A MULTISCALE VARIANCE STABILIZATION FOR
BINOMIAL SEQUENCE PROPORTION ESTIMATION

Matthew A. Nunes and Guy P. Nason

Imperial College, University of Bristol

Abstract: There exist many different wavelet methods for classical nonparametric
regression in the statistical literature. However, techniques specifically designed
for binomial intensity estimation are relatively uncommon. In this article, we pro-
pose a new technique for the estimation of the proportion of a binomial process.
This method, called the Haar-NN transformation, transforms the data to be ap-
proximately normal with constant variance. This reduces the binomial proportion
problem to the usual ‘function plus normal noise’ regression model and thus any
wavelet denoising method can be used for the intensity estimation. We demonstrate
that our methodology possesses good Gaussianization and variance-stabilizing prop-
erties through extensive simulations, comparing it to traditional transformations.
Further, we show that cycle-spinning can improve the performance of our technique.
We also explore the efficacy of our method in a real application.

Key words and phrases: Binomial random variable, Gaussianization, Haar-Fisz,
sequence probability estimation, variance stabilization.

1 Introduction

Wavelet transforms are now widely used as mathematical tools for applications
such as data compression, density estimation and nonparametric regression. In
particular, they can be used to estimate underlying signals from noisy observa-
tions, with many of these shrinkage techniques assuming that the corrupting noise
is Gaussian. For detailed discussions of the mathematical aspects of wavelets,
see Mallat (1989); Daubechies (1992); Nason and Silverman (1994); Vidakovic
(1999); for thorough coverage of wavelet shrinkage estimation, see Donoho and

This article investigates the problem of estimating the proportion parameter
associated with a sequence of binomial random variables (a binomial process)
using a wavelet-based transform. The usual regression model takes the following form: we observe the data, \( v = (v_0, v_1, \ldots, v_{N-1}) \) at equally-spaced timepoints assumed to be in the unit interval, where \( N = 2^J \). Our assumption is that the \( N \) observations \( \{v_k\} \) are modelled as a sequence of binomial random variables \( X_k \), where we assume the variables to be independent: \( X_k \sim \text{Bin}(n_k, p_k) \) for \( k \in \{0, \ldots, N-1\} \), where \( n_k \) is assumed known for each \( k \). Our aim is to try and estimate the unknown proportion vector \( p = (p_0, p_1, \ldots, p_{N-1}) \) from the observations \( \{v_k\} \). We assume \( p_k = P(k/N) \) for \( k \in \{0, \ldots, N-1\} \), where \( P \) denotes an underlying binomial proportion function.

In practice, this type of problem is difficult since the noise is not Gaussian, but more importantly the variance of the ‘noise’ depends on the mean, unlike the Gaussian situation: we have \( E(X_k) = n_k p_k \) and \( \text{Var}(X_k) = n_k p_k q_k \) (with \( q_k = 1 - p_k \)).

One approach is to transform the data so that it is variance-stabilized and approximately normal; a denoiser suitable for Gaussian noise is then applied and the data is transformed back to obtain an estimate of the proportion. One such transform is Anscombe’s inverse sine transformation (Anscombe, 1948), reviewed in the next section. Existing methodology for Haar-Fisz variance stabilization and Gaussianization has been successful for Poisson data (see for example Fryzlewicz and Nason (2004); Nason and Bailey (2008)). The Haar-Fisz transform cannot be used directly on binomial data as the variance is not stabilized. However, we introduce a modified transform that does.

In our simulations, we will compare the algorithm with Anscombe’s inverse sine transformation (Anscombe, 1948) and also the Freeman-Tukey averaged inverse sine transformation (Freeman and Tukey, 1950) when investigating Gaussianizing and variance-stabilizing properties.

Our method exhibits many benefits, namely:

1. It is shown to possess good Gaussianizing and variance-stabilizing properties;

2. It outperforms traditional Gaussianizing transformations in difficult cases, for example, when the binomial size is small or the binomial proportion is extreme;
3. It is computationally simple and easy to code;

4. Since it is an effective variance-stabilizing ‘Gaussianizer’, a wide range of smoothing methods can be used to obtain a proportion estimate.

This article is organized as follows. Section 2 reviews estimation methods for binomial processes, including a discussion of the Haar-Fisz transform and its motivation from the Fisz transform (Fisz, 1955). Section 3 proposes a new Gaussianizing transform called the NN transform for binomially distributed random variables. Section 4 adapts our new transform for use on binomial data and explores its properties. We also propose a technique for proportion estimation from a binomial sequence in Section 5. Section 6 concludes and outlines ideas for further work.

2 Review of work on binomial proportion estimation

We now give a brief outline of work in the literature for binomial process proportion estimation problems.

