Helix modelling through the Mardia-Holmes model framework and an extension of the Mardia-Holmes model

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Abstract

For noisy two-dimensional data, which are approximately uniformly distributed near the circumference of an ellipse, Mardia & Holmes (1980) developed a model to fit the ellipse. In this paper we adapt their methodology to the analysis of helix data in three dimensions. If the helix axis is known, then the Mardia-Holmes model for the circular case can be fitted after projecting the helix data onto the plane normal to the helix axis. If the axis is unknown, an iterative algorithm has been developed to estimate the axis. The methodology is illustrated using simulated protein α-helices. We also give a multivariate version of the Mardia-Holmes model which will be applicable for fitting an ellipsoid and in particular a cylinder.

Keywords and phrases. Fitted ellipse, Fitted circle, Principal component analysis, Helix axis, Maximum likelihood, Least squares

1 Introduction

A mathematical helix is a curve in three dimensional space, of the form

\[ f(t) = \begin{bmatrix} r \cos t \\ r \sin t \\ ct \end{bmatrix} \]  

(e.g., O’Neill, 1997, p. 16), augmented by an arbitrary rotation and shift in \( \mathbb{R}^3 \), as the “time” \( t \) ranges through the real line. This helix is called “right-handed” since when looked at from above, \( x_1 \) and \( x_2 \) move in in a counter-clockwise direction around a circle as \( t \) increases, i.e. as the axis position \( x_3 \) gets closer to to observer.

A statistical helix is obtained from (1) by adding noise at equally spaced time points \( t_i = i\beta \) to give data

\[ x_i = f(t_i) + \epsilon_i, \quad i = 1, \ldots, n, \]

(2)
where \( \epsilon_i \) are small noise terms, typically modelled by independent isotropic normal distributions,

\[
\epsilon_i \sim N_3(0, \sigma^2 I_3).
\]

The structural parameters of the helix data are

- the radius \( r > 0 \);
- the pitch \( 2\pi c \) (the amount of vertical movement after one rotation around the helix); and
- the turn angle \( \beta \).

An important application of helix models is to secondary protein structure, where a common structure is the right-handed \( \alpha \)-helix, (see e.g. [Campbell & Farrell, 2009]). A protein \( \alpha \)-helix can treated as a data set of “landmarks” lying near a helix by focusing on specific atoms such as \( C_\alpha \) atoms.

An important task when presented with helix data is to estimate the axis. Various statistical methods have been proposed in the literature. Mardia et al. (2018) used maximum likelihood estimates under various assumptions about the parameters. In particular if \( \beta \) is known, it is also possible to use a modified least squares algorithm to compute the MLE; this particular algorithm was called OptLS by Alfahad et al. (2018) and this name will be used in this paper. There are many compositional methods to calculate the axis; see for examples, Åqvist (1986) and Rotfit by Christopher et al. (1996).

In this paper, we develop a new method, by adapting the Mardia & Holmes (1980) (M-H) model for data in the plane. The paper is laid out as follows. In Section 2 the MH model for data in the plane is reviewed. Then in Section 3 the MH model is adapted to estimate the helix axis for three-dimensional data using a projection into the plane. Section 4 illustrates the use of the model on some simulated data.

## 2 Mardia-Holmes model

Mardia & Holmes (1980) (M-H) model was originally designed to analyze megalithic data, in particular stones clustered uniformly around an ellipse, or as a special case, a circle. The M-H model has several parameters:

- a concentration parameter \( \kappa > 0 \) describing how closely the data points are concentrated around an ellipse;
- a location parameter in the plane \( \mathbf{a} = (a_1, a_2)^T \) representing the centre of the ellipse; and
- a \( 2 \times 2 \) matrix \( \Sigma \) used to specify the ellipse as a quadratic form,

\[
(y - a)^T \Sigma^{-1} (y - a) = 1.
\]
The M-H model treats $n$ data points in the plane $x_1, \ldots, x_n$ as independent observations from the density

$$f(y) = C(\kappa)|\Sigma|^{-1/2}\exp\left\{ -\frac{1}{2\kappa}(y - a)^T \Sigma^{-1}(y - a) - 1 \right\},$$

(4)

where $C(\kappa) = (\kappa/2\pi)^{1/2}/\{\pi \Phi(\kappa/2)\}$ is the normalization constant. This model has its mode on the circumference of the ellipse, that is, the values of $y$ satisfying (3).

