

The model assumes changes in arterial wall stretch are proportionate to filtered blood pressure,  $\dot{\bar{p}} = \alpha(-\bar{p} + p)$  where  $\alpha$  is a gain,  $\bar{p}$  is the filtered blood pressure, and  $p$  is the patient's measured blood pressure. From  $\bar{p}$ , we can predict the nervous

system firing rate,  $n = \sum_i n_i + N$ ,  $i = 1, 2$  where  $N$  is a baseline firing rate and  $n_i$  corresponds to the firing rate of nerve fibers of type  $i$ . The firing rates for nerves of type  $i$  are computed as:

$$\frac{dn_i}{dt} = \kappa_i \frac{d\bar{p}}{dt} \frac{n(M - n)}{(M/2)^2} - \frac{n_i}{\tau_i}, i = 1, 2 \quad (1)$$

where  $M$  is the maximum firing rate, and  $\tau_i$  is the time scale for nerves of type  $i$ . The firing rate information is compiled by the central nervous system, which then determines the sympathetic and parasympathetic outputs,  $f_{sym}$  and  $f_{par}$ , respectively. The parasympathetic output is given by  $f_{par} = n/M$ , while sympathetic output takes the form:

$$f_{sym} = \frac{1 - n(t - \tau_d)/M}{1 + \beta f_{par}} \quad (2)$$

With these outputs, we can determine the dimensionless concentrations of acetylcholine,  $c_{ach}$  and noradrenaline,  $c_{nor}$ :

$$\frac{dc_j}{dt} = \frac{f_i - c_j}{\tau_j} \quad (3)$$

where each  $\tau_j$  represents a time scale. Finally, the heart rate is calculated from  $h_0$ , the intrinsic heart rate, and  $m_{nor}$  and  $m_{ach}$ , which are weights for the contributions of acetylcholine and norepinephrine to heart rate  $h = h_0(1 + m_{nor}c_{nor} - m_{ach}c_{ach})$ .

## Results

### One Dimensional Optimization of Parameters

We minimized averaged the mean squared error per patient using the Nelder Mead algorithm as implemented in Julia package NLOpt. We forced all of the parameters to be non-negative as to be biologically correct. The original and estimated values of the parameters are shown in Table 1.

Within the estimated parameter set, the value of  $N$ , the baseline firing rate increased, and both  $k_1$  and  $\tau_1$ , representing a change in the response rate of the faster firing baroreceptors in the model. Baroreceptors are generally divided into three groups, depending on their transmission speeds (on the order of half a second, five seconds, and five hundred seconds), but this model only includes two types.<sup>2</sup> The increase in  $\tau_1$  and the decrease in  $\tau_2$  in the estimated parameter set may be the result of oversimplification.

The baseline heart rate ( $h_0$ ) decreased slightly, to 88 bpm, from the initial 100 bpm. Both  $\tau_{ach}$  and  $m_{ach}$ , which determine how acetylcholine plays into the model, decreased dramatically in the estimated parameter set, with the reduction in  $m_{ach}$  reducing the effects of a change in acetylcholine on heart rate, and the decrease in  $\tau_{ach}$  increasing the rate of acetylcholine change. The estimated parameter set reduced the averaged mean squared error to 352 from 1167. As seen in Figure 1, the estimated parameters slightly overestimate heart rate for this patient, but they perform far better than the original parameters, which severely underestimate the heart rate. This behavior is typical of the model on patients in this study.

$k_2$  and  $\beta$  were held constant as to reduce the search space, as done by Olufsen and Ottesen. Additionally, when they were allowed to vary during the optimization, the parameter set generated had very small values for  $m_{ach}$  and  $m_{nor}$ , resulting in a predicted heart rate that was basically constant at  $h_0$ . While this set of the parameters did minimize the MSE, it did not capture the intrinsic variation in heart rate.  $\alpha$ , the parameter used to smooth the pressure data was held constant at 1.5 to smooth the data with a minimal phase shift. The maximum firing rate,  $M$ , was held constant, as it only appears in this system of equations by normalizing  $n$ . The sympathetic nervous system delay,  $\tau_d$ , was held constant, owing to the propagation of discontinuities.<sup>8</sup>

### Clustering

We clustered the patients based on their age, average heart rate, and SAPS (Simplified Acute Physiology) score, a measure that estimates a patient's risk of death within an intensive care unit.<sup>9</sup> We used the patient's average SAPS since some patients had multiple admissions resulting in more than one blood pressure-heart rate track. Through the use of the Clustering Julia package, we created up to 26 clusters based on these variables, and scored each cluster with the sum of its silhouettes, where a higher score means that each member of the cluster is more similar to the other members of the clusters.<sup>10</sup> We found that grouping the patients into two clusters gave the highest score and therefore the best clustering. The sum of silhouettes as a function of number of clusters is shown in 5, and the patients by cluster in 2. Cluster 1 patients ( $n = 165$ ), shown in white, tend to have a lower average heart rate (73 BPM compared to 88 BPM), and be older than patients in cluster 2 ( $n = 108$ ) (69 years vs 59 years, on average).

## Multidimensional Optimization

We used the Julia language POETs package, which combines simulated annealing with Pareto optimality to generate families of best parameters.<sup>11</sup> Using the two clusters formed by k-means, we minimized the averaged mean squared error to create these parameter families. We utilized a monotonically decreasing cooling schedule with five iterations at each temperature. The trade off curve generated using  $\alpha = .9$  is shown in 8, and with  $\alpha = .5$  in 9. We used the parameter families from the slower cooling for further analysis. To decrease the time necessary to perform the simulated annealing, we utilized Julia's transparent parallelization capabilities. With the @parallel (+) operator, we were able to calculate patient's mean squared errors in parallel. The speed up from parallelization is shown in 6. We then selected the ten best sets of parameters from each cluster to examine the performance of the model with the new parameters. A sample patient from cluster 1 is shown in 3, and from cluster 2 in 4. The new parameter families reduced the averaged mean squared error even further than the parameters estimated using Nelder Mead-the ten best families for cluster 1 reduced the averaged mean squared error to 135 or less, and for cluster two, the averaged mean squared error was reduced to 178, or less.

Both of the families had fairly similar values for  $m_{nor}$  and  $m_{ach}$ , however, cluster 1 had a larger value of  $N$ , the resting firing rate than cluster 2. Cluster 1 contains the older patients, on average, suggesting that the resting firing rate may be age dependent. The differences in average heart rate between the clusters apparent in the clustering are apparent in the difference in  $h_0$  between the two clusters, with cluster 2 having a faster base line heart rate, at  $1.749 \pm .05$  beats per second, corresponding to  $104.95 \pm 3$  beats per minute, compared to  $74.4 \pm 4$  beats per minute for cluster 1.

