Probability distributions for measures of placental shape and morphology

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Abstract

Birthweight at delivery is a standard cumulative measure of placental growth, but is a crude summary of other placental characteristics, such as, e.g., the chorionic plate size, and the shape and position of the umbilical cord insertion. Distributions of such measures across a cohort reveal information about the developmental history of the chorionic plate which is unavailable from an analysis based solely on the mean and standard deviation. Various measures were determined from digitized images of chorionic plates obtained from the pregnancy, infection, and nutrition study, a prospective cohort study of preterm birth in central North Carolina between 2002 and 2004. Centroids (geometric centers) and umbilical cord insertions were taken directly from the images. Chorionic plate outlines were obtained from an interpolation based on a Fourier series, while eccentricity (of the best-fit ellipse), skewness, and kurtosis were determined from the method of moments. Histograms of each variable were compared against the normal, lognormal, and Lévy distributions. Only a single measure (eccentricity) followed a normal distribution. All others followed lognormal or ‘heavy-tailed’ distributions for moderate to extreme deviations from the mean, where the relative likelihood far exceeded those of a normal distribution.

Keywords: placenta, chorionic plate, shape analysis, morphology, distributions

1. Introduction

The placenta is the interface across which all oxygen and nutrients are exchanged between mother and fetus. Understanding the development and function of the human placenta is crucial to gaining insight into the environment of the developing fetus, whose health is thought to be an important influence on childhood and lifelong health (Barker 1995).
The placenta is conventionally thought to develop uniformly outward from the site of the umbilical cord insertion, leading to an approximately circular shape. However, while circular placentas are infrequently observed, recent work (Salafia et al 2010) has suggested that the ‘average’ placental shape within a cohort is, in fact, close to circular, though there remains some debate on this issue (Pathak et al 2010, Nelson and Burton 2010). The ability of the chorionic plate to extend laterally uniformly outward from the cord insertion is due, in part, to the suitability of the maternal uteroplacental environment. Any deficiencies in that environment can have adverse effects on placental and, by extension, fetal development. Consequently, the analysis of the deviations of mature placental chorionic surface shapes from ‘regularity’ (circular, or otherwise) can provide information about the uterine environment and possibly provide indicators about the health of the child.

The structure of the mature placenta is geometrically complex. The umbilical cord is usually attached near the center of the placenta, but this is not always the case; eccentric, marginal and velamentous cords inserted onto the extraplacental membranes are not rare (Benirschke et al 2006). From the point of the cord insertion onto the chorionic plate, the fetal chorionic vascular system branches and spreads laterally across the chorionic plate. At later stages in the branching and extension of chorionic surface vessels, veins and arteries dive down into the placenta and continue branching to contribute to disk thickness. The chorionic surface outline of the delivered placenta is a culmination of lateral placental vascular growth.

A mature placenta can take many different shapes, from near-circular to multi-lobed to star-shaped. There is little or no explanation as to why such variations of placental shapes exist, apart from ‘trophotropism’ (Ramos-Arroyo et al 1988, Cunningham et al 1997, Benirschke and Kaufman 2000), an argument which says, in effect, that ‘the placenta grows where it can and does not grow where it cannot’. There is no data about whether shape variations are associated with particular complications or subsequent health problems. One of the main goals of the present study is to understand the genesis, development, and evolution of mature placental chorionic surface shape from the distributions of various measures of placental shape. The shape of a placental chorionic surface or, indeed, any two-dimensional object, can be characterized by area, perimeter, compactness (perimeter squared divided by area), eccentricity (of a bounding ellipse), elongation and rectangularity (of a bounding box), etc. In addition, the chorionic plate outline can be analyzed in terms of its ‘roughness’ and ‘correlation’, both of which are standard measures used in the statistical analysis of rough surfaces (Barabási and Stanley 1995). The eccentricity and orientation of the best-fit ellipse, skewness, and kurtosis can be calculated from the lower-order moments of the chorionic plate (Teague 1980, Prokop and Reeves 1992), and the distance between the umbilical cord insertion and the centroid, which provides an indication about how the placenta developed with respect to the umbilical cord, is extracted directly from the images. The roughness and correlation function are based on a Fourier representation of each chorionic plate outline.

Although an ideal placental shape is expected to be regular, if only to minimize the cost of maintaining its vascular network, deviations from regularity can be quite pronounced, as noted above, and are not uncommon. This indicates that the lateral growth of the placental chorionic surface is not typically a uniform process, but has an element of randomness in many, if not most pregnancies, that is, different regions of the placental chorionic surface may develop at different random rates. The potentially important corollary to this is that the ‘fetal programming’ hypothesis may be germane to the majority of births, since few placentas are round with perfectly central cords. Various measures can and have been extracted from digitized images of placentas (Salafia et al 2005) and plotted as distributions, but an analysis of their distributions has yet to be reported. Our fundamental premise is that the form of
these distributions can provide information about the statistical properties of these measures that encode the underlying developmental properties that led to these distributions. Attaining a better understanding of the timing of development of placental chorionic surface shape features, which may reflect early perturbations of placental vascular growth (Salafia et al 2010), may clarify how risk of the wide range of diseases that have been associated with gestational pathology develops or, when in subsequent pregnancies of that mother, surveillance might be expected to be useful in the identification of recurrence, since there is a low but finite risk of recurrence after preeclampsia (McDonald et al 2009), preterm birth (Iams 2010), fetal growth restriction (Kinzler and Kaminsky 2007), stillbirth (Reddy 2007), or even miscarriage (Flint and Gibb 1996, Regan and Rai 2000).

