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Pali Sen
*University of North Florida*

Mary Anderson
*University of North Florida*

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# Simulation Study Of Chemical Inhibition Modeling

Pali Sen
Department of Mathematics and Statistics
University of North Florida

Mary Anderson
Department of Mathematics and Statistics
University of North Florida

The combined effects of the activities of different chemicals are of interest of this study. We simulate for the synthetic data, and fit experimental data for three models and estimate the parameters. We assess the fit of the synthetic data and the experimental data by comparing the coefficients of variation for the parameter estimates and identify the best model for the inhibition process.

Key words: Additive model, coefficient of variation, combination model, product model

## Introduction

Pharmacological data deal with the study of chemicals in a body. Researchers are interested in the distributions of these chemicals and their retention times. Studies by clinicians (e.g., Wagner, 1988; Bass, 1988; Beck, 1988) on the specific activities of chemicals under various conditions are examples. Thakur (1988), Matis (1988), and Jacquez (1985), to name a few, developed methods to study the dynamic behavior of chemicals using tools in mathematical modeling.

Sen and Mohr (1990), and Sen, Bell, and Mohr (1992) studied the distribution of a chemical in a body and modeled its activities as nonlinear time-dependent functions. In this paper we develop mathematical models of two chemicals in order to study the inhibition effects of one chemical on the other. This inhibition between two chemicals may be indicated by suppression or amplification of their individual effects. The specific activities of two interacting chemicals are measured on laboratory animals during an experiment.

Three models are developed here for study: an additive model, a product model, and a combination model. The purpose of the study is to select the best model from these three models, to describe the inhibition effect of two interacting chemicals and to interpret the observed data. A simulation study of the models and their parameter estimation using the synthetic data is described in the result section. A numerical example of the evaluation of the models is also presented in the result section.

Contact information for both authors is: Department of Mathematics and Statistics, University of North Florida Jacksonville, FL, 32224. Telephone: (904) 620-2846, Fax No. (904) 620-2818. E-mail: psen@unf.edu. The authors thank the referees for many good suggestions on content and presentation.

## Methodology

Consider a chemical flow in a body and its concentration changes at different times and at different points. We observe the flow discretely at a certain location in the body and at certain times, and we visualize a one-compartment model with a single input and output from the system. After the initial dose of a chemical is injected into the system, some amount of it will escape the compartment and the chemical itself will slowly decay over time. We assume the rate changes in concentration, p(t), of the chemical at any time in the body will follow the differential equation given below.

$$dp(t)/dt = -\alpha p(t) + f(t), \qquad (2.1)$$

where $\alpha$ is the rate at which the absorbed chemical leaves the system. f(t) is a decreasing function of

the chemical applied initially, which enters the system and is assumed to have the form

$$f(t) = d\, e^{-\beta t}, \qquad (2.2)$$

where d is the initial amount of the input, and β is the rate of absorption of the chemical. The solution of the equation (2.1) may be extended for two chemicals, since they follow essentially the same equation. Hence the solution of equation (2.1) for each chemical is written as,

$$p_i(t) = d_i\, (\exp(-\beta_i t) - \exp(-\alpha_i t))/(\alpha_i - \beta_i), \qquad (2.3)$$

for i = 1, 2.

We now consider an 'activator-inhibitor' system for the combined concentrations, p(t), of the activity levels, which consists of two chemicals that each exhibits the mutual effect of inhibiting the other's formation , Edelstein - Keshet, (1989). By selecting models for each of the combining effects, we have models that take the following forms:

Model 1: $p(t) = p_1(t) - p_2(t).$ (2.4)

Model 2: $p(t) = p_1(t) * p_2(t).$ (2.5)

Model 3: $p(t) = p_1(t) - p_2(t) + p_1(t) * p_2(t)$ (2.6)

The rationale for these models is based on the physiological combination effects of two chemicals. Sometimes the combined effects produce a reduction, and at other times a surge in the activity levels, depending on the chemical balance of the concentration levels. The negative sign in (2.4) indicates inhibition of the first chemical by the second**,** which is an antagonistic effect. Next, we consider the product model since the combination may alternatively cause the effects to rise. The product of the two equations is similar to an interaction effect, which we believe is a competitor for model 1. The third model is a combination of models 1 and 2, which intuitively may be viewed as a synergistic effect. We want to achieve a trend to identify a best inhibition model using experimental and synthetic data.

