PROBABILITY THEORY AND MULTIEXPONENTIAL SIGNALS, HOW ACCURATELY CAN THE PARAMETERS BE DETERMINED?

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ABSTRACT. Estimating the amplitudes and decay rate constants of exponentially decaying signals is an important problem in science. Understanding how the uncertainty in the parameter estimates depends on the experimental parameters is important as an aid in understanding how to improve the reliability of the parameter estimates. In this paper, probability theory has been applied to this problem with the intent of understanding the relevant experimental parameters. In the case of a single exponential, the uncertainty in the estimated decay rate depends directly on the three halves power of the true decay rate constant, inversely on the signal-to-noise ratio, and inversely on the square root of the number of data values. The uncertainty in the amplitude estimate depends directly on the square root of the true decay rate constant, directly on the noise level, and inversely on the square root of the number of data values. The case of two exponentials has also been analyzed with similar results. However, here the presence of the second signal introduces interference effects which make the estimate more uncertain.

1. Introduction

Exponentially decaying signals occur in many branches of science and engineering. In chemistry the concentrations of the reactants in first order reactions decay exponentially. The same is true in physics for the radioactive nuclear decay and in Nuclear Magnetic Resonance (NMR) for the magnetization of an excited nucleus. Exponentials are also used to model both storage and release of drugs and other exogenous substances, like metabolic tracers, from compartments within the body. In all of these examples, the value of the amplitudes and decay rate constants, contain the information about the dynamics of interest. Various methods have been used to estimate these parameters. Some of these include curve stripping (measuring the slope of the line in a semi-log plot), nonlinear least squares, Proney method's, linear prediction, and Bayesian probability theory. Of these methods, Bayesian probability theory offers a unique opportunity to understand how the parameter estimates depend on experimental parameters because it provides an estimate of the uncertainty in the parameter estimates. The techniques and procedures used in this paper have been applied previously to exponentially decaying sinusoidal models [1], to chirped sinusoids [2], and to gaussian point spread functions [3]. When the results of the Bayesian analysis have been compared to more traditional techniques, it has been observed that the traditional methods depend on the experimental parameters in much the same way as the parameter estimates from probability theory [4,5]. Consequently, the results derived from probability theory should also be indicative of the behaviour of the estimate from more traditional techniques.

This paper addresses questions of the form "How does the uncertainty in the decay rate constant depend on the sampling time, the number of data points, the signal-to-noise ratio and the true decay rate constant of the signal?" In sections 2 and 3 the uncertainty in the parameter estimates for the decay rate constant and amplitude are determined for the single exponential model. Similarly, in sections 4 and 5 the uncertainty in the parameter estimates are determined for the two (or bi-) exponential model. A different calculation is needed to determine the uncertainty in the parameter estimates for each parameter, though each of these calculations follows the same general outline. First, a data set $D \equiv \{d_1, \ldots, d_N\}$ is postulated. This data has been sampled from a time series $y(t)$ at discrete times t_i $(1 \le i \le N)$. The time series $y(t)$ is assumed to be the sum of two terms, a signal plus noise:

$$d_i = y(t_i) = f(t_i) + e_i \quad (1 \le i \le N), \tag{1}$$

where the signal $f(t)$ is taken to be of the form

$$f(t_i) = \sum_{j=1}^{m} = B_j G_j(t_i) = \sum_{j=1}^{m} B_j \exp\{-\alpha_j t_i\}. \tag{2}$$

The model signal is given by

$$f(t_i) = \sum_{j=1}^{m} B_j \exp\{-\alpha_j t_i\} \tag{3}$$

where e_i represents the value of the noise at time t_i, B_j is the amplitude of jth signal, α_j is the decay rate constant, and m is the number of exponentials. The cases of m=1 and m=2 will be considered in this paper. In the second step of the calculation, the posterior probability density for the parameter of interest (the decay rate constant or amplitude) is computed. Next, a functional form of the data is postulated, and finally the parameter estimates are derived in the (mean $\pm$ standard deviation) form. These estimates explicitly demonstrate the dependence on the experimental parameters and what must be done to make more precise estimates.

