracellular scaffolds in NGF-induced Erk1/2 signaling (`examples/ECM_differences`)

These models require the freely available toolboxes

- AMICI for simulation (`http://icb-dcm.github.io/AMICI/`)
- PESTO for the parameter estimation (`http://icb-dcm.github.io/PESTO/`)
- SPToolbox for the sigma-point approximation (`http://icb-dcm.github.io/SPToolbox/`)

2.1 Conversion reaction

In this example, models incorporating only the **mean** (model_RRE.m), and models incorporating **mean and variance** (e.g., model_SP_k3.m) are implemented. The latter allow for cell-to-cell variability of certain parameters of the model and incorporate the sigma-point approximation to obtain the statistical properties of the individual subpopulations.

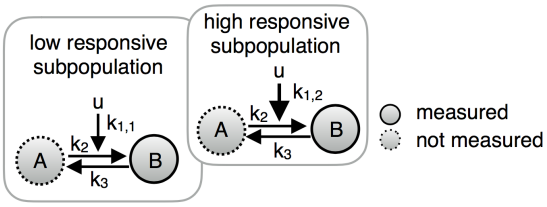

Figure 1 Model for the conversion process.

2.2 Differential protein expression

In this example, models incorporating the **mean and variance** (e.g., model_SP_k3.m) are implemented and compared. The first model (main_SP_ODEMM_1D.m) only analyzes the marginal distributions of multivariate measurements, whereas the second model (main_SP_ODEMM_2D.m) exploits the correlation structures. For both models, the sigma-point approximation is employed.

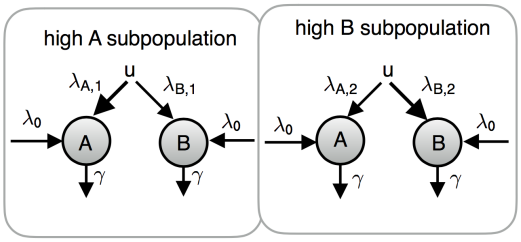

Figure 2 Model for differential protein expression.

2.3 Intrinsic noise for a two stage model of gene expression

For this example, we obtained the mean and variance using the moment-closure approximation provided by the toolbox CERENA.

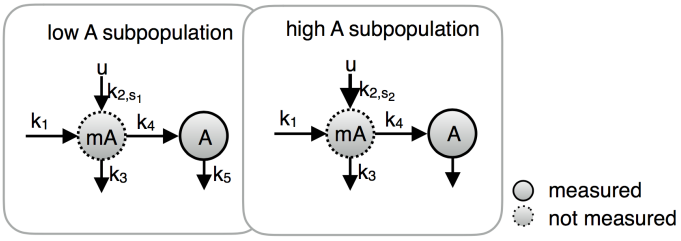

Figure 3 Model for the two stage model of gene expression.

3 File Index

3.1 File List

Here is a list of all documented files with brief descriptions:

4 File Documentation

4.1 collectConditions.m File Reference

This function collects all different conditions regarding input/differences between subpopulations/experiments and timepoints.

Functions

- mlhsSubst< mlhsInnerSubst< matlabtypesubstitute, conditions >,mlhsInnerSubst< matlabtypesubstitute, D > > collectConditions (matlabtypesubstitute D, matlabtypesubstitute M)

  This function collects all different conditions regarding input/differences between subpopulations/experiments and timepoints.

4.1.1 Detailed Description

This function collects all different conditions regarding input/differences between subpopulations/experiments and timepoints.

4.1.2 Function Documentation

4.1.2.1 mlhsSubst< mlhsInnerSubst< matlabtypesubstitute, conditions >,mlhsInnerSubst< matlabtypesubstitute, D > > collectConditions (matlabtypesubstitute *D,* matlabtypesubstitute *M*)

This function collects all different conditions regarding input/differences between subpopulations/experiments and timepoints.

USAGE

[conditions,D] = collectConditions(D,M)

Parameters

D	data struct
M	model struct

Return values

conditions	conditions struct
D	updated data struct

Required fields of D:

- `t` -- time vector
- `u` -- vector of stimulations

Required fields of M:

- `n_subpop` -- number of subpopulations
- `u{s,e}` — input vector capturing differences between subpopulations and experiments

Generated fields of D:

- `c` -- n_subpop x (n_u + n_differences) matrix linking condition to data

Generated fields of conditions:

- `input` -- (n_u + n_differences) x 1 input vector
- `time` -- 1 x n_t time vector
- `sigma` -- 1 x n_t vector of sigmas for condition c

Definition at line 17 of file collectConditions.m.

Referenced by logLikelihood(), and plotODEMix().

4.2 computeMixtureProbability.m File Reference

Robust calculation of a mixture distribution likelihood.

Functions

- mlhsInnerSubst< matlabtypesubstitute, varargout > computeMixtureProbability (matlabtypesubstitute varargin)

  Robust calculation of a mixture distribution likelihood.

4.2.1 Detailed Description

Robust calculation of a mixture distribution likelihood.

4.2.2 Function Documentation

4.2.2.1 mlhsInnerSubst< matlabtypesubstitute, varargout > computeMixtureProbability (matlabtypesubstitute *varargin*)

Robust calculation of a mixture distribution likelihood.

USAGE

[logp,dlogpdxi] = computeMixtureProbability(w,q_i,H_i)
[logp] = computeMixtureProbability(w,q_i)

Parameters

varargin	`1 computeMixtureProbability ( w, q_i, H_i )` *Required Parameters for varargin:* • w (1 x n_s) vector with weights w_s • q_i (n x n_s) matrix with log(p_i) for every column • H_i (n x n_xi x n_s) s.th. d(w_i∗p_i)/dxi = p_i∗H_i

Return values

logp	1x1 scalar of loglikelihood
dlogpdxi	n_xi x 1 vector of gradient

Definition at line 17 of file computeMixtureProbability.m.

Referenced by logLikelihood().

4.3 distributions/logn/func_dmudxi_logn_mean.m File Reference

This function calculates the derivative of μ of the (multivariate) log-normal distribution for the case of linking the mean of the observables to the mean of the (multivariate) log-normal distribution.

