Alternating Weighted Least Squares Parameter Estimation for Biological S-Systems

Li-Zhi Liu†, Fang-Xiang Wu* and Wen-Jun Zhang‡
†*‡Department of Mechanical Engineering, *‡Division of Biomedical Engineering,
University of Saskatchewan, 57 Campus Dr., Saskatoon, SK, S7N 5A9, Canada
* Corresponding author: faw341@mail.usask.ca

***Abstract*—The S-system, which is a set of nonlinear ordinary differential equations and derived from the generalized mass action law, is a consistent model to describe various biological systems. Parameters in S-systems contain important biological information and yet can not be obtained directly from experiments. Therefore, the parameter estimation methods are a choice to estimate parameters in S-systems. However, the parameter estimation for this model turns out to be a complex nonlinear optimization problem. A novel method, alternating weighted least squares (AWLS), is proposed in this paper to estimate the parameters in S-systems. The fast deterministic AWLS method takes advantage of the special structure of the S-system model and reduces solving the nonlinear optimization problem into alternately solving weighed least squares problems which have analytical solutions. The effectiveness of AWLS is demonstrated by the simulation studies and the results show that the AWLS outperforms the existing alternating regression method.**

I. Introduction

Biological systems, such as metabolic pathways and genetic regulatory networks, consist of many components and the interactions between them. One task of systems biology is to reveal the interactions and the biological functions those interactions may result in [1]. Instead of focusing on individual components, systems biology applies system engineering methods and principles to study all components and their interactions as parts of a biological system. Such a systematic view provides an insight into the control and optimization of parts of the system while considering the effects those may have on the whole system. It may lead to the discovery of new properties of a biological system, which helps understand the mechanisms of biological systems, and valuable clues and new ideas in practical areas such as disease treatment and drug design [2].

Many mathematical models have been proposed to describe the molecular biological systems based on biochemical principles. Most models are nonlinear in both parameters and system state variables [1], [3]. Estimation of parameters in those models are thus formulated as nonlinear optimization problems which generally have no analytical solutions. One popular model is the S-system, which is nonlinear and derived from the generalized mass action law [3].

An S-system with N components is a type of power-law formalism and typically a group of nonlinear ordinary differential equations in the following format:

$$\dot{X}_i = \alpha_i \prod_{j=1}^{N} X_j^{g_{ij}} - \beta_i \prod_{j=1}^{N} X_j^{h_{ij}}, \quad i = 1, \ldots, N, \qquad (1)$$

where X_i represents the concentration of metabolite i, whose changes are the difference between production and degradation, α_i and β_i are non-negative rate constants, and g_{ij} and h_{ij} are real-valued kinetic orders. It is an effective mathematical framework to characterize and analyze the molecular biological systems and their system dynamics. The representation of this model maps the dynamical and topological information of the system onto its parameters.

Parameter estimation and structure identification of S-system models are extremely difficult and challenging tasks, where the parameter estimation usually occurs after or in the process of structure identification. As the estimation of parameters in S-systems is a nonlinear problem, in principle, all algorithms for nonlinear optimization problems can be used, for example, Gauss-Newton iteration method, and its variants such as Box-Kanemasu interpolation method, Levenberg damped least squares method, and Marquardt's method [4]. However, these methods are initial-sensitive and most of them need to calculate the inverse of the Hessian which costs computation effort.

Several numerical methods have been proposed in the literature to estimate the parameters in S-systems, most of which are based on heuristics. For example, Kikuchi et al. [5] employed a genetic algorithm to infer the S-systems. Gonzalez et al. [6] showed the effectiveness of the simulated annealing technique. Voit and Almeida [7] developed an ANN-based method to identify the structure and estimate the parameters of S-systems. Ho et al. [8] and Wang et al. [9] respectively proposed an intelligent two-stage evolutionary algorithm and an unified approach to estimate the parameters in S-systems. Those methods are computationally expensive and do not sufficiently take the special model structure of the S-system into account.

Wu and Mu [10] introduced a separable parameter estimation method which takes advantage of the structure of the S-system model, i.e., one group of parameters is linear in model while the other group is nonlinear. This method has been extended to the case when system topology is unknown with a genetic algorithm by Liu et al. [11], [12]. One observation

978-1-4673-4398-5/12/$31.00 ©2012 IEEE

of the S-system is that if the parameters in one term on the right hand side of (1) is known, this term can be moved to the left side and a linear model is obtained by taking logarithm of both sides. Based on this observation, an alternating regression (AR) method was proposed by Chou et al. [13], which reduces the nonlinear estimation problem into the iterative procedures of linear regression. However, the objective of the iterations is vague and the necessary and sufficient criteria for convergence are not known. Inspired by the idea of AR, Vilela et al. [14] proposed a novel method based on eigenvector optimization of a matrix formed from multiple regression equations of the linearized decoupled S-systems, which, however, involves an nonlinear optimization problem.

