

# Robust Parameter Identification with Adaptive Sparse Grid-based Optimization for Nonlinear Systems Biology Models

Maia M. Donahue, Gregory T. Buzzard, and Ann E. Rundell

**Abstract**—A major limiting step in the creation of systems biology models is the determination of appropriate parameter values that fit available experimental data. Parameter identification is hindered by the experimental difficulties in examining biological systems and the growing size and complexity of nonlinear models. In addition, the majority of systems biology models are ‘sloppy,’ allowing many parameter sets to fit the data. Typically, these sets are only distinguished by their quantitative fit, with the goal to minimize the least square error between simulation and data. Instead of this single-minded focus on error, parameter sets can also be distinguished by the model’s relative robustness to parameter changes with that set. Robustness of a model in general has been explored, but choosing model parameters based on relative robustness is fairly new. This choice is reasonable both from the biological perspective, in that a system would be more resistant to mutations with robust parameters, and from the modeling prospective, in that robust parameters could allow easier re-fitting of the model to new data. A sparse grid-based parameter identification method has been recently developed for nonlinear models with large uncertain parameter spaces. Sparse grid parameter identification has the added benefit of storing information about the entire global parameter space, unlike commonly used stochastic methods and most deterministic algorithms. This information can be exploited for a robustness analysis that requires no additional model simulations or manipulation of the model equations. Herein, sparse grid-based identification is extended to include a novel parameter robustness analysis method that can be applied to any type of quantitative model.

## I. INTRODUCTION

INCREASINGLY, mathematical models are being used to provide insight into cellular processes [1]. However, the determination of appropriate parameter values presents a significant challenge to the creation of models [2]. Systems biology models are becoming larger and more complex, often requiring tens to hundreds of parameters. Very few of these have values that have been experimentally determined, due to the difficulty of measuring such information as kinetic rates and binding and diffusion constants [3]. An additional difficulty is that the majority of biological models are ‘sloppy’: they have parameters with orders of magnitude different sensitivities and high parameter correlations [4]. As

a result, many different sets of parameter values are capable of replicating experimental data.

Parameter values are most typically determined through search: either locally from an initial guess or globally over the possible parameter space using stochastic (such as the genetic algorithm) or deterministic (convex) methods. All of these methods can suffer from local minimum trap, poor convergence rates, and high computational cost [5]. The intent of searching is purely to find values that allow the model to acceptably fit the experimental data; while finding the globally optimum parameter set is typically the goal, this is difficult to achieve and does not guarantee that the found parameter values represent the true values of the biological system. In addition, these searches typically examine only a very small part of the parameter space.

As discussed by Gutenkunst et al, the actual parameter values of a model are far less important than the ability to replicate behavior [4]. Therefore, the model’s behavior should be as independent as possible from the parameter values. Physiologically, a robust biological system would be more resilient to perturbations and may be less likely to depend on certain parameters to maintain their exact values in order to achieve the desired cellular behavior. From a modeling point of view, fitting robust parameters would make the model easier to fit to new data, as required changes to parameter values would be less likely to damage the fit to the old data sets. In the context of control, the parameters to be optimized are the control inputs and it is desirable that the inputs be designed such that small errors in implementation would not result in large output errors. Therefore, a more valuable approach would consider not only the predicted performance at parameter values, but also the robustness of that performance to perturbations.

Recently sparse grid interpolation approaches have been developed that support deterministic global optimization for the minimization of functions with bounded mixed derivatives [6]. These methods are currently being refined for efficiently solving large dimension problems, more than 10 uncertain parameters [7]. Sparse grid-based approaches represent an opportunity to combine, without additional computation, parameter identification and robustness.

This paper is organized in two main parts. In the background section, adaptive sparse grid-based optimization, is applied to identify model parameters and its performance is compared with a global, stochastic optimization method are described. In the second part, the parameter robustness concepts and the methods of determining relative robustness are introduced and demonstrated with examples using both

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M. D. Donahue is with the Weldon School of Biomedical Engineering, Purdue University, West Lafayette, IN 47906

G. T. Buzzard is with the Mathematics department, Purdue University, West Lafayette, IN USA.

A. E. Rundell is with the Weldon School of Biomedical Engineering, Purdue University, West Lafayette, IN 47906 USA; e-mail: rundell@purdue.edu.

three and 18 unknown model parameters.

