

**POINTWISE BINOMIAL APPROXIMATION IN
A MODEL OF SOMATIC CELL HYBRID**

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Abstract: This paper uses Stein's method to give a non-uniform bound for approximating the distribution of the number of pairs of chromosomes for which the Hamming distance is less than some fixed Hamming distance d by the binomial distribution with parameters $|\Gamma| = 253$ and $p \in (0, 1)$. Two numerical examples have been given to illustrate the obtained result.

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1. Introduction

It is well known that somatic cell hybrids can be used to assign particular human genes to specific human chromosomes, see [2, 3, 11, 12, 13]. The potential of human gene localization by rodent-human somatic cell hybrids has been confirmed since the pioneering work of [13]. These somatic cell hybrids are formed by fusing normal diploid human somatic cells with permanently transformed rodent cells. The resulting hybrid somatic cells retrain all of the rodent chromosomes while losing random subsets of the human chromosomes. A few

generation after cell fusion, a collection of different hybrid clones are analyzed for the expression of the human gene and for the presence of each of the 24 distinct human chromosomes. The chromosomes bearing the interested gene are consistently present in the hybrid clones expressing the gene and consistently absent in that clones not expressing it. From this pattern one can assign the gene to the particular chromosome. Since somatic hybrid clones are usually created from human female cells, the chromosome types of this interesting consist of 22 autosomes and the X chromosome.

This study follows the mathematical models for the design of hybrid clone panels in [4, 5]. Let m denote the number of hybrid clones in a panel. When each clone in the panel is assayed for the presence of each of 23 chromosomes, we need to construct a karyotype matrix of this panel. This matrix consists of m rows and 23 columns and its entry in the row i and column j is 1 if the clone i contains chromosome j and it is 0 otherwise, as seen in Fig. 1, which depicts a karyotype matrix of a hybrid panel with $m = 9$. Similarly, we need to construct an additional test column of 0's and 1's when each clone is assayed for the presence of a given human gene. Barring assay errors or failure of critical assumptions in [4, 5], the test column will uniquely match one of the columns of the matrix. In this case the gene is assigned to the corresponding chromosome. If two columns of the karyotype matrix of a panel are identical, then the gene assignment becomes ambiguous for any gene lying on one of the two corresponding chromosomes.

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0 1 0 1 0 0 0 1 0 0 0 0 0 0 1 0 1 1 0 1 1 1 1
1 0 1 0 1 1 0 0 1 0 0 0 0 1 0 0 1 0 1 0 1 1 1
0 1 1 1 1 0 1 0 0 0 0 0 1 0 0 1 1 0 1 1 0 1 1
1 1 1 0 0 1 1 0 0 1 0 1 0 0 0 1 1 1 0 0 1 0 1
0 0 0 1 1 1 1 0 0 0 1 1 1 1 1 0 1 0 0 0 1 1 0
0 1 1 1 1 1 1 1 1 1 1 0 0 0 0 0 1 0 0 0 0 0 0
0 0 1 0 1 0 1 1 0 1 1 1 0 0 0 0 1 1 1 1 1 0 0
0 0 0 1 0 1 1 1 0 0 0 1 0 1 1 1 1 0 1 0 1 0 1
1 0 0 0 1 1 0 0 0 1 0 1 1 0 1 0 1 0 1 1 0 0 1

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Fig. 1. A karyotype matrix of a somatic cell hybrid panel

