Convergence Dynamics of Biochemical Models To The Global Optimum

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***Abstract*-Stochastic nature of convergence of steady state stochastic global optimization methods causes several seemingly attractive approaches to reduce the length of the optimization procedure.**
The properties of convergence dynamics of evolutionary programming (EP) and particle swarm (PS) are studied optimizing yeast glycolysis by COPASI software adjusting parameters of one, five, ten and fifteen reactions with five identical runs for each case.
Results indicate the potential and risks of shortening the optimization time improving the possibilities of systematic search of adjustable parameter combinations. The choice of optimization method depending on the model size and the number of adjustable parameters should be based on number of tests on the convergence quality, speed and repeatability.

Keywords: bioprocess design, dynamic modelling, kinetic parameters, optimization, convergence dynamics.

I. INTRODUCTION

The mission of systems biology and synthetic biology in metabolic engineering tasks [16] is to facilitate the development of new bioprocesses by the help of *in silico* procedures thus reducing 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 [16, 6] to increase the profitability.

The most typical approach to representing biochemical networks is through 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 [3]. The expected increase of the size of dynamic models [12] 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.

The numerical methods are used in optimization tasks of biochemical networks. They can be divided in local and global optimum seeking methods [16,4]. 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 [5,17]. Therefore, 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 [5,17].

Currently the growing computational power leads to the systematic scanning approach [18] of all possible combinations of adjustable parameters. Still, the combinatorial explosion of adjustable parameter sets force to look for efficient technologies to reduce necessary time either by rejecting some combinations of adjustable parameters or by reducing time for estimation of each combination. Following approaches may seem to be attractive: 1) quick determination of the best value of objective function using one long optimization run or several shorter ones, 2) reduce the optimization time assuming that the convergence dynamics will stay the same using the same model, software and optimization method and it's settings, 3) switch between several optimization methods to converge faster to the best value (could be equal to the global optimum) or/and 4) find the fastest method for given model using several test runs with different methods.

Dynamic yeast glycolysis model [10] and COPASI [11] 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. Five optimization runs of two stochastic optimization methods [17]: evolutionary programming (EP) and particle swarm (PS) are compared optimizing values of reaction speed related parameters of one, five, ten and fifteen enzymes.

It is concluded that not all methods converge to the best value (may be equal to the global optimum) even using long (more than five days) optimization runs indicating that optimization length do not compensate drawbacks of optimization method that stagnates in a local optimum. Performance of a method may strongly depend on the number of optimized reactions within the same model using the same optimization tool, optimization method and it's settings. Poor performance of optimization method in case of one set of adjustable parameters does not necessarily mean that performance will be poor in case of other set of adjustable parameters.

II. MATERIALS AND METHODS

Yeast glycolysis model [10] downloaded from Biomodels data base [15] 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

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$$K = \frac{Ethanol\ flow}{Glucose\ uptake} + 5 * Ethanol\ flow \quad (1)$$

Concentrations of enzymes catalyzing 15 reactions were chosen as adjustable parameters [16]. Four numbers of reactions (1, 5, 10 and 15) were optimized to see the influence of the solution space on the convergence properties of objective function to the global optimum. The sequence of modified reactions was chosen in decreasing order of the module of flux control coefficients of ethanol flow (Table 1) obtained using Metabolic Control Analysis [7,8,13] for the steady state found for initial values of the model using COPASI. It was expected that the reactions with highest influence on the main product (ethanol) flow will be at the beginning of the list.

TABLE I
SEQUENCE OF MODIFIED REACTIONS

Sequence number accordingly MCA	Use in optimization experiment sets of 1, 5, 10 and 15 reactions	Reaction name	Module of flux control coefficient for Ethanol flow	Adjustable model parameters
1	1,5,10,15	HK	7.92e-01	V3m
2	5,10,15	ADH	1.84e-01	V12m
3	5,10,15	consum	5.21e-02	k23
4	5,10,15	lpGlyc	3.13e-02	V15m
5	5,10,15	PFK	2.81e-02	V5m
6	10,15	GAPDH	2.01e-02	V8f, V8r
7	10,15	Storage	1.89e-02	k22
8	10,15	TIM	9.18e-03	V7f, V7r
9	10,15	PK	5.20e-03	V10m
10	10,15	GlcTrans	4.37e-03	V2f, V2r
11	15	PGI	2.32e-03	V4f, V4r
12	15	lpPEP	1.72e-03	k1, k2
13	15	PDC	7.82e-16	V11m
14	15	ALD	4.04e-16	V6f
15	15	AK	2.13e-18	k1, k2