## Local Sensitivity Using Finite Differences

The derivatives of all parameters were estimated using central differences.

$$\frac{dh}{d\theta_j} = \frac{h(\theta_0 + \frac{e_j}{2}) - h(\theta_0 - \frac{e_j}{2})}{\delta} \quad (4)$$

where  $\delta = 10^{-8} * \theta_j$  and  $e_j$  is a vector of length  $\delta$  in the  $j^{th}$  direction. To collapse the time dimension, we calculated overall state sensitivity coefficients.<sup>12</sup>

$$S_{0j}(t) = \frac{1}{n_s} p_j \left( \sum_{k=1}^{n_t} \sum_{i=1}^{n_s} \left[ \frac{1}{x_i} \frac{dx_i(t_k)}{dp_j} \right]^2 \right)^{1/2} \quad (5)$$

where  $n_s = 1$ , as  $h$  is the only state variable and  $n_t$  is the number of time points available for that patient. We calculated sensitivities of parameters that were optimized and not that of those held constant.

## Single Objective Sensitivity

From the original values provided by Olufsen and Ottesen, we found that  $h_0$  was the most sensitive parameter, followed by  $N$ ,  $m_{ach}$ , and  $m_{nor}$  in that order, of the parameters estimated. Of the four most sensitive equations, three of them ( $h_0$ ,  $m_{ach}$  and  $m_{nor}$ ) appear directly in the equation for heart rate, and  $N$  indirectly appears, as both  $c_{ach}$  and  $c_{nor}$  are functions of  $N$ . The four estimated parameters that were the most sensitive in our study were among the five most sensitive parameters found by Olufsen and Ottesen, as seen in 3. However,  $k_2$  showed a very high degree of sensitivity in both the original and estimated parameter set, even more so than any of the estimated parameters. It also had the highest variance in sensitivity, due to the fact that some patients exhibited a sensitivity to  $k_2$  that was an order of magnitude larger than the mean.

Between the estimated and the original parameters, the sensitivity of  $h_0$  barely changed, but  $N$  became much less sensitive in the estimated parameter set and  $m_{ach}$  increased in sensitivity. This apparent change in sensitivity originates from the method of calculation, where the sum is divided by the value of the parameter. As  $N$  increased in the estimated parameter set, dividing by this new value decreased the overall state sensitivity coefficient, while the opposite is true for  $m_{ach}$ .

## Multiobjective Sensitivity

For the multiobjective case, we used the same finite differences, but averaged them not only over the patients, but over the families of parameters-the ten best for each cluster. As with the single objective case,  $h_0$  is the most sensitive parameter, followed by  $N$ , as seen in 7 for both clusters, but  $N$  is about two times as sensitive in cluster 2 as in cluster one, whereas  $h_0$  has nearly the same sensitivity for both clusters. If one were to rank the parameters by sensitivity, the ordering of the four most sensitive parameters between the two clusters is identical, however,  $\tau_{nor}$  in cluster 2 is approximately an order of magnitude less sensitive than in cluster 1 and  $\tau_{ach}$  is nearly three orders of magnitude less sensitive in cluster 2 compared to cluster 1. Of the parameters held constant during optimization,  $k_2$  showed the highest degree of sensitivity in both clusters, which corresponds to the sensitivity found in the single objective case.

If we were to compare to the parameters estimated by Nelder Mead, we find similar sensitivities in  $h_0$  and  $N$  as well as in  $m_{ach}$  and  $m_{nor}$ . The sensitivities in all of the  $\tau$ s included in the model is much smaller in the multiobjective case than in the

single objective case. Part of this difference in sensitivity may arise from the differences in value found for these parameters by the different methods of optimization.

### Global Sensitivity

We used the Morris method of sampling to generate a family of parameter sets, ranging from  $\pm 25\%$  of the nominal parameter values, with the exception of  $h_0$ , which was bounded between  $[.8, 2.0]$ , corresponding to a resting heart rate between 48 and 120 bpm.<sup>13</sup> We found that this range of parameters resulted in physiologically acceptable heart rates. As heart rates are a function of time, it was necessary for us to collapse the time dimension to perform sensitivity analysis. We used fPCA (functional principal component analysis) to convert the heart rate curves into weights ( $\omega_i$ ) and eigenfunctions ( $\xi_i(t)$ ) so that  $h_j(t) = \sum_i \omega_i \xi_i(t)$ , and then performed sensitivity analysis on the weights generated for each patient.<sup>14</sup> We then grouped the patients by cluster, and calculated the average of  $\mu^*$ , the estimate of the mean of distribution of the absolute values of the elementary effects. For each cluster, we calculated the overall standard deviation,  $\sigma$ , by summing all of the variances and then taking the square root.<sup>7</sup> The results are shown in 10 and 11. The results are nearly identical between the two clusters, with the ranking of the six most sensitive parameters (as given by the largest values of  $\mu^*$ ) being the same in both clusters, with  $m_{nor}$  being the parameter with the largest effect on the model's output. The parameter with the largest standard deviation, indicative of it depending on other parameters in the model, was the resting heart rate.

### Discussion

We estimated three sets of parameters that can be used to predict heart rates of patients in intensive care units. The accuracy of the model was much improved when patients were grouped by their characteristics. This improvement in accuracy is likely mostly based on that the resting heart rate of the patients in clusters more accurately matched  $h_0$ , the resting heart rate in the model, since  $h_0$  was shown to be the most sensitive parameter in the model.

We discovered that one of the parameters found to be fairly insensitive in previous work,  $k_2$ , was surprisingly sensitive in this work. It was held constant during optimization as previous work pointed to it being a very insensitive parameter, but it proved to be very sensitive in all cases. Future work may involve estimating a better value for the gain on this type of baroreceptor.

The model used has several shortcomings. This model oversimplifies the process of heart rate regulation. It does not include cardiac sympathetic afferent reflex, which is sensitive to both mechanical and chemical inputs.<sup>15</sup> It can only be used for short time scales, as it does not include the slower acting renin-angiotensin-aldosterone system, which determines blood volume, and therefore blood pressure.<sup>1</sup> The model only considers two vasoactive agents when there are many more and does not attempt to capture the effects of respiration rate. Nevertheless, it does capture the dynamics of the system at short time scales.

### Methods

All calculations were carried out Ubuntu 16.04 using Julia version 0.4.5, with 7.7 GB of available RAM on a Intel Core i7-6700 CPU @ 3.40GHz. Differential equations were solved using the ODE package, with solvers ode23 and ode78, with an absolute and relative tolerance of  $10^{-8}$ . Single objective optimization was performed using the Nelder Mead algorithm, as implemented in the Julia package NLOpt, and multiobjective optimization was performed using the POETs package. FPCA calculations were carried out through the use of the Rcall package using the R package FDAPace.

Since pressure data was given in a discrete format, we linearly interpolated between values when necessary, as pressure is an input to the system of differential equations. We used the pressure data recorded at 1 Hz as well as the heart rate data at 1 Hz from the MIMIC II Waveform Database, numerics section. We extracted data from the database using rdsamp and stored it locally as text files that were then read into the model.