We observe, in Fig. 1, that every pair of columns in the panel differs at least three entries. This level of redundancy is useful for assigning the gene to a particular chromosome, such as if a single assay error is made in creating a test column for a human gene, then the program of gene assignment must be successful. In practice, the level of redundancy is random. Minimum Hamming

distance is a natural measure of the redundancy of a panel. Let c_s^m denote the column s of the karyotype matrix of a random panel with m hybrid clones. Then the Hamming distance $\rho(c_s^m, c_t^m)$ between two columns c_s^m and c_t^m from a random panel is just the number of entries in which they differ. When somatic cell hybrid panels are randomly created, the following assumptions should be satisfied. First, each human chromosome is lost or retained independently during the formation of a stable clone. Second, there is a common retention probability $p_0 \in (0, 1)$ applying to all chromosome pairs. Third, different clones behave independently in their patterns. Let $\Gamma = \{\alpha = \{s, t\} : 1 \leq s \neq t \leq 23\}$. For any two distinct columns c_s^m and c_t^m , define $Y_{\{s,t\}}$ to be the indicator of the event $\rho(c_s^m, c_t^m) < d$, where d is some fixed Hamming distance. For each $\alpha \in \Gamma$, the probability $\mathbb{P}(Y_\alpha = 1)$ is

$$p = \sum_{i=0}^{d-1} \binom{m}{i} \wp^i (1 - \wp)^{m-i},$$

where $\wp = 2p_0(1 - p_0)$ is the probability that c_s^m and c_t^m differ in any entry. Let $X = \sum_{\alpha \in \Gamma} Y_\alpha$ be the number of pairs of chromosomes for which the Hamming distance $\rho(c_s^m, c_t^m)$ less than d . For each $\alpha \in \Gamma$, let $\Gamma_\alpha = \{\beta \in \Gamma : \alpha \cap \beta \neq \emptyset\}$ be a neighborhood of dependence for α . It is observed that Y_α and Y_β are independent if $\alpha \cap \beta = \emptyset$, that is, Y_α is independent of all of the Y_β for $\beta \notin \Gamma_\alpha$. Let

$$b_1 = \sum_{\alpha \in \Gamma} \sum_{\beta \in \Gamma_\alpha \setminus \{\alpha\}} \mathbb{E}(Y_\alpha Y_\beta). \quad (1.1)$$

In 2005, Teerapabolarn and Neammanee [9] used the Stein-Chen method to give a non-uniform bound in approximating the point probabilities of the number of pairs of chromosomes for which the Hamming distance $\rho(c_s^m, c_t^m)$ less than some fixed Hamming distance d by the Poisson distribution with mean $\lambda = |\Gamma|p = 253p$ as follows:

$$\left| \mathbb{P}(X = x_0) - \frac{e^{-\lambda} \lambda^{x_0}}{x_0!} \right| \leq \min \left\{ \frac{1}{x_0}, \lambda^{-1} \right\} [\lambda \min\{1, 43p\} + \min\{\lambda, b_1\}], \quad (1.2)$$

where $x_0 \in \{1, \dots, 253\}$, and

$$\left| \mathbb{P}(X = 0) - e^{-\lambda} \right| \leq \lambda^{-2} (\lambda + e^{-\lambda} - 1) \max\{43\lambda p, b_1\}. \quad (1.3)$$

This paper uses Stein's method for binomial approximation to give a non-uniform bound in approximating the point probabilities of X by the binomial distribution with parameters $|\Gamma| = 253$ and p .

2. Method

We will prove our main result by Stein's method, which was first developed and applied in the setting of the binomial distribution by Stein [7]. The Stein's equation for the binomial distribution with parameters $n \geq 1$ and $p = (1 - q) \in (0, 1)$, for given h , is defined by

$$(n - x)pg(x + 1) - qxg(x) = h(x) - \mathcal{B}_{n,p}(h), \quad (2.1)$$

where $\mathcal{B}_{n,p}(h) = \sum_{k=0}^n h(k) \binom{n}{k} p^k q^{n-k}$ and g and h are bounded real-valued functions defined on $\{0, 1, \dots, n\}$.

