IDENTIFICATION OF PARAMETERS FOR LARGE-SCALE MODELS IN SYSTEMS BIOLOGY

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ABSTRACT. Inverse problem for the identification of the parameters for large-scale systems of nonlinear ordinary differential equations (ODEs) arising in systems biology is analyzed. In a recent paper in Mathematical Biosciences, 305(2018), 133-145, the authors implemented the numerical method suggested by one of the authors in J. Optim. Theory Appl., 85, 3(1995), 509-526 for identification of parameters in moderate scale models of systems biology. This method combines Pontryagin optimization or Bellman’s quasilinearization with sensitivity analysis and Tikhonov regularization. We suggest modification of the method by embedding a method of staggered corrector for sensitivity analysis and by enhancing multi-objective optimization which enables application of the method to large-scale models with practically non-identifiable parameters based on multiple data sets, possibly with partial and noisy measurements. We apply the modified method to a benchmark model of a three-step pathway modeled by 8 nonlinear ODEs with 36 unknown parameters and two control input parameters. The numerical results demonstrate geometric convergence with a minimum of five data sets and with minimum measurements per data set. Software package qlopt is developed and posted in GitHub. MATLAB package AMIGO2 is used to demonstrate advantage of qlopt over most popular methods/software such as lsqnonlin, fmincon and nl2sol.

1. INTRODUCTION

Systems Biology is an actively emerging interdisciplinary field whose mission is to reveal and understand the global properties of biological or bioengineering systems through complex interaction of a large number of cells or organisms. One of the major challenges of systems biology is to develop predictive mathematical models described by large numbers of nonlinear ordinary differential equations based on experimental data. The quantitative features of such models are
characterized by a large number of parameters. Identification of parameters through noisy measurements is an ill-posed inverse problem and it requires the development of delicate regularization techniques [1]. Solving inverse problems in systems biology is an actively growing research field [2, 3, 4, 5, 6, 7, 8, 9, 10]. We refer to the survey article [6] for references. In a recent paper [11] the authors implemented the numerical method introduced by one of the authors in [12, 13]. The iterative method combines ideas of Pontryagin optimization or Bellman quasilinearization with sensitivity analysis and Tikhonov regularization. Extensive computational analysis pursued in [11] demonstrated that the method is very well adapted to canonical models of system biology with moderate size parameter sets and has a quadratic convergence. Software package qlopt was developed and posted in GitHub [15]. The MATLAB package AMIGO2 [16] was used to demonstrate the high competitiveness of qlopt with the most popular software packages, including lsqnonlin, fmincon, nl2sol.

However, direct adaptation and scalability of the method to inverse problems with significantly large size was not as effective. The goal of this paper is to suggest the modification of the method which is effective at solving the inverse problem on the identification of parameters for large scale models in systems biology. The modification is twofold.

- Method of staggered corrector [17] is embedded into the step of calculation of the sensitivity vectors. More precisely, instead of solving the linearized system and associated sensitivity system, we first solve the original system through quasilinearization [18], and then use its solution to solve the linear sensitivity system corresponding to the original nonlinear system. We use the software package CVODES [19] to implement the method of staggered corrector into our algorithm.

- Multi-objective optimization is enhanced into the method which allows for the application of the method to large-scale models with a practically non-identifiable set of parameters based on multiple data sets, possibly with partial and noisy measurements.

2. DESCRIPTION OF THE METHOD

Consider a dynamical system:

\[
\frac{dx}{dt} = f(t, x, u, v), \quad t_0 \leq t \leq t_1
\]

(1)

\[
x(t_0) = x^0 \in \mathbb{R}^n,
\]

(2)
where
\[ x = x(t) = (x_1(t), x_2(t), \ldots, x_n(t)) : [t_0, t_1] \to \mathbb{R}^n \]
is the state vector,
\[ u = (u_1, u_2, \ldots, u_m) \in \mathbb{R}^m \]
is the unknown parameter vector,
\[ v = (v_1, v_2, \ldots, v_p) \in \mathbb{R}^p \]
is the control input parameter vector, and
\[ f = (f_1(t, x, u, v), f_2(t, x, u, v), \ldots, f_n(t, x, u, v)) : [t_0, t_1] \times \mathbb{R}^n \times \mathbb{R}^m \times \mathbb{R}^p \to \mathbb{R}^n \]
is a continuous vector function with continuous derivatives
\[ \frac{\partial f}{\partial x}, \frac{\partial f}{\partial u}. \]

Consider the inverse problem of finding the parameter \( u \) given \( D \) measurements for the state vector \( x \) corresponding to \( D \) fixed values of the control vector \( v \):
\[ x = x^d(t) = x^d(t; u) := x(t, u^d), \quad d = 1, \ldots, D \]
on an interval \( t_0 \leq t \leq t_1 \), where \( x^d(t_0) = x^0 \).

Given the initial guess \( u_0 \) of the unknown parameter \( u \), we implement quasilinearization of (1) and at each fixed iteration \( N = 1, 2, \ldots \) we find the solution as a limit
\[ x^d_{N,p}(t) = \lim_{p \to \infty} x^d_{N,p}(t), \quad t_0 \leq t \leq t_1, \tag{3} \]
where \( x^d_{N,p} \) solves the linear system of ODEs in \([t_0, t_1]\) with \( u = u_{N-1} \):
\[ \frac{dx^d_{N,p}}{dt} = f(t, x^d_{N,p-1}, u, v^d) + J(t, x^d_{N,p-1}, u, v^d)(x^d_{N,p} - x^d_{N,p-1}), \tag{4a} \]
\[ x^d_{N,p}(t_0) = x^0, \tag{4b} \]
where
\[ J(t, x, u, v) = \frac{\partial f(t, x, u, v)}{\partial x} \]
is the \( n \times n \) Jacobian matrix. It is well known that the convergence \( \[ \] \) has a quadratic rate \( \[ \] \). Given the initial guess \( u_0 \) of the unknown parameter \( u \), we identify at every step of the iteration a new approximation
\[ u_N = u_{N-1} + \Delta u, \tag{5} \]
which minimizes the $L_2$-norm of the residues
\[ \mathcal{R} = x^d(t, u) - x_N^d(t, u_N). \]

We have
\[ \mathcal{R} = \Delta x_N^d(t) - U_N^d \Delta u + o(|\Delta u|), \quad \text{as } |\Delta u| \to 0, \]

where
\[ \Delta x_N^d(t) = x^d(t, u) - x_N^d(t, u_{N-1}), \]

$U_N^d$ is an $n \times m$ sensitivity matrix with columns
\[ U_{N}^{d,j} = \left( \frac{\partial x_N^d(t, u_{N-1})}{\partial u^j} \right), \quad j = 1, \ldots, m. \]

$U_N^d$ solves the matrix differential system
\[
\frac{dU_N^d}{dt} = \frac{\partial}{\partial u} f(t, x_N^d, u_{N-1}, v^d) + J(t, x_N^d, u_{N-1}, v^d)U_N^d, \quad t_0 \leq t \leq t_1
\]
\[ U_N^d(t_0) = 0, \]

where $x_N^d$ is the solution of (1), (2) with $u = u_{N-1}, v = v^d$ as it is constructed in (3). Finding $x_N^d, U_N^d$ from (3), (4), (7) form the method of staggered corrector [17].

To find $\Delta u$, we minimize the multi-objective function
\[ J(\Delta u) = \sum_{d=1}^{D} ||\Delta x_N^d - U_N^d \Delta u||_2^{2} L_N^2(t_0, t_1), \]

where $L_N^2(t_0, t_1)$ is a Hilbert space of vector functions $g : (t_0, t_1) \to \mathbb{R}^n$ with inner product
\[ (g, h)_{L_N^2(t_0, t_1)} = \int_{t_0}^{t_1} g^T h dt. \]

We have
\[ J_N'(\Delta u) = 2 \sum_{d=1}^{D} \int_{t_0}^{t_1} \left( (U_N^d)^T U_N^d \Delta u - (U_N^d)^T \Delta x_N^d \right) dt, \]
\[ J_N''(\Delta u) = 2 \sum_{d=1}^{D} \int_{t_0}^{t_1} (U_N^d)^T U_N^d dt. \]

Therefore, minimum $\Delta u$ satisfies the following system of linear algebraic equations
\[ A_N \Delta u = P_N, \]
where
\[ A_N = \sum_{d=1}^{D} \int_{t_0}^{t_1} (U_N^d)^T U_N^d dt = \left( a_{N}^{ij} \right)_{i,j=1}^{m} \]
is an \(m \times m\) symmetric matrix with elements
\[ a_{N}^{ij} = \sum_{d=1}^{D} \int_{t_0}^{t_1} \left( \frac{\partial x_N^d(t,u_{N-1})}{\partial u^i} \right)^T \frac{\partial x_N^d(t,u_{N-1})}{\partial u^j} dt, \]
and
\[ P_N = \sum_{d=1}^{D} \int_{t_0}^{t_1} (U_N^d)^T \Delta x_N dt = \left( p_N^j \right)_{j=1}^{m} \]
is an \(m\)-vector with elements
\[ p_N^j = \sum_{d=1}^{D} \int_{t_0}^{t_1} \left( \frac{\partial x_N^d(t,u_{N-1})}{\partial u^j} \right)^T (x^d(t,u) - x_N^d(t,u_{N-1})) dt \]
In fact, \(A_N\) is a sum of Gram matrices of vectors \(U_{N}^{d,j}\), and
\[ a_{N}^{ij} = \sum_{d=1}^{D} (U_{N}^{d,i} , U_{N}^{d,j} )_{L_2^2(t_0,t_1)}. \]
It is known [20] that
\[ det(A_N) = \sum_{d=1}^{D} \Gamma(U_{N}^{d,1} ,..., U_{N}^{d,m}) \geq 0 \]
and it is positive, that is to say, \(A_N\) is non-singular, if and only if the vectors \(U_{N}^{d,j}, j = 1, ..., m\) are linearly independent at least for one \(d = 1, ..., D\).

Hence, we suggest the following modification of the numerical algorithm from [12].

2.1. Algorithm.

(1) Initialize \(u_0\) and set \(N = 1\).
(2) Set \(x_{N,0}^d(t)\) and find \(x_{N}^d(t,u_{N-1})\) via quasilinearization from (3),(4).
(3) Having \(x_{N}^d(\cdot,u_{N-1})\) find sensitivity matrices \(U_{N}^{d}\) by solving linear ODE systems (7).
(4) Find \(\Delta u\) by solving linear algebraic equations system (9) and update the new value \(u_N\) of the parameter using (5).
(5) If satisfactory accuracy is achieved, then terminate the process, otherwise replace $N$ with $N + 1$ and go back to Step 2. As termination criteria, the smallness of either of the expressions

$$|u_{N-1} - u_N|, \ J_N(\Delta u), \ \sum_{d=1}^D ||x^d(\cdot) - x^d_N(\cdot, u_N)||_{L^2}$$

can be used.

2.2. Regularization. As in [11] we implement two types of Tikhonov regularization. Type I regularization is performed by replacing the function (8) with

(10) $$\sum_{d=1}^D \left( ||\Delta x_N^d - U_N^d \Delta u||_{L^2}^2 \right) + \alpha |\Delta u|^2.$$ 

This yields the following linear system instead of (9)

(11) $$(A_N + \alpha I)\Delta u = P_N$$

where $I$ is the identity matrix and $\alpha$ is a regularization parameter. Type II regularization is performed by replacing the function (8) with

(12) $$\sum_{d=1}^D ||\Delta x_N^d - U_N^d \Delta u||_{L^2}^2 + \alpha |u_{N-1} + \Delta u - u^*|^2$$

where $u^*$ is a known vector expected to be close to the true value of the unknown parameter. This implies the following linear system instead of (9):

(13) $$(A_N + \alpha I)\Delta u = P_N + \alpha (u^* - u_{N-1}).$$

2.3. Identifiability. Convergence of the algorithm is connected to the identifiability of unknown parameters. In fact, $d$th Gram matrix summand of $A_N$ in (9) is the so called Fisher information matrix (FIM) for the ODE system (1), which characterizes the information content of the experimental measurement in the $d$th data set. Singularity of $A_N$ is equivalent to linear dependence of the sensitivity vectors $U_N^{d,j}, j = 1, ..., m$ for all $d = 1, ..., D$, which is the indication of the presence of the non-identifiable parameters. On the contrary, non-singularity of $A_N$ is equivalent to identifiability of parameters. If $A_N$ is non-singular but det$A_N$ is sufficiently small, then for computer simulation $A_N$ is treated as a singular matrix [10, 21, 22]. Our two regularization algorithms are developed to address such practical non-identifiability cases. A major factor for the convergence of the algorithm for the identification of practically non-identifiable parameters is the increase of number of data sets $D$. Specifically, there is a minimum
number of data sets with different inputs of control parameters for experimental design needed to relieve the parameter correlations and acquire suitable measurement data for unique parameter estimation [23].

