AutoRepar: supplementary information

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This document gives supplementary details of the application of AutoRepar to the four case studies analysed in the main text of the following papers:

1. "Repairing dynamic models: a method to obtain identifiable and observable reparameterizations with mechanistic insights", G Massonis, JR Banga, AF Villaverde. *arXiv preprint* arXiv:2012.09826
2. "AutoRepar: a method to obtain identifiable and observable reparameterizations of dynamic models with mechanistic insights", G Massonis, JR Banga, AF Villaverde. *International Journal of Robust and Nonlinear Control*.

The analysed models are listed in the following table of contents:

Contents

Each model is analysed step-by-step, by means of explanations and mathematical expressions. The output of the AutoRepar procedure executed in the STRIKE-GOLDD toolbox is shown in Boxes. In all cases, to reparameterize the models one must first modify the 'modelname' field in the file options.m, and then simply execute AutoRepar.m in the Matlab command line, i.e.:

```
>> AutoRepar
```

The AutoRepar procedure proceeds in three steps: first, it analyses the structural identifiability and observability (SIO) of the model by executing the function STRIKE_GOLDD.m; second, it searches for the Lie symmetries that cause the lack of SIO by calling Lie_Symmetry.m; third, it reparameterizes the model to remove the symmetries.

1 Vajda1989 model

To analyse this model we choose its file in options.m:

```
modelname ='Vajda1989';
```

Then we run AutoRepar from Matlab's command line:

```
>> AutoRepar
```

The first step in the reparameterization procedure is the observability and identifiability analysis. It is performed by calling the STRIKE-GOLDD function, which produces the following output:

BOX 1. STRIKE-GOLDD

>>> RESULTS SUMMARY:

>>> The model is structurally unidentifiable.
>>> These parameters are identifiable:
[t1, t4]
>>> These parameters are unidentifiable:
[t2, t3]

>>> These states are observable (and their initial conditions, if considered unknown, are identifiable):
x2
>>> These states are directly measured:
x1
>>> These unmeasured inputs are observable:
[w, w_d1]

Total execution time: $3.548690e + 00$

The additional variable in the unmeasured inputs vector, w_{d1}, represents its derivative. It is automatically created by STRIKE-GOLDD if we specify in the file *options.m* a minimum of one non-zero derivative of w to treat it like a time-dependent input, i.e.:

```
opts.nnzDerW = 1;
```

Once the results summary is printed, the difference between the dimension of the augmented vector and the rank is computed. When this result is zero, the model is FISPO; in this case a message appears on the screen and the program ends. When it is not zero, the number of necessary reparameterizations is calculated and the Lie_Symmetry is called. This is the case for the Vajda1989 model. The output of the Lie_Symmetry function is shown in the box below:

BOX 2. Lie_Symmetry.

>>> The Vajda1989 model requires 1 transformation(s).
Searching for symmetries of Vajda1989...
Elapsed time is 110.699343 seconds.

>>> Reparameterization #1:
Generator #1 has 1 possible reparameterization(s)
Generator #2 has 0 possible reparameterization(s)
Generator #3 has 2 possible reparameterization(s)

For the infinitesimal generator #1 the following parameters can be removed:
(1): t2
⟶ Affected variables: [w; t2]

For the infinitesimal generator #2 the following parameters can be removed:

For the infinitesimal generator #3 the following parameters can be removed:
(1): t2
⟶ Affected variables: [x2; t2; t3]
(2): t3
⟶ Affected variables: [x2; t2; t3]

The three infinitesimal generators obtained with the Lie symmetries program are:

$$X = x_1 x_2 \frac{\partial}{\partial w} - \frac{\partial}{\partial \theta_2} \ , \tag{1}$$

$$X = x_1^2 \frac{\partial}{\partial w} - \frac{\partial}{\partial \theta_1} \ , \tag{2}$$

$$X = x_2 \frac{\partial}{\partial x_2} - \theta_2 \frac{\partial}{\partial \theta_2} + \theta_3 \frac{\partial}{\partial \theta_3} \ . \tag{3}$$

Since it is only possible to remove parameters from the model (not states nor unknown inputs), only θ_2 can be chosen for the first infinitesimal generator (1). In this case, it is possible to reformulate the model without inferring in the other non-observable variables (θ_3 and $x2$).

The second infinitesimal generator (2) does not lead to any possible reparameterization because it only involves one parameter, θ_1, which is identifiable and therefore cannot be removed.

The last infinitesimal generator (3) has two possibilities: θ_2 (t2) o θ_3 (t3). Both options imply reformulating x_2, leading to a complete transformation of the three non-observable variables.

This information is printed as follows: number of generators, possible parameters to remove per generator, and affected variables (i.e. the variables that will be transformed).

At this point, the user must introduce the chosen generator and, if it has multiple possibilities, the parameter to remove. Let us choose the first generator:

BOX 3. User input.
Enter the generator that you want to use:
1

When the chosen generator only has one possible reparameterization, it is not necessary to introduce it, as it happens in this example: choosing the infinitesimal generator (1) entails removing the parameter θ_2 (t2). Thus, AutoRepar automatically removes it from the model and performs the transformations that make the model FISPO.