For $A \subseteq \{0, 1, \dots, n\}$, let $h_A : \{0, 1, \dots, n\} \rightarrow \mathbb{R}$ be defined by

$$h_A(x) = \begin{cases} 1 & \text{if } x \in A, \\ 0 & \text{if } x \notin A. \end{cases} \quad (2.2)$$

Following [1], let $g_A : \mathbb{N} \cup \{0\} \rightarrow \mathbb{R}$ satisfy (2.1), where $g_A(0) = g_A(1)$ and $g_A(x) = g_A(n)$ for $x \geq n$. For $A = \{x_0\}$, $x_0 \in \{0, 1, \dots, n\}$, the solution $g_{x_0} = g_{\{x_0\}}$ of (2.1) can be written as

$$g_{x_0}(x) = \begin{cases} -\frac{\binom{n}{x_0} p^{x_0-x} \mathcal{B}_{n,p}(h_{C_{x-1}})}{x \binom{n}{x} q^{x_0-(x-1)}} & \text{if } x_0 \geq x \geq 1, \\ \frac{\binom{n}{x_0} p^{x_0-x} \mathcal{B}_{n,p}(1-h_{C_{x-1}})}{x \binom{n}{x} q^{x_0-(x-1)}} & \text{if } x_0 < x, \end{cases} \quad (2.3)$$

where $C_x = \{0, \dots, x\}$.

Before proving our main result, we need to set the following properties.

Lemma 2.1. *For $x_0 \in \{1, \dots, 253\}$, let $\Delta g_{x_0}(x) = g_{x_0}(x + 1) - g_{x_0}(x)$ and $n \geq 2$. Then the following inequalities hold:*

$$\sup_{x \geq 1} |\Delta g_{x_0}(x)| \leq \min \left\{ \frac{1 - p^n}{qx_0}, \frac{1 - p^{n+1} - q^{n+1}}{(n+1)pq} \right\} \quad ([10]) \quad (2.4)$$

and

$$-\frac{np - (1 - q^n)}{(n-1)np^2} \leq \sup_{x \geq 1} \Delta g_0(x) \leq 0. \quad ([8]) \quad (2.5)$$

3. Result

The following theorem is our main result, which can be derived by Stein's method

Theorem 3.1. *Let $x_0 \in \{1, \dots, 253\}$, $b_2 = \sum_{\alpha \in \Gamma} \sum_{\beta \in \Gamma_\alpha \setminus \{\alpha\}} \mathbb{E}(|p - Y_\alpha| Y_\beta)$, and $q = 1 - p$. Then we have the following:*

$$\left| \mathbb{P}(X = x_0) - \binom{253}{x_0} p^{x_0} q^{253-x_0} \right| \leq \min \left\{ \frac{1 - p^{253}}{qx_0}, \frac{1 - p^{254} - q^{254}}{254pq} \right\} \times \min \{506pq, b_2\} \quad (3.1)$$

and

$$-\frac{253p - 1 + q^{253}}{6} \leq \mathbb{P}(X = 0) - q^{253} \leq \frac{(253p - 1 + q^{253})b_1}{63756p^2}. \quad (3.2)$$

Proof. Let $n = |\Gamma| = 253$, $X_\alpha = X - Y_\alpha$, $W_\alpha = \sum_{\beta \in \Gamma_\alpha \setminus \{\alpha\}} Y_\beta$ and $Z_\alpha = X - Y_\alpha - W_\alpha = \sum_{\beta \notin \Gamma_\alpha} Y_\beta$. First we shall show that (3.1) holds. Substituting $h = h_{x_0}$ and taking expectation in (2.1), we have

$$\mathbb{P}(X = x_0) - \binom{n}{x_0} p^{x_0} q^{n-x_0} = \mathbb{E}[(n - X)pg(X + 1) - qXg(X)], \quad (3.3)$$

where $g = g_{x_0}$ is defined in (2.3). Because $\mathbb{P}(Y_\alpha = 1) = p$ for all α and using the result of Soon [6] on pp. 708, the equation (3.3) can be written as

$$\mathbb{P}(X = x_0) - \binom{n}{x_0} p^{x_0} q^{n-x_0} = \sum_{\alpha \in \Gamma} p \mathbb{E}[g(X_\alpha + 1)] - \mathbb{E}[Xg(X)]. \quad (3.4)$$