3. Results and Discussions

We tested the method on a benchmark model of a biological network for a three-step pathway modeled by 8 nonlinear ODEs describing 8 metabolic concentrations and 36 parameters $p_i, i = 1, \ldots, 36$ ([2]):

$$
\begin{align*}
\dot{x}_1 &= \frac{p_1}{1 + \left(\frac{p_2}{p_5}\right)^{p_3} + \left(\frac{p_4}{S}\right)^{p_5}} - p_6 x_1 \\
\dot{x}_2 &= \frac{p_7}{1 + \left(\frac{p_8}{p_9}\right)^{p_9} + \left(\frac{p_{10}}{x_7}\right)^{p_{11}}} - p_{12} x_2 \\
\dot{x}_3 &= \frac{p_{13}}{1 + \left(\frac{p_{14}}{p_{15}}\right)^{p_{15}} + \left(\frac{p_{16}}{x_8}\right)^{p_{17}}} - p_{18} x_3 \\
\dot{x}_4 &= \frac{p_{19} x_1}{p_20 + x_1} - p_{21} x_4 \\
\dot{x}_5 &= \frac{p_{22} x_2}{p_{23} + x_2} - p_{24} x_5 \\
\dot{x}_6 &= \frac{p_{25} x_3}{p_{26} + x_3} - p_{27} x_6 \\
\dot{x}_7 &= \frac{p_{28} x_4 \left(S - x_7\right)}{p_{29} \left(1 + \frac{s}{p_{29}} + \frac{x_7}{p_{30}}\right)} - \frac{p_{31} x_5 \left(x_7 - x_8\right)}{p_{32} \left(1 + \frac{x_7}{p_{32}} + \frac{x_8}{p_{33}}\right)} \\
\dot{x}_8 &= \frac{p_{31} x_5 \left(x_7 - x_8\right)}{p_{32} \left(1 + \frac{x_7}{p_{32}} + \frac{x_8}{p_{33}}\right)} - \frac{p_{34} x_6 \left(x_8 - P\right)}{p_{35} \left(1 + \frac{x_8}{p_{35}} + \frac{P}{p_{36}}\right)}
\end{align*}
$$

Two parameters $P$ and $S$ are control input parameters specified by the experimental design. The unknown parameters $p_i$ are correlated, but their functional relationship with one another is dependent on the input parameters $P$ and $S$, and in general parameters are practically identifiable with multiple data sets. In [24], the inverse problem was analyzed with 16 noise-free data sets, and in [25] with 16 both noise-free and noisy data sets. The results demonstrated strong parameter correlations in several groups, with accurate parameter values identified in [25]. Parameter correlations were analyzed in [23]. It is demonstrated that correlated parameters are practically non-identifiable for
a single data set and at least 5 data sets with different control inputs are required to uniquely estimate the 36 parameters of this model.

For our experiments we used the common values for the initial conditions \( (6.6667e-1, 5.7254e-1, 4.1758e-1, 4.0e-1, 3.6409e-1, 2.9457e-1, 1.419e-1, 0.3464e-1) \), with \( t_0 = 0 \) and \( t_1 = 120 \). We implemented the 16 input parameters given in AMIGO2 \cite{16} and 5 input parameters given in \cite{23} for our experiments. We chose the regularization parameter \( \alpha \) as a function of the residual:

\[
\sum_{d=1}^{D} C||x^d - x^d_N||^2_{L_2}
\]

where \( C, \gamma > 0 \) are chosen experimentally.

3.1. Numerical Results with Noise-free Data Sets. We applied the numerical method to identify the 36 parameters with 16 and 5 data sets. We generated simulated measurements for each data set by solving the system of 8 nonlinear ODEs with true values of 36 parameters. We chose the number of time data points for each of the 8 components of the system either at 240 or at 20 uniformly distributed time grid points in the segment \([0, 120] \). Computational cost of each iteration per one data set consists of iterative solution of the system of 8 nonlinear ODEs through quasilinearization; solving a system of 288 linear ODEs to identify sensitivity matrix-function; calculation of 1332 integrals for entries of the matrix \( A_N \) and vector \( P_N \); and finally solving system of 36 linear algebraic equations to find the increment of the parameters. In Table 1 and Figure 1 we demonstrate the results for 16 data sets with 240 time points. Rapid convergence to the true solution happens in only 7 iterations. Next we applied the method with 5 data sets. Though it required 3 extra iterations, Table 2 and Figure 2 demonstrate the rapid convergence of the method with reduced error.

Next we applied the method by choosing measurements at 20 time grid points for each of the 8 components. The results are demonstrated for 16 and 5 data sets in Tables 3 and 4, respectively. The algorithm converges in the same number of iterations with respect to the number of data sets, while maintaining around the same level of accuracy, as demonstrated in Figures 3 and 4.

3.2. Effect of the Regularization Parameter \( \alpha \). The choice of the regularization parameter \( \alpha \) is an important factor which significantly improves the convergence rate and computational cost of the algorithm. To demonstrate the existence of the optimal non-trivial value of \( \alpha \) at every fixed step \( N \), we considered profiles of \( \alpha \) vs \( |u_{N-1} + \Delta u - u^*| \), where
| \( \bar{u} \) | \( \bar{u}_0 \) | \( \bar{u}_2 \) | \( \bar{u}_4 \) | \( \bar{u}_7 \) | \( \bar{u} \) |
|---|---|---|---|---|---|
| \( p_1 \) | 1.250 00 | 1.246 39 | 0.952 77 | 1.001 14 | 1 |
| \( p_2 \) | 1.250 00 | 1.001 45 | 1.000 12 | 1.000 01 | 1 |
| \( p_3 \) | 2.500 00 | 2.012 51 | 2.000 11 | 1.999 91 | 2 |
| \( p_4 \) | 1.250 00 | 0.987 74 | 1.000 12 | 0.999 99 | 1 |
| \( p_5 \) | 2.500 00 | 2.004 16 | 1.999 71 | 1.999 96 | 2 |
| \( p_6 \) | 1.250 00 | 1.250 30 | 0.952 72 | 1.001 14 | 1 |
| \( p_7 \) | 1.250 00 | 1.285 21 | 0.969 97 | 1.000 60 | 1 |
| \( p_8 \) | 1.250 00 | 0.991 18 | 1.000 32 | 1.000 01 | 1 |
| \( p_9 \) | 2.500 00 | 2.009 61 | 1.999 47 | 2.000 10 | 2 |
| \( p_{10} \) | 1.250 00 | 1.011 87 | 0.999 95 | 1.000 00 | 1 |
| \( p_{11} \) | 2.500 00 | 1.921 66 | 1.997 80 | 1.999 97 | 2 |
| \( p_{12} \) | 1.250 00 | 1.280 11 | 0.970 01 | 1.000 60 | 1 |
| \( p_{13} \) | 1.250 00 | 1.247 89 | 1.021 28 | 1.000 46 | 1 |
| \( p_{14} \) | 1.250 00 | 1.039 07 | 1.000 54 | 1.000 07 | 1 |
| \( p_{15} \) | 2.500 00 | 2.023 76 | 2.000 26 | 2.000 42 | 2 |
| \( p_{16} \) | 1.250 00 | 0.956 82 | 0.999 21 | 0.999 92 | 1 |
| \( p_{17} \) | 2.500 00 | 2.032 21 | 2.000 05 | 2.000 05 | 2 |
| \( p_{18} \) | 1.250 00 | 1.307 97 | 1.021 35 | 1.000 55 | 1 |
| \( p_{19} \) | 0.125 00 | 0.083 56 | 0.099 73 | 0.100 01 | 0.1 |
| \( p_{20} \) | 1.250 00 | 0.937 93 | 1.000 10 | 1.000 17 | 1 |
| \( p_{21} \) | 0.125 00 | 0.080 52 | 0.099 73 | 0.100 00 | 0.1 |
| \( p_{22} \) | 0.125 00 | 0.052 33 | 0.095 84 | 0.100 00 | 0.1 |
| \( p_{23} \) | 1.250 00 | 0.797 97 | 0.996 37 | 0.999 97 | 1 |
| \( p_{24} \) | 0.125 00 | 0.051 19 | 0.096 12 | 0.100 00 | 0.1 |
| \( p_{25} \) | 0.125 00 | 0.096 90 | 0.099 41 | 0.100 00 | 0.1 |
| \( p_{26} \) | 1.250 00 | 0.958 03 | 1.001 01 | 1.000 05 | 1 |
| \( p_{27} \) | 0.125 00 | 0.098 49 | 0.099 32 | 0.099 99 | 0.1 |
| \( p_{28} \) | 1.250 00 | 0.949 33 | 1.000 96 | 0.999 98 | 1 |
| \( p_{29} \) | 1.250 00 | 1.170 61 | 1.000 23 | 0.999 77 | 1 |
| \( p_{30} \) | 1.250 00 | 1.445 02 | 0.991 61 | 0.999 71 | 1 |
| \( p_{31} \) | 1.250 00 | 1.003 15 | 1.000 47 | 1.000 05 | 1 |
| \( p_{32} \) | 1.250 00 | 1.134 35 | 1.003 18 | 0.999 76 | 1 |
| \( p_{33} \) | 1.250 00 | 1.119 95 | 0.995 90 | 0.999 37 | 1 |
| \( p_{34} \) | 1.250 00 | 1.075 49 | 1.000 04 | 0.999 91 | 1 |
| \( p_{35} \) | 1.250 00 | 1.139 16 | 1.002 07 | 0.999 83 | 1 |
| \( p_{36} \) | 1.250 00 | 1.021 51 | 0.999 32 | 0.999 87 | 1 |
| \( \alpha \) | 3.312 63 | 0.066 38 | 1.910 27×10^{-7} | |