One approach to the binomial problem is to transform the observations so that the transformed data can be assumed to be (at least approximately) normally distributed. For the binomial distribution, Anscombe (1948) suggests the following. If \( \{x_i\} \) are realizations from i.i.d. binomial random variables \( X_i \sim \text{Bin}(n,p) \), then the transformed data \( A x_i = \sin^{-1} \sqrt{(x_i + c)/(n + 2c)} \) will be distributed ‘more normally’. Anscombe states that the value \( c = \frac{3}{8} \) is optimal for \( \mu \) and \( n - \mu \) large (where \( \mu \) is the mean of the binomial distribution). The asymptotic mean of the transform is approximately \( \bar{A} \mu = \sin^{-1} \sqrt{(8m + 3)/(8n + 6)} \), and the variance will be stabilized at \( \frac{1}{4}(n + 1)^{-1} \) for this value of \( c \). Though computationally efficient, Anscombe’s transformations used in conjunction with such traditional wavelet methods are reported to oversmooth and not perform well when intensities are low (Antoniadis and Sapatinas, 2001).

Freeman and Tukey (1950) discusses a similar transform, the averaged inverse sine function \( B x_i = \sin^{-1} \sqrt{x_i/(n + 1)} + \sin^{-1} \sqrt{(x_i + 1)/(n + 1)} \), with asymptotic mean approximately \( B \mu \). This transform is said to have variance stabilization around \( (n + \frac{1}{2})^{-1} \) for almost all cases when the binomial mean is at least one, though it is difficult to use as a pre- and postprocessor since it does not have
a unique inverse function.

Nonparametric regression techniques for proportions usually assume that the underlying proportion function has a certain degree of smoothness. For example, recent work on generalized linear models (Hastie and Tibshirani, 1990; Fan and Gijbels, 1995) assume that the proportion function $P(x)$ follows the relation $g(P(x)) = s(x)$, where $g$ is a monotone smooth function called the link function, and $s(x)$ is a smooth function which is estimated by methods suitable for smooth (continuous) regression functions. Different assumptions and estimation techniques for $s(x)$, and also link function choice are discussed in Fan and Gijbels (1995); Fan, Heckman and Wand (1995). For a more involved discussion of generalized linear models, see for example Hastie and Tibshirani (1990); McCullagh and Nelder (1989).

Kolaczyk and Nowak (2005) presents a multiscale generalized linear model for the estimation of functions in a general one-dimensional nonparametric regression setting. Piecewise polynomials defined on recursive partitionings of the unit interval are used to construct estimators of the regression function, optimizing a penalized likelihood criterion to choose a piecewise polynomial fit.

Altman and MacGibbon (1998) uses cross-validation for the bandwidth selection in kernel estimators for either fixed or random design binary regression. The asymptotic risk of the kernel estimators is shown to have good convergence properties under certain smoothness conditions on the regression function.

Antoniadis and LeBlanc (2000) considers linear wavelet smoothers for the irregular design binary regression situation. A generalized linear model with identity link function is imposed on the regression function, and via usual wavelet projection an estimator of the smooth model function $s(x)$ is obtained. A particular form of empirical wavelet coefficient is proposed to obtain smoother regression estimators, and the adaptive choice of resolution parameter in resulting wavelet series expansions is implemented in the binary regression context. The estimator is then modified to give a suitable estimator of the regression function $P(x)$. The estimator is shown to have good asymptotic properties and is computationally faster than traditional local polynomial estimators.

Wavelet shrinkage is used in the modulation estimator methodology by Antoniadis and Sapatinas (2001), extending the idea to obtain smooth estimates
for data from exponential families with quadratic variance functions, including
the binomial distribution. An estimator of the risk is formed by assuming the
function estimate to be a diagonal linear shrinker and using a cross-validation
approach. The function estimate is then constructed using a minimizer of the
risk estimate.

Sardy, Antoniadis and Tseng (2004) proposes a generalization of the WaveShrink
wavelet smoother (Donoho and Johnstone, 1994) to include a range of non-
Gaussian distributions such as the binomial and Bernoulli distributions. The
procedure uses interpoint algorithms to find the solution to a penalized log-
likelihood problem based on the $l^1$-norm of the wavelet coefficients in a wavelet
estimator representation.

Fryzlewicz and Nason (2004) introduces the Haar-Fisz transformation, combi-
ning the Haar wavelet transform and a result by Fisz (1955), which asserts the
asymptotic normality of a special ratio of Poisson random variables. The result
motivates the authors to propose a method for Poisson intensity estimation, us-
ing the Haar-Fisz technique as a pre- and postprocessing tool for Poisson data.
The algorithm consists of performing the Haar wavelet transform to count data,
and then modifying the wavelet coefficients according to Fisz (1955). Inverting
the Haar wavelet transform after the modification creates a variance stabilizing
transform. The algorithm has been used successfully for its gaussianizing and
variance stabilizing properties.