Placental growth has been shown to be empirically modeled by the growth of a fractal by diffusion-limited aggregation (Yampolsky et al 2008). From this phenomenology, we can consider the notion of a random walk (Feller 1968), where a ‘walker’ takes small sequential steps to the left or right, each chosen randomly with equal probability. As the number of steps increases, the distribution of possible distances from the walker’s initial position approaches a normal distribution. An alternative version of a random walk is based on independent random relative increments which, as the number of steps increases, leads to a lognormal distribution (Limpert et al 2001). Finally, a random walk with step sizes that decay as a power law for large step lengths is known as a ‘Lévy flight’. The likelihood of a large step is much greater than for a random walk, which has the effect of enhancing the rate of displacement compared to a random walk, and the resulting displacements follow a Lévy distribution (Tsallis 1997).

2. Methods and materials

2.1. The placental cohort

The data set for our analysis is obtained from the digital images of placentas collected from the pregnancy, infection, and nutrition study, a cohort study of women recruited at mid-pregnancy from an academic health center in central North Carolina. The study population and recruitment techniques are described in detail elsewhere (Kaufman et al 2003). Beginning in March 2002, all women recruited into this study were requested to consent to a detailed placental examination. As of 1 October, 2004, 1159 women (94.6%) consented to such examination and 1014 (87.4%) had placentas collected and photographed for image analysis. Of these, 1008 (99%) were suitable for analysis.

Placental gross examinations, histology reviews, and image analyses were performed at EarlyPath Clinical and Research Diagnostics, a New York State-licensed histopathology facility under the direct supervision of Dr Carolyn Salafia. The institutional review board from the University of North Carolina at Chapel Hill approved this protocol. The fetal surface of each placenta was wiped dry and placed on a clean surface, after which the extraplacental membranes and umbilical cord were trimmed from the placenta.

The fetal surface was photographed together with the laboratory identification number and a 3 cm section of a plastic ruler in the field of view using a standard high-resolution digital camera with a minimum image size of 2.3 megapixels. A trained observer captured the Cartesian coordinates that marked the site of the umbilical cord insertion and a series of such coordinates along the perimeter of the fetal surface. The perimeter coordinates were captured at intervals of no greater than 1 cm, with additional coordinates if it appeared essential to accurately capture the shape of the fetal surface.
Table 1. Measures of the chorionic plate that are calculated in this paper. Against the name of each measure is its symbol, definition, and a formula expressed in terms of moments $\mu_{ij}$ of the region bounded by the chorionic plate outline (appendix B) or the Fourier coefficients $a_n$ and $b_n$ of the outline (appendix A). The fundamental mathematical definitions of these measures, from which the formulas in this table are derived, are given in appendices A and B.

| Name           | Symbol | Definition                                                                 | Formula |
|----------------|--------|-----------------------------------------------------------------------------|---------|
| Area           | $A$    | Area within chorionic plate outline                                         | $\mu_{00}$ |
| Centroid       | $(x_c, y_c)$ | Geometric center of area within chorionic plate outline                     | \( \left( \frac{\mu_{30}}{\mu_{00}}, \frac{\mu_{03}}{\mu_{00}} \right) \) |
| Eccentricity   | $e$    | Eccentricity of bounding ellipse                                            | \( \sqrt{1 - \frac{b_n^2}{a_n^2}} \) |
| Skewness       | $(S_x, S_y)$ | Asymmetry of image projections onto $x$- and $y$-axes                         | \( \left( \frac{\mu_{30}}{\mu_{00}^{3/2}}, \frac{\mu_{03}}{\mu_{00}^{3/2}} \right) \) |
| Kurtosis       | $(K_x, K_y)$ | Peakedness relative to normal distribution of image projections onto $x$- and $y$-axes | \( \frac{\mu_{40}}{\mu_{20}^2} - 3, \frac{\mu_{04}}{\mu_{02}^2} - 3 \) |
| Roughness      | $W$    | Standard deviation of chorionic outline from the average radius             | \( \sqrt{\frac{1}{N} \sum_{n=1}^{N} (a_n^2 + b_n^2)} \) |

2.2. Measures of chorionic plate shape and morphology

A Fourier series (appendix A) is used to interpolate between the discrete points captured along the perimeter of the chorionic plate (section 2.1), resulting in a smooth outline. A Fourier series is a sum of trigonometric functions (sines and cosines) whose coefficients measure the deviation of the outline from circularity. The lower-order Fourier coefficients capture information about the gross shape, whereas higher order coefficients are required to accurately recreate rapidly-varying perimeters or those with significant deviations from circularity, such as lobes and protrusions. The distance between data points describing each chorionic plate perimeter can vary depending on how rapidly the perimeter changes. Using higher Fourier terms for the rapidly-varying sections of perimeter has the unfortunate effect of introducing unwanted oscillations in slowly-varying sections of the outline. By creating linearly-interpolated points between actual data points, this effect can be suppressed, and both features of the perimeter are correctly reproduced by the Fourier series. Effectively, the numerical integrations required to calculate the Fourier coefficients are undertaken with smaller trapezia. We use 20 coefficients to fully capture all perimeter information without introducing spurious oscillations. While introducing linearly interpolated points makes assumptions about the data, the original images indicate that the placental perimeter does not vary rapidly between the data points. Additionally, our approach is expected to be more accurate than simply connecting the perimeter data with straight segments. Both the Fourier coefficients of the outline and the moments of the region surrounded by the outline are used to calculate measures of the shape and morphology of the chorionic plate. Table 1 summarizes the measures and their formulas. Details of the computational methods may be found in (Gill 2012).

