GEARS: The Goodwin Oscillator example

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The Goodwin oscillator example in GEARS performs parameter estimation on the Goodwin oscillator model. The Goodwin oscillator model Goodwin (1965), is a fairly generic model with the variables $\{x_1, x_2, x_3\}$ representing RNA, protein and then some end product respectively. We consider the model in the form as described by equations 1-6 and figure 1.

$$\frac{dx_1}{dt} = \frac{k_1 \cdot K_i^n}{K_i^n + x_3^n} - k_2 \cdot x_1 \tag{1}$$

$$\frac{dx_2}{dt} = k_3 \cdot x_1 - k_4 \cdot x_2 \tag{2}$$

$$\frac{dx_3}{dt} = k_5 \cdot x_2 - k_6 \cdot x_3 \tag{3}$$
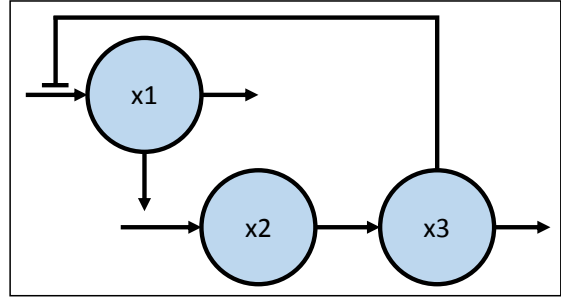
$$x_{1-3}(t_0, \boldsymbol{\theta}) = x_{1-3,0} \tag{4}$$

Figure 1: A visualisation of the structure of the Goodwin Oscillator model.

$$\boldsymbol{y}_F(t_i) = [x_1(t_i), x_3(t_i)] \text{ and } \boldsymbol{y}_V(t_i) = [x_1(t_i), x_2(t_i), x_3(t_i)] \tag{5}$$

$$\boldsymbol{\theta} = \{k_{1-6}, K_i, n\} \text{ where } \{k_{1-6}, K_i\} \in [10^{-3}, 10^3] \text{ and } n \in [1, 12] \tag{6}$$

Where $\boldsymbol{y}_F$ is the observation function for the fitting procedure and $\boldsymbol{y}_V$ is the observation function for the cross-validation procedure. Synthetic data was generated for the Goodwin oscillator model for parameter values $\{k_{1-6}, K_i, n\} = \{1, 0.1, 1, 0.1, 1, 0.1, 1, 10\}$ for the initial conditions $x_{1-3,0} = [0.1, 0.2, 2.5]$. This data was generated with a standard deviation

of 10% of the nominal signal level and a detection threshold of 0.1. This set-up for generating data was used to set up one fitting set of data and two data sets for cross-validation. Initial conditions for the cross-validation sets were varied randomly within a meaningful range.

A selection of the expected results achieved by running the GO example in `GEARS` can be found below. For the full collection of the expected results of the example please consult the expected results folder in the GO example folder.

One issue that especially affects the GO model is a lack of identifiability. The Goodwin oscillator contains a number of identifiability issues for a number of different parameters. One particular case of this is the high correlation between parameters k_1 and K_i which can be seen in figure 3. The GO model also has some structural identifiability issues with parameter k_3 and k_5 when the state x_2 is not observed.

| Parameter	Value	Confidence (95%)	Coeff of variation (%)	Bounds status
k_1	85.4695	± 101.1419	60.3759	Bounds not active
k_2	0.1257	± 0.02272827	9.22635	Bounds not active
k_3	0.8131	± 0.4246396	26.6465	Bounds not active
k_4	0.1364	± 0.04167118	15.5852	Bounds not active
k_5	0.8234	± 0.6647931	41.1939	Bounds not active
k_6	0.0506	± 0.02286852	23.0398	Bounds not active
K_i	0.7656	± 0.06074743	4.04812	Bounds not active
n	12	± 1.897339	8.06692	Upper bound active

Table 1: A summary of the regularised results from the `GEARS` analysis of the GO model.

| Experiment	Regularised estimation	Non-regularised estimation
Fitting experiment	4.8119	4.2876

Table 2: The NRMSEs calculated for the fitting of the GO model.

| Experiment	Regularised estimation	Non-regularised estimation
All experiments	18.2	19.047
Experiment 1	17.285	21.999
Experiment 2	19.07	15.545