If $\Sigma = \rho^2 I_2$, $\rho^2 > 0$, and $I_2$ is the $2 \times 2$ identity matrix, then ellipse in (3) reduces to a circle of radius $\rho$.

The circular version of the M-H model is the appropriate version for helix data. If data $\{x_i\}$ follow the helix model (1)-(2), then the projected data

$$y_i = \begin{bmatrix} y_{i1} \\ y_{i2} \end{bmatrix} = \begin{bmatrix} x_{i1} \\ x_{i2} \end{bmatrix}$$

will approximately follow the M-H model.

The adjective “approximately” is needed for two reasons. (i) The angular parts of the helix data (i.e. $\theta_i = \text{atan2}(x_{i2}, x_{i1}), i = 1, \ldots, n$) are not i.i.d.; the distribution of $\theta_i$ depends on $t_i$. However, provided $\beta/2\pi$ is not a simple fraction, we expect the $\theta_i$ to be well spread around the circle.

(ii) The radial part of the helix distribution (i.e. the distribution of $(x^2_{i1} + x^2_{i2})^{1/2}$ from (2) is not quite the same as the radial part of the M-H distribution (i.e. the distribution of $(y^2_{i1} + y^2_{i2})^{1/2}$ from (4). However, the two radial distributions will be very similar under high concentration, i.e. if $\kappa$ is large, by matching the parameters $\kappa = 1/\sigma^2$.

Estimation in the M-H model can be done by maximum likelihood. However, since the MLEs do not exist in closed form, an iterative algorithm is needed. The simplest procedure is to choose plausible initial estimates and then to use a black box optimization algorithm (e.g. the function nlm in R) to carry out the maximization.

Here is a set of choices of initial estimates for the circular case, given data $\{y_i\}$:

- Estimate $a$ by $\hat{a}_{\text{init}}$, the vector mean of the data.
- Estimate $\rho$ by $\hat{\rho}_{\text{init}}$, the average distance between the data and $\hat{a}_{\text{init}}$, i.e. $n^{-1} \sum |y_i - \hat{a}_{\text{init}}|$.
- Estimate $\kappa$ by the reciprocal of the sample variance of the radial part of the centered data,

$$1/\hat{\kappa}_{\text{init}} = \text{var}\{|y_i - \hat{a}_{\text{init}}|\}.$$
where \( \mathbf{u}, \mathbf{v}, \mathbf{w} \) are three-dimensional orthonormal vectors. In particular, \( \mathbf{w} \) is the helix axis. Further, \( R = [u \ v \ w] \) is a \( 3 \times 3 \) rotation matrix. The vector \( \mathbf{b} \) represents the shift term. The rotated errors \( \mathbf{e}_i = R\mathbf{e}_i \) still follow independent isotropic normal distributions, \( \mathbf{e}_i \sim N_3(0, \sigma^2 I_3) \).

If \( R \) is a possible estimate of the rotation matrix, then the first two components of the rotated data

\[
\mathbf{y}_i = \begin{bmatrix} y_{i1} \\ y_{i2} \end{bmatrix} = \begin{bmatrix} (R^T \mathbf{x}_i)_1 \\ (R^T \mathbf{x}_i)_2 \end{bmatrix}
\]

will approximately follow the M-H model. Since the fit of the M-H model is invariant under rotations in the plane, the maximized M-H log likelihood for the \( \{\mathbf{y}_i\} \) depends only on the third column of \( R \), i.e. \( \mathbf{w} \), and not on the relative orientation of the first two columns. Hence write \( MLL(\mathbf{w}) \) for the maximized M-H log likelihood, depending on the choice of helix axis \( \mathbf{w} \).