In this paper, an alternating weighted least squares (AWLS) method is proposed. AWLS is a fast deterministic method and aims at reducing the nonlinear optimization problem into a series of easily solved problems, the idea of which is similar as AR's [13]. AWLS starts from the nonlinear least squares objective which can be approximated by a quadratic function with the assumption that part of the parameters are known. The approximated function turns out to be a weighted least squares problem which has an analytical solution. With the solution of the approximated problem, the other part of the parameters can also be estimated or further updated by forming another weighted least squares problem. AWLS takes advantage of the special form of S-systems and has a more clear objective than AR.

Briefly, the paper is organized as follows. In Section II, the AWLS method is introduced and derived. In Section III, the AWLS approach is applied to estimate the parameters of S-systems. The performance of AWLS is also compared with that of AR. Finally, in Section IV, conclusions are drawn and some future works along this research are pointed out.

II. Alternating Weighted Least Squares

Consider a biological system with N components described by an S-system in (1). For each component X_i, time series data consisting of n time points, $x_{i1}, x_{i2}, \ldots, x_{in}$, are assumed to be observed. The purpose is to estimate the parameters in (1) from these observed data. We substitute the derivative of X_i at each time t with the estimated slope, S_{it}, so that the original coupled differential equations are decoupled into $n \times N$ uncoupled algebraic equations [7], [14]:

$$S_{it} = \alpha_i \prod_{j=1}^{N} x_{jt}^{g_{ij}} - \beta_i \prod_{j=1}^{N} x_{jt}^{h_{ij}}, \tag{2}$$

where $i = 1, \ldots, N$ and $t = 1, \ldots, n$. The estimation of slopes is a crucial step and may have effects on the final results. To increase the accuracy, the five-point numerical derivative method is employed in this study, i.e.,

$$S_{it} = \frac{-x_{i,t+2} + 8x_{i,t+1} - 8x_{i,t-1} + x_{i,t-2}}{12\Delta t}, \tag{3}$$

where Δt is the length of sampling step.

Generally, the sum of least squares is used as a criterion to determine the values of parameters, i.e., parameters in each equation i of (1) are estimated by minimizing the following objective:

$$J_i(\alpha_i, \beta_i, g_i, h_i) = \sum_{t=1}^{n} \left[S_{it} - \alpha_i \prod_{j=1}^{N} x_{jt}^{g_{ij}} + \beta_i \prod_{j=1}^{N} x_{jt}^{h_{ij}} \right]^2, \tag{4}$$

where $g_i = [g_{i1}, \ldots, g_{iN}]^T$ and $h_i = [h_{i1}, \ldots, h_{iN}]^T$. Suppose values of β_i and h_i are given and let

$$D_{it} = S_{it} + \beta_i \prod_{j=1}^{N} x_{jt}^{h_{ij}} \text{ and } P_{it} = \alpha_i \prod_{j=1}^{N} x_{jt}^{g_{ij}}.$$

Then, we have

$$\begin{aligned}
J_i(\alpha_i, \beta_i, g_i, h_i) &= \sum_{t=1}^{n} (D_{it} - P_{it})^2 \\
&= \sum_{t=1}^{n} \left[e^{\log D_{it}} \left(1 - e^{\log P_{it} - \log D_{it}} \right) \right]^2 \\
&= \sum_{t=1}^{n} \left[D_{it} \left(\log D_{it} - \log P_{it} + o(\log D_{it} - \log P_{it}) \right) \right]^2 \\
&= \sum_{t=1}^{n} D_{it}^2 \left(\log D_{it} - \log P_{it} \right)^2 + o\left(\sum_{t=1}^{n} D_{it}^2 \left(\log D_{it} - \log P_{it} \right)^2 \right).
\end{aligned}$$

From (2), D_{it} and P_{it} should be close and in the third equality above, the first order Taylor approximation is applied. The last equality shows that $J_i(\alpha_i, \beta_i, g_i, h_i)$ can be minimized if the first term is small enough. Hence, the last term can be omitted.

