Looking at Whole Genomes – Information, growth & evolution

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Plan of talk

• Genome and Life
• How did genome grow (life evolve) so quickly
• Textual spectral width & Shannon information
• Universality class of genomes
• Model for genome growth
• Self-similarity & randomness
• Substitution and duplication rates
• Discussion – implication in biology & evolution
~ Life is the splendid expression genome – the ultimate organization of information
Life is highly diverse and complex

Tree of Life
W.F. Doolittle

We are here
And it took a long time to get here now

4 billion yrs ago
Two approaches to Life Science

1. Local - “Biology”
   - Individual, specificity, uniqueness

2. Global - “Physics/Math/Stats”
   - Class, generality, universality, model

Today we take the GLOBAL route
Genome Growth, Entropy & Second law of Thermodynamics

~ How did genomes generate information stochastically
Evolution of Genomes and the Second Law of Thermodynamics

- **Genomes**
  - Grew and evolved (mainly) **stochastically**, modulated by natural selection
  - Bigger genomes carry more information than smaller ones

- **The second law of thermodynamics:**
  - the entropy of closed system can never decrease
  - a system that grows stochastically tends to acquire entropy
  - Increased randomness → more entropy

- **Shannon information**
  - Information decreases with increasing entropy
How did evolution fight against the Second Law?

• Genomes are not closed systems, but the 2nd law does make it difficult for the genome to simultaneously:
  • grow stochastically
  • acquire more information
    • lose entropy
    • gain order

• We propose an answer to this question
Genomes as Text - Spectral Width & Shannon Information

~ genomes have far more information than random sequences
Genomes are BIG

A stretch of genome from the X chromosome of Homo sapien


The complete genome has 2,000,000 such Pages

1 tgctgagaaa acataaagctg tgtttctcct tccccaaag acacttcgca gcccctcttg
61 ggatccagcg cagcgcaagg taagccagat gcctcgtctg ttgcccctcc tgtgggccgt
121 ctcctctcac gecgcgcgc cactggggca cctggtgca ac tgtcaggag gctgagctgc
181 aaaccccaat gaggggcagg tgtctcggga gacgtgcttc ccacacgccc atctttctgc
241 cccgcgcttt gaggcttccc aggcgcctct ttgcaccctc ccctagcagg aacatgcgcgt
301 tgtccctctc gacgcggtca agcttcgcct gataataggta aggttctttgc gctgagcgg
361 gatgtgctca ttcgctctcc ttcgagggg gattctggag tccacatgaa tttgaggtgt
421 gacactgtcctgcaacggg gcgcggccac tcacctcccac ctcctccttc catcttcgtc
481 ttcgtgtatt aagcaggggcc gctcaggggc ctgtaacttg gagaagttat ccccgtcctgc
541 agagttcgg gctctgcgtt ttgatttctg ttcctggct ccagcagggg aagcagcctgc
601 ttggaatgc tgaattaggg attttcaggg ccactgctgc ccagatatca aatttcctga
661 cattaagat acgtgagag tctaatgcgt atttcttctta aaaaaaaaaaa acacacacac
721 aaaaaaaaaa acacacacac atcgtacttta atagatcca tgtctataag acaagaggaac
781 acctcctgcg atatagcttg gacctcgggc agcgtgcggc agttaacttg cagttctccc
841 taaaatgaca aagctacac gcgcggcctga caaatttacat gcttgtgcgct tccccaatg
901 tattttttct atctttggct catttatttgc catttctcctt caccctgcctgc
961 aggttcagc gattctcggg cctcagcctgc ccaatagcgt gggaggagag gcacccgcgt
1021 tgtatgcccccg ttaattttgt tattttttag ctagaggttg ttctgtcctg tgtgccccgg
1081 tttgctgaa ctcctgtcct caggtgatcc gcctgccttg gcctcctcgc gtttgggaggt
1141 gcacagcctag gcaccccgcc ccagcgcagg aatctatgcc tttgcttggg aatatttcag
1201 tccactgcgg ccagcagcctg aggaaaaaca gtttgcagcct gcacccgcaac ccctgtaagaag
1261 taaattgaga aaatttgtga attaagaaca tgggtcgcgg gttgggtctgg aatatttttaag
1321 cccacctgc gcgcggttgc cgtgcttttt gtattttctg cttacatcgc gttggtcttg
1381 tagttatggtt tctaataagtc gacgctcaga gactgcagc cggctagct caaatataaata
1441 gatattttata atttatacag tctatagcgt ggaatgccgg gcagctgcagc cggctagct
1501 egaaactgac ttatagctg gcgtcagcgc gcgtcagcgc gcgtcagcgc gcgtcagcgc
Genome as text - Frequencies of k-mers