2. Estimating Decay Rate Constant: One Exponential Case

The first calculation involves determining how the uncertainty in the estimated decay rate constant depends on the experimental parameters. From Eq. (3), the model equation for the single exponential, $m = 1$, is

$$d_i = B_1 \exp\{-\alpha_1 t_i\} + e_i \quad (1 \le i \le N). \tag{4}$$

The posterior probability has been derived previously [6] and the results will simply be given here. Using bounded uniform priors, for both the amplitude and decay rate constant, the posterior probability density for the decay rate constant is given by

$$P(\alpha_1|\sigma, D, I) \propto \exp\left\{\frac{(d\cdot G)^2}{2\sigma^2 G\cdot G}\right\}, \tag{5}$$

where a number of irrelevant constants have been dropped and "·" means sum over discrete times:

$$d\cdot G \equiv \sum_{i=1}^{N} d_i G(t_i) = \sum_{i=1}^{N} d_i \exp\{-\alpha_1 t_i\}, \tag{6}$$

and

$$G\cdot G \equiv \sum_{i=1}^{N} G_i^2 = \sum_{i=1}^{N} \exp(-2\alpha_1 t_i) \approx \frac{1}{2\alpha_1}. \tag{7}$$

The approximation in this equation assumes that $2\alpha_1 N$ is large compared to one; i.e., the signal decays away over the total sampling time, and that the sum may be approximated by an integral. To motivate the integral approximation, suppose the dimensionless decay rate constant is 0.01, that uniform sampling is used, and the time series is sampled for three e-folding times to obtain 300 data values; then the exact sum gives 50.3764, while the approximation gives 50.0. The approximation introduces an error of 0.75%.

The next step in the calculation is to postulate a functional form for the data. If the true values of the amplitude and decay rate constant are $\hat{B}_1$ and $\hat{\alpha}_1$ respectively, then the data are given by

$$d(t_i) = \hat{B}_1 \exp\{-\hat{\alpha}_1 t_i\} + e_i \quad (1 \le i \le N) \tag{8}$$

and

$$\begin{aligned} d\cdot G &= \sum_{i=1}^{N} d_i \exp\{-\alpha_1 t_i\} \\ &= \sum_{i=1}^{N} \hat{B}_1 \exp\{-(\hat{\alpha}_1 + \alpha_1)t_i\} + \sum_{i=1}^{N} e_i \exp\{-\alpha_1 t_i\} \\ &\approx \frac{\hat{B}_1}{\alpha_1 + \hat{\alpha}_1}, \end{aligned} \tag{9}$$

where the projection of the model onto the noise was assumed small compared to the projection of the model onto the signal (effectively the high signal-to-noise case). For the postulated data, the posterior probability density for the decay rate constant becomes

$$P(\alpha_1|\sigma, D, I) \propto \exp\left\{\frac{2\alpha_1 \hat{B}_1^2}{2\sigma^2(\alpha_1 + \hat{\alpha}_1)^2}\right\}. \tag{10}$$

The maximum of the posterior probability occurs at $\alpha_1 = \hat{\alpha}_1$; the true value of the parameter. Taylor expanding the exponent about this maximum gives

$$P(\alpha_1|\sigma, D, I) \propto \exp\left\{-\frac{(\alpha_1 - \hat{\alpha}_1)^2 \hat{B}_1^2}{16\sigma^2\hat{\alpha}_1^3}\right\}, \tag{11}$$

from which one obtains

$$(\alpha_1)_{est} = \hat{\alpha}_1 \pm \sqrt{8}\frac{\sigma}{\hat{B}_1}(\hat{\alpha}_1)^{3/2} \tag{12}$$

as the (mean $\pm$ standard deviation) estimate of the decay rate constant.