Table 1. The evolution of the parameters at select iterations, with 16 data sets, \( t_0 = 0, t_1 = 120, \Delta t = 0.5 \), i.e. 240 time points. Regularization parameter \( \alpha \) was determined using (14) where \( C = 0.009 \) and \( \gamma = 2 \).
| $\vec{u}$ | $\vec{u}_0$ | $\vec{u}_3$ | $\vec{u}_6$ | $\vec{u}_{10}$ | $\vec{u}$ |
|---------|-----------|-----------|-----------|-----------|---------|
| $p_1$   | 1.250 00 | 1.234 03 | 1.049 71 | 1.000 20 | 1       |
| $p_2$   | 1.250 00 | 0.979 74 | 0.999 53 | 1.000 22 | 1       |
| $p_3$   | 2.500 00 | 2.023 80 | 2.001 55 | 1.999 51 | 2       |
| $p_4$   | 1.250 00 | 0.912 42 | 0.999 17 | 0.999 99 | 1       |
| $p_5$   | 2.500 00 | 1.663 10 | 1.997 80 | 1.999 99 | 2       |
| $p_6$   | 1.250 00 | 1.232 31 | 1.049 80 | 1.000 20 | 1       |
| $p_7$   | 1.250 00 | 1.246 83 | 1.080 49 | 1.000 49 | 1       |
| $p_8$   | 1.250 00 | 0.980 26 | 1.002 02 | 0.999 97 | 1       |
| $p_9$   | 2.500 00 | 2.015 11 | 1.996 19 | 2.000 09 | 2       |
| $p_{10}$| 1.250 00 | 0.999 49 | 0.999 71 | 1.000 00 | 1       |
| $p_{11}$| 2.500 00 | 1.983 55 | 2.001 73 | 1.999 89 | 2       |
| $p_{12}$| 1.250 00 | 1.246 23 | 1.080 87 | 1.000 48 | 1       |
| $p_{13}$| 1.250 00 | 1.237 32 | 1.196 26 | 1.001 72 | 1       |
| $p_{14}$| 1.250 00 | 0.986 99 | 0.997 80 | 1.000 06 | 1       |
| $p_{15}$| 2.500 00 | 2.011 17 | 2.008 52 | 1.999 88 | 2       |
| $p_{16}$| 1.250 00 | 0.982 42 | 1.006 48 | 0.999 87 | 1       |
| $p_{17}$| 2.500 00 | 2.016 85 | 1.985 51 | 2.000 20 | 2       |
| $p_{18}$| 1.250 00 | 1.256 95 | 1.189 65 | 1.001 84 | 1       |
| $p_{19}$| 0.125 00 | 0.091 76 | 0.098 68 | 0.100 00 | 0.1     |
| $p_{20}$| 1.250 00 | 1.007 99 | 0.999 59 | 1.000 06 | 1       |
| $p_{21}$| 0.125 00 | 0.090 38 | 0.098 69 | 0.099 99 | 0.1     |
| $p_{22}$| 0.125 00 | 0.091 38 | 0.099 16 | 0.100 00 | 0.1     |
| $p_{23}$| 1.250 00 | 0.984 00 | 1.003 81 | 1.000 03 | 1       |
| $p_{24}$| 0.125 00 | 0.092 23 | 0.098 92 | 0.100 00 | 0.1     |
| $p_{25}$| 0.125 00 | 0.101 22 | 0.098 94 | 0.100 00 | 0.1     |
| $p_{26}$| 1.250 00 | 1.017 51 | 1.002 23 | 0.999 96 | 1       |
| $p_{27}$| 0.125 00 | 0.100 32 | 0.098 79 | 0.100 00 | 0.1     |
| $p_{28}$| 1.250 00 | 0.991 74 | 0.997 03 | 0.999 99 | 1       |
| $p_{29}$| 1.250 00 | 1.177 39 | 1.031 58 | 1.000 11 | 1       |
| $p_{30}$| 1.250 00 | 1.385 90 | 1.060 47 | 1.000 25 | 1       |
| $p_{31}$| 1.250 00 | 1.052 83 | 1.006 24 | 1.000 04 | 1       |
| $p_{32}$| 1.250 00 | 1.157 74 | 1.020 31 | 1.000 01 | 1       |
| $p_{33}$| 1.250 00 | 1.154 41 | 1.036 05 | 0.999 94 | 1       |
| $p_{34}$| 1.250 00 | 1.096 91 | 1.016 50 | 1.000 07 | 1       |
| $p_{35}$| 1.250 00 | 1.151 20 | 1.022 09 | 1.000 10 | 1       |
| $p_{36}$| 1.250 00 | 1.014 71 | 1.010 37 | 1.000 08 | 1       |
| $\alpha$| 0.334 78 | 0.039 64 | 2.517 84×10⁻⁴|

Table 2. The evolution of the parameters at select iterations, with 5 data sets, $t_0 = 0$, $t_1 = 120$, $\Delta t = 0.5$, i.e., 240 time points. Regularization parameter $\alpha$ was determined using (14) where $C = 0.25$ and $\gamma = 1$. 
| $\vec{u}$ | $\vec{u}_0$ | $\vec{u}_2$ | $\vec{u}_4$ | $\vec{u}_7$ | $\vec{u}$ |
|----------|-----------|-----------|-----------|-----------|-----------|
| $p_1$    | 1.250 00  | 1.25513   | 0.92712   | 1.000 86  | 1         |
| $p_2$    | 1.250 00  | 0.99986   | 1.000 03  | 1.000 01  | 1         |
| $p_3$    | 2.500 00  | 1.97179   | 1.99992   | 1.999 91  | 2         |
| $p_4$    | 1.250 00  | 0.99014   | 0.99990   | 0.999 99  | 1         |
| $p_5$    | 2.500 00  | 1.95854   | 1.99986   | 1.999 97  | 2         |
| $p_6$    | 1.250 00  | 1.25268   | 0.92718   | 1.000 85  | 1         |
| $p_7$    | 1.250 00  | 1.29547   | 0.92150   | 1.000 50  | 1         |
| $p_8$    | 1.250 00  | 0.99811   | 1.000 02  | 1.000 01  | 1         |
| $p_9$    | 2.500 00  | 1.98785   | 2.000 08  | 2.000 10  | 2         |
| $p_{10}$ | 1.250 00  | 1.01373   | 0.99998   | 1.000 00  | 1         |
| $p_{11}$ | 2.500 00  | 1.99704   | 1.99989   | 1.999 97  | 2         |
| $p_{12}$ | 1.250 00  | 1.29427   | 0.92141   | 1.000 50  | 1         |
| $p_{13}$ | 1.250 00  | 1.26093   | 0.93061   | 1.000 51  | 1         |
| $p_{14}$ | 1.250 00  | 1.01331   | 1.000 00  | 1.000 06  | 1         |
| $p_{15}$ | 2.500 00  | 1.94676   | 1.99989   | 2.000 40  | 2         |
| $p_{16}$ | 1.250 00  | 0.98555   | 1.000 00  | 0.999 93  | 1         |
| $p_{17}$ | 2.500 00  | 1.97327   | 2.000 03  | 2.000 04  | 2         |
| $p_{18}$ | 1.250 00  | 1.27617   | 0.93014   | 1.000 59  | 1         |
| $p_{19}$ | 0.125 00  | 0.08431   | 0.09971   | 0.100 01  | 0.1       |
| $p_{20}$ | 1.250 00  | 0.98182   | 1.00011   | 1.000 14  | 1         |
| $p_{21}$ | 0.125 00  | 0.07762   | 0.09964   | 0.100 00  | 0.1       |
| $p_{22}$ | 0.125 00  | 0.08656   | 0.09997   | 0.100 00  | 0.1       |
| $p_{23}$ | 1.250 00  | 0.95621   | 0.99984   | 0.999 96  | 1         |
| $p_{24}$ | 0.125 00  | 0.08549   | 0.09998   | 0.100 00  | 0.1       |
| $p_{25}$ | 0.125 00  | 0.08525   | 0.09999   | 0.100 00  | 0.1       |
| $p_{26}$ | 1.250 00  | 0.98425   | 0.99970   | 1.000 07  | 1         |
| $p_{27}$ | 0.125 00  | 0.08221   | 0.09999   | 0.099 99  | 0.1       |
| $p_{28}$ | 1.250 00  | 0.90785   | 0.99926   | 0.999 99  | 1         |
| $p_{29}$ | 1.250 00  | 1.10587   | 0.99988   | 0.999 78  | 1         |
| $p_{30}$ | 1.250 00  | 1.34339   | 1.00104   | 0.999 68  | 1         |
| $p_{31}$ | 1.250 00  | 1.00717   | 0.99972   | 1.000 04  | 1         |
| $p_{32}$ | 1.250 00  | 1.09481   | 0.99945   | 0.999 78  | 1         |
| $p_{33}$ | 1.250 00  | 0.98646   | 0.99990   | 0.999 38  | 1         |
| $p_{34}$ | 1.250 00  | 0.99117   | 0.99966   | 0.999 90  | 1         |
| $p_{35}$ | 1.250 00  | 1.04746   | 0.99934   | 0.999 82  | 1         |
| $p_{36}$ | 1.250 00  | 0.97497   | 1.00030   | 0.999 87  | 1         |
| $\alpha$ | 2.01103   | 0.00932   | 2.688 09 × 10^{-8} |         |         |

Table 3. The evolution of the parameters at select iterations, with 16 data sets, $t_0 = 0$, $t_1 = 120$, $\Delta t = 6.0$, i.e. 20 time points. Regularization parameter $\alpha$ was determined using (14) where $C = 0.005$ and $\gamma = 2$. 
$\mathbf{\bar{u}}$ | $\mathbf{\bar{u}_0}$ | $\mathbf{\bar{u}_3}$ | $\mathbf{\bar{u}_6}$ | $\mathbf{\bar{u}_{10}}$ | $\mathbf{\bar{u}}$
---|---|---|---|---|---
$p_1$ | 1.25000 | 1.24688 | 0.99921 | 1.00116 | 1
$p_2$ | 1.25000 | 0.92935 | 0.99979 | 1.00021 | 1
$p_3$ | 2.50000 | 2.28328 | 2.00063 | 1.99954 | 2
$p_4$ | 1.25000 | 1.17855 | 0.99961 | 0.99998 | 1
$p_5$ | 2.50000 | 2.54456 | 1.99867 | 1.99998 | 2
$p_6$ | 1.25000 | 1.25620 | 0.99932 | 1.00116 | 1
$p_7$ | 1.25000 | 1.24492 | 1.08625 | 1.00215 | 1
$p_8$ | 1.25000 | 0.95158 | 1.00008 | 0.99996 | 1
$p_9$ | 2.50000 | 2.08014 | 2.00019 | 2.00010 | 2
$p_{10}$ | 1.25000 | 0.98508 | 0.99965 | 0.99999 | 1
$p_{11}$ | 2.50000 | 2.01634 | 1.99938 | 1.99988 | 2
$p_{12}$ | 1.25000 | 1.25964 | 1.08645 | 1.00215 | 1
$p_{13}$ | 1.25000 | 1.21353 | 1.05666 | 1.00014 | 1
$p_{14}$ | 1.25000 | 1.00315 | 0.99943 | 1.00000 | 1
$p_{15}$ | 2.50000 | 2.29280 | 2.00308 | 2.00004 | 2
$p_{16}$ | 1.25000 | 0.93760 | 1.00160 | 1.00001 | 1
$p_{17}$ | 2.50000 | 2.10338 | 1.99518 | 1.99998 | 2
$p_{18}$ | 1.25000 | 1.29358 | 1.05726 | 1.00013 | 1
$p_{19}$ | 0.12500 | 0.08487 | 0.09916 | 0.09998 | 0.1
$p_{20}$ | 1.25000 | 1.14647 | 0.99984 | 1.00005 | 1
$p_{21}$ | 0.12500 | 0.07581 | 0.09918 | 0.09998 | 0.1
$p_{22}$ | 0.12500 | 0.07177 | 0.09903 | 0.09999 | 0.1
$p_{23}$ | 1.25000 | 1.00612 | 1.00240 | 1.00006 | 1
$p_{24}$ | 0.12500 | 0.06955 | 0.09888 | 0.09998 | 0.1
$p_{25}$ | 0.12500 | 0.10117 | 0.09949 | 0.10002 | 0.1
$p_{26}$ | 1.25000 | 1.02453 | 1.00054 | 0.99992 | 1
$p_{27}$ | 0.12500 | 0.10125 | 0.09945 | 0.10002 | 0.1
$p_{28}$ | 1.25000 | 1.01681 | 0.99809 | 0.99995 | 1
$p_{29}$ | 1.25000 | 1.26465 | 1.01660 | 1.00039 | 1
$p_{30}$ | 1.25000 | 1.34510 | 0.97913 | 1.00110 | 1
$p_{31}$ | 1.25000 | 1.11417 | 1.00248 | 1.00010 | 1
$p_{32}$ | 1.25000 | 1.24486 | 1.00895 | 1.00017 | 1
$p_{33}$ | 1.25000 | 1.11535 | 1.00955 | 1.00032 | 1
$p_{34}$ | 1.25000 | 1.21463 | 1.00509 | 1.00022 | 1
$p_{35}$ | 1.25000 | 1.31790 | 1.00739 | 1.00027 | 1
$p_{36}$ | 1.25000 | 0.97429 | 1.00480 | 1.00018 | 1
$\alpha$ | 2.95829 | 0.01168 | 4.00464×10⁻⁷

Table 4. The evolution of the parameters at select iterations, with 5 data sets, $t_0 = 0$, $t_1 = 120$, $\Delta t = 6.0$, i.e. 20 time points. Regularization parameter $\alpha$ was determined using (14) where $C = 0.25$ and $\gamma = 2$. 
Figure 1. The average error at each iteration corresponding to Table 1.