## II. BACKGROUND

### A. Adaptive sparse grid-based optimization

Sparse grid interpolation builds a grid of support nodes in a patterned manner in the parameter space and evaluates the model at each point. An error-controlled interpolated function is created by combining basis functions at the support nodes to approximate the cost function evaluated over the entire parameter space. It has been shown that the error of the interpolating function strongly depends upon the degree of the bounded mixed derivative (smoothness) and is a weak function of the dimension of the problem,  $O(N^{-k}(\log N)^{(k+1)(d-1)})$ , where  $N$  is the number of function

evaluations performed on the sparse grid at the support nodes,  $k$  is the interpolation depth, and  $d$  is the dimension of the parameter space [8]. Hence these methods are considered nearly optimal (up to a logarithmic factor) [8] and are significantly better than those of quasi-Monte Carlo algorithms,  $O(N^{-1}(\log N)^d)$  [9]. A uniform sparse grid cannot

avoid a logarithmic dependence of the error on dimension; however, adaptive sparse grids sample most along the dimension of greatest importance as ascertained by the ability of samples in that direction to decrease the estimated interpolation error (Fig. 1) [9]. This “problem-adjusted refinement” [10] most effectively reduces the computational costs for the optimization on models whose roughness is confined to a subset of the dimensions of the uncertain space and it does no worse than the uniform sparse grid methods.

The search for acceptable parameter values is performed on the interpolated function. Typically, a search along a polynomial-based interpolation function is significantly faster than a search involving repeated numerical integrations of a model, see Fig 2.

### B. The Mitogen-Activated Protein Kinase cascade

The mitogen-activated protein kinase (MAPK) cascade is a serine/threonine phosphorylation cascade that is highly conserved in eukaryotic cells and has been considered an exemplar system for systems biology studies [12, 13]. The cascade transduces signals from the cell surface to the nucleus and therefore plays a key role in regulating cellular behavior. Therefore, it was determined that the MAPK cascade is a good example for demonstrating the adaptive sparse grid optimization algorithm.

For this work, it was important to use a model that could exactly replicate an example data set so that model structure errors could be neglected. The most straightforward approach is to take a published model and create a mock data set by simulating the model. The Wolkenhauer et al model [14] was chosen because the equations were available, the states displayed interesting dynamics, and it was not so large as to make computational time a factor in creating examples. The model consists of four nonlinear

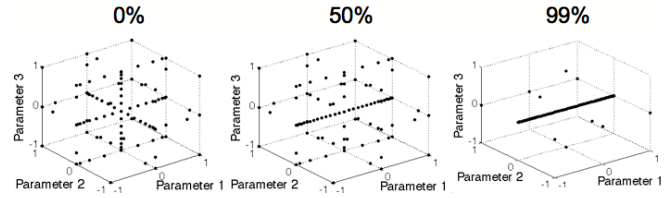


Fig. 1. Examples of three-dimensional adaptive Chebyshev sparse grids, with increasing degree of adaptivity from left to right, generated with the Sparse Grid toolbox [11]. This figure demonstrates that the parameter along the x-axis is more important to decreasing interpolation error than the parameters along the y-axis or z-axis.