Functions

- mlhsInnerSubst< matlabtypesubstitute, dmudxi > func_dmudxi_logn_mean (matlabtypesubstitute t, matlabtypesubstitute x, matlabtypesubstitute dxdxi, matlabtypesubstitute Sigma, matlabtypesubstitute dSigmadxi, matlabtypesubstitute xi, matlabtypesubstitute u, matlabtypesubstitute dim)

  This function calculates the derivative of μ of the (multivariate) log-normal distribution for the case of linking the mean of the observables to the mean of the (multivariate) log-normal distribution.

4.3.1 Detailed Description

This function calculates the derivative of μ of the (multivariate) log-normal distribution for the case of linking the mean of the observables to the mean of the (multivariate) log-normal distribution.

4.3.2 Function Documentation

4.3.2.1 mlhsInnerSubst< matlabtypesubstitute, dmudxi > func_dmudxi_logn_mean (matlabtypesubstitute *t,* matlabtypesubstitute *x,* matlabtypesubstitute *dxdxi,* matlabtypesubstitute *Sigma,* matlabtypesubstitute *dSigmadxi,* matlabtypesubstitute *xi,* matlabtypesubstitute *u,* matlabtypesubstitute *dim*)

This function calculates the derivative of μ of the (multivariate) log-normal distribution for the case of linking the mean of the observables to the mean of the (multivariate) log-normal distribution.

Parameters

t	time vector (not used, included for consistency and possible extensions)
x	vector of the means and covariances (not used, included for consistency and possible extensions)
dxdxi	derivatives of the means and covariances
Sigma	(not used, included for consistency and possible extensions)
dSigmadxi	(not used, included for consistency and possible extensions)
xi	parameter vector (not used, included for consistency and possible extensions)
u	input/stimulus (not used, included for consistency and possible extensions)
n_dim	dimension of measurements

Return values

dmudxi	derivative of μ of the (multivariate) log-normal distribution

Definition at line 17 of file func_dmudxi_logn_mean.m.

4.4 distributions/logn/func_dmudxi_logn_median.m File Reference

This function calculates the derivative of μ of the (multivariate) log-normal distribution for the case of linking the mean of the observables to the median of the (multivariate) log-normal distribution. This should only be used for the case of using only a mechanistic description of the means of the observables.

Functions

- mlhsInnerSubst< matlabtypesubstitute, dmudxi > func_dmudxi_logn_median (matlabtypesubstitute t, matlabtypesubstitute x, matlabtypesubstitute dxdxi, matlabtypesubstitute Sigma, matlabtypesubstitute dSigmadxi, matlabtypesubstitute xi, matlabtypesubstitute u, matlabtypesubstitute dim)

  This function calculates the derivative of μ of the (multivariate) log-normal distribution for the case of linking the mean of the observables to the median of the (multivariate) log-normal distribution. This should only be used for the case of using only a mechanistic description of the means of the observables.

4.4.1 Detailed Description

This function calculates the derivative of μ of the (multivariate) log-normal distribution for the case of linking the mean of the observables to the median of the (multivariate) log-normal distribution. This should only be used for the case of using only a mechanistic description of the means of the observables.

4.4.2 Function Documentation

4.4.2.1 mlhsInnerSubst< matlabtypesubstitute, dmudxi > func_dmudxi_logn_median (matlabtypesubstitute *t,* matlabtypesubstitute *x,* matlabtypesubstitute *dxdxi,* matlabtypesubstitute *Sigma,* matlabtypesubstitute *dSigmadxi,* matlabtypesubstitute *xi,* matlabtypesubstitute *u,* matlabtypesubstitute *dim*)

This function calculates the derivative of μ of the (multivariate) log-normal distribution for the case of linking the mean of the observables to the median of the (multivariate) log-normal distribution. This should only be used for the case of using only a mechanistic description of the means of the observables.

Parameters

t	time vector (not used, included for consistency and possible extensions)
x	vector of the means and covariances (not used, included for consistency and possible extensions)
dxdxi	derivatives of the means and covariances
Sigma	(not used, included for consistency and possible extensions)
dSigmadxi	(not used, included for consistency and possible extensions)
xi	parameter vector (not used, included for consistency and possible extensions)
u	input (not used, included for consistency and possible extensions)
n_dim	dimension of measurement

Return values

dmudxi	derivative of μ of the (multivariate) log-normal distribution

Definition at line 17 of file func_dmudxi_logn_median.m.

4.5 distributions/logn/func_dsigma2dxi_logn.m File Reference

This function calcuatates the derivative of σ^2 in case of univariate measurements and a log-normal distribution assumption.

Functions

- mlhsInnerSubst< matlabtypesubstitute, dsigma2dxi > func_dsigma2dxi_logn (matlabtypesubstitute t, matlabtypesubstitute x, matlabtypesubstitute dxdxi, matlabtypesubstitute xi, matlabtypesubstitute varargin)

  This function calcuatates the derivative of σ^2 in case of univariate measurements and a log-normal distribution assumption.

4.5.1 Detailed Description

This function calcuatates the derivative of σ^2 in case of univariate measurements and a log-normal distribution assumption.

4.5.2 Function Documentation

4.5.2.1 mlhsInnerSubst< matlabtypesubstitute, dsigma2dxi > func_dsigma2dxi_logn (matlabtypesubstitute *t,* matlabtypesubstitute *x,* matlabtypesubstitute *dxdxi,* matlabtypesubstitute *xi,* matlabtypesubstitute *varargin*)

This function calcuatates the derivative of σ^2 in case of univariate measurements and a log-normal distribution assumption.