The infinitesimal generator (1) leads to the following reparameterized input function and parameter:

$$w^* = x_1 x_2 \varepsilon + w,\ \theta_2^* = -\varepsilon + \theta_2$$

The program removes θ_2 by finding an expression for ε by which $\theta_2^* = 1$. In this case this expression is given by:

$$\varepsilon = \theta_2 - 1\ ,$$

which provides the following reparameterization:

$$w + x_1 x_2(\theta_2 - 1),\ 1\ .$$

The output shown on the screen is:

BOX 4. AutoRepar.
You have chosen the parameter t2 from the infinitesimal generator:
[0, 0, x1*x2, 0, -1, 0, 0]

>>> Transformed variables:
x1 $\longleftarrow$ x1
x2 $\longleftarrow$ x2
w $\longleftarrow$ w + x1*x2*(t2 - 1)
t1 $\longleftarrow$ t1
t2 $\longleftarrow$ 1
t3 $\longleftarrow$ t3
t4 $\longleftarrow$ t4
>>> Reformulated model:
f:
$t1 * x1^2 + x2 * x1 + w$
$t3 * x1^2 + t4 * x2 * x1$

h:
x1

>>> The model reparameterization has been completed successfully

---

The new FISPO model is:
f:
$t1 * x1^2 + x2 * x1 + w$
$t3 * x1^2 + t4 * x2 * x1$

h:
x1

2 Pharmacokinetic model (PK)

To reparameterize this model, we choose it in the options.m file:

```
modelname ='PK_unknown_input';
```

We also set the following options:

```
opts.ansatz = 3;
opts.degree = 3;
opts.ode_n = 1;
```

The latter option is only available for Matlab R2020a and later versions. Then we run AutoRepar from Matlab's command line:

```
>> AutoRepar
```

obtaining the following output:

BOX 1. STRIKE-GOLDD.

>>> RESULTS SUMMARY:

>>> The model is structurally unidentifiable.
>>> These parameters are identifiable:
[k4, k5, k6]
>>> These parameters are unidentifiable:
[k1, k2, k3, k7, s2, s3]

>>> These states are unobservable (and their initial conditions, if considered unknown, are unidentifiable):
[x1, x2, x3, x4]
>>> These unmeasured inputs are unobservable:
[u1, u1_d1]
Total execution time: $1.047922e+01$

The pharmacokinetic model requires two reparameterizations. The first search finds four infinitesimal generators:

BOX 2. Lie_Symmetry.

>>> The PK_unknown_input model requires 2 transformation(s).
Searching for symmetries of PK_unknown_input...
Elapsed time is 96.517125 seconds.

>>> Reparameterization #1:
Generator #1 has 3 possible reparameterization(s)
Generator #2 has 3 possible reparameterization(s)
Generator #3 has 2 possible reparameterization(s)
Generator #4 has 1 possible reparameterization(s)

For the infinitesimal generator #1 the following parameters can be removed:
(1): k2
⟶ Affected variables: [x3; u1; k2; k3; k7; s3]
(2): k3
⟶ Affected variables: [x3; u1; k2; k3; k7; s3]
(3): s3
⟶ Affected variables: [x3; u1; k2; k3; k7; s3]

For the infinitesimal generator #2 the following parameters can be removed:
(1): k3
⟶ Affected variables: [x2; x4; u1; k3; k7; k1; s2]
(2): k1
⟶ Affected variables: [x2; x4; u1; k3; k7; k1; s2]
(3): s2
⟶ Affected variables: [x2; x4; u1; k3; k7; k1; s2]

For the infinitesimal generator #3 the following parameters can be removed:
(1): k2
⟶ Affected variables: [x1; u1; k2; k1]
(2): k1
⟶ Affected variables: [x1; u1; k2; k1]

For the infinitesimal generator #4 the following parameters can be removed:
(1): k3
⟶ Affected variables: [x1; u1; k3; k7]

The complete infinitesimal generators expressions are defined by:

$$X = x_3 \frac{\partial}{\partial x_3} + k_2 x_1 \frac{\partial}{\partial u} + k_2 \frac{\partial}{\partial k_2} + k_3 \frac{\partial}{\partial k_3} - k_3 \frac{\partial}{\partial k_7} - s_3 \frac{\partial}{\partial s_3}, \tag{4}$$

$$X = x_2 \frac{\partial}{\partial x_2} + x_4 \frac{\partial}{\partial x_4} + k_1 x_1 \frac{\partial}{\partial u} + k_1 \frac{\partial}{\partial k_1} - k_3 \frac{\partial}{\partial k_3} + k_3 \frac{\partial}{\partial k_7} - s_2 \frac{\partial}{\partial s_2}, \tag{5}$$

$$X = x_1 \frac{\partial}{\partial x_1} + (u - k_1 x_1 - k_2 x_1) \frac{\partial}{\partial u} - k_1 \frac{\partial}{\partial k_1} - k_2 \frac{\partial}{\partial k_2}, \tag{6}$$

$$\begin{aligned} X = x_2 \frac{\partial}{\partial x_2} + (k_1 x_1 + x_2(k_1 + k_2 - k_3 - k_6 - k_7) + k_5 x_4) \frac{\partial}{\partial u} - \\ - k_2 \frac{\partial}{\partial k_3} + (k_1 + k_2) \frac{\partial}{\partial k_7} \end{aligned} \tag{7}$$

The generator (6) will be used for the first reparameterization, in order to involve the fewest states and parameters. For this infinitesimal generator it is only possible to remove k_2 or k_1; we will chose the second one.