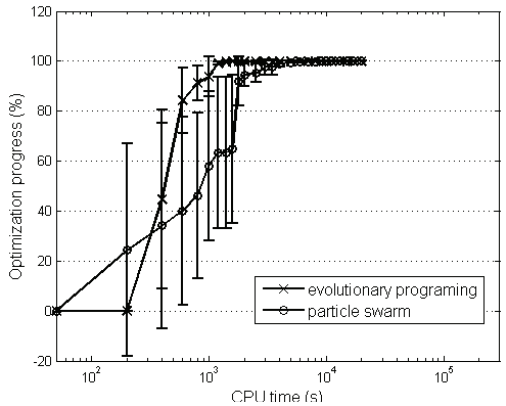
COPASI [11], build 30, is used as optimization tool. Two global stochastic optimization methods are applied: 1) evolutionary programming [9,1,2] with following method parameters: Number of Generations: 30000; Population Size: 20; Random Number Generator: 1; Seed: 0 and particle swarm [14] with following 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.

Progress of convergence to the best value of objective function was recorded as time series of CPU time and best objective function values. 5e+05 seconds (or 5.8 days) of CPU time were used in case of slowly converging optimizations. Five optimization experiments were performed for each number of reactions 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.

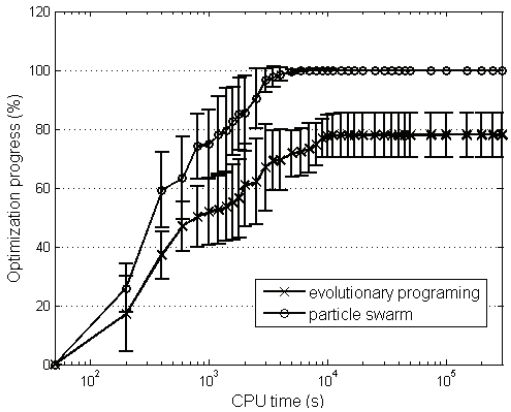
III. RESULTS

The performance of Evolutionary Programming (EP) and Particle Swarm (PS) methods is presented in the Figure 1 for different size of adjustable parameter sets: 1, 5, 10 and 15. The convergence curves are normalized the way that 0% value of objective function correspond to the steady state of unchanged model (K=4.99) while 100% correspond to the best value of objective function found in any run of identical optimization run: 5.02 optimizing one reaction (Fig.1a), 6.38 optimizing 5 reactions (Fig.1b), 6.48 optimizing 10 reactions (Fig.1c) and 12.73 optimizing 15 reactions (Fig.1d). The presented optimization progress dynamics correspond to identical initial models for both methods.

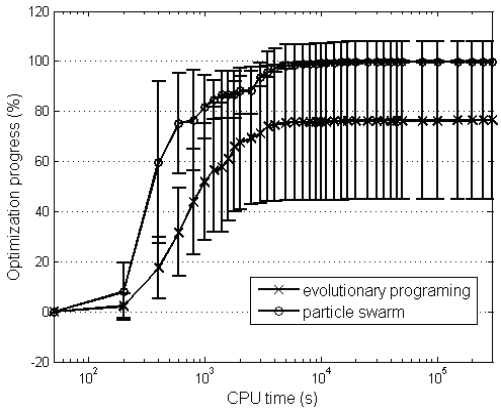
a)



b)



c)



d)

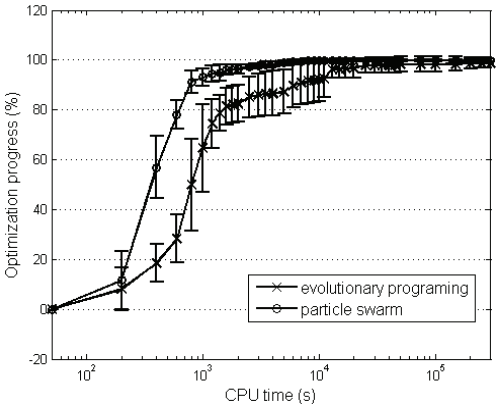


Fig. 1. Average normalized convergence speed of evolutionary programming and particle swarm optimization methods (error bars represent standard deviation of five experiments): a – one reaction optimization, b – five reaction optimization, c – ten reaction optimization, d – fifteen reaction optimization.

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 [16,4,5,17]. Particle swarm method has converged to objective function values that are close to the best value in all cases within 3500 seconds of CPU time that correspond roughly to one hour. EP had a good convergence in case of one reaction and satisfactory convergence in case of 15 reactions (Fig.1). EP for 5 and 10 reactions had a poor convergence with high standard deviation values (Fig.2).