### References

1. Boron, W. F. & Boulpaep, E. L. *Medical physiology* (Elsevier Health Sciences, 2016).
2. Olshansky, B., Sabbah, H. N., Hauptman, P. J. & Colucci, W. S. Parasympathetic nervous system and heart failure pathophysiology and potential implications for therapy. *Circulation* **118**, 863–871 (2008).
3. Ottesen, J. T. Modelling of the baroreflex-feedback mechanism with time-delay. *Journal of mathematical biology* **36**, 41–63 (1997).
4. NEGATIVE, A. B. A. A. Reflexes that control cardiovascular function (1999).
5. Oparil, S., Zaman, M. A. & Calhoun, D. A. Pathogenesis of hypertension. *Annals of internal medicine* **139**, 761–776 (2003).

6. Olufsen, M. S. & Ottesen, J. T. A practical approach to parameter estimation applied to model predicting heart rate regulation. *Journal of mathematical biology* **67**, 39–68 (2013).
7. Saeed, M. *et al.* Multiparameter intelligent monitoring in intensive care ii (mimic-ii): a public-access intensive care unit database. *Critical care medicine* **39**, 952 (2011).
8. Baker, C. T. & Paul, C. A. Pitfalls in parameter estimation for delay differential equations. *SIAM Journal on Scientific Computing* **18**, 305–314 (1997).
9. Le Gall, J.-R., Lemeshow, S. & Saulnier, F. A new simplified acute physiology score (saps ii) based on a european/north american multicenter study. *Jama* **270**, 2957–2963 (1993).
10. Rousseeuw, P. J. Silhouettes: a graphical aid to the interpretation and validation of cluster analysis. *Journal of computational and applied mathematics* **20**, 53–65 (1987).
11. Bassen, D., Vilkhovoy, M., Minot, M., Butcher, J. T. & Varner, J. D. Jupoets: A constrained multiobjective optimization approach to estimate biochemical model ensembles in the julia programming language. *bioRxiv* 056044 (2016).
12. Stelling, J., Gilles, E. D. & Doyle, F. J. Robustness properties of circadian clock architectures. *Proceedings of the National Academy of Sciences of the United States of America* **101**, 13210–13215 (2004).
13. Morris, M. D. Factorial sampling plans for preliminary computational experiments. *Technometrics* **33**, 161–174 (1991).
14. Sumner, T., Shephard, E. & Bogle, I. A methodology for global-sensitivity analysis of time-dependent outputs in systems biology modelling. *Journal of The Royal Society Interface* **9**, 2156–2166 (2012).
15. Du, Y.-H. & Chen, A. F. A “love triangle” elicited by electrochemistry: complex interactions among cardiac sympathetic afferent, chemo-, and baroreflexes. *Journal of Applied Physiology* **102**, 9–10 (2007).

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## Author contributions statement

Must include all authors, identified by initials, for example: A.A. conceived the experiment(s), A.A. and B.A. conducted the experiment(s), C.A. and D.A. analysed the results. All authors reviewed the manuscript.

## Additional information

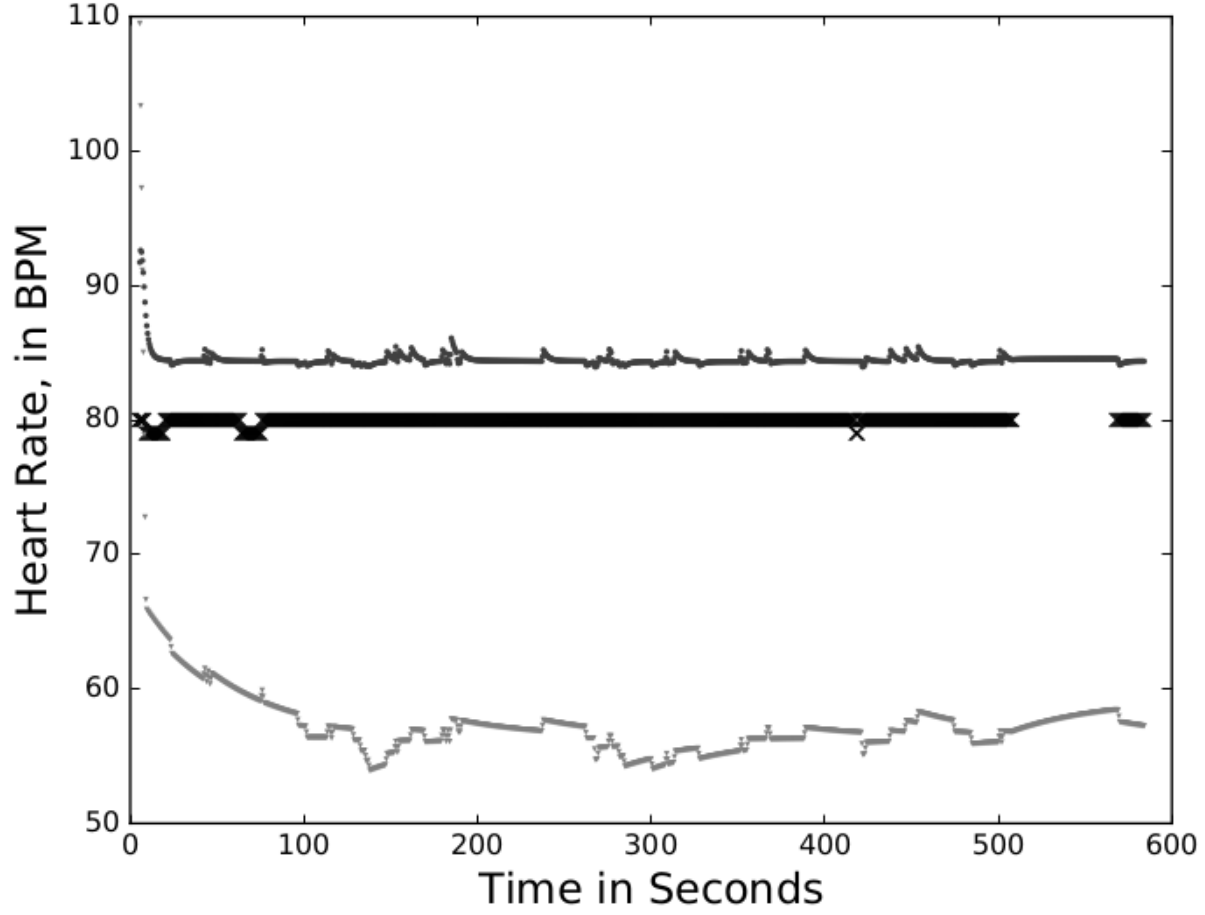
To include, in this order: **Accession codes** (where applicable); **Competing financial interests** (mandatory statement). The corresponding author is responsible for submitting a [competing financial interests statement](#) on behalf of all authors of the paper. This statement must be included in the submitted article file.

