Convergence Dynamics of Biochemical Pathway Steady State Stochastic Global Optimization

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Abstract-The **stochastic nature of convergence of steady state stochastic global optimization methods in design optimization tasks with steady state precondition is a hardly predictable step in development of industrially efficient strains of microorganisms.**
The properties of convergence dynamics of evolutionary programming (EP) and particle swarm (PS) depending on complexity of kinetic equations within the same model are studied optimizing yeast glycolysis for ethanol production by COPASI software adjusting parameters of three combinations of five reactions out of fifteen enzymatic reactions.
Results indicate significant differences in the convergence dynamics between different combinations. 50-fold difference in convergence time as well as possible stagnation at local optima was observed. The choice of optimization method and duration of optimization runs should be based on number of tests on the convergence quality, speed and repeatability.

I. INTRODUCTION

The mission of systems biology and synthetic biology in tasks of metabolic engineering [17] is to facilitate the development of new bioprocesses aiming for the best instead of just a better process. One of phases in this optimisation process are the computational procedures helping to reduce the amount of necessary biological experiments which are more costly both in terms of time and resources. In case of biotechnological processes optimal steady state accordingly to a set of criteria usually is sought [7,17] to increase the profitability of industrial process. Different types of mathematical models can be applied [25] accordingly to the peculiarities of the process of interest and available information. The growing number of available stoichiometric [20, 23] and dynamic [16] models support the *in silico* optimization approach.

Search of the most profitable steady state applying flux balance analysis for constraint-based stoichiometric models [21] and genome scale reconstructions [22] with thousands of reactions give valuable insight in the interactions of various flows. Disadvantage of the stoichiometric approach is the fact that kinetic parameters of reactions are not taken into account [25] and concentrations of reactants, details of transition processes cannot be calculated. Therefore dynamic models are necessary to assess the industrial feasibility of the metabolically engineered biochemical system taking into account the peculiarities of the available equipment, stability of the process in a steady state as well as in transition processes.

The most typical approach representing biochemical networks is a set of coupled deterministic ordinary differential equations intended to describe the network and the production and consumption rates for the individual species involved in the network [4]. The expected increase of the size of dynamic models [13] will facilitate their application. The main disadvantage in case of optimization of dynamic model is the lack of analytical optimization solutions to solve systems of nonlinear differential equations.

Quite high number of numerical methods can be applied in optimization tasks of biochemical networks. They can be divided in local and global optimum seeking methods [5,17]. Usually the global optimization methods are used to avoid stagnation of the solution in local minimum. There are two classes of global numerical optimization methods: deterministic ones and the stochastic ones. The advantage of some of deterministic methods is the guaranteed reach of global optima for the price of unknown computation time [6,18]. Still the stochastic global optimization methods are the most popular in optimization tasks of biochemical networks due to their universality and relatively fast convergence to the global optima close value [6,18] in spite of not guaranteed reaching of global optima.

The convergence of global stochastic optimization methods is analyzed in case of parameter estimation tasks [3,4,5,17,18] while just first attempts are made in design optimization tasks [19] where the properties of metabolic pathways are changed with the aim of enhancing the production of some metabolite of interest [17,18]. Importance of the convergence speed and reliability is critical in design problems of biochemical networks where even relatively small number (5-15) of adjustable parameters of the model cause high number of combinations to be explored, for instance, in case when minimal number of adjustable parameters is sought to reach necessary level of the objective function. Thus, in case of several hundreds or thousands of adjustable parameter combinations the number of optimization runs does not seem attractive. Therefore, often biologists are the ones which generate ideas to be tested on the model before the biological experiments are started. This

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approach can lead to the limitation of the search space due to the experience and habits of biologists and may cause wrong conclusions about the best industrially feasible steady state solutions [7] for particular biochemical network.

Currently the growing computational power leads to the systematic scanning approach [24] of all possible combinations of adjustable parameters. Still, the combinatorial explosion of adjustable parameter sets force to look for efficient technologies to reduce the total optimisation time either by rejecting some combinations of adjustable parameters or by reducing time for estimation of best value of objective function for each combination. Dynamic yeast glycolysis model [11] and COPASI [12] optimization features are used to test reliability of the above mentioned approaches to reduce optimization time in case of combinatorial explosion due to high number of adjustable parameters.