By the fact that each Y_α takes on values of 0 and 1, we can express

$$\begin{aligned} \mathbb{E}[Xg(X)] &= \sum_{\alpha \in \Gamma} \mathbb{E}[Y_\alpha g(X_\alpha + 1)] \\ &= \sum_{\alpha \in \Gamma} \mathbb{E}[Y_\alpha f(Z_\alpha + 1)] + \sum_{\alpha \in \Gamma} \mathbb{E}[Y_\alpha (g(Z_\alpha + W_\alpha + 1) - g(Z_\alpha + 1))]. \end{aligned}$$

Hence, by the independence of Y_α and Z_α ,

$$\begin{aligned} \sum_{\alpha \in \Gamma} p \mathbb{E}[g(X_\alpha + 1)] - \mathbb{E}[Xg(X)] &= \sum_{\alpha \in \Gamma} \{ \mathbb{E}[p(g(Z_\alpha + W_\alpha + 1) - g(Z_\alpha + 1))] \\ &\quad - \mathbb{E}[Y_\alpha (g(Z_\alpha + W_\alpha + 1) - g(Z_\alpha + 1))] \} \end{aligned}$$

$$\begin{aligned}
&= \sum_{\alpha \in \Gamma} \mathbb{E}\{(p - Y_\alpha) \\
&\quad \times [g(Z_\alpha + W_\alpha + 1) - g(Z_\alpha + 1)]\}. \quad (3.5)
\end{aligned}$$

From (3.4) and (3.5) , we can obtain

$$\begin{aligned}
\left| \mathbb{P}(X = x_0) - \binom{n}{x_0} p^{x_0} q^{n-x_0} \right| &\leq \sum_{\alpha \in \Gamma} \mathbb{E}[|p - Y_\alpha| |g(Z_\alpha + W_\alpha + 1) - g(Z_\alpha + 1)|] \\
&\leq \sum_{\alpha \in \Gamma} |\sup_{x \geq 1} \Delta g(x)| \mathbb{E}[|p - Y_\alpha| W_\alpha] \\
&\leq \min \left\{ \frac{1 - p^n}{qx_0}, \frac{1 - p^{n+1} - q^{n+1}}{(n+1)pq} \right\} \\
&\quad \times \sum_{\alpha \in \Gamma} \sum_{\beta \in \Gamma_\alpha \setminus \{\alpha\}} \mathbb{E}(|p - Y_\alpha| Y_\beta) \quad (\text{by (2.4)})
\end{aligned}$$

and it is clear that

$$\begin{aligned}
\left| \mathbb{P}(X = x_0) - \binom{n}{x_0} p^{x_0} q^{n-x_0} \right| &\leq \sum_{\alpha \in \Gamma} \sup_{x \geq 1} |\Delta g(x)| \mathbb{E}|p - Y_\alpha| \\
&\leq 506pq \min \left\{ \frac{1 - p^n}{qx_0}, \frac{1 - p^{n+1} - q^{n+1}}{(n+1)pq} \right\}.
\end{aligned}$$

Therefore, by putting $n = 253$, (3.1) holds.

We will prove the result in (3.2). For $x_0 = 0$, (2.1) is of the form

$$\mathbb{P}(X = 0) - q^n = \mathbb{E}[(n - X)pg(X + 1) - qXg(X)], \quad (3.6)$$

where $g = g_0$ is defined in (2.3). It follows from (3.5) that

$$\begin{aligned}
\mathbb{P}(X = 0) - q^n &= \sum_{\alpha \in \Gamma} \mathbb{E}\{(Y_\alpha - p)[g(Z_\alpha + 1) - g(Z_\alpha + W_\alpha + 1)]\}, \\
\mathbb{P}(X = 0) - q^n &\geq - \sum_{\alpha \in \Gamma} \mathbb{E}\{p[g(Z_\alpha + 1) - g(Z_\alpha + W_\alpha + 1)]\} \\
&\geq - \sum_{\alpha \in \Gamma} \sup_{x \geq 1} |\Delta g(x)| p \mathbb{E}(W_\alpha) \\
&\geq - \frac{np - 1 + q^n}{(n-1)np^2} \sum_{\alpha \in \Gamma} \sum_{\alpha \in \Gamma_\alpha \setminus \{\alpha\}} p^2 \quad (\text{by (2.5)}) \\
&= - \frac{42(np - 1 + q^n)}{n - 1} \quad (3.7)
\end{aligned}$$