**Table 1.** Original and estimated parameter values. The bolded parameters were held constant.

Parameter	$\alpha$	$N$	$M$	$k_1$	$k_2$	$\tau_1$	$\tau_2$	$\tau_{ach}$	$\tau_{nor}$	$\beta$	$h_0$	$m_{nor}$	$m_{ach}$	$\tau_d$
Original Value	<b>1.5</b>	75	<b>120</b>	1.5	<b>0.5</b>	0.5	250	0.5	0.5	<b>6</b>	1.67	0.96	0.7	<b>7</b>
Parameter Estimations from MIMIC II Data	<b>1.5</b>	107.33	<b>120</b>	41.139	<b>0.5</b>	14.062	202.925	2.94E-05	8.156	<b>6</b>	1.474	0.165	5.20E-02	<b>7</b>

**Table 2.** Average parameter values for the 10 best sets per cluster. Data is reported as mean  $\pm$  stdev. Bolded columns were held constant.

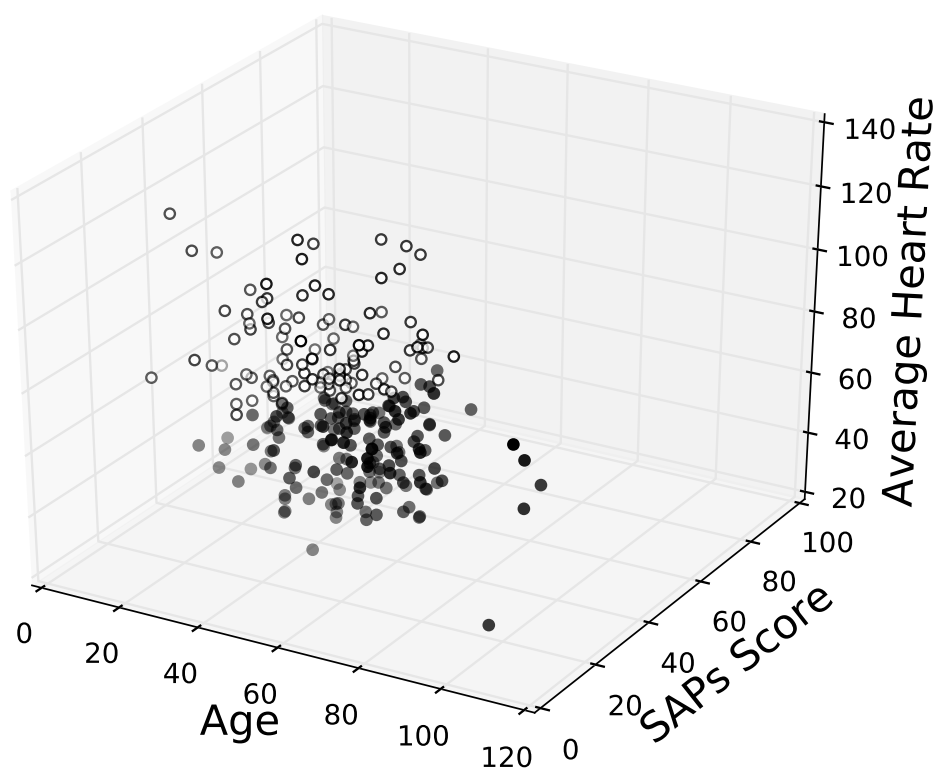
Cluster	$\alpha$	$N$	$M$	$k_1$	$k_2$	$\tau_1$	$\tau_2$	$\tau_{ach}$	$\tau_{nor}$	$\beta$	$h_0$	$m_{nor}$	$m_{ach}$	$\tau_d$
1	<b>1.5</b>	50.36 $\pm$ 9	<b>120</b>	.9566 $\pm$ .3	<b>0.5</b>	.1854 $\pm$ .13	127.31 $\pm$ 46	.5968 $\pm$ .4	.3176 $\pm$ .06	<b>6</b>	1.245 $\pm$ .006	.1816 $\pm$ .02	.0434 $\pm$ .004	<b>7</b>
2	<b>1.5</b>	37.98 $\pm$ 9	<b>120</b>	1.379 $\pm$ .7	<b>0.5</b>	.3621 $\pm$ .11	82.88 $\pm$ 33	.1410 $\pm$ .06	.1688 $\pm$ .04	<b>6</b>	1.749 $\pm$ .05	.1609 $\pm$ .02	.0962 $\pm$ .06	<b>7</b>



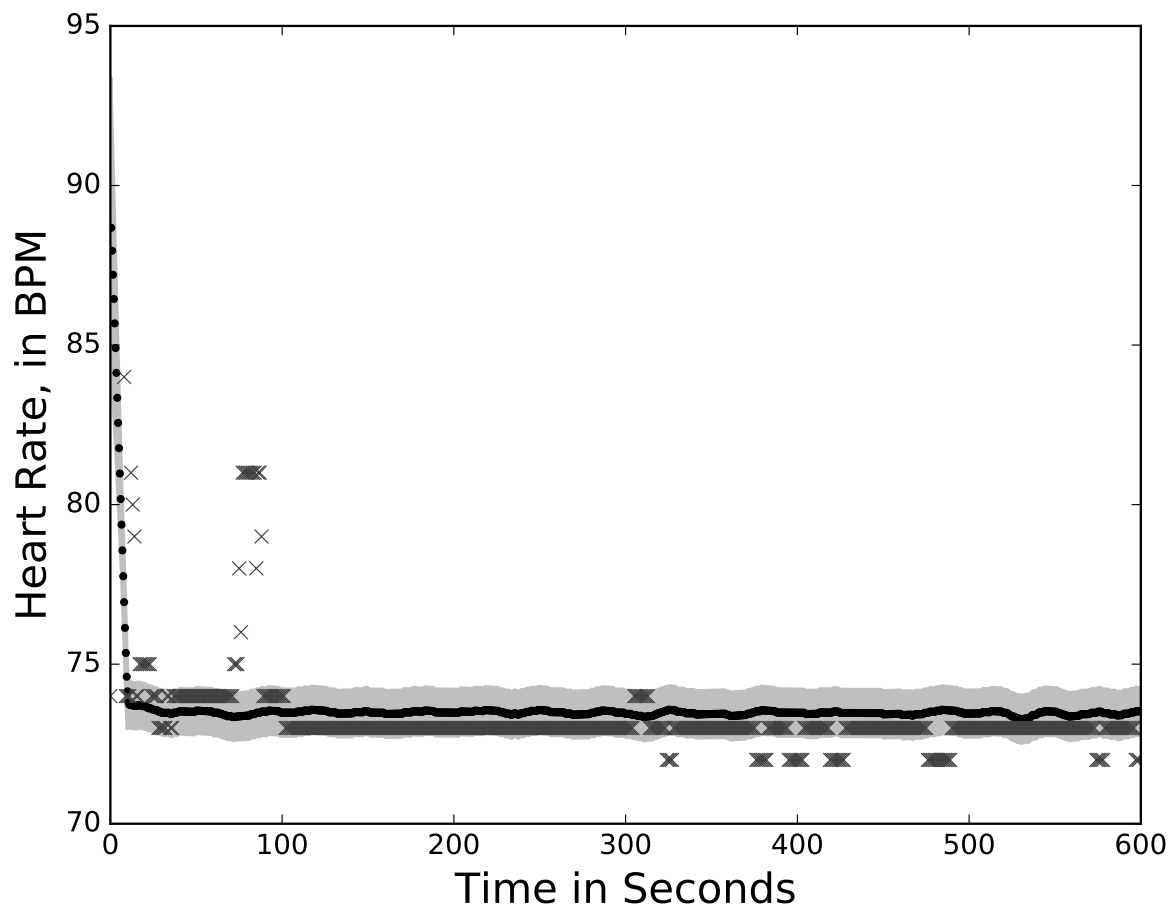
**Figure 1.** The black xs are the measured heart rate, the dark gray is the model prediction using the original parameters and the light gray is the model prediction using the original parameters.