All of the above methods are suitable for binomial proportion estimation.
However, the methods based on generalized linear models often have the decision
of link choice to make; others assume some degree of regularity of the underly-
proportion function or produce estimates belonging to a certain smoothness class.
The use of interpoint algorithms in Sardy, Antoniadis and Tseng (2004) can be
computationally expensive. The aim of the method presented in this paper is to
take advantage of the computational efficiency and flexibility of transformations
such as Anscombe but improve performance in cases of low intensity.
3 The NN variance-stabilizing transform

3.1 The transform and its theoretical properties

The Haar-Fisz transform (outlined in Section 2) is motivated by the observation that applying the Fisz theorem (Fisz, 1955) to pairs of Poisson random variables results in an asymptotic normal distribution with unit variance.

However, for binomial variables, there is no choice of Fisz exponent which produces a constant asymptotic variance and so the variance cannot be stabilized by the usual Fisz transform (even in the limited case of equal trial probabilities and equal binomial sizes). Hence we propose a different Gaussianizing transform, similar to the Fisz transform (Fisz, 1955), with which asymptotic normality with stabilized variance can be obtained. We will then use this result in a similar way to the Haar-Fisz technique to propose an algorithm for binomial proportion estimation.

In our new transform, we divide the Haar difference $X_2 - X_1$ by its standard error, $\sqrt{\text{var}(X_1) + \text{var}(X_2)}$. This essentially uses the observations from $X_1$ and $X_2$ as estimates for the individual binomial means $n_r p$ ($r = 1, 2$) and combines them in the expression for the standard error. We first state our alternative theorem to the Fisz theorem (Fisz, 1955), the proof of which can be found in Appendix A of Nunes and Nason (2008).

**Theorem 3.1.** Let $X_r \sim \text{Bin}(n_r, p_r)$, for $r = 1, 2$ with $p_r \in (0, 1)$ (fixed). Let us denote, for $r = 1, 2$,

$$m_r = E(\xi_r), \quad \sigma_r^2 = \text{Var}(\xi_r), \quad \text{and} \quad \psi = \sqrt{\sigma_1^2 + \sigma_2^2}. \tag{3.1}$$

If the random variables $X_1$ and $X_2$ are independent and

$$\lim_{n_1, n_2 \to \infty} m_1/m_2 = 1, \tag{3.2}$$

then the random variable defined by

$$\zeta_B(n_1, n_2) = \frac{X_2 - X_1}{\left(\frac{X_1 + X_2}{n_1 + n_2} (n_1 + n_2 - (X_1 + X_2))\right)^{1/2}}$$
is asymptotically normal $N(m_B, \sigma_B^2)$ when $n_1, n_2 \to \infty$, where

$$m_B = \frac{m_2 - m_1}{\left(\frac{m_1 + m_2}{m_1 + n_2} (n_1 + n_2 - (m_1 + m_2))\right)^{1/2}} \quad (3.3)$$

and

$$\sigma_B = \frac{\psi}{\left(\frac{m_1 + m_2}{m_1 + n_2} (n_1 + n_2 - (m_1 + m_2))\right)^{1/2}} \quad (3.4)$$

In the definition of $\zeta_B$, we assume that the random variable takes the value zero when both $X_1$ and $X_2$ are zero.

Let us now consider a specific case of this result. Suppose $X_r \sim Bin(n_r, p)$ for $r = 1, 2$, i.e. the binomial random variables have equal trial probabilities. Due to Theorem 3.1, the random variable $\zeta_B(X_1, X_2)$ will be asymptotically normal with mean \((n_2 - n_1)/(n_1 + n_2))(p/q)^{1/2}\), but with unit variance when $n_1, n_2 \to \infty$. In other words, using the transform $\zeta_B(X_1, X_2)$ will stabilize the variance of the asymptotic distribution. Note also, that if in addition we impose the constraint that the binomial sample sizes are equal (i.e. $n_1 = n_2$), the asymptotic distribution will be $N(0,1)$.

### 3.2 Gaussianization and variance-stabilization properties of the NN transform

In this section we demonstrate through simulations how well the transform $\zeta_B$ can bring binomial data closer to normality, whilst stabilizing the variance of the data.

In some of the simulations below, we compare properties of our transform with that of Anscombe’s angular transformation and the Freeman-Tukey transformation outlined in Section 2. We follow a similar approach to these simulations as Fryźlewicz and Nason (2004). However, since the size of the binomial means depends on the trial success probability, $p$, as well as the binomial size, $n$, the effect of both of these parameters feature in our simulations.

Let $X_r \sim B(n, p_r)$ for $r = 1, 2$. For each experiment, we sampled $10^5$ values of $X_r$ for various binomial sizes and for each probability lattice point ($p_1, p_2$), where $p_r$ ranged from 0 to 1 in steps of 0.05. The binomial samples were then used
to compute $10^5$ values of the random variable $\zeta_B(X_1, X_2)$, denoted $z_n(p_1, p_2)$. For the comparisons with the Anscombe and Freeman-Tukey inverse sine transformations, the values of the binomial variable corresponding to the larger of the two probabilities $p_r$ was used. Since these transformations work better for larger means, doing this is favourable to Anscombe and Freeman-Tukey.