USAGE: dsigma2dxi = func_dsigma2dxi_logn(t,x,dxdxi,xi)
dsigma2dxi = func_dsigma2dxi_logn(t,x,dxdxi,xi,noise,dnoisedxi,'additive')
dsigma2dxi = func_dsigma2dxi_logn(t,x,dxdxi,xi,noise,dnoisedxi,'multiplicative')

Parameters

t	time vector (not used, included for consistency and possible extensions)
x	vector of the means and variances (not used, included for consistency and possible extensions)
dxdxi	derivatives of the means and variances
xi	parameter vector(not used, included for consistency and possible extensions)
varargin	• noise: parameters for measurement noise • dnoisedxi: derivative of measurement noise • noisemodel: 'multiplicative' or 'additive'

Return values

dsigma2dxi	derivative of σ^2 of a log-normal distribution

Definition at line 17 of file func_dsigma2dxi_logn.m.

4.6 distributions/logn/func_dSigmadxi_logn.m File Reference

This function maps the means and covariances of the observables for a subpopulation to Σ of the multivariate log-normal distribution.

Functions

- mlhsInnerSubst< matlabtypesubstitute, dSigmadxi > func_dSigmadxi_logn (matlabtypesubstitute t, matlabtypesubstitute x, matlabtypesubstitute dxdxi, matlabtypesubstitute xi, matlabtypesubstitute n_dim, matlabtypesubstitute varargin)

  This function maps the means and covariances of the observables for a subpopulation to Σ of the multivariate log-normal distribution.

4.6.1 Detailed Description

This function maps the means and covariances of the observables for a subpopulation to Σ of the multivariate log-normal distribution.

4.6.2 Function Documentation

4.6.2.1 mlhsInnerSubst< matlabtypesubstitute, dSigmadxi > func_dSigmadxi_logn (matlabtypesubstitute *t,* matlabtypesubstitute *x,* matlabtypesubstitute *dxdxi,* matlabtypesubstitute *xi,* matlabtypesubstitute *n_dim,* matlabtypesubstitute *varargin*)

This function maps the means and covariances of the observables for a subpopulation to Σ of the multivariate log-normal distribution.

USAGE

```
dSigmadxi = func_dSigmadxi_logn(t,x,dxdxi,xi,n_n_dim)
dSigmadxi = func_dSigmadxi_logn(t,x,dxdxi,xi,n_n_dim,noise,dnoisedxi,'multiplicative')
dSigmadxi = func_dSigmadxi_logn(t,x,dxdxi,xi,n_n_dim,noise,dnoisedxi,'additive')
```

Definition at line 17 of file func_dSigmadxi_logn.m.

4.7 distributions/logn/func_Sigma_logn.m File Reference

This function maps the means and covariances to Σ of a (multivariate) log-normal distribution.

Functions

- mlhsInnerSubst< matlabtypesubstitute, Sigma > func_Sigma_logn (matlabtypesubstitute t, matlabtypesubstitute x, matlabtypesubstitute xi, matlabtypesubstitute n_dim, matlabtypesubstitute varargin)

  This function maps the means and covariances to Σ of a (multivariate) log-normal distribution.

4.7.1 Detailed Description

This function maps the means and covariances to Σ of a (multivariate) log-normal distribution.

4.7.2 Function Documentation

4.7.2.1 mlhsInnerSubst< matlabtypesubstitute, Sigma > func_Sigma_logn (matlabtypesubstitute *t,* matlabtypesubstitute *x,* matlabtypesubstitute *xi,* matlabtypesubstitute *n_dim,* matlabtypesubstitute *varargin*)

This function maps the means and covariances to Σ of a (multivariate) log-normal distribution.

USAGE

```
Sigma = func_Sigma_logn(t,x,xi,n_dim)
Sigma = func_Sigma_logn(t,x,xi,n_dim,noise,'additive')
Sigma = func_Sigma_logn(t,x,xi,n_dim,noise,'multiplicative')
```

Definition at line 17 of file func_Sigma_logn.m.

4.8 distributions/logn/logoflognpdf.m File Reference

Modified version of MATLAB function LOGNPDF such that the log-density is returned.

Functions

- mlhsInnerSubst< matlabtypesubstitute, logy > logoflognpdf (matlabtypesubstitute x, matlabtypesubstitute mu, matlabtypesubstitute sigma)

  Modified version of MATLAB function LOGNPDF such that the log-density is returned.

4.8.1 Detailed Description

Modified version of MATLAB function LOGNPDF such that the log-density is returned.

4.8.2 Function Documentation

4.8.2.1 mlhsInnerSubst< matlabtypesubstitute, logy > logoflognpdf (matlabtypesubstitute *x,* matlabtypesubstitute *mu,* matlabtypesubstitute *sigma*)

Modified version of MATLAB function LOGNPDF such that the log-density is returned.

LOGNPDF Lognormal probability density function (pdf). Y = LOGNPDF(X,MU,SIGMA) returns values at X of the lognormal pdf with distribution parameters MU and SIGMA. MU and SIGMA are the mean and standard deviation, respectively, of the associated normal distribution. The size of Y is the common size of the input arguments. A scalar input functions as a constant matrix of the same size as the other inputs.

Default values for MU and SIGMA are 0 and 1 respectively.

See also

LOGNCDF, LOGNFIT, LOGNINV, LOGNLIKE, LOGNRND, LOGNSTAT.

Definition at line 17 of file logoflognpdf.m.

Referenced by logLikelihood().

4.9 distributions/logn/logofmvnpdf.m File Reference

Modified version of MATLAB function MVNPDF such that the log-density is returned.

Functions

- mlhsInnerSubst< matlabtypesubstitute, y > logofmvnpdf (matlabtypesubstitute X, matlabtypesubstitute Mu, matlabtypesubstitute Sigma)

  Modified version of MATLAB function MVNPDF such that the log-density is returned.

4.9.1 Detailed Description

Modified version of MATLAB function MVNPDF such that the log-density is returned.

4.9.2 Function Documentation

4.9.2.1 mlhsInnerSubst< matlabtypesubstitute, y > logofmvnpdf (matlabtypesubstitute *X,* matlabtypesubstitute *Mu,* matlabtypesubstitute *Sigma*)

Modified version of MATLAB function MVNPDF such that the log-density is returned.

MVNPDF Multivariate normal probability density function (pdf). Y = MVNPDF(X) returns the probability density of the multivariate normal distribution with zero mean and identity covariance matrix, evaluated at each row of X. Rows of the N-by-D matrix X correspond to observations or points, and columns correspond to variables or coordinates. Y is an N-by-1 vector.