Computationally, the proposed models in (2.4), (2.5), and (2.6) yield different combinations of exponential terms. To simplify the notations, we use α, β, γ, δ instead of $\alpha_1$, $\beta_1$, $\alpha_2$, $\beta_2$. Here, γ represents the rate at which the second chemical leaves the system and δ is the rate at which the second chemical is absorbed in the system. The initial input ($d_i$) is considered to be of the same amount, d, for both the chemicals. We write equations (2.4), (2.5), and (2.6) in the following equations.

$$p(t) = d[\exp(-\beta t) - \exp(-\alpha t)]/(\alpha - \beta) - d[\exp(-\delta t) - \exp(-\gamma t)]/(\gamma - \delta). \qquad (2.7)$$

$$p(t) = d^2[\exp(-(\beta t + \gamma t)) - \exp(-(\beta t + \delta t)) - \exp(-(\alpha t + \gamma t)) + \exp(-(\alpha t + \delta t))]/(\alpha-\beta)(\delta-\gamma). \qquad (2.8)$$

$$p(t) = d[\exp(-\beta t) - \exp(-\alpha t)]/(\alpha - \beta) - d[\exp(-\delta t) - \exp(-\gamma t)]/(\gamma - \delta) + d^2[\exp(-(\beta t + \gamma t)) - \exp(-(\beta t + \delta t)) - \exp(-(\alpha t + \gamma t)) + \exp(-(\alpha t + \delta t))]/(\alpha-\beta)(\delta-\gamma). \qquad (2.9)$$

The above equations are similar even though the combinations of the parameters are different in each equation. Each equation in (2.7) – (2.9) consists of four parameters. We compare the fit of the generated curves with the observed values and then study the errors of estimation for each fitted curve.

## Results

We want to compare the models by generating data from the respective equations for a period of time. We simulate the models with four unknown parameters and for thirteen time points. d is a proportionality constant and may be set to any number. A value of d = 10 units is considered for the analysis. The random numbers are generated for ten sets of data at each time point 0, 30, ...360. The system of random numbers is perturbed by a sigma of 1 unit. The Monte Carlo method of the program is written using Fortran language and the Levenberg -Marquardt is used to fit the model parameters (Press, 1986). The initial guesses of the parameters and the first derivatives of the parameters are supplied in order for the nonlinear equations to converge when a chi-square value has

reached to a pre set number. Convergence implies that the best estimates of the parameters have been obtained, under the assumption that the model is adequate. Two convergence criteria are used here.

1) Continue iterative method until the parameter values on successive iterations stabilize. This can be measured by the size of the each parameter increment relative to the previous parameter value.
2) Continue till relative change in sum of squares on successive iterations is small.

Compliance with both criteria does not guarantee convergence; instead it could indicate a lack of progress. Often a small pivot element will generate a large correction in the parameter values, which will then be rejected. This near degeneracy of the minimum causes the parameters to fluctuate around a value (a local minimum) without ever converging to a global minimum.

Table 1 gives the estimated parameter values along with their standard errors for the data generated using the additive model for initial estimates of the parameters $\alpha = .0699$, $\beta = .0173$, $\gamma = .3742$, and $\delta = .057$, with respective parameter estimates $\hat{\alpha} = .0958$, $\hat{\beta} = .00535$, $\hat{\gamma} = .420862$, $\hat{\delta} = .0228$. The change in the Chi-Squares is from 186326.5 to 110324.7 with a 41% drop in the value.