- Genome is a text of four letters – A,C,G,T
- Frequencies of k-mers characterize the whole genome
  - E.g. counting frequencies of 7-mers with a “sliding window”
  - Frequency set \( \{f_i \mid i = 1 \text{ to } 4^k\} \)

\[ N(\text{GTTCACC}) = N(\text{GTTCACC}) + 1 \]
A “Chaos Game”

For k-mers, $2^k$ by $2^k$ pixels, one spot gives color-code frequency of occurrence for each k-mer

Has “fractals”

BL Hao, HCL & SY Zhang
Prominent pattern of portrait determined by frequency of short oligonucleotides (words). (1) low CTAG; (2) A+T-rich; (3) AT-rich & high AC, CA, GT, TG; (4) high AA, TT.
“Fractal” (pattern of red squares) caused by extreme under-representation of the palindrome ACGT

$k=8$

Fig. 7. The location of csg-tagged strings in $K = 6$ to 9 frames.
Given freq. set \{f_i\}, define

**k-spectrum**
\{n_f | f=1,2,\ldots\}
\[ \sum_i f_i = \sum_i f n_f \]

Relative spectral width

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**Example:**
6-spectrum of *B. subtilis*

![Graph showing frequency distribution](image)

- **Width (2x Std. Deviation)**
- **Mean frequency**
Shannon entropy

- **Shannon entropy** for a system frequency set \( \{f_i| \Sigma_i f_i=L\} \) or a spectrum \( \{n_f\} \) is

\[
H = - \Sigma_i f_i/L \log (f_i/L) = - \Sigma_f n_f f/L \log (f/L)
\]

- Suppose there are \( \tau \) types of events: \( \Sigma_i = \tau \). Then \( H \) has **maximum value** when every \( f_i \) is equal to \( N/\tau \):

\[
H_{\text{max}} = \log \tau
\]

- For a genomic \( k \)-frequency set: \( \tau = 4^k \), \( L = \) genome length.

\[
H_{\text{max}} = 2k \log 2
\]
Shannon information & relative spectral width

- **Shannon information**: information is *decrease* in $H$: define
  \[ R = \log \tau - H \]

- Relation to *relative spectral width* (for unimodal distribution)
  \[ R = \sigma^2/2 + O(\sigma^3) \]

- Shannon information and relative spectral width are equivalent measures

Shannon called $R/H_{\text{max}}$ redundancy; Gatlin (1972) called $R$ divergence.
Huge difference between genomes and random sequences

Black: genome of *E. coli*  
Green: matching random sequence  
(Red: model sequence)
Genomes violently disobey large-systems rule

- Random sequence: width $\sim L^{1/2}$, hence
  $\sigma \sim 1/L^{1/2} \rightarrow 0$ for large $L$
  - i.e., large systems have sharply defined averages

- Genomes: $\sigma_{\text{genome}} >> \sigma_{\text{random}}$
  - Widths of genomes do not decrease with $L$

- Genomes have far more (Shannon) information than random sequences
$R = \log \tau - H$ is a good definition

Table 1: Shannon entropy $H$ and information $R$ in units of $\log 2$ in the $k$-spectra of the genome sequence of *P. aerophilum* and of the random sequence obtained by randomizing the genome. $R_{ex}$ is the expected information in a random sequence. Sequences have AT/CG= 50/50