BOX 3. User input.
Enter the generator that you want to use:
3
Enter the number of the parameter to be removed (in order of output per screen):
2

The expression of this parameters under one-parameter Lie group of transformations is:

$$\begin{aligned} x_1^* &= x_1 \exp(\varepsilon), \\ u^* &= x_1(k_1 + k_2) + \exp(\varepsilon)(u - x_1(k_1 + k_2)), \\ k_1^* &= k_1 \exp(-\varepsilon), \\ k_2^* &= k_2 \exp(-\varepsilon) \end{aligned}$$

The next step is to obtain an expression for $\exp(\varepsilon)$ through which the parameter k_1 disappears from the model and is introduced in the other states and parameters. The method sets the new expression of the parameter, k_1^*, to 1, and:

$$k_1^* = k_1 \exp(-\varepsilon) = 1 \longrightarrow \exp(\varepsilon) = k_1$$

The new expressions, without $\exp(\varepsilon)$, are:

$$\begin{aligned} x_1^* &= x_1 k_1, \\ u^* &= x_1(k_1 + k_2) + k_1(u - x_1(k_1 + k_2)), \\ k_2^* &= \frac{k_2}{k_1} \end{aligned}$$

These new variables are replaced in the model, leading to:

BOX 4. AutoRepar.
You have chosen the parameter k1 from the infinitesimal generator:
[x1, 0, 0, 0, u1 - k1*x1 - k2*x1, -k2, 0, 0, -k1, 0, 0]

>>> Transformed variables:
x1 ⟵ k1*x1
x2 ⟵ x2
x3 ⟵ x3
x4 ⟵ x4
u1 ⟵ k1*(u1 - k1*x1 - k2*x1 + (x1*(k1 + k2))/k1)
k2 ⟵ k2/k1
k3 ⟵ k3
k7 ⟵ k7
k1 ⟵ 1
s2 ⟵ s2
s3 ⟵ s3
>>> Equations of the reformulated model:
f:
$u1 - x1 * (k2 + 1)$
$x1 + k5 * x4 - x2 * (k3 + k6 + k7)$
$k2 * x1 + k3 * x2 - k4 * x3$
$k6 * x2 - k5 * x4$

h:
$s2 * x2$
$s3 * x3$

The first set of transformations has been completed, and there is one reparameterization remaining. Therefore, the process starts again, analysing the SIO of the reformulated model. The new SIO analysis yields that, by performing the transformations, three parameters have become structurally identifiable: $k2$, $k3$, and $k7$. Hence, in the pending reparameterization only $s2$ or $s3$ can be removed. The following boxes show the output of the SIO and Lie symmetries analyses:

BOX 5. STRIKE-GOLDD.

>>> RESULTS SUMMARY:

>>> The model is structurally unidentifiable.
>>> These parameters are identifiable:
[k2, k3, k7]
>>> These parameters are unidentifiable:
[s2, s3]

>>> These states are unobservable (and their initial conditions, if considered unknown, are unidentifiable):
[x1, x2, x3, x4]
>>> These unmeasured inputs are unobservable:
[u1, u1_d1]
Total execution time: $3.066803e + 00$

BOX 6. Lie_Symmetry.

Searching for symmetries of New_Model...
Elapsed time is 45.969603 seconds.

>>> Reparameterization #2:
Generator #1 has 1 possible reparameterization(s)
Generator #2 has 1 possible reparameterization(s)
Generator #3 has 0 possible reparameterization(s)

For the infinitesimal generator #1 the following parameters can be removed:
(1): s3
⟶ Affected variables: [x3; u1; k2; k3; k7; s3]

For the infinitesimal generator #2 the following parameters can be removed:
(1): s2

⟶ Affected variables: [x1; x2; x4; u1; k2; k3; k7; s2]

For the infinitesimal generator #3 the following parameters can be removed:

The expressions of the new infinitesimal generators are given by:

$$X = x_3\frac{\partial}{\partial x_3} + k_2 x_1\frac{\partial}{\partial u} + k_2\frac{\partial}{\partial k_2} + k_3\frac{\partial}{\partial k_3} - k_3\frac{\partial}{\partial k_7} - s_3\frac{\partial}{\partial s_3}, \tag{8}$$

$$\begin{aligned} X = {} & x_1\frac{\partial}{\partial x_1} + x_2\frac{\partial}{\partial x_2} + x_4\frac{\partial}{\partial x_4} + (u - k_2 x_1)\frac{\partial}{\partial u} - k_2\frac{\partial}{\partial k_2} - \\ & - k_3\frac{\partial}{\partial k_3} + k_3\frac{\partial}{\partial k_7}, \end{aligned} \tag{9}$$

$$\begin{aligned} X = {} & x_2\frac{\partial}{\partial x_1} + (x_1 + x_2(1 + k_2 - k_3 - k_6 - k_7) + k_5 x_4)\frac{\partial}{\partial u} - \\ & - k_2\frac{\partial}{\partial k_3} + (k_2 + 1)\frac{\partial}{\partial k_7} \end{aligned} \tag{10}$$

As explained above, only parameters that are unidentifiable can be removed; adding this condition to the impossibility of reparameterization for states and/or input functions, as happens in the third generator, only two possibilities remain: the first and second infinitesimal generators.

The generator (8) has been chosen since it has fewer states in its expression and, therefore, fewer variables will need to be transformed.

> **BOX 7. User input.**
> Enter the generator that you want to use:
> 1

In this case, these is a non-elementary transformation for k_7, the expression of which is calculated by solving ODEs:

$$\begin{aligned} \widetilde{x_3} &= x_3 s_3, \\ \widetilde{k_2^*} &= k_2^* s_3, \\ \widetilde{k_3} &= s_3 k_3, \\ \widetilde{k_7} &= k_3(1 - s_3) + k_7 \end{aligned}$$

Since there are no more reparameterizations left, the resulting FISPO model is printed and the program end:.