and

$$\begin{aligned}
\mathbb{P}(X = 0) - q^n &\leq \sum_{\alpha \in \Gamma} \mathbb{E}\{Y_\alpha [g(Z_\alpha + 1) - g(Z_\alpha + W_\alpha + 1)]\} \\
&\leq \sum_{\alpha \in \Gamma} \sup_{x \geq 1} |\Delta g(x)| \mathbb{E}(Y_\alpha W_\alpha) \\
&\leq \frac{np - 1 + q^n}{(n - 1)np^2} \sum_{\alpha \in \Gamma} \sum_{\alpha \in \Gamma_\alpha \setminus \{\alpha\}} \mathbb{E}(Y_\alpha W_\alpha) \quad (\text{by (2.5)}) \\
&= \frac{(np - 1 + q^n)b_1}{(n - 1)np^2}. \tag{3.8}
\end{aligned}$$

Hence, by (3.7) and (3.8) and setting $n = 253$, we have (3.2). \square

4. Numerical Examples

We give two numerical examples to illustrate the result of Theorem 3.1.

Example 4.1. For $p_0 = 0.5$, it follows from Lange [5] that Y_α and Y_β are independent for each $\alpha \in \Gamma$ and $\beta \in \Gamma_\alpha \setminus \{\alpha\}$. Thus, we have $\mathbb{E}(Y_\alpha Y_\beta) = p^2$ and $\mathbb{E}(|p - Y_\alpha| Y_\beta) = 2p^2q$. Since $n = |\Gamma| = 253$ and $|\Gamma_\alpha| = 43$, $b_1 = 10,626p^2$ and $b_2 = 21,252p^2q$. Therefore, when $p_0 = 0.5$, $d = 3$ and $m = 20$, we get $p = 0.000201225$, $q^{253} = 0.950359335$, $np = 253p = 0.050909996$, $b_1 = 0.000430264$ and $b_2 = 0.000860528q$, and a non-uniform bound on the binomial approximation is of the form

$$\left| \mathbb{P}(X = x_0) - \binom{253}{x_0} p^{x_0} q^{253-x_0} \right| \leq \begin{cases} 0.000838989 & \text{if } x_0 = 1, \\ \frac{0.000860528}{x_0} & \text{if } x_0 = 2, \dots, 253, \end{cases}$$

and for $x_0 = 0$,

$$-0.000211555 \leq \mathbb{P}(X = 0) - 0.950359335 \leq 0.000211555.$$

That is, the probability approximation of the Hamming distance equals or exceeds 3 is

$$0.950147780 \leq \mathbb{P}(X = 0) \leq 0.950570890.$$

By comparing numerical results in (3.1) and (3.2) with (1.2) and (1.3), the binomial result is better than the Poisson result in [9].

In case of $X = 0$, the another interesting is estimating the probability $\mathbb{P}(X > 0)$ or $1 - \mathbb{P}(X = 0)$. We can apply (3.2) in the Theorem 3.1 to obtain

$$1 - q^{253} - \frac{(253p - 1 + q^{253})b_1}{63756p^2} \leq 1 - \mathbb{P}(X = 0) \leq 1 - q^{253} + \frac{253p - 1 + q^{253}}{6}$$

and we can show some representative binomial estimate of the probabilities $\mathbb{P}(X > 0)$ for $p_0 = 0.5$ in Table 4.1.