**Simulations of the variance.** The sample variance was computed over the $10^5$ samples of $\zeta_B$ arising from the samples of $X_1$ and $X_2$ for each point $(p_1, p_2)$. Figure 3.1 gives a series of contour plots of the sample variance for each of the binomial sizes $n = 1, 25, 100$, renormalized so that the asymptotic distribution will have unit variance. The plots show a “flattening” of the surface peaks as the binomial size increases, with the variance of the peak approaching one. In fact, this feature happens most near the line $p_1 = p_2$. This reflects the observation that equal binomial probabilities will result in an asymptotic distribution with unit variance.

![Figure 3.1: Contour plots showing the sample variance of $\zeta_B$ across the binomial probability lattice for different binomial sizes: $n = 1$ (top left); $n = 25$ (top right); $n = 100$ (bottom).](image-url)
To further examine the case when the two binomial proportions are equal, we display this graphically for $\zeta_B$, Anscombe’s transformation $A$, and the Freeman-Tukey transformation $B$, on the interval $p_1 = p_2 \in (0, 1)$, for increasing $n$. Figure 3.2 plots the squared residual of the variance from one against the (equal) binomial proportion. From this plot, it is more obvious that for small binomial sizes, our transform has variance closer to one for low and high proportions, especially when compared against Anscombe’s transformation, although the Freeman-Tukey comes quite close to our transform. It is comparable to the two competitors for the middle half interval (0.25,0.75). For larger $n$, all three transforms do well at stabilizing the variance at one.

**Gaussianization simulations.** For judging the relative Gaussianizing properties of the transform $\zeta_B$, we computed the Kolmogorov-Smirnov statistics for $\zeta_B$ and for the two competitor transformations over the binomial proportion lattice. Lower Kolmogorov-Smirnov statistics are representative of samples which are...
more Gaussian. Figure 3.3 shows contour plots of the difference in Kolmogorov-Smirnov statistics between Anscombe’s transform and $\zeta_B$. A positive difference in these plots corresponds to our transform being more Gaussian. The corresponding plot for the difference between the Freeman-Tukey transform and $\zeta_B$ is very similar.

![Contour plots showing the difference between Kolmogorov-Smirnov statistics computed on Anscombe samples with binomial probability $\max(p_1, p_2)$ for different binomial sizes: $n = 1$ (top left); $n = 10$ (top right); $n = 25$ (bottom). Positive contours indicate that $\zeta_B$ is closer to Gaussian than Anscombe. Biggest difference for $n = 1$ is 0.657 at $(p_1, p_2) = (0.5, 1)$.](image1)

The overall trend is that the difference in Kolmogorov-Smirnov statistics is positive for small and moderate binomial sizes, irrespective of the binomial proportions $p_1$ and $p_2$. This demonstrates that our transform has better Gaussianization properties than both Anscombe and the Freeman-Tukey transformation. As expected, as the binomial size becomes high, the differences between the Kolmogorov-Smirnov statistics becomes negligible, due to both transforms having good Gaussianizing properties. However, examining the statistics further, the means of the statistics for $\zeta_B$ are lower compared to those of its competitors.
(for all values of the binomial size, $n$). This indicates that the transformed data using our transform is more Gaussian than those of the Anscombe or Freeman-Tukey transforms. More graphical evidence for the simulations in Section 3.2 can be found in Nunes and Nason (2008).

4 The Haar-NN transform for binomial random variables

4.1 The transform

The Haar discrete wavelet transform. The Haar-Fisz transform combines a Gaussianizing transform with the Haar discrete wavelet transform. The Haar discrete wavelet transform (DWT) is performed on an input data vector $v$ by iterating the steps

$$c_{j,k} = \frac{(c_{j+1,2k} + c_{j+1,2k+1})}{2} \quad \text{and} \quad d_{j,k} = \frac{(c_{j+1,2k} - c_{j+1,2k+1})}{2},$$

for $j = J - 1, \ldots, 0$. The inverse DWT can be expressed in the two equations

$$c_{j+1,2k} = c_{j,k} + d_{j,k} \quad \text{and} \quad c_{j+1,2k+1} = c_{j,k} - d_{j,k}.$$

Note that the forward and inverse steps described above translate into using wavelet filters $\frac{1}{\sqrt{2}}(1, 1)$ and $\frac{1}{\sqrt{2}}(1, -1)$. This differs from the Haar filters used in many descriptions of the Haar transform, which make the Haar basis orthonormal.

We now introduce an algorithm similar to the Haar-Fisz transform described in Section 2, based on the asymptotic result from the preceding section. Suppose we have an observed vector $v=(v_0, v_1, \ldots, v_{N-1})$ of length $N = 2^J$, with $0 \leq v_i \leq n_k$, for some integers $n_k$. The algorithm is as follows.