To estimate \( \mathbf{w} \) we maximize \( MLL(\mathbf{w}) \) over \( \mathbf{w} \). As in the last section it is necessary to use an iterative numerical method such as the R routine \texttt{nlm}, starting from an initial estimate of \( \mathbf{w} \).

A suitable initial estimate \( \mathbf{w}_{\text{init}} \) can be found using e.g. modified principal component analysis or OptLS (Alfahad et al., 2018) or Rotfit (Christopher et al., 1996).

A unit vector is a constrained vector in three dimensions. For optimization purposes, it is helpful to represent it using unconstrained two-dimensional coordinates. For example, once an initial estimate has been selected, we can rotate the data so that the initial estimate points to the north pole, \( [0 \ 0 \ 1] \) and represent deviations about the north pole using stereographic coordinates \( \mathbf{p} = (p_1, p_2)^T \), say, where \( \mathbf{w} \) can be written in terms of \( \mathbf{p} \) as follows:

\[
\begin{align*}
\mathbf{w}_1 &= \frac{2p_1}{1 + p_1^2 + p_2^2}, \\
\mathbf{w}_2 &= \frac{2p_2}{1 + p_1^2 + p_2^2}, \\
\mathbf{w}_3 &= \frac{-1 + p_1^2 + p_2^2}{1 + p_1^2 + p_2^2}.
\end{align*}
\]

Then define a function

\[
f(p_1, p_2) = MLL(\mathbf{w})
\]

and maximize this function numerically starting at \( \mathbf{p} = \mathbf{0} \).

Note that the M-H procedure involves a nested use of numerical optimization. At the inner level, numerical optimization is used to maximize the M-H log likelihood, assuming the helix axis \( \mathbf{w} \) is given, yielding a maximized log likelihood \( MLL(\mathbf{w}) \). At the outer level, we maximize (6) over \( \mathbf{p} \), i.e. over the choice of \( \mathbf{w} \).

We now apply the method to estimate the axis for two real helices (Helices 7 and 8 from Mardia et al (2018)). For Helix 7 the estimated axis is \( (0.591, -0.795, 0.133)^T \) and for Helix 8 the estimated axis is \( (0.336, 0.516, -0.788)^T \). Their estimates from OptLS are respectively \( (0.601, -0.789, 0.129)^T \) and \( (0.318, 0.537, -0.780)^T \). The cosine and their angle for the two cases are \( 0.9999315, \theta = 0.01170463; 0.9995821, \theta = 0.0289111 \) These indicate that for the two cases, these estimates are very similar. The next section, examines their mean square error through a simulation study.
4 Simulation

In this section, we illustrate our M-H procedure for estimating the helix axis on 100 simulated helices that mimic a protein α-helix for different choices of sample size \( n \) and parameter values \( r, c, \) and \( \sigma^2 \) (with \( \beta = 2\pi/3.6 \)) and compare with OptLS procedure. For more details of protein α-helix see Mardia (2013), Branden & Tooze (1999) and Creighton (1993). We have 100 estimates of the helix axis \( \hat{w}_{M-H,i} \) by the M-H procedure and \( \hat{w}_{Opt,i} \) by the OptLS method. To calculate the accuracy of these estimates, we define the mean square errors (MSEs) in terms of the means of the inner products,

\[
\text{MSE}_{M-H} = 1 - \frac{1}{100} \sum_{i=1}^{100} \hat{w}_{M-H,i} \hat{w}_0^T, \quad \text{MSE}_{Opt} = 1 - \frac{1}{100} \sum_{i=1}^{100} \hat{w}_{Opt,i} \hat{w}_0^T,
\]