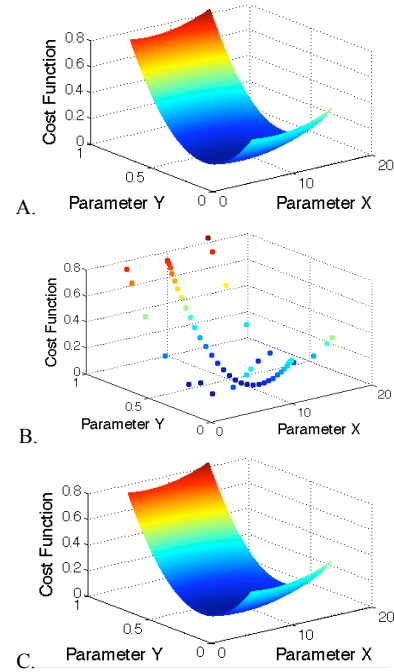


Fig. 2. Comparison of meshes created by actual cost function evaluations and from an interpolated cost function for a two-parameter search of a polynomial  $f(x, y) = 2(y - 0.4)^2 + .002(x - 7.5)^2$ . A. This mapping of the cost function was created from a 500x500 evenly spaced grid of parameter sets, for a total of 250000 function evaluations. B. The 53 adaptive sparse support nodes used to create the interpolated function, generated by the Sparse Grid Toolbox [11]. C. An evenly spaced 500x500 grid of parameter sets was created and evaluated by the interpolated function, creating an identical mapping to A that only required the 53 model evaluations used to create the support nodes. Local searches starting from the lowest cost function point from either full grid were able to find the optimal parameters (0.4, 7.5). As can be seen, if evaluating the function required numerical integration, the use of sparse grid interpolation would save significant computational time.

ordinary differential equation (ODEs) and 18 parameters. For these examples, mock experimental data was generated by simulating the model with the published (nominal) parameter values. The mock data consisted of seven, error-free, time points of the simulations for two of the four states (phosphorylated MAPK and MAPKK) and the examples utilize either just the MAPK data set or both data sets.

### C. Parameter Identification

The main goal in most modeling projects is to identify parameter values, which can be a difficult problem in the case of large, nonlinear models. Therefore, the ability of adaptive sparse grid interpolation to optimize model

parameters was demonstrated with the chosen MAPK model. The adaptive sparse grid optimization performance was compared to the performance of a standard stochastic optimization method, the genetic algorithm (GA), with an increasing number of model evaluations. The general optimization process is described below, followed by sections providing implementation details for the adaptive sparse grid and GA algorithms, respectively.

The fit of parameter points to this mock data set was calculated using the least square error formula:

$$F(p) = \log\left(\sum_{j=1}^q \sum_{i=1}^{n_j} [y_j(p, t_i) - \hat{y}_{j,i}]^2\right), \quad (1)$$

where  $q$  is the number of states with experimental data,  $n_j$  is the number of experimental time points for state  $j$ ,  $\hat{y}_{j,i}$  is the data for state  $j$  at time  $i$ ,  $y_j(p, t_i)$  is the simulated model output for state  $j$  at time  $i$  for parameter set  $p$ . The goal of optimization was to find the parameter set,  $p$ , in the 18-dimensional parameter space, that minimized the value of the cost function,  $F(p)$ , with both MAPK and MAPKK data included. The sparse grid method, due to symmetry, automatically evaluates the center point of the parameter space. Therefore, in order to avoid biasing the sparse grid towards the nominal parameter values, a new center point was created by selecting a random initialization point within an order of magnitude above and below the actual values. The parameter search range for both the sparse grid and GA was assigned from an order of magnitude smaller than this initial point to an order of magnitude larger.

#### 1) Adaptive sparse grid-based optimization

Sparse grids in log space and interpolants were created using the Sparse Grid Toolbox for Matlab [11], (for detailed methods see [15]). Chebyshev polynomial basis functions were used with 100% adaptive grids. Local searches were performed in the parameter space on both the interpolated and actual cost function from the grid point that returned the lowest cost function.

#### 2) Genetic Algorithm

The Matlab genetic algorithm was utilized [16]. For each example, the maximum number of generations was limited in order to limit the number of model evaluations to the desired level. All other options, including a population size of 20, were kept at their defaults. The GA was run five independent times for each number of evaluations allowed (because of its stochastic nature, each outcome is different), followed by local searches from the returned point.

#### 3) Comparison of adaptive sparse grid and GA based optimization

The resulting cost function value (the least squared error or LSE) was calculated for the adaptive sparse grid-based optimization method and the GA for increasing numbers of model evaluations. The results are shown in Fig. 3. For the adaptive sparse grid method, the total number of model evaluations was the sum of the number of grid points and the

number of evaluations performed by the local searches. For the GA method, the number of model evaluations was the sum of the evaluations used by the GA and the local searches. The results of the searches were averaged and the error bars in Fig. 3 represent the standard deviations of the results. Clearly, adaptive sparse grid interpolation can be applied for parameter identification, and can outperform standard methods such as the GA. Though adaptive sparse grid-based interpolation can be successfully applied to parameter identification, the process should not end with optimized parameter values but also examine the relative robustness of the points in the parameter space. The following section discusses finding and analyzing robust parameter values.