Y = MVNPDF(X,MU) returns the density of the multivariate normal distribution with mean MU and identity covariance matrix, evaluated at each row of X. MU is a 1-by-D vector, or an N-by-D matrix, in which case the density is evaluated for each row of X with the corresponding row of MU. MU can also be a scalar value, which MVNPDF replicates to match the size of X.

Y = MVNPDF(X,MU,SIGMA) returns the density of the multivariate normal distribution with mean MU and covariance SIGMA, evaluated at each row of X. SIGMA is a D-by-D matrix, or an D-by-D-by-N array, in which case the density is evaluated for each row of X with the corresponding page of SIGMA, i.e., MVNPDF computes Y(I) using X(I,:) and SIGMA(:,:,I). If the covariance matrix is diagonal, containing variances along the diagonal and zero covariances off the diagonal, SIGMA may also be specified as a 1-by-D matrix or a 1-by-D-by-N array, containing just the diagonal. Pass in the empty matrix for MU to use its default value when you want to only specify SIGMA.

If X is a 1-by-D vector, MVNPDF replicates it to match the leading dimension of MU or the trailing dimension of SIGMA.

Example

```
mu = [1 -1]; Sigma = [.9 .4; .4 .3];
[X1,X2] = meshgrid(linspace(-1,3,25)<tt>, linspace(-3,1,25)</tt>);
X = [X1(:) X2(:)];
p = mvnpdf(X, mu, Sigma);
surf(X1,X2,reshape(p,25,25));
```

See also

MVTPDF, MVNCDF, MVNRND, NORMPDF. Copyright 1993-2011 The MathWorks, Inc.

Definition at line 17 of file logofmvnpdf.m.

Referenced by logLikelihood().

4.10 distributions/norm/func_dmudxi_norm.m File Reference

This function calculates the derivative of μ of the (multivariate) normal distribution.

Functions

- mlhsInnerSubst< matlabtypesubstitute, dmudxi > func_dmudxi_norm (matlabtypesubstitute t, matlabtypesubstitute x, matlabtypesubstitute dxdxi, matlabtypesubstitute Sigma, matlabtypesubstitute dSigmadxi, matlabtypesubstitute xi, matlabtypesubstitute u, matlabtypesubstitute n_dim)

  This function calculates the derivative of μ of the (multivariate) normal distribution.

4.10.1 Detailed Description

This function calculates the derivative of μ of the (multivariate) normal distribution.

4.10.2 Function Documentation

4.10.2.1 mlhsInnerSubst< matlabtypesubstitute, dmudxi > func_dmudxi_norm (matlabtypesubstitute *t,* matlabtypesubstitute *x,* matlabtypesubstitute *dxdxi,* matlabtypesubstitute *Sigma,* matlabtypesubstitute *dSigmadxi,* matlabtypesubstitute *xi,* matlabtypesubstitute *u,* matlabtypesubstitute *n_dim*)

This function calculates the derivative of μ of the (multivariate) normal distribution.

Parameters

t	time vector (not used, included for consistency and possible extensions)
x	vector of means and variances (not used, included for consistency and possible extensions)
dxdxi	derivatives of means and variances
Sigma	(not used, included for consistency and possible extensions)
dSigmadxi	(not used, included for consistency and possible extensions)
xi	parameter vector (not used, included for consistency and possible extensions)
u	input (not used, included for consistency and possible extensions)
n_dim	dimension of measurement

Return values

dmudxi	derivative of μ of the (multivariate) normal distribution.

Definition at line 17 of file func_dmudxi_norm.m.

4.11 distributions/norm/func_dsigma2dxi_norm.m File Reference

This function calculates the derivative of σ^2 in case of univariate measurements and a normal distribution assumption.

Functions

- mlhsInnerSubst< matlabtypesubstitute, dsigma2dxi > func_dsigma2dxi_norm (matlabtypesubstitute t, matlabtypesubstitute x, matlabtypesubstitute dxdxi, matlabtypesubstitute xi, matlabtypesubstitute varargin)

  This function calculates the derivative of σ^2 in case of univariate measurements and a normal distribution assumption.

4.11.1 Detailed Description

This function calculates the derivative of σ^2 in case of univariate measurements and a normal distribution assumption.

4.11.2 Function Documentation

4.11.2.1 mlhsInnerSubst< matlabtypesubstitute, dsigma2dxi > func_dsigma2dxi_norm (matlabtypesubstitute *t,* matlabtypesubstitute *x,* matlabtypesubstitute *dxdxi,* matlabtypesubstitute *xi,* matlabtypesubstitute *varargin*)

This function calculates the derivative of σ^2 in case of univariate measurements and a normal distribution assumption.

USAGE: dsigma2dxi = func_dsigma2dxi_norm(t,x,dxdxi,xi) dsigma2dxi = func_dsigma2dxi_norm(t,x,dxdxi,xi,noise,dnoisedxi, 'additive')

Parameters

t	time vector (not used, included for consistency and possible extensions)
x	vector of the means and variances of the observables (not used, included for consistency and possible extensions)
dxdxi	derivatives of the means and variances of the obsevables
xi	parameter vector(not used, included for consistency and possible extensions)
varargin	• noise: parameter for measurement noise • dnoisedxi: derivative of measurement noise • noisemodel: (so far only 'additive' supported)

Return values

dsigma2dxi	derivative of σ^2 of the normal distribution.

Definition at line 17 of file func_dsigma2dxi_norm.m.

4.12 distributions/norm/func_dSigmadxi_norm.m File Reference

This function maps the means and variances to Σ of the multivariate normal distribution.

Functions

- mlhsInnerSubst< matlabtypesubstitute, dSigmadxi > func_dSigmadxi_norm (matlabtypesubstitute t, matlabtypesubstitute x, matlabtypesubstitute dxdxi, matlabtypesubstitute xi, matlabtypesubstitute n_dim, matlabtypesubstitute varargin)

  This function maps the means and variances to Σ of the multivariate normal distribution.