<table>
<thead>
<tr>
<th>$k$</th>
<th>Random sequence</th>
<th>Genome sequence</th>
<th>$R_{gen}/R_{ran}$</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>$H$</td>
<td>$R$</td>
<td>$R_{ex}$</td>
</tr>
<tr>
<td>2</td>
<td>3.9999</td>
<td>5.90 E-6</td>
<td>5.77 E-6</td>
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<tr>
<td>3</td>
<td>5.9999</td>
<td>3.72 E-5</td>
<td>3.46 E-5</td>
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<tr>
<td>4</td>
<td>7.9999</td>
<td>1.72 E-4</td>
<td>1.62 E-4</td>
</tr>
<tr>
<td>5</td>
<td>9.9993</td>
<td>7.26 E-4</td>
<td>7.53 E-4</td>
</tr>
<tr>
<td>6</td>
<td>11.999</td>
<td>2.94 E-3</td>
<td>2.90 E-3</td>
</tr>
<tr>
<td>7</td>
<td>13.988</td>
<td>1.18 E-3</td>
<td>1.17 E-3</td>
</tr>
<tr>
<td>8</td>
<td>15.955</td>
<td>4.78 E-2</td>
<td>4.71 E-2</td>
</tr>
<tr>
<td>9</td>
<td>17.798</td>
<td>2.02 E-1</td>
<td>1.88 E-1</td>
</tr>
<tr>
<td>10</td>
<td>19.xxx</td>
<td>x.xx E-1</td>
<td>5.24 E-1</td>
</tr>
</tbody>
</table>
When $A+T \neq C+G$, $k$-spectrum is superposition of $k+1$ subspectra.

Random sequence: (A) Single peak when $A+T$ and $C+G$ same. (B) Otherwise split into $k+1$ "$m$" peaks, $m=0$ to $k$. Under each $m$ peak is spectrum of subset of $k$-mers with $m$ A+T's.

(C) Detail of subspectrum of $m=2$ set. Otherwise split into $k+1$ "$m$" peaks, $m=0$ to $k$. Under each $m$ peak is spectrum of $k$-mer with $m$ A+T's.
### Information in 70/30 sequences

Table 2: Shannon information of subspectra $\mathcal{F}_{k,m}$ from the genome *C. muridarum* and corresponding random sequence. Sequences have AT/CG= 70/30

<table>
<thead>
<tr>
<th>$k$, $m$</th>
<th>$\bar{f}_m$</th>
<th>$R_{C_{mur}}$</th>
<th>$R_{random}$</th>
<th>$R_{ex}$</th>
<th>$\frac{R_{gen}}{R_{ran}}$</th>
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<tr>
<td>2, 1</td>
<td>52,500</td>
<td>7.39 E-3</td>
<td>5.12 E-6</td>
<td>4.76 E-6</td>
<td>1440</td>
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<td>3, 2</td>
<td>18,375</td>
<td>2.07 E-2</td>
<td>2.13 E-5</td>
<td>2.04 E-5</td>
<td>963</td>
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<td>4, 2</td>
<td>2,756</td>
<td>8.58 E-2</td>
<td>1.75 E-4</td>
<td>1.50 E-4</td>
<td>490</td>
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<td>5, 3</td>
<td>964</td>
<td>1.10 E-1</td>
<td>5.10 E-4</td>
<td>4.86 E-4</td>
<td>216</td>
</tr>
<tr>
<td>6, 3</td>
<td>145</td>
<td>2.04 E-1</td>
<td>3.42 E-3</td>
<td>3.34 E-3</td>
<td>60</td>
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<tr>
<td>7, 4</td>
<td>50.6</td>
<td>2.61 E-1</td>
<td>9.90 E-3</td>
<td>9.72 E-3</td>
<td>26</td>
</tr>
<tr>
<td>8, 4</td>
<td>7.60</td>
<td>4.79 E-1</td>
<td>6.59 E-2</td>
<td>6.53 E-2</td>
<td>7.3</td>
</tr>
<tr>
<td>9, 5</td>
<td>2.65</td>
<td>3.05 E-1</td>
<td>1.89 E-1</td>
<td>1.88 E-1</td>
<td>1.6</td>
</tr>
<tr>
<td>9, 7</td>
<td>14.5</td>
<td>3.03 E-1</td>
<td>3.43 E-2</td>
<td>3.43 E-2</td>
<td>8.8</td>
</tr>
<tr>
<td>10, 6</td>
<td>0.93</td>
<td>1.02 E 0</td>
<td>5.44 E-1</td>
<td>5.37 E-1</td>
<td>1.9</td>
</tr>
<tr>
<td>10, 8</td>
<td>5.06</td>
<td>4.24 E-1</td>
<td>0.99 E-1</td>
<td>0.99 E-1</td>
<td>6.2</td>
</tr>
</tbody>
</table>
Reduced spectral width & Shannon information

