

On the Benefits of Multimodal Optimization for Metabolic Network Modeling

Marcel Kronfeld, Andreas Dräger, Moritz Aschoff, Andreas Zell

Center for Bioinformatics Tübingen
Eberhard Karls University Tübingen
Sand 14, D-72076 Tübingen, Germany

{marcel.kronfeld, andreas.draeger, moritz.aschoff, andreas.zell}@uni-tuebingen.de

Abstract: The calibration of complex models of biological systems requires numerical simulation and optimization procedures to infer undetermined parameters and fit measured data. The optimization step typically employs heuristic global optimization algorithms, but due to measurement noise and the many degrees of freedom, it is not guaranteed that the identified single optimum is also the most meaningful parameter set. Multimodal optimization allows for identifying multiple optima in parallel. We consider high-dimensional benchmark functions and a realistic metabolic network model from systems biology to compare evolutionary and swarm-based multimodal methods. We show that an extended swarm based niching algorithm is able to find a considerable set of solutions in parallel, which have significantly more explanatory power. As an outline of the information gain, the variations in the set of high-quality solutions are contrasted to a state-of-the-art global sensitivity analysis.

1 Introduction

The parameter estimation for mathematical models of biological systems is a demanding task. For complex systems of differential equations, for example, usually there is hardly any previous knowledge on the required model type and its parameterization. Often, numerical simulation and heuristic optimization of the measurement fit is the only way of inferring a parameter set that reproduces the measured data and thus the only way of judging the model's ability to represent the measurements. [Ban08]

This approach brings with it certain ambiguities due to measurement noise and system complexity, which not only means that the target function is non-convex (multimodal) but also entails the existence of distinct parameter sets fitting the data with a very similar quality. This renders the assumption that global optimization methods find the vicinity of the global optimum very quickly [BCPB⁺08, RFEB06] rather challengeable. Moreover, the local optima may be so similar that they can hardly be discriminated with respect to biological significance—a fact usually ignored in parameter estimation, where mostly artificial data and low-scale noise are used. One way of delivering more evidence on model properties and biological importance lies in model sensitivity [STCR04]. On the one hand, it is usually observed that biological systems are relatively robust towards small changes,

e.g., in concentration of substances involved in a biochemical reaction system. On the other hand, there may be single parameter changes that disturb the system significantly more than others, and if a mathematical model was able to predict these sensitivities, it would increase its biological relevance. This motivates the idea to not only search for one optimum but for a set of different high-quality solutions, to compare them and test for common dependencies and sensitivities. This can be achieved by multimodal optimization (MMO) methods [SD06], which, however, are often developed on simple benchmarks. We thus perform preliminary tests on difficult benchmarks before tackling the computationally much more expensive application. The target system, a metabolic network of the industrially important *Corynebacterium glutamicum*, has been modeled using Generalized Mass Action Kinetics (GMAK) and examined by unimodal optimization [DKZ⁺09]. In the work at hand, MMO is applied to find sets of high-quality local optima of the biochemical model. We contrast the parameter distribution of identified optima with a global sensitivity analysis to show how, thereby, possibly new biological implications can be drawn.

2 Heuristic Multimodal Optimization

Researchers often face nonlinear, non-convex problems the derivative of which is infeasible to compute. In these cases, modern stochastic metaheuristic optimization methods are an apt choice, because they have a higher chance to locate the global optimum compared to classical local search methods [Ban08]. This is mostly because, instead of only looking at a single possible solution at a time, a whole set (“population”) is processed, which converges on the global optimum with higher probability. Two particularly successful optimization techniques are biologically inspired. In Evolutionary Algorithms (EAs), candidate solutions in \mathbb{R}^n are assigned a quality measure, and better ones are selected, recombined and mutated hoping to produce better individuals from good ones. In Particle Swarm Optimization (PSO), a candidate solution $x \in \mathbb{R}^n$ (“particle”) is assigned a “velocity” vector. x is accelerated towards (i) the best position the particle itself has come across so far (p^h) and (ii) the best position in a particle neighborhood (p^n). Formally: $v_i(t+1) = \omega v_i(t) + \phi_1 r_1 (p_i^h - x_i) + \phi_2 r_2 (p_i^n - x_i)$ for all vector components i , where ω and $\phi_{1/2}$ are control parameters, while $r_{1/2} \sim U(0, 1)$ provide for randomization. A comprehensive introduction to EAs and PSO is given in [Eng02].