The area bounded by the chorionic outline provides a cumulative measure of the development of the placenta at delivery. No information is provided about the shape or morphology of the chorionic plate—this is contained in higher moments of this outline. The skewness measures the asymmetry with respect to the mean of projections of the outline.
onto the x- and y-axes, viewed as distributions. The kurtosis measures the peakedness or flatness of these projections relative to that of a normal distribution, whose kurtosis has the value 3. A positive (resp., negative) kurtosis means that the distribution is more (resp., less) peaked than a normal distribution. Each chorionic plate has also been represented by an ellipse, whose eccentricity and orientation are determined by the zeroth and first moments of the outline.

The chorionic plate outline provides complementary information to the moment analysis. The measure we use is the roughness, which is a standard quantity used to characterize fluctuating interfaces. The roughness, defined in (A.5), is an average over the chorionic plate outline of root-mean-squared deviations from an average radius. Thus, roughness measures the ‘width’ of the deviations of the outline from a circle. A small roughness indicates a narrow width, which corresponds to an approximately circular outline, while a large width results from larger deviations from circularity, such as those of lobed or star-shaped outlines.

2.3. Probability distributions

When calculated for all of the placentas in our cohort, the measures compiled in table 1 yield ranges of values that can be represented as distributions, that is, the relative frequencies of the outcomes of the measures. These distributions embody information about the developmental characteristics of placentas, which can be identified by comparing them with distributions that are associated with particular types of processes. The distribution functions that we use in this paper are summarized below, with details provided in appendix C.

The most common probability distribution is the Gaussian, or normal, distribution. The probability density of this distribution is completely characterized by its mean and standard deviation. Normal distributions are so common because of the central limit theorem, which states that, under quite weak conditions, such distributions are the cumulative result of a large number of additive random events (Feller 1968). A related distribution is the lognormal, which is the probability of a variable whose logarithm is normally distributed (Limpert et al 2001). The lognormal is a skewed distribution, which occurs when averages are low, variances comparatively large, and values of the quantity being measured cannot be negative. This distribution is the cumulative result of a large number of multiplicative random events.

A qualitatively different distribution from the normal and lognormal distributions is the symmetric Lévy distribution (Tsallis 1997). The main distinguishing characteristic of Lévy distributions is that the probability of extreme variations decays like a power of that variation, as indicated in (C.7). Hence, the occurrence of such variations is far more likely than for a normal distribution, which decays exponentially for extreme variations. For this reason, Lévy distributions are called ‘heavy tailed’. Lévy distributions arise from additive random events which may involve quite large changes. In contrast, the events that result in the normal and lognormal distributions are comparatively small.

3. Results

3.1. Interpolation of chorionic plate outlines

Figure 1 shows typical fits to the data points of chorionic plate outlines obtained with the method described in appendix A. Two types of outlines are shown: one with a single-valued and one with a multi-valued radius. A single-valued radius means that a line emanating from the centroid intersects each point on the perimeter only once, while a multi-valued radius function may intersect the perimeter more than once. In the latter case, the perimeter folds
back on itself, and the corresponding chorionic plate has lobes or some other irregular shape. Note the irregular spacing of the points along the perimeter, as described in section 2.1. The outline with the single-valued radius has a regular shape, so relatively few data points are needed. However, the outline with the multi-valued radius has intervals where more points are needed to describe regions of greater curvature, which can occur for a small protrusion or, as in this case, a large morphological entity such as a lobe. This is reflected in the number of terms that must be included in the Fourier series to produce an accurate interpolation. The series for the outline with the single-valued radius required fewer terms than that for the outline with the multi-valued radius because regions of larger curvature mean that more rapidly-varying trigonometric functions must be included in the interpolation.

3.2. Chorionic plate area

The distribution of areas $A$ bounded by the outlines of the chorionic plates is shown as a histogram in figure 2. These histograms were constructed by first defining normalized areas as the original areas $A$ divided by the average area $A_{av}$ of the cohort. These data points are grouped into contiguous ‘bins’ of width 0.1, a choice dictated by the balance between the inherent statistical fluctuations in such a limited sample against the smoothness of the resulting relative frequency profile. Choosing a width of 0.05 produced a somewhat noisier distribution but did not substantially alter any of the fits. The relative frequencies $f$ are obtained.

Figure 1. Interpolations of two chorionic plate outlines that have been determined by the method described in appendix A. The origin of the data points for each outline has been shifted to its centroid. The original data points of a smooth featureless outline and its centroid are indicated by the open circles, with the interpolation shown by the broken curve. Closed circles mark the original data points and centroid and the solid curve shows the interpolation for an outline with a multi-valued radius function.
Figure 2. Histogram of chorionic plate areas shown as the relative frequencies of bins of normalized areas on linear (a), (c), (e) and logarithmic (b), (d), (f) scales for relative frequencies. These are compared with (a), (b) the normal distribution, (c), (d) the lognormal distribution, and (e), (f) and an optimized Lévy distribution, each of which is shown by a solid curve.

by dividing the fraction of the total number of data points within each bin by the bin width, so the shaded area in the histogram in figure 2 is equal to 1. This way of plotting histograms, which eliminates the units of the quantities being plotted, allows distributions of different measures to be compared directly, as well as providing the conceptual convenience of having the mean at 1.