**Table 3.** Average Overall State Sensitivity Coefficients For Single Objective Case

Parameter set	$S_{\alpha}$	$S_N$	$S_M$	$S_{k_1}$	$S_{k_2}$	$S_{\tau_1}$	$S_{\tau_2}$	$S_{\tau_{ach}}$	$S_{\tau_{por}}$	$S_{\beta}$	$S_{h_0}$	$S_{m_{ach}}$	$S_{m_{mor}}$	$S_{\tau_d}$
original parameters	$3.99 \pm 2$	$15.26 \pm 4$	$.0069 \pm .002$	$.0792 \pm .04$	$142.61 \pm 30$	$.0739 \pm .04$	$.0156 \pm .004$	$.0540 \pm .013$	$0.00055 \pm 4E-4$	$.113 \pm .13$	$19.9 \pm 6$	$.574 \pm .7$	$14.6 \pm 4$	$.085 \pm .09$
estimated parameters	$78 \pm 250$	$2.24 \pm 5$	$.329 \pm .6$	$.89 \pm 3$	$86 \pm 400$	$1.20 \pm 4$	$.61 \pm 3$	$0.52 \pm 2$	$4.34 \pm 1.9$	$.52 \pm 5$	$20.1 \pm 6$	$6.79 \pm 2$	$.83 \pm 1.9$	$4.13E-7 \pm 3E-6$