First note that dimensionless units have been used. The conversion to dimensional units is given by

$$\alpha_1{}' = \frac{\alpha_1 N}{\pi \Delta t} \tag{13}$$

where α_1' is the corresponding dimensional decay rate constant and Δt is the sampling time. Converting the (mean $\pm$ standard deviation) estimate to dimensional quantities one obtains

$$(\alpha_1')_{est} = \hat{\alpha}_1' \pm \frac{\sigma}{\hat{B}_1}\sqrt{\frac{8\pi\Delta t}{N}}(\hat{\alpha}_1')^{3/2}. \tag{14}$$

A number of conclusions can be drawn from this expression about estimating the decay rate constant:

1. The estimated decay rate constant is equal to the true decay rate constant i.e., as the noise goes to zero, the parameter estimate goes smoothly to the true parameter value.
2. Increasing the signal-to-noise ratio ($\sigma/\hat{B}_1$) reduces the uncertainty in the estimated decay rate constant.
3. For a fixed acquisition time, increasing the sampling time decreases precision of the estimate: sampling fewer data values over the region where the signal is large decreases the precision of the estimate.
4. Conversely, increasing the number of data points (decreasing the sampling time) improves the precision of the estimate for the decay rate constant.
5. The more rapidly a signal decays the worse the precision of the estimate. Rapidly decaying signals effectively reduce the number of relevant data.

To make the decay rate estimate more precise one can either improve the signal-to-noise ratio, or gather more data values over the region where the signal is large. However, these comments apply only to the decay rate constant. They do not necessarily apply to the amplitude of the signal. To determine if they apply, the same type of calculation must be repeated for the amplitude of the signal, a task to which we now turn our attention.

3. Estimating Amplitude: One Exponential Case

To determine how the amplitude estimate depends on the experimental parameters, the calculation presented in the previous section must be repeated using the posterior probability for the amplitude as the starting point. Given the model, Eq. (4), the posterior probability for the amplitude is given by

$$P(B_1|\sigma, D, I) \propto \int d\alpha_1 \exp\left\{-\frac{B_1^2 G\cdot G - 2B_1 d\cdot G}{2\sigma^2}\right\} \tag{15}$$

where some irrelevant constants have been dropped, and no closed form solution for the integral is known to the authors. For the single exponential model and the postulated data, the posterior probability density for the amplitude becomes

$$P(B_1|\sigma, D, I) \propto \exp\left\{-\frac{(B_1 - \hat{B}_1)^2}{4\sigma^2\hat{\alpha}_1}\right\} \tag{16}$$

where some irrelevant constants were dropped and a gaussian approximation was used to evaluate the integral over α_1. Examining Eq. (16), the (mean $\pm$ standard deviation) amplitude estimate is given by:

$$(B_1)_{est} = \hat{B}_1 \pm \sigma\sqrt{2\hat{\alpha}_1}. \quad (17)$$

The conversion to dimensional units was given in Eq. (13), from which one obtains

$$(B_1')_{est} = \hat{B}_1' \pm \sigma\sqrt{\frac{2\pi\Delta t\hat{\alpha}_1'}{N}}. \quad (18)$$

A number of conclusions can be drawn from this expression about estimating the amplitude:

1. The estimated amplitude is equal to the true amplitude. As the noise goes to zero, the parameter estimate goes smoothly to the true parameter value.
2. The uncertainty in the estimate does not depend on the signal-to-noise ratio, but varies directly with the noise standard deviation σ. Once a signal is above the noise level one should be able to detect and estimate its amplitude.
3. The uncertainty in the estimate has the same dependence on the sampling time and the total number of data values as the decay rate constant.
4. The uncertainty in the estimate increases as the true decay rate constant increases; but unlike the uncertainty estimate of the decay rate constant, the dependence is on the square root of the true decay rate constant, instead of the three-halves power. Consequently, the uncertainty in the estimated amplitude does not deteriorate as quickly as the uncertainty in the estimated decay rate constant.

Unlike the uncertainty in the estimated decay rate constant, the uncertainty in the estimated amplitude does not depend on the signal-to-noise level; rather it depends only on the noise standard deviation. Increasing the signal strength will not make the amplitude estimate more precise. Only decreasing the noise level or increasing the sampling rate can do that. However, increasing the signal intensity will result in a smaller fractional error.