For multimodal optimization specifically, the population diversity is boosted to allow multiple optima to be occupied in parallel. Early methods such as *sharing*, *crowding* or *clearing* [SD06, Mah95] accomplish this by punishing similarity within the EA population. Recent approaches emphasize *niching* by explicitly forming sub-populations, e.g., using clustering in EA [SSUZ03] or sub-swarm-formation in PSO [BEvdB03]. The sub-populations are to cumulate around local optima in a self-organizing way, while a diverse main-population may keep exploring the search space. Current works often report swarm methods to be superior to other methods [BEvdB03, ÖY07], which fail especially in higher dimensions [SD06] and in lower dimensions may be outperformed by simple multi-start Hill-Climbing (HC) [SSUZ03]. As swarm-based methods showed to be more promising on the target model than traditional methods [DKZ⁺09], such as HC or Genetic Algo-

Name	Function	Domain	Parameters
$f_{M6}(\vec{x})$	$= 1 - \sin(30x_1^3)\sin(25x_2^2x_1)$	$[0, 1]^2$	
$f_{M10}(\vec{x})$	$= 1 - \frac{1}{n} \sum_{i=1}^n [1 - \sin^6(5\pi x_i)]$	$[0, 1]^n$	
$f_{SR}(\vec{x})$	$= \sum_{i=1}^n (z_i^2 - 10 \cos(2\pi z_i) + 10)$	$[-5, 5]^n$	$\vec{z} = \vec{x} - \vec{o}$ for shifted optimum \vec{o}
$f_{M13}(\vec{x})$	$= cn - \sum_{i=1}^n x_i \sin \sqrt{ x_i }$	$[-512.03, 511.97]^n$	$c = 418.9829$

Table 1: Preliminary benchmark functions.

rithms (GA), we concentrate on swarm-based niching in comparison to clustering EAs.

Typically, an MM approach introduces new parameters to the optimization procedure. The Clustering-Based Niching EA (CBNEA, [SSUZ03]) performs density-based clustering with a strategy parameter σ on the population. Since the selection drives the population towards areas of better fitness, it is expected that clusters form around local optima. Each cluster is decoupled from the main population and evolved with an Evolution Strategy (ES) or a GA to identify a local optimum. We employ CBNES with $\sigma = 0.1$ and a (μ, λ) -ES with $\frac{\mu}{\lambda} = \frac{3}{10}$, simple uniform step-size mutation ($p_m = 1$) and one-point-crossover ($p_c = 0.5$). The real-valued CBNGA only differs in the selection method, which is tournament selection on groups of four instead of elitistic ES-selection, so its selective pressure is lower.

The NichePSO algorithm [EvL07] forms niches by looking for particles having a fitness standard deviation σ below a threshold δ for k iterations. Any such particle forms a sub-swarm with its closest neighbor, and they are again decoupled from the main swarm. To allow for distributed sub-swarm formation, the neighborhood attraction is deactivated in the main swarm ($\phi_1 = 1.2$, $\phi_2 = 0$), whereas sub-swarm particles are fully connected. The inertness factor ω is linearly decreased, and sub-swarms are merged if they overlap. In [ÖY07], a maximum merge distance is introduced to avoid too large sub-swarms, a problem of the original NichePSO. ANPSO is a further extension which adaptively sets the allowed sub-swarm radius to the average of each particle's distance to its closest neighbor [BL06]. ANPSO also reintroduces neighborhood attraction for the main swarm ($\phi_2 = 0.6$) to enforce global search.

We extend the niching PSO variants by a deactivation strategy [SSUZ03]: when a sub-swarm converges, its best position is stored and the particles are reinitialized. Similar to sub-swarm creation, we deactivate a sub-swarm if all its particles have a fitness standard deviation below a threshold ϵ_{deact} for k iterations. We set $\epsilon_{deact} = \delta$ ($\delta = 10^{-4}$ in NichePSO [EvL07]). Deactivation enhances exploration and allows the algorithm to identify more optima than the initial swarm size.

Conclusively, we test the following algorithms with a population size of 200: NichePSO with standard parameters, enhanced NichePSO (*NPSO**, [EvL07]), ANPSO with standard parameters [BL06], and an ANPSO variant which employs the SPSO-strategy for the main-swarm using the adaptive swarm-size parameter defined by ANPSO (*ANPSO**). The *ANPSO** strategy parameters are set to $\phi_1 = 1.2$, $\phi_2 = 1.2$, and $\omega = 0.73$.