This study assumes the structure of the system, i.e., the positions of nonzero kinetic orders, is available. From this information, some entries in g_i and h_i are known to be zeros. Let $\tilde{g}_i = [g_{ij_1}, \ldots, g_{ij_p}]^T$ and $\tilde{h}_i = [h_{i\ell_1}, \ldots, h_{i\ell_q}]^T$ denote the vectors of nonzero kinetic orders in g_i and h_i, respectively. α_i and $\tilde{g}_i$ can be estimated by solving the optimization problem

$$\begin{aligned}
\underset{\alpha_i, \tilde{g}_i}{\text{minimize}} \quad & \sum_{t=1}^{n} \left(S_{it} + \beta_i \prod_{j=1}^{N} x_{jt}^{h_{ij}} \right)^2 \left[\log \left(S_{it} + \beta_i \prod_{j=1}^{N} x_{jt}^{h_{ij}} \right) \right. \\
& \left. - \log \alpha_i - \sum_{k=1}^{p} g_{ij_k} \log x_{j_k t} \right]^2,
\end{aligned} \tag{5}$$

which is a weighted least squares problem. Let

$$\begin{aligned}
&\mathbf{W}(\beta_i, h_i) = \text{diag}(D_{i1}^2, \ldots, D_{in}^2), \\
&\mathbf{Y}(\beta_i, h_i) = \left[\log D_{i1}, \ldots, \log D_{in} \right]^T, \\
&\mathbf{\Gamma}_i = [\zeta_i, \tilde{g}_i^T]^T, \text{ where } \zeta_i = \log \alpha_i,
\end{aligned}$$

and

$$\mathbf{X}_{g,i} = \begin{bmatrix} 1 & \log x_{j_1 1} & \ldots & \log x_{j_p 1} \\ 1 & \log x_{j_1 2} & \ldots & \log x_{j_p 2} \\ \vdots & \vdots & \vdots & \vdots \\ 1 & \log x_{j_1 n} & \ldots & \log x_{j_p n} \end{bmatrix}.$$

978-1-4673-4398-5/12/$31.00 ©2012 IEEE

Then, (5) becomes

$$\underset{\boldsymbol{\Gamma}_i}{\text{minimize}} \quad \|\mathbf{W}(\beta_i,h_i)^{\frac{1}{2}}[\mathbf{Y}(\beta_i,h_i)-\mathbf{X}_{g,i}\boldsymbol{\Gamma}_i]\|_2^2, \tag{6}$$

and the analytical solution is

$$\begin{aligned}\widehat{\boldsymbol{\Gamma}}_i &= (\mathbf{X}_{g,i}^T\mathbf{W}(\beta_i,h_i)\mathbf{X}_{g,i})^{-1}\mathbf{X}_{g,i}^T\mathbf{W}(\beta_i,h_i)\mathbf{Y}(\beta_i,h_i),\\ \hat{\alpha}_i &= \exp(\hat{\zeta}_i).\end{aligned} \tag{7}$$

Similarly, when α_i and g_i are given, β_i and $\tilde{h}_i$ can be estimated from

$$\underset{\boldsymbol{\Theta}_i}{\text{minimize}} \quad \|\mathbf{W}(\alpha_i,g_i)^{\frac{1}{2}}[\mathbf{Y}(\alpha_i,g_i)-\mathbf{X}_{h,i}\boldsymbol{\Theta}_i]\|_2^2, \tag{8}$$

where $E_{it}=\alpha_i\prod_{j=1}^N x_{jt}^{g_{ij}}-S_{it}$,

$$\mathbf{X}_{h,i}=\begin{bmatrix}1 & \log x_{\ell_1 1} & \dots & \log x_{\ell_q 1}\\ 1 & \log x_{\ell_1 2} & \dots & \log x_{\ell_q 2}\\ \vdots & \vdots & \vdots & \vdots\\ 1 & \log x_{\ell_1 n} & \dots & \log x_{\ell_q n}\end{bmatrix},$$

and

$$\begin{aligned}&\mathbf{W}(\alpha_i,g_i)=\text{diag}(E_{i1}^2,\dots,E_{in}^2),\\ &\mathbf{Y}(\alpha_i,g_i)=[\log E_{i1},\dots,\log E_{in}]^T,\\ &\boldsymbol{\Theta}_i=[\eta_i,\tilde{h}_i^T]^T,\ \text{where } \eta_i=\log\beta_i.\end{aligned}$$

The corresponding analytical solution is

$$\begin{aligned}\widehat{\boldsymbol{\Theta}}_i &= (\mathbf{X}_{h,i}^T\mathbf{W}(\alpha_i,g_i)\mathbf{X}_{h,i})^{-1}\mathbf{X}_{h,i}^T\mathbf{W}(\alpha_i,g_i)\mathbf{Y}(\alpha_i,g_i),\\ \hat{\beta}_i &= \exp(\hat{\eta}_i).\end{aligned} \tag{9}$$

Based on the derivations above, we can see that when part of the parameters in an S-system are known, the rest can be estimated by solving a weighted least squares problem. Thus, given the initial values of one part of the parameters, all parameters in the S-system can be iteratively estimated by alternately solving weighted least squares problems. The objective value J_i is reduced in each iteration and the estimated parameters are obtained when the iterations converge. The proposed AWLS method for each equation i is:

Require: The structure of the system and initial values of β_i and $\tilde{h}_i$,
1: **repeat**
2: Estimate α_i and $\tilde{g}_i$ by (7) with known β_i and $\tilde{h}_i$,
3: Estimate β_i and $\tilde{h}_i$ by (9) with known α_i and $\tilde{g}_i$,
4: **until** a stopping criteria is met.