where the inner products are sample means,

\[
\hat{w}_{M-H} = \frac{1}{100} \sum_{i=1}^{100} \hat{w}_{M-H,i}, \quad \hat{w}_{Opt} = \frac{1}{100} \sum_{i=1}^{100} \hat{w}_{Opt,i},
\]

and \( \hat{w}_0 = (0, 0, 1)^T \) is the axis pointing to north pole. Let \( \theta \) be the angle between the estimated axis \( \hat{w}_{M-H} \) (or \( \hat{w}_{Opt} \)) and \( \hat{w}_0 \). If this angle vanishes, \( \theta = 0 \), then the estimated axis is a perfect fit, then the inner product is 1 (Deville et al., 2008), so that the MSE is equal to zero.

We illustrate the algorithm with an example of one simulated dataset that mimics a long protein α helix, where \( n = 30, r = 2.3, c = 5.4/(2\pi), \beta = 2\pi/3.6, \sigma^2 = 0.001 \), and the true axis is \( \hat{w}_0 = (0, 0, 1)^T \). We also estimate the axis of this dataset by OptLS. The estimated helix axis by M-H procedure is \( \hat{w}_{M-H} = (-5.9 \times 10^{-4}, 3.2 \times 10^{-4}, 0.9999999)^T \) and the estimated helix axis by OptLS is \( \hat{w}_{Opt} = (-3.8 \times 10^{-4}, 3.0 \times 10^{-4}, 0.9999998)^T \). The MSE by M-H procedure is \( 2.3 \times 10^{-7} \) and the MSE by OptLS is \( 1.1 \times 10^{-7} \). This result shows that OptLS is more accurate than M-H algorithm as the MSE is smaller by a factor of two.

Table 1 shows the MSE for six different simulated datasets. These data sets have been constructed with a variety of parameter choices. Set 2 mimics a long protein α helix \( (n = 30) \) and set 3 mimics short protein α helix \( (n = 12) \). The remaining data sets are modified versions of these sets. In particular, the error variance has been decreased for set 1 from \( \sigma^2 = 0.05 \) to \( \sigma^2 = 0.001 \) and increased for set 4 from \( \sigma^2 = 0.05 \) to \( \sigma^2 = 0.10 \). Sets 5 and 6 are fatter helices (changing \( r = 2.3 \) to \( r = 7 \)); in addition for set 5, the pitch parameter \( c \) has been reduced (from \( c = 5.4/(2\pi) = 0.859 \) to \( c = 0.63/(2\pi) = .1 \)). The parameter \( \beta = 2\pi/3.6 \) is fixed for all these sets.

In each case the MSE of M-H is at least a factor of two larger than the MSE of OptLS. From this result we conclude that the OptLS is generally much more accurate than the M-H procedure. This is partly expected for the reasons (i) and (ii) given in Section 2. Further, we are comparing only these two methods but of course there are other methods, mainly computational.
Table 1: Comparison between M-H and OptLS procedures by the mean square error.

|       | set 1     | set 2     | set 3     | set 4     | set 5     | set 6     |
|-------|-----------|-----------|-----------|-----------|-----------|-----------|
| n     | 30        | 30        | 12        | 12        | 12        | 12        |
| r     | 2.3       | 2.3       | 2.3       | 2.3       | 7         | 7         |
| c     | $\frac{5.4}{(2\pi)}$ | $\frac{5.4}{(2\pi)}$ | $\frac{5.4}{(2\pi)}$ | $\frac{5.4}{(2\pi)}$ | $\frac{0.63}{(2\pi)}$ | $\frac{5.4}{(2\pi)}$ |
| $\sigma^2$ | 0.001    | 0.05      | 0.05      | 0.1       | 0.05      | 0.05      |
| M-H   | $2.8 \times 10^{-7}$ | $1.5 \times 10^{-5}$ | $2.4 \times 10^{-4}$ | $4.5 \times 10^{-4}$ | $1.2 \times 10^{-2}$ | $2.3 \times 10^{-4}$ |
| OptLS | $1.2 \times 10^{-7}$ | $0.5 \times 10^{-5}$ | $1.4 \times 10^{-4}$ | $2.8 \times 10^{-4}$ | $0.01 \times 10^{-2}$ | $0.8 \times 10^{-4}$ |