Table 1 -Parameter estimates for three models for the first set of simulated data± indicates asymptotic standard errors

| Model | α | β | γ | δ |
|---|---|---|---|---|
| **Additive** | .096± .000028 | .005± .000001 | .421 ± .00018 | .023 ± .000056 |
| **Product** | .0019± 26.5040 | .0083± 26.5040 | 15.19± 26.5040 | -.0014± 26.5040 |
| **Combination** | 5.816± .000516 | .00009± .000004 | .0002± .0000015 | .0078± .000019 |

Table 2 gives the estimated parameter values along with their standard errors for the data generated using the combination model for initial estimates of the parameters $\alpha = .0818$, $\beta = .0108$, $\gamma = .0114$, and $\delta = .114$ with respective parameter estimates $\hat{\alpha} = .845261$, $\hat{\beta} = .00622$, $\hat{\gamma} = .00669$, $\hat{\delta} = 3.145268$. The change in the Chi-Squares is a 99% drop in the value.

Table 2 -Parameter estimates for three models for the second set of simulated data± indicates asymptotic standard errors.

| Model | α | β | γ | δ |
|---|---|---|---|---|
| **Additive** | .1396± .00012 | .0004± .00003 | .3087 ± .00043 | .0015 ± .00003 |
| **Product** | .0016± 77.223 | .3669± 77.229 | 5.445± 78.636 | -.0013± 77.224 |
| **Combination** | .845± .000939 | .006± .00003 | -.007± .00003 | 3.145± .00503 |

Tables 1 and 2 show some similarity in the estimates of the parameters. We have obtained the convergence criteria by all three models for the above two sets of parameters. It was extremely difficult to find the initial estimates of the parameters for the product model, but we included it in the analysis as well. The additive and the combination models both gave very good estimates of the standard errors, but the product model had the estimated standard errors very large to indicate the convergence might have reached locally. The data were generated using the additive and the combination models and both sets of data converged for both models 1 and 3 with good sets of parameter estimates, but neither set worked well for the product model. The coefficients of variation for estimated parameters fitted from the simulation data were calculated by dividing the standard errors of estimation by the estimated parameters for the sets given in the accompanying tables.

Once the validity of the models has been established, we want to see how the three models compare at each other, we use the estimated parameter values from the tables to draw the curves for all three models and place them on the same axes. Figure 1 shows that all three graphs basically follow the same pattern but in figure 2 the product model shows a slight fluctuation from the other two curves, and the combination model

separates from the other two at the end of 360 minutes. These pictures confirm that all three models are equally good in describing the chemical inhibition process.

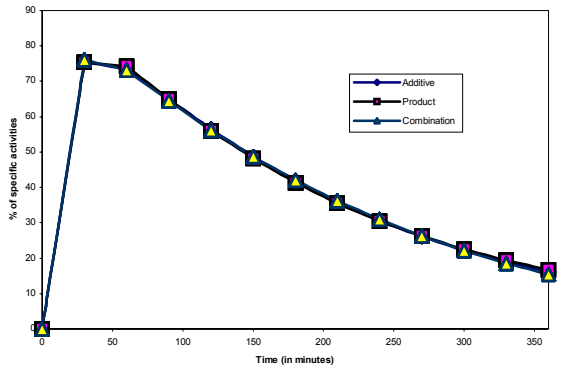


Figure 1. Simulated curves for three models using the parameter estimates in Table 1.

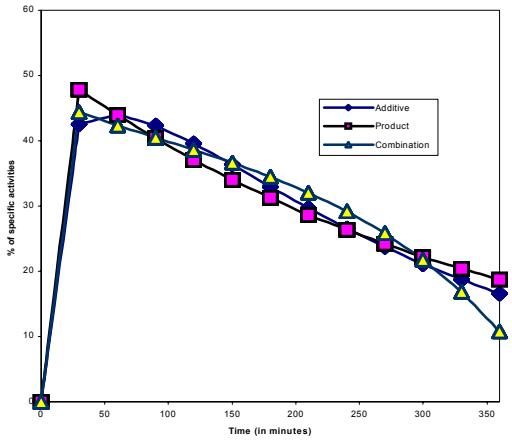


Figure 2. Simulated curves for three models using the parameter estimates in Table 2.