Figure 2. The average error at each iteration corresponding to Table 2.

$u^*$ is the true solution. Figures 5 and 6 correspond to iterations 2 and 4 respectively for the results demonstrated in Table 1. Similarly, Figures 7 and 8 correspond to iterations 3 and 6 respectively for the results from Table 2. In each example there is a clear minimum which is the best choice of the regularization parameter. The bullets on the graph corresponds to our choice of the regularization parameter according to the residual method (14). In fact, optimal or nearly optimal choice of the regularization parameter significantly increases convergence rate of the method from geometric to be close to quadratic convergence (see Section 3.7). The residual method provides a close, but not necessarily optimal value of $\alpha$. This analysis demonstrated that there is room for
improvement of the convergence rate of the algorithm through implementation of a more effective method for the search of regularization parameter $\alpha$ without significantly affecting computational cost.

3.3. Convergence vs. Number of Data Points. The method is very robust and convergence is still the case if the number of data points is reduced to a single time measurement at the end of the time interval for each of the 8 components of the system. Figure 3 demonstrates the dependence of the number of time measurements for each component...
on the average error

\[
\frac{1}{D} \sum_{d=1}^{D} \| x^d - x_N^d \|_{L_2^n}
\]

calculated at the final iteration in the experiment with \( D = 5 \) data sets. Three graphs correspond to three different settings of the relative and absolute tolerances for CVODES. Decrease of the latter increases the overall accuracy of the result. Similar dependence in the experiment with 16 data sets and with CVODES tolerance being set up at \( 1E - 6 \) is demonstrated in Figure 10. Some of the variation in the chart can be attributed to error accumulation and noise. Table 5 demonstrates the final values of 36 parameters in a numerical experiment with \( D = 5 \)
data sets with 1, 20 and 240 time measurements for each of the 8 components.

3.4. Convergence vs. Number of Data Sets. Our numerical analysis confirms the result of [23] that at least 5 data sets with different control inputs are required to uniquely estimate the 36 parameters of this model. Tables 6 and 7 demonstrate the results of the numerical experiments when the number of data sets vary from 1 to 5, and time measurements for each of the 8 components of the system is 240 and 20 respectively. Table 6 demonstrates that when the number of data sets increases from 1 to 5 with accuracy $10^{-3}$, the number of identified parameters increases as 22, 27, 32, 34 and 36 accordingly, provided that
Table 5. The evolution of the parameters as the number of time points increase, from 1 to 5. Where 5 data sets were considered, $u_0 = 1.25 u$. In each case regularization parameter $\alpha$ is chosen near optimally.
Table 7 demonstrates that with 20 time measurements the same number increases as 11, 24, 32, 33, 36.

3.5. **Range of convergence.** We define the range of convergence as a neighborhood of the true solution $\mathbf{u}$ in $\mathbb{R}^{36}$ such that for any $\mathbf{u}_0$ chosen from it, the sequence $\mathbf{u}_N$ constructed according to our algorithm...
| $\bar{u}$ | 1         | 2         | 3         | 4         | 5         | $\bar{u}$ |
|-------|-----------|-----------|-----------|-----------|-----------|-----------|
| $p_1$ | 0.99359   | 0.99453   | 1.00448   | 0.99909   | 1.00200   | 1         |
| $p_2$ | 1.24980   | 1.23815   | 1.19979   | 0.87369   | 1.00022   | 1         |
| $p_3$ | 2.49967   | 2.49266   | 2.46999   | 2.34286   | 1.99951   | 2         |
| $p_4$ | 1.25353   | 1.31690   | 1.14607   | 1.00297   | 0.99999   | 1         |
| $p_5$ | 2.49633   | 2.48044   | 1.89147   | 1.99534   | 1.99999   | 2         |
| $p_6$ | 1.00008   | 1.00008   | 1.00000   | 1.00018   | 1.00020   | 1         |
| $p_7$ | 0.99965   | 0.99776   | 0.99923   | 1.00009   | 1.00049   | 1         |
| $p_8$ | 1.24971   | 0.87782   | 0.99884   | 0.99993   | 0.99997   | 1         |
| $p_9$ | 2.49954   | 2.30979   | 1.99950   | 2.00018   | 2.00009   | 2         |
| $p_{10}$ | 0.99951 | 0.99913   | 0.99986   | 1.00000   | 1.00000   | 1         |
| $p_{11}$ | 2.00150 | 1.99937   | 2.00014   | 1.99982   | 1.99989   | 2         |
| $p_{12}$ | 1.00188 | 0.99891   | 0.99926   | 1.00007   | 1.00048   | 1         |
| $p_{13}$ | 0.99856 | 1.00410   | 0.99797   | 1.00149   | 1.00172   | 1         |
| $p_{14}$ | 1.24973 | 0.88085   | 0.99989   | 1.00190   | 1.00061   | 1         |
| $p_{15}$ | 2.49957 | 2.30093   | 1.99961   | 1.99944   | 1.99988   | 2         |
| $p_{16}$ | 0.99914 | 1.00139   | 1.00130   | 0.99952   | 0.99987   | 1         |
| $p_{17}$ | 1.99959 | 1.99593   | 1.99959   | 2.00079   | 2.00020   | 2         |
| $p_{18}$ | 1.00052 | 1.00338   | 0.99782   | 1.00194   | 1.00184   | 1         |
| $p_{19}$ | 0.99998 | 0.10001   | 0.10001   | 0.10001   | 0.10000   | 0.1       |
| $p_{20}$ | 0.99967 | 1.00004   | 1.00008   | 1.00111   | 1.00006   | 1         |
| $p_{21}$ | 0.99999 | 0.10001   | 0.10000   | 0.10000   | 0.99999   | 0.1       |
| $p_{22}$ | 0.10004 | 0.10001   | 0.10001   | 0.10001   | 0.10000   | 0.1       |
| $p_{23}$ | 1.00043 | 1.00002   | 0.99998   | 1.00000   | 1.00003   | 1         |
| $p_{24}$ | 0.10001 | 0.10001   | 0.10001   | 0.10001   | 0.10000   | 0.1       |
| $p_{25}$ | 0.10001 | 0.10002   | 0.10003   | 0.09998   | 0.10000   | 0.1       |
| $p_{26}$ | 0.99991 | 0.99993   | 0.99995   | 0.99997   | 0.99996   | 1         |
| $p_{27}$ | 0.10001 | 0.10003   | 0.10003   | 0.09998   | 0.10000   | 0.1       |
| $p_{28}$ | 1.02525 | 1.00006   | 0.99992   | 1.00003   | 0.99999   | 1         |
| $p_{29}$ | 1.27902 | 1.00028   | 0.99963   | 0.99975   | 1.00011   | 1         |
| $p_{30}$ | 1.24784 | 0.99980   | 0.99944   | 0.99940   | 1.00025   | 1         |
| $p_{31}$ | 1.00036 | 1.00023   | 0.99936   | 0.99997   | 1.00004   | 1         |
| $p_{32}$ | 1.00124 | 0.99979   | 1.00009   | 0.99979   | 1.00001   | 1         |
| $p_{33}$ | 1.00000 | 0.99814   | 1.00436   | 0.99956   | 0.99994   | 1         |
| $p_{34}$ | 1.00036 | 0.99980   | 1.00010   | 0.99990   | 1.00001   | 1         |
| $p_{35}$ | 1.01094 | 0.99973   | 1.00052   | 0.99986   | 1.00010   | 1         |
| $p_{36}$ | 1.25907 | 0.99929   | 1.00098   | 0.99997   | 1.00008   | 1         |

**Table 6.** The evolution of the parameters against the number of data sets, from 1 to 5. Where $\bar{u}_0 = 1.25u$, $t_0 = 0$, $t_1 = 120$, $\Delta t = 0.5$, giving us 240 time points. In each case $\alpha$ was determined using (14).

Converges to $\bar{u}$. Consider the rectangular prism neighborhood of $\bar{u}$:

$$P_{\tau}^\omega = \{p \in \mathbb{R}^{36} : \tau u_i \leq p_i \leq \omega u_i, \ i = 1, ..., 36\}$$
where $\tau$ and $\omega$ are two positive real numbers satisfying $\tau < 1 < \omega$. Numerical analysis demonstrates that for our model example, $P_{0.65}$ is the largest rectangular prism contained in the convergence range according to the algorithm accompanied by Type I regularization. Tables 8 and 9.
Figure 11. Distribution of the average residual error for several noise levels. Each run had 240 time points.

and [9] demonstrate the convergence with initial iteration $u_0$ chosen at extremes of $P_{0.65}$, namely $0.5u$ and $1.65u$ respectively.

Careful implementation of Type II regularization allows significant expansion of the convergence range. In fact, by selecting $u^*$ at the extremes of $P_{0.5}$, namely $u^* = 0.5u$ and $u^* = 1.65u$ we increased the convergence range to $P_{0.03}$ according to the algorithm accompanied by Type II regularization. Table 10 demonstrates the results of convergence of the method with Type II regularization when $u^* = 0.5u$, and initial iteration is chosen as 0.03u. Table 11 demonstrates the results when $u^* = 1.65u$, and initial iteration is chosen as 1001u.

3.6. Convergence with Noisy Measurements. We pursued numerical experiments with simulated noisy data with Gaussian noise

$$y_i = x_i^d(t; u) + px_i^d(t; u)\nu_i, \quad i = 1, ..., n$$

where $p$ is a percentage and $\nu_i$ is a random variable with standard normal distribution:

$$\nu_i \sim N(0,1).$$

Tables 12, 13, and 14 demonstrate the convergence in the experiment with 5 data sets and 240 noisy time measurements with $p = 1, 2$ and 5 respectively. In Figures 11 and 12 we show the box plot based on 100 simulations for the residual and parameter vector error dependence on the noise percentage $p$. Similar results with 20 noisy time measurements are given in Tables 15, 16 and 17.

3.7. Rate of convergence. To estimate the convergence rate $\gamma$ from the relation

$$|u_{k+1} - u_k| \sim C|u_k - u_{k-1}|^\gamma$$
\[ \vec{u} \quad \vec{u}_0 \quad \vec{u}_3 \quad \vec{u}_6 \quad \vec{u}_9 \quad \vec{u} \]