- Recall $k$-spectrum superposition of $k+1$ peaks
- For each peak, define
  \[ M_\sigma = (\sigma_{\text{genome}}/\sigma_{\text{random}})^2 \]
  and
  \[ M_R = R_{\text{genome}}/R_{\text{genome}} \]
- For whole $k$-spectrum, define reduced spectral width (RSW $M_\sigma$) and reduced Shannon information (RSI $M_R$) averaged over subspectra
  \[ M_\sigma(Q) = <\sigma^2/\sigma_{\text{random}}^2>, \quad M_R(Q) = <R/R_{\text{random}}> \]
- Expect
  \[ M_\sigma(Q) \sim M_R(Q), \quad M_\sigma(Q_{\text{ran}}) \sim M_R(Q_{\text{ran}}) \sim 1 \]
Testing $M_R (Q_{ran}) \sim 1$

(A) Random “matches” of 155 microbial genomes; $k=2-10$

(B) 100-replica matches of 155 microbial genomes; $k=2-10$
A look at Complete Genomes

~ A universality is discovered
Complete Genomes are diverse

**Fractional (A+T) content $\rho$**

- **Prokaryotes**
- **Eukaryotes**
- **PF**: *Plasmodium falciparum* (A eukaryotic Malaria causing parasite)

**Sequence length $L$ (bases)**
Measurements

• Measure (by computation)
  - reduced spectral widths $M_\sigma$
  - reduced Shannon information $M_R$
  - $k$-spectra, $k = 2$ to $10$
  - 282 complete sequences (155 microbial genomes and 127 eukaryotic chromosomes)

• Results
  - $M_\sigma \sim M_R$
  - Plot $M_\sigma$ versus $L$, sequence length
Results: color coded by organisms

Each point from one k-spectrum of one sequence; >2500 data points. Black crosses are microbials. Data shifted by factor $2^{10-k}$. 
Data from 14 *Plasmodium* chromosomes excluded; ~2400 data points. For each $k$, 268 data points form a narrow $M_\sigma \sim L$ "$k$-band".
$k$-bands

- $M_R$ is very large
- For each $k$ all data (268 sequences) form a $k$-band
  - $M_R/L \sim \text{universal constant}$ (i.e., same for ALL genomes)
A Universality Class

- Each $k$-band defines a universal constant $L/M \sim \text{constant} = L_r$ (Effective root-sequence length)
- Obeys $\log L_r(k) = a k + B$
  - 1989 pieces of data given be two parameters.
  - $a = 0.398 \pm 0.038$
  - $B = 1.61 \pm 0.11$
- Defines a universal class
- Plasmodium has separate class:
  - $a = 0.146 \pm 0.012$

Black: genome data; green: artificial
Replicas & Root-Sequence Length

~ How to create information stochastically
Replica & universal root-sequence length

- Take random root-sequence of length $L_r$ and replicate to length $L$ of some genome, then full sequence will have
  $$M_R = L/L_r \quad \text{(for any k)}$$

- Or, any sequences obtained by replication of the root-sequence (i.e. a replica) will have
  $$L/M_R = L_r$$

- A set of replicas of variable lengths all replicated from (not necessarily the same) random root-sequences of length $L_r$ will have $k$-independent universal $L/M_R = L_r$
RSI in an m-replica is multiplied m times

(A) Random “matches” of 155 microbial genomes; \( k=2-10 \)
(B) 100-replica matches of 155 microbial genomes; \( k=2-10 \)
Reduced Shannon information
In Replicas

