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Journal Name:	<u>British Journal of Mathematics & Computer Science</u>
Manuscript Number:	2013_BJMCS_7800
Title of the Manuscript:	Constrained Stochastic Space Search Method for Parameter Estimation in Biological Networks
Type of the Article	Original Research Article

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SDI Review Form 1.6

PART 1: Review Comments

	Reviewer's comment	Author's comment (if agreed with reviewer, correct the manuscript and highlight that part in the manuscript. It is mandatory that authors should write his/her feedback here)
<u>Compulsory</u> REVISION comments	1. It is not clear for me why CSSS method is used for the comparison of ICRS/DS method in this paper. Because there are other stochastic search algorithm in the literature such as simulated annealing, tabu search or genetic search. So is ICRS/DC already better than those methods so that the author(s) choose(s) this algorithm to compare with CSSS? 2. It can be presented how the order of convergence changes with respect to the increase in the dimension of networks. Hence we can understand the advantage of CSSS over ICRS/DS in realistically large or moderately large biological systems. 3. In the literature part, there is no information about other stochastic search algorithms and hybrid search algorithms. Because of this reason I cannot see why CSSS is chosen among those methods (i.e. among other stochastic and hybrid search method). 4. On line 226-229, it is written that if we change the selected initial values, the convergence of both algorithms becomes worse. So does it mean that for arbitrary initial values or for other choices as initials, both algorithms perform almost equally? If it is, it is not very clear for me	I would like to thank the reviewer for the useful comments and suggestions to help improve the manuscript. 1. A justification for the use of CSSS has been provided in the manuscript. 2. It is difficult to directly deduce the order of convergence with respect to the increase in the dimension of networks from this study. Establishing such a link requires a different study aimed at addressing this specific problem, particularly with respect to deducing how CSSS and ICRS/DS perform for realistically large or moderately large biological systems. 3. Additional insight into other stochastic algorithms has been provided in the introduction section of the revised manuscript. However, at it still remains difficult basing on this study to directly compare those methods to the CSSS proposed in this manuscript – since most of the other stochastic optimization methods are rarely used in the context of parameter estimation in biological network, but on machine learning and pattern recognition in physical systems. 4. Additional sentences have been added



SDI Review Form 1.6

	the advantage of this method over CSSS in every situation. 5. Here the fit is shown when $\Delta t=0.05$. So the observed time points are very close. So how the performance of both methods changes if the observations are collected when $\Delta t=1$ or higher values? Do the plots in Figure 2 change in this case? 6. Do(es) the author(s) show the performance of both algorithms in large or moderately large networks? Because it seems that the current application is valid for small toy system. Moreover a small application via a real dataset, if such data are available, can be interesting.	in the manuscript to clarify on this comment. [see page 10]. 5. Often the data sampling frequency is based on the suspected dynamics in the time course profile and objective of the research question being considered. Some gene transcription profiles have order dynamics higher than 3, and while some show oscillatory dynamics – in which case an appropriate data sampling time steps have to be decided upon to capture such dynamics. 6. The performance of both algorithms has so far only been tested on a small and synthetic. Indeed it would be interesting to have it tested on real data and on an up-scaled system that is relatively larger, perhaps tens or hundreds of network components. However, as can already be seen from this work, the problem of accurately identifying the parameters might only get worse – just like with any other method. The larger the network, the more the number of parameters, and therefore the higher the chances of correlations and bias in estimating them.
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SDI Review Form 1.6

<u>Minor</u> REVISION comments	1. The set of reaction or simple figure of the system described in Equation 9 can be given. Because we cannot see how we produce the set of equation in (9). 2. How do(es) the author(s) decide on $\alpha=0.05$? Is it chosen arbitrarily? 3. The meaning of each term in Table 1 can be briefly described in the caption as it can help the reader to understand the pseudo-codes better. 4. The available data used in section 3 and figure 2 are described shortly at the beginning of section 3.1 such as how many data points are observed for each time point? How many genes are used and how many parameters do we need to estimate? 5. The meanings of 0.0191 for ICRS/DS and 0.0170 for CSSS (line 218) are not given. Those can be explained. 6. Could the author(s) also show the plot for the number of unsuccessful iterations like in Figure 1? 7. The y-axis of Figure 1, 6 and 7 cannot be read at all.	1. An explanation in response to issue number 1 regarding eq. (9), has been provided in the manuscript. [Page 9-10]. 2. Yes, these value is chosen arbitrarily, however it is also not unrealistic since noise levels in time course data are about 5% to even 10% or higher... 3. The meaning of some extra terms has been added in the caption of Table 1 as requested. 4. Subsection 3.1 contains additional lines explaining the requested clarification. [page 8] 5. These values are explained on page 9. 6. Figures 6 and 7 do provide sufficient information to address this question. The CSSS is much faster compared to the ICRS/DS, hence, less unsuccessful iterations for the CSSS unlike the ICRS/DS. 7. The readability of the legends and axis of all the figures in the manuscript has been improved as requested by the reviewer.
<u>Optional/General</u> comments	I consider that the paper is interesting to suggest a better performed algorithm in ODE type of inference. Whereas before accepting for publication, certain revision listed above is needed.	