Earlier research has demonstrated that convergence dynamics strongly depend on the number of adjustable parameters as well as on the optimization method [19]. This article is devoted to the comparison of convergence dynamics in case of different combinations of fixed number of adjustable parameters. Therefore convergence dynamics of three different combinations with five enzymes out of fifteen enzymatic reactions are compared to find out if one can generalize that convergence properties depend just on the number of adjustable parameters or it can not be generalized due to the influence of choice of particular parameters within the combination. Five optimization runs with identical start conditions of two stochastic optimization methods [18]: evolutionary programming (EP) and particle swarm (PS) are compared optimizing values of reaction speed related parameters.

In two adjustable parameter combinations out of three both EP and PS converged to the optima within 400 seconds demonstrating similar performance in terms of repeatability of five optimization runs with identical start parameters.

The third combination demonstrated slow convergence within about 20000 seconds for both EP and PS. Still EP reached the optima just in one case out of five while the other runs of EP for this combination of adjustable parameters reached just 37-82% of optima. EP stagnated at local optima until 50000 seconds when the optimization runs were interrupted.

It is concluded that generalisation of convergence dynamics of optimisation runs even for the same number of adjustable parameters within the same model can cause inadequate conclusions about the necessary duration of optimisation to reach the best value as well as risk to stagnate at a local optima. Adjustable parameters of reactions with high flux control coefficients for the objective function related flux may be related to the increased convergence speed in case of steady state optimisation or even to stagnation at local optima. Good performance of optimization method in case of one set of adjustable parameters does not necessarily mean that performance will be good in case of other set of adjustable parameters even if the number of parameters stay the same.

II. MATERIALS AND METHODS

Yeast glycolysis model [11] downloaded from Biomodels data base [16] is used as a test model for optimization. The model contains 2 compartments, 24 reactions and 25 metabolites. Objective function in all optimization runs was

$$K = \frac{Ethanol\ flow}{Glucose\,uptake} + 5 * Ethanol\ flow$$

Concentrations of 15 enzymes catalyzing 15 reactions were available to include in three combinations of 5 adjustable parameters [17].

Three combinations of adjustable parameters were created: 1) five reactions with the smallest number of parameters in kinetic equations (combination C1), 2) five reactions with the highest number of parameters in kinetic equations (combination C2) and 3) five reactions with the largest MCA coefficients (combination C3). The reactions in combination C3 were chosen in decreasing order of the module of flux control coefficients of ethanol flow obtained using Metabolic Control Analysis [8,9,14] for the steady state found for initial values of the model using COPASI.

As a result C1 consists of concentrations of enzymes of ATP consumption, storage, phosphoenolpyruvate synthesis, adenylate kinase, pyruvate decarboxylase with number of parameters in kinetic equation 2; 2; 3; 3 and 3 correspondingly. Combination C2 consists of concentrations of phosphoglucoisomerase, triosephosphate isomerase, glucose uptake, aldolase, glyceraldehyde 3-phosphate dehydrogenase with number of parameters in kinetic equations 6; 6; 8; 8 and 8 correspondingly. Combination C3 consists of concentrations of hexokinase, alcohol dehydrogenase, ATP consumption, glycerol synthesis, phosphofructokinase with module of MCA flux control coefficients 0.792; 0.184; 0.0521; 0.0313 and 0.0281 correspondingly. The fifteenth reaction which was not used in any combination was pyruvate kinase.

