Determining the distribution of word matches between Markovian sequences

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Definition of D_2

Given two sequences from a finite alphabet

$$A := (A_1, A_2, \ldots, A_m) \text{ and } B := (B_1, B_2, \ldots, B_n),$$

D_2 is the number of matches of words (including overlaps) of prespecified length k between two given sequences.

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Example: consider these two sequences and $k = 7 \ldots$

A: ATGCTTTGCTAGCGCTATGCTTTCGCAAACTCAT

B: ATGCTTTTAAAACCGAGCTGGTCAGCGCTAAGCGCT

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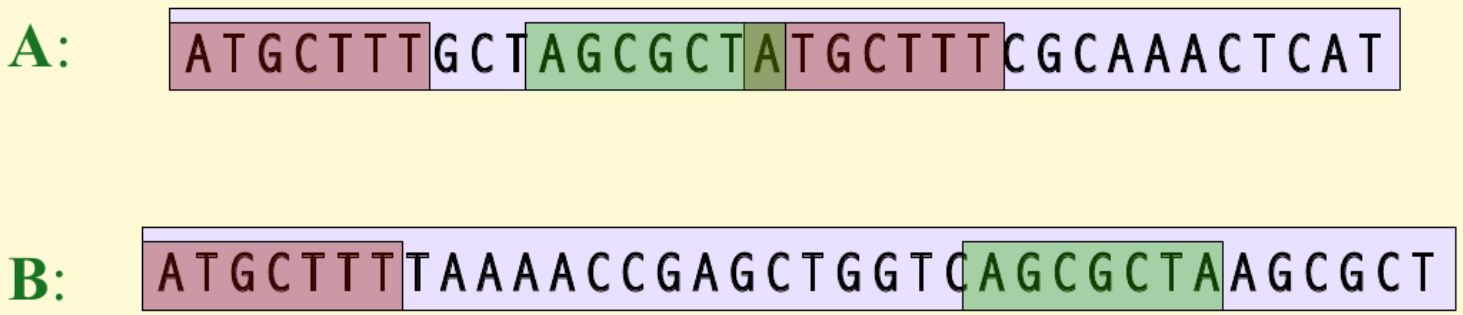

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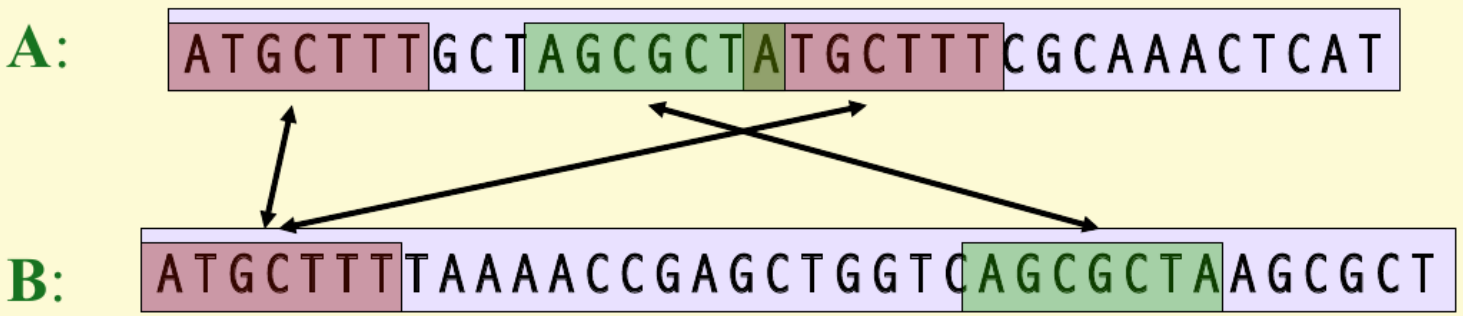


In this example, for $k = 7, D_2 = 3$.