| \(p_1\) | 0.500 00 | 0.626 17 | 0.977 72 | 0.999 47 | 1 |
| \(p_2\) | 0.500 00 | 0.845 63 | 1.001 65 | 1.000 32 | 1 |
| \(p_3\) | 1 | 2.076 52 | 1.995 80 | 1.999 29 | 2 |
| \(p_4\) | 0.500 00 | 0.982 50 | 0.999 14 | 1.000 01 | 1 |
| \(p_5\) | 1 | 1.932 98 | 1.997 47 | 2.000 07 | 2 |
| \(p_6\) | 0.500 00 | 0.626 18 | 0.977 57 | 0.999 46 | 1 |
| \(p_7\) | 0.500 00 | 0.671 52 | 0.953 50 | 0.999 08 | 1 |
| \(p_8\) | 0.500 00 | 1.030 58 | 1.003 00 | 0.999 62 | 1 |
| \(p_9\) | 1 | 1.924 56 | 1.991 37 | 2.000 95 | 2 |
| \(p_{10}\) | 0.500 00 | 1.016 32 | 0.999 80 | 1.000 00 | 1 |
| \(p_{11}\) | 1 | 1.840 23 | 2.002 84 | 1.999 17 | 2 |
| \(p_{12}\) | 0.500 00 | 0.670 29 | 0.952 89 | 0.999 01 | 1 |
| \(p_{13}\) | 0.500 00 | 0.516 68 | 0.707 44 | 1.000 20 | 1 |
| \(p_{14}\) | 0.500 00 | 0.473 02 | 1.005 27 | 0.999 93 | 1 |
| \(p_{15}\) | 1 | 1.960 05 | 1.881 36 | 2.000 36 | 2 |
| \(p_{16}\) | 0.500 00 | 0.700 85 | 0.999 72 | 1.000 26 | 1 |
| \(p_{17}\) | 1 | 2.056 85 | 1.993 58 | 1.999 49 | 2 |
| \(p_{18}\) | 0.500 00 | 0.568 75 | 0.714 15 | 1.000 02 | 1 |
| \(p_{19}\) | 0.050 00 | 0.089 72 | 0.101 10 | 0.100 02 | 0.1 |
| \(p_{20}\) | 0.500 00 | 0.833 64 | 1.003 21 | 1.000 04 | 1 |
| \(p_{21}\) | 0.050 00 | 0.099 51 | 0.100 88 | 0.100 01 | 0.1 |
| \(p_{22}\) | 0.050 00 | 0.108 31 | 0.096 63 | 0.100 04 | 0.1 |
| \(p_{23}\) | 0.500 00 | 0.936 75 | 0.992 31 | 1.000 00 | 1 |
| \(p_{24}\) | 0.050 00 | 0.109 96 | 0.097 34 | 0.100 05 | 0.1 |
| \(p_{25}\) | 0.050 00 | 0.115 36 | 0.098 59 | 0.099 98 | 0.1 |
| \(p_{26}\) | 0.500 00 | 0.960 17 | 1.005 82 | 0.999 94 | 1 |
| \(p_{27}\) | 0.050 00 | 0.119 98 | 0.098 42 | 0.099 98 | 0.1 |
| \(p_{28}\) | 0.500 00 | 0.936 87 | 1.004 24 | 1.000 05 | 1 |
| \(p_{29}\) | 0.500 00 | 1.079 54 | 0.937 32 | 0.999 45 | 1 |
| \(p_{30}\) | 0.500 00 | 1.038 93 | 0.819 93 | 0.998 21 | 1 |
| \(p_{31}\) | 0.500 00 | 0.884 89 | 0.983 66 | 0.999 80 | 1 |
| \(p_{32}\) | 0.500 00 | 1.167 25 | 0.955 38 | 0.999 53 | 1 |
| \(p_{33}\) | 0.500 00 | 1.340 60 | 0.919 58 | 0.999 42 | 1 |
| \(p_{34}\) | 0.500 00 | 0.969 34 | 0.960 23 | 0.999 70 | 1 |
| \(p_{35}\) | 0.500 00 | 1.118 84 | 0.943 11 | 0.999 61 | 1 |
| \(p_{36}\) | 0.500 00 | 1.000 13 | 0.974 24 | 0.999 93 | 1 |
| \(\alpha\) | 1.165 91 | 0.015 85 | 10000 |

Table 8. The evolution of the parameters at select iterations, with 5 data sets, \((\vec{u}_0 = 0.5\vec{u}, t_0 = 0, t_1 = 120, \Delta t = 0.5\), i.e., 240 time points. Regularization parameter \(\alpha\) was chosen near optimally.
| $\vec{u}$ | $\vec{u}_0$ | $\vec{u}_4$ | $\vec{u}_8$ | $\vec{u}_{13}$ | $\vec{u}$ |
|--------|--------|--------|--------|--------|--------|
| $p_1$  | 1.650 00 | 1.651 55 | 1.105 82 | 0.999 94 | 1 |
| $p_2$  | 1.650 00 | 0.911 54 | 1.000 60 | 1.000 24 | 1 |
| $p_3$  | 3.300 00 | 2.116 07 | 1.980 43 | 1.999 48 | 2 |
| $p_4$  | 1.650 00 | 1.378 18 | 0.996 26 | 1.000 00 | 1 |
| $p_5$  | 3.300 00 | 3.344 76 | 1.988 21 | 2.000 03 | 2 |
| $p_6$  | 1.650 00 | 1.662 44 | 1.107 68 | 0.999 94 | 1 |
| $p_7$  | 1.650 00 | 1.627 98 | 1.040 04 | 1.000 10 | 1 |
| $p_8$  | 1.650 00 | 0.589 71 | 1.007 24 | 0.999 87 | 1 |
| $p_9$  | 3.300 00 | 2.593 96 | 1.983 75 | 2.000 35 | 2 |
| $p_{10}$ | 1.650 00 | 1.001 20 | 0.999 99 | 1.000 00 | 1 |
| $p_{11}$ | 3.300 00 | 2.196 28 | 2.009 80 | 1.999 68 | 2 |
| $p_{12}$ | 1.650 00 | 1.680 34 | 1.043 09 | 1.000 07 | 1 |
| $p_{13}$ | 1.650 00 | 1.608 93 | 1.025 38 | 1.004 22 | 1 |
| $p_{14}$ | 1.650 00 | 0.711 96 | 1.047 66 | 0.999 94 | 1 |
| $p_{15}$ | 3.300 00 | 2.903 15 | 2.006 76 | 2.000 28 | 2 |
| $p_{16}$ | 1.650 00 | 0.894 84 | 0.690 99 | 1.000 21 | 1 |
| $p_{17}$ | 3.300 00 | 1.592 31 | 1.976 13 | 1.999 58 | 2 |
| $p_{18}$ | 1.650 00 | 1.758 23 | 1.334 72 | 1.004 03 | 1 |
| $p_{19}$ | 0.165 00 | 0.076 35 | 0.096 25 | 0.100 00 | 0.1 |
| $p_{20}$ | 1.650 00 | 1.331 64 | 1.001 50 | 1.000 06 | 1 |
| $p_{21}$ | 0.165 00 | 0.061 66 | 0.096 28 | 0.100 00 | 0.1 |
| $p_{22}$ | 0.165 00 | 0.036 06 | 0.096 63 | 0.100 01 | 0.1 |
| $p_{23}$ | 1.650 00 | 0.805 53 | 1.003 14 | 1.000 02 | 1 |
| $p_{24}$ | 0.165 00 | 0.048 02 | 0.096 48 | 0.100 01 | 0.1 |
| $p_{25}$ | 0.165 00 | 0.149 16 | 0.097 29 | 0.099 98 | 0.1 |
| $p_{26}$ | 1.650 00 | 1.856 89 | 0.990 51 | 1.000 00 | 1 |
| $p_{27}$ | 0.165 00 | 0.088 91 | 0.097 23 | 0.099 98 | 0.1 |
| $p_{28}$ | 1.650 00 | 0.993 90 | 0.989 12 | 1.000 03 | 1 |
| $p_{29}$ | 1.650 00 | 1.672 35 | 1.073 18 | 0.999 77 | 1 |
| $p_{30}$ | 1.650 00 | 1.761 73 | 0.681 67 | 0.999 43 | 1 |
| $p_{31}$ | 1.650 00 | 1.268 86 | 1.016 22 | 0.999 94 | 1 |
| $p_{32}$ | 1.650 00 | 1.644 15 | 1.036 45 | 0.999 79 | 1 |
| $p_{33}$ | 1.650 00 | 0.790 45 | 1.050 41 | 0.999 67 | 1 |
| $p_{34}$ | 1.650 00 | 1.599 15 | 1.023 03 | 0.999 89 | 1 |
| $p_{35}$ | 1.650 00 | 2.159 08 | 1.016 68 | 0.999 85 | 1 |
| $p_{36}$ | 1.650 00 | 1.348 86 | 1.027 74 | 0.999 98 | 1 |
| $\alpha$ | 2.511 89 | 0.015 85 | 10 000 |

Table 9. The evolution of the parameters at select iterations, with 5 data sets, ($u_0 = 1.650u$, $t_0 = 0$, $t_1 = 120$, $\Delta t = 0.5$, i.e. 240 time points. Regularization parameter $\alpha$ was chosen near optimally.
| $\vec{u}$ | $\vec{u}_0$  | $\vec{u}_4$  | $\vec{u}_8$  | $\vec{u}_{14}$ | $\vec{u}$  |
|-----------|-------------|-------------|-------------|-------------|-------------|
| $p_1$     | 0.030 00   | 0.737 22   | 0.963 90   | 0.999 97   | 1           |
| $p_2$     | 0.030 00   | 1.151 14   | 1.200 73   | 1.000 24   | 1           |
| $p_3$     | 0.060 00   | 1.521 36   | 1.600 84   | 1.999 46   | 2           |
| $p_4$     | 0.030 00   | 0.875 46   | 0.959 86   | 0.999 99   | 1           |
| $p_5$     | 0.060 00   | 1.714 22   | 1.929 22   | 2.000 02   | 2           |
| $p_6$     | 0.030 00   | 0.721 20   | 0.960 67   | 0.999 97   | 1           |
| $p_7$     | 0.030 00   | 0.618 66   | 0.873 71   | 0.999 93   | 1           |
| $p_8$     | 0.030 00   | 0.772 75   | 1.037 86   | 0.999 99   | 1           |
| $p_9$     | 0.060 00   | 2.005 89   | 1.748 46   | 2.000 02   | 2           |
| $p_{10}$  | 0.030 00   | 0.927 44   | 0.994 64   | 1.000 00   | 1           |
| $p_{11}$  | 0.060 00   | 1.362 25   | 2.003 13   | 1.999 98   | 2           |
| $p_{12}$  | 0.030 00   | 0.559 49   | 0.857 17   | 0.999 92   | 1           |
| $p_{13}$  | 0.030 00   | 0.536 88   | 0.942 79   | 1.000 20   | 1           |
| $p_{14}$  | 0.030 00   | 0.487 66   | 1.146 86   | 0.999 99   | 1           |
| $p_{15}$  | 0.060 00   | 1.538 62   | 1.306 04   | 2.000 07   | 2           |
| $p_{16}$  | 0.030 00   | 1.094 39   | 0.963 92   | 1.000 05   | 1           |
| $p_{17}$  | 0.060 00   | 1.722 93   | 2.038 11   | 1.999 92   | 2           |
| $p_{18}$  | 0.030 00   | 0.462 46   | 1.075 06   | 1.000 15   | 1           |
| $p_{19}$  | 0.003 00   | 0.083 86   | 0.089 04   | 0.100 00   | 0.1         |
| $p_{20}$  | 0.030 00   | 0.982 14   | 0.836 52   | 1.000 00   | 1           |
| $p_{21}$  | 0.003 00   | 0.080 36   | 0.096 23   | 0.100 00   | 0.1         |
| $p_{22}$  | 0.003 00   | 0.140 84   | 0.051 69   | 0.100 00   | 0.1         |
| $p_{23}$  | 0.030 00   | 0.806 69   | 0.622 62   | 1.000 00   | 1           |
| $p_{24}$  | 0.003 00   | 0.156 23   | 0.065 42   | 0.100 00   | 0.1         |
| $p_{25}$  | 0.003 00   | 0.141 18   | 0.030 62   | 0.100 01   | 0.1         |
| $p_{26}$  | 0.030 00   | 0.654 61   | 0.184 16   | 0.999 96   | 1           |
| $p_{27}$  | 0.003 00   | 0.177 86   | 0.047 64   | 0.100 01   | 0.1         |
| $p_{28}$  | 0.030 00   | 0.521 97   | 0.936 34   | 1.000 00   | 1           |
| $p_{29}$  | 0.030 00   | 0.813 26   | 0.545 62   | 0.999 89   | 1           |
| $p_{30}$  | 0.030 00   | 0.267 79   | 0.658 22   | 0.999 76   | 1           |
| $p_{31}$  | 0.030 00   | 0.420 73   | 0.889 45   | 0.999 95   | 1           |
| $p_{32}$  | 0.030 00   | −0.207 56   | 0.796 60   | 0.999 87   | 1           |
| $p_{33}$  | 0.030 00   | 0.654 63   | 0.733 92   | 0.999 84   | 1           |
| $p_{34}$  | 0.030 00   | 0.475 66   | 1.047 39   | 0.999 90   | 1           |
| $p_{35}$  | 0.030 00   | 0.064 48   | 1.204 62   | 0.999 85   | 1           |
| $p_{36}$  | 0.030 00   | 0.894 14   | 1.134 25   | 0.999 96   | 1           |
| $\alpha$ | 0.100 00   | 0.012 59   | 1×10^{-6}  |             |             |

Table 10. The evolution of the parameters at select iterations, with 5 data sets, type 2 regularization, ($u_0 = 0.03u$, $t_0 = 0$, $t_1 = 120$, $\Delta t = 0.5$, i.e. 240 time points. Regularization parameter $\alpha$ was chosen near optimally.
Table 11. The evolution of the parameters at select iterations, with 5 data sets, type 2 regularization, \((u_0 = 1001, t_0 = 0, t_1 = 120, \Delta t = 0.5\), i.e. 240 time points. Regularization parameter \(\alpha\) was chosen near optimally.