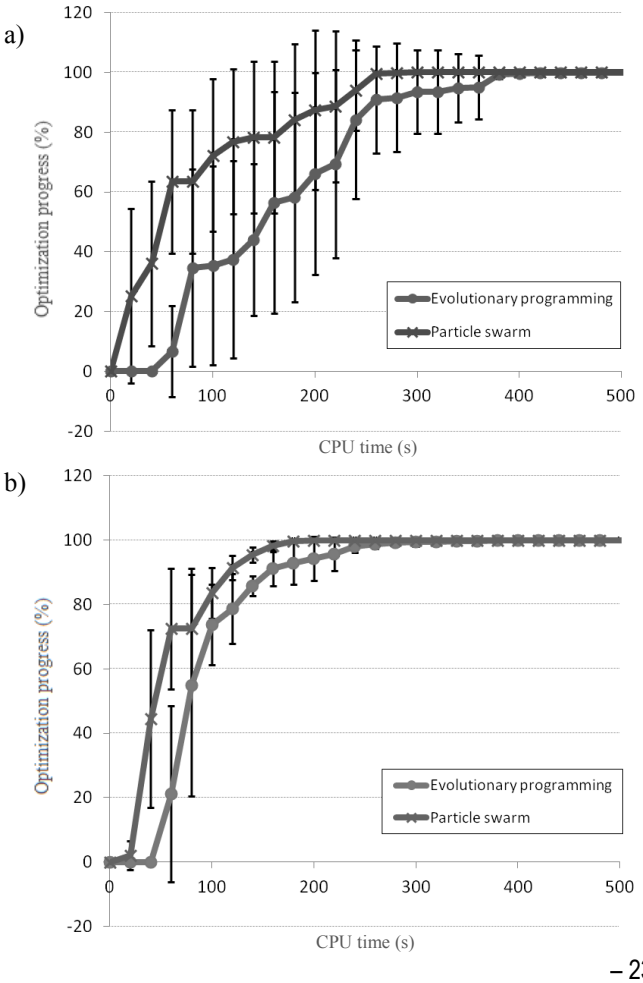
COPASI [12], build 30, is used as optimization tool. Two global stochastic optimization methods are applied: 1) evolutionary programming [1,2,10] with following method parameters: Number of Generations: 30000; Population Size: 20; Random Number Generator: 1; Seed: 0 and particle swarm [15] with following method parameters: Iteration Limit: 2000; Swarm Size: 50; Std. Deviation: 1e-06; Random Number Generator: 1; Seed: 0. The values of adjustable parameters were allowed to change within a wide range from -99% up to 1000% from their initial values. “Steady state” subtask of optimization was chosen.

Discretisation of time series of convergence progress was performed using convergence analysis software ConvAn (available at: http://www.biosystems.lv/index.php?option=com_content&view=category&layout=blog&id=44&Itemid=70).

Progress of convergence to the best value of objective function was recorded as time series of CPU time and best objective function values. Optimization experiments of 50000 seconds (or 13.9 hours) of CPU time were performed. Five optimization experiments were performed for each of three combinations for each optimization method on a server running 64-bit Microsoft Windows Server 2008 Standard Service Pack 2 operating system. Server has 4x QuadCore Intel Xeon MP E7330 2400 MHz CPU and 32,768 MB of RAM. Several optimization experiments were run in parallel. Single processor per task was used as COPASI does not support optimization with parallel task distribution.

II. RESULTS

The performance of Evolutionary Programming (EP) and Particle Swarm (PS) methods is presented in the Figure 1 for all the three combinations of five parameters: C1, C2 and C3. The convergence curves are normalized the way that 0% value of objective function correspond to the steady state of initial model before optimization (K=4.99) while 100% correspond to the best value of objective function found in any run of particular combinations: 6.81 optimizing combination C1 (Fig.1a), 5.12 optimizing C2 (Fig.1b) and 6.38 optimizing C3 (Fig.1c).