In this paper, the stopping criteria is

$$\frac{\|\gamma^{(k)}-\gamma^{(k-1)}\|_2}{\|\gamma^{(k)}\|_2}<\theta, \tag{10}$$

or the number of iterations is greater than 10,000, i.e., not convergent. Here, θ is a preset threshold and $\gamma^{(k)}=[\hat{\alpha}_i^{(k)},\hat{\beta}_i^{(k)},\hat{g}_i^{(k)T},\hat{h}_i^{(k)T}]^T$, i.e., the parameter estimations in the kth iteration.

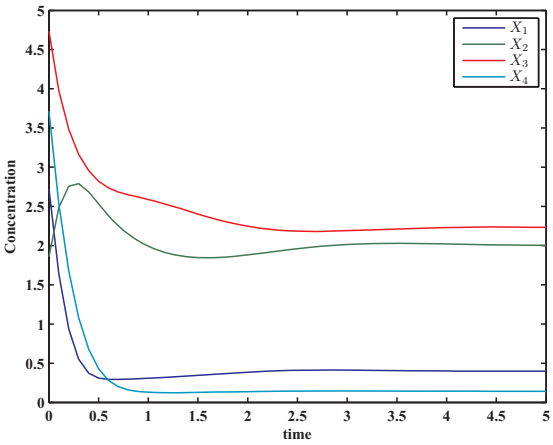

Fig. 1. Time series data of the 4-dimensional model.

III. Simulation and Comparison

A. Parameter Estimation

1) 4-dimensional model: Consider the following S-system of 4 metabolites [3]:

$$\begin{aligned}\dot{X}_1 &= 12X_3^{-0.8}-10X_1^{0.5},\\ \dot{X}_2 &= 8X_1^{0.5}-3X_2^{0.75},\\ \dot{X}_3 &= 3X_2^{0.75}-5X_3^{0.5}X_4^{0.2},\\ \dot{X}_4 &= 2X_1^{0.5}-6X_4^{0.8}.\end{aligned} \tag{11}$$

The noise-free time series data are obtained by numerically solving the S-system with an initial condition $X(0)=[x_{10},x_{20},x_{30},x_{40}]^T$. The data are sampled at time points in the interval $[0,5]$ with $\Delta t=0.1$.

In this example, the data are generated with $X(0)=[2.7255,1.8601,4.7343,3.7162]^T$ whose elements are randomly chosen in $[0,5]$. The time series data are shown in Fig. 1, from which we can see all states of X_i's are eventually in the steady states. The AWLS method is applied to estimate the parameters from these data with the initial values for β_i and h_i chosen by

$$(\beta_i^{\text{init}};h_i^{\text{init}})=(\beta_i^{\text{true}};h_i^{\text{true}})(1+\sigma\varepsilon), \tag{12}$$

where ε is a standard Gaussian random variable and σ is a positive constant. Since (4) is a nonlinear optimization problem, to avoid falling into the local optimum, we apply AWLS 100 times initiated with different values and choose the best one as the final solution. Here, we set $\sigma=90\%$, the objective values $J_i^{(k)}$ for each equation i in each iteration k are illustrated in Fig. 2. It can be seen that the objective values decrease with the increase of iteration steps. Table I shows the estimated results, from which we can see that the estimated values are quite close to their true values and the optimal objective values are all very small.

978-1-4673-4398-5/12/$31.00 ©2012 IEEE

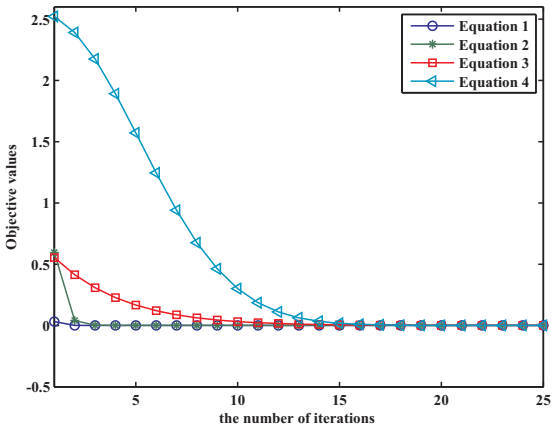

Fig. 2. Objective values over various numbers of iterations in AWLS.