• Squares: $M_R$ in
  $m$-replicas
  - root-sequence length 300
  - 260 replicas match profiles of genomes
  - sky: $k=2$,
  - purple: $k=3$
  - blue: $k=4$-10

• Crosses: $M_R(k=2)$ in genomes

• Replicas like genomes, but lack $k$-dependence
A Model for Genome Growth & Evolution

~ How did life create information stochastically
A Hypothesis for Genome Growth

- Random early growth
  - Random b/c has no information

- Followed by
  1. random segmental duplication and
  2. random mutation

Self copying – strategy for retaining and multiple usage of hard-to-come-by coded sequences (i.e. genes)
The Minimal Model

• Start with length $L_0$

• Segmental duplication is **maximally stochastic** and grow to full length $L$
  – random selection of site of copied segment
  – weighed random selection $g(l)$ of length of copied segment
  – random selection of insertion site of copied segment
  – Biologists: **replicative translocation**

• Mutation is standard single-point replacement (no insertion and deletion)
  – Point mutation at rate of $r$ per base
\[ \chi^2 = \langle \left[ \frac{(L_r)_{\text{model}} - (L_r)_{\text{gen}}}{\Delta (L_r)_{\text{gen}}} \right]^2 \rangle \]

Model parameter search: favors very small \( L_0 \)
• Best parameters (preliminary; after non-exhaustive search)
  – $L_0 \sim 8\, b$
  – $r \sim 0.95\sim 1.1$ (mutations per 100 $b$)
  – $g(l)$: equal probability $0 < l < l_x$
    $l_x = 250\sim 2000$ if current seq. length $L_c < 2\, Mb$
    $l_x = 10000$ if $L_c > 2\, Mb$

• Generated model sequence set with same length and composition profile as complete genome set

• Computed $k$-spectra, $M_\sigma$, $M_R$, $L_r$, etc.
5-spectra of “genomes” with different base compositions

Green – random
Black – genome
Orange – model

(A) 50/50
(B) 60/40
(C) 70/30
Universality classes

Reduced Shannon information

Reduced spectral width

Red & blue symbols are from (same) model sequences
Self-Similarity in Genomes

~ Genomes emulates self-organized critical systems
Are genomes self similar?

- Very small $L_{eff}$ suggests genomes has very high duplication content.
- Our model based on maximally stochastic segmental duplication reproduce empirical $k$-spectra and $L_{eff}$.
- If genomes are sufficiently uniform, then genome should exhibit whole-genome property on a scale of $\sim L_{eff}$
  
  $\frac{M_{\sigma}(k)}{l} \sim \frac{(RSW \text{ of whole genome})}{L} \sim L_{eff}(k)$
$M_R(k)$ in 8 randomly selected segments of length $l = L/2^n$

Figure 1: RSW ($M_\sigma$) of $k$-spectra, $k=2$ to 10, of segments from the 246 Mb chromosome 1 of H. sapiens. Lengths of the segments are $1/2^n$ of full length, $n=1$ to 21, and for each length eight segments are randomly selected. Data for which segment length is less than $4^k$ are not included. Data for the same $k$ forms a $k$-band approximately linear in $L$ (red line), and each data point has been multiplied by factor of $2^{10-k}$ to delineate the $k$-bands for better viewing.
• Given genome length \( L \) and RSW \( \mathcal{M}_\sigma \)
• Randomly select set of 25 segments of length \( l \) labeled \( i \) and compute \( \mathcal{M}_{\sigma i} \) of segments
• Define

\[
\chi^2(l) = \frac{1}{25} \sum_{i=1}^{n} \left( \frac{\log \frac{L \mathcal{M}_{\sigma i}}{l \mathcal{M}_{\sigma}}}{\log 2} \right)^2
\]

• If \( \chi^2 < 1 \) then on average \( \mathcal{M}_{\sigma i}/l \) within factor of 2 of \( \mathcal{M}_\sigma/L \)
• Find
  - \( L_u \): segment length above which all sets have \( \chi^2 < 1 \)
  - \( L_d \): segment length below which all sets have \( \chi^2 > 1 \)
\( L_u \) and \( L_d, k=5 \), all complete sequences

