LEARN

“A Lyapunov-enabled analysis of biochemical reaction networks”

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We describe the prerequisites of `LEARN` , the basic subroutines offered in `LEARN` and few example runs.

1 Prerequisites

`LEARN` runs on MATLAB with the optimization toolbox. Also, it utilizes the `cvx` package. The latest version of `cvx` is available on the link `http://cvxr.com/cvx/download/`. After download, the user must run `cvx_setup`. After `cvx_setup` reporting that `cvx` is successfully installed, `LEARN` should run without issues.

2 List of Subroutines

The following subroutines are available. Note that all the subroutines below take Γ as an input which is the stoichiometry matrix of the network. If the network has an autocatalytic reaction then both matrices A, B need to be entered. (see the Methods section in the main text)

2.1 Basic subroutines

- `LEARNmain(Gamma)`: Prints a basic report on the network. Examples will follow.
- `flag=IsConservative(Gamma)`: Checks if the network is conservative. The output is either 0 or 1.
- `flag=IsAS1(Gamma)`: Checks if the stoichiometry matrix has a positive vector in its kernel. The output is either 0 or 1.
- `flag=checkSiphons(Gamma)`: Checks if there are critical siphons. The output is either 0 or 1.
- `flag=checkMnetwork(Gamma)`: Checks if the network is an M-network. The output is either 0 or 1.

2.2 Necessary Conditions

- `flag=checkSiphonCondition(Gamma)`: Checks if the network violates the critical siphon necessary condition (Theorem 8). The output is either 0 or 1.
- `flag=SignPatternCheck(Gamma)`: Checks if the network violates the sign pattern necessary condition [**?**, Theorem 9]. The output is either 0 or 1.
- `flag=checkPmatreix(Gamma)`: Checks if the network violates the P matrix necessary condition [**?**, Theorem 8]. The output is either 0 or 1.
- `flag=RobustNondegeneracy(Gamma)`: Checks if the network has a robustly non-degenerate Jacobian (Theorem 7). This only applies to networks that pass the P matrix test. The output is either 0 or 1.

2.3 Construction of RLFs

- `C=ConstructGraphical(Gamma)`: Checks if the network admits an RLF as given in Theorem 4. The output is C. If the method fails then C will be an empty matrix.
- `C=ConstructIterate(Gamma)`: Checks if the network admits an RLF as given in Theorem 3. The output is C. If the method fails then C will be an empty matrix.
- `[C,cvx]=ConstructLP(Gamma,H2,w,c)`: Checks if the network admits an RLF as given in Theorem 2. The last three inputs are optional. The output is C and the flag `cvx` to indicate whether the RLF is convex. The second input is H_2 which are optional rows to add to the partitioning matrix $H = \Gamma$. The default value for H_2 is an empty matrix. The third input is w and it is a flag to constrain the search to weighted ℓ_1 RLFs. The default value is 0. The fourth input is a flag to constrain the RLF to be convex. The default value is 0.
- `[C,cvx]=ConstructLPauto(A,B,H2,w,c)`: Checks if an *autocatalytic* network admits an RLF as given in Theorem 2. The remaining input structure is similar to the previous subroutine.
- `[C,cvx]=ConstructCoP(Gamma,H2,c)`: Checks if the network admits an RLF as given in Theorem 5. The last two inputs are optional. The output is C and a flag `cvx` to indicate whether the RLF is convex. The second input is H_2 which are optional rows to add to the partitioning matrix $H = \Gamma$. The default value for H_2 is an empty matrix. The third input is a flag to constrain the RLF to be convex. The default value is 0.

2.4 Checking a candidate RLF

- `flag=CheckRLF(Gamma,C)`: Checks if $\tilde{V} = \max_k c_k^T r$ is an RLF for a network with the stoichiometry matrix Γ.

3 Examples

3.1 The double processive PTM cycle

This is the form of the input to `LEARN` for the network depicted in Fig. 9-b.

```
Gamma=[
-1     1     0     0     0     0     0     1;
-1     1     0     0     0     0     1     0;
 1    -1    -1     0     0     0     0     0;
 0     0     0    -1     1     0     1     0;
 0     0     0    -1     1     0     0     1;
 0     0     0     1    -1    -1     0     0;
 0     0     1     0     0     0    -1     0;
 0     0     0     0     0     1     0    -1];
LEARNmain(Gamma)
```

