Repetition length in random sequences

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Motivation

Many repetitive structures in genomic sequences:

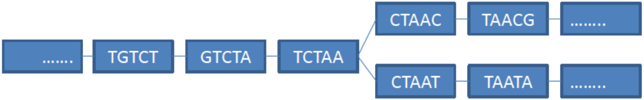
- microsatellites
- DNA transposons
- long terminal repeats
- long interspersed nuclear elements
- ribosomal DNA
- short interspersed nuclear elements

Treangen&Salzberg2012: half of the genome : repetitive elements.

Applications : assembly, de Bruijn graphs, ...

Assembly strategies 

de Bruijn graph.



- Reads $\rightarrow$ k-mers
- Node $=$ one k-mer
- Edge $\rightarrow$ 1 $(k-1)$-mer

State of the art

Model: trie versus (word,sequence) repetition

Deviations from uniformity

- **Flajolet&Nigel** : binary alphabet Σ; uniform Bernoulli model:
  - almost all words of length $\leq k$ appear.
  - almost no word of length $> k$ appear.
- **Park&al. 2009**; binary alphabet; biased Bernoulli model: transition domain for trie profile: "many" words of length k appear.

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General alphabets ?

State of the art

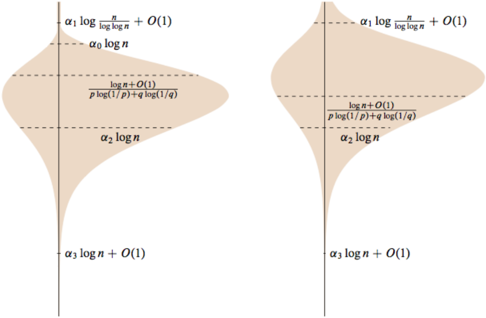

Figure 5: *The silhouettes of the expected external (left) and internal (right) profiles of an asymmetric trie* ($p = 0.75$)*. Note that the right subtrees of the asymmetric trie have more nodes than their left siblings since* $p > 1/2$*. Also, the first few levels contain almost no external nodes, but are almost full of internal nodes.*

Method

Analytic combinatorics

- functional equation on a generating function, or an induction.
- asymptotics of coefficients of G.F. (Mellin, saddle point; ...)
- Bernoulli-Poisson cycle

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- probability $\Rightarrow$ coefficients
- Lagrange multipliers

Words and tries

Axiom: repeat $\Leftrightarrow$ internal node

Words and tries

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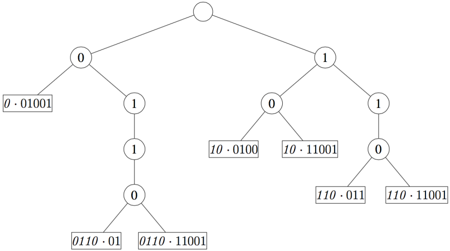
Unique k-mer :

wa : once; w : twice; $|wa| = k$

- In the sequence : $wa \cdots wb$
  w : (right) maximal repeat
- In a trie :
  w : internal node ; w : leaf

Myriad virtues of Tries (and Suffix arrays)



Notations

n words OR sequence of length n

$$
\begin{aligned}
B(n,k) &= \#\text{unique } k\text{-mers} \\
\mu(n,k-1) &= E(B(n,k)) \\
\alpha &= \frac{k}{\log n}
\end{aligned}
$$

Notations

n words OR sequence of length n

$$
\begin{aligned}
B(n,k) &= \#\text{unique } k\text{-mers} \leq n \\
\mu(n,k-1) &= E(B(n,k)) \sim B(n,k)\text{: LLN} \\
\alpha &= \frac{k}{\log n} \quad 0 \cdots \infty
\end{aligned}
$$

Notations

n words OR sequence of length n
Σ alphabet $\chi_1, \cdots, \chi_V$
Probabilities: $p_1, \cdots, p_V$

$$\beta_i = \log \frac{1}{p_i} \quad .$$

$$p_{min} = \min\{p_i; 1 \le i \le V\} \quad \text{and} \quad \alpha_{min} = \frac{1}{\log \frac{1}{p_{min}}} = \frac{1}{\max(\beta_i)}$$
$$p_{max} = \max\{p_i; 1 \le i \le V\} \quad \text{and} \quad \alpha_{max} = \frac{1}{\log \frac{1}{p_{max}}} = \frac{1}{\min(\beta_i)}$$

k-mers classification

Barycentric coordinates & objective function

$$\rho(k_1, \cdots, k_V) = \sum_{i=1}^{V} \frac{k_i}{k} \beta_i - \frac{1}{\alpha} \quad . \tag{1}$$

