DATA SHEET

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Remarks:
SENSITIVITIES FOR FREE: CMA-ES BASED SENSITIVITY ANALYSIS

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We present a novel method for parameter sensitivity identification based on the Covariance Matrix Adaptation Evolutionary Strategy (CMA-ES) optimization procedure [1]. Our method directly uses the information that is acquired during an optimization process to provide local and global parameter sensitivity estimates with no additional evaluations of the cost function. To demonstrate the performance of the method, we consider a complex example from cell biology, namely a TCR-activated signal transduction network. For this network, different global sensitivity indices are known [2].

The CMA-ES is a powerful evolutionary algorithm for non-linear, non-convex optimization problems. It has successfully been applied in a variety of domains ranging from lens design in optics [3] over computation of Nash equilibria in economics [4] to design of cancer chemotherapies [5]. Moreover, the CMA-ES has demonstrated unique performance in robust parameter estimation for biochemical network models [6].

The CMA-ES comprises a local sampling with a multivariate normal distribution to form the new generation of sampling points. The covariance matrix of the sample distribution is hereby continuously adapted in order to bias the search toward the most likely direction of the global optimum [7]. For each generation, this allows us to estimate a local sensitivity measure, centered around the mean position of the particles at that generation. Our estimator uses the classical coefficient of determination, corresponding to a good measure for a local linearization of the objective function. In order to reconstruct a rank-based measure for first order sensitivity indices we compute a weighted average of the local sensitivities along the CMA search path. The weights are determined by an importance sampling of the local indices. In each generation of the optimizer, the common weight of the sampling points is given by the determinant of the current CMA covariance matrix.

The proposed novel sensitivity measure hence reads:

$$S_j = \sum_{g=1}^{g_n} \text{det}(C_g) \text{corr}(F(x_1^g, \ldots, x_p^g), x_j^g)^2$$

with:

- \(g\) Index of the generation
- \(n_g\) Number of generation during the search
- \(C_g\) Covariance matrix of the gth generation
- \(p\) Dimension of the parameter space
- \(S_j\) First order rank-based sensitivity index for parameter \(j\)
- \(\{x_1^g, \ldots, x_p^g\}\) Sampling points of generation \(g\)
- \(F(\cdot)\) Objective function

As a benchmark problem, we study a TCR-activated Erk-MAPK signal transduction pathway in biological cells. The pathway model consists of a set of 24 ordinary differential equations with 49 free parameters. After estimating the model parameters with a genetic algorithm, Zhang and Rundell [2] derived parameter sensitivities using a variety of methods, including Sobol’s method and Extended FAST [8], using 200 000 sample points. In order to test our parameter sensitivity scheme we evaluate a total of 70 000 sample points. This is done in three independent CMA-ES runs. The first run uses the optimal parameter set proposed in Ref. [2] as a starting point and includes 30 000 sampling points. The other two runs start at two different random points in parameter space, running over 20 000 samples each. These two runs are conducted with non-adaptive scaling of the covariance matrix, in order to improve the global sampling. The global parameter sensitivity indices of each run are normalized and summed up to give the overall global parameter sensitivity indices as shown in Fig. 1. Given the reduced sample size our results are in good agreement (correlation coefficient 0.69) with the Extended FAST total effect indices (Fig. 2), which are considered the benchmark sensitivity measure. In addition, our CMA-ES optimization has found a new set of model parameters that significantly improve the model quality.
Figure 1: Parameter sensitivity ranks derived from the CMA-based sensitivity analysis given a total of 70,000 sample points.

Figure 2: Parameter sensitivity ranks derived from Extended FAST total effect indices given a total of 200,000 sample points. The indices have been taken from [2].

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References


