Structural identifiability and observability analysis of the carotenoid pathway model

In this example we analyse the carotenoid pathway model from Bruno et al. (*Journal of experimental botany*, 67(21):5993–6005, 2016). This model has 7 states, 13 parameters, and no inputs. The experimental setup is such that there are 6 experimental conditions and in each of them there is a different output, i.e. a different state is measured (one state is measured in two experiments and there are 2 states that are never measured). Hence we analyse the structural identifiability and observability for each experiment separately.

We begin by installing STRIKE-GOLDD:

```
clear
clc
cd('options_files')
copyfile("options_*","../../strike-goldd/STRIKE-GOLDD")
cd('../../strike-goldd/STRIKE-GOLDD')
install
```

```
STRIKE-GOLDD (v3.0) folders added to the path
```

Then we run the analysis for the first experiment:

```
STRIKE_GOLDD('options_bruno1.m')
```

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>>> STRIKE-GOLDD toolbox 3.0
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Analyzing the bruno_1_beta1 model...

>>> The model contains:
7 states:
[beta; cry; zea; beta10; OHbeta10; betaio; OHbetaio]
2 outputs:
[beta; beta10]
0 known inputs:

0 unknown inputs:

6 parameters:
[kbeta; kcryOH; kcrybeta; kzea; kbeta10; kOHbeta10]

>>> Building the observability-identifiability matrix requires at least 6 Lie derivatives
    Calculating derivatives: 1 2 3 4 5 6
>>> Observability-Identifiability matrix built with 6 Lie derivatives
    (calculated in 9.943310e-02 seconds)
>>> Calculating rank...
    Rank = 6 (calculated in 2.067180e-02 seconds)
>>> Observability-Identifiability matrix built with 7 Lie derivatives
    (calculated in 1.339515e-01 seconds)
>>> Calculating rank...
    Rank = 6 (calculated in 2.205100e-02 seconds)
   => Parameter kbeta is structurally identifiable
   => Parameter kcryOH is structurally unidentifiable
   => Parameter kcrybeta is structurally unidentifiable
   => Parameter kzea is structurally unidentifiable
   => Parameter kbeta10 is structurally identifiable
   => Parameter kOHbeta10 is structurally unidentifiable
   => State cry is unobservable
   => State zea is unobservable
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   => State OHbeta10 is unobservable
   => State betaio is unobservable
   => State OHbetaio is unobservable

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>>> RESULTS SUMMARY:
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>>> The model is structurally unidentifiable.
>>> These parameters are identifiable:
     [kbeta, kbeta10]
>>> These parameters are unidentifiable:
     [kOHbeta10, kcryOH, kcrybeta, kzea]

>>> These states are unobservable (and their initial conditions, if considered unknown, are unidentifiable):
     [OHbeta10, OHbetaio, betaio, cry, zea]
>>> These states are directly measured:
     [beta; beta10]
Total execution time: 9.294923e-01
```

The analysis yields that from this experiment alone, only two parameters (kbeta, kbeta10) are structurally identifiable. Since their values are constant across all experiments, we can consider them known in the 2nd and subsequent experiments. We include this assumption in the file 'options_bruno2.m', which analyses the SIO of the model from the 2nd experiment:

```
STRIKE_GOLDD('options_bruno2.m')
```

```
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>>> STRIKE-GOLDD toolbox 3.0
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Analyzing the bruno_2_beta2 model...

>>> The model contains:
7 states:
[beta; cry; zea; beta10; OHbeta10; betaio; OHbetaio]
2 outputs:
[beta; beta10]
0 known inputs:

0 unknown inputs:

5 parameters:
[kcryOH; kcrybeta; kzea; kOHbeta10; szea]

>>> Building the observability-identifiability matrix requires at least 5 Lie derivatives
    Calculating derivatives: 1 2 3 4 5
>>> Observability-Identifiability matrix built with 5 Lie derivatives
    (calculated in 6.105650e-02 seconds)
>>> Calculating rank...
    Rank = 5 (calculated in 1.703570e-02 seconds)
>>> Observability-Identifiability matrix built with 6 Lie derivatives
    (calculated in 7.662820e-02 seconds)
>>> Calculating rank...
    Rank = 5 (calculated in 2.092510e-02 seconds)
   => Parameter kcryOH is structurally unidentifiable
   => Parameter kcrybeta is structurally unidentifiable
   => Parameter kzea is structurally unidentifiable
   => Parameter kOHbeta10 is structurally unidentifiable
   => Parameter szea is structurally identifiable
   => State cry is unobservable
   => State zea is unobservable
```