Table 4.1. Binomial Estimate of $\mathbb{P}(X > 0)$

| d | m | Lower Bound | Estimate | Upper Bound |
|-----|-----|-------------|----------|-------------|
| 1 | 10 | 0.21433 | 0.21901 | 0.22369 |
| 1 | 15 | 0.00769 | 0.00769 | 0.00770 |
| 1 | 20 | 0.00024 | 0.00024 | 0.00024 |
| 1 | 25 | 0.00001 | 0.00001 | 0.00001 |
| 2 | 10 | 0.63780 | 0.93494 | 1.00000 |
| 2 | 15 | 0.11502 | 0.11624 | 0.11745 |
| 2 | 20 | 0.00505 | 0.00505 | 0.00506 |
| 2 | 25 | 0.00020 | 0.00020 | 0.00020 |
| 3 | 10 | 0.00000 | 1.00000 | 1.00000 |
| 3 | 15 | 0.55339 | 0.60779 | 0.66220 |
| 3 | 20 | 0.04943 | 0.04964 | 0.04985 |
| 3 | 25 | 0.00245 | 0.00246 | 0.00246 |

It is observed that the estimates are more accurate when m is increasing or the lower and upper bounds are close to the estimates when m is large. By comparison between lower and upper bounds, our estimates of $\mathbb{P}(X > 0)$ are better than the estimates of [5] on pp. 257. When the retention probability $p_0 \neq 0.5$, it follows from [5] that, for a random panel with m clones and regardless of which $\beta \in \Gamma_\alpha \setminus \{\alpha\}$ is chosen,

$$\mathbb{E}(Y_\alpha Y_\beta) = \sum_{d_{12}=0}^{d-1} \sum_{d_{13}=0}^{d-1} x_{m,d_{12},d_{13}}, \quad (4.1)$$

where $x_{m,d_{12},d_{13}} = \mathbb{P}(\rho(c_1^m, c_2^m) = d_{12}, \rho(c_1^m, c_3^m) = d_{13})$. We can compute $x_{m,d_{12},d_{13}}$ from the recurrence relation, for $m \geq 1$,

$$\begin{aligned} x_{m,d_{12},d_{13}} &= p_0(1 - p_0)(x_{m-1,d_{12}-1,d_{13}} + x_{m-1,d_{12},d_{13}-1} + x_{m-1,d_{12}-1,d_{13}-1}) \\ &\quad + (1 - 3p_0(1 - p_0))x_{m-1,d_{12},d_{13}}, \end{aligned} \quad (4.2)$$

where the initial conditions are

$$x_{0,d_{12},d_{13}} = \begin{cases} 1 & \text{if } d_{12} = d_{13} = 0, \\ 0 & \text{otherwise.} \end{cases}$$

Example 4.2. Suppose that $p_0 = 0.3$, $d = 3$ and $m = 25$, then we have $p = 0.0002149$, $q^{253} = 0.947076372$, $np = 253p = 0.0543697$, $\mathbb{E}(Y_\alpha Y_\beta) = 0.00000022184$, $b_1 = 0.0023573$ and $b_2 \leq 10$, $626p^2 + qb_1 = 0.00284752$. A non-uniform bound for approximating the point probabilities of X by the binomial distribution with parameters $n = |\Gamma| = 253$ and $p = 0.0002149$ is

$$\left| \mathbb{P}(X = x_0) - \binom{253}{x_0} p^{x_0} q^{253-x_0} \right| \leq \begin{cases} 0.002772582 & \text{if } x_0 = 1, \\ \frac{0.002848136}{x_0} & \text{if } x_0 = 2, \dots, 253, \end{cases}$$

and for $x_0 = 0$,

$$-0.000241012 \leq \mathbb{P}(X = 0) - 0.947076372 \leq 0.001157740,$$

and the probability approximation of the Hamming distance equals or exceeds $d = 3$ is

$$0.94683536 \leq \mathbb{P}(X = 0) \leq 0.948234112.$$

This numerical result is also better than the numerical result of the Poisson approximation in (1.2) and (1.3).

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