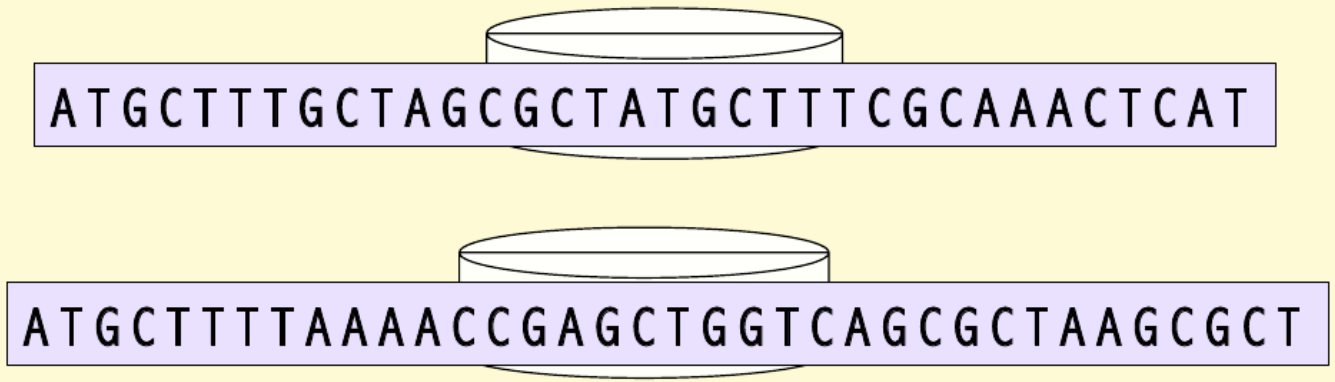
Our previous results

(with Sue Wilson, Ruth Kantorovitz, and Junmei Jing)

We have exact formulas for $\mathbf{E}(\boldsymbol{D_2})$ (simple) and $\mathbf{Var}(\boldsymbol{D_2})$ (complicated), and accurate approximations for the distribution of $\boldsymbol{D_2}$ for the case of sequences composed of i.i.d. letters;
i.e. each letter drawn independently from the same distribution.

Periodic boundary conditions

To simplify the calculations (avoiding 'edge effects'), we imposed periodic boundary conditions:



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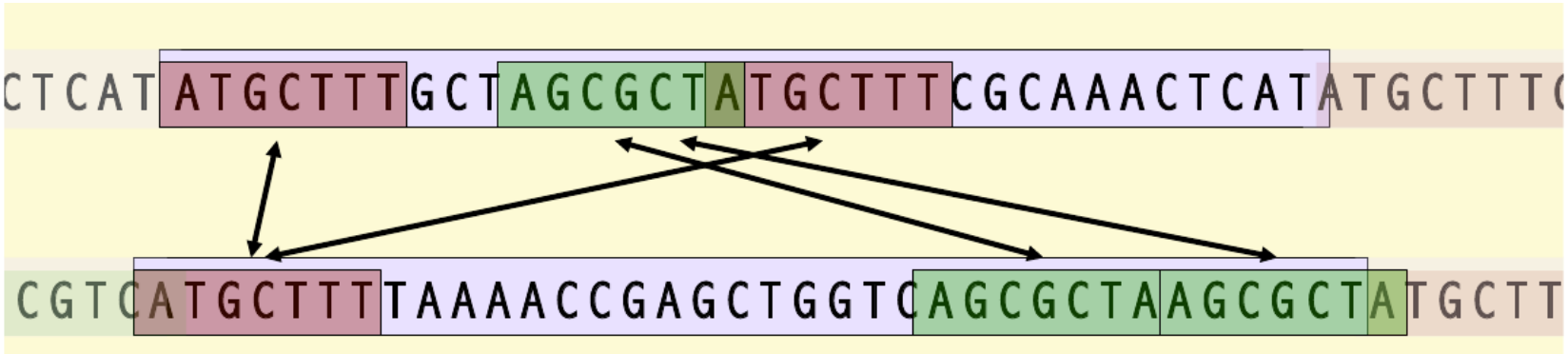

Now, for $k = 7$ we have $D_2 = 4$.