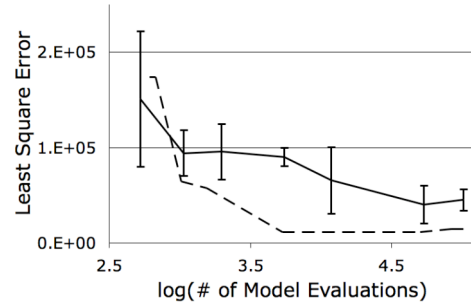


Fig. 3. For a MAPK model [14], a comparison of the performance, indicated by the least squared error (LSE) between the model simulations and the mock data set, of the adaptive sparse grid-based optimization (dotted line) and the GA (solid line). The uncertain parameter space had a dimension of 18 and both MAPK and MAPKK data was included in the cost function. The adaptive sparse grid method consistently performed better than the GA for larger numbers of model simulations. The GA results are the average of at least five runs, with the error bars representing the standard deviation of the results. For implementation details, see Background.

### III. ROBUSTNESS

Robustness is referred to in different contexts, such as the robustness of Bayesian or Boolean networks [17], the robustness of steady states (i.e. changes to bifurcation points and oscillations) due to changes in parameter values [18], and the robustness of signal aspects such as time, duration, and amplitude to changes in parameter values [19]. Typically, studies focus on the robustness of a model as a whole over the global parameter space [20]. The relative robustness of a model in different areas of the parameter space has been less examined. For instance, Chaves et al [21] mathematically described the robustness of disparate areas of the parameter space to achieve the desired steady states, but relied on a simplified version of the model and approximations to decrease the dimension of the parameter space to five.

Adaptive sparse grids present a valuable platform for examining robustness in a computationally efficient manner. During the parameter identification process, grids store information about the cost function behavior over the entire parameter space. In addition, the error-controlled interpolant provides a means to examine the parameter space without additional, and costly, model evaluations. In order to

demonstrate the calculation of robustness of parameter points using sparse grids, illustrative examples in three dimensions are given for the MAPK model [14], followed by examples utilizing the full, 18 dimensional, uncertain parameter space.

#### A. Methods

For each example, a Chebyshev grid and interpolant were created using the methods described in Background. After the creation of the grid and the interpolant, the parameter points,  $p$ , of the global parameter space,  $\Omega$ , were sorted by cost function value (Eq. 1) and a cut-off value, or threshold, was determined. The choice of threshold is dependent on the problem and the desired maximum deviation from the data points. The grid points with cost functions below the threshold make up the set of acceptable grid points,  $p_{\omega}$ , in the acceptable space,  $\omega$ , which is made up of one or more subspaces of  $\Omega$ .

The goal of the robustness analysis is to determine the amount of parameter change allowed from each point before leaving  $\omega$ . This amount of change is quantified by the minimum Euclidean distance from each point to the nearest boundary of  $\omega$ . This distance is determined by utilizing quadratic approximations when suitable (in locally convex areas of  $\omega$ ) and constrained local searches when not. Therefore, a quadratic approximation of the interpolated space was created at each  $p_{\omega}$ .

$$f(x) \approx f(p) + \nabla f(p)^T (x - p) + \frac{1}{2!} (x - a)^T \nabla^2 f(p) (x - p), \quad (2)$$

where  $\nabla$  is the gradient and  $\nabla^2$  is the Hessian matrix. For convex quadratic approximations (with all eigenvalues of the Hessian greater than zero), the eigenvectors of the Hessian provide the stiff and soft directions of the acceptable parameter space ellipsoid. The width of the space in each direction is proportional to the inverse of the corresponding eigenvalue. The distance that can be traveled in a direction is found by stepping in that direction with a step size proportional to the inverse of the eigenvalue until the threshold is reached, the crosspoint. For a parameter space of dimension  $D$ , there are  $2D$  directions that can be utilized (the eigenvectors and their opposite directions.) The number of directions chosen is a trade-off between accuracy and computational time. For these examples, the eigenvectors corresponding to the two stiffest directions were chosen, resulting in four directions from each point. For points with nonconvex approximations (where one or more of the eigenvalues were less than or equal to zero), the crosspoint is found by a constrained local search from that point. A second crosspoint is found by stepping along in the opposite direction, using a stepsize proportional to the distance to the first crosspoint. Fig. 4 demonstrates with a test function that the crosspoints lie along the contour lines of the cost function at the threshold level. The most robust point,  $p_R$ , was defined as the point farthest from any crosspoint. Therefore, for each acceptable point, the minimum distance