Superimposed on the area histogram are the normal (figure 2(a)) and lognormal (figure 2(c)) distributions with mean and standard deviation determined from the data, in the latter case using (C.3) and (C.4), and an optimized fit to a Lévy distribution (figure 2(e)), which yielded the parameters $\alpha = 1.62 \pm 0.02$ and $\gamma = 0.046 \pm 0.04$ in (C.5). This fit was obtained by the least squares method, in which a Lévy distribution was calculated at the center of each bin, and the sum of the squares of the differences between these values and those of
Figure 3. Histograms of the roughness (A.6). A linear plot is shown in (a) and the corresponding plot with a logarithmic frequency scale in (b), with the frequencies associated with each bin indicated by points. Each histogram is compared with a lognormal distribution, which is indicated by the solid curve.

The bins was minimized by varying $\alpha$ and $\gamma$. Figures 2(b), (d), (f) show the same distributions plotted on a logarithmic scale for the frequencies (but maintaining the same linear scale for the areas). Such plots are used to accentuate the extreme variations of data (the ‘tails’ of the relative frequencies) to assess how various distributions account for this regime. Note that, according to (C.7), the fit in figure 2(c), yields a probability for large deviations from the mean decreases as $(A/A_{\text{av}})^{-2.62}$.

3.3. Perimeter roughness

The perimeter roughness (A.5) provides a measure of the shape of the chorionic plate. Figure 3(a) shows the histogram of this quantity using the normalization in figure 2, i.e. roughness divided by its average over the cohort and its frequencies defined such that the sum of the shaded regions is equal to 1. The bin width for the histogram was again taken as 0.1. Also shown is a lognormal distribution whose mean and standard deviation were determined from the data by using (C.3) and (C.4). Figure 3(b) shows the histograms and corresponding lognormal distributions plotted on a logarithmic scale for the frequencies. The tails of this distribution extends to much larger values than the area distributions in figure 2, so the semi-logarithmic plots provide correspondingly more information about the distribution. The histogram is significantly skewed, so only the lognormal distribution is appropriate, as both the normal and Lévy distributions are symmetric.

3.4. Distance between the centroid and the umbilical cord insertion

As the placenta grows outwards from a central point, the position of the umbilical cord insertion relative to the centroid of the placenta, which is a measure of the centrality of this point, provides information about the isotropy of placental development. If the umbilical cord insertion is close to the centroid, then the placenta has, on average, grown outwards more symmetrically than if the cord insertion is displaced appreciably from the centroid. This does not imply that the chorionic plate is circular in this case, just that lateral growth was not skewed in any direction. The histogram of the distances between the centroid and the umbilical cord insertion is show in figure 4, plotted with the distances divided by their average, with frequencies that sum to 1. The data have been grouped into bins of width 0.1. Superimposed on the histograms are the lognormal distribution whose mean and standard deviation are determined from the data by using (C.3) and (C.4). Note that, in common with
Figure 4. (a) Histogram of the distances between the centroid and the umbilical cord insertion compared with the lognormal distribution. (b) Semi-logarithmic plot of the histogram and distributions in (a), with the bin frequencies represented by points.

Table 2. Mean ($\mu$), standard deviation ($\sigma$), and range of placental measures calculated from moment-based methods, as described in appendix B, compared with those determined in Salafia et al (2010).

| Measure                                      | Moments | Salafia et al 2010 |
|----------------------------------------------|---------|--------------------|
| Chorionic plate area (cm$^2$)                | $\mu$   | $\sigma$ | Range     | $\mu$   | $\sigma$ | Range     |
| Major axis (cm)                              | 21      | 3.3       | 10–48     | 21      | 3.3       | 12–43     |
| Minor axis (cm)                              | 17      | 2.3       | 7–27      | 18      | 2.4       | 9–29      |
| Radius of circle with the same area as the chorionic plate (cm) | 9.5     | 1.1       | 4.1–14.9  | 9.4     | 1.1       | 5.8–13.8  |
| Distance between cord insertion to chorionic plate centroid (cm) | 3.7     | 2.3       | 0.01–24.6 | 3.6     | 2.4       | 0.1–23.7  |

the histograms in figure 3, the histogram of the distances is highly skewed, with a long tail, so only the lognormal distribution is appropriate.

3.5. Placental shape

The moment expansion method described in appendix B has been used to calculate the best-fit ellipse for the chorionic plate of each placenta in the cohort. Best-fit ellipses are created to have the same size, orientation, and eccentricity, as the image, with its center at the centroid of the image. Table 2 compares various measures determined from the moments of the chorionic plate outline with the corresponding quantities calculated in Salafia et al (2010). The placentas in Salafia et al (2010) were oriented such that ‘the chorionic plate margin nearest the site of membrane rupture was positioned at 6 o’clock’. The data used in this work is from the same digitized source, and thus oriented in the same way. However, this orientation does not affect any of our conclusions.

Figure 5 shows several placentas and their best-fit ellipses. Some outlines fit their ellipse quite well. These correspond to chorionic plates with regular shapes. But for chorionic plates that have irregular shapes with pronounced lobes and other protrusions, the ellipses do not provide as good a fit. As expected from the discussion in appendix B, such placentas have appreciable higher-order moments to account for their irregularities. In such cases, quantities derived from higher-order moments, such as skewness (third-order) and kurtosis (fourth-order) provide appreciable additional information about placental shape. The extent to which
the ellipse accounts for the shape of the chorionic plate can also be used to estimate the roughness. Any part of the chorionic outline that lies within the ellipse or crosses its boundary contributes to the roughness, as is apparent from (A.5).