The simulation study is convincing enough for us to look further into the models using the real data. The data used for this study were collected at the Ohio State University pharmacological laboratory in Columbus, Ohio. Researchers administered two chemicals, morphine and midazolam, to laboratory rats. The experiment is to study the effects of two chemicals, Midazolam and Morphine when they are administered simultaneously. A high dose of Morphine, a common anesthetic agent, may have an irreversible side effect on the body. Midazolam has been shown to either increase or decrease spinal activity depending on the relative combined concentration of morphine and midazolam , Niv (1988); Tejwani, (1990). Also midazolam has been shown to have minimal side effects even with high dosages.

The purpose of their study for the combination effects was to see the effects of morphine in high doses when applied with varying dose levels of midazolam. Researchers especially want to determine if a combination level of two chemicals can produce the desired anesthetic effect that reaches high within 50 minutes to 100 minutes and gets out of the system within 3 hours. The experimenters used a group of five to six laboratory rats to administer midazolam at three levels and morphine at the same three levels as a 3X3 factorial design.

The combined effects of those two chemicals were observed on the rats. The concentration levels for each chemical were used at 10μg (low), 20μg (moderate), and 30μg (high) and each of the nine combinations of the concentrations. The numbing effects of the combined chemicals were recorded by measuring the tail flickering of the rats. These measurements, known as the specific activities, represent the percentage increase over the baseline values of the anesthetic effects, which are due to the chemicals. Higher measurement readings indicate a stronger effect of the chemicals.

The average percentages of the maximal possible effects on tail flickering of these animals were measured. A high number indicated the effect of analgesia (anesthetic effect) was strongly present. A descriptive study of the data has been published in one of the pharmacological journals, Rattan (1991).

Nonlinear regression fits of the models to the data are obtained using the Marquardt method. The estimates of the parameters are also obtained. The procedure is iterative based on the least squares method. The initial guess for each parameter is supplied and a known value of the initial amount (d) of 10 units is used for each level of the chemicals for the observed thirteen time points. The coefficients of variation for estimated parameters fitted from the data are calculated for the converged sets.

To avoid repetition and lack of any further meaningful information, only three selected combination levels of midazolam and morphine are presented here**.** The tables 3, 4, and 5 show the estimates of the four parameters with their corresponding asymptotic standard errors of estimation.

A well-known result is that the method of maximum likelihood asymptotically produces an estimated density, which is closest to the true density in the information sense. Maximizing the log- likelihood is equivalent to minimizing the expected logarithmic difference between the two densities. Akaike (1974) has suggested an estimate of the approximate loss between the true normal density and the approximating density. This estimate uses the maximum log-likelihood of the observation vector minus the number of parameters. Akaike's information criterion (AIC) is a useful statistic for statistical model evaluation and has been widely accepted in some areas of statistics, Bozdogan (1987). It is calculated for each selected model as AIC = (n)ln($SSE^s$/n) + 2k, SAS (1990). A low value for AIC indicates a better fit.

We notice in table 5, the combination data of both high levels of concentrations (Mor30 and Mid30), fit with AIC values equal to 28.89 for the additive model, and 34.07 for the combination model, those are the smallest among all other AIC values. The AIC values are in the similar range in the table 3 for the combination data of low morphine with high midazolam concentrations (Mor10 and Mid30). For the combination data of medium morphine with low midazolam concentrations (Mor20 and Mid10) in table 4, the AIC values are relatively high but similar for the additive model and the combination model and even higher for the product model.

We compare the standard errors of the parameter estimates in these tables. In tables 3 and 4 only the combination model has reliable estimated standard errors, and in table 5 models 1 and 3 have reliable estimated standard errors. So the combination model is the only one that is holding steady for the data.