```
   => State OHbeta10 is unobservable
   => State betaio is unobservable
   => State OHbetaio is unobservable

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>>> RESULTS SUMMARY:
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>>> The model is structurally unidentifiable.
>>> These parameters are identifiable:
     szea
>>> These parameters are unidentifiable:
     [kOHbeta10, kcryOH, kcrybeta, kzea]

>>> These states are unobservable (and their initial conditions, if considered unknown, are unidentifiable):
     [OHbeta10, OHbetaio, betaio, cry, zea]
>>> These states are directly measured:
     [beta; beta10]
Total execution time: 8.397040e-01
```

The second analysis yields that szea is structurally identifiable. This parameter also appears in the 4th experiment, but not in the remaining ones. Hence we only include it as a 'parameter already classified as identifiable' (along with kbeta, kbeta10) in the options file of the 4th experiment.

We run 'options_bruno3.m', which analyses the SIO of the model from the 3rd experiment:

```
STRIKE_GOLDD('options_bruno3.m')
```

```
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>>> STRIKE-GOLDD toolbox 3.0
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Analyzing the bruno_3_cry model...

>>> The model contains:
7 states:
[beta; cry; zea; beta10; OHbeta10; betaio; OHbetaio]
3 outputs:
[cry; beta10; OHbeta10]
0 known inputs:

0 unknown inputs:

4 parameters:
[kcryOH; kcrybeta; kzea; kOHbeta10]

>>> Building the observability-identifiability matrix requires at least 3 Lie derivatives
    Calculating derivatives: 1 2 3
>>> Observability-Identifiability matrix built with 3 Lie derivatives
    (calculated in 4.499600e-02 seconds)
>>> Calculating rank...
    Rank = 9 (calculated in 1.181310e-02 seconds)
>>> Observability-Identifiability matrix built with 4 Lie derivatives
    (calculated in 6.032350e-02 seconds)
>>> Calculating rank...
    Rank = 9 (calculated in 1.384950e-02 seconds)
   => Parameter kcryOH is structurally identifiable
   => Parameter kcrybeta is structurally identifiable
   => Parameter kzea is structurally identifiable
   => Parameter kOHbeta10 is structurally identifiable
   => State beta is observable
   => State zea is observable
   => State betaio is unobservable
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   => State OHbetaio is unobservable

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>>> RESULTS SUMMARY:
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>>> The model is structurally identifiable:
    All its parameters are structurally identifiable.
>>> These states are observable (and their initial conditions, if considered unknown, are identifiable):
     [beta, zea]
>>> These states are unobservable (and their initial conditions, if considered unknown, are unidentifiable):
     [OHbetaio, betaio]
>>> These states are directly measured:
     [cry; beta10; OHbeta10]
Total execution time: 6.814883e-01
```

All the remaining parameters are structurally locally identifiable. Thus, the model is structurally locally identifiable from the available experiments.

The observability of the model states depends on the experiment. However, it can be seen that two states are never observable. To this end, let us analyse the model assuming that all the states that are measured in the different experiments can be simultaneously measured:

```
STRIKE_GOLDD('options_bruno_five_outputs.m')
```

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>>> STRIKE-GOLDD toolbox 3.0
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Analyzing the bruno_five_outputs model...

>>> The model contains:
7 states:
[beta; cry; zea; beta10; OHbeta10; betaio; OHbetaio]
5 outputs:
[beta; cry; zea; beta10; OHbeta10]
0 known inputs:

0 unknown inputs:

0 parameters:


>>> Building the observability-identifiability matrix requires at least 1 Lie derivatives
    Calculating derivatives: 1
>>> Observability-Identifiability matrix built with 1 Lie derivatives
    (calculated in 2.339820e-02 seconds)
>>> Calculating rank...
    Rank = 5 (calculated in 6.224600e-03 seconds)
>>> Observability-Identifiability matrix built with 2 Lie derivatives
    (calculated in 3.773030e-02 seconds)
>>> Calculating rank...
    Rank = 5 (calculated in 7.942200e-03 seconds)
   => State betaio is unobservable
   => State OHbetaio is unobservable

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>>> RESULTS SUMMARY:
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>>> The model is structurally identifiable:
```

```
    All its parameters are structurally identifiable.
>>> These states are unobservable (and their initial conditions, if considered unknown, are unidentifiable):
     [OHbetaio, betaio]
>>> These states are directly measured:
     [beta; cry; zea; beta10; OHbeta10]
Total execution time: 4.144091e-01
```

As can be seen, the two unmeasured states (OH-Beta-io and Beta-io) are non-observable, despite all the parameters being structurally identifiable. This is because their initial conditions are unknown.