| \(\vec{u}\) | \(\vec{u}_0\) | \(\vec{u}_4\) | \(\vec{u}_7\) | \(\vec{u}\) |
|-----------|-----------|-----------|-----------|-----------|
| \(p_1\)   | 1001      | 0.99921   | 0.99998   | 1         |
| \(p_2\)   | 1001      | 0.90059   | 0.99881   | 1         |
| \(p_3\)   | 2002      | 1.92905   | 2.00044   | 2         |
| \(p_4\)   | 1001      | 0.98549   | 1.00001   | 1         |
| \(p_5\)   | 2002      | 1.96085   | 1.99999   | 2         |
| \(p_6\)   | 1001      | 1.00029   | 0.99999   | 1         |
| \(p_7\)   | 1001      | 0.76439   | 0.99999   | 1         |
| \(p_8\)   | 1001      | 0.98905   | 1.00000   | 1         |
| \(p_9\)   | 2002      | 2.02527   | 2.00002   | 2         |
| \(p_{10}\)| 1001      | 0.99728   | 1.00000   | 1         |
| \(p_{11}\)| 2002      | 1.97481   | 1.99999   | 2         |
| \(p_{12}\)| 1001      | 0.77572   | 0.99999   | 1         |
| \(p_{13}\)| 1001      | 1.36472   | 1.00044   | 1         |
| \(p_{14}\)| 1001      | 0.97024   | 0.99999   | 1         |
| \(p_{15}\)| 2002      | 1.78165   | 2.00013   | 2         |
| \(p_{16}\)| 1001      | 1.10567   | 0.99998   | 1         |
| \(p_{17}\)| 2002      | 1.84612   | 1.99989   | 2         |
| \(p_{18}\)| 1001      | 1.20949   | 1.00045   | 1         |
| \(p_{19}\)| 100.1     | 0.09930   | 0.10000   | 0.1       |
| \(p_{20}\)| 1001      | 0.94542   | 1.00002   | 1         |
| \(p_{21}\)| 100.1     | 0.09601   | 0.10000   | 0.1       |
| \(p_{22}\)| 100.1     | 0.08655   | 0.10000   | 0.1       |
| \(p_{23}\)| 1001      | 0.95080   | 1.00000   | 1         |
| \(p_{24}\)| 100.1     | 0.08932   | 0.10000   | 0.1       |
| \(p_{25}\)| 100.1     | 0.08688   | 0.10001   | 0.1       |
| \(p_{26}\)| 1001      | 0.93134   | 0.99995   | 1         |
| \(p_{27}\)| 100.1     | 0.09067   | 0.10001   | 0.1       |
| \(p_{28}\)| 1001      | 0.99472   | 0.99999   | 1         |
| \(p_{29}\)| 1001      | 1.03188   | 1.00004   | 1         |
| \(p_{30}\)| 1001      | 0.96256   | 1.00009   | 1         |
| \(p_{31}\)| 1001      | 1.01905   | 0.99997   | 1         |
| \(p_{32}\)| 1001      | 0.95544   | 1.00001   | 1         |
| \(p_{33}\)| 1001      | 0.92948   | 1.00014   | 1         |
| \(p_{34}\)| 1001      | 0.92008   | 0.99998   | 1         |
| \(p_{35}\)| 1001      | 0.76293   | 0.99997   | 1         |
| \(p_{36}\)| 1001      | 1.01246   | 1.00001   | 1         |

\(\alpha\) \(7.94328 \times 10^{-6}\) \(1 \times 10^{-6}\)
| $\bar{u}$ | $\bar{u}_0$ | $\bar{u}_2$ | $\bar{u}_4$ | $\bar{u}_7$ | $\bar{u}$ |
|--------|--------|--------|--------|--------|--------|
| $p_1$  | 1.250 00 | 0.789 04 | 1.040 88 | 1.040 97 | 1       |
| $p_2$  | 1.250 00 | 0.993 03 | 1.032 34 | 1.031 97 | 1       |
| $p_3$  | 2.500 00 | 1.988 62 | 1.933 01 | 1.932 79 | 2       |
| $p_4$  | 1.250 00 | 1.046 23 | 1.002 35 | 1.004 12 | 1       |
| $p_5$  | 2.500 00 | 2.114 53 | 2.003 68 | 2.003 39 | 2       |
| $p_6$  | 1.250 00 | 0.789 08 | 1.039 67 | 1.039 57 | 1       |
| $p_7$  | 1.250 00 | 0.824 96 | 0.988 02 | 0.986 74 | 1       |
| $p_8$  | 1.250 00 | 0.919 25 | 0.993 26 | 0.993 25 | 1       |
| $p_9$  | 2.500 00 | 2.027 46 | 2.029 58 | 2.029 62 | 2       |
| $p_{10}$ | 1.250 00 | 1.009 97 | 0.999 02 | 0.998 88 | 1       |
| $p_{11}$ | 2.500 00 | 1.911 15 | 1.990 23 | 1.990 23 | 2       |
| $p_{12}$ | 1.250 00 | 0.816 64 | 0.986 67 | 0.987 96 | 1       |
| $p_{13}$ | 1.250 00 | 0.707 89 | 0.459 16 | 0.469 48 | 1       |
| $p_{14}$ | 1.250 00 | 0.894 43 | 1.017 10 | 1.018 39 | 1       |
| $p_{15}$ | 2.500 00 | 2.201 23 | 1.808 08 | 1.808 33 | 2       |
| $p_{16}$ | 1.250 00 | 1.253 07 | 0.954 10 | 0.946 78 | 1       |
| $p_{17}$ | 2.500 00 | 1.744 86 | 2.153 86 | 2.152 66 | 2       |
| $p_{18}$ | 1.250 00 | 0.583 65 | 0.505 58 | 0.495 46 | 1       |
| $p_{19}$ | 0.125 00 | 0.088 69 | 0.099 79 | 0.100 30 | 0.1     |
| $p_{20}$ | 1.250 00 | 0.956 18 | 0.997 90 | 0.998 50 | 1       |
| $p_{21}$ | 0.125 00 | 0.090 58 | 0.099 91 | 0.100 34 | 0.1     |
| $p_{22}$ | 0.125 00 | 0.090 72 | 0.099 08 | 0.099 22 | 0.1     |
| $p_{23}$ | 1.250 00 | 1.018 70 | 0.998 60 | 0.998 03 | 1       |
| $p_{24}$ | 0.125 00 | 0.088 61 | 0.099 16 | 0.099 28 | 0.1     |
| $p_{25}$ | 0.125 00 | 0.096 33 | 0.102 09 | 0.100 91 | 0.1     |
| $p_{26}$ | 1.250 00 | 0.985 43 | 0.978 91 | 0.977 71 | 1       |
| $p_{27}$ | 0.125 00 | 0.096 14 | 0.103 66 | 0.102 36 | 0.1     |
| $p_{28}$ | 1.250 00 | 0.994 57 | 1.006 54 | 1.009 39 | 1       |
| $p_{29}$ | 1.250 00 | 1.265 78 | 0.966 40 | 0.967 31 | 1       |
| $p_{30}$ | 1.250 00 | 1.380 33 | 0.904 21 | 0.904 65 | 1       |
| $p_{31}$ | 1.250 00 | 1.047 86 | 1.016 39 | 1.015 68 | 1       |
| $p_{32}$ | 1.250 00 | 1.190 24 | 0.955 82 | 0.955 52 | 1       |
| $p_{33}$ | 1.250 00 | 1.064 94 | 0.845 88 | 0.845 80 | 1       |
| $p_{34}$ | 1.250 00 | 1.114 11 | 0.990 74 | 0.988 49 | 1       |
| $p_{35}$ | 1.250 00 | 1.260 31 | 0.983 26 | 0.983 13 | 1       |
| $p_{36}$ | 1.250 00 | 1.025 84 | 0.976 96 | 0.977 59 | 1       |
| $\alpha$ | 1.847 85 | 0.002 33 | $1 \times 10^6$ | |

Table 12. The evolution of the parameters at select iterations, with 1% noise, 5 data sets, $t_0 = 0$, $t_1 = 120$, $\Delta t = 0.5$, i.e. 240 time points.
Table 13. The evolution of the parameters at select iterations, with 3% noise, 5 data sets, $t_0 = 0$, $t_1 = 120$, $\Delta t = 0.5$, i.e. 240 time points.
| $\bar{u}$ | $\bar{u}_0$ | $\bar{u}_2$ | $\bar{u}_5$ | $\bar{u}$ |
|----------|-------------|-------------|-------------|---------|
| $p_1$    | 1.250 00    | 0.936 20    | 0.936 11    | 1       |
| $p_2$    | 1.250 00    | 0.944 61    | 0.945 13    | 1       |
| $p_3$    | 2.500 00    | 2.064 18    | 2.064 39    | 2       |
| $p_4$    | 1.250 00    | 1.136 18    | 1.134 88    | 1       |
| $p_5$    | 2.500 00    | 2.330 24    | 2.330 26    | 2       |
| $p_6$    | 1.250 00    | 0.931 29    | 0.931 00    | 1       |
| $p_7$    | 1.250 00    | 0.867 59    | 0.868 22    | 1       |
| $p_8$    | 1.250 00    | 0.852 49    | 0.850 89    | 1       |
| $p_9$    | 2.500 00    | 2.139 89    | 2.140 03    | 2       |
| $p_{10}$ | 1.250 00    | 1.043 83    | 1.045 17    | 1       |
| $p_{11}$ | 2.500 00    | 2.168 59    | 2.169 29    | 2       |
| $p_{12}$ | 1.250 00    | 0.871 24    | 0.871 14    | 1       |
| $p_{13}$ | 1.250 00    | 0.763 35    | 0.764 16    | 1       |
| $p_{14}$ | 1.250 00    | 0.910 83    | 0.910 98    | 1       |
| $p_{15}$ | 2.500 00    | 2.283 58    | 2.283 55    | 2       |
| $p_{16}$ | 1.250 00    | 1.293 85    | 1.293 52    | 1       |
| $p_{17}$ | 2.500 00    | 1.888 27    | 1.888 35    | 2       |
| $p_{18}$ | 1.250 00    | 0.569 72    | 0.568 71    | 1       |
| $p_{19}$ | 0.125 00    | 0.077 53    | 0.070 03    | 0.1     |
| $p_{20}$ | 1.250 00    | 1.008 31    | 1.008 06    | 1       |
| $p_{21}$ | 0.125 00    | 0.075 65    | 0.068 54    | 0.1     |
| $p_{22}$ | 0.125 00    | 0.017 23    | 0.034 80    | 0.1     |
| $p_{23}$ | 1.250 00    | 1.314 92    | 1.315 34    | 1       |
| $p_{24}$ | 0.125 00    | 0.014 09    | 0.029 05    | 0.1     |
| $p_{25}$ | 0.125 00    | 0.118 24    | 0.117 68    | 0.1     |
| $p_{26}$ | 1.250 00    | 0.899 60    | 0.899 77    | 1       |
| $p_{27}$ | 0.125 00    | 0.132 36    | 0.132 99    | 0.1     |
| $p_{28}$ | 1.250 00    | 0.926 57    | 0.923 79    | 1       |
| $p_{29}$ | 1.250 00    | 1.278 54    | 1.278 20    | 1       |
| $p_{30}$ | 1.250 00    | 1.277 17    | 1.276 82    | 1       |
| $p_{31}$ | 1.250 00    | 0.996 67    | 0.999 61    | 1       |
| $p_{32}$ | 1.250 00    | 1.257 49    | 1.257 01    | 1       |
| $p_{33}$ | 1.250 00    | 1.148 58    | 1.149 00    | 1       |
| $p_{34}$ | 1.250 00    | 1.027 45    | 1.026 67    | 1       |
| $p_{35}$ | 1.250 00    | 1.196 09    | 1.196 72    | 1       |
| $p_{36}$ | 1.250 00    | 1.002 67    | 1.002 32    | 1       |
| $\alpha$| 89.125 09    | 1 $\times 10^6$ |            |         |