Markovian sequences

The i.i.d. is not realistic. Real DNA sequences are more realistically modelled as Markovian (up to fifth order).

For first order:

$$\mathbf{Prob}(A_{i+1} = u \mid A_i = v) = M_{u,v},$$
$$u, v \in \{A, C, G, T\}$$

where

$$0 \leqslant M_{u,v} \leqslant 1; \quad \sum_v M_{u,v} = 1.$$

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First problem:
How do we define periodic boundary conditions for a Markovian sequence?

Markov chain with periodic boundary conditions

Define a Markov chain

$$\ldots X_{n-1}, X_n, X_1, X_2, \ldots, X_n, X_1, X_2, \ldots$$

with periodic boundary conditions (PBCs) via the following algorithm:

1. Choose X_1 from any distribution $\pi(u), u \in \{1, \ldots, d\}$, where $0 \leqslant \pi(u) \leqslant 1; \sum_u \pi(u) = 1$. Thus $\mathbf{Pr}(X1 = u) = \pi(u)$.

2. Choose $X_2, \ldots, X_{n+1}$ via the Markov matrix M, $\mathbf{Pr}(X_{i+1} = v \mid X_1 = u) = M_{u,v}, i = 1, \ldots, n$.

3. If $X_{n+1} = X_1$, accept $X_1, X_2, \ldots, X_n$, otherwise return to Step 1 and repeat the procedure.

No privileged starting point

We further wish to restrict the definition to repeating Markov chains with no privileged starting point, by which we mean

$$\mathbf{Pr}(X = x) = \mathbf{Pr}\left(X = (x_{i+1} \dots x_n, x_1 \dots x_i)\right),$$
$$\text{for all } i = 1, \dots, n-1,$$
$$\text{where } X = (X_1 X_2 \dots X_n).$$

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Theorem 1

X has no privileged starting point if and only if $\pi(u)$ is a uniform distribution: $\pi(u) = 1/d, u = 1, \dots, d$.

Probability of a specific sequence

Corollary 2

If $\boldsymbol{X}$ is a Markov chain with no privileged starting point, the probability of any given sequence $\boldsymbol{x} = (\boldsymbol{x_1 x_2 \dots x_n})$ is

$$\mathbf{Pr}(\boldsymbol{X} = \boldsymbol{x}) = \frac{\boldsymbol{M_{x_1,x_2} M_{x_2,x_3} \cdots M_{x_n,x_1}}}{\mathbf{tr}(\boldsymbol{M^n})}$$

Mean of D_2

For two sequences A and B of length m and n, both generated using the matrix M, and word length k,

$$\mathbf{E}(D_2) = \frac{mn \operatorname{tr}\left[(M^{m-k+1} \circ M^{n-k+1})(M \circ M)^{k-1}\right]}{\operatorname{tr}(M^m) \operatorname{tr}(M^n)},$$

where $\circ$ indicates the Hadamard product of matrices

$$(P \circ Q)_{r,s} = P_{r,s} Q_{r,s}.$$

Mean of D_2

Given two sequences
$A = (A_1, A_2, \ldots, A_m)$ and $B = (B_1, B_2, \ldots, B_n)$,
define the word-match indicator

$$I_{i,j} = \begin{cases} 1 & \text{if } k\text{-word at position } i \text{ in } A \text{ matches} \\ & \quad k\text{-word at position } j \text{ in } B, \\ 0 & \text{otherwise.} \end{cases}$$

Then

$$D_2 = \sum_{i=1}^{m} \sum_{j=1}^{n} I_{i,j}$$

and

$$\mathrm{E}(D_2) = \sum_{i=1}^{m} \sum_{j=1}^{n} \mathrm{E}(I_{i,j}) = \sum_{i=1}^{m} \sum_{j=1}^{n} \Pr(I_{i,j} = 1).$$