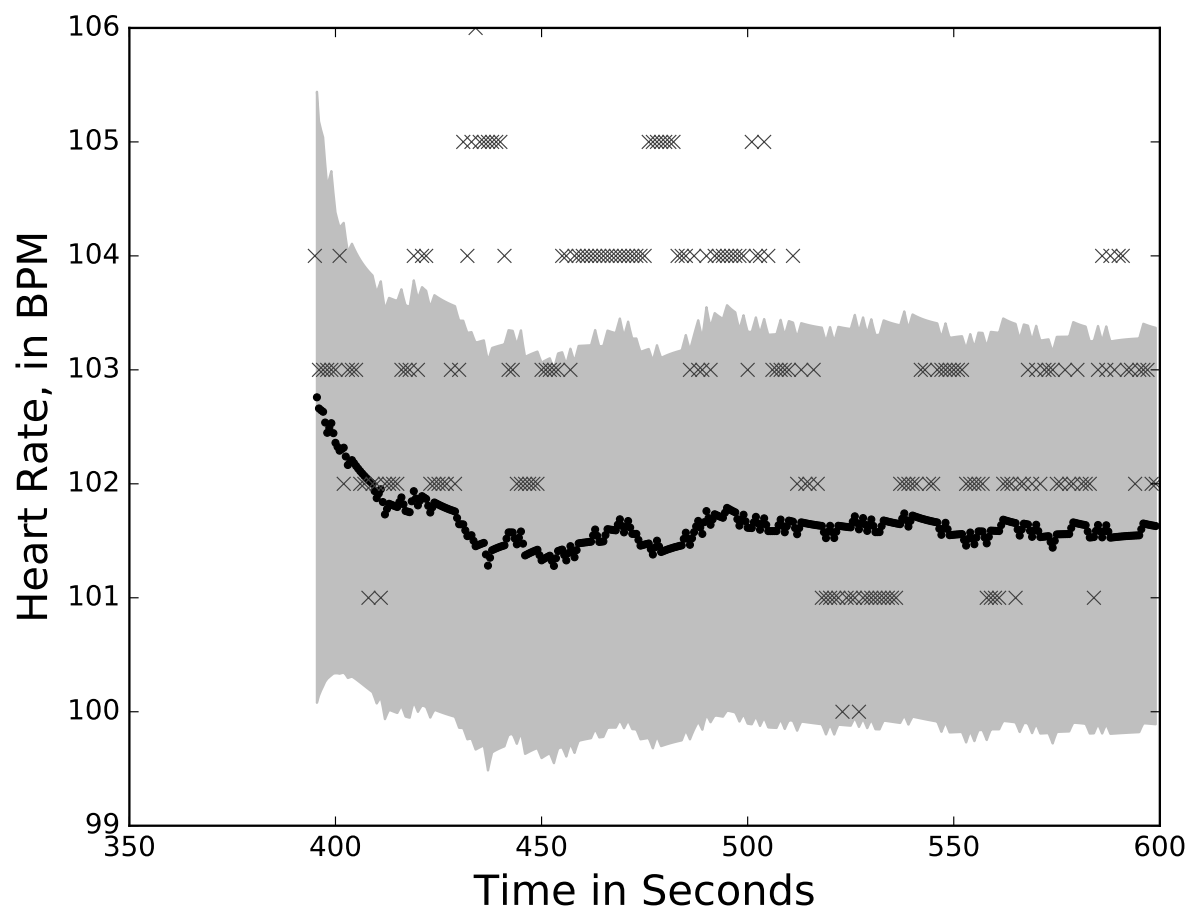


**Figure 2.** The patients, clustered into two groups.

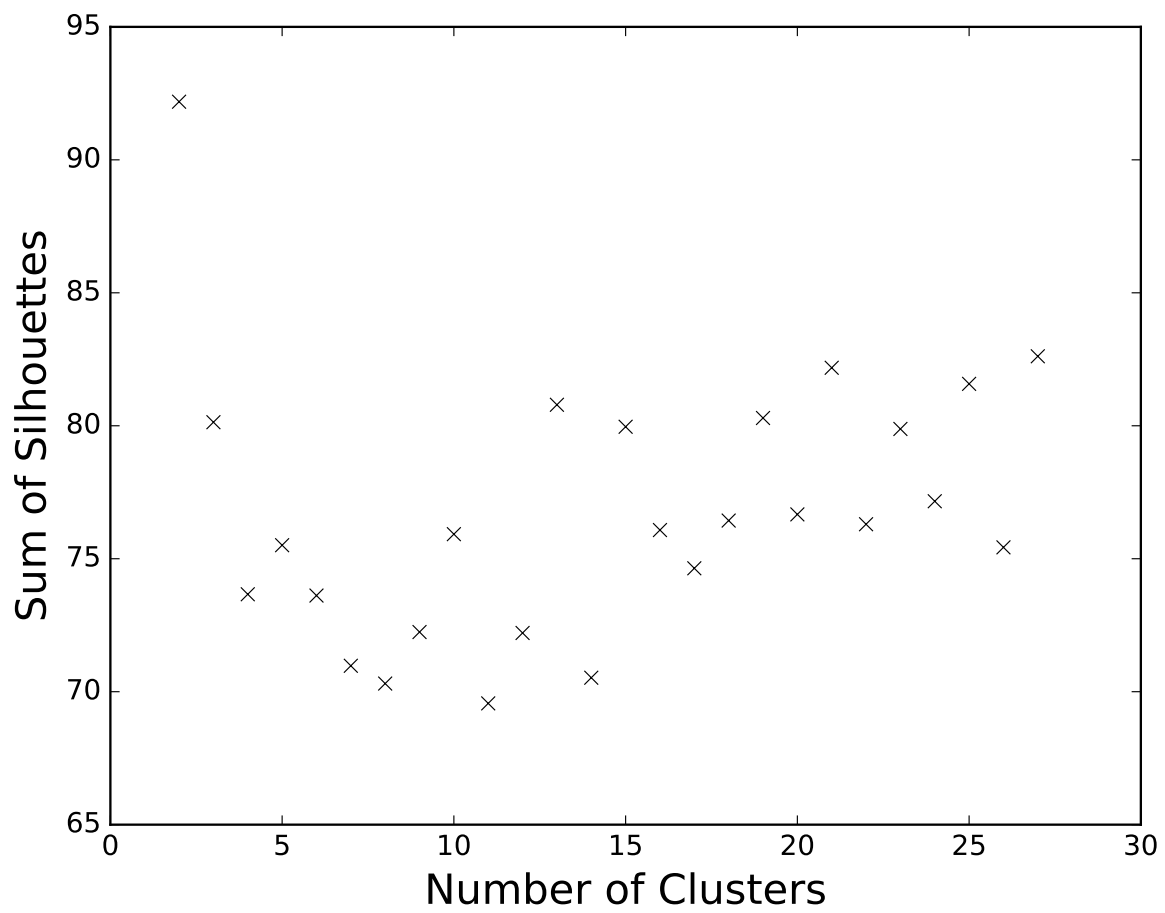


**Figure 3.** Performance of the model on a patient in cluster 1. The x represent the true heart rate, the black dots are the mean model prediction from the family of best parameter sets, and the grey gives a 95% confidence interval.

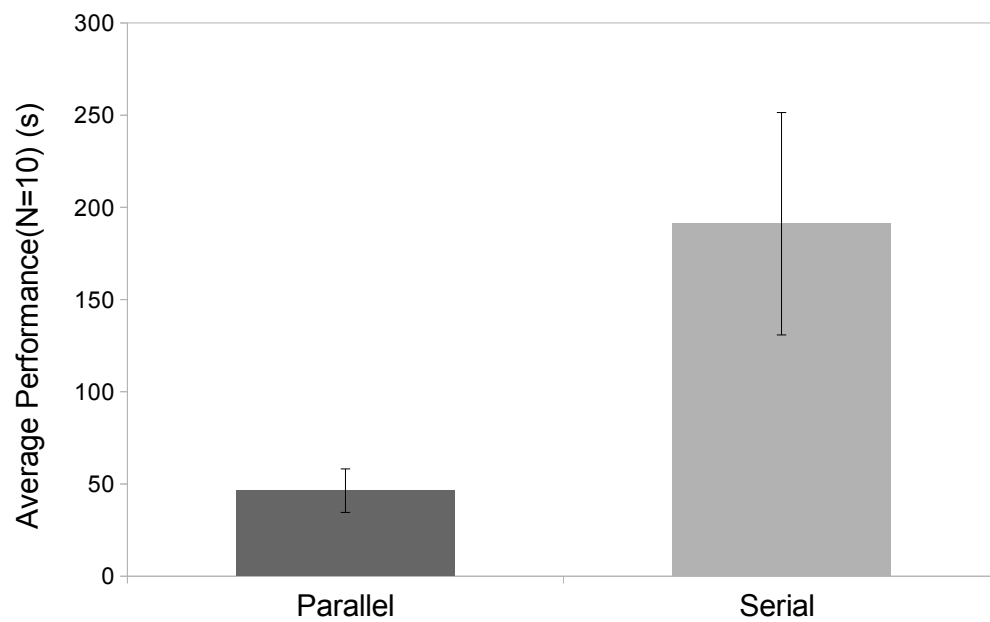




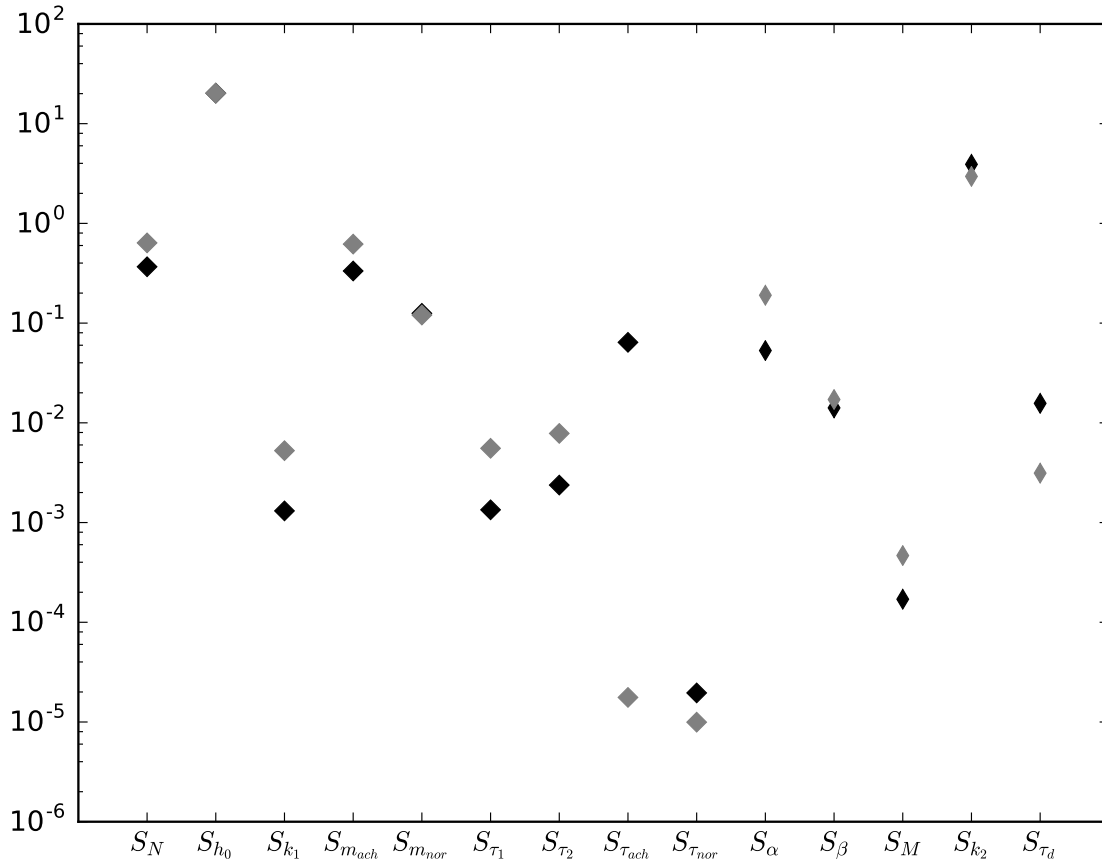
**Figure 4.** Performance of the model on a patient in cluster 2. The x represent the true heart rate, the black dots are the mean model prediction from the family of best parameter sets, and the grey gives a 95% confidence interval.