BOX 8. AutoRepar.
You have chosen the parameter s3 from the infinitesimal generator:
[0, 0, x3, 0, k2*x1, k2, k3, -k3, 0, -s3]
>>> Transformed variables:
x1 $\longleftarrow$ x1
x2 $\longleftarrow$ x2
x3 $\longleftarrow$ s3*x3
x4 $\longleftarrow$ x4
u1 $\longleftarrow$ u1 - k2*x1 + k2*s3*x1
k2 $\longleftarrow$ k2*s3
k3 $\longleftarrow$ k3*s3
k7 $\longleftarrow$ k3 + k7 - k3*s3
s2 $\longleftarrow$ s2
s3 $\longleftarrow$ 1
>>> Equations of the reformulated model:
f:
$u1 - x1 * (k2 + 1)$
$x1 + k5 * x4 - x2 * (k3 + k6 + k7)$
$k2 * x1 + k3 * x2 - k4 * x3$
$k6 * x2 - k5 * x4$

h:
$s2 * x2$
x3

>>> The model reparameterization has been completed successfully

---

The new FISPO model is:
f:
$u1 - x1 * (k2 + 1)$
$x1 + k5 * x4 - x2 * (k3 + k6 + k7)$
$k2 * x1 + k3 * x2 - k4 * x3$
$k6 * x2 - k5 * x4$

h:
$s2 * x2$
$x3$

3 βIG model

To analyse the βIG model with a known input, we set in the options file:

```
modelname ='BIG_known_input';
```

(To analyse the βIG model with an unknown input, we would select `modelname ='BIG_known_input'`. Here we only show the results for the known input case.) The first output of the program is the result of the SIO analysis performed by the STRIKE-GOLDD function:

BOX 1. STRIKE-GOLDD.

>>> RESULTS SUMMARY:

>>> The model is structurally unidentifiable.
>>> These parameters are identifiable:

>>> These parameters are unidentifiable:
[P, si]
>>> These states are unobservable (and their initial conditions, if considered unknown, are unidentifiable):
[B, I]
>>> These states are directly measured:
G
>>> These inputs are known:
u
Total execution time: $7.750776e + 00$

Then the Lie_Symmetry program searches for symmetries in the model with the specific conditions given by the option file. The βIG model needs two reformulations to become FISPO. Two generators are found by the program, the mathematical expressions of which are:

$$X = I\frac{\partial}{\partial I} + P\frac{\partial}{\partial P} - si\frac{\partial}{\partial si} \tag{11}$$

$$X = B\frac{\partial}{\partial B} - P\frac{\partial}{\partial P} \tag{12}$$

The changes of variable associated to those infinitesimals generators are:

$$I^* = I\exp(\varepsilon),\ \ si^* = si\exp(-\varepsilon),\ \ P^* = P\exp(\varepsilon); \tag{13}$$

$$B^* = B\exp(\varepsilon),\ \ P^* = P\exp(-\varepsilon) \tag{14}$$

The first infinitesimal generator has two options : si or P, both of them involve I. The second generator has only one possible reparameterization.

BOX 2. Lie_Symmetry.

>>> The 1D_BIG model requires 2 transformation(s).
Searching for symmetries of 1D_BIG...
Elapsed time is 13.674026 seconds.

Reparametrization #1:
Generator #1 has 2 possible reparametrization(s)
Generator #2 has 1 possible reparametrization(s)

For the infinitesimal generator #1 the following parameters can be removed:
(1): P
⟶ Affected variables: [I; P; si]
(2): si
⟶ Affected variables: [I; P; si]

For the infinitesimal generator #2 the following parameters can be removed:
(1): P
⟶ Affected variables: [B; P]

At this point, the user must introduce the generator (the second one, in this case) and the parameter to be removed taking into account their order. For the βIG model this choices are:

BOX 3. User input.
Enter the generator that you want to use:
1

The transformed variables are calculated by isolating ε of the expression (13) for one parameter, i.e.:

$$P^* = P\exp(\varepsilon) = 1 \longrightarrow \exp(-\varepsilon) = P;$$

and then, replacing $\exp(\varepsilon)$ in the other variables:

$$B^* = BP,\ P^* = 1\ .$$

AutoRepar computes those transformations and lists them with the reformulated model.

BOX 4. AutoRepar.
You have chosen the parameter P from the infinitesimal generator:
[0, B, 0, P, 0]

>>>Transformed variables:
G ⟵ G
B ⟵ B*P
I ⟵ I
P ⟵ 1
si ⟵ si
>>> Equations of the reformulated model:
f:
$u - G*(c + I*si)$
$B*(8608480567731125/(590295810358705651712*((42/(5*G))^(17/10) + 1)) - 1/(57600*(((5*G)/24)^(17/2) + 1)))$
$(B*G^2)/(G^2 + a^2) - I*g$

h:
G

βIG requires one more reparameterization in order to become FISPO. The program will start the process again automatically.

BOX 5. STRIKE-GOLDD.