Note that the stoichiometry matrix Γ can be easily written from a list of reactions. The output of LEARN is as follows:

```
--------------------------------
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   gmail.com}

LEARN tries to construct a Robust Lyapunov Function for a given
   reaction network.
--------------------------------
The network has 8 species and 8 reactions.
The stoichiometric space is 5-dimensional.
The network has a positive vector in the kernel of the stoichiometry
    matrix, i.e. it has the potential for positive steady states.
The network is conservative.
The network has no critical siphons. It is structurally persistent.
--------------------------------
LEARN will check some necessary conditions
Necessary Condition # 1 ....
The critical siphon necessary condition is satisfied.
Necessary Condition # 2 ....
The sign pattern necessary condition is satisfied.
Necessary Condition # 3 ....
The P matrix necessary condition is satisfied.
--------------------------------
LEARN will search for a PWL RLF
Method # 1: Graphical Method ..
This is an M-network. The graphical criteria will be checked

Success!! A PWL RLF has been found.
The following is always a Lyapunov function for any monotone
   kinetics: V(x)=|| C*R(x) ||_infty,
where C is given as follows:
0        0        1        0        0       -1        0        0
0        0        1        0        0        0       -1        0
0        0        1        0        0        0        0       -1
-1       1        1        0        0        0        0        0
```

```
0         0        1       -1        1        0        0        0
0         0        0        0        0        1       -1        0
0         0        0        0        0        1        0       -1
-1        1        0        0        0        1        0        0
0         0        0       -1        1        1        0        0
0         0        0        0        0        0        1       -1
-1        1        0        0        0        0        1        0
0         0        0       -1        1        0        1        0
-1        1        0        0        0        0        0        1
0         0        0       -1        1        0        0        1
1        -1        0       -1        1        0        0        0

The robust non-degeneracy test is passed.
Since the network is conservative and with no critical siphons then
   the following holds:
There exists a unique positive globally asymptotically stable steady
    state  in each stoichiometric class.
--------------------------------
Method # 2: Iterative Method ..
Success!! A PWL RLF has been found.
The following is always a Lyapunov function for any monotone
   kinetics: V(x)=|| C*R(x) ||_infty,
where C is given as follows:
-1        1        0        0        0        0        0        1
-1        1        0        0        0        0        1        0
1        -1       -1        0        0        0        0        0
0         0        0       -1        1        0        1        0
0         0        0       -1        1        0        0        1
0         0        0        1       -1       -1        0        0
0         0        1        0        0        0       -1        0
0         0        0        0        0        1        0       -1
0         0        0        0        0        0       -1        1
0         0       -1        0        0        0        0        1
-1        1        0        0        0        1        0        0
0         0        0        0        0       -1        1        0
0         0        1       -1        1        0        0        0
0         0       -1        0        0        1        0        0
-1        1        0        1       -1        0        0        0

The robust non-degeneracy test is passed.
Since the network is conservative and with no critical siphons then
   the following holds:
There exists a unique positive globally asymptotically stable steady
    state  in each stoichiometric class.
--------------------------------
Method # 3: Linear Programming Method ..
The partition matrix H is set to the default choice H=the
   stoichiometry matrix ..
```

```
This method for constructing a PWL RLF has failed.
THE END.
```

3.2 The double distributive PTM cycle

This is the output of `LEARNmain` for the network depicted in Fig. 9-d.

```
--------------------------------
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   gmail.com}

LEARN tries to construct a Robust Lyapunov Function for a given
   reaction network.
--------------------------------
The network has 9 species and 12 reactions.
The stoichiometric space is 6-dimensional.
The network has a positive vector in the kernel of the stoichiometry
    matrix, i.e. it has the potential for positive steady states.
The network is conservative.
The network has no critical siphons. It is structurally persistent.
--------------------------------
LEARN will check some necessary conditions
Necessary Condition # 1 ....
The critical siphon necessary condition is satisfied.
Necessary Condition # 2 ....
The sign pattern necessary condition is satisfied.
Necessary Condition # 3 ....
The P matrix necessary condition is violated. A PWL RLF does not
   exist
--------------------------------
LEARN will search for a PWL RLF
Method # 1: Graphical Method ..
This is not an M-network. Method # 1 is not applicable.

--------------------------------
Method # 2: Iterative Method ..
This method for constructing a PWL RLF has failed.
--------------------------------
Method # 3: Linear Programming Method ..
The partition matrix H is set to the default choice H=the
   stoichiometry matrix ..
This method for constructing a PWL RLF has failed.
THE END.
```

3.3 The McKeithan Network

This is the output of `LEARNmain` for the network depicted in Fig. 11-a.

```
--------------------------------
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LEARN tries to construct a Robust Lyapunov Function for a given
   reaction network.
--------------------------------
The network has 5 species and 6 reactions.
The stoichiometric space is 3-dimensional.
The network has a positive vector in the kernel of the stoichiometry
    matrix, i.e. it has the potential for positive steady states.
The network is conservative.
The network has no critical siphons. It is structurally persistent.
--------------------------------
LEARN will check some necessary conditions
Necessary Condition # 1 ....
The critical siphon necessary condition is satisfied.
Necessary Condition # 2 ....
The sign pattern necessary condition is satisfied.
Necessary Condition # 3 ....
The P matrix necessary condition is satisfied.
--------------------------------
LEARN will search for a PWL RLF
Method # 1: Graphical Method ..
This is not an M-network. Method # 1 is not applicable.

--------------------------------
Method # 2: Iterative Method ..
Success!! A PWL RLF has been found.
The following is always a Lyapunov function for any monotone
   kinetics: V(x)=|| C*R(x) ||_infty,
where C is given as follows:
-1       1       0       0       1       1
-1       1       0       0       1       1
1       -1      -1       0       0       0
0        0       1      -1      -1       0
0        0       0       1       0      -1
0        0      -1       0       1       1
-1       1       1      -1       0       1
-1       1       0       1       1       0

The robust non-degeneracy test is passed.
Since the network is conservative and with no critical siphons then
   the following holds:
There exists a unique positive globally asymptotically stable steady
    state  in each stoichiometric class.
--------------------------------
```

```
Method # 3: Linear Programming Method ..
The partition matrix H is set to the default choice H=the
   stoichiometry matrix ..
Success!! A PWL RLF has been found.
The following is always a Lyapunov function for any monotone
   kinetics: V(x)=|| C*R(x) ||_infty,
where C is given as follows:
0        0        0        1        0       -1
0        0        1       -1       -1        0
0        0        1       -0       -1       -1
1       -1       -1        0        0        0
1       -1       -1        1        0       -1
1       -1       -0       -1       -1        0
1       -1       -0       -0       -1       -1

The robust non-degeneracy test is passed.
Since the network is conservative and with no critical siphons then
   the following holds:
There exists a unique positive globally asymptotically stable steady
    state  in each stoichiometric class.
THE END.
```

References