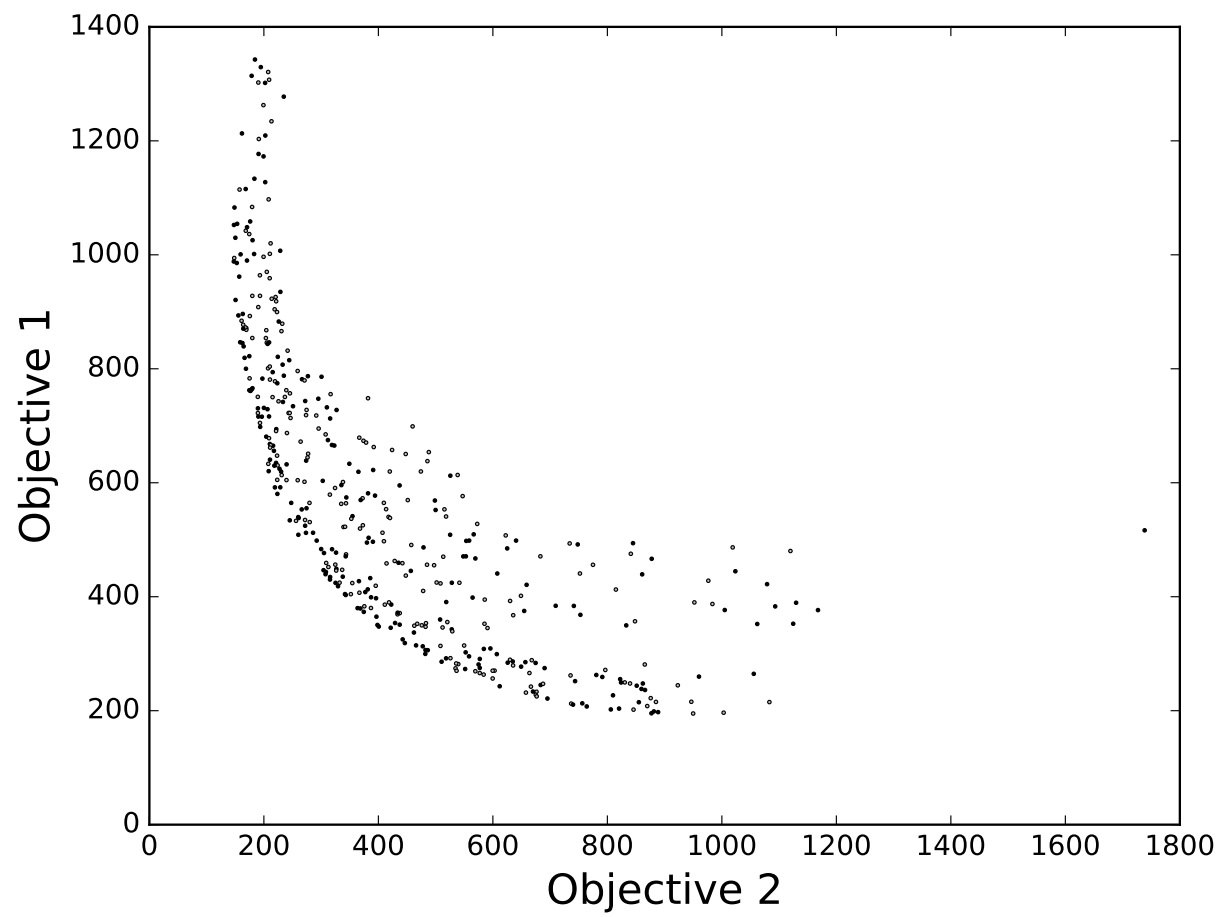
**Figure 5.** Sum of silhouettes as function of number of clusters



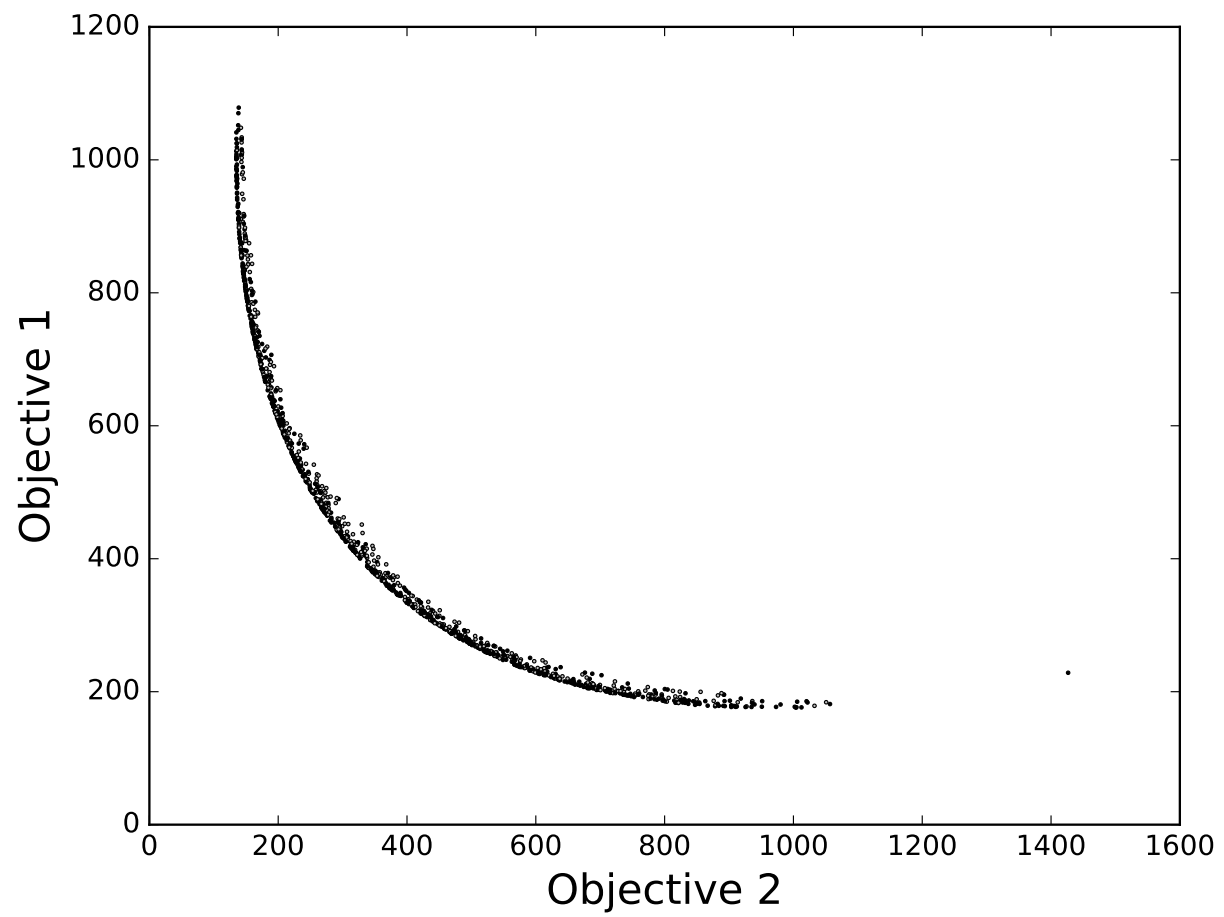
**Figure 6.** Switching from serial to parallel computation resulted in a significant speed up. In parallel operation, six cores were used.