$\sum_{i=1}^{V} \frac{k_i}{k} \beta_i \in [\min(\beta_i), \max(\beta_i)]$

k-mers classification

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A k-mer $w\chi_i$ is said

- a *common k-mer* if $\rho(k_1, \cdots, k_V) < 0$;
- a *transition k-mer* if $\rho(k_1, \cdots, k_V) \geq 0$ and its ancestor is a common k-mer;
- a *rare k-mer* , otherwise.

k-mers classification

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- a *transition k-mer* if $\rho(k_1, \cdots, k_V) \geq 0$ and its ancestor is a common k-mer; $E(w\chi_i) \leq 1, E(w) > 1$
- a *rare k-mer* ; $E(w) \leq 1$

k-mers classification

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- a *rare k-mer* ; $E(w) \leq 1$

Main contribution for each given level k :transition nodes.

Combinatorial sums

$$\mu(n,k) = n \sum_{k_1+\cdots k_V=k} \binom{k}{k_1,\cdots,k_V} \phi(k_1,\cdots,k_V)\psi_n(k_1,\cdots,k_V) \tag{2}$$

$\phi(k_1,\cdots,k_V) = p_1^{k_1}\cdots p_V^{k_V}$
$\psi\ : \sum_{i=1}^{V} p_i[(1-\phi(k_1,\cdots,k_V)p_i)^{n-1} - (1-\phi(k_1,\cdots,k_V))^{n-1}]$

Combinatorial sums

$$\mu(n,k) = n \sum_{k_1+\cdots k_V=k} \binom{k}{k_1,\cdots,k_V} \phi(k_1,\cdots,k_V)\psi_n(k_1,\cdots,k_V)$$

$\phi(k_1,\cdots,k_V)p_i = p_1^{k_1}\cdots p_V^{k_V}p_i$: $P(w\chi_i)$
ψ : $\sum_{i=1}^V p_i[(1-\phi(k_1,\cdots,k_V)p_i)^{n-1} - (1-\phi(k_1,\cdots,k_V))^{n-1}]$
$(1-\phi(k_1,\cdots,k_V)p_i)^{n-1}$: no other $w\chi_i$
$(1-\phi(k_1,\cdots,k_V))^{n-1}$: at least an other w

Combinatorial sums

$$S(k) = n \sum_{D_k(n)} \binom{k}{k_1 \cdots k_V} \phi(k_1, \cdots, k_V)\psi_n(k_1, \cdots, k_V) \ ;$$

$$T(k) = n \sum_{E_k(n)} \binom{k}{k_1 \cdots k_V} \phi(k_1, \cdots, k_V)\psi_n(k_1, \cdots, k_V) \ .$$

Tech: two diff. approx. when

- w : rare or transition
- w : common

Computable for moderate k.

Lagrange multipliers

Large Deviation Principle

$$
\begin{aligned}
np_1^{k_1} \cdots p_V^{k_V} &= e^{-k\rho(k_1,\cdots,k_V)} \\
\binom{k}{k_1, \cdots, k_V} \phi(k_1, \cdots, k_V) &\to e^{-k\sum_i \frac{k_i}{k} \log \frac{k_i}{k}}
\end{aligned}
$$

Dominating contribution $S(k), T(k)$: $\rho(k_1, \cdots, k_V) = 0.$

Large Deviation principle

Main contribution

For each given level k :transition nodes.

Maximization problem

$\sim \max\{-\sum_{i=1}^{V} \frac{k_i}{k} \log \frac{k_i}{k}; \rho(k_1, \cdots, k_V) = 0\}$

Rewrite :

$\max\{\sum_{i=1}^{V} \theta_i \log \frac{1}{\theta_i}; \sum_{i=1}^{V} \theta_i = 1; \sum_{i=1}^{V} \beta_i \theta_i = \frac{1}{\alpha}; 0 \leq \theta_i \leq 1\}$

Lagrange multipliers and Large Deviation Principle

Lagrange multipliers

$\max\{\sum_{i=1}^{V} \theta_i \log \frac{1}{\theta_i}; \sum_{i=1}^{V} \theta_i = 1; \sum_{i=1}^{V} \beta_i \theta_i = \frac{1}{\alpha}; 0 \leq \theta_i \leq 1\}$