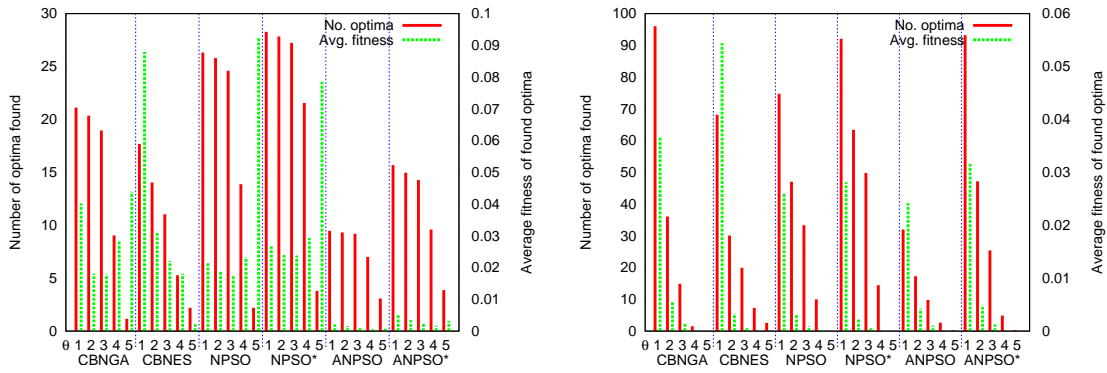


Figure 1: Number of optima identified and their average fitness for f_{M6} (left) and f_{M10} (right).

3 Preliminary Evaluation

We selected 5 diverse, multimodal functions to delineate some characteristics of the MM methods, listed in Tab. 1. f_{M6} is 2-dimensional and has 33 local optima which are unevenly spaced, whereas f_{M10} has 5^n optima of equal fitness distributed evenly; we set $n = 5$. f_{SR} (shifted Rastrigin's) has numerous local optima in a global basin of attraction. f_{M13} (Schwefel's sine root) has numerous local optima and no global basin of attraction. For the latter two we test $n \in \{10, 30\}$. All functions are treated as minimization problems with the solution at $f(\vec{x}^*) = 0$. To measure optimization performance, we look at the number of known optima found with several accuracy thresholds θ_i and the average fitness of the optima. Specifically, we compare $\theta \in \{0.05, 0.01, 0.005, 0.001, 0.0001\}$ and expect that fewer optima are found with decreasing θ corresponding to increasing accuracy.

For f_{SR} and f_{M13} we did not presume knowledge of local optima. The performance criteria for f_{SR}/f_{M13} are based on post processing: the suggested solutions are clustered and the best representative of each cluster C_i is interpreted as candidate solution c_i . Each c_i is refined using a Nelder-Mead-Simplex (NMS) local search started in the close neighborhood of c_i . In case the NMS converges without moving away by more than θ from c_i , the candidate is classified as being locally optimal. The number of solutions found in this way gives a relative measure on how well algorithms converge on a specific benchmark. Additionally, we look at the average fitness of the suggested solutions without regarding convergence state, because for difficult functions, often no close convergence is reached.

Benchmark Results: For each MMO method under consideration, we averaged the results of 25 runs à $5,000 \cdot n$ evaluations. Figures 1-2 show the number of optima found (left axis, more is better) and their average fitness (right axis, less is better), for each method and the five different thresholds. As can be seen in Fig. 1, NichePSO tends to find more optima than the CBN and ANPSO methods, but with worse fitness values. For f_{SR} the quality delivered by NichePSO is hardly acceptable.

CBN and ANPSO usually reach better fitness and higher accuracy than NichePSO, which invests equally in both good and bad optima. This, too, can be attributed to the absence of