4.12.1 Detailed Description

This function maps the means and variances to Σ of the multivariate normal distribution.

4.12.2 Function Documentation

4.12.2.1 mlhsInnerSubst< matlabtypesubstitute, dSigmadxi > func_dSigmadxi_norm (matlabtypesubstitute *t,* matlabtypesubstitute *x,* matlabtypesubstitute *dxdxi,* matlabtypesubstitute *xi,* matlabtypesubstitute *n_dim,* matlabtypesubstitute *varargin*)

This function maps the means and variances to Σ of the multivariate normal distribution.

USAGE

```
dSigmadxi = func_dSigmadxi_norm(t,x,dxdxi,xi,n_n_dim)
dSigmadxi = func_dSigmadxi_norm(t,x,dxdxi,xi,n_n_dim,noise,dnoisedxi,'additive')
```

Definition at line 17 of file func_dSigmadxi_norm.m.

4.13 distributions/norm/func_Sigma_norm.m File Reference

This function maps the means and variances to Σ of the multivariate normal distribution.

Functions

- mlhsInnerSubst< matlabtypesubstitute, Sigma > func_Sigma_norm (matlabtypesubstitute t, matlabtypesubstitute x, matlabtypesubstitute xi, matlabtypesubstitute n_dim, matlabtypesubstitute varargin)

  This function maps the means and variances to Σ of the multivariate normal distribution.

4.13.1 Detailed Description

This function maps the means and variances to Σ of the multivariate normal distribution.

4.13.2 Function Documentation

4.13.2.1 mlhsInnerSubst< matlabtypesubstitute, Sigma > func_Sigma_norm (matlabtypesubstitute *t,* matlabtypesubstitute *x,* matlabtypesubstitute *xi,* matlabtypesubstitute *n_dim,* matlabtypesubstitute *varargin*)

This function maps the means and variances to Σ of the multivariate normal distribution.

USAGE

```
Sigma = func_Sigma_norm(t,x,xi,n_dim,noise,'additive')
```

Parameters

t	time vector
x	vector including means and variances
xi	(not used, included for consistency and possible extensions)
n_dim	dimension of measurement
varargin	• noise: parameter for measurement noise • noisemodel: (so far only 'additive' supported)

Return values

Sigma	(n_t x n_dim x n_dim) Σ of the multivariate normal distribution.

Definition at line 17 of file func_Sigma_norm.m.

4.14 distributions/norm/logofnormpdf.m File Reference

Modified version of MATLAB function NORMPDF such that the log-density is given back.

Functions

- mlhsInnerSubst< matlabtypesubstitute, logy > logofnormpdf (matlabtypesubstitute x, matlabtypesubstitute mu, matlabtypesubstitute sigma)

  Modified version of MATLAB function NORMPDF such that the log-density is given back.

4.14.1 Detailed Description

Modified version of MATLAB function NORMPDF such that the log-density is given back.

4.14.2 Function Documentation

4.14.2.1 mlhsInnerSubst< matlabtypesubstitute, logy > logofnormpdf (matlabtypesubstitute *x*, matlabtypesubstitute *mu*, matlabtypesubstitute *sigma*)

Modified version of MATLAB function NORMPDF such that the log-density is given back.

NORMPDF Normal probability density function (pdf). Y = NORMPDF(X,MU,SIGMA) returns the pdf of the normal distribution with mean MU and standard deviation SIGMA, evaluated at the values in X. The size of Y is the common size of the input arguments. A scalar input functions as a constant matrix of the same size as the other inputs.

Default values for MU and SIGMA are 0 and 1 respectively.

See also

NORMCDF, NORMFIT, NORMINV, NORMLIKE, NORMRND, NORMSTAT.

Definition at line 17 of file logofnormpdf.m.

Referenced by logLikelihood().

4.15 generateODEMM.m File Reference

This function generates a file that defines the ODE-constrained mixture model.

Functions

- mlhsInnerSubst< matlabtypesubstitute, varargout > generateODEMM (matlabtypesubstitute D, matlabtypesubstitute M, matlabtypesubstitute parameters, matlabtypesubstitute conditions, matlabtypesubstitute varargin)

  This function generates a file that defines the ODE-constrained mixture model.
- mlhsInnerSubst< matlabtypesubstitute, retstr > **mtoc_subst_generateODEMM_m_tsbus_cotm_↩replace_xi_x_u** (matlabtypesubstitute symexpr)
- mlhsInnerSubst< matlabtypesubstitute, str_dzdxi > **mtoc_subst_generateODEMM_m_tsbus_cotm↩_getStrDerivative2Terms** (matlabtypesubstitute sym_expr, matlabtypesubstitute x, matlabtypesubstitute dxdxi, matlabtypesubstitute xi)
- mlhsInnerSubst< matlabtypesubstitute, str_dzdxi > **mtoc_subst_generateODEMM_m_tsbus_cotm_↩getStrDerivative3Terms** (matlabtypesubstitute deriv_name, matlabtypesubstitute sym_expr, matlabtypesubstitute s, matlabtypesubstitute e, matlabtypesubstitute x, matlabtypesubstitute dxdxi, matlabtypesubstitute sigma, matlabtypesubstitute dsigmadxi, matlabtypesubstitute xi)

4.15.1 Detailed Description

This function generates a file that defines the ODE-constrained mixture model.

4.15.2 Function Documentation

4.15.2.1 mlhsInnerSubst< matlabtypesubstitute, varargout > generateODEMM (matlabtypesubstitute *D,* matlabtypesubstitute *M,* matlabtypesubstitute *parameters,* matlabtypesubstitute *conditions,* matlabtypesubstitute *varargin*)

This function generates a file that defines the ODE-constrained mixture model.