>>> RESULTS SUMMARY:

>>> The model is structurally unidentifiable.
>>> These parameters are identifiable:

>>> These parameters are unidentifiable:
si
>>> These states are unobservable (and their initial conditions, if considered unknown, are unidentifiable):
[B, I]
>>> These states are directly measured:
G
>>> These inputs are known:
u
Total execution time: $1.667467e + 00$

After this output, the Lie_Symmetries is called again and only one generator with one possible reparameterization is found:

$$X = B\frac{\partial}{\partial B} + I\frac{\partial}{\partial I} - si\frac{\partial}{\partial si} \ , \tag{15}$$

leading to the following expressions of one parameter Lie group of transformations:

$$\widetilde{B} = B\exp(\varepsilon),\ \widetilde{I} = I\exp(\varepsilon),\ \widetilde{si} = si\exp(-\varepsilon)$$

The only possible reparameterization is given by

$$\widetilde{si} = si\exp(-\varepsilon) = 1 \longrightarrow si = \exp(\varepsilon),$$

resulting in these new states:

$$\widetilde{B} = Bsi,$$
$$\widetilde{I} = Isi.$$

In this case, no input is needed from the user, and the final information is printed on the screen:

BOX 6. Lie_Symmetry and AutoRepar.

Searching for symmetries of New_Model...
Elapsed time is 6.574515 seconds.

>>> Reparametrization #2:
Generator #1 has 1 possible reparametrization(s)

For the infinitesimal generator #1 the following parameters can be removed:
(1): si
$\longrightarrow$ Affected variables: [B; I; si]
You have chosen the parameter si from the infinitesimal generator:
[0, B, I, -si]
>>> Transformed variables:
G $\longleftarrow$ G
B $\longleftarrow$ B*si
I $\longleftarrow$ I*si
si$\longleftarrow$ 1
>>> Equations of the reformulated model:
f:
$u - G * (I + c)$
$B*(8608480567731125/(590295810358705651712*((42/(5*G))^{(}17/10)+1)) - 1/(57600*(((5*G)/24)^{(}17/2)+1)))$
$(B*G^2)/(G^2+a^2) - I*g$

h:
G

>>> The model reparameterization has been completed successfully

---

The new FISPO model is:
f:
$u - G * (I + c)$
$B*(8608480567731125/(590295810358705651712*((42/(5*G))^{(}17/10)+1)) - 1/(57600*(((5*G)/24)^{(}17/2)+1)))$
$(B*G^2)/(G^2+a^2) - I*g$

h:
G

4 NF-κB

If the SIO analysis of a model has already been performed by running the file STRIKE_GOLDD.m, there is no need to repeat the calculations when performing the automatic reparameterization. We illustrate this feature with this model. Assuming that a mat-file called id_results_NFKB.mat exists, which contains the SIO results, we set the following options in options.m:

```
opts.use_existing_results = 1;
opts.results_file = 'id_results_NFKB.mat';
```

Since this bypasses the need to perform the SIO analysis again, the first output of AutoRepar.m is now the number of necessary reparameterizations and the results of Lie_Symmetry:

BOX 1. Lie_Symmetry.

>>> The NFKB model requires 3 transformation(s).
Searching for symmetries of NFKB...
Elapsed time is 1301.381253 seconds.

>>> Reparameterization #1:
Generator #1 has 2 possible reparameterization(s)
Generator #2 has 1 possible reparameterization(s)
Generator #3 has 2 possible reparameterization(s)
Generator #4 has 7 possible reparameterization(s)

For the infinitesimal generator #1 the following parameters can be removed:
(1): k0
⟶ Affected variables: [u1; k0; k1]
(2): k1
⟶ Affected variables: [u1; k0; k1]

For the infinitesimal generator #2 the following parameters can be removed:
(1): k0
⟶ Affected variables: [u1; k0]
For the infinitesimal generator #3 the following parameters can be removed:
(1): k6
⟶ Affected variables: [x7; k6; k8]
(2): k8
⟶ Affected variables: [x7; k6; k8]

For the infinitesimal generator #4 the following parameters can be removed:
(1): s1
⟶ Affected variables: [x1; x2; x3; x4; x5; x6; x8; x9; x10; s1; s2; s3; s4; k6; k8; k10]
(2): s2
⟶ Affected variables: [x1; x2; x3; x4; x5; x6; x8; x9; x10; s1; s2; s3; s4; k6; k8; k10]
(3): s3
⟶ Affected variables: [x1; x2; x3; x4; x5; x6; x8; x9; x10; s1; s2; s3; s4; k6; k8; k10]
(4): s4
⟶ Affected variables: [x1; x2; x3; x4; x5; x6; x8; x9; x10; s1; s2; s3; s4; k6; k8; k10]
(5): k6
⟶ Affected variables: [x1; x2; x3; x4; x5; x6; x8; x9; x10; s1; s2; s3; s4; k6; k8; k10]
(6): k8
⟶ Affected variables: [x1; x2; x3; x4; x5; x6; x8; x9; x10; s1; s2; s3; s4; k6; k8; k10]
(7): k10
⟶ Affected variables: [x1; x2; x3; x4; x5; x6; x8; x9; x10; s1; s2; s3; s4; k6; k8; k10]