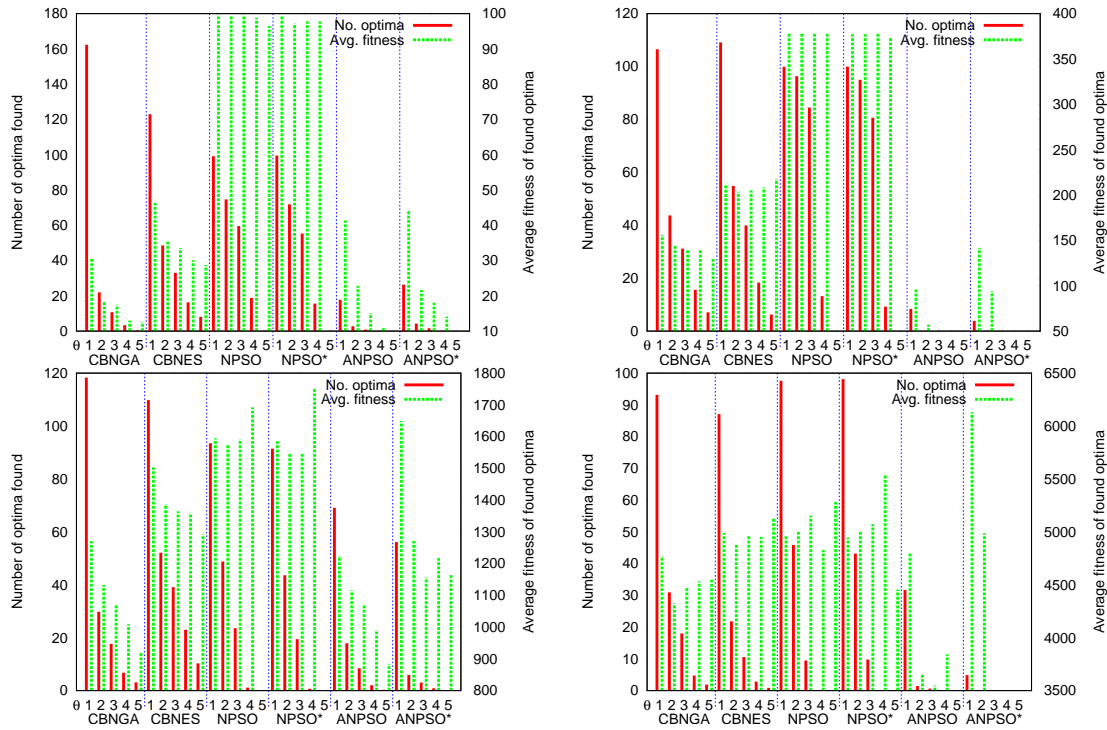


Figure 2: f_{SR} (top) and f_{M13} (bottom) in 10-D (left) and 30-D (right).

a main swarm for global search in NichePSO. To rate the statistical significance, we performed Student’s t-tests on all pairs of algorithms testing the null hypotheses that, for each benchmark and threshold, they (i) find the same number of optima and (ii) reach the same fitness quality. For a condensed comparison, we scored $+1(-1)$ for the superior (inferior) algorithm whenever that hypothesis could be significantly rejected at a 5% level. Table 2 shows the summed-up scores for the number of optima (left) and the fitness quality (right). A positive number k in line A_i and column A_j means that algorithm A_i was significantly better than algorithm A_j in k more cases than the other way around. The tests support the conclusions that the CBN variants find slightly fewer optima than NPSO with better fitness values. Also, ANPSO* finds more optima than ANPSO, whereas both find significantly fewer optima than the other algorithms with better fitness values.

For the more difficult benchmarks f_{SR} and f_{M13} , some algorithms do not find any optimum with certain accuracies θ_i , which can be seen from missing fitness bars, e.g., for ANPSO on f_{SR} -30-D and $\theta \in \{0.005, 0.001, 0.0001\}$. Yet this is not equal to bad performance when looking beyond the convergence state. For Tab. 3, the resulting populations were clustered, a cluster’s best particle interpreted as local solution, and their average number, mean and minimum fitness values are displayed. Since on $f_{SR/M13}$, CBNES was outperformed by CBNGA, and NPSO* performed very similar to NPSO, those are omitted.

The comparison indicates that, although ANPSO does not converge closely on the local optima resulting in fewer identified optima in Fig. 2, it produces good fitness values across the sub-swarms. As can be expected, NichePSO is competitive on f_{M13} , but not on f_{SR} ,

	CG	CE	NP	NP*	AP	AP*	CG	CE	NP	NP*	AP	AP*
CBNGA	0	-7	-7	-4	21	15	0	15	12	14	-11	-4
CBNES	7	0	-1	-1	26	17	-15	0	13	11	-14	-7
NPSO	7	1	0	0	18	16	-12	-13	0	-1	-17	-9
NPSO*	4	1	0	0	19	20	-14	-11	1	0	-17	-10
ANPSO	-21	-26	-18	-19	0	-2	11	14	17	17	0	10
ANPSO*	-15	-17	-16	-20	2	0	4	7	9	10	-10	0

Table 2: Significance scores regarding No. optima found (left) and fitness (right).