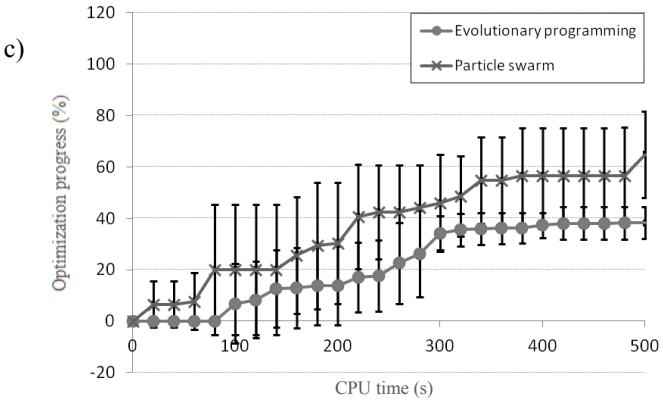
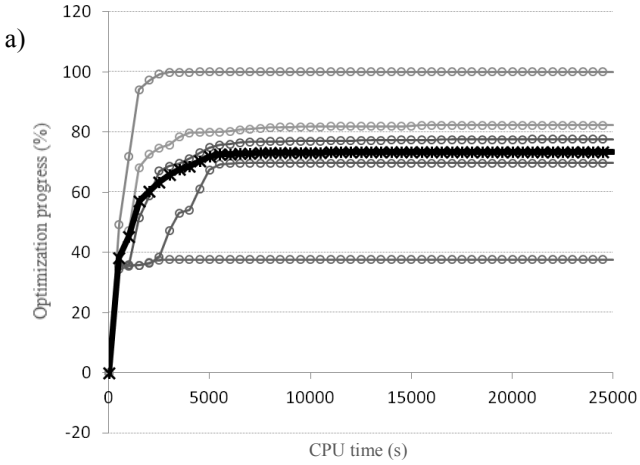


Figure 1. Average normalized convergence speed of evolutionary programming and particle swarm optimization methods until 500 seconds of CPU time (error bars represent standard deviation of five experiments): a – combination C1, b – combination C2 and c – combination C3.

A. *Convergence to the best value of the objective function*

Stochastic numerical methods do not guarantee reach of global optimum. Therefore, we use term „best value" to describe best objective function value that has been observed for particular number of optimized reactions independent on the optimization method. The best value may be global optimum but that is not guaranteed [5,6,17, 18].

PS method has converged to objective function values that are close to the best value in all cases. In cases C1 and C2 all the runs reached the best value within 300 seconds of CPU time. In the case of C3 the best value was reached by all the five optimization runs much later – after about 20000 seconds (Fig.2b). EP had a good convergence in case of C1 and C2 reaching the best value in all runs within 400 seconds. In case of C3 EP method reached the best value only in one optimization run while the other four stayed within range 37-82% of the best value (Fig.2a). The stagnation of all the runs started at CPU time of about 20000 seconds.



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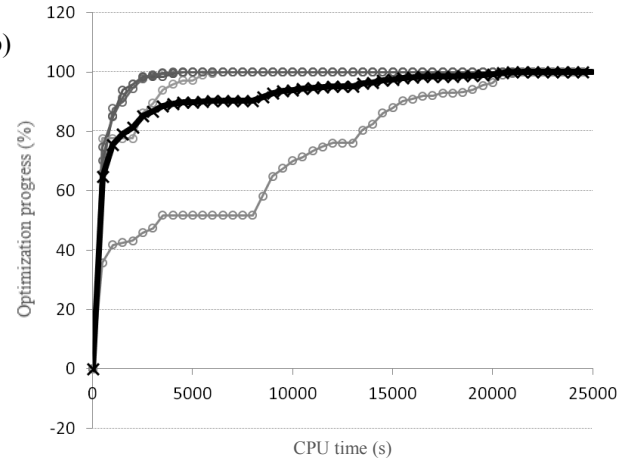

Figure 2. EP optimization experiments of combination C3 for evolutionary programming (a) and particle swarm (b) methods until 25000 seconds of CPU time. Line with crosses represents the mean values, lines with rings show dynamics of individual optimizations.

B. Dynamics of standard deviation

Standard deviations of EP and PS are similar in cases C1 and C2. Still the PS optimization method demonstrates slightly better performance.

In case of C3 the EP method has very poor performance even within 50000 seconds of CPU: stagnation starts at about 10000 seconds at very different levels thus causing very large value of standard deviation.

PS method is more reliable in the C3 case. One run out of five converges very slow compared to the other four still reaching the best value.

III. DISCUSSION

The aim of the experiment is to test the nature of behaviour of optimization methods and results may not be biologically relevant. The behaviour of one model and two different stochastic global optimization methods are tested to evaluate the nonlinearity features of the model as well as possibility to generalize experience of optimization gained optimizing the same model with the same optimization method and tool.