The first study of symmetries finds the following infinitesimal generators:

$$X = -u\frac{\partial}{\partial u} + k_0\frac{\partial}{\partial k_0} + k_1\frac{\partial}{\partial k_1}\ , \tag{16}$$

$$X = u^2\frac{\partial}{\partial u} + \frac{\partial}{\partial k_0}\ , \tag{17}$$

$$X = -x_7\frac{\partial}{\partial x_7} - k_6\frac{\partial}{\partial k_6} + k_8\frac{\partial}{\partial k_8}\ , \tag{18}$$

$$\begin{aligned} X = -x_1\frac{\partial}{\partial x_1} - x_2\frac{\partial}{\partial x_2} - x_3\frac{\partial}{\partial x_3} - x_4\frac{\partial}{\partial x_4} - x_5\frac{\partial}{\partial x_5} - \\ - x_6\frac{\partial}{\partial x_6} - x_7\frac{\partial}{\partial x_7} - x_8\frac{\partial}{\partial x_8} - x_9\frac{\partial}{\partial x_9} - x_{10}\frac{\partial}{\partial x_{10}} + \\ + s_1\frac{\partial}{\partial s_1} + s_2\frac{\partial}{\partial s_2} + s_3\frac{\partial}{\partial s_3} + s_4\frac{\partial}{\partial s_4} + k_{10}\frac{\partial}{\partial k_{10}}\ . \end{aligned} \tag{19}$$

We will consider the infinitesimal generator (16) for the first reparameterization:

BOX 2. User input.
Enter the generator that you want to use:
1
Enter the number of the parameter to be removed (in order of output per screen):
1

BOX 3. AutoRepar.
You have chosen the parameter k0 from the infinitesimal generator:
[0, 0, 0, 0, 0, 0, 0, 0, 0, 0, u1, 0, 0, 0, 0, -k0, -k1, 0, 0, 0]

>>> Transformed variables:
u1 $\longleftarrow$ k0*u1
k0 $\longleftarrow$ 1
k1 $\longleftarrow$ k1/k0
>>> Equations of the reformulated model:
f:

$k11 * x10 - x1 * (k1p + (k1 * u1)/(u1 + 1))$
$x1 * (k1p + (k1 * u1)/(u1 + 1)) - k2 * x2$
$k2 * x2 - k3 * x3$
$k2 * x2 - k4 * x4$
$k3 * rhovol * x3 - k5 * x5$
$k5 * x5 - k10 * x6 * x9$
$k6 * x6 - k7 * x7$
$k8 * x7 - k9 * x8$
$k9 * rhovol * x8 - k10 * x6 * x9$
$k10 * x6 * x9 - k11 * rhovol * x10$
h:

$I0cyt + s1 * (x1 + x2 + x3)$
$I0nuc + s2 * (x5 + x6 + x10)$
$s3 * (x2 + x3)$
$s4 * (x2 + x4)$

The output shown above corresponds to the following replacements:

$$
\begin{aligned}
&k_0^* = k_0 \exp(\varepsilon) = 1 \longrightarrow \exp(\varepsilon) = \frac{1}{k_0}\ ; \\
&u^* = u \exp(-\varepsilon) \longrightarrow u^* = u k_0, \\
&k_1^* = k_1 \exp(\varepsilon) \longrightarrow k_1^* = \frac{k_1}{k_0}.
\end{aligned}
$$

As it is still necessary to perform two reparameterizations, STRIKE-GOLDD is called once again (this time it is not possible to use the option of loading an existing results file):

BOX 4. STRIKE-GOLDD.

>>> RESULTS SUMMARY:

>>> The model is structurally unidentifiable.
>>> These parameters are identifiable:
k1
>>> These parameters are unidentifiable:
[k10, k6, k8, s1, s2, s3, s4]

>>> These states are unobservable (and their initial conditions, if considered unknown, are unidentifiable):
[x1, x10, x2, x3, x4, x5, x6, x7, x8, x9]
>>> These unmeasured inputs are observable:
[u1, u1_d1]
Total execution time: $8.882646e + 01$

This new analysis reveals that the parameter k_1 has become identifiable with the first reformulation. With this new information, a new search for symmetries is carried out, and the number of remaining reparameterizations is updated:

BOX 5. Lie_Symmetry.

Searching for symmetries of New_Model...
Elapsed time is 490.589714 seconds.

>>> Reparameterization #2:
Generator #1 has 0 possible reparameterization(s)
Generator #2 has 2 possible reparameterization(s)
Generator #3 has 7 possible reparameterization(s)
For the infinitesimal generator #1 the following parameters can be removed:
For the infinitesimal generator #2 the following parameters can be removed:
(1): k6
$\longrightarrow$ Affected variables: [x7; k6; k8]
(2): k8
$\longrightarrow$ Affected variables: [x7; k6; k8]
For the infinitesimal generator #3 the following parameters can be removed:
(1): s1
$\longrightarrow$ Affected variables: [x1; x2; x3; x4; x5; x6; x8; x9; x10; s1; s2; s3; s4; k6; k8; k10]
(2): s2
$\longrightarrow$ Affected variables: [x1; x2; x3; x4; x5; x6; x8; x9; x10; s1; s2; s3; s4; k6; k8; k10]
(3): s3
$\longrightarrow$ Affected variables: [x1; x2; x3; x4; x5; x6; x8; x9; x10; s1; s2; s3; s4; k6; k8; k10]
(4): s4
$\longrightarrow$ Affected variables: [x1; x2; x3; x4; x5; x6; x8; x9; x10; s1; s2; s3; s4; k6; k8; k10]
(5): k6
$\longrightarrow$ Affected variables: [x1; x2; x3; x4; x5; x6; x8; x9; x10; s1; s2; s3; s4; k6; k8; k10]
(6): k8
$\longrightarrow$ Affected variables: [x1; x2; x3; x4; x5; x6; x8; x9; x10; s1; s2; s3; s4; k6; k8; k10]
(7): k10
$\longrightarrow$ Affected variables: [x1; x2; x3; x4; x5; x6; x8; x9; x10; s1; s2; s3; s4; k6; k8; k10]