Figure 6(a), (c), (e) shows histograms of the eccentricities and the $x$- and $y$-projections of the skewness and kurtosis compared with normal distributions with the same means and variances. The bin sizes were 0.04 for the eccentricity and kurtosis and 0.05 for the skewness. Figure 6(b), (d), (f) compares the histograms with optimized Lévy distributions using the procedure described in section 3.2. The optimized parameters are $\alpha = 2$ and $\gamma = 0.012$ for the eccentricity, $\alpha = 1.6$ and $\gamma = 0.009$ for the skewness, and $\alpha = 1.75$ and $\gamma = 0.0036$ for
Figure 6. Histograms of the eccentricities of the best-fit ellipses compared with (a) a normal and (b) an optimized Lévy distribution. Histograms of the skewness of the chorionic plate, projected onto the x- and y-axes (shown as shaded and unshaded bins, respectively) compared with the (c) normal and (d) an optimized Lévy distribution. Histograms of the kurtosis of the chorionic plate, projected onto the x- and y-axes (shown as shaded and unshaded bins, respectively) compared with the (e) normal and (f) an optimized Lévy distribution. The fits in (c)–(f) were obtained by averaging over the x- and y-projections of each quantity.

the kurtosis, with the same error bars as in section 3.2. For the skewness and kurtosis, the fits were carried out for the averages over their x- and y-projections.

4. Discussion

There are large variations in the characteristics of mature placental shapes. How do these variations arise? The uterine environment plays a part, for example, in cases where ‘trophotropism’ suggests that the placenta can differentially grow, effectively migrating to a
Table 3. Summary of best-fit distributions for the measures in table 1, as well as the distance between the centroid and the umbilical cord insertion.

| Measure                        | Best fit | Comments                                                                 |
|--------------------------------|----------|---------------------------------------------------------------------------|
| Area                           | Lévy     | Normal distribution for small values, Lévy distribution for moderate to large values |
| Roughness                      | Lognormal| Power law (‘heavy’) tail                                                  |
| Centroid–umbilical cord distance| Lognormal| Poor fit near peak of histogram                                           |
| Eccentricity                   | Normal   | Optimized Lévy distribution also yields normal distribution               |
| Skewness                       | Lévy     | Average over x- and y-directions                                          |
| Kurtosis                       | Lévy     | Average over x- and y-directions                                          |

more suitable location in the uterus. However, there may also be manifestations of randomness within placental growth. The chorionic plate outline of the mature placenta reflects, in essence, a summary of the effects of all factors that can impact the lateral expansion of the chorionic surface. Identifying whether a placental measure follows one of the distributions in appendix C or another distribution is important for assessing the statistical properties of lateral growth or the processes underlying growth. The results we described in the preceding section are summarized in table 3.

4.1. Chorionic plate area

The Gaussian and lognormal distributions provide good accounts of the gross shape of the histogram of chorionic plate areas, but underestimate the peak near the mean (figure 2(a)). The larger positive deviations from the mean of the area are better described by the lognormal distribution, but the Lévy distribution provides a discernibly better overall fit to the entire histogram than either the normal or lognormal distributions (figure 2(c)). In particular, the Lévy distribution gives a much better account of the peak near the mean and at large positive deviations from the mean, where the decay is much slower than for the normal distribution. This can be seen directly in figure 2(b), (d), where we plot the logarithm of the frequencies in figure 2(a), (c) against the normalized area. In this coordinate system, the normal distribution appears as an inverted parabola, as follows from (C.1). Figure 2(b), (d) clearly shows that the lognormal distribution provides a good fit for moderate positive deviations from the mean, but that the Lévy distribution provides a much better fit at all large positive deviations from the mean. The normal distribution, however, provides a better description of the data at values below the mean.

To appreciate the consequences of the better fit provided by the Lévy distribution, we return to the notion of a random walk (Feller 1968), where a ‘walker’ takes small sequential steps to the left or right, each chosen randomly with equal probability. As previously noted, as the number of steps increases, the distribution of possible distances from the walkers initial position approaches a normal distribution. Lévy distributions arise from random walks with step sizes chosen from a distribution for which step sizes decay as a power law for large step lengths. Hence, the likelihood of a large step is much greater than for a random walk. This has the effect of enhancing the rate of displacement compared to a random walk. The fits in figure 2 thereby suggest that placentas whose chorionic plate area is much smaller than the mean, which follow a normal distribution, developed by a series of small independent random steps. Placentas with a chorionic area that is much larger than the mean, however, developed
Figure 7. Log–log plot of the histogram in figure 3(a), with the bin frequencies represented as dots. The line represents an optimized linear fit to the tail of the distribution, yielding a slope of $-3.47$. The quality of this fit suggests that the tail of the distribution has a power law decay, as in (C.6).

by large steps, or a series of smaller correlated steps. In either case, the growth of placentas with a large chorionic area is manifestly inconsistent with normal behavior.

4.2. Perimeter roughness

The skewed histogram in figure 3 means that symmetric distributions are not appropriate, so we have focused on the lognormal distribution. This distribution provides a reasonable fit to the data, though there are evident discrepancies. However, as the semi-logarithmic plot in figure 3(b) shows, while the lognormal distribution accurately accounts for moderate positive deviations from the mean, extreme deviations (the tails) show systematic differences from this distribution.

An analysis of this regime is shown in figure 7, where a log–log plot of the data in figure 2(a) is compared with a linear fit to the tail of the distribution. Bearing in mind that there are fewer placentas for extreme values, so the scatter in the data is correspondingly greater than for smaller values, the linear fit provides an acceptable account of the tail. The significance of this becomes apparent when we refer to the power law behavior of the tails of the Lévy distribution in (C.6). The linear fit in figure 7 shows that the tails of this histogram is indeed consistent with a power law decay. Although this is indicative of the wild fluctuations associated with Lévy distributions, we have not been able to fit such a distribution to the entire range of the data. Nevertheless, the analysis in figure 7 is very suggestive, though we must conclude this discussion with a word of caution. Linear fits to log–log plots typically rely on several decades (i.e. powers of ten on a log–log plot) of data to enable a firm conclusion to be drawn about the existence of power law tails. Our analysis is based on less than half a decade, which is the nature of the measures we are using, so our conclusions must be tempered accordingly.

4.3. Distance between the centroid and the umbilical cord insertion

The lognormal distribution in figure 4 provides a good account of the profile of the histogram of distances between the centroid and the umbilical cord insertion, apart from the main peak of the histogram, which is overestimated by approximately 10%. Even more significant is the fit in figure 4(b), which shows that the lognormal distribution provides an excellent account of the tail of the histogram. Hence, we conclude that the distribution associated with this quantity, when
measured in mature placentas across a cohort, is the cumulative result of small multiplicative random steps. This, in turn, leads to two further considerations. Consider first the fact that a vasculogenic zone is already evident at the fifth week of development (Kliman 1998). Thus, in the early stages of development, we expect that the centroid of the developing chorionic plate and umbilical cord insertion are strongly correlated. However, as further development occurs, random factors diminish this correlation, eventually producing the uncorrelated behavior seen in figure 4. Why is the distribution lognormal, rather than normal? Chemical reactions and, by extension, biochemical reactions, are inherently multiplicative processes (Limpert et al 2001) because concentrations of particular species must be simultaneously present at a specific location for development to occur. The amount of each quantity, which varies across the placenta, determines the extent to which development occurs. The comparisons in figure 4 suggests that these spatial variations are random.

4.4. Placental shape

The most striking result in figure 6 is how well the normal distribution accounts for the eccentricities of the best-fit ellipses across the cohort. This is confirmed by the optimized Lévy distribution, which has \( \alpha = 2 \) and a standard deviation of \( \sqrt{2} \gamma = 0.0155 \), the latter comparing well with the value \( \sigma = 0.0149 \) obtained directly from the data. Hence, the eccentricity may be regarded as being normally distributed. The shape of the skewness is also described moderately well by a normal distribution, though the large deviations from the mean are better accounted for by the Lévy distribution. For the kurtosis, the normal distribution accounts for the width of the distribution, but underestimates the height of the peak near the mean and, of course, does not account for the occurrence of large deviations from the mean. Here, the Lévy distribution provides the superior description.

5. Summary

Placental weight is a standard measure of placental development and is often used as a primary indicator of fetal health. But weight is just one way that factors affect the developmental history of a placenta. Other measures have been presented before (Salafia et al 2005) and are revisited here in light of their distributions. Working from interpolations between data points obtained from digitized images of the cohort described in Kaufman et al (2003), we have calculated several measures of chorionic plate morphology, including its area, the roughness of the outline, the distance between the centroid and the umbilical cord insertion, and several shape parameters.

Our focus here is determining the extent to which the distributions of placental measures are described by normal or lognormal distributions, in other words, the extent to which the fluctuations of these measures result from the sum or product, respectively, of relatively independent factors. In fact, we found that normal distributions provide an accurate account only of the distribution of the eccentricities of the best-fit ellipses. Taken together, the results presented here demonstrate how an analysis of a cohort can reveal fundamental aspects in the development of placentas. The deviations from normal or lognormal behavior, in particular, provide the most direct indication of the presence of correlations in the development of the placenta. Large deviations from mean behavior are not simply the result of mild independent fluctuations, as normal or lognormal distributions would imply, but embody the wild fluctuations that lead to power law decay.

While we have focused entirely on geometric and morphological features in this paper, other characteristics of the chorionic plate would also benefit from our analysis, especially
those which take account of vasculature. Indeed, the correlation between placenta shape and any clinical outcome must address the question of function, which necessitates a more highly resolved analysis, delving into the vasculature (Seong et al 2013) and transport properties (Gill et al 2011). Such studies are in progress and will be reported in future publications.

**Appendix A. Fourier series for the chorionic plate outline**

The chorionic plate outline is represented by a set of points with coordinates \((x_k, y_k)\), for \(k = 1, \ldots, N\) obtained from the digitized images (section 2.1). To eliminate any bias in the data, we first calculate the coordinates of the centroid by taking the average of each perimeter coordinate:

\[
x_c = \frac{1}{N} \sum_{k=1}^{N} x_k, \quad y_c = \frac{1}{N} \sum_{k=1}^{N} y_k.
\]  

(A.1)

The centroid is taken as the origin of coordinates for the points along the chorionic outline. The radius \(r\) is specified in terms of the length \(s\) along the perimeter, which has length \(L\). The Fourier series for \(r(s)\) is

\[
r(s) = r_{av} + \sum_{n=1}^{N} \left[ a_n \cos \left( \frac{2\pi sn}{L} \right) + b_n \sin \left( \frac{2\pi sn}{L} \right) \right].
\]  

(A.2)

where the Fourier coefficients are

\[
a_n = \frac{2}{L} \sum_{k=1}^{N} r_k \cos \left( \frac{2\pi s_k n}{L} \right),
\]  

(A.3)

\[
b_n = \frac{2}{L} \sum_{k=1}^{N} r_k \sin \left( \frac{2\pi s_k n}{L} \right),
\]  

(A.4)

in which \(r_k\) is the radius of the \(k\)th data point at a distance \(s_k\) along the perimeter. The corresponding series for the coordinates \((x(s), y(s))\) of the perimeter are of the same form as (A.2), but with \(x_k\) and \(y_k\) in turn replacing \(r_k\) in (A.3) and (A.4).

The interpolation of the chorionic plate outline can be used to calculate several measures associated with the deviations of this outline from circularity. The roughness \(W\) of this outline is defined as the root-mean-squared deviations from its average radius \(r_{av}\):

\[
W = \left\{ \frac{1}{L} \int_{0}^{L} [r(s) - r_{av}]^2 \, ds \right\}^{1/2},
\]  

(A.5)

in which \(r(s)\) is the distance from the centroid to the chorionic plate outline at a point \(s\) along the outline and \(L\) is the length of the outline. The roughness is expressed in terms of the coefficients in (A.3) and (A.4) as

\[
W = \left[ \frac{1}{2} \sum_{n=1}^{\infty} (a_n^2 + b_n^2) \right]^{1/2}.
\]  

(A.6)

**Appendix B. Moments of chorionic plate shape**

An alternative to the contour-based analysis of chorionic plate shape using the Fourier series in appendix A is the area-based approach of moments. We define a function \(f(x, y)\) that takes the
value 1 within the chorionic plate area and the value 0 outside this area. The \((p, q)\)th moment \(\mu_{p,q}\) of the enclosed area is defined as

\[
\mu_{p,q} = \iint x^p y^q f(x, y) \, dx \, dy,
\]

where \(p, q = 0, 1, 2, \ldots\). If all of the moments are calculated, then the original shape can be restored. In practice, only lower-order moments, for which \(p + q \leq 4\) are typically used.

The zeroth-order moment \(\mu_{0,0}\) determines the area \(A\) of the chorionic plate,

\[
A = \mu_{0,0} = \iint f(x, y) \, dx \, dy,
\]

and the coordinates \((x_c, y_c)\) of the centroid are expressed in terms of \(\mu_{0,0}\) the first-order moments \(\mu_{1,0}\) and \(\mu_{0,1}\) as

\[
x_c = \frac{1}{A} \iint x f(x, y) \, dx \, dy = \frac{\mu_{1,0}}{\mu_{0,0}},
\]

\[
y_c = \frac{1}{A} \iint y f(x, y) \, dx \, dy = \frac{\mu_{0,1}}{\mu_{0,0}}.
\]

The zeroth- and second-order moments determine the best-fit ellipse. This ellipse is centered at the centroid of the chorionic plate and its semi-major and semi-minor axes \(a\) and \(b\), respectively, are the perpendicular lines that pass through the centroid for which the second-order central moments about these lines are maximum and minimum, respectively. The semi-major and semi-minor axes are given by (Teague 1980)

\[
a = \sqrt{\frac{1}{2} \left( \mu_{2,0} + \mu_{0,2} + \left( (\mu_{2,0} - \mu_{1,2})^2 + 4\mu_{2,1}^2 \right)^{1/2} \right) \mu_{0,0}^{-1}},
\]

\[
b = \sqrt{\frac{1}{2} \left( \mu_{2,0} + \mu_{0,2} - \left( (\mu_{2,0} - \mu_{1,2})^2 + 4\mu_{2,1}^2 \right)^{1/2} \right) \mu_{0,0}^{-1}},
\]

where the tilt angle \(\phi\) of the ellipse, measured counterclockwise with respect to the original coordinate axes, is (Teague 1980)

\[
\phi = \frac{1}{2} \tan^{-1} \left( \frac{2\mu_{1,1}}{\mu_{2,0} - \mu_{0,2}} \right).
\]

The convention is that \(\phi\) is the angle between the \(x\)-axis and the semi-major axis, where, by definition, \(a \geq b\). The eccentricity \(e\) of the best-fit ellipse is given by the usual formula:

\[
e = \sqrt{1 - \frac{b^2}{a^2}}.
\]

Higher-order moments include quantities such as skewness and kurtosis of \(x\)- and \(y\)-projections of the placental shape (for example, the \(x\)-projection is the image obtained by summing over all pixels in the \(x\)-direction). Expressions for these quantities are compiled in table 1.

### Appendix C. Probability density functions

The probability density function \(p(x)\) of a continuous random variable represents the relative likelihood that the random variable occurs at a given point \(x\). The probability density function
The probability density of the normal distribution is
\[ p_1(x; \mu, \sigma) = \frac{1}{\sqrt{2\pi\sigma^2}} \exp\left[\frac{-(x-\mu)^2}{2\sigma^2}\right], \tag{C.1} \]
in which \( \mu \) is the mean and \( \sigma \) the standard deviation. The corresponding quantity for the lognormal distribution is
\[ p_2(x; \mu, \sigma) = \frac{1}{x\sqrt{2\pi\sigma^2}} \exp\left[\frac{-(\ln x - \mu)^2}{2\sigma^2}\right], \tag{C.2} \]
where \( \mu \) is the mean and \( \sigma \) the standard deviation for \( \ln x \). These are related to the mean \( \mu' \) and variance \( \sigma'^2 \) of a random variable that is lognormally distributed by
\[ \mu = \ln(\mu') - \frac{1}{2} \ln\left(1 + \frac{\sigma'^2}{\mu'^2}\right), \tag{C.3} \]
\[ \sigma^2 = \ln\left(1 + \frac{\sigma'^2}{\mu'^2}\right). \tag{C.4} \]
The probability density function of the Lévy distribution
\[ p_3(x; \alpha, \gamma) = \frac{1}{\pi} \int_0^{\infty} e^{-\gamma k^\alpha} \cos(kx) \, dk, \tag{C.5} \]
where \( 0 < \alpha \leq 2 \) and \( \gamma > 0 \) is a width parameter. The Lévy distribution is known in closed form only for \( \alpha = 1 \) and \( \alpha = 2 \), with the latter yielding the normal distribution in the form
\[ p_3(x; 2, \gamma) = \frac{1}{\sqrt{4\pi\gamma}} \exp\left(-\frac{x^2}{4\gamma}\right), \tag{C.6} \]
which is a normal distribution with \( \mu = 0 \) and \( \sigma^2 = 2\gamma \). In all other cases the Lévy distribution must be evaluated numerically.