Earlier research [19] comparing the same model and optimization methods optimizing one, five, ten and fifteen reactions with has indicated that there are significant differences in performance of EP and PS methods. This research concentrates on generalisation risks of convergence properties for different combinations of equal number of adjustable parameters of the same model that is optimised with the same optimization methods.

Therefore three combinations of five adjustable parameters (one per reaction) were compared. The adjustable parameters were V or k [19] depending on the type of reaction kinetics. The combinations of adjustable parameters in case of C1 and C2 were chosen linking the number of parameters in the kinetic equation of the reaction with it's complexity expecting and with features of it's optimization. The combination of adjustable parameters C3 was chosen assuming that the reactions with the highest flux control coefficients should have the largest influence on the ethanol flow which is the main parameter in the objective function.

The most important clearly visible conclusion is that the same optimization methods, number of adjustable parameters within the same model does not guarantee the same convergence properties. Several conclusions can be made.

1. PS method is reliable in terms of convergence to the best value of the objective function at least within performed optimisation runs. At the same time there are no evidences that it can be generalised.

2. EP method is working reliably in some combinations of adjustable parameters performing as good as PS method (C1 and C2). Still the performance of EP with combination C3 clearly demonstrate that EP method is not reliable in terms of convergence and long optimization runs can not help there. The stagnation can be very explicit and very far from the best value.

3. Combinations C1 and C2 were performing very similar way with both methods. Still the standard error in case of C2 was much smaller independent on the optimization method. Authors can not explain this phenomenon.

4. The combination C3 demonstrated completely different optimization features: about 50-fold increase in convergence time (until all the runs reach the best value) in case of PS and stagnation starting from 20000 seconds of CPU time in case of EP. This behaviour can be explained by peculiarities of steady state condition which was set as a subtask of optimization task within COPASI software. We suppose that high flux control coefficients lead to quick loss of steady state feature even in small steps from the initial steady state of the model. Therefore the number of steady state giving combinations of parameters is very limited thus increasing the convergence time. Still we have no explanation for the heavy stagnation of the EP method. Interestingly that all the four not successful runs of EP start the stagnation at value 35% of the best value while none of PS runs stagnates at the same level.

Thus, the assumption that stochastic methods reach the global optima close value in reasonable computation times [6,18] may be dangerous at least in some cases. The lack of significant progress after 20,000 seconds of CPU time in any optimization experiment indicate that long or even very long optimization not always can compensate the drawbacks of the method or/and peculiarities of the model. At the same time this conclusion cannot be generalized to other methods which are not tested. It can not be generalised even to the PS and EP as only one combination of method settings is tested.

The above mentioned features of optimization experiments may be caused by different factors like optimization method, nonlinearity of the model causing multimodalities [6] at particular combinations of adjustable parameters.

IV. CONCLUSION

Convergence tests of two global stochastic optimization methods (particle swarm and evolutionary programming) performing steady state task indicate that the same number of adjustable parameters even within the same model can have completely different convergence features as increased convergence time and even failure of convergence.

The convergence speed between three combinations of five adjustable parameters was within range of 500 till 25000 seconds of CPU time thus indicating 50-fold difference.

Successfully converging methods in case of one combination may fail in case of other combination with the same number of adjustable parameters of the same model. Thus good convergence in case of one combination does not guarantee the same for other combinations.

Slow convergence has been found for a set of adjustable parameters which are related to the concentrations of enzymes with high flux control coefficients for the objective function related flux. Authors hypothesize that high flux control coefficients lead to quick loss of steady state feature even in small distance from the initial state of the model. Therefore the number of steady state giving combinations of parameters is very limited thus increasing the convergence time.

Application of a single stochastic global optimization method raise risks of failure to find the best possible value of objective function. Long optimization runs do not always ensure convergence to the best value of the objective function and do not compensate the poor convergence properties of optimization methods for a particular model.

Normalized curves of convergence dynamics in all the optimization experiments demonstrate asymptotic behaviour.

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