USAGE

M = generateODEMM(D,M,parameters,conditions,options)

Parameters

D	data struct
M	model struct
parameters	parameters struct
conditions	conditions struct obtained by collectConditions.m
varargin	`1 generateODEMM ( ..., options )` *Required Parameters for varargin:* • options (options for the generation)

Required fields of M:

- `name --` name of the model
- `model --` simulation file with input (T,theta,u) (e.g., generated by amiwrap of the toolbox AMICI), the first output needs to be the status of thesimulation (whether it failed or not) the 4th the simulation output, and the 6th the sensitivities
- `sim_type --` simulation type ('RRE' for a mechanistic description of the mean, e.g., by reaction rate equations, 'HO' for a mechanistic description of the mean and covariance, e.g., by moment-closure approximation or sigma-point approximation)
- `n_subpop --` number of subpopulations
- `distribution{s,e}` — distribution assumption
  = 'norm' for normal distribution assumption
  = 'logn_median' for log-normal distribution assumption when mean of simulation linked to median of distribution
  = 'logn_mean' for log-normal distribution assumption when mean of simulation is % linked to mean of distribution
- `mean_ind{s,e}` — indices of simulation output describing the mean of the measurand(s) of experiment e
- `var_ind{s,e}` — indices of simulation output describing the variance (empty if RREs used)
- `u{s,e}` — input vector describing differences between subpopulations and experiments
- `sym --` symbolic description of properties of the model with fields
  - w{s,e}: weights of subpopulation s in experiment e
  - theta: parameter needed for simulation of individual subpopulations
  - scaling{r,e}: scaling factor for replicate r in experiment e, if the replicates are not considered seperately, use r=1
  - offset{r,e}: offset parameter for replicate r in experiment e

Required fields of D:

- `conditions --` obtained by collectConditions.m

Required fields of parameters:

Optional fields of options:

- `write_parameter --` write parameter definition in file (true by default)
- `measurement_noise --` if measurement noise is included
  = true
  = false (default)
- `replicates --` if individual replicates are modeled = true
  = false (default)
- `sigmas --` parametrization of the variance in case of using only a mechanistic description of the mean
  = 'condition-dependent': (default) assign sigma for every time point
  = 'time-independent': sigma stays the same for subpopulation and some dosage
  = 'only-one': only one sigma for everything

Definition at line 17 of file generateODEMM.m.

4.16 getLognMeanVar.m File Reference

This function calculations the mean and variances, and the corresponding derivatives of a multivariate log-normal distribution given the parameters μ and Σ.

Functions

- mlhsSubst< mlhsInnerSubst< matlabtypesubstitute, Zout >,mlhsInnerSubst< matlabtypesubstitute, varargout > > getLognMeanVar (matlabtypesubstitute Z, matlabtypesubstitute n_dim, matlabtypesubstitute varargin)

  This function calculations the mean and variances, and the corresponding derivatives of a multivariate log-normal distribution given the parameters μ and Σ.

4.16.1 Detailed Description

This function calculations the mean and variances, and the corresponding derivatives of a multivariate log-normal distribution given the parameters μ and Σ.

4.16.2 Function Documentation

4.16.2.1 mlhsSubst< mlhsInnerSubst< matlabtypesubstitute, Zout >,mlhsInnerSubst< matlabtypesubstitute, varargout > > getLognMeanVar (matlabtypesubstitute *Z,* matlabtypesubstitute *n_dim,* matlabtypesubstitute *varargin*)

This function calculations the mean and variances, and the corresponding derivatives of a multivariate log-normal distribution given the parameters μ and Σ.

USAGE

[Zout] = getLognMeanVar(Z,n_dim)
[Zout,dZdthetaout] = getLognMeanVar(Z,n_dim,dZdtheta)

Parameters

Z	(n_dim + n_dim(n_dim+1)/2) x n_t vector with μ and Σ
n_dim	dimension of the multivariate log-normal distribution
varargin	`1 getLognMeanVar ( ..., dZdtheta )` *Required Parameters for varargin:* • dZdtheta ((n_dim + n_dim(n_dim+1)/2) x n_theta x n_t derivative)

Return values

Zout	(n_dim + n_dim(n_dim+1)/2) x n_t vector with mean and coariance
dZdthetaout	derivative of Zout

Definition at line 17 of file getLognMeanVar.m.

Referenced by logLikelihood(), and plotODEMix().

4.17 getRREsigmas.m File Reference

This function defines the parameters needed for the parametrization of the variances in case Reaction Rate Equations are used for the mechanistic description of the means.

Functions

- mlhsSubst< mlhsInnerSubst< matlabtypesubstitute, parameters >,mlhsInnerSubst< matlabtypesubstitute, conditions >,mlhsInnerSubst< matlabtypesubstitute, varargout > > getRREsigmas (matlabtypesubstitute parameters, matlabtypesubstitute conditions, matlabtypesubstitute varargin)

  This function defines the parameters needed for the parametrization of the variances in case Reaction Rate Equations are used for the mechanistic description of the means.

4.17.1 Detailed Description

This function defines the parameters needed for the parametrization of the variances in case Reaction Rate Equations are used for the mechanistic description of the means.

4.17.2 Function Documentation

4.17.2.1 mlhsSubst< mlhsInnerSubst< matlabtypesubstitute, parameters >,mlhsInnerSubst< matlabtypesubstitute, conditions >,mlhsInnerSubst< matlabtypesubstitute, varargout > > getRREsigmas (matlabtypesubstitute *parameters,* matlabtypesubstitute *conditions,* matlabtypesubstitute *varargin*)

This function defines the parameters needed for the parametrization of the variances in case Reaction Rate Equations are used for the mechanistic description of the means.

USAGE

[parameters,conditions] = getRREsigmas(parameters,conditions)
[parameters,conditions,D] = getRREsigmas(parameters,conditions,options,D,M)

Parameters

parameters	parameters struct
conditions	conditions struct (see collectConditions.m)
varargin	`1 getRREsigmas ( ..., options, D, M )` *Required Parameters for varargin:* • options • D data struct (see logLikelihood.m) • M model struct (see generateODEMM.m)

Return values

parameters	updated parameters struct
conditions	updated conditions struct
D	updated data struct

Required fields of parameters:

Optional fields of options:

- `sigmas --`
  = 'condition-dependent': (default) assign sigma for every time point
  = 'time-dependent': one sigma for every subpopulation and time point
  = 'only-one': only one sigma for everything
  = 'subpopulation-specific': for every subpopulation one sigma

- `boundaries --` boundaries for optimization for the sigma parameters with fields
  - min
  - max

Generated fields of parameters:

- `names --` names for sigma parameters are added

Generated fields of D:

- `sigma --` (if n_dim = 1)
- `Sigma --` (if n_dim = 2)

Definition at line 17 of file getRREsigmas.m.