The calculations presented in this and the previous section show how the uncertainty in the amplitude and decay rate constant depend on the experimental parameters. These estimates are valid for high signal-to-noise data containing a single exponentially decaying signal that decays away in the acquisition time. They are not valid for truncated signals or for data that contain more than a single exponential. Both of these shortcomings are easily corrected by repeating the calculations and making the appropriate assumptions. For truncated data one would not expect any new phenomena to appear. All that one would expect is a more general formula applicable under wider circumstances. However, for the two exponential case one would expect new phenomena to appear. In particular, one would expect to find interference phenomena. To see how the presence of the second exponential affects the parameter estimates these calculations must be repeated for the two exponential model.

4. Estimating Decay Rate Constant: Two Exponential Case

In the next two sections the analysis presented for the single exponential case is generalized to the two exponential case. The question considered in this section is "How accurately can one of the decay rate constants be estimated given data that contain two exponentially decaying signals?" The model equation for such data may be written as

$$d_i = B_1 \exp\{-\alpha_1 t_i\} + B_2 \exp\{-\alpha_2 t_i\} + e_i \quad (1 \le i \le N). \quad (19)$$

Using uniform priors, for the amplitudes and decay rate constants, and assuming the noise standard deviation (σ) is known, the posterior probability density for one of the decay rate constants independent of the value of the other decay rate constant is given by

$$P(\alpha_1|\sigma, D, I) \propto \int d\alpha_2 \exp\left\{\frac{m\overline{h^2}}{2\sigma^2}\right\} \tag{20}$$

where some irrelevant constants have been dropped. The quantity $\overline{h^2}$ is given by

$$\overline{h^2} = \frac{2\alpha_1\alpha_2(\alpha_1+\alpha_2)^2}{(\alpha_1-\alpha_2)^2}\left\{\frac{S_1^2}{2\alpha_2} - \frac{2S_1S_2}{\alpha_1+\alpha_2} + \frac{S_2^2}{2\alpha_1}\right\} \tag{21}$$

with

$$S_1 = d\cdot\exp\{-\alpha_1 t\} \quad \text{and} \quad S_2 = d\cdot\exp\{-\alpha_2 t\}. \tag{22}$$

Postulating two exponential data given by

$$d(t_i) = \hat{B}_1\exp\{-\hat{\alpha}_1 t\} + \hat{B}_2\exp\{-\hat{\alpha}_2 t\} + e_i \quad (1\le i\le N), \tag{23}$$

where $\hat{B}_1$ and $\hat{\alpha}_1$ are the true amplitude and decay rate constant of the first exponential, and $\hat{B}_2$ and $\hat{\alpha}_2$ are the true amplitude and decay rate constant of the second exponential, then S_1 and S_2 are given approximately by

$$S_1 = \frac{\hat{B}_1}{\alpha_1+\hat{\alpha}_1} + \frac{\hat{B}_2}{\alpha_1+\hat{\alpha}_2} \quad \text{and} \quad S_2 = \frac{\hat{B}_1}{\alpha_2+\hat{\alpha}_1} + \frac{\hat{B}_2}{\alpha_2+\hat{\alpha}_2}. \tag{24}$$

The maximum of the posterior probability density again occurs at $\hat{\alpha}_1$; the true value of the parameter. Taylor expanding the exponent about this maximum gives

$$P(\alpha_1|\sigma, D, I) \propto \exp\left\{-\frac{(\alpha_1-\hat{\alpha}_1)^2\hat{B}_1^2(\hat{\alpha}_1-\hat{\alpha}_2)^4}{8\sigma^2\hat{\alpha}_1^3(\hat{\alpha}_1+\hat{\alpha}_2)^4}\right\} \tag{25}$$

where some irrelevant constants have been dropped, and the integral was evaluated in the gaussian approximation. From Eq. (25) one obtains