The three infinitesimal generators are:

$$X = -u(u+1)\frac{\partial}{\partial u} + \widetilde{k}_1\frac{\partial}{\partial k_1}, \tag{20}$$

$$X = -x_7\frac{\partial}{\partial x_7} - k_6\frac{\partial}{\partial k_6} + k_8\frac{\partial}{\partial k_8}, \tag{21}$$

$$\begin{aligned} X = &-x_1\frac{\partial}{\partial x_1} - x_2\frac{\partial}{\partial x_2} - x_3\frac{\partial}{\partial x_3} - x_4\frac{\partial}{\partial x_4} - x_5\frac{\partial}{\partial x_5} - \\ &- x_6\frac{\partial}{\partial x_6} - x_7\frac{\partial}{\partial x_7} - x_8\frac{\partial}{\partial x_8} - x_9\frac{\partial}{\partial x_9} - x_{10}\frac{\partial}{\partial x_{10}} + \\ &+ s_1\frac{\partial}{\partial s_1} + s_2\frac{\partial}{\partial s_2} + s_3\frac{\partial}{\partial s_3} + s_4\frac{\partial}{\partial s_4} + k_{10}\frac{\partial}{\partial k_{10}}\ . \end{aligned} \tag{22}$$

Only the second and third infinitesimal generator can be selected, because the first one is composed by the input function and one identifiable parameter. We choose the second infinitesimal generator and its first parameter (k_6):

> **BOX 6. User input.**
> Enter the generator that you want to use:
> 2
> Enter the number of the parameter to be removed (in order of output per screen):
> 1

The one parameter Lie group of transformation is given by:

$$\begin{aligned} \widetilde{x_7} &= x_7 \exp(-\varepsilon), \\ \widetilde{k_6} &= k_6 \exp(-\varepsilon), \\ \widetilde{k_8} &= k_8 \exp(\varepsilon) \end{aligned}$$

To remove the parameter k_6 from the model it is necessary to find an expression for $\exp(\varepsilon)$ with which $\widetilde{k_6} = 1$:

$$\widetilde{k_6} = k_6 \exp(-\varepsilon) = 1 \longrightarrow k_6 = \exp(\varepsilon)$$

This leads to the following expressions:

$$\begin{aligned} \widetilde{x_7} &= \frac{x_7}{k_6}, \\ \widetilde{k_8} &= k_8 k_6 \end{aligned}$$

BOX 7. AutoRepar.
You have chosen the parameter k6 from the infinitesimal generator:
[0, 0, 0, 0, 0, 0, x7, 0, 0, 0, 0, 0, 0, 0, 0, 0, k6, -k8, 0]
>>> Transformed variables:
x1 $\longleftarrow$ x1
x2 $\longleftarrow$ x2
x3 $\longleftarrow$ x3
x4 $\longleftarrow$ x4
x5 $\longleftarrow$ x5
x6 $\longleftarrow$ x6
x7 $\longleftarrow$ x7/k6
x8 $\longleftarrow$ x8
x9 $\longleftarrow$ x9
x10 $\longleftarrow$ x10
u1 $\longleftarrow$ u1
s1 $\longleftarrow$ s1
s2 $\longleftarrow$ s2
s3 $\longleftarrow$ s3
s4 $\longleftarrow$ s4
k1 $\longleftarrow$ k1
k6 $\longleftarrow$ 1
k8 $\longleftarrow$ k6*k8
k10 $\longleftarrow$ k10
>>> Equations of the reformulated model:

f:
$k11 * x10 - x1 * (k1p + (k1 * u1)/(u1 + 1))$
$x1 * (k1p + (k1 * u1)/(u1 + 1)) - k2 * x2$
$k2 * x2 - k3 * x3$
$k2 * x2 - k4 * x4$
$k3 * rhovol * x3 - k5 * x5$
$k5 * x5 - k10 * x6 * x9$
$x6 - k7 * x7$
$k8 * x7 - k9 * x8$
$k9 * rhovol * x8 - k10 * x6 * x9$
$k10 * x6 * x9 - k11 * rhovol * x10$

h:
$I0cyt + s1 * (x1 + x2 + x3)$
$I0nuc + s2 * (x5 + x6 + x10)$
$s3 * (x2 + x3)$
$s4 * (x2 + x4)$

Next, the SIO of the reparameterized model is analysed:

BOX 8. STRIKE-GOLDD.

\>>> RESULTS SUMMARY:

\>>> The model is structurally unidentifiable.
\>>> These parameters are identifiable:
[k1, k8]
\>>> These parameters are unidentifiable:
[k10, s1, s2, s3, s4]

\>>> These states are unobservable (and their initial conditions, if considered unknown, are unidentifiable):
[x1, x10, x2, x3, x4, x5, x6, x7, x8, x9]
\>>> These unmeasured inputs are observable:
[u1, u1_d1]
Total execution time: $9.297018e + 01$

After the second reparameterization, one more parameter has become identifiable: $k8$. One more reparameterization is needed, since five parameters are still unidentifiable (s_1, s_2, s_3, s_4, and k_{10}). Hence a new search for symmetries is carried out:

BOX 9. Lie_Symmetry.

Searching for symmetries of New_Model...
Elapsed time is 208.236640 seconds.