4.18 getScalingFactors.m File Reference

Calculates scaling factors for replicates such that the distance between the means in log-space are minimal.

Functions

- mlhsInnerSubst< matlabtypesubstitute, s > getScalingFactors (matlabtypesubstitute varargin)
  Calculates scaling factors for replicates such that the distance between the means in log-space are minimal.

4.18.1 Detailed Description

Calculates scaling factors for replicates such that the distance between the means in log-space are minimal.

4.18.2 Function Documentation

4.18.2.1 mlhsInnerSubst< matlabtypesubstitute, s > getScalingFactors (matlabtypesubstitute *varargin*)

Calculates scaling factors for replicates such that the distance between the means in log-space are minimal.

USAGE

s = getScalingFactors(ExpC)
s = getScalingFactors(ExpC_1,ExpC_2)

Parameters

varargin	`1 getScalingFactors ( ExpC )` *Required Parameters for varargin:* • ExpC struct of experiments

Return values

s	(1 x n_r) vector including scaling factor for every replicate

Required fields of ExpC:

- `name --` string specifying the conditions
- `time --` time point of measurement
- `stimulus --` stimulus for measurement
- `replicate --` struct of replicates
  - name: string specifying the replicate
  - measurands: names of measurands
  - ndata: matrices under different conditions (one row represents one observed cell with the data in the order of the measurands. The different rows provide measurement data for different cells)

Definition at line 17 of file getScalingFactors.m.

4.19 getSigmaPointApp_status_mod.m File Reference

Modified version of the getSigmaPointApp.m function of the SPToolbox.

Functions

- mlhsSubst< mlhsInnerSubst< matlabtypesubstitute, status >,mlhsInnerSubst< matlabtypesubstitute, SP > > getSigmaPointApp_status_mod (matlabtypesubstitute varargin)

  Modified version of the getSigmaPointApp.m function of the SPToolbox.

4.19.1 Detailed Description

Modified version of the getSigmaPointApp.m function of the SPToolbox.

4.19.2 Function Documentation

4.19.2.1 mlhsSubst< mlhsInnerSubst< matlabtypesubstitute, status >,mlhsInnerSubst< matlabtypesubstitute, SP > > getSigmaPointApp_status_mod (matlabtypesubstitute *varargin*)

Modified version of the getSigmaPointApp.m function of the SPToolbox.

Generated fields of SP:

Definition at line 17 of file getSigmaPointApp_status_mod.m.

Referenced by testSigmaPointApp_mod().

4.20 install_ODEMM.m File Reference

Script that adds the required paths to the MATLAB search path.

Functions

- noret::substitute install_ODEMM ()
  Script that adds the required paths to the MATLAB search path.

4.20.1 Detailed Description

Script that adds the required paths to the MATLAB search path.

4.21 load_plot_settings.m File Reference

Functions to set font sizes and colors for the visualization.

Functions

- noret::substitute load_plot_settings ()
  Functions to set font sizes and colors for the visualization.

4.21.1 Detailed Description

Functions to set font sizes and colors for the visualization.

4.22 logLikelihood.m File Reference

This function evaluates the likelihood function for a given model, data and parameter vector.

Functions

- mlhsInnerSubst< matlabtypesubstitute, varargout > logLikelihood (matlabtypesubstitute xi, matlabtypesubstitute M, matlabtypesubstitute D, matlabtypesubstitute varargin)

  This function evaluates the likelihood function for a given model, data and parameter vector.

4.22.1 Detailed Description

This function evaluates the likelihood function for a given model, data and parameter vector.

4.22.2 Function Documentation

4.22.2.1 mlhsInnerSubst< matlabtypesubstitute, varargout > logLikelihood (matlabtypesubstitute *xi,* matlabtypesubstitute *M,* matlabtypesubstitute *D,* matlabtypesubstitute *varargin*)

This function evaluates the likelihood function for a given model, data and parameter vector.

USAGE

[...] = logLikelihood(xi,M,D,options,conditions,I)
[...] = logLikelihood(xi,M,D,options,conditions)
[...] = logLikelihood(xi,M,D,options)
[logL] = logLikelihood(...)
[logL, dlogL] = logLikelihood(...)

Parameters

xi	parameter values
M	model struct
D	data struct
varargin	`1 logLikelihood ( ..., options, conditions, I )` *Required Parameters for varargin:* • options struct • conditions generated by function collectConditions.m • I indices for which of the data the likelihood function should be evaluated

Return values

logL	log-likelihood value
dlogL	gradient of log-likelihood function

Required fields of M:

- `n_subpop --` number of subpopulations

- `model --` simulation file with input (T,theta,u) (e.g., generated by amiwrap), the first output needs to be the status of the simulation, the 4th the simulation output and the 6th the sensitivities (n_t x n_obs x n_theta)
- `mean_ind --` indices of output for mean
- `var_ind --` indices of output for variances (empty if using RREs)
- `theta --` parameters needed for simulation dependend on xi and u the following fields of M are generated by generate_ODEMM
- `distribution{s,e}` — distribution assumption
  = 'norm': normal distribution assumption
  = 'logn_median': log-normal distribution assumption, mean of simulation linked to median of distribution
  = 'logn_mean': log-normal distribution assumption, mean of simulation linked to mean of distribution

  The following fields are automatically added by generateODEMM.m
- `dthetadxi --` gradient of theta
- `mu{s,e}` — specification of mixture parameter mu for subpopulation s and experiment e
- `dmudxi{s,e}` — gradient of mu
- `sigma{s,e}` — specification of mixture parameter σ (M.Sigma in multivariate case (covariance matrix))
- `dsigmadxi{s,e}` — gradient of sigma (M.dSigmadxi in multivariate case)
- `w{s,e}` — specification of weights w_s
- `dwdxi{s,e}` — gradient of weights
- `scaling{r,e}` — scaling parameter of replicate r in experiment e
- `dscalingdxi{r,e}` — gradient of scaling
- `offset{r,e}` — offset
- `doffsetdxi{r,e}` — gradient of offset