$$(\alpha_1)_{est} = \hat{\alpha}_1 \pm 2\sqrt{\frac{\sigma^2\hat{\alpha}_1^3(\hat{\alpha}_1+\hat{\alpha}_2)^4}{\hat{B}_1^2(\hat{\alpha}_1-\hat{\alpha}_2)^4}} \tag{26}$$

as the (mean $\pm$ standard deviation) estimate of the decay rate constant. The conversion to dimensional units was given in Eq. (13), from which one obtains

$$(\alpha_1')_{est} = \hat{\alpha}_1' \pm 2\frac{\sigma}{\hat{B}_1}\frac{(\hat{\alpha}_1+\hat{\alpha}_2)^2}{(\hat{\alpha}_1-\hat{\alpha}_2)^2}\sqrt{\frac{\pi\Delta t}{N}}(\hat{\alpha}_1')^{3/2}. \tag{27}$$

Similarly, for the other decay rate constant one finds,

$$(\alpha_2')_{est} = \hat{\alpha}_2' \pm 2\frac{\sigma}{\hat{B}_2}\frac{(\hat{\alpha}_1+\hat{\alpha}_2)^2}{(\hat{\alpha}_1-\hat{\alpha}_2)^2}\sqrt{\frac{\pi\Delta t}{N}}(\hat{\alpha}_2')^{3/2}. \tag{28}$$

A number of conclusions can be drawn from this expression about estimating the decay rate constant when the signal is known to consist of two exponentials:

1. The estimated decay rate constant go smoothly to the true value of this parameter as the noise level goes to zero.
2. The uncertainty in the estimated value of the decay rate constant depends only on the signal-to-noise ratio of the component of interest and is independent of the signal-to-noise ratio of the other component.
3. Except for the quadratic ratio, the uncertainty in the estimated parameters has the same dependence on the experimental parameters as in the single exponential case.
4. As the true values of the decay rate constants become comparable the uncertainty in the estimated values for both decay rate constants increases rapidly.

To gain some insight into this last item, suppose the dimensionless decay rate constants are 0.01 and 0.02. Then the uncertainty in the estimated parameters is a factor of 9 worse than if the decay rate constants were well separated. Additionally, suppose N=300, corresponding to an acquisition time of three e-foldings for the longer component, and both exponentials have the same amplitude, then to resolve each of the two decay rate constants at one standard deviation the signal-to-noise ratio must be approximately 10 for each component, or 20 total. But this assumes $N = 300$ data values. If the number of data values is low, for example $N = 30$, then the uncertainty in the estimated parameters increases $\sqrt{10}$. To compensate, the signal-to-noise ratio must be increased to 35 for each component, or 70 total. The presence of the second experimental signal increases the uncertainty in the parameter estimates. But note that when the decay rate constants are very different the uncertainty in the parameter estimates reduce to the single exponential case. So potentially if one can modify the experiment so that one component in very much different from the other, one can reduce the uncertainty in the estimated value of the longer lived component.

5. Estimating Amplitude: Two Exponential Case

The question considered in this section is "How accurately can one of the amplitudes be estimated given data that are known to contain two exponentially decaying signals?" The model equation for this data was given in Eq. (19). The posterior probability for B_1 is given by

$$P(B_1|\sigma, D, I) \propto \int d\alpha_1 d\alpha_2 \exp\left\{-\frac{(B_1 - \mathcal{B})^2}{2\sigma^2}\right\} \tag{29}$$

where some irrelevant constants have been dropped, no closed solution for the integral is known to the authors, and

$$\mathcal{B} = \frac{2\alpha_1(\alpha_1 + \alpha_2)^2}{\alpha_1^2 + \alpha_2^2}\left[d \cdot \exp\{-\alpha_1 t\} + (\frac{2\alpha_2}{\alpha_1 + \alpha_2})d \cdot \exp\{-\alpha_2 t\}\right]. \tag{30}$$