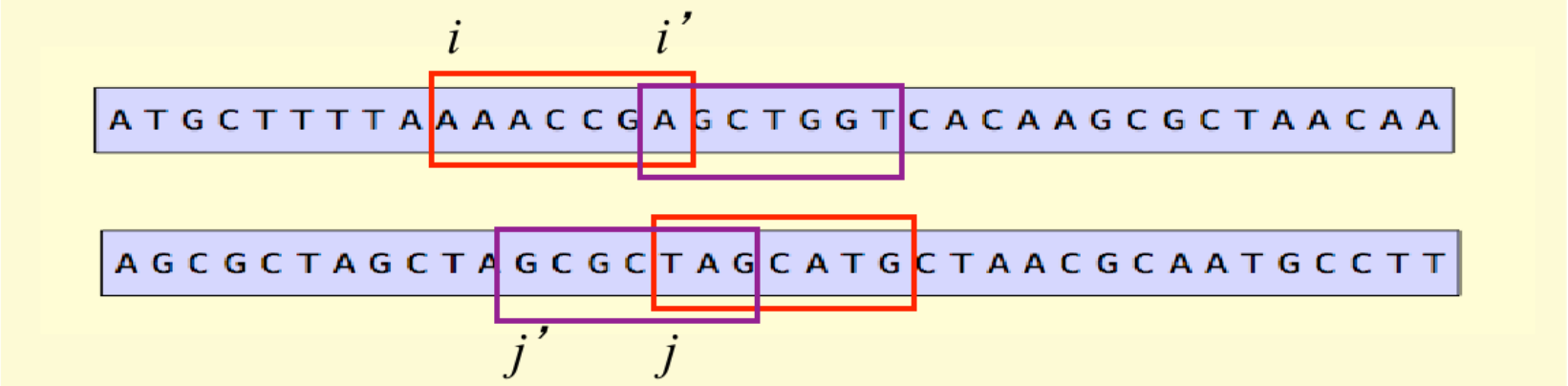
Variance of D_2

The variance of D_2 is much harder but can be done, at least for Markov order 1:

$$\mathbf{Var}(D_2) = \mathbf{Var}\left(\sum_{i,j} I_{i,j}\right) = \mathbf{E}\left(\left(\sum_{i,j} I_{i,j}\right)^2\right) - \left(\mathbf{E}\left(\sum_{i,j} I_{i,j}\right)\right)^2$$

$$= \left(\sum_{i,j,i',j'} \mathbf{E}(I_{i,j}, I_{i',j'})\right) - \mathbf{E}(D_2)^2.$$

The difficult part is $\mathbf{E}(I_{i,j}, I_{i',j'})$, the probability of word matches like this:



Variance of D_2

The formula for $\mathbf{Var}(D_2)$ with periodic boundary conditions and Markov order 1 is complicated . . .

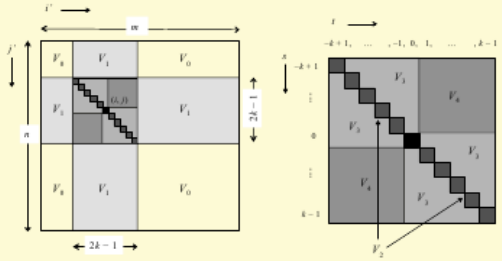


Figure 2: Contributions to $\mathrm{Var}(D_2)$ via the sum in Eq. (24). The left-hand diagram shows the (i', j')-plane for a fixed value of (i, j), shown as the black square. The right-hand diagram is an expanded view of the 'accordion' region $-k+1 \le s, t \le k-1$, where $t = i' - i$ and $s = j' - j$ up to PBCs.

and j' in sequence $\mathbf{Y}$,

$$
\begin{aligned}
E(D_2{}^2) &= \sum_{i,i'=1}^{m} \sum_{j,j'=1}^{n} E(I_{ij} I_{i'j'}) \\
&= \sum_{i,i'=1}^{m} \sum_{j,j'=1}^{n} \mathrm{Prob}\,(I_{ij} = 1, I_{i'j'} = 1) \\
&= V_0 + V_1 + V_2 + V_3 + V_4. \qquad (24)
\end{aligned}
$$

The partitioning reflects the degree of overlap between words in each of the two sequences, and is illustrated in Fig. 2. We assume $m, n \ge 2k$, which will almost certainly be the case in any biological application.