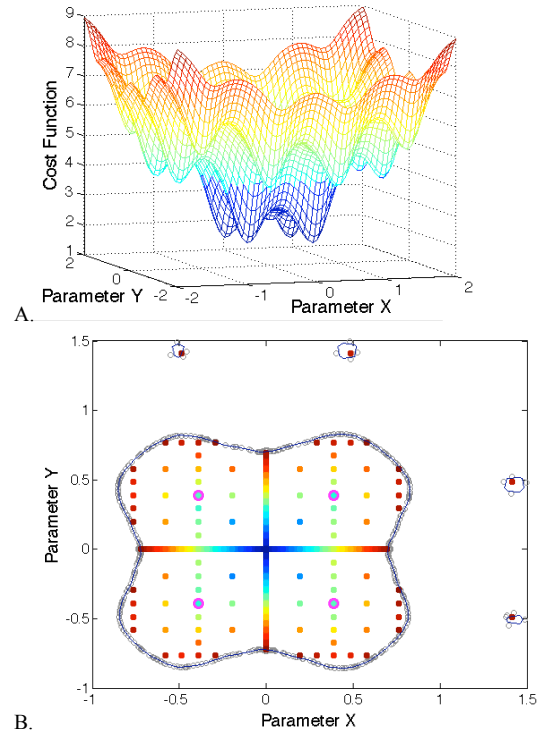


Fig. 4. An illustration of the robustness analysis in two dimensions on a test function (a modified Ackely's Path function:  $f(x, y) = -20e^{-0.2\sqrt{\frac{1}{2}(x^2 + y^2)}} - e^2 \frac{1}{2}(\cos(2\pi x - 3) + \cos(2\pi y - 3)) + 20 + e$ ) [22]. A. A mesh of the global parameter space,  $\Omega$ , showing four optimal minima surrounding one local minima with a higher cost function. B. The acceptable points (with a threshold of 4) are color-coded by robustness (blue: high, red: low). The most robust points are blue and centered at (0,0) while the four optimal points are circled in purple. The gray circles identify the crosspoints which align with the contour lines (solid blue lines) of the function at the threshold level. The circles perfectly align with the contour lines, making the blue line difficult to see for the acceptable region centered on (0,0).

was found and considered its 'robustness value' (where a higher value corresponds to a more robust point):

$$R_p = \min_i(d_{p,i}) \quad (3)$$

where  $R_p$  is the robustness of the parameter point  $p$ ,  $d_{p,i}$  is the distance to the crosspoint  $i$  from point  $p$ .

Sensitivity analyses (SA) were also performed on the model with the cost function (Eq. 1) defining the model output and the unknown parameters for both the three-dimensional and 18 dimensional cases as the inputs. Extended FAST [23] was used to estimate both the main effects attributed to each unknown parameter and the total effects which includes interactions effects between the unknown parameters. This global SA was performed over the entire global parameter space,  $\Omega$ , as well as over the local neighborhood of both the best ( $p_B$ ) and the most robust points ( $p_R$ ). (The local neighborhood was considered to be +/- 1% of the parameter values.) Local sensitivity analyses were not performed as they quantify the effects from variation in each parameter one-at-a-time and do not consider parameter interactions which are known to be significant for systems biology models that consider biochemical reactions [24].



## B. Results

### 1) Robustness in three dimensions

This example was limited to three dimensions in order to allow illustrations. Three of the model parameters were labeled ‘unknown’ (parameters 1-3) while the others were fixed at the model’s nominal values. The grid created was half an order of magnitude less to half an order of magnitude more in each direction from a randomly selected point within +/- 30% of the nominal values. The grid was created first with the MAPK data and MAPKK data considered in the cost function (Eq. 1). The threshold was arbitrarily set at 6.9 or  $\log(1E3)$ .