Table 3 -Parameter estimates of three models for low level of Morphine± indicates asymptotic standard errors. * = Concentration Level.

| Level* | α | β | γ | δ | AIC |
|---|---|---|---|---|---|
| **Mor10 Mid30 Model 1** | .0383 ± 2.469 | .0382 ± 2.4645 | .3771 ± 617.19 | .3765 ± 616.3 | 56.42318072 |
| **Mor10 Mid30 Model 2** | .2005 ± 0.0000 | .1748 ± 263.9 | .0001 ± 27.961 | -.1400± 74.52 | 53.15877737 |
| **Mor10 Mid30 Model 3** | .0809 ± .0423 | .0168 ± .0178 | .0120 ± .0152 | .1431 ± .0676 | 53.46542876 |

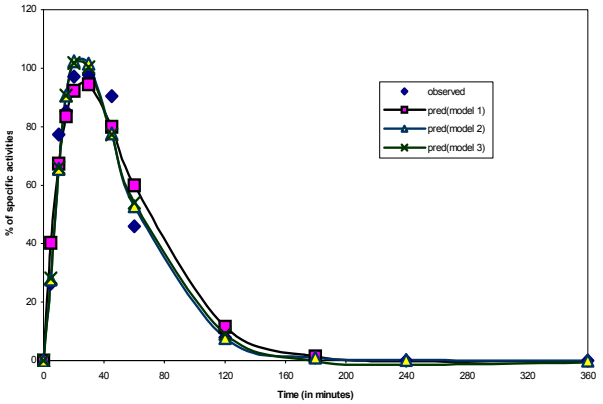


Figure 3. Distribution of Morphine 10µg and Midazolam 30µg with predicted models.

Table 4 -Parameter estimates of three models for medium level of Morphine ± indicates asymptotic standard errors.

| Level* | α | β | γ | δ | AIC |
|---|---|---|---|---|---|
| **Mor20 Mid10 Model 1** | .0836 ± .0050 | .0027 ± .0005 | 67739± .0000 | 47398± .0000 | 64.50291081 |
| **Mor20 Mid10 Model 2** | -.0286 ± .0016 | .4917 ± 6.972 | .0299 ± 0.0000 | .4951 ± 7.8581 | 74.11086129 |
| **Mor20 Mid10 Model 3** | .1445 ± .0876 | .0012 ± .0008 | .0094 ± 0.0130 | .1828 ± .1063 | 63.81358576 |

*Note:* * = Concentration Level.

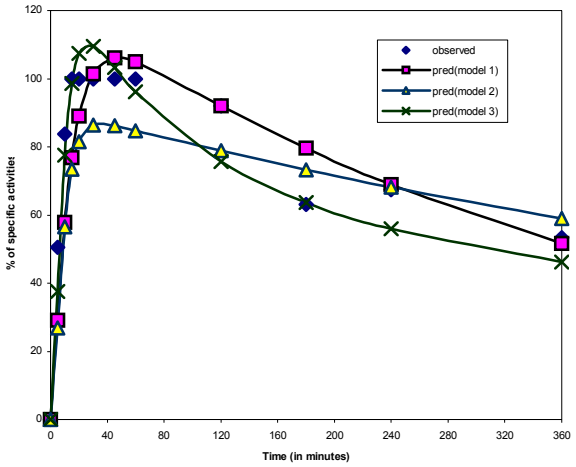


Figure 4. Distribution of Morphine 20µg and Midazolam 10µg with predicted models.