**Figure 3:** \( L_u \) (the length above which all segments are similar to the genome; green bars) and \( L_d \) (the length below which no segment is similar to the genome; red bars) for \( k=5 \) for all complete sequences in the main universality class. The blue (yellow) line is the position of \( L_{\text{max}} \) (\( L_{\text{min}} \)).
Figure 4: \( L_u \) (green bars) and \( L_d \) (red bars) for \( k = 2, 4, 6 \) and 8; see caption for Fig. 3 for more detailed description.
Average Results

<table>
<thead>
<tr>
<th>$k$</th>
<th>$L_u$</th>
<th>$L_d$</th>
<th>$L_u$</th>
<th>$L_d$</th>
<th>$L_u$</th>
<th>$L_d$</th>
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<tbody>
<tr>
<td>2</td>
<td>4.20±2.18 E2</td>
<td>1.63±1.26 E3</td>
<td>5.43±3.69 E2</td>
<td>1.12±1.12 E3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>9.62±4.43 E2</td>
<td>2.08±1.65 E3</td>
<td>1.20±0.84 E3</td>
<td>1.70±1.50 E3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>2.35±0.92 E3</td>
<td>4.88±3.89 E3</td>
<td>2.66±1.55 E3</td>
<td>3.47±2.61 E3</td>
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<tr>
<td>5</td>
<td>6.39±2.03 E3</td>
<td>1.18±0.91 E4</td>
<td>6.15±3.17 E3</td>
<td>7.54±4.39 E3</td>
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<tr>
<td>6</td>
<td>1.63±0.48 E4</td>
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<td>8</td>
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<td>1.76±1.62 E5</td>
<td>1.10±0.45 E5</td>
<td>1.20±0.55 E5</td>
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- Prokaryotes: $L_u \sim L_d$
- Prokaryotes $L_d \sim$ Eukaryotes $L_d$
- Eukaryotes: $L_u$ significantly $> L_d$
Average $L_u$ and $L_d$ versus $k$
Compare $L_{eff}$ ($L_r$) with similarity length

Table 3: Comparison of $4^k$ and mean values of $L_r(k)$ and $L_{sim}(k)$.

<table>
<thead>
<tr>
<th>$k$</th>
<th>$4^k$</th>
<th>$\langle L_r \rangle$</th>
<th>$\langle L_{sim} \rangle$</th>
</tr>
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<tbody>
<tr>
<td>2</td>
<td>16</td>
<td>310±200</td>
<td>690±570</td>
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<td>3</td>
<td>64</td>
<td>680±350</td>
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<td>1690±760</td>
<td>2820±1700</td>
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<td>65536</td>
<td>89500±43000</td>
<td>109000±44000</td>
</tr>
</tbody>
</table>

- $L_{sim}$ is the average of prokaryotic $L_u$ and $L_d$ eukaryotic $L_d$
- $L_{sim}$ barely $L_r$ > barely > $4^k$,
- Hence genomes are almost maximally self-similar
Compare genomic and model $L_{sim}$

Note: Model predates data

But model has smaller spread

Model is too smooth
Texture of genome are rougher than model.

Black: *E. coli*; blue: random; green: model.

Along length of genome (E. coli)
Randomness in Genomes

~ Genomes are not random
But they are generated by a highly random process
• Intervals (spatial or temporal) between adjacent random uncorrelated events have an exponential distribution
• In a random sequence, intervals of identical words are exponential
• What is the word-interval distribution in a (non-random) genome?
Interval distribution is exponential in random sequence as expected. **But also in genome!**

And in the model sequence (not surprising, because growth mechanism is maximally stochastic).
All \(k\)-mers in E. Coli, \(k=1-6\).

\[ N(d) = N_0 \exp(-a\,d) \]

Each data point from one \(k\)-mer; each \(k\) has \(4^k\) pts. \(\overline{d}_\sigma\) is average \(d\) from sequence. In ran. sequence for each \(k\), all \(\overline{d}_\sigma\) are the same.
For biased composition ($p$ not 0.5), data concentrated at $k+1$ points for each $k$, but are spread out in genomes.
41 microbial genomes longer than 4 Mb

\[ m = a \bar{d}_\sigma \]

A from exponential Fit; \( \bar{d}_\sigma \) is average \( d \) from sequence.