Table 3: The NRMSEs calculated for the cross-validation of the GO model.
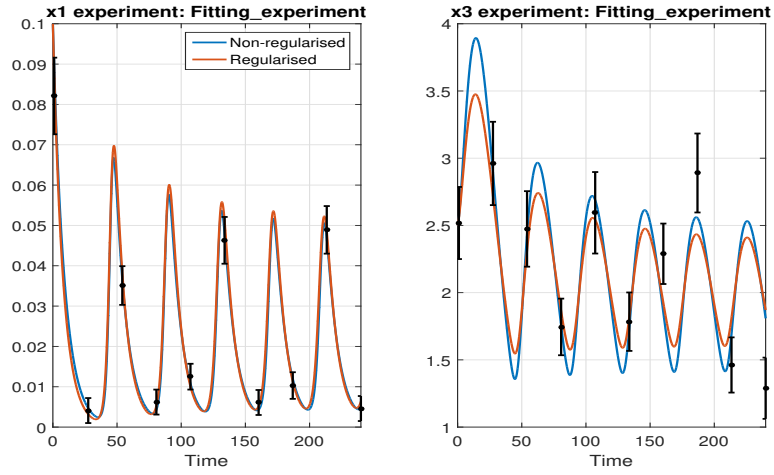
(a) A comparison of the GO model fits with and without regularisation.
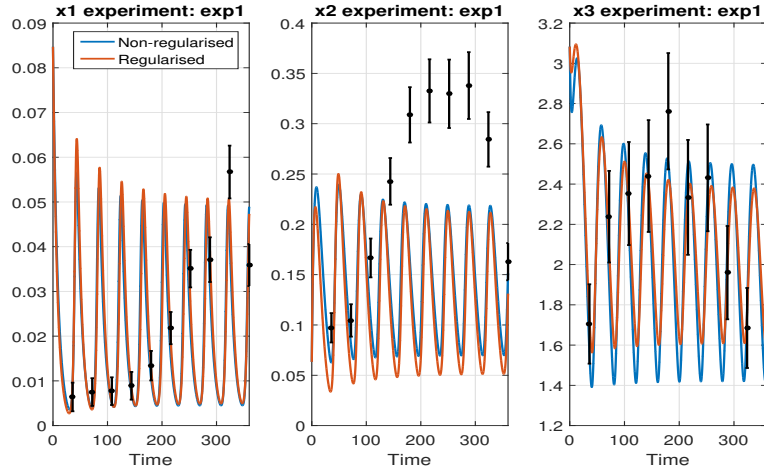
(b) A comparison of the GO model predictions for the first cross-validation data set with and without regularisation.
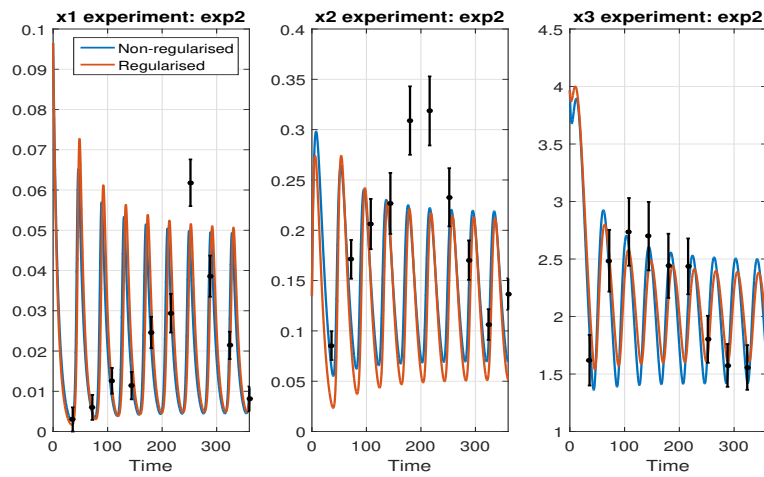
(c) A comparison of the GO model predictions for the second cross-validation data set with and without regularisation.

Figure 2: Figures showing the comparison between the regularised and non-regularised fits for both fitting and cross-validation.
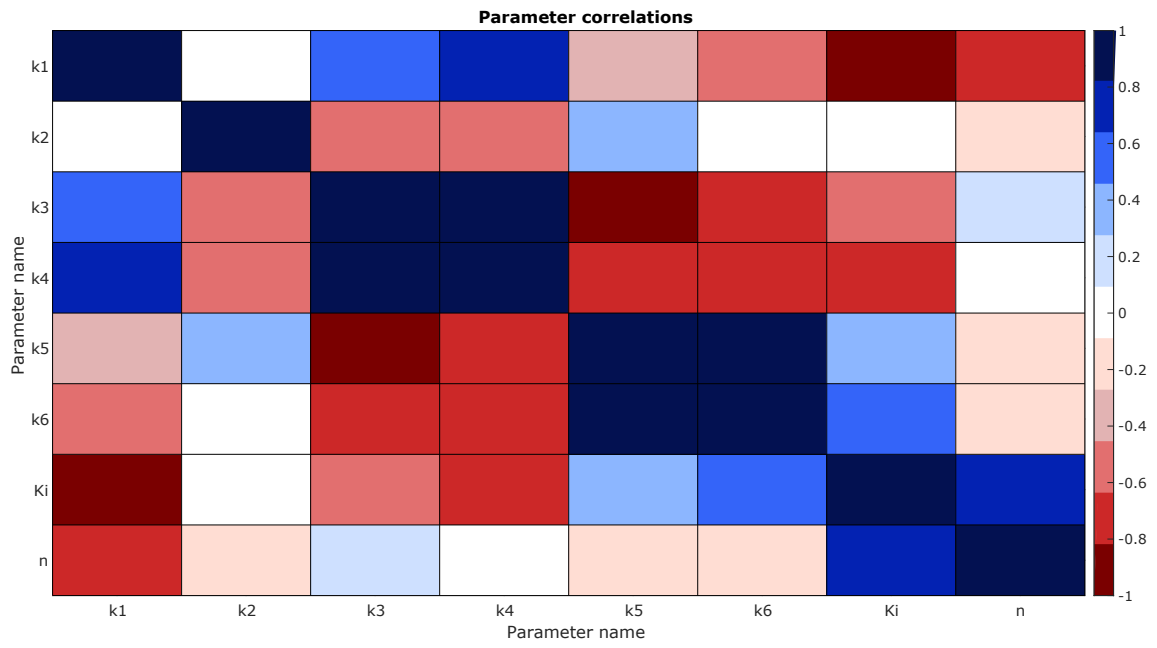
Figure 3: The correlation matrix of the Goodwin oscillator at the estimated parameter values.

References

Goodwin, B. C. (1965). Oscillatory behavior in enzymatic control processes. *Advances in enzyme regulation*, 3:425–429.