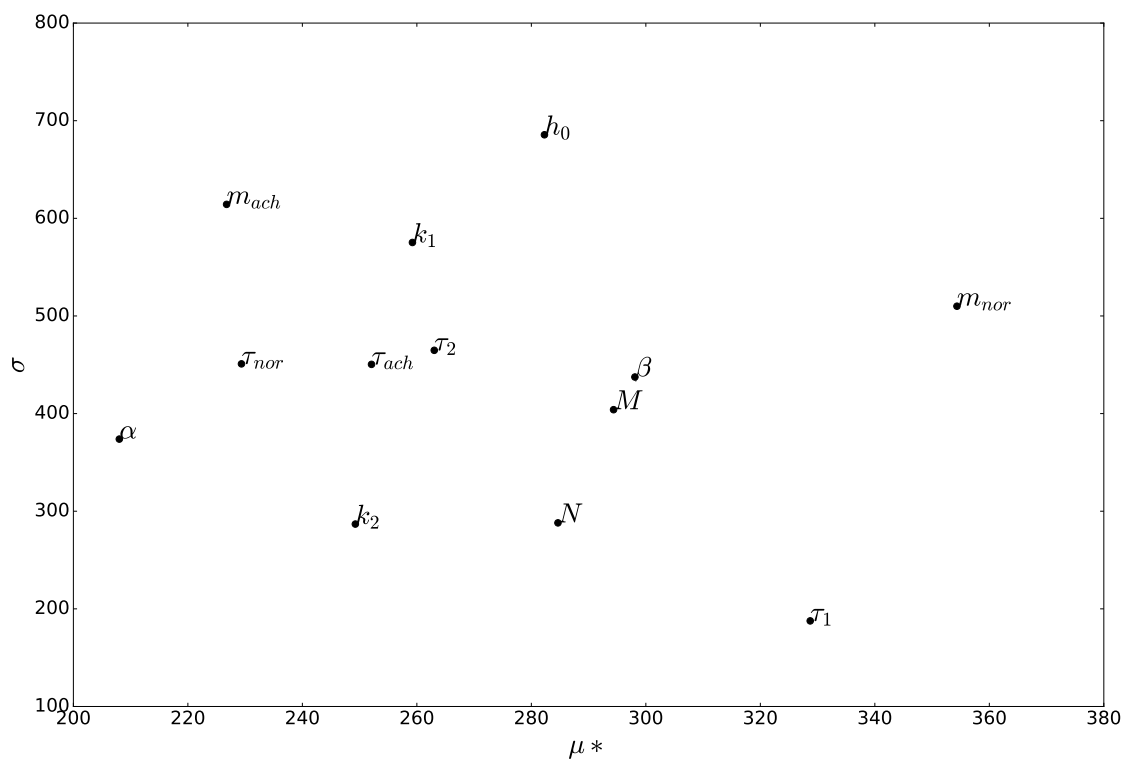
**Figure 7.** The black marks are from cluster 1, the grey marks represent cluster 2. Error bars are omitted for the sake of clarity. Parameters represented by an square were allowed to vary, and parameters represented by a diamond were held constant.



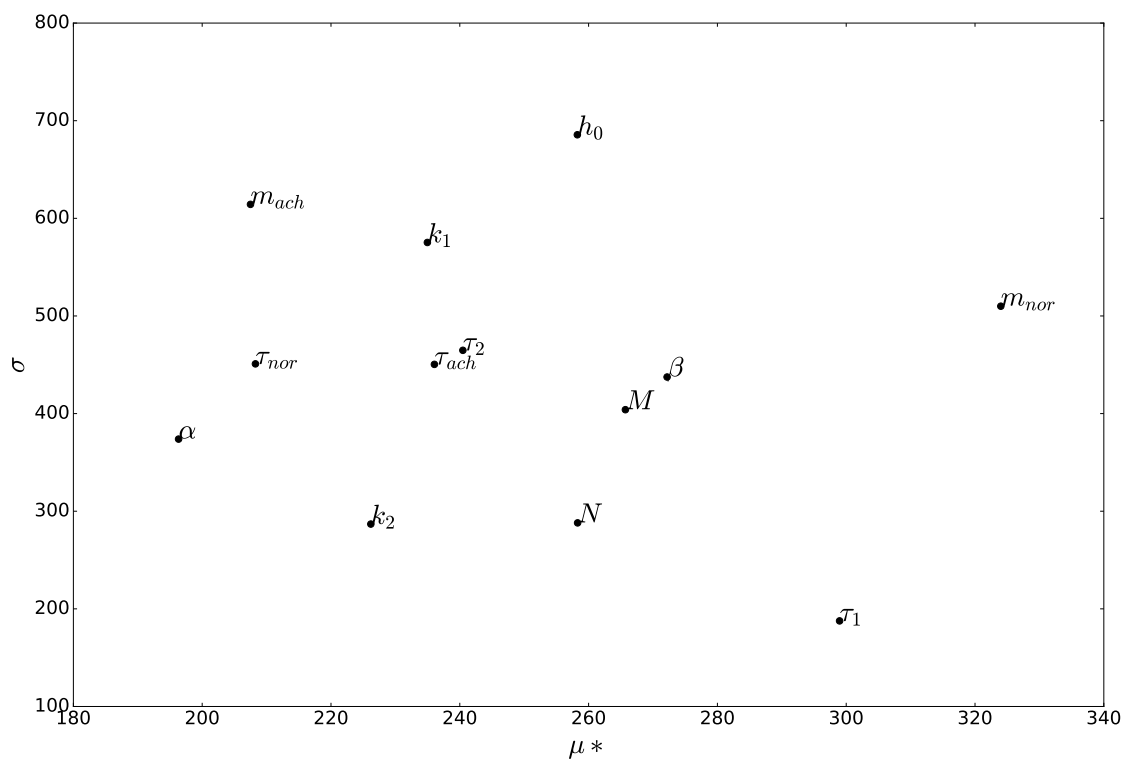
**Figure 8.** The black dots represent the rank 0, or best parameter sets, and the grey dots represent rank 1-4 parameter sets.



**Figure 9.** The black dots represent the rank 0, or best parameter sets, and the grey dots represent rank 1-4 parameter sets.



**Figure 10.** Cluster 1 Morris Plot, with N =100



**Figure 11.** Cluster 2 Morris Plot, with N =100