	Algorithm	Avg. #Opt		Avg. Mean Fit.		Avg. Min. Fit.	
		10D	30D	10D	30D	10D	30D
f_{SR}	HC-100	100.00	100.0	80.25	351.4	42.52	207.8
	CBNGA	185.60	255.7	39.60	219.2	6.12	50.2
	NPSO	100.60	101.4	100.70	380.7	23.90	187.2
	ANPSO	17.76	123.1	92.17	221.6	12.33	57.8
	ANPSO*	15.72	17.0	48.38	269.1	11.69	100.2
f_{M13}	HC-100	100.00	100.0	2082.9	7838.0	1175.7	4110.6
	CBNGA	102.36	120.4	1407.2	5926.4	569.2	3785.1
	NPSO	100.00	100.2	1614.1	4966.6	660.0	3231.8
	ANPSO	76.08	170.3	1265.4	5935.7	612.7	3081.3
	ANPSO*	40.80	51.1	1067.1	5285.4	417.0	2693.4

Table 3: Clustered results on f_{SR} and f_{M13} in 10 / 30 dimensions.

whose global basin of attraction suits the global search components of CBN and ANPSO.

4 The Metabolic Network

Figure 3 shows the reaction pathway of the valine (Val) and leucine (Leu) biosynthesis in *C. glutamicum* according to [DKZ⁺09]. The metabolic pathway starts with the formation of 2-ketoisovalerate (KIV) from pyruvate (Pyr) in three reaction steps [CFF⁺08]. At the KIV node the pathway branches: Two parallel reactions produce Val and one forms 2-isopropylmalate (2-IPM), the starting substance for the Leu production. Both Val and Leu can be used for biomass production or secreted into the culture medium—the industrially interesting outcome. Val and Leu inhibit their production rates in four feedback loops. The competition of both products for the secretory protein is modeled by inhibition: Val inhibits the secretion of Leu and vice versa. Additionally, Val inhibits reactions R_{1-3} while Leu inhibits R_7 (Tab. 4). The fast reaction $2\text{-IPM} \rightleftharpoons 3\text{-IPM}$ is assumed to process in equilibrium and combined with $3\text{-IPM} + \text{NAD}^+ \rightarrow 2\text{-I}_3\text{OS} + \text{NADH}_2$ and $(2\text{S})\text{-2-isopropyl-3-oxosuccinate (2-I}_3\text{OS)} \rightarrow 2\text{-ketoisocaproate (KIC)} + \text{CO}_2$, which only depend on the concentration of 2-IPM, introducing the symbol IPM for both derivatives.

Reaction	Parameters (fw/bw/ihb)	Reaction	Parameters (fw/bw/ihb)
R_1 $2 \text{Pyr} \rightleftharpoons \text{AcLac} + \text{CO}_2$	p_0, p_{10}, p_{18}	R_2 $\text{AcLac} + \text{NADPH}_2 \rightleftharpoons \text{DHIV} + \text{NADP}^+$	p_1, p_{11}, p_{19}
R_3 $\text{DHIV} \rightleftharpoons \text{KIV} + \text{H}_2\text{O}$	p_2, p_{12}, p_{20}	R_4 $\text{KIV} + \text{Gln} \rightleftharpoons \text{Val} + \alpha\text{KG}$	$p_3, p_{13}, -$
R_5 $\text{KIV} + \text{Ala} \rightleftharpoons \text{Val} + \text{Pyr}$	$p_4, p_{14}, -$	R_6 $\text{Val} \longrightarrow \text{Val}_{\text{ext}}$	$p_5, -, p_{21}$
R_7 $\text{KIV} + \text{AcCoA} \rightleftharpoons \text{IPM} + \text{CoA}$	p_6, p_{15}, p_{22}	R_8 $\text{IPM} + \text{NAD}^+ \rightleftharpoons \text{KIC} + \text{NADH}_2 + \text{CO}_2$	$p_7, p_{16}, -$
R_9 $\text{KIC} + \text{Gln} \rightleftharpoons \text{Leu} + \alpha\text{KG}$	$p_8, p_{17}, -$	R_{10} $\text{Leu} \longrightarrow \text{Leu}_{\text{ext}}$	$p_9, -, p_{23}$

Table 4: The reaction system. All except R_6 and R_{10} are modeled reversibly [DKZ⁺09]. We refer to Dihydroxy-isovalerate as DHIV, Acetyl-CoA as AcCoa, Acetolactate as AcLac, α -Ketoglutaric Acid as α KG; cf. Sec. 4.