We will write a Hadamard product of q factors, $M \circ \ldots \circ M$, using the shorthand notation $M^{\circ q}$. With this notation, the contributions to the variance are:

$$
\begin{aligned}
V_0 = {} & \frac{mn}{\mathrm{tr}\,(M^m)\mathrm{tr}\,(M^n)} \times \\
& \sum_{r=0}^{m-2k} \sum_{s=0}^{n-2k} \mathrm{tr}\left[(M^{r+1} \circ M^{s+1})(M \circ M)^{k-1} \times \right. \\
& \left. (M^{m-2k-r+1} \circ M^{n-2k-s+1})(M \circ M)^{k-1} \right], \qquad (25)
\end{aligned}
$$

$$
\begin{aligned}
V_1 = {} & \frac{mn}{\mathrm{tr}\,(M^m)\mathrm{tr}\,(M^n)} \times \\
& \left\{ \sum_{r=0}^{n-2k} \left[\mathrm{tr}\left\{ [(M \circ M \circ M)^{k-1} \circ (M^{r+1})^T] \times \right. \right. \right. \\
& \left. \left. \left. (M^{m-k+1} \circ M^{n-2k-r+1}) \right\} \right. \right. \\
& \left. \left. + 2 \sum_{r=1}^{k-1} \mathrm{tr}\left\{ (M \circ M)^r \times \right. \right. \right. \\
& \left. \left. \left. [(M \circ M \circ M)^{k-r-1} \circ (M^{r+1})^T] \times \right. \right. \right. \\
& \left. \left. \left. (M \circ M)^r (M^{m-k-r+1} \circ M^{n-2k-s+1}) \right\} \right] \right. \\
& \left. + \text{the same with } m \text{ and } n \text{ interchanged.} \right\}, \qquad (26)
\end{aligned}
$$

$$
\begin{aligned}
V_2 = {} & \frac{mn}{\mathrm{tr}\,(M^m)\mathrm{tr}\,(M^n)} \times \\
& \left\{ \mathrm{tr}\left[(M^{m-k+1} \circ M^{n-k+1})(M \circ M)^{k-1} \right] \right. \\
& \left. + 2 \sum_{t=1}^{k-1} \mathrm{tr}\left[(M^{m-k-t+1} \circ M^{n-k-t+1}) \times \right. \right. \\
& \left. \left. (M \circ M)^{k+t-1} \right] \right\}, \qquad (27)
\end{aligned}
$$

$$
\begin{aligned}
V_3 = {} & \frac{2mn}{\mathrm{tr}\,(M^m)\mathrm{tr}\,(M^n)} \times \\
& \sum_{t=1}^{k-1} \sum_{s=0}^{t-1} \mathrm{tr}\left[(M \circ M)^t Q (M \circ M)^s \times \right. \\
& (M^{m-k-t+1} \circ M^{n-k-s+1} + \\
& \left. M^{n-k-t+1} \circ M^{m-k-s+1}) \right], \qquad (28)
\end{aligned}
$$

where

$$
Q = \begin{cases} (M^{\circ(2\nu+3)})^{\rho-1} \circ [(M^{\circ(2\nu+1)})^{t-s-\rho+1}]^T & \text{if } \rho > 0, \\ (M^{\circ(2\nu+1)})^{t-s-1} \circ (M^{\circ(2\nu-1)})^T & \text{if } \rho = 0, \end{cases} \qquad (29)
$$

and

$$
\nu = \left\lfloor \frac{k-s}{t-s} \right\rfloor, \qquad \rho = (k-s) \bmod (t-s). \qquad (30)
$$