The grid points in  $\omega$  are shown in Fig. 5, color-coded by cost function (where dark blue are the best, or lowest cost function, points) in Fig. 5A and by robustness in Fig. 5B (where blue points are the most robust, or highest  $R_p$ ). It can be seen that the best parameter points can overlap with the most robust points. The lowest cost function point,  $p_B$  ranked 158 out of 1900 points in robustness, but the second lowest cost function point ranked 2<sup>nd</sup>.

To examine the effect of experimental data availability on the robustness analysis, the grid was recreated for the parameters with only MAPK data considered in the cost function (Eq. 1). In this case,  $p_B$  ranked 123 out of 866 points in robustness. To demonstrate the difference in robustness of  $p_B$  and  $p_R$ , five random and independent perturbations were generated with as much as +/- 10% of the nominal parameter values. These five independent perturbations were added to both  $p_B$  and  $p_R$  and in each case the model was simulated with the new parameter values, with results shown in Fig. 6A and B for  $p_B$  and  $p_R$ , respectively.

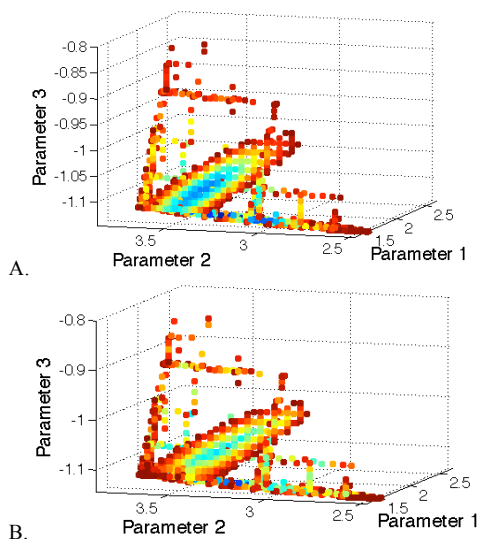


Fig. 5. Analysis of three dimensions of a MAPK model, with MAPK and MAPKK data included in the cost function. Parameters 1-3 were assumed ‘unknown.’ A Chebyshev grid was generated. The acceptable points of the grid were plotted by cost function (A), where all the acceptable points are below 6.9 or  $\log(1E3)$ , and by robustness (B), where the most robust are in blue. It can be seen in this case robust grid points can align with the grid points with the lowest cost functions. The best grid point was ranked 158 in robustness out of 1900 points, while the most robust grid point was 48<sup>th</sup> in cost function.

### 2) Robustness in 18 dimensions

For the 18-dimensional example in the case where only MAPK data was considered in the cost function (Eq. 1),  $\omega$  contained 130 grid points. The robustness analysis showed that  $p_B$  was ranked 7<sup>th</sup> in robustness. For the case where MAPKK data was also considered,  $p_B$  was ranked 2<sup>nd</sup> in robustness out of 45 points.

### 3) Sensitivity Analysis

Sensitivity analyses (using extended FAST [23]) were performed on the global parameter space and in the local neighborhoods of the best and the most robust grid points. There was no correlation between the sensitivity rankings of parameters and the allowable amount of parameter change in the directions of those parameters from  $p_B$  and  $p_R$  or the sum of the allowable parameter changes of all points in  $\omega$ . As an example, the results for the 18-dimensional case where only MAPK data is included in the cost function are shown in Table 1 (results not shown for the other examples). This is to be expected as the robustness of a parameter point combines both local and global information, as the travelable distances can vary significantly. In order to compare the sensitivities of the parameters at particular points to the travelable distances in the parameters’ directions from the points, the sensitivity analyses would have to be performed over the below-threshold area (light blue in Fig. 4) around each point. Hence the output of a traditional sensitivity analysis and this robustness analysis differ in the information they convey. In addition, the selection of a robust parameter point over the most optimal would have no effect on the parameters’ global sensitivities, as the global cost function is not affected.