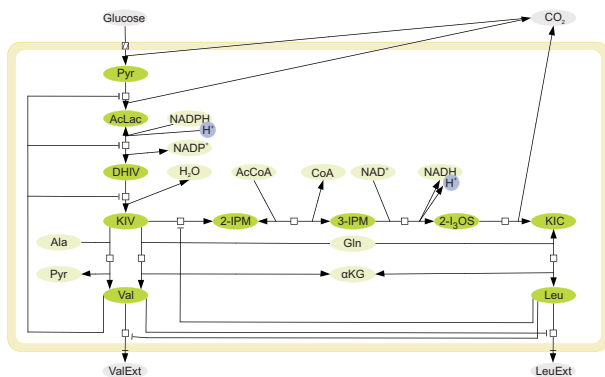


Figure 3: Val/Leu synthesis model [DKZ⁺09].

Algo-	Avg.	Best
rithm	#Opt	fit.
MSHC	0	36.13
CBNGA	2	22.88
NPSO*	3	22.68
ANPSO*	110	21.05

Figure 4: No. of interesting optima found (GMAKr model).

In an experiment by Magnus *et al.*, a glucose shock was caused after a starvation period to a *C. glutamicum* culture [MHOT06]. Over a time span of 25 s, 47 samples were taken for 13 metabolites on the pathway, which serve as target system output in the optimization. While Magnus *et al.* used LinLog kinetics, we model the system based on a reversible Generalized Mass Action Kinetics formulation (GMAKr) [DKZ⁺09]. Table 4 outlines the component reactions, of which all but R_6 and R_{10} —the secretion out of the cell—are considered to be reversible. Conclusively, there are 24 velocity (forward/backward) and inhibition factors to be optimized with respect to how well the measured data can be reproduced by the GMAK model. Due to the strong backwards coupling in the network and necessary numerical integration, the model is computationally expensive and highly nonlinear. Moreover, a noticeable ratio of possible parameters are unstable, which is why they are initialized around velocity values typically observed.

Results on the Metabolic Network: The benchmark evaluation in Sec. 3 shows that ANPSO tends to find fewer optima of higher quality compared to NPSO and CBN methods, especially for the complex 30-D f_{M13} function (Tab. 3). We therefore assume ANPSO to locate multiple high-quality solutions for *C. glutamicum*'s Val/Leu synthesis network.

We allow a number of 500 individuals for 500,000 evaluations per run with 5 runs per

algorithm. Global optimization reaches fitness values near 20 – 23, so we define a fitness threshold of $\Theta = 25$ below which solutions are said to be interesting. Tab. 4 lists the number of such solutions found in 5 runs for the multi-start hill-climber (MSHC), CBNGA and the swarm-based variants. All population-based approaches clearly outperform the hill-climber, yet only ANPSO* identifies a noticeable number of distinct optima per run. The relatively bad performance of CBNGA compared to the benchmarks is consistent with earlier results on the considered system [DKZ⁺09]. The performance difference between NichePSO and ANPSO suggests that the local solutions of the target function lie within larger areas of relatively good fitness values which can be exploited by ANPSO.

It should be noted that earlier studies reached better single fitness values using global optimization, e.g., RSE 20.334 [DKZ⁺09]. However, due to the measurement noise, the single optimal parameter set for a deterministic model will hardly be the most biologically plausible one—it might even be a “phantom optimum” resulting from numerical inaccuracies. A large set of high-quality solutions contains more information and is a basis for analyses of properties hard to handle during optimization. For example, biological systems are known to be stable: they operate within steady-states to which they return after small perturbations [HS96, pp. 40–52]. Thermodynamic validity as well as global or local sensitivity indices can also be regarded for the fitted parameter sets. An exemplary analysis follows in the next section. Compared to [DKZ⁺09], we demonstrate that a multimodal optimization approach delivers a set of high-quality solutions at a remarkably lower computational cost, since multiple high-quality solutions can be identified within single runs, while global optimizers are designed to converge on a single solution.