Finally,

$$
V_4 = \frac{2mn}{\mathrm{tr}\,(M^m)\mathrm{tr}\,(M^n)} \sum_{r,t=1}^{k-1} \mathrm{tr}\, U, \qquad (31)
$$

where

$$
U = \begin{cases}
\left\{ (M^{\circ(2\nu+1)})^{t-1} \circ (M^{m-k-r+1})^T \right\} M^{\circ 2\nu} \times \\
\quad \left\{ (M^{\circ(2\nu+1)})^{r-1} \circ (M^{n-k-r+1})^T \right\} M^{\circ 2\nu} \\
\qquad \text{if } \zeta = 0, \\
\left\{ (M^{\circ(2\nu+1)})^{r-\zeta+1} \circ M^{m-k-t+1} \right\} \times \\
(M^{\circ(2\nu+2)})^{\zeta-1} \times \\
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\quad (M^{\circ(2\nu+2)})^{\zeta-1} \\
\qquad \text{if } 0 < \zeta \le r, t, \\
\left\{ (M^{\circ(2\nu+3)})^{\zeta-r-1} \circ (M^{m-k-t+1})^T \right\} \times \\
(M^{\circ(2\nu+2)})^r \left\{ (M^{\circ(2\nu+1)})^{t-\zeta+1} \circ M^{n-k-r+1} \right\} \\
\quad \times (M^{\circ(2\nu+2)})^r \\
\qquad \text{if } r < \zeta \le t, \\
\{\text{as above with } m \text{ and } n \text{ interchanged} \\
\quad \text{and } r \text{ and } t \text{ interchanged}\} \\
\qquad \text{if } t < \zeta \le r, \\
\left\{ (M^{\circ(2\nu+3)})^{\zeta-r-1} \circ (M^{m-k-t+1})^T \right\} \times \\
(M^{\circ(2\nu+2)})^{t+r-\zeta+1} \times \\
\quad \left\{ (M^{\circ(2\nu+3)})^{\zeta-t-1} \circ (M^{n-k-r+1})^T \right\} \times \\
\quad (M^{\circ(2\nu+2)})^{t+r-\zeta+1} \\
\qquad \text{if } r, t < \zeta,
\end{cases}
$$

and

$$
\nu = \left\lfloor \frac{k}{r+t} \right\rfloor, \qquad \zeta = k \bmod (r+t). \qquad (32)
$$

. . . but is easily evaluated.

Verification by simulation

1. For a given order 1 Markov matrix, generate 10,000 random pairs of Markovian sequences with periodic boundary conditions (R scripts).

2. Obtain the value of $\boldsymbol{D_2}$ for each pair (SAFT program, written in C).

3. Compare empirical cumulative distribution function of $\boldsymbol{D_2}$ with that of Normal and Pólya-Aeppli (compound Poisson) distributions using theoretical $\mathbf{E}(\boldsymbol{D_2})$ and $\mathbf{Var}(\boldsymbol{D_2})$ (R scripts).

Generation of sequences

Sequences are generated by using the algorithm shown previously.

Seemingly more efficient algorithms, such as continuing with $\boldsymbol{X_{n+2}, X_{n+3}, \ldots}$ until $\boldsymbol{X_k}$ matches $\boldsymbol{X_{n+k}}$ can yield different distributions.

Calculating D_2

The SAFT program was written to compare a given sequence against a database of sequences, by calculating D_2 for each pair.

The program was adapted to take two lists of sequences $\mathcal{A}, \mathcal{B}$, and determine D_2 for each corresponding pair $\mathcal{A}_k, \mathcal{B}_k$.