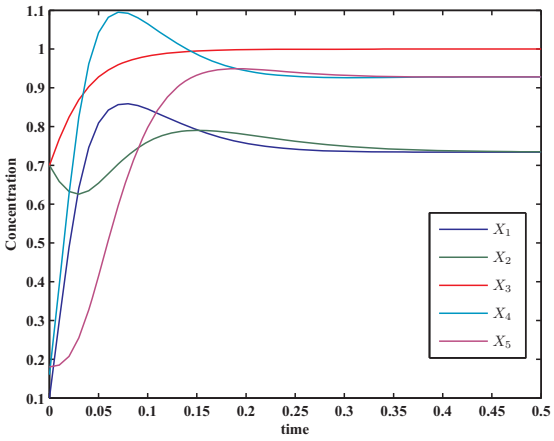

Fig. 3. Time series data of the 5-dimensional model.

TABLE I
ESTIMATED RESULTS OF THE 4-DIMENSIONAL MODEL.

Parameter	True Value	Estimation	Relative Error	Objective Value
α_1	12	12.0922	0.77%	1.4754×10^{-4}
β_1	10	10.1040	1.04%	
g_{13}	0.8	0.7893	1.34%	
h_{11}	0.5	0.4936	1.29%	
α_2	8	7.9851	0.19%	2.0490×10^{-4}
β_2	3	2.9830	0.57%	
g_{21}	0.5	0.5025	0.50%	
h_{22}	0.75	0.7522	0.29%	
α_3	3	3.0205	0.68%	1.8454×10^{-4}
β_3	5	5.0550	1.10%	
g_{32}	0.75	0.7531	0.41%	
h_{33}	0.5	0.4963	0.73%	
h_{34}	0.2	0.1996	0.22%	
α_4	2	2.0081	0.41%	1.0699×10^{-4}
β_4	6	5.9883	0.19%	
g_{41}	0.5	0.5157	3.13%	
h_{44}	0.8	0.8045	0.57%	

2) 5-dimensional model: A benchmark 5-dimensional model [14], [15] is considered,

$$\begin{aligned}
\dot{X}_1 &= 5X_3X_5^{-1} - 10X_1^2, \\
\dot{X}_2 &= 10X_1^2 - 10X_2^2, \\
\dot{X}_3 &= 10X_2^{-1} - 10X_2^{-1}X_3^2, \\
\dot{X}_4 &= 8X_3^2X_5^{-1} - 10X_4^2, \\
\dot{X}_5 &= 10X_4^2 - 10X_5^2.
\end{aligned} \tag{13}$$

The data used in this example are generated with the initial condition $X(0) = [0.1, 0.7, 0.7, 0.16, 0.18]^T$, the same in Yang et al. [15]. Fig. 3 shows the time series data that are sampled in the interval $[0, 0.5]$ with $\Delta t = 0.01$. Note that the states of all variables quickly converge to the steady state. Hence, only limited information on the dynamics of the system is contained in the data. We run AWLS 100 times with different initial values obtained from (12) with $\sigma = 80\%$ and select the best one as the solution. The results in Table II show the effectiveness of AWLS: estimated values of parameters are close to the true values and the optimal objective values are all very small.

TABLE II
ESTIMATED RESULTS OF THE 5-DIMENSIONAL MODEL.

Parameter	True Value	Estimation	Relative Error	Objective Value
α_1	5	4.8473	3.05%	6.0840×10^{-4}
β_1	10	9.8529	1.47%	
g_{13}	1	1.1337	13.37%	
g_{15}	-1	-1.0316	3.16%	
h_{11}	2	2.0443	2.21%	
α_2	10	10.0039	0.04%	8.0113×10^{-4}
β_2	10	9.9626	0.37%	
g_{21}	2	2.0049	0.25%	
h_{22}	2	1.9898	0.51%	
α_3	10	9.9699	0.30%	1.5504×10^{-4}
β_3	10	9.9711	0.29%	
g_{32}	-1	-0.9686	3.14%	
h_{32}	-1	-0.9684	3.16%	
h_{33}	2	2.0411	2.05%	
α_4	8	7.5653	5.43%	1.1×10^{-3}
β_4	10	9.5512	4.49%	
g_{43}	2	2.1869	9.35%	
g_{45}	-1	-1.0490	4.90%	
h_{44}	2	2.0824	4.12%	
α_5	10	9.9910	0.09%	1.4×10^{-3}
β_5	10	9.9770	0.23%	
g_{54}	2	2.0121	0.60%	
h_{55}	2	1.9917	0.42%	