Implicit equation solution

Let τ_α be the unique real root of the equation

$$\frac{1}{\alpha} = \frac{\sum_{i=1}^{V} \beta_i e^{-\beta_i \tau}}{\sum_{i=1}^{V} e^{-\beta_i \tau}} \tag{2}$$

Let ψ be the function defined in $[\alpha_{min}, \alpha_{ext}]$ as

$$\alpha_{min} \leq \alpha \leq \bar{\alpha} \quad : \quad \psi(\alpha) = \tau_\alpha + \alpha \log(\sum_{i=1}^{V} e^{-\beta_i \tau_\alpha}) \;\; ;$$

$$\bar{\alpha} \leq \alpha \quad : \quad \psi(\alpha) = 2 - \alpha \log \frac{1}{\sigma_2} \;\; .$$

Results and interpretation

0 —— α_{min} —— $\tilde{\alpha}$ —— $\bar{\alpha}$ —— α_{max} —— α_{ext} ——

- $\alpha \leq \alpha_{min}$: **all nodes are common** : $\frac{\log \mu(n,k)}{\log n} \leq 0$.
- **common, transition and rare** :
- **all nodes are rare**
  - $\alpha_{max} \leq \alpha \leq \alpha_{ext}$: LLN

$$\frac{\log \mu(n,k)}{\log n} = \psi_2(\alpha) = 2 - \alpha \log \frac{1}{\sigma_2}$$

  - $\alpha \geq \alpha_{ext}$:

$$\frac{\log \mu(n,k)}{\log n} \leq 0$$

Results and interpretation

0 ——— α_{min} ——— $\tilde{\alpha}$ ——— $\bar{\alpha}$ ——— α_{max} ——— α_{ext} ———

common, transition and rare

- $\alpha_{min} \leq \alpha \leq \tilde{\alpha}$: transition k-mers increase

$$\frac{\log \mu(n,k)}{\log n} = \psi_1(\alpha)$$

- $\tilde{\alpha} \leq \alpha \leq \bar{\alpha}$: transition k-mers decrease

$$\frac{\log \mu(n,k)}{\log n} = \psi_1(\alpha)$$

- $\bar{\alpha} \leq \alpha_{max}$: transition k-mers decrease

$$\frac{\log \mu(n,k)}{\log n} = \psi_2(\alpha) = 2 - \alpha \log \frac{1}{\sigma_2}$$

Simulations

k	observed $B(k+1)$	predicted $S(k)$	$T(k)$	$\mu(N,k)$	observed $\frac{\log B(k+1)}{\log N}$	asymptotic $\psi(\alpha)$	$\psi(\alpha)+\xi(\alpha)$	
11	0.29	0.0	0.3	0.3	-0.0803			
12	7.91	0.0	8.3	8.3	0.1341			
13	87.87	0.1	86.9	87.1	0.2902	**0.0843**	*0.0012*	k_{min}
14	552.88	1.2	550.3	551.5	0.4094	**0.3340**	*0.2485*	
15	2456.77	86.6	2366.4	2453.0	0.5061	**0.4962**	*0.4085*	
16	8269.20	209.4	8069.1	8278.5	0.5848	**0.6181**	*0.5282*	
17	22516.20	406.1	22097.7	22503.8	0.6497	**0.7136**	*0.6218*	
18	51085.15	4823.8	46267.2	51091.0	0.7028	**0.7897**	*0.6960*	
19	99387.01	6636.1	92717.6	99353.7	0.7460	**0.8504**	*0.7549*	
20	169303.03	37415.5	131882.6	169298.1	0.7805	**0.8984**	*0.8013*	
21	256358.10	42003.9	214454.4	256458.3	0.8074	**0.9357**	*0.8370*	
22	349801.23	137615.9	212264.2	349880.1	0.8276	**0.9635**	*0.8634*	
23	434625.83	134807.6	299824.7	434632.4	0.8416	**0.9830**	*0.8814*	
24	495572.93	122283.1	373279.8	495562.8	0.8501	**0.9949**	*0.8919*	
25	522788.19	255284.4	267476.3	522760.7	0.8536	**0.9998**	*0.8955*	$\tilde{k}$
26	513374.76	211204.2	302252.5	513456.7	0.8524	**0.9982**	*0.8926*	
27	472126.51	315154.7	157087.0	472241.6	0.8470	**0.9906**	*0.8838*	
28	408946.76	242583.4	166360.3	408943.7	0.8377	**0.9772**	*0.8692*	
29	335080.05	273441.0	61579.7	335020.7	0.8248	**0.9582**	*0.8491*	
30	260999.29	198163.4	62712.5	260875.9	0.8086	**0.9339**	*0.8236*	
31	194100.36	137502.0	56463.1	193965.1	0.7894	**0.9043**	*0.7930*	$\bar{k}$
32	138437.13	122218.3	16090.9	138309.2	0.7675	**0.8699**	*0.8136*	
33	95017.33	80937.1	14067.8	95004.9	0.7431	**0.8346**	*0.7783*	