For the two exponential model and the postulated data, Eq. (23), the posterior probability density for the amplitude is given approximately by

$$P(B_1|\sigma, D, I) \propto \exp\left\{-\frac{(B_1 - \hat{B}_1)^2}{4\sigma^2\hat{\alpha}_1}\left[\frac{\hat{\alpha}_1 - \hat{\alpha}_2}{\hat{\alpha}_1 + \hat{\alpha}_2}\right]^2\right\} \tag{31}$$

where the integrals were evaluated using a gaussian approximation. Examining Eq. (31) the (mean ± standard deviation) amplitude estimate is given by

$$(B_1)_{est} = \hat{B}_1 \pm \sigma \left| \frac{\hat{\alpha}_1 + \hat{\alpha}_2}{\hat{\alpha}_1 - \hat{\alpha}_2} \right| \sqrt{2\hat{\alpha}_1}. \tag{32}$$

The conversion to dimensional units was given in Eq. (13), from which one obtains

$$(B_1')_{est} = \hat{B}_1' \pm \sigma \left| \frac{\hat{\alpha}_1 + \hat{\alpha}_2}{\hat{\alpha}_1 - \hat{\alpha}_2} \right| \sqrt{\frac{2\pi\Delta t\hat{\alpha}_1'}{N}}. \tag{33}$$

Similarly, for the other amplitude one finds,

$$(B_2')_{est} = \hat{B}_2' \pm \sigma \left| \frac{\hat{\alpha}_1 + \hat{\alpha}_2}{\hat{\alpha}_1 - \hat{\alpha}_2} \right| \sqrt{\frac{2\pi\Delta t\hat{\alpha}_2'}{N}}. \tag{34}$$

A number of conclusions can be drawn about estimating the amplitudes when the signal is known to consist of two exponentials:

1. The estimated amplitudes go smoothly to the true values of the amplitudes as the noise level goes to zero.
2. The uncertainty in the amplitude estimate does not depend on the signal-to-noise ratio but varies directly with the noise standard deviation σ. Again, once a signal is above the noise level one should be able to detect and estimate its parameters.
3. Except for the interference factor in front of the square root, the uncertainty in the estimated parameters have the same dependence on the sampling time, the total number of data values and the true decay rate constant as in the single exponential case.
4. As the true values of both decay rate constants become comparable, the uncertainty in the estimated parameters increase. But, the uncertainty in the estimated amplitudes does not increase as rapidly as the uncertainty in the estimated decay rate constant.

To obtain a better understanding of this last item suppose $\alpha_1 = 0.01$, $\alpha_2 = 0.02$ and $N = 300$, (the same values used previously) then the uncertainty in the amplitude estimate is 3 times larger than for the corresponding single exponential case. As the true values of the decay rate constants approach each other the amplitude uncertainty becomes large. However, the signal-to-noise ratio has not changed. If the individual amplitudes cannot be determined there must be some quantity that is still well determined. That quantity is the sum of the two amplitudes. The difference in amplitudes is undetermined. Conversely, if the two decay rate constants are very different, the uncertainty in the amplitude estimate reduces to that found in the single exponential case.

6. Summary

In this paper, probability theory has been used to obtain an understanding of how the uncertainty in the estimated parameters depends on experimental parameters. For decay rate constants, there are two ways to reduce the uncertainty in the estimated parameters: increase the signal-to-noise ratio or increase the sampling rate while holding the acquisition time constant; e.g., take more data over the time one has a signal. For amplitudes a similar result holds for taking more data, but not for increasing the signal-to-noise level. To reduce the uncertainty in the estimated amplitudes, one must decrease the noise level. A potentially much harder condition to fulfill. In the case of data containing two exponentials, probability theory shows how the uncertainty in the parameter estimates depend on the presence of the other exponential. For such data probability theory indicates that the uncertainty in the parameter estimates may be reduced by modifying the experiment in such a way as to separate the true decay rate constants. However, barring this last alternative, there are only two fundamental ways to reduce the uncertainty in the estimated parameters: decrease the noise level (thereby increasing the signal-to-noise of the data) or take more data over the region where the signal is large.

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