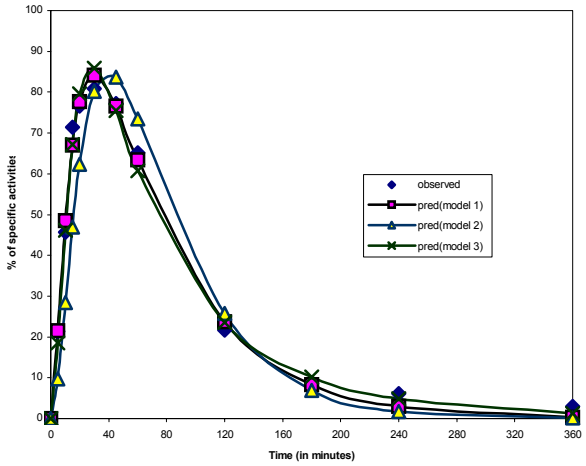


Figure 5. Distribution of Morphine 30µg and Midazolam 30µg with predicted models.

Table 5 -Parameter estimates of three models for high level of Morphine± indicates asymptotic standard errors.

| Level* | α | β | γ | δ | AIC |
|---|---|---|---|---|---|
| **Mor30 Mid30 Model 1** | .0699 ± .0082 | .0173 ± .0020 | .3742 ± .1141 | .0570 ± .0489 | 28.89092708 |
| **Mor30 Mid30 Model 2** | .0796 ± 0.0000 | .0705 ± 14528 | .0288 ± 701.31 | -.0446 ± 1396 | 68.71982797 |
| **Mor 30 Mid 30 Model 3** | .0818 ± .0286 | .0108 ± .0235 | .0114 ± .0396 | .1141 ± .0267 | 34.07428277 |

*Note*: * = Concentration Level.

Figures 3 – 5, refer to the respective tables 3 - 5, show the actual data with the estimated fitted lines by the models 1, 2, and 3. The estimated parameter values from the tables are used to draw the respective fitted curves and placed them with the original data points. Figure 3 shows a very close fit by all three curves, figure 4 shows very different fit by all three of them and figure 5 again shows very good fit by all three models.

We now focus on the estimated values to decide how good these fits are. Tables 3 - 5 show a lack of reliability in the measurements of the coefficients of variation by the product model for all of its estimated parameter values. They are quite large, indicating that the convergence may have reached locally, which is also the case with the simulation results for the product model, even though it fit the experimental data in figures 3 and 5. Table 3 shows only the combination model with a set of reasonable coefficients of variation for it's estimated parameter values but all curves fit data well. The standard errors for estimated parameter values for the other two models are large in Table 3. For the combination and addition models in table 5, the parameter estimates are extremely good with mostly low coefficients of variation, and all three models fit well. The estimated standard errors with the low coefficients of variation may be used to make the confidence intervals for the parameters for the combination model.

## Conclusion

The AIC criteria has been criticized in literature for adding two times the number of parameters of the model in the calculation, but we overcome this criticism by having equal number of parameters for each model. The AIC values are used heavily in the literature for model comparisons, but how low is a value to be considered for a good fit. Our studies show that the values range from 28.89 to 74.11 for the set of data that we have used. It is then reasonable to suggest that this range of AIC values meet the standards since they meet the convergence criteria for the study.

However to select a best model, only the AIC criteria may not be enough, the estimated parameter values also play a key role in determining a good model. One does not need to do the testing of hypothesis to decide if the estimated values are acceptable or not, as the coefficients of variation are instant indicators for the decision. The coefficients of variation for the estimated parameters are always large for the product model, but they are low for the combination model with no exception, indicating that the combination model is probably a better choice. This indicates that the coefficients of variation should also be considered for the choice of a model.

When we look into the simulation of the models, we find that all three models generate extremely similar patterns. The data under study contain a lot of variations for measurements and has only thirteen time points for each set. This may contribute to some of the convergence problems for model 1, which sometimes produces unusable estimates of the parameters in tables 3 and 4. Otherwise the simulation results in tables 1 and 2 are perfectly fine for the additive model. The combination model always did extremely well for fitting the data, estimating the parameters with low coefficients of variations, but producing the AIC values similar to the other two models.