1. Perform the Haar DWT on $v$ to obtain the vector $(c_0, d_0, d_1, \ldots, d_{J-1})$. As each level is produced, modify the coefficients by defining

$$f_{j,k} = \frac{d_{j,k}}{\sqrt{(c_{j,k}(n_{j+1,k-1} + n_{j+1,k} - 2^{J-1}c_{j,k}))/(n_{j+1,k-1} + n_{j+1,k})}},$$

(4.1)

2. Perform the inverse Haar DWT on the vector $(c_0, f_0, f_1, \ldots, f_{J-1})$. Call the result $u$.

In the above, $n_{j+1,k-1}$ and $n_{j+1,k}$ are the recursive pairwise sums of the binomial sizes as the DWT levels are produced, and $f_{j,k} = 0$ if the denominator
in (4.1) is zero. When the binomial sizes are equal, that is, \( n_k = n \ \forall k \), the modification in step 1 simplifies to

\[
f_{j,k} = \begin{cases} 
0 & \text{if } c_{j,k} = 0 \text{ or } c_{j,k} = n, \\
d_{j,k} / \sqrt{(c_{j,k}(n - c_{j,k})) / n} & \text{otherwise}
\end{cases}
\]

(4.2)

We denote this transform by \( \mathbf{u} = \mathcal{F}_B \mathbf{v} \). As with the usual Haar-Fisz transform, \( \mathcal{F}_B \) can be inverted by “undoing” the steps 1 and 2.

Let us examine the effect of the modification in step 1 of the above procedure. For clarity, we will use the simplified modification (4.2). Consider the coefficients \( v_0 \) and \( v_1 \). The modified detail coefficient \( d_{J-1,0} \) is produced by

\[
f_{J-1,0} = \frac{(v_1 - v_0) / 2}{\left( \left( (v_0 + v_1) (n - \frac{v_0 + v_1}{2}) \right) / 2n \right)^{1/2}} = \frac{(v_1 - v_0)}{\left( \left( (v_0 + v_1) (2n - (v_0 + v_1)) \right) / n \right)^{1/2}}.
\]

Similarly the next coarsest level coefficient is

\[
f_{J-2,0} = \frac{((v_0 + v_1) - (v_3 + v_4))}{\left( \left( (v_0 + \cdots + v_3) (4n - (v_0 + \cdots + v_3)) \right) / n \right)^{1/2}}.
\]

This computation is similar for every coefficient within a level, and for each DWT decomposition level. If the data vector \( \mathbf{v} \) is representative of observations from i.i.d. binomial random variables \( X_k \sim Bin(n, p) \), then the modified detail coefficients can be expressed as \( f_{j,k} = 2^{-(J-j)} \zeta_B(Y_1, Y_2) \), where \( Y_1 \) and \( Y_2 \) are both sums of \( 2^{J-j} \) of the random variables \( X_k \), and thus are binomially distributed as well. Since the application of the inverse Haar transform is identical for \( \mathcal{F}_B \mathbf{v} \) as for \( \mathcal{F} \mathbf{v} \), after performing the transform \( \mathcal{F}_B \mathbf{v} \), the original data can be expressed as linear combinations of quantities of the form \( \zeta_B(Y_1, Y_2) \) for binomial random variables \( Y_1 \) and \( Y_2 \). This also applies to the more general (4.1). It is analogous to the Haar-Fisz transform (see Section 2.2 in Fryełewicz and Nason (2004)). Thus \( \mathcal{F}_B \mathbf{v} \) represents a diagonal transformation of \( \mathbf{v} \), that is, there is one transformed value for each \( v_i \).
4.2 Finite sample Gaussianization and Variance stabilization properties of the Haar-NN transform

The following investigation compares the Gaussianization and variance-stabilizing properties of the transform $F_B$ introduced in Section 4, with Anscombe’s transformation, the Freeman-Tukey transformation, and the identity transformation. Again, we follow an approach similar to Fryzlewicz and Nason (2004).

For these simulations, we have chosen a binomial proportion vector, $p$ of length $N = 1024$ sampled from a (normalized and stretched) version of the well-known Blocks test signal of Donoho and Johnstone (1994) (see Figure 5.1). For each binomial size we will denote by $\lambda := np$ the mean intensity vector corresponding to $n$. It should be noted that although the mean vector depends on the binomial size, $n$, this is not included in the notation explicitly, since it will be obvious from the context which value of $n$ we will use. A sample path generated from binomial random variables with the mean vector $\lambda$ will be denoted by $v$. As expected, a sample path takes the value 1 more often when $p$ is near 1, and hits zero more frequently when $p$ is near zero.

**Gaussianizing simulations.** We compared the Gaussianizing properties of the different transforms by considering the Q-Q plots of $v - \lambda$ (identity transform), $Av - A\lambda$ (Anscombe), $Bv - B\lambda$ (Freeman-Tukey) and $F_Bv - F_B\lambda$ (Haar-NN), averaged over 100 sample paths, $v$. These paths were created from the mean vector $\lambda$ for various binomial sizes. Figure 4.1 shows this comparison for the binomial sizes $n = 1, 5$ and 25.

For the lowest binomial sizes, namely $n = 1$ and 2, the raw data (marked in black) is quite “stepped”. This is expected since the data are discrete. The Anscombe-transformed data and those transformed by Freeman-Tukey transformation still exhibit this characteristic, whilst for our transform, $F_B$, they have lost most of this stepped character; the data lies closer to a straight line, showing that the data is more Gaussian. Moreover, the data is closer to the solid line (which has a slope of 1), which indicates a variance of one. As $n$ increases, the Q-Q lines become similar, although it can be said that our transform displays slightly better Gaussianization (and also variance-stabilization), since the quantile points do not deviate from the (solid) straight line as much as the other transforms, especially at the tails. For large $n$, all three transforms do very well.
Figure 4.1: Q-Q plot comparison for four different transforms, averaged over 100 paths sampled from binomial variables with sizes \( n = 1 \) (top left), \( n = 5 \) (top right) and \( n = 25 \) (bottom) and proportion vector \( p; \ v - \lambda \) (black); \( A v - A \lambda \) (red); \( B v - B \lambda \) (blue); \( F_B v - F_B \lambda \) (green). Solid line has slope 1, indicating unit variance.

at bringing the data to normality. Furthermore, the variance is very close to one. However, this is mostly expected due to the high value of \( n \), since at this large binomial size, the Central Limit Theorem comes into effect.

**Variance simulations.** To assess how well the transformations \( A, B \) and \( F_B \) force the data to have variance nearer to one, we plotted the squared residual \( |A v - A \lambda|^2, |B v - B \lambda|^2 \) and \( |F_B v - F_B \lambda|^2 \) for the Anscombe transform, Freeman-Tukey transform and our transform (respectively), rescaled by their respective asymptotic variances. The residuals were averaged over 1000 sample paths, which were generated from the mean intensity vector \( \lambda \) for a range of binomial sizes. When performance is optimal, the squared residuals stabilize at one when the proportion is nonzero, since the squared residuals form an estimate of the variance. Examples of the squared residuals for the three transforms are given in Figures 4.2 and 4.3 for \( n = 1 \) and 25.

When the binomial size is small, the simulations show that our transform does much better than the competitors, \( A \) and \( B \), at stabilizing the sample path.
variances. For example, for $n = 1$, the Anscombe transform has the squared residual in the range 0.2 to 0.6, and the Freeman-Tukey transform has the squared residual in the range 0.4 to 0.9, whereas for our transform, the residual is nearer 1 for most of the sample path range. Further, our transform does relatively well compared to Anscombe and slightly better than Freeman-Tukey when the binomial proportion is small, that is in the three non-zero ‘troughs’. However, there is a degree of erratic behaviour near the discontinuities in the proportion vector. Moderate binomial sizes have the competitor transformations beginning to achieve similar stabilization as our transform; when $n$ is large, all three transforms do very well at variance stabilization, though Anscombe can be considered to do slightly better in performance in this case, due to the occasional downward spikes in the Haar-NN transform (see Figure 4.3).
Figure 4.3: Squared residuals for different Gaussianizing transforms, averaged over 1000 sample paths from binomial variables with size $n = 25$ and proportion vector $p$: $|Av - A\lambda|^2$ (top left); $|Bv - B\lambda|^2$ (top right); $|FBv - FB\lambda|^2$ (right). Dashed line shows ideal (unit) residual where intensity $\in (0,1)$.

5 Binomial proportion estimation

Motivated by these observations about the properties of the transform $FB$, we now propose an algorithm for probability curve estimation for a binomial sequence.

Suppose $v = (v_0, \ldots, v_{N-1})$ is a vector of observations of length $N = 2^J$ from a binomial process with size $n$ and unknown probability vector $p$.

1. Perform the transform $FB$ on $v$ to produce $u = FBv$. The vector $u$ should be approximately normally distributed with constant variance.

2. Use any denoiser suitable for handling Gaussian noise with constant variance.

3. Invert the Haar-NN transform to obtain the estimate of the binomial probability vector.
5.1 Simulation Study

A simulation study was performed to assess the curve estimation procedure above. Several proportion functions were chosen to be estimated, each exhibiting different properties. These were the Sinlog function in Antoniadis and LeBlanc (2000); a scaled and reflected version of the $P_2$ function described in Antoniadis and LeBlanc (2000) (denoted here by $P_3$) and the modified Blocks proportion from Section 4.2. These test functions are shown in Figure 5.1. More details of these functions can be found in Nunes and Nason (2008).

These functions were sampled on regular grids of length $N = 128, 256, 512$ and 1024. The sampled vectors were then used to create binomial sample paths using the sample vectors to define the binomial trial probabilities, i.e. $p_i = P_j(t_i)$ for $i = 1, \ldots, n$ and each proportion function $P_j$ (Sinlog, $P_3$ and Blocks). For each grid length/binomial size combination, 1000 sample paths were created. These sample paths were then denoised using the estimation procedure described at the beginning of this section (transform-denoise-invert) with both $\mathcal{F}_B$ and $\mathcal{A}$ as pre- and post-processors in steps 1 and 3 of the procedure. In the denoising step, the DWT was used with Daubechies’ Least Asymmetric wavelet with 8 vanishing
moments and universal soft thresholding. A comparison was also made to the wavelet shrinkage method of Antoniadis and Sapatinas (2001), denoted AS. All methods were optimized over the resolution level.

**Cycle-spinning.** We also implemented a variant of our method using cycle-spinning. Since the Haar-NN transform is translation invariant, cycle-spinning can be used to gain performance improvements (Fryźlewicz and Nason, 2004). In this case, the binomial vector is shifted before denoising and the estimate is shifted back afterwards. Estimates from different shifts are then averaged to obtain an overall estimator of the proportion function. We have used 50 shifts as suggested in Fryźlewicz and Nason (2004). Performing cycle-spinning with Anscombe’s transformation would not give any performance gain since this transformation commutes with the shift operator.

For each method, and for different binomial sizes and signal lengths, the averaged mean square error (x 10^4) between the estimates and the sampled proportion function were recorded. For the binomial size regimes, we used different fixed binomial sizes of n_k = n ≡ 1, 5, 10, as well as randomly generated binomial sizes; r_1 indicates where binomial sizes were uniformly generated from n_k ∈ {1, 5, 10} and r_2 denotes random generation of binomial sizes from n_k ∈ {2, 4, 6}. For brevity, only signal lengths N = 256 and N = 1024 are shown.

<table>
<thead>
<tr>
<th>Binomial regime</th>
<th>P_3 Blocks</th>
<th>Sinlog</th>
<th>Binomial regime</th>
<th>P_3 Blocks</th>
<th>Sinlog</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>3.3</td>
<td>5.7</td>
<td>5</td>
<td>0.7</td>
<td>0.9</td>
</tr>
<tr>
<td>5</td>
<td>0.5</td>
<td>0.5</td>
<td>10</td>
<td>67.0</td>
<td>55.4</td>
</tr>
<tr>
<td>r_1</td>
<td>34.6</td>
<td>26.8</td>
<td>5</td>
<td>0.5</td>
<td>0.5</td>
</tr>
<tr>
<td>r_2</td>
<td>1303.6</td>
<td>1300.4</td>
<td>10</td>
<td>67.0</td>
<td>55.4</td>
</tr>
</tbody>
</table>

Table 5.1: AMSE (×10^4) simulation results for different binomial size regimes and signals described in the text: signal length N = 256.

Table 5.2: AMSE (×10^4) simulation results for different binomial size regimes and signals described in the text: signal length N = 1024.
The results of the simulation study are very encouraging. When the binomial size is fixed, our algorithm outperforms the Anscombe across the different signals all of the time, and beats the Antoniadis and Sapatinas (2001) method in a lot of cases. For the randomly-generated binomial sizes (regimes $r_1$ and $r_2$), the $AS$ technique does not perform well, and Anscombe performs better than our regular method. However, the performance gain from using our method combined with cycle-spinning for these regimes is clear: there is an improvement over our regular method and over Anscombe. The relative performance of the Haar-NN transform seems to increase as the signal length increases. Initial investigation into other thresholding techniques indicate that there could be further improvements with our method.

5.2 Application: DNA Isochore detection

There has been substantial work in the field of bioinformatics in recent years, and the quest to improve existing methods and computational techniques is also of great importance. In particular, DNA sequencing and gene expression methods are a couple of the topics in this area. One important problem in these areas is the modelling and prediction of isochore clusters in DNA sequence data (Bernardi, 2000). In this section we hope to use the Gaussianizing and variance stabilizing properties of the Haar-NN method for this application.

**Biological background to the isochore problem.** DNA sequences are strings (polymers) of nucleotides, chemical compounds which play important biological rôles. Each nucleotide is characterized by its nitrogen base, represented by a letter: A (adenine); C (cytosine); G (guanine); and T (thymine). These four nucleotide bases come from two compound base pair groups, namely *purines* (adenine and thymine) and *pyrimidines* (cytosine and guanine), differing in structure. For a more detailed discussion of the structure of DNA, see any introductory text on genomics, for example Brown (2002). G+C content can be seen as the ratio between the number of pyrimidine nucleotides to the total number of nucleotides in a DNA segment.

A school of thought in bioinformatics accepts an *isochore* model for DNA, which asserts that chromosome DNA sequences are mosaics of long DNA segments of (fairly) homogenous G+C content in adjacent segments (Oliver, Carpena,
Hackenberg and Bernaola-Galvan, 2004); under this model, the G+C content mosaics differs for different organisms, especially between warm- and cold-blooded vertebrates (Bernardi, 2000), and so prediction is of obvious interest, for example, in organism classification applications.

**IsoFinder: an existing approach to the isochore problem.** In Oliver, Carpena, Hackenberg and Bernaola-Galvan (2004) and Zhang and Chen (2004), a procedure of sequential hypothesis testing is implemented to attempt to model the distribution of G+C cluster sizes of a DNA sequence.