One of the most important characteristics of Lévy distributions is that the probability density of extreme variations of a random variable follows a power law:
\[ p_3(x; \alpha, \gamma) \rightarrow |x|^{-\alpha-1} \text{ as } |x| \rightarrow \infty. \tag{C.7} \]

References

Barabási A L and Stanley H E 1995 Fractal Concepts in Surface Growth (Cambridge: Cambridge University Press)

Barker D J 1995 Fetal origins of coronary heart disease Br. Med. J. 311 171–4

Benirschke K and Kaufmann P 2000 Pathology of the Human Placenta 4th edn (New York: Springer) pp 778–85

Benirschke K, Kaufmann P and Baergen R N 2006 Anatomy and Pathology of the Umbilical Cord 5th edn (New York: Springer) p 403 (table 12.1)

Cunningham F G, MacDonald P, Gant N, Leveno K J, Gilstrap L C, Hankins G D V and Clark S L 1997 William’s Obstetrics 20th edn (Stanford, CT: Appleton and Lange) pp 765–7

Feller W 1968 An Introduction to Probability Theory and its Applications vol 1 3rd edn (New York: Wiley)

Flint S and Gibb D M 1996 Recurrent second trimester miscarriage Curr. Opin. Obst. Gynecol. 8 449–53

Gill J S 2012 Morphology and vascular transport in the human placenta PhD thesis Imperial College London

Gill J S, Salafia C M, Grebenkov D and Vvedensky D D 2011 Modeling oxygen transport in human placental terminal villi J. Theor. Biol. 294 33–41
Iams J D and Berghella V 2010 Care for women with prior preterm birth Am. J. Obstet. Gynecol. 203 89–100

Kaufman J S, Dole N, Savitz D A and Herring A H 2003 Modeling community level effects on preterm birth Ann. Epidemiol. 13 377–84

Kinzler W L and Kaminsky L 2007 Fetal growth restriction and subsequent pregnancy risks Semin. Perinatol. 31 126–34

Kliman H J 1998 Umbilical cord Encyclopedia of Reproduction vol 4 ed E Knobil and J Neill (New York: Academic) pp 585–96

Limpert E, Stahel W A and Abbt M 2001 Log-normal distributions across the sciences: keys and clues BioScience 51 341–52

McDonald S, Best C and Lam K 2009 The recurrence risk of severe de novo preeclampsia in singleton pregnancies: a population-based cohort Br. J. Obstet. Gynaecol. 116 1578–84

Nelson D M and Burton G J 2010 Does a picture of the human placenta predict the future? Placenta 31 943

Pathak S, Hook E, Hackett G, Murdoch E, Sebire N J, Jessop F and Lees C 2010 Cord coiling, umbilical cord insertion and placental shape in an unselected cohort delivering at term: relationship with common obstetric outcomes Placenta 31 963–8

Prokop R J and Reeves A P 1992 A survey of moment-based techniques for unoccluded object representation and recognition CVGIP, Graph. Models Image Process. 54 438–60

Ramos-Arroyo M A, Ulbright T M, Yu P L and Christian J C 1988 Twin study: relationship between birth weight, zygosity, placentation, and pathologic placental changes Acta Genet. Med. Genellol. (Roma) 37 229–38

Reddy U M 2007 Prediction and prevention of recurrent stillbirth Obstet. Gynecol. 110 1151–64

Regan L and Rai R 2000 Epidemiology and the medical causes of miscarriage Best Pract. Res. Clin. Obstet. Gynaecol. 14 839–54

Salafia C M, Maas E, Thorp J M, Eucker B, Pezzullo J C and Savitz D A 2005 Measures of placental growth in relation to birth weight and gestational age Am. J. Epidemiol. 162 991–8

Salafia C M, Yampolsky M, Misra D P, Shlakhter O, Haas D, Eucker B and Thorp J 2010 Placental surface shape, function, and effects of maternal and fetal vascular pathology Placenta 31 958–62

Seong R-K, Getreuer P, Li Y, Girardi T, Salafia C M and Vvedensky D D 2013 Statistical geometry and topology of the human placenta Advances in Applied Mathematics, Modeling, and Computational Science (Fields Institute Communications vol 66) ed R Melnik and I Kotsireas (New York: Springer) pp 187–208

Teague M R 1980 Image analysis via the general theory of moments J. Opt. Soc. Am. 70 920–30

Tsallis C 1997 Lévy distributions Physics World 10 July pp 42–5

Yampolsky M, Salafia C M, Shlakhter O, Haas D, Eucker B and Thorp J 2008 Modeling the variability of shapes of a human placenta Placenta 29 790–7