Table 14. The evolution of the parameters at select iterations, with 5% noise, 5 data sets, $t_0 = 0$, $t_1 = 120$, $\Delta t = 0.5$, i.e. 240 time points.
| $\vec{u}$ | $\vec{u}_0$ | $\vec{u}_2$ | $\vec{u}_4$ | $\vec{u}_6$ | $\vec{u}$ |
|----------|-------------|-------------|-------------|-------------|------|
| $p_1$    | 1.250 00    | 1.123 56    | 1.129 08    | 1.129 07    | 1    |
| $p_2$    | 1.250 00    | 0.912 06    | 0.893 12    | 0.893 12    | 1    |
| $p_3$    | 2.500 00    | 2.361 38    | 2.370 12    | 2.370 12    | 2    |
| $p_4$    | 1.250 00    | 1.153 81    | 1.154 43    | 1.154 42    | 1    |
| $p_5$    | 2.500 00    | 2.481 35    | 2.485 82    | 2.485 82    | 2    |
| $p_6$    | 1.250 00    | 1.133 77    | 1.138 47    | 1.138 47    | 1    |
| $p_7$    | 1.250 00    | 0.917 57    | 0.912 97    | 0.912 96    | 1    |
| $p_8$    | 1.250 00    | 0.853 65    | 0.883 40    | 0.883 39    | 1    |
| $p_9$    | 2.500 00    | 2.150 99    | 2.110 38    | 2.110 38    | 2    |
| $p_{10}$ | 1.250 00    | 0.986 18    | 0.991 18    | 0.991 19    | 1    |
| $p_{11}$ | 2.500 00    | 2.106 48    | 2.063 96    | 2.063 97    | 2    |
| $p_{12}$ | 1.250 00    | 0.928 24    | 0.918 05    | 0.918 06    | 1    |
| $p_{13}$ | 1.250 00    | 0.867 92    | 0.856 57    | 0.856 57    | 1    |
| $p_{14}$ | 1.250 00    | 0.954 25    | 0.951 15    | 0.951 14    | 1    |
| $p_{15}$ | 2.500 00    | 2.379 82    | 2.369 63    | 2.369 63    | 2    |
| $p_{16}$ | 1.250 00    | 1.146 56    | 1.138 75    | 1.138 75    | 1    |
| $p_{17}$ | 2.500 00    | 1.841 38    | 1.801 38    | 1.801 38    | 2    |
| $p_{18}$ | 1.250 00    | 0.771 34    | 0.769 00    | 0.769 01    | 1    |
| $p_{19}$ | 0.125 00    | 0.089 38    | 0.086 19    | 0.086 02    | 0.1  |
| $p_{20}$ | 1.250 00    | 1.082 97    | 1.063 48    | 1.063 48    | 1    |
| $p_{21}$ | 0.125 00    | 0.084 05    | 0.083 05    | 0.083 05    | 0.1  |
| $p_{22}$ | 0.125 00    | 0.036 81    | 0.048 03    | 0.048 07    | 0.1  |
| $p_{23}$ | 1.250 00    | 1.159 68    | 1.123 86    | 1.123 86    | 1    |
| $p_{24}$ | 0.125 00    | 0.034 24    | 0.045 08    | 0.045 09    | 0.1  |
| $p_{25}$ | 0.125 00    | 0.061 91    | 0.073 88    | 0.073 83    | 0.1  |
| $p_{26}$ | 1.250 00    | 1.123 06    | 1.093 39    | 1.093 40    | 1    |
| $p_{27}$ | 0.125 00    | 0.057 15    | 0.068 23    | 0.068 31    | 0.1  |
| $p_{28}$ | 1.250 00    | 0.956 12    | 0.957 38    | 0.957 36    | 1    |
| $p_{29}$ | 1.250 00    | 1.305 80    | 1.312 11    | 1.312 11    | 1    |
| $p_{30}$ | 1.250 00    | 1.316 10    | 1.325 85    | 1.325 85    | 1    |
| $p_{31}$ | 1.250 00    | 1.067 06    | 1.049 70    | 1.049 71    | 1    |
| $p_{32}$ | 1.250 00    | 1.229 93    | 1.232 79    | 1.232 79    | 1    |
| $p_{33}$ | 1.250 00    | 1.000 75    | 0.974 78    | 0.974 78    | 1    |
| $p_{34}$ | 1.250 00    | 1.123 94    | 1.093 78    | 1.093 78    | 1    |
| $p_{35}$ | 1.250 00    | 1.371 62    | 1.378 17    | 1.378 17    | 1    |
| $p_{36}$ | 1.250 00    | 0.935 57    | 0.912 49    | 0.912 48    | 1    |
| $\alpha$ | 10          | 39.810 72    | $1 \times 10^4$ |            |      |

**Table 15.** The evolution of the parameters at select iterations, with 1% noise, 5 data sets, $t_0 = 0$, $t_1 = 120$, $\Delta t = 6.0$, i.e. 20 time points.
| $\bar{u}$ | $\bar{u}_0$ | $\bar{u}_2$ | $\bar{u}_5$ | $\bar{u}$ |
|---------|---------|---------|---------|---------|
| $p_1$   | 1.250 00 | 1.005 97 | 1.000 97 | 1       |
| $p_2$   | 1.250 00 | 0.887 30 | 0.938 81 | 1       |
| $p_3$   | 2.500 00 | 2.226 31 | 2.232 82 | 2       |
| $p_4$   | 1.250 00 | 1.169 73 | 1.153 28 | 1       |
| $p_5$   | 2.500 00 | 2.450 10 | 2.455 69 | 2       |
| $p_6$   | 1.250 00 | 1.002 28 | 1.005 88 | 1       |
| $p_7$   | 1.250 00 | 0.920 88 | 0.915 86 | 1       |
| $p_8$   | 1.250 00 | 0.817 40 | 0.860 84 | 1       |
| $p_9$   | 2.500 00 | 2.243 15 | 2.262 64 | 2       |
| $p_{10}$| 1.250 00 | 1.048 16 | 0.998 36 | 1       |
| $p_{11}$| 2.500 00 | 2.307 72 | 2.324 45 | 2       |
| $p_{12}$| 1.250 00 | 0.933 04 | 0.937 63 | 1       |
| $p_{13}$| 1.250 00 | 0.918 00 | 0.908 13 | 1       |
| $p_{14}$| 1.250 00 | 0.905 25 | 0.982 28 | 1       |
| $p_{15}$| 2.500 00 | 2.390 16 | 2.381 59 | 2       |
| $p_{16}$| 1.250 00 | 1.148 38 | 1.140 19 | 1       |
| $p_{17}$| 2.500 00 | 1.933 01 | 1.900 71 | 2       |
| $p_{18}$| 1.250 00 | 0.802 91 | 0.800 10 | 1       |
| $p_{19}$| 0.125 00 | 0.074 70 | 0.087 04 | 0.1     |
| $p_{20}$| 1.250 00 | 1.144 66 | 1.121 85 | 1       |
| $p_{21}$| 0.125 00 | 0.066 57 | 0.080 44 | 0.1     |
| $p_{22}$| 0.125 00 | 0.035 92 | 0.034 49 | 0.1     |
| $p_{23}$| 1.250 00 | 1.361 50 | 1.355 23 | 1       |
| $p_{24}$| 0.125 00 | 0.029 14 | 0.028 46 | 0.1     |
| $p_{25}$| 0.125 00 | 0.169 80 | 0.189 21 | 0.1     |
| $p_{26}$| 1.250 00 | 0.933 39 | 0.919 06 | 1       |
| $p_{27}$| 0.125 00 | 0.183 29 | 0.206 01 | 0.1     |
| $p_{28}$| 1.250 00 | 1.008 91 | 1.001 98 | 1       |
| $p_{29}$| 1.250 00 | 1.333 56 | 1.316 59 | 1       |
| $p_{30}$| 1.250 00 | 1.277 13 | 1.283 33 | 1       |
| $p_{31}$| 1.250 00 | 1.154 32 | 1.130 49 | 1       |
| $p_{32}$| 1.250 00 | 1.330 92 | 1.337 43 | 1       |
| $p_{33}$| 1.250 00 | 1.109 17 | 1.104 11 | 1       |
| $p_{34}$| 1.250 00 | 1.146 50 | 1.121 97 | 1       |
| $p_{35}$| 1.250 00 | 1.218 65 | 1.246 92 | 1       |
| $p_{36}$| 1.250 00 | 1.095 10 | 1.070 38 | 1       |
| $\alpha$| 232.630 51 | $1 \times 10^4$ |

Table 16. The evolution of the parameters at select iterations, with 3% noise, 5 data sets, $t_0 = 0$, $t_1 = 120$, $\Delta t = 6.0$, i.e. 20 time points.
The evolution of the parameters at select \( t \).

| \( \bar{u} \) | \( \bar{u}_0 \) | \( \bar{u}_3 \) | \( \bar{u}_6 \) | \( \bar{u}_9 \) | \( \bar{u} \) |
|---|---|---|---|---|---|
| \( p_1 \) | 1.250 00 | 1.23274 | 1.23364 | 1.23364 | 1 |
| \( p_2 \) | 1.250 00 | 0.96011 | 0.96048 | 0.96050 | 1 |
| \( p_3 \) | 2.500 00 | 2.29121 | 2.29133 | 2.29133 | 2 |
| \( p_4 \) | 1.250 00 | 1.16850 | 1.16806 | 1.16803 | 1 |
| \( p_5 \) | 2.500 00 | 2.54519 | 2.54557 | 2.54557 | 2 |
| \( p_6 \) | 1.250 00 | 1.24253 | 1.24231 | 1.24231 | 1 |
| \( p_7 \) | 1.250 00 | 1.06647 | 1.06849 | 1 |
| \( p_8 \) | 1.250 00 | 1.04851 | 1.04940 | 1.04939 | 1 |
| \( p_9 \) | 2.500 00 | 2.36006 | 2.36006 | 2 |
| \( p_{10} \) | 1.250 00 | 1.01487 | 1.01256 | 1.01254 | 1 |
| \( p_{11} \) | 2.500 00 | 2.22898 | 2.22857 | 2.22857 | 2 |
| \( p_{12} \) | 1.250 00 | 1.09028 | 1.08864 | 1.08861 | 1 |
| \( p_{13} \) | 1.250 00 | 1.08753 | 1.08866 | 1.08866 | 1 |
| \( p_{14} \) | 1.250 00 | 1.02046 | 1.02179 | 1.02177 | 1 |
| \( p_{15} \) | 2.500 00 | 2.44899 | 2.44896 | 2.44896 | 2 |
| \( p_{16} \) | 1.250 00 | 1.06005 | 1.05929 | 1.05930 | 1 |
| \( p_{17} \) | 2.500 00 | 2.20058 | 2.20056 | 2.20057 | 2 |
| \( p_{18} \) | 1.250 00 | 0.96611 | 0.96486 | 0.96486 | 1 |
| \( p_{19} \) | 0.125 00 | 0.06452 | 0.07859 | 0.07844 | 0.1 |
| \( p_{20} \) | 1.250 00 | 1.22288 | 1.22252 | 1.22251 | 1 |
| \( p_{21} \) | 0.125 00 | 0.05467 | 0.06778 | 0.06764 | 0.1 |
| \( p_{22} \) | 0.125 00 | 0.05890 | 0.05704 | 0.05706 | 0.1 |
| \( p_{23} \) | 1.250 00 | 1.18359 | 1.18339 | 1.18339 | 1 |
| \( p_{24} \) | 0.125 00 | 0.05299 | 0.05157 | 0.05159 | 0.1 |
| \( p_{25} \) | 0.125 00 | 0.05258 | 0.05256 | 0.05266 | 0.1 |
| \( p_{26} \) | 1.250 00 | 1.32704 | 1.32706 | 1.32707 | 1 |
| \( p_{27} \) | 0.125 00 | 0.04976 | 0.04989 | 0.04907 | 0.1 |
| \( p_{28} \) | 1.250 00 | 1.04149 | 1.04141 | 1.04137 | 1 |
| \( p_{29} \) | 1.250 00 | 1.45677 | 1.45721 | 1.45719 | 1 |
| \( p_{30} \) | 1.250 00 | 1.21605 | 1.21602 | 1.21601 | 1 |
| \( p_{31} \) | 1.250 00 | 1.02227 | 1.02229 | 1.02229 | 1 |
| \( p_{32} \) | 1.250 00 | 1.20559 | 1.20559 | 1.20559 | 1 |
| \( p_{33} \) | 1.250 00 | 1.22659 | 1.22666 | 1.22666 | 1 |
| \( p_{34} \) | 1.250 00 | 1.29687 | 1.29706 | 1.29707 | 1 |
| \( p_{35} \) | 1.250 00 | 1.36691 | 1.36682 | 1.36682 | 1 |
| \( p_{36} \) | 1.250 00 | 1.28031 | 1.28061 | 1.28060 | 1 |
| \( \alpha \) | 92.61187 | \( 1 \times 10^4 \) | \( 1 \times 10^4 \) |