Required fields of D:

- `n_dim --` dimension of the measurements
- `t --` 1 x n_t vector of timepoints
- `u --` n_maxu x n_u vector of inputs with n_maxu: maximal number of inputs simulatenously used
- `y --` n_u x n_t x n_cells x n_dim data matrix (only needed if replicates are merged and already scaled), dim is the dimension of the measurement
- `c --` n_subpop x (n_u + n_differences) corresponding condition (automatically added by calling collectCondition.m)
- `replicate(r).y` — n_u x n_t x n_cells x n_dim data matrix of replicate r in experiment e (only needed if individual replicates should be fitted)

Optional fields of options:

- `use_robust --` robust calculation of mixture probability
  = true: uses reformulation (default)
  = false: classical calculation (not recommended)
- `simulate_musigma --` true if simulation directly provides ...
- `negLogLikelihood --` true if negativev log-likelihood required
- `replicates --` true if replicates are fitted individually

Definition at line 17 of file logLikelihood.m.

References collectConditions(), computeMixtureProbability(), getLognMeanVar(), logoflognpdf(), logofmvnpdf(), and logofnormpdf().

4.23 plotODEMix.m File Reference

Routine to plot the ODE-constrained mixture model.

Functions

- mlhsInnerSubst< matlabtypesubstitute, varargout > plotODEMix (matlabtypesubstitute varargin)

  Routine to plot the ODE-constrained mixture model.
- mlhsInnerSubst< matlabtypesubstitute, str_dose > **mtoc_subst_plotODEMix_m_tsbus_cotm_getStr↩Dose** (matlabtypesubstitute D, matlabtypesubstitute e, matlabtypesubstitute d)
- noret::substitute **mtoc_subst_plotODEMix_m_tsbus_cotm_evalModel** (matlabtypesubstitute xi, matlabtypesubstitute M, matlabtypesubstitute D, matlabtypesubstitute e, matlabtypesubstitute r, matlabtypesubstitute d, matlabtypesubstitute X_c, matlabtypesubstitute options, matlabtypesubstitute conditions)
- mlhsSubst< mlhsInnerSubst< matlabtypesubstitute, lim >,mlhsInnerSubst< matlabtypesubstitute, hists >,mlhsInnerSubst< matlabtypesubstitute, grids > > **mtoc_subst_plotODEMix_m_tsbus_cotm_set↩YminmaxHists** (matlabtypesubstitute D, matlabtypesubstitute e, matlabtypesubstitute d, matlabtypesubstitute options, matlabtypesubstitute ind)
- noret::substitute **mtoc_subst_plotODEMix_m_tsbus_cotm_evalPdf** (matlabtypesubstitute M, matlabtypesubstitute D, matlabtypesubstitute e, matlabtypesubstitute d, matlabtypesubstitute k, matlabtypesubstitute options, matlabtypesubstitute legendflag, matlabtypesubstitute ind, matlabtypesubstitute lim, matlabtypesubstitute hists, matlabtypesubstitute grids, matlabtypesubstitute plotModel, matlabtypesubstitute plotData)

4.23.1 Detailed Description

Routine to plot the ODE-constrained mixture model.

4.23.2 Function Documentation

4.23.2.1 mlhsInnerSubst< matlabtypesubstitute, varargout > plotODEMix (matlabtypesubstitute *varargin*)

Routine to plot the ODE-constrained mixture model.

USAGE

[...] = plotODEMix(D,M,xi)
[...] = plotODEMix(D,M,xi,I,options)
[...] = plotODEMix(D,M,xi,I,options,tu_ind)
[fh] = plotODEMix(...)
[fh,fhm] = plotODEMix(...)

Parameters

varargin	• D: data struct • M: model struct • xi: parameter vector • I: (optional) indices for which the data and model should be visualized, the whole data set is visualized if I = [] • options: plotting options • tu_ind{e}: struct of indices for the time points/doses for which the data and model should be visualized

Return values

fh	struct of function handles for each data set
fhm	struct of function handles for the plots of the marginals

Definition at line 17 of file plotODEMix.m.

References collectConditions(), and getLognMeanVar().

4.24 printParams.m File Reference

Help function to print parameters names and values.

Functions

- noret::substitute printParams (matlabtypesubstitute parameters, matlabtypesubstitute varargin)
  Help function to print parameters names and values.

4.24.1 Detailed Description

Help function to print parameters names and values.

4.24.2 Function Documentation

4.24.2.1 noret::substitute printParams (matlabtypesubstitute *parameters,* matlabtypesubstitute *varargin*)

Help function to print parameters names and values.

USAGE

[] = printParams(parameters,xi)

Parameters

parameters	parameters struct
varargin	`1 printParams ( ..., xi )` *Required Parameters for varargin:* • xi parameter values printed together with parameter names

Required fields of parameters:

- `name --` struct with names of parameters

Definition at line 17 of file printParams.m.

4.25 testSigmaPointApp_mod.m File Reference

Modified version of the testSigmaPointApp_status.m function of the SPToolbox.

Functions

- mlhsInnerSubst< matlabtypesubstitute, SP > testSigmaPointApp_mod (matlabtypesubstitute varargin)
  Modified version of the testSigmaPointApp_status.m function of the SPToolbox.

4.25.1 Detailed Description

Modified version of the testSigmaPointApp_status.m function of the SPToolbox.

4.25.2 Function Documentation

4.25.2.1 mlhsInnerSubst< matlabtypesubstitute, SP > testSigmaPointApp_mod (matlabtypesubstitute *varargin*)

Modified version of the testSigmaPointApp_status.m function of the SPToolbox.

Generated fields of SP:

Definition at line 17 of file testSigmaPointApp_mod.m.

References getSigmaPointApp_status_mod().

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