The procedure works as follows. The G+C content of the sequence is counted, and a $t$-statistic is used to assess the significance of the difference in mean G+C values on either side of a sliding pointer moving along the DNA sequence. After heterogeneity is filtered out, the information is used to split the original sequence into two distinct regions of differing G+C mean value. This method is then repeated on successive blocks until the original sequence is divided into a number of regions with significantly different mean G+C levels. These obtained clusters are predictions of isochores of the original DNA sequence. This method is known as the *IsoFinder* procedure.

**Haar-NN transform approach to the isochore problem.** Let us consider a DNA sequence. Since we are interested in the sections of the strand containing G+C content, we can view the DNA section as a binary sequence with a corresponding sequence of indicator values at each nucleotide site, showing whether or not a particular nucleotide comes from the pyrimidine (G or C) base pair: for an unseen strand, if we assume each molecule along the sequence is from one of the two nucleotide base pairs independently, we can assign Bernoulli random variables at the nucleotide sites. Suppose we have a DNA sequence of length $n = 2^J$. Let $X_k$ indicate the type of nucleotide $k$. Then $X_k \sim \text{Bernoulli}(p_k)$, and so $P(\text{nucleotide } k \text{ has G+C content}) = P(X_k = 1) = p_k$ and $P(\text{nucleotide } k \text{ has A+T content}) = P(X_k = 0) = 1 - p_k = q_k$. Estimating equal $p_k$ for long consecutive sequences of $k$ indicate regions of equal G+C content, and is representative of an isochore.

**Example.** To test the G+C proportion estimation procedure, a chromosome strand was acquired from the Wellcome Trust Sanger Institute Human Genome Sequencing Group, namely the chromosome 20 of the human genome (available
online from the website http://www.sanger.ac.uk/HGP/). To make it feasible to process this data with our method, the sequence strands were cropped to $2^{21} = 2097152$ bases, and then converted into binary sequences indicating G+C content as outlined above.

In the denoising step of the algorithm in Section 5, we used the Haar DWT with Sureshrink thresholding (Donoho and Johnstone, 1995), with primary resolution level 3. However, we modified the smoothing procedure. Recall that in the IsoFinder procedure, there is an in-place heterogeneity filtering. This is usually applied to filter out isochores of less than 3 kilobases from the resulting isochore maps, so that these map estimates resemble mammalian genomes (Oliver, Carpena, Hackenberg and Bernaola-Galvan, 2004). To mimic this filtering, in the denoising step of the procedure, we set the finest 11 detail coefficient levels to zero (after thresholding) before inverting the discrete wavelet transform. This has the effect of ensuring that isochore regions of less than $2^{11} = 2048$ bases do not feature in our estimates of G+C content produced after inversion of the wavelet transform.

As a comparison to our procedure, the IsoFinder method was also applied to the cropped nucleotide sequence, using the online IsoFinder implementation (which can be found at http://bioinfo2.ugr.es/IsoF/isofinder.html). Figure 5.2 was created using this web interface.

Figure 5.2: Isochore map of chromosome 20 of the human genome, as estimated by the Isofinder procedure (with 3 kilobase filtering).
Figures 5.2 and 5.3 give estimates for the (unknown) isochore profile of chromosome 20 for the two procedures. Whilst the estimates produced using our method are more “spiky” and show shorter isochore regions, the estimates for both procedures exhibit similar overall features. It should be noted here that our estimates use SureShrink thresholding, with no consideration for the effect of the primary resolution level. More complex thresholding procedures could produce more homogeneous estimates. Also, our method uses a low kilobase filtering compared to the IsoFinder procedure (due to being constrained to a power of two) so is more likely to produce estimates which exhibit less homogeneity.

6 Conclusions

This article has proposed a new transform, $\zeta_B$, that possesses variance-stabilizing properties for binomial random variables. An asymptotic result was established about this transform, and simulations for different binomial sizes and probabilities were performed to investigate how well it Gaussianizes and stabilizes the variance compared to current normalizing transforms. The results indicate that our transform does very well for smaller binomial sizes, $n$, and/or for extreme
binomial proportions.

Section 4 introduced a new modified Haar transform using our Gaussianizing transform. This was compared to the Anscombe transform also, and it was found to again outperform the traditional transformation for smaller binomial sizes and/or binomial proportions nearer the boundaries of the interval (0,1). This improvement for small \( n \) and extreme proportions is important, since in practice, large binomial sizes and “nice” success probabilities could be unrealistic. This evidence of good properties lead us to suggest an algorithm for binomial proportion curve estimation. Investigations show error improvements over competitors, especially when adopting cycle-spinning, with better performance in all but a few cases. The technique was then applied to isochore prediction.

Software code that implements our Haar-NN transform is freely available at the CRAN R software archive as an R package. It can also be found at

http://www.stats.bris.ac.uk/ maman/computerstuff/Binfisz.html.

Acknowledgment

Nunes and Nason were both partially supported by EPSRC Grant D005221/1 and the UK Government.

References