Still, in case of one reaction the EP demonstrated the best performance both in terms of speed and reaching the best value while PS was better in case of five, ten and fifteen reactions.

a)

b)

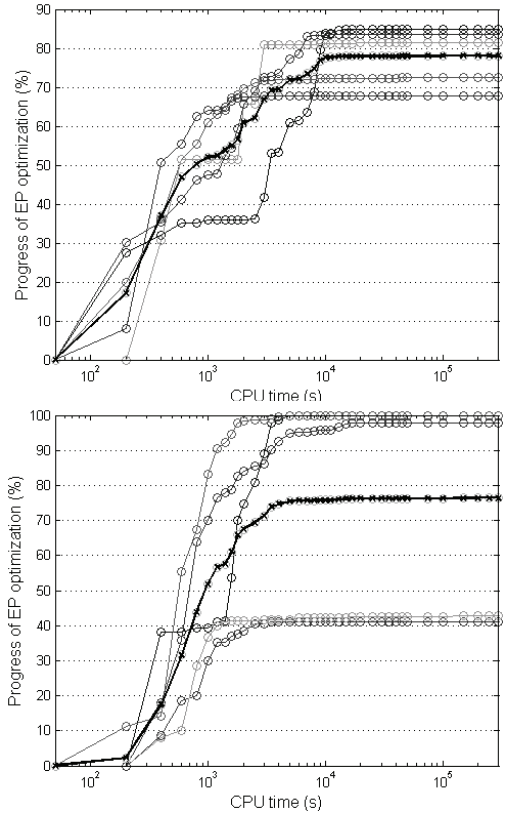


Fig. 2. EP optimization experiments for five (a) and ten (b) reactions. Line with crosses represents the mean values, lines with rings show dynamics of individual optimizations.

B. Stagnation at local optimum

PS do not stagnate at local optimums and converge successfully to the best value. In case of five and ten reaction optimization with EP the five experiments demonstrate interesting behaviour. Three of five reaction experiments optimizing five reactions with EP reach the best value while two experiments stagnate at the level of approximately 40% of the best value. None of the five experiments optimizing 10 reactions reach the best value. All of them lay within range of 67-85%. The length of optimization did not change the stagnating behaviour: no significant changes have happened within time period from 1e+04 seconds (approx. 2.7 hours) until 5e+05 seconds (approx. 5.8 days) of CPU time.

C. Dynamics of standard deviation

Standard deviations of PS curves are close to zero latest 10,000 seconds of CPU time from the start or earlier. In case of EP there are no significant changes of standard deviation starting from 10,000 seconds of CPU time except of small changes in case of optimization of 15 reactions.

IV. 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.

While there were no surprises regarding the behaviour of PS regarding the fact of convergence to the best value and reduction of standard error during optimization it is interesting that convergence speed is similar in case of one, five, ten and fifteen reactions in spite of tremendous increase of the solution space from one to fifteen dimensions. Still, it is unclear how the steady state precondition has reduced the solution space.

The performance of EP seems to be very promising and better than PS if one starts the comparison from optimizing one reaction which is the only case where EP performs slightly better than PS. The rest of experiments with five, ten and fifteen reactions state that it would be wrong to decide that EP is a generally better optimization method and one should prefer it to PS. In case of single reaction optimization based preference of EP a number of wrong conclusions might be made:

- in case of five reactions the 85% of best value would be detected as 100%, thus, giving misleading impression about the optimization potential,

- in case of ten reactions the shape of the progress of objective function values of the curves in Fig.2b where just 40% of the best value are reached seems to be converged to the best value (100%) while in fact they do not indicate even half of the potential.

Thus, the assumption that stochastic methods reach the global optima close value in reasonable computation times [5,17] may be dangerous at least in some cases. The lack of significant progress after 10,000 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. None of performed 40 experiments demonstrated significant improvement after the first 10,000 seconds. At the same time this conclusion cannot be generalized to other methods which are not tested.

EP demonstrates interesting features regarding tendencies of the method when number of optimized reactions increase. Looking at one, five and ten reaction optimizations one can conclude that the method is not applicable to a big number of optimized reactions. The fourth group of experiments with 15 optimized reactions perform much better than in case of five and ten reactions. Thus, even that tendency cannot be generalized.

Perhaps variations of parameters of the optimization method would give better performance but it is significant effort due to combinatorial problems with values of method parameters.

Experiments also indicate that it is very critical to pay attention to the determination of the best value that might be also the global optimum. It has sense to test several methods with several optimization runs to avoid possible stagnation of the objective function value at local optimum.

V. CONCLUSION

Convergence tests of two global stochastic optimization methods performing steady state task indicate some peculiarities of convergence behaviour that should be tested more systematically to increase the reliability of this popular class of optimization methods. The assumption that stochastic global optimization methods in case of design optimization of a biochemical network reach the global optima close value in reasonable computation times [5,17] is true in most cases but exceptions are well possible. Several optimization runs with particular optimization method, model, software tool and set of optimization method parameters should be performed to find out the most appropriate method for particular optimization task. Generalization and extrapolation of optimization behaviour can cause several misleading conclusions: 1) too low best value of the objective function and 2) too long or too short estimation of optimization time needed to reach objective function value that is close to the best one.

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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