Conclusion: words are randomly generated in genomes. Emulated by growth model.
Evolution rates

~ Putting time in our model
• Identify substitutions and duplications by sequence similarity ("blasting")

• **Substitution rate**
  - $K$: substitution per site between two homologous sequences
  - $T$: divergence time of two sequences
  - Subst. rate $r_S = K/2T$ (/site/unit time)

• **Duplication rate**
  - $N$: number of duplication events per site
  - Duplication rate $r_D = N/T$ (/site/unit time)
Some data on rates for human

• Data
  – Estimated silent site substitute rates for plants and animals range from 1 to 16 (/site/By) (Li97)
  – Humans: $r_S \sim 2$ (Lynch00) or 1 (Liu03) /site/By.
  – Animal gene duplication rate $\sim 0.01$ (0.002 to 0.02) per gene per My (Lynch00)
  – Human (coding region $\sim 3\%$ of genome) translates to 3.9/Mb/My.
  – Human retrotransposition event rate $\sim 2.8$/Mb/My (Liu03)

• Estimate rates for human

  $r_S \sim 2$ /site/By, \quad r_D \sim 3.4$/Mb/My

• Human genome grew 15-20% last 50 My (Liu03)

• References
Rates from growth model

• Arguments
  – Can estimate substitution and duplication rate if assign total growth time
  – Human genome still growing last 50 My
  – Hence assume total growth time for human genome $T \sim 4$ By

• Get rates average over $T$
  
  $<r_S> \sim 0.25$ site/By, $<r_D> \sim 0.50$ Mb/My

• About 7~8 time smaller than recent sequence divergence estimates
Bridging the two estimates

• Rates are **per length**; hence lower when genome is shorter

• Sequence divergence rates $r_{S,D}$ for last DT~50 My are terminal rates

• Model rates $\langle r_{S,D} \rangle$ averaged over whole growth history, *hence $\langle r_{S,D} \rangle$ less than $r_{S,D}$*

• Assume constant (intrinsic) rate $r_c$ and genome grew exponentially with time

\[ L(t) = L_0 \exp(T/\tau) \]
• Number of events in interval $dt$ at time $t$ is
  \[ dN(t) = r_0 L(t) \, dt \]
• $<r>$ is average over whole $T$, $r$ is average over last $\Delta t \sim 0$
• Have $\tau/T \ll 1$ (because $<r>/r \ll 1$) and $\Delta t/\tau \ll 1$,
• Then
  \[ r \sim r_0, \quad <r> \sim r_0 \, \tau/T \]
• Then from $\tau/T \sim <r>/r \sim 1/8$
  \[ \tau \sim 0.5 \text{ By}, \quad L_0 \sim 1 \text{ Mb}. \]
Very roughly, constant rates in human
- site substitution: $r_S \sim 2 \text{/site/By}$,
- segmental duplication $r_D \sim 3.4/\text{Mb/My}$,

Growth
- $L(t) \sim 0.001 (Bb) L_0 \exp(t/0.5 \text{(By)})$

Remarks
- grew by $\sim 12\%$ last $50\text{My}$
- Liu et al. grew by $\sim 15\%-19\%$ last $50\text{My}$
- Does not imply $L=1 \text{ Mb at } t=0$
- Does imply at $t \ll 500\text{My}, L \sim 1 \text{ Mb}$
Genomes are close to being self-organized critical systems

Evolution mostly driven by neutral events
Summary of results

• Genomes are large systems with small-system statistics

• Shannon information of complete genomes exhibit **universal lengths**; genomes belongs to single **universality class**

• Data consistent with simple growth model based on **maximally stochastic segmental duplication and random point mutation**
  – For **human genome**, site substitution and segmental duplication **per site per time rates** consistent w/ those extracted by sequence divergence methods