Parameter Distribution: Fig. 5 (a) shows the variations within a set of 21 interesting solutions found in one ANPSO* run. They are contrasted with an Extended Fourier Amplitude Sensitivity Test (EFAST) on the target function (Fig. 5 (b)). Several correlations are obvious: some parameters of low sensitivity, such as p_5 and p_{11} , vary over several orders of magnitude in the set of optimized solutions, while others with a very high total effect such as p_3 , p_8 , and p_{13} receive very similar values. The sensitivity analysis implies that of parameters p_3 and p_4 , which correspond to the parallel reactions R_4 and R_5 , p_3 shows much higher sensitivity. The variations in the high-quality solutions are very small for p_3 and larger for p_4 , leading to the conclusion that R_4 is dominant among the two.

More interesting observations come up from variations in the optimized set that seem unexpected from the global sensitivities: While p_1 and p_{15} have a very similar total effect, p_1 has a considerably larger variance in the optimized set. This indicates that reaction R_7 , of which p_{15} is the backwards velocity parameter, is as important as expected from the global sensitivity analysis, while R_2 at the entrance of the production cycle is less sensitive for biologically relevant parameters. Yet comparing p_4 and p_5 , both of which exhibit very low global sensitivity, depicts that p_5 varies over a much larger scale than p_4 in the optimized set. This indicates that R_5 , of which p_4 is the forward velocity, is of more relative importance than R_6 . Looking back at Tab. 4 and Fig. 3 this turns out to be plausible, as R_5 consumes the central KIV which is a key substance at the crossing of the network, while R_6 —and with it p_5 —“only” affects the transport of Val out of the cell, having no recurrent effects on the system.

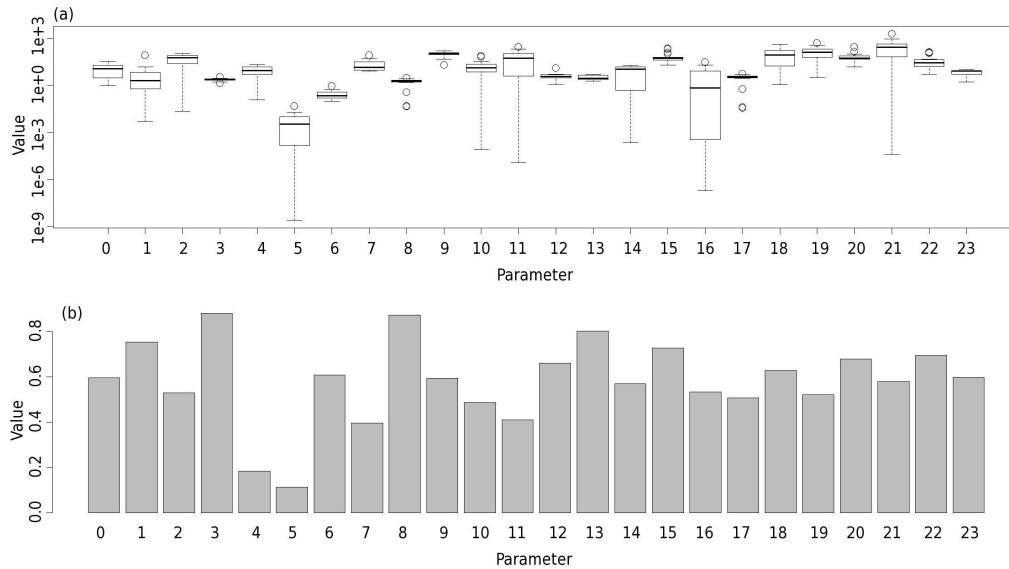


Figure 5: Parameter value distribution (a) and sensitivity total effect per parameter (b).

5 Conclusion

Multimodal optimization techniques aim at finding several local optima of an unknown target function in parallel. As they are usually developed on low-dimensional benchmarks, we looked at a set of current methods and benchmarked them on high-dimensional functions, finding that clustering EA approaches as well as the adaptive swarm-based approach ANPSO are able to find multiple solutions with sensible fitness values, where an adapted version, ANPSO*, was especially successful on the most complex benchmark function. The standard NichePSO approach lacks a globally searching main swarm and is mostly unable to compete on functions with many local optima on large-scale basins of attraction. The subsequent application on a GMAK model of a metabolic network representing the Leu/Val-synthesis of *C. glutamicum* showed that ANPSO* finds a considerable number of distinct high-quality solutions in parallel, while CBN and NichePSO widely fail. This can be attributed to the rather exploitative nature of ANPSO. Since default GA and ES strategies showed to be inferior to swarm-methods on the GMAK model earlier [DKZ⁺09], the success of ANPSO over the CBNEA variants is consistent. The analysis of parameter variations of a set of local optima compared to a global sensitivity analysis allowed several interesting interpretations which indicate that multimodal optimization can be a useful tool for assessing the results of heuristic parameter estimation in systems biology.