3) 6-dimensional model: In this example, the AWLS method is applied to estimate the parameters in the following

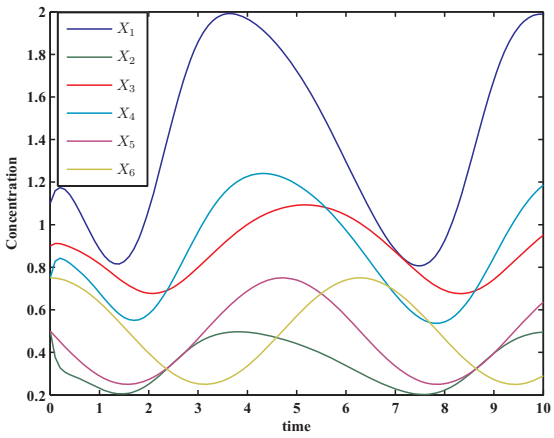

Fig. 4. Time series data of the 6-dimensional model.

6-dimensional S-system [15]:

$$\begin{aligned}
\dot{X}_1 &= 10X_3^{-2}X_5 - 5X_1^{0.5},\\
\dot{X}_2 &= 5X_1^{0.5} - 10X_2^{0.5},\\
\dot{X}_3 &= 2X_2^{0.5} - 1.25X_3^{0.5},\\
\dot{X}_4 &= 8X_2^{0.5} - 5X_4^{0.5},\\
\dot{X}_5 &= 0.5 - X_6,\\
\dot{X}_6 &= X_5 - 0.5.
\end{aligned} \tag{14}$$

The noise-free time series data are generated with the initial condition $X(0) = [1.1, 0.5, 0.9, 0.75, 0.5, 0.75]^T$ which matches that in Yang et al. [15]. Fig. 4 illustrates the time series data which are sampled in the interval $[0, 10]$ with $\Delta t = 0.1$. Fig. 4 also shows the periodic oscillating behavior of the data. The initial values for β_i and h_i are also chosen by (12) with $\sigma = 50\%$. The solution shown in Table III is the best one among 100 runs of AWLS with different initial values. The results in Table III indicate that the estimated parameters are close to their true values and the optimal objective values are all very small.

B. Comparison

The performances of AWLS and AR [13] are compared based on the previous 4-dimensional model (11) in the following procedure: (i) Fix a value of σ and randomly generate an initial condition $X(0)$ in $[0, 5]$. (ii) Obtain the noise-free data in the interval $[0, 5]$ with $\Delta t = 0.1$. (iii) Generate 100 initial values of $(\beta_i; h_i)$ by (12). (iv) Apply AWLS and AR to each equation i with each initial value, respectively. Therefore, each method has 100 results for each equation. (v) Remove those results which do not satisfy $\alpha_i, \beta_i \in [0.1, 12]$ or $g_{ij}, h_{ij} \in [-2, 3]$ (cf. [3], [14]) or not converge. Choose the result which has the the minimum objective value as the best one. (vi) For each method, put the best results of each equation together to form the final solution of the S-system. We run the aforementioned procedure (i)–(vi) with different $X(0)$'s and different σ's. In this experiment, we have 30 different $X(0)$'s and for each $X(0)$, σ's vary from 0 to 1 with step 0.1. Thus, each method has 30×11 results. We denote the results

TABLE III
ESTIMATED RESULTS OF THE 6-DIMENSIONAL MODEL.

Parameter	True Value	Estimation	Relative Error	Objective Value
α_1	10	10.4440	4.44%	2.0×10^{-3}
β_1	5	5.5333	10.67%	
g_{13}	-2	-1.8332	8.43%	
g_{15}	1	0.9163	8.37%	
h_{11}	0.5	0.4580	8.40%	
α_2	5	5.3370	6.74%	7.3143×10^{-4}
β_2	10	10.3732	3.73%	
g_{21}	0.5	0.4793	4.14%	
h_{22}	0.5	0.4794	4.12%	
α_3	2	2.0485	2.42%	1.8097×10^{-4}
β_3	1.25	1.3000	4.00%	
g_{32}	0.5	0.4835	3.29%	
h_{33}	0.5	0.4840	3.20%	
α_4	8	7.9549	0.56%	1.2×10^{-3}
β_4	5	5.0024	0.05%	
g_{42}	0.5	0.4934	1.33%	
h_{44}	0.5	0.4932	1.35%	
α_5	0.5	0.4928	1.43%	1.3908×10^{-5}
β_5	1	0.9957	0.43%	
h_{56}	1	1.0160	1.60%	
α_6	1	0.9955	0.45%	1.5696×10^{-5}
β_6	0.5	0.4925	1.51%	
g_{65}	1	1.0170	1.70%	

for the lth data, which are generated by $X^l(0)$, and $\sigma = \tau$ from AWLS and AR by $\gamma_{AWLS}^{(l,\tau)}$ and $\gamma_{AR}^{(l,\tau)}$, respectively, where $l = 1, \ldots, 30$ and $\tau = 0, 0.1, \ldots, 1.0$.