Simulations

	observed	predicted			observed	asymptotic		
k	$B(k+1)$	$S(k)$	$T(k)$	$\mu(N,k)$	$\frac{\log B(k+1)}{\log N}$	$\psi(\alpha)$	$\psi(\alpha)+\xi(\alpha)$	
12	7.91	0.0	8.3	8.3	0.1341			
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27	472126.51	315154.7	157087.0	472241.6	0.8470	**0.9906**	*0.8838*	
29	335080.05	273441.0	61579.7	335020.7	0.8248	**0.9582**	*0.8491*	
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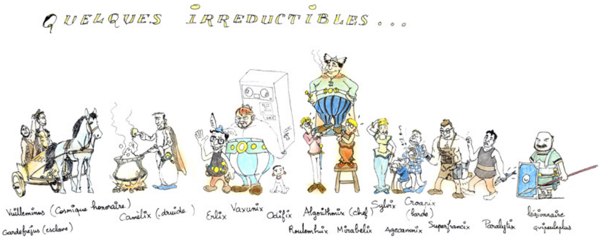
32	138437.13	122218.3	16090.9	138309.2	0.7675	**0.8699**	*0.8136*	$\bar{k}$
34	63082.67	60397.1	2744.6	63141.7	0.7165	**0.7993**	*0.7430*	
36	25679.21	23888.2	1817.4	25705.6	0.6582	**0.7286**	*0.6724*	
38	9645.84	9455.0	194.2	9649.2	0.5948	**0.6580**	*0.6018*	
40	3433.87	3426.4	12.1	3438.5	0.5278	**0.5874**	*0.5311*	
42	1188.84	1189.0	0.3	1189.3	0.4590	**0.5167**	*0.4605*	
43	692.28	694.8	0.2	695.0	0.4240	**0.4814**	*0.4252*	
44	402.75	405.1	0.0	405.1	0.3889	**0.4461**	*0.3899*	k_{max}
46	135.42	137.0	0.0	137.0	0.3182	**0.3755**	*0.3192*	
48	44.69	46.2	0.0	46.2	0.2463	**0.3048**	*0.2486*	
50	14.57	15.6	0.0	15.6	0.1737	**0.2342**	*0.1780*	
52	4.76	5.2	0.0	5.2	0.1012	**0.1636**	*0.1073*	
54	1.74	1.8	0.0	1.8	0.0359	**0.0929**	*0.0367*	
56	0.64	0.6	0.0	0.6	-0.0289	**0.0223**	*-0.0339*	
57	0.32	0.3	0.0	0.3	-0.0739	**-0.0130**		k_{ext}
59	0.16	0.1	0.0	0.1	-0.1188	**-0.0836**		
61	0.08	0.0	0.0	0.0	-0.1637	**-0.1543**		

Extensions

- Right to left maximality
- Maximal repeats
- Markov model
- Errors

Thank you !



team-project
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A basic scheme

$$
\begin{array}{rcccl}
\mathcal{R}: f(n) = \sum \cdots & \rightarrow & f(n) \sim \cdots : \mathcal{R} \\
\downarrow & 1983 & \downarrow \\
\mathcal{C}: F(z) = \sum_n f(n) z^n & \rightarrow & f(n) \sim \cdots : (\textit{singularities!})\, \mathcal{C}
\end{array}
$$

Generating functions

Combinatorial object and a size : trees, words, ...
Generating functions :

$$
\begin{aligned}
F(z) &= \sum_n f(n) z^n \ \textit{ordinary} \\
&= \sum_n f(n) \frac{z^n}{n!} \quad \textit{exponential}
\end{aligned}
$$

algebraic or probability

monovariate or multivariate

A systematic approach

$$\{f_n\}_{n\geq 1} \leftrightarrow F(z) = \sum_n f_n z^n$$

Induction: Recursive combinatorial properties

$\Downarrow$

Functional equation on $F(z)$

$\Downarrow$

Asymptotics :

n large: $f_n \sim \beta_n \rho^{-n}$

where ρ is the root of some algebraic equation.