TABLE 1: SENSITIVITY ANALYSIS VS ROBUSTNESS

SA	$\Omega$	pB	pR	Robust-ness	$\omega$	pB	pR
Most	15	1	7	Least	14	15	1
	1	2	10		4	14	2
	13	7	4		16	4	3
	3	10	2		3	16	4
	14	4	1		17	3	10
	18	17	13		1	6	12
	11	6	11		2	13	14
	12	13	6		10	17	16
	6	14	14		12	11	17
	8	11	17		6	1	11
	10	15	15		13	2	7
	16	12	12		15	10	6
	2	3	3		11	12	15
	7	16	16		7	5	8
	9	8	8		5	7	9
5	18	9	18	8	5		
4	9	18	9	9	18		
Least	17	5	5	Most	8	18	13

For the 18 dimensional case where only MAPK data was considered in the cost function, sensitivity analyses were performed on both the entire parameter space,  $\Omega$ , and in the local neighborhoods (+/- 1%) of the best ( $p_B$ ) and most robust ( $p_R$ ) points. The results, by parameter number, are shown in order of the model being most sensitive to least sensitive to the parameter. These results are compared to the allowable parameter changes (in both the positive and negative directions) summed over all the acceptable points,  $p_{\omega}$ , and from  $p_B$  and  $p_R$ . The highest correlation coefficient among these six vectors is 0.51, between the local neighborhood sensitivities around  $p_B$  and  $p_R$ .

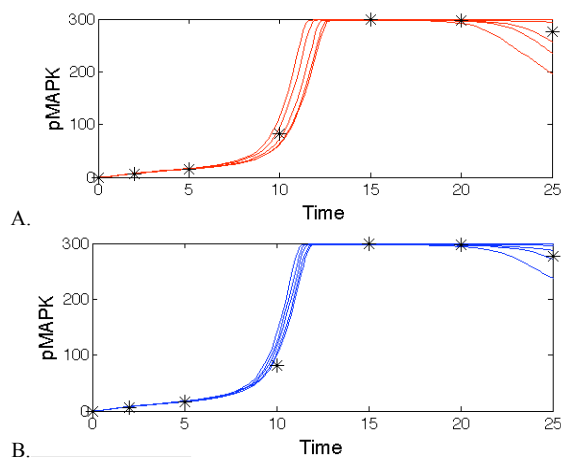


Fig. 6. Perturbation of  $p_B$  and  $p_R$  for the three-dimensional case with only MAPK data considered. A. Simulation results of five random perturbations of the best point. B. Simulation results when the robust point is subjected to the same five percentage perturbations. The mock data is shown with stars.

#### IV. CONCLUSIONS AND FUTURE WORK

Adaptive sparse grid-based optimization provides, in a computationally efficient manner, sets of parameter values that support acceptable model simulation replication of experimental data. For a MAPK model with 18 parameters [14], the sparse grid method showed a faster decrease in least squared error with increasing model evaluations than did the GA. In addition, the optimization process retains important information that describes the cost function over the entire uncertain parameter space. This information can be explored to determine, without additional model evaluations or manipulation of the model equations, the relative robustness of grid points in the acceptable parameter space. As discussed, this information should be considered when choosing parameters for models where many combinations of parameters can replicate experimental data, due to correlations and poor identifiability. The proposed process to identify the most robust parameter values resulted in ranking the parameters differently than traditional sensitivity analysis: the most robust parameter values were not necessarily the least sensitive parameter values. In summary, we purport that instead of focusing on identifying the parameter values that give the lowest cost function value possible, the focus should be on selecting parameter values such that the model output will be robust to parameter perturbations.

For the examples herein, the model was exactly identical to the “experimental” system and therefore, the nominal parameters were the correct ones. As such, it is expected that increasing the amount of available data would push the lowest cost function points toward the nominal parameter values and increase the relative robustness of the lowest cost function points, as was seen in the examples. This trend is not expected to occur where models are gross abstractions of biological systems and experimental data is noisy, as is typically the case. Currently, the most computationally costly steps in this analysis are the local searches from the points with nonconvex quadratic approximations. Therefore,

future work will focus on establishing more reliable methods for analyzing nonconvex points.

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