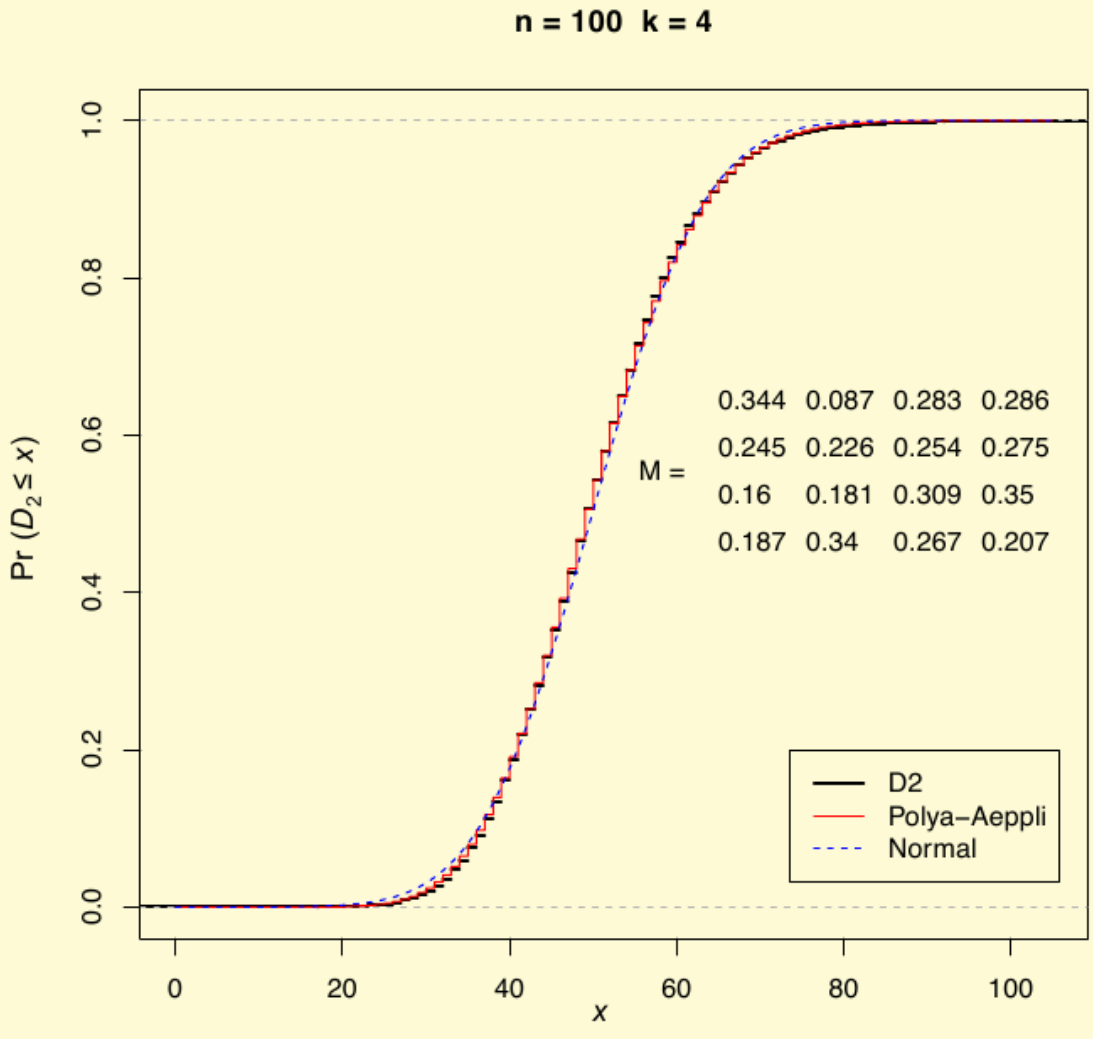
Comparing against known distributions

The R statistical system was used to

- Use the `t.test` function in R to compare the empirical and theoretical mean values.
- Use the `qchisq` function in R to produce a confidence interval for the variance, and test the variance using this interval.
- Use the `ks.test` function in R to compare the empirical distribution of $\boldsymbol{D_2}$ against the Normal and the Pólya-Aeppli distributions, using the theoretical mean and variance. The R function `pPolyaAeppli` was written for this purpose.
- Plot cumulative distributions.

Results for one random Markov matrix

Randomly chosen Markov matrix *M*



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