5 Appendix: Extension of Mardia and Holmes Model

Mardia and Holmes’s bivariate model can be extended to any dimension on replacing the ellipse by an ellipsoid. Namely, let $X$ be a random vector in $d$ dimension then their distribution has the probability density function (p.d.f.)

$$f(x; \mu, \Sigma, \kappa) = C(\kappa)|\Sigma|^{-1/2} \exp\left\{-\frac{1}{2} \kappa((x - \mu)^T \Sigma^{-1} (x - \mu) - 1)^2\right\}$$

(7)

where $x$ is dimension $d$ the concentration parameter $\kappa > 0$; $\mu$ takes any value in $R^d$ and $\Sigma$ is a positive definite matrix. It turns out that the normalizing constant is given by a parabolic cylindrical function and is given below. For the right cylinder, the two small eigenvalues are equal a priori. The axis is the $z$-axis if we take the largest eigenvalue as the third one; that is a thin and long ellipsoid so may be relevant "tangentially" though the multivariate Mardia-Holmes model will be useful for any inference related to fitting an ellipsoid.

We will use the general summary of elliptic family by Azzilini(2014,pp.168-169) of which this is a member but not studied. Let us write

$$r^2 = (x - \mu)^T \Sigma^{-1} (x - \mu).$$

Then the pdf can be rewritten as

$$f(x; \mu, \Sigma, \kappa) = C(\kappa)|\Sigma|^{-1/2} p(r^2)$$

(8)

where

$$C(\kappa) = \Gamma(d/2)/(2\pi^{d/2} b(\kappa)),$$

with

$$b(\kappa) = \int_0^\infty r^{d-1} p(r^2) \, dr \text{ and } p(r^2) = \exp\left\{-\frac{1}{2} \kappa(r^2 - 1)^2\right\}.$$ 

We need now to evaluate $b(\kappa)$ given by

$$b(\kappa) = \int_0^\infty r^{d-1} \left\{\exp\left\{-\frac{1}{2} \kappa(r^2 - 1)^2\right\}\right\} \, dr.$$
In fact, it can be expressed in terms of the parabolic cylindrical function defined by (see, Abramowitz and Stegun, 1965, Chapter 9, p.688).

\[ U(a, z) = \frac{1}{\Gamma(a + \frac{1}{2})} \exp \left( -\frac{1}{2}z^2 \right) \int_0^{\infty} s^{a-\frac{1}{2}} \exp \left( -\frac{1}{2}s^2 - zs \right) ds. \]

We have

\[ b(\kappa) = \frac{\Gamma(a + \frac{1}{2}) \exp(-\frac{\kappa}{2})}{2\kappa^{\frac{d+1}{4}}} U(a, -\sqrt{\kappa}), \quad (9) \]

where \( a = (d - 1)/2 \). Note that if \( d = 2n \) then \( a = n - \frac{1}{2} \) and if \( d = 2n + 1 \) then \( a = n \). For \( d = 3 \), we have \( a = 1 \).

We now summaries a few properties The mode of the distribution is given by

\[ (x - \mu)^T \Sigma^{-1} (x - \mu) = 1. \]

Further,

\[ E(X) = \mu, \quad E(X - \mu)(X - \mu)^T = \alpha \Sigma, \quad (10) \]

where \( \alpha \) is a function of \( \kappa \). The most general equation of ellipsoid is given by

\[ (x - \mu)^T \Sigma^{-1} (x - \mu) = 1 \]

so 1 in the LHS does NOT need any adjustments. It can be noted that the model works to fit a general ellipsoid when there is a very high probability of concentration around

\[ (x - \mu)^T \Sigma^{-1} (x - \mu) = 1 \]

where \( \Sigma \) is positive definite.

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