>>> Reparameterization #3:
Generator #1 has 0 possible reparameterization(s)
Generator #2 has 5 possible reparameterization(s)

For the infinitesimal generator #1 the following parameters can be removed:

For the infinitesimal generator #2 the following parameters can be removed:
(1): s1
⟶ Affected variables: [x1; x2; x3; x4; x5; x6; x7; x8; x9; x10; s1; s2; s3; s4; k10]
(2): s2
⟶ Affected variables: [x1; x2; x3; x4; x5; x6; x7; x8; x9; x10; s1; s2; s3; s4; k10]
(3): s3
⟶ Affected variables: [x1; x2; x3; x4; x5; x6; x7; x8; x9; x10; s1; s2; s3; s4; k10]
(4): s4
⟶ Affected variables: [x1; x2; x3; x4; x5; x6; x7; x8; x9; x10; s1; s2; s3; s4; k10]
(5): k10
⟶ Affected variables: [x1; x2; x3; x4; x5; x6; x7; x8; x9; x10; s1; s2; s3; s4; k10]

The search for symmetries reported above finds two infinitesimal generators:

$$X = -u(u+1)\frac{\partial}{\partial u} + k_1\frac{\partial}{\partial k_1}, \tag{23}$$

$$\begin{aligned} X = &-x_1\frac{\partial}{\partial x_1} - x_2\frac{\partial}{\partial x_2} - x_3\frac{\partial}{\partial x_3} - x_4\frac{\partial}{\partial x_4} - x_5\frac{\partial}{\partial x_5} - \\ &- x_6\frac{\partial}{\partial x_6} - x_7\frac{\partial}{\partial x_7} - x_8\frac{\partial}{\partial x_8} - x_9\frac{\partial}{\partial x_9} - x_{10}\frac{\partial}{\partial x_{10}} + \\ &+ s_1\frac{\partial}{\partial s_1} + s_2\frac{\partial}{\partial s_2} + s_3\frac{\partial}{\partial s_3} + s_4\frac{\partial}{\partial s_4} + k_{10}\frac{\partial}{\partial k_{10}}\ . \end{aligned} \tag{24}$$

Only the last infinitesimal generator can be selected, because is the only one that incorporates unidentifiable parameters. From it, we choose to remove parameter k_{10}:

BOX 10. User input.
Enter the generator that you want to use:
2
Enter the number of the parameter to be removed (in order of output per screen):
5

The new expressions for states and parameters are given by:

$$\overline{x_i} = x_i k_{10} \text{ for } i = 1, ..., 10 \ ,$$
$$\overline{s_j} = \frac{s_j}{k_{10}} \text{ for } j = 1, .., 4$$

After this new transformation, state x_7 has been reparameterized twice.

Lastly, AutoRepar performs the remaining transformations and yields the reparameterized model, which is FISPO:

BOX 11. AutoRepar.
You have chosen the parameter k10 from the infinitesimal generator:
[x1, x2, x3, x4, x5, x6, x7, x8, x9, x10, 0, -s1, -s2, -s3, -s4, 0, 0, -k10]

>>> Transformed variables:
x1 $\longleftarrow$ x1/k10
x2 $\longleftarrow$ x10/k10
x3 $\longleftarrow$ s1*k10
x4 $\longleftarrow$ s2*k10
x5 $\longleftarrow$ s3*k10
x6 $\longleftarrow$ s4*k10
x7 $\longleftarrow$ k10*k10
x8 $\longleftarrow$ x2/k10
x9 $\longleftarrow$ x3/k10
x10 $\longleftarrow$ x4/k10
u1 $\longleftarrow$ u1
s1 $\longleftarrow$ x5/k10
s2 $\longleftarrow$ x6/k10
s3 $\longleftarrow$ x7/k10
s4 $\longleftarrow$ x8/k10
k1 $\longleftarrow$ k1
k8 $\longleftarrow$ k8
k10 $\longleftarrow$ 1
>>> Equations of the reformulated model:

f:
$k11 * x10 - x1 * (k1p + (k1 * u1)/(u1 + 1))$
$x1 * (k1p + (k1 * u1)/(u1 + 1)) - k2 * x2$
$k2 * x2 - k3 * x3$
$k2 * x2 - k4 * x4$
$k3 * rhovol * x3 - k5 * x5$
$k5 * x5 - x6 * x9$
$x6 - k7 * x7$
$k8 * x7 - k9 * x8$
$k9 * rhovol * x8 - x6 * x9$
$x6 * x9 - k11 * rhovol * x10$
h:

$I0cyt + s1 * (x1 + x2 + x3)$
$I0nuc + s2 * (x5 + x6 + x10)$
$s3 * (x2 + x3)$
$s4 * (x2 + x4)$

>>> The model reparameterization has been completed successfully

The new FISPO model is:
f:
$k11 * x10 - x1 * (k1p + (k1 * u1)/(u1 + 1))$
$x1 * (k1p + (k1 * u1)/(u1 + 1)) - k2 * x2$
$k2 * x2 - k3 * x3$
$k2 * x2 - k4 * x4$
$k3 * rhovol * x3 - k5 * x5$
$k5 * x5 - x6 * x9$
$x6 - k7 * x7$
$k8 * x7 - k9 * x8$
$k9 * rhovol * x8 - x6 * x9$
$x6 * x9 - k11 * rhovol * x10$
h:

$I0cyt + s1 * (x1 + x2 + x3)$
$I0nuc + s2 * (x5 + x6 + x10)$
$s3 * (x2 + x3)$
$s4 * (x2 + x4)$