Table 17. The evolution of the parameters at select iterations, with 5% noise, 5 data sets, \( t_0 = 0 \), \( t_1 = 120 \), \( \Delta t = 6.0 \), i.e. 20 time points.
Figure 12. Distribution of the parameter error for the three step metabolic network at several noise levels. Each run had 240 time steps.

we plot \( \log |\mathbf{u}_{k+1} - \mathbf{u}_k| \) vs. \( \log |\mathbf{u}_k - \mathbf{u}_{k-1}| \) and find a line of best fit to identify \( \gamma \) and \( C \). Figures 13 and 14 demonstrate the outcome. For the numerical experiment from Table 1 we have \( \gamma = 1.6104, C = 3.1622E-3 \), and for results from Table 2 we have \( \gamma = 1.1674, C = 6.3271E-1 \). The difference in convergence rate of two examples is in particular due to choice of the regularization parameter \( \alpha \). Almost optimal choice of \( \alpha \), as it is demonstrated in Figures 5 and 6 vs. Figures 7 and 8, causes higher convergence rate for the numerical experiment in Table 1 vs. Table 2. We expect theoretical convergence rate of the method is quadratic [12].

3.8. Convergence with Partial Measurements. We tested the convergence of the method when only some of the components of the system have available measurements or partial measurements. In this case the inverse problem must be solved with partial observations. A typical result is demonstrated in Table 18 and Figure 15. We considered our numerical experiment with 5 data sets, and with 20 time measurements of only components 3, 4, 5, and 7. As can be seen from Table 18 and Figure 15, the iteration converges to the true solution, but some small error is present in the final value of the parameter vector.

3.9. Comparison with \textit{lsqnonlin} and \textit{nl2sol}. As in our previous paper [11] we are comparing our method \textit{glopt} with the most popular methods available as open software [16, 26, 27] such as

- Levenberg-Marquardt algorithm and trust-region-reflective method (function \textit{lsqnonlin} in MatLab) [28].
The evolution of the parameters at select iterations was determined using (14) where $\gamma = 2$. The table below shows the estimated parameters at different iterations.

| $\vec{u}$ | $\vec{u}_0$ | $\vec{u}_3$ | $\vec{u}_6$ | $\vec{u}_{11}$ | $\vec{u}$ |
|----------|------------|------------|------------|--------------|--------|
| $p_1$    | 1.250 00  | 1.230 25   | 1.225 92   | 1.000 68     | 1      |
| $p_2$    | 1.250 00  | 0.991 90   | 1.057 14   | 0.998 55     | 1      |
| $p_3$    | 2.500 00  | 2.276 34   | 1.989 15   | 2.000 00     | 2      |
| $p_4$    | 1.250 00  | 1.097 82   | 0.941 10   | 1.001 34     | 1      |
| $p_5$    | 2.500 00  | 2.350 05   | 1.988 15   | 2.000 04     | 2      |
| $p_6$    | 1.250 00  | 1.293 94   | 1.254 39   | 0.999 53     | 1      |
| $p_7$    | 1.250 00  | 1.257 00   | 1.310 13   | 0.965 15     | 1      |
| $p_8$    | 1.250 00  | 0.998 80   | 1.028 75   | 1.033 83     | 1      |
| $p_9$    | 2.500 00  | 1.980 25   | 2.019 45   | 2.000 30     | 2      |
| $p_{10}$ | 1.250 00  | 0.936 13   | 0.967 15   | 0.967 10     | 1      |
| $p_{11}$ | 2.500 00  | 2.069 48   | 1.986 34   | 1.999 61     | 2      |
| $p_{12}$ | 1.250 00  | 1.247 68   | 1.195 33   | 0.993 36     | 1      |
| $p_{13}$ | 1.250 00  | 1.147 72   | 1.137 17   | 1.001 72     | 1      |
| $p_{14}$ | 1.250 00  | 1.155 33   | 1.082 80   | 0.999 56     | 1      |
| $p_{15}$ | 2.500 00  | 2.473 03   | 2.092 53   | 1.998 73     | 2      |
| $p_{16}$ | 1.250 00  | 0.934 64   | 0.922 53   | 1.000 00     | 1      |
| $p_{17}$ | 2.500 00  | 2.328 48   | 2.109 30   | 2.000 96     | 2      |
| $p_{18}$ | 1.250 00  | 1.336 11   | 1.266 14   | 1.001 42     | 1      |
| $p_{19}$ | 0.125 00  | 0.092 35   | 0.108 09   | 0.099 69     | 0.1    |
| $p_{20}$ | 1.250 00  | 1.278 25   | 1.228 58   | 0.994 82     | 1      |
| $p_{21}$ | 0.125 00  | 0.078 65   | 0.095 77   | 0.100 01     | 0.1    |
| $p_{22}$ | 0.125 00  | 0.086 13   | 0.105 16   | 0.107 45     | 0.1    |
| $p_{23}$ | 1.250 00  | 1.253 27   | 1.266 85   | 1.115 16     | 1      |
| $p_{24}$ | 0.125 00  | 0.076 54   | 0.097 40   | 0.100 05     | 0.1    |
| $p_{25}$ | 0.125 00  | 0.070 30   | 0.091 74   | 0.099 87     | 0.1    |
| $p_{26}$ | 1.250 00  | 1.280 15   | 0.931 29   | 0.998 81     | 1      |
| $p_{27}$ | 0.125 00  | 0.060 80   | 0.094 31   | 0.099 97     | 0.1    |
| $p_{28}$ | 1.250 00  | 1.086 58   | 0.999 40   | 0.999 89     | 1      |
| $p_{29}$ | 1.250 00  | 1.389 87   | 1.122 43   | 0.999 52     | 1      |
| $p_{30}$ | 1.250 00  | 1.202 39   | 1.386 69   | 0.998 86     | 1      |
| $p_{31}$ | 1.250 00  | 1.144 17   | 1.112 45   | 0.999 48     | 1      |
| $p_{32}$ | 1.250 00  | 1.241 77   | 1.181 59   | 0.997 38     | 1      |
| $p_{33}$ | 1.250 00  | 1.199 01   | 1.192 94   | 0.994 90     | 1      |
| $p_{34}$ | 1.250 00  | 1.213 85   | 1.029 19   | 1.001 24     | 1      |
| $p_{35}$ | 1.250 00  | 1.398 01   | 1.062 88   | 1.002 33     | 1      |
| $p_{36}$ | 1.250 00  | 0.881 37   | 1.023 79   | 1.001 36     | 1      |
| $\alpha$ | 1.372 35  | 0.469 27   | 3.118 46×10⁻⁶ |            |        |

**Table 18.** The evolution of the parameters at select iterations, with 5 data sets, 4 out of 8 states, $t_0 = 0$, $t_1 = 120$, $\Delta t = 6.0$, i.e. 20 time points. Regularization parameter $\alpha$ was determined using (14) where $C = 0.5$ and $\gamma = 2$. 
An adaptive non-linear least-squares algorithm (function *nl2sol* in MatLab) [29].

We used model example provided by AMIGO2, which had 16 data sets with each component evaluated at 21 time points giving a total of 2688 data points. We ran each algorithm 20 times and recorded the average relative error of the parameter values (r.e.), the median number of objective function evaluations (f.e.), the average computational time (c.t.), and the median number of iterations (n.i.). The results are demonstrated in Table 19. All three methods have a comparable relative error. In terms of required number of iterations, our method is comparable to *nl2sol*, and both have a clear advantage over *lsqnonlin*. 

**Figure 13.** The convergence rate graph corresponding to Table 1 where \( r = 1.6104 \) and \( C = 3.1622E - 3 \).

**Figure 14.** The convergence rate graph corresponding to Table 2 where \( r = 1.1674 \) and \( C = 6.3271E - 1 \).
Figure 15. The average error at each iteration corresponding to Table 18.

| metric | qlopt     | lsqnonlin | nl2sol    |
|--------|-----------|-----------|-----------|
| r.e.   | $4.271 \times 10^{-4}$ | $3.236 \times 10^{-5}$ | $4.354 \times 10^{-4}$ |
| n.i.   | 8         | 16        | 7         |
| c.t. (s)| 1.389     | 7.656     | 5.043     |
| f.e.   | 8         | 593       | 299       |

Table 19. Comparison of several local optimization methods against the presented method for the three step metabolic network. The initial guess was $u_0 = 1.25u$ the relative errors (r.e.), the number of iterations (n.i.), mean of the computational time (c.t.) of 20 runs, and the number of function evaluations (f.e.). We considered the data sets provided by AMIGO2 which contained 16 datasets evaluated a 21 time values giving us a total of 2688 data points.

In terms of computational time and function evaluations our method has an enormous advantage over both methods. It should be noted that our software package qlopt is using C++ and Eigen, which gives an advantage over MatLab-based methods with respect to computational time.
4. Conclusions

This paper develops the numerical method for solving inverse problem on the identification of parameters for large scale models in systems biology. It is an essential modification adapted for large scale problems of the method introduced by one of the authors in [12], and successfully implemented by authors for solving inverse problems in systems biology with moderate size parameters in [11]. The iterative method combines ideas of Pontryagin optimization or Bellman quasilinearization with sensitivity analysis and Tikhonov regularization. For the adaptation and scalability of the method and our software package qlopt to inverse problems with significantly large size of the parameter set, a twofold modification is pursued: method of staggered corrector [17] is embedded into the step for sensitivity analysis, and the software package CVODES [19] is connected with our software package qlopt; and multi-objective optimization is enhanced into the method which allows for the application of the method to large-scale models with a practically non-identifiable set of parameters based on multiple data sets, possibly with partial and noisy measurements. The modified method is applied to a benchmark model of a biological network for a three-step pathway modeled by 8 nonlinear ODEs describing 8 metabolic concentrations with 36 unknown parameters, and two control input parameters specified by the experimental design. Extensive analysis demonstrates that the modified method is extremely well adapted to large scale problems. The main conclusions of the paper can be summarized as follows:

- There is a minimum number of data sets with different control parameter inputs required to achieve geometric convergence and unique identifiability of parameters for large-scale problems. The method has a geometric convergence and high accuracy for the benchmark model if at least five data sets with different control parameter inputs are used.
- Increase of data sets beyond the minimum doesn’t significantly affect convergence rate and accuracy, but possibly affects the computational cost.
- The method is extremely robust in terms of required number of time measurements for components of the system for every data set. For the benchmark model, high accuracy is achieved if the number of time measurements is between 1 and 240 in a segment [0,120].
- Optimal choice of the Tikhonov regularization parameter significantly increases the convergence rate and precision.
• The method is robust with respect to noisy measurements. Simulating up to 5% Gaussian noise in a benchmark model does not affect the convergence rate, but only adds some additional error to final output in accordance with the noise level.
• Implementation of the Type II Tikhonov regularization significantly increases the convergence range of the algorithm.
• Method is robust with respect to partial measurements. Application to the benchmark model with measurements of only four components instead of eight demonstrates convergence with slightly reduced but still quite high accuracy.
• The method is highly competitive and has an advantage over popular methods such as \texttt{lsqnonlin, fmincon, nl2sol} in terms of computational time, number of iterations and function evaluations.
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