AWLS and AR are compared from two perspectives: the estimation error (EstErr) and the objective value (ObjVal).

$$\text{EstErr}^{(l,\tau)} = \frac{\|\gamma^{(l,\tau)} - \gamma_{true}\|_2^2}{\|\gamma_{true}\|_2^2}, \quad \text{ObjVal}^{(l,\tau)} = \sum_{i=1}^{N} J_i(\gamma^{(l,\tau)})$$

Fig. 5 shows the mean estimation errors of AWLS and AR with respect to each value of σ, respectively. Fig. 6 describes the mean objective values with respect to each value of σ. We can see that both the mean estimation error and the mean objective value grow with the increase of σ. In addition, both the mean estimation error and mean objective value of AWLS are in general less than those of AR, especially for large σ's.

To further confirm the conclusion, note that there are totally 330 cases (30 $X^k(0)$'s and 11 σ's) and in each case, the initial values for AWLS and AR are the same. Therefore, the 330 $\text{EstErr}^{(l,\tau)}$'s and 330 $\text{ObjVal}^{(l,\tau)}$'s of AWLS can be compared with those of AR, respectively, by paired hypothesis tests. The null hypotheses for the estimation error and the objective value are:

$$H_0 : \text{EstErr of AWLS} \geq \text{EstErr of AR};$$
$$H_0 : \text{ObjVal of AWLS} \geq \text{ObjVal of AR}.$$

We perform the paired t-test and paired Wilcoxon signed-rank test for the estimation error and objective value, respectively.

978-1-4673-4398-5/12/$31.00 ©2012 IEEE

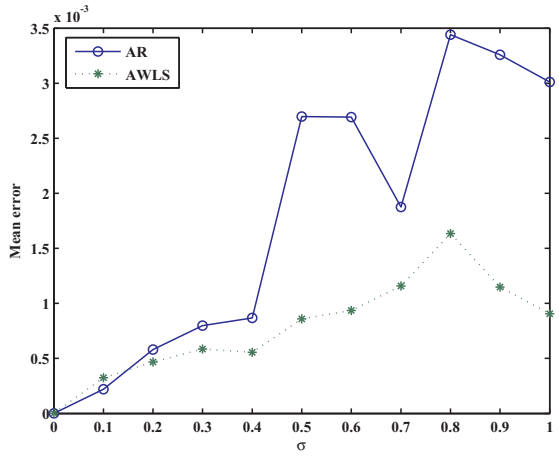

Fig. 5. Comparison of AWLS and AR w.r.t. mean estimation errors.

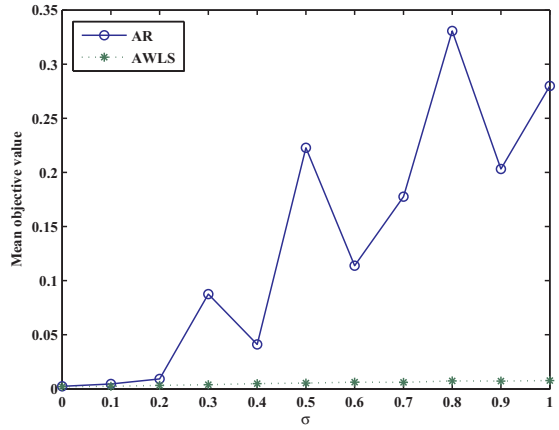

Fig. 6. Comparison of AWLS and AR w.r.t. mean objective values.

The null hypothesis of paired Wilcoxon test is similar as that of paired t-test but on medians and no normality assumption is required. The hypothesis test results are shown in Table IV, in which the p-values indicate that the estimation error and objective value of AWLS are significantly less than those of AR. Therefore, AWLS outperforms AR.

IV. Conclusions

This paper has proposed an AWLS method to estimate the parameters in biological S-systems. AWLS takes advantage of the special structure of S-systems and is a fast deterministic method with low computational cost. The superb efficiency comes from the reduction of the complex nonlinear optimization problem into alternating weighted least squares problems. There is no need to compute the inverse of the Hessian matrix and only part of the parameters require initial values. The dimension of search space of parameters are hence reduced. The simulation results show that AWLS can find the values of parameters in S-systems and AWLS outperform AR, i.e., it has less estimation error and objective value than those of AR.