References

- [Ban08] J. R. Banga. Optimization in computational systems biology. *BMC Systems Biology*, 2:47, May 2008.

- [BCPB⁺08] E. Balsa-Canto, M. Peifer, J. R. Banga, J. Timmer, and C. Fleck. Hybrid optimization method with general switching strategy for parameter estimation. *BMC Systems Biology*, 2:26, Mar. 2008.
- [BEvdB03] R. Brits, A.P. Engelbrecht, and F. van den Bergh. Scalability of Niche PSO. In *The IEEE Swarm Intelligence Symp. SIS '03. Proc. of*, pp. 228 – 234, 2003.
- [BL06] S. Bird and X. Li. Adaptively choosing niching parameters in a PSO. In *GECCO '06: Proc. of the 8th annual conf. on Genetic and evolutionary computation*, pp. 3–10, New York, NY, USA, 2006. ACM.
- [CFF⁺08] R. Caspi, H. Foerster, C. A. Fulcher, P. Kaipa, M. Krummenacker, M. Latendresse, S. Paley, S. Y. Rhee, A. G. Shearer, C. Tissier, T. C. Walk, P. Zhang, and P. D. Karp. The MetaCyc Database of metabolic pathways and enzymes and the BioCyc collection of Pathway/Genome Databases. *Nucleic Acids Research*, 36(Database issue):D623–D631, Jan. 2008.
- [DKZ⁺09] A. Dräger, M. Kronfeld, M. J. Ziller, J. Supper, H. Planatscher, J. B. Magnus, M. Oldiges, O. Kohlbacher, and A. Zell. Modeling metabolic networks in *C. glutamicum*: a comparison of rate laws in combination with various parameter optimization strategies. *BMC Systems Biology*, 3:5, Jan. 2009.
- [Eng02] A. Engelbrecht. *Computational Intelligence: An Introduction*. Halsted, New York, NY, USA, 2002.
- [EvL07] A. Engelbrecht and N. H. van Loggerenberg. Enhancing the NichePSO. In D. Srinivasan and L. Wang, eds., *2007 IEEE Cong. on Evolutionary Comp.*, pp. 2297–2302, Singapore, 2007. IEEE Computational Intelligence Society, IEEE Press.
- [HS96] R. Heinrich and S. Schuster. *The Regulation of Cellular Systems*. Chapman and Hall, New York, NY, 1996.
- [Mah95] S. W. Mahfoud. *Niching Methods for Genetic Algorithms*. PhD thesis, University of Illinois at Urbana-Champaign, Champaign, IL, USA, 1995.
- [MHOT06] J. B. Magnus, D. Hollwedel, M. Oldiges, and R. Takors. Monitoring and Modeling of the Reaction Dynamics in the Valine/Leucine Synthesis Pathway in *Corynebacterium glutamicum*. *Biotech. Progress*, 22:1071–1083, 2006.
- [ÖY07] E. Özcan and M. Yilmaz. Particle Swarms for Multimodal Optimization. In *ICAN-NGA: Int. Conf. on Adaptive and Natural Computing Algorithms*, pp. 366–375, 2007.
- [RFEB06] M. Rodriguez-Fernandez, J. A. Egea, J. R. Banga. Novel metaheuristic for parameter estimation in nonlinear dynamic biological systems. *BMC Bioinf.*, 7:483, Nov. 2006.
- [SD06] G. Singh and K. Deb. Comparison of multi-modal optimization algorithms based on evolutionary algorithms. In *GECCO '06: Proc. of the 8th annual conf. on Genetic and evolutionary computation*, pp. 1305–1312, New York, NY, USA, 2006. ACM.
- [SSUZ03] F. Streichert, G. Stein, H. Ulmer, and A. Zell. A Clustering Based Niching EA for Multimodal Search Spaces. In *Proc. of Evolution Artificielle (LNCS 2935)*, pp. 293–304. Springer, 2003.
- [STCR04] A. Saltelli, S. Tarantola, F. Campolongo, and M. Ratto. *Sensitivity Analysis in Practice: A Guide to Assessing Scientific Models*. Halsted, New York, NY, USA, 2004.