• Genomes are not random but are essentially **randomly generated**
  – Has high degree of self-similarity, almost **SOC** systems

• Model permits **universal or multiple ancestor** as well as **huge species diversity**
Stochastic Duplication/replication was superb evolutionary strategy
- A most efficient way to:
  - Grow and accumulate information
  - Escape rule of large systems

Duplication/replication and mutations were mostly selectively neutral
- because measure not sensitive to coding
- most of eukaryotic genomes are non-coding parts
- Eukaryotes and prokaryotes belong to the same universality

Corroborates Kimura’s neutral theory of molecular evolution (1968, 1983)
- based on polymorphisms of genes
- most mutations on genes were selectively neutral
Shannon information versus biological information

• Large Shannon information is necessary condition for rich biological information

• Growth by random duplication provides an basis allowing natural selection to fine-tune, via natural selection, Shannon information into biological information

• The adaptation of the strategy of growth by random duplication by itself may be a consequence of natural selection
Are genes “spandrels”?

• Spandrels
  – In **architecture**. The roughly triangular space between an arch, a wall and the ceiling
  – In **evolution**. Major category of important evolutionary features that were originally side effects and did not arise as adaptations *(Gould and Lewontin 1979)*

• The duplications may be what the arches, walls and ceilings are to spandrels and the genes are the decorations in the spandrels
Great debated in palaeontology and evolution - Dawkins & others vs. (the late) Gould & Eldridge: evolution went gradually and evenly vs. by stochastic bursts with intervals of stasis

Our model provides genetic basis for both. Mutation and small duplication induce gradual change; occasional large duplication can induce abrupt and seemingly discontinuous change
The RNA World

- RNA was discovered in early 80’s to have enzymatic activity – ribozymes can splice and replicate DNA sequences (Cech et al. (1981), Guerrier-Takada et al. 1983)

- The RNA world conjecture – early had no proteins, only RNAs, which played the dual roles of genotype and phenotype

- Some present-day ribozymes are very small; smallest hammerhead ribozyme only 31 nucleotides; ribozymes in early life need not be much larger
In our model the small initial size of the genome necessarily implies an early RNA world.

A genome 200~300 nt long is long enough to code the many small ribozymes (but not proteins) needed to propagate life.

Origin of this initial genome not addressed in the model. It (or its precursor) could have arisen spontaneously - artificial ribozymes have been successfully isolated from pools of random RNA sequences (Ekland et al. 1995).

Present-day ribozyme can be as small as 31 nt; there could be smaller earlier ones.
Growth by duplication may provide partial answers to:

• How did life evolve so rapidly?
• How have genes been duplicated at the high rate of about 1% per gene per million years? *(Lynch 2000)*
• Why are there so many duplicate genes in all life forms? *(Maynard 1998, Otto & Yong 2001)*
• The chromosome exchanges that characterize mammalian and plant radiations. *(O’Brien et al. 1999; Grant, et al. 2000)*
• Was duplicate genes selected because they contribute to genetic robustness? *(Gu et al. 2003)*
  – Likely not; Most likely high frequency of occurrence duplicate genes is a spandrel
Many more questions to answer

• **Tracing natural selection**
  – Can we show conclusively growth by stochastic duplication is faster than selection driven (at gene level) growth?
  – Can we extend the method to say anything about evolution of genes? (Introduce roughness in genome?)

• **Time scale**
  – When did growth happen? At what rate? How did growth stabilize? Has it stabilized?
  – When and how did the codons form? When did protein arise?

• **Phylogeny**
  – Is the model useful for using whole genomes to build trees?
  – If so will the result agree with alignment bases analysis?

• **Universal ancestor**
  – Was there a Universal Ancestor? Or were there a group of Ancestors?
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For copies, see http://sansan.phy.ncu.edu.tw/~hclee/pub/selected.html
Computation Biology Laboratory (2003)
Thank you for your attention
• Present-day ribozyme can be as small as 31 nt; there could be smaller earlier ones.
• The average duplicated segment length of 25 nt in the model is very short compared to present-day genes that code for proteins, but likely represents a good portion of the length of a typical ribozyme encoded in the early universal genome of the RNA world.