In this study, the structure of the system is assumed to be known. One direction of the future work is to extend AWLS with Lasso approach [16], [17] to infer the S-system without knowing the system structure.

TABLE IV
Paired t-test (t) and paired Wilcoxon signed-rank test (V).

	t	df	p-value	V	p-value
EstErr	3.9859	329	4.143e-05	34151	3.985e-05
ObjVal	5.1832	329	1.907e-07	36958	1.321e-08

Acknowledgment

This study is supported by Natural Science and Engineering Research Council of Canada (NSERC).

References

[1] E. Klipp, R. Herwig, A. Kowald, C. Wierling, and H. Lehrach, *Systems Biology in Practice: Concepts, Implementation and Application*. Wiley-VCH, May 2005.

[2] T. S. Gardner, D. di Bernardo, D. Lorenz, and J. J. Collins, "Inferring Genetic Networks and Identifying Compound Mode of Action via Expression Profiling," *Science*, vol. 301, no. 5629, pp. 102–105, 2003.

[3] E. O. Voit, *Computational Analysis of Biochemical Systems: A Practical Guide for Biochemists and Molecular Biologists*. Cambridge University Press, Sep. 2000.

[4] J. V. Beck and K. J. Arnold, *Parameter estimation in engineering and science*. Wiley New York, 1977.

[5] S. Kikuchi, D. Tominaga, M. Arita, K. Takahashi, and M. Tomita, "Dynamic modeling of genetic networks using genetic algorithm and S-system," *Bioinformatics*, vol. 19, no. 5, pp. 643–650, 2003.

[6] O. R. Gonzalez, C. Kper, K. Jung, P. C. Naval, and E. Mendoza, "Parameter estimation using Simulated Annealing for S-system models of biochemical networks," *Bioinformatics*, vol. 23, no. 4, pp. 480–486, 2007.

[7] E. O. Voit and J. Almeida, "Decoupling dynamical systems for pathway identification from metabolic profiles," *Bioinformatics*, vol. 20, no. 11, pp. 1670–1681, 2004.

[8] S.-Y. Ho, C.-H. Hsieh, F.-C. Yu, and H.-L. Huang, "An Intelligent Two-Stage Evolutionary Algorithm for Dynamic Pathway Identification From Gene Expression Profiles," *Computational Biology and Bioinformatics, IEEE/ACM Transactions on*, vol. 4, no. 4, pp. 648 –704, oct.-dec. 2007.

[9] H. Wang, L. Qian, and E. Dougherty, "Inference of gene regulatory networks using S-system: a unified approach," *Systems Biology, IET*, vol. 4, no. 2, pp. 145 –156, march 2010.

[10] F.-X. Wu and L. Mu, "Separable Parameter Estimation Method for Nonlinear Biological Systems," in *Bioinformatics and Biomedical Engineering , 2009. ICBBE 2009. 3rd International Conference on*, june 2009, pp. 1 –4.

[11] L. Liu, F. Wu, and W. Zhang, "Inference of Biological S-system Using Separable Estimation Method and Genetic Algorithm," *Computational Biology and Bioinformatics, IEEE/ACM Transactions on*, in press.

[12] L.-Z. Liu, F.-X. Wu, L.-L. Han, and W. Zhang, "Structure identification and parameter estimation of biological S-systems," in *Bioinformatics and Biomedicine (BIBM), 2010 IEEE International Conference on*, dec. 2010, pp. 329 –334.

[13] I.-C. Chou, H. Martens, and E. Voit, "Parameter estimation in biochemical systems models with alternating regression," *Theoretical Biology and Medical Modelling*, vol. 3, no. 1, p. 25, 2006.

[14] M. Vilela, I.-C. Chou, S. Vinga, A. Vasconcelos, E. Voit, and J. Almeida, "Parameter optimization in S-system models," *BMC Systems Biology*, vol. 2, no. 1, p. 35, 2008.

[15] X. Yang, J. E. Dent, and C. Nardini, "An S-System Parameter Estimation Method (SPEM) for biological networks," *J Comput Biol*, vol. 19, no. 2, pp. 175–187, Feb 2012. [Online]. Available: http://dx.doi.org/10.1089/cmb.2011.0269

[16] B. Efron, T. Hastie, I. Johnstone, and R. Tibshirani, "Least Angle Regression," *Annals of Statistics*, vol. 32, pp. 407–499, 2004.

[17] R. Tibshirani, "Regression Shrinkage and Selection Via the Lasso," *Journal of the Royal Statistical Society, Series B*, vol. 58, pp. 267–288, 1994.

978-1-4673-4398-5/12/$31.00 ©2012 IEEE