This study indicates that there are a number of conceivable reasons why a particular model should be chosen. Beyond the reasonable AIC values, we looked into the fit and the coefficients of variation for estimating the parameters. This study showed that the reliable estimates of the parameter values were obtained from the combination model always, from the additive model sometimes and none of the times from the product model. The fit of the models are extremely close in two of the three graphs shown here. The models 1 and 2 have the potential for simpler interpretation of an inhibition model as being either an additive or a multiplicative in nature, but as we have seen the estimated parameter values are not always reliable, whereas a combination of the two models produces reliable estimates of the parameters.

In conclusion we would like to remark that AIC criteria are a very simple technique to identify the goodness of fit, but we need other statistical techniques as well to evaluate a model. This paper addresses the issue to identify a model that will best describe the inhibition process, even though that may not be a flawless model for the entire process. The models are based on simple approach to the physical description of the inhibition process with a few parameters. The data we have used for the numerical example may be modeled by much complicated equations than these models can describe. Any chemical interaction is a complicated process but the observable data points are restricted. Moreover, this type of experiment requires live subjects for study, which makes it harder to collect a large set of data. The proposed models have only four parameters to estimate and require a moderate size of the data set. In real experimental process if more data is available, the initial equation set up must be more elaborate before the three proposed models could be introduced. The simulation results and the numerical example show that the combination model better describe the inhibition effects of two chemicals.

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# Combining Quantum Mechanical Calculations And A $\chi^2$ Fit In A Potential Energy Function For The $CO_2 + O^+$ Reaction

Ellen F. Sawilowsky
Detroit, Michigan

In order to compute a highly accurate statistical rate constant for the $CO_2 + O^+$ reaction, it is necessary to first calculate the potential energy of the system at many different geometric configurations. Quantum mechanical calculations are very time-consuming, making it difficult to obtain a sufficient number to allow for accurate interpolation. The number of quantum mechanical calculations required can be significantly reduced by using known relations in classical physics to calculate energy for configurations where the oxygen is relatively far from the $CO_2$. A chi-squared fit to quantum mechanical points is obtained for these configurations, and the resulting parameters are used to generate an equation for the potential energy. This equation, combined with an interpolated set of quantum mechanical points to give the potential energy for configurations where the molecules are closer together, allows all configurations to be calculated accurately and efficiently.

Key words: Potential energy surface, $\chi^2$ fit

## Introduction

The reaction of carbon dioxide with the $O^+$ oxygen ion is of interest because experimental rate measurements show that at low energies the rate is constant at the expected value, but at high energies the rate steadily decreases to values below the expected rate (Viggiano, et al.,1992). RRKM rate calculations were done for the purpose of explaining this experimentally observed decrease (Forst, 1973).

In order to calculate the rate of reaction using statistical rate theories such as RRKM theory, the potential energy of the reacting molecules must be known at any geometric configuration that might be found near the transition state. This refers to the small portion of the potential surface that is near the maximum point on the minimum-energy path.

Ellen Sawilowsky has a Ph. D. in physical chemistry from Case Western Reserve University. She has previously published in journals such as the *Journal of Physical Chemistry* and *Abstracts of the Papers of the American Chemical Society*. Her email address is ell@chemist.com.

The accuracy of a rate calculation is directly related to the accuracy of the potential surface employed, and a good potential is needed if the rate calculation is to be highly accurate. Because calculating the potential energy at any one configuration involves time-consuming quantum mechanical calculations, constructing the potential surface with energies for all probable configurations near the transition state using quantum mechanical calculations becomes an impossible task. Instead, it is common to do calculations at judiciously chosen configurations and use interpolation to obtain good approximations for the energies of configurations for all other geometries.

The potential is split into long and short-range portions in order to further reduce the number of quantum mechanical calculations. *Ab initio* quantum mechanical calculations were done for the short-range portion only. At separation distances of 6.9 Å or greater, the long-range portion of the potential is invoked. It consists of a fit to the long range *ab initio* points with a functional form, which is a parameterized variation of the ion-induced dipole plus quadrupole potential: