Lecture Two

Genome: Information Carrier at the "Edge of Chaos"

HC Lee
National Central University

Life at the edge of chaos

- Edge of chaos
  - Computational system
  - Cellular automata
  - Transition to criticality
- Life at the Edge of chaos
  - Life involves complex computation
  - Technical apparatus for description still missing
- Genome as Life
  - Chaos as a state of near randomness
  - Textual complexity of a genome represent computational ability
  - Dynamics of genome evolution

Terminology & Notations

- Consider genome with fractional AT-content *p* (then fractional GC-content *q=1-p*
  - When *p*>0.5, there will be more AT-rich words than GC-rich words
- Partition *k*-letters words (*k*-mer) into sets, called *m*-sets $\mathcal{S}_m$, *m=0,1,…,k;* elements in $\mathcal{S}_m$ are *k*-mers with *m* ATs, $\bigcup_m S_m = S$
- Total number of kinds of *k*-mers is $\tau=4^k$, of kinds of *k*-mers in m-set is τ_m. Let u be a *k*-mer,

$$L_m = \sum_{u \in S_m} f_u \qquad \sum_{u \in S} f_u = L-k+1 \qquad \sum_{u \in S} f_u = \sum_m L_m = L$$

$$\tau_m = \binom{k}{m} 2^k, \qquad L_m^{\{\infty\}} = L\binom{k}{m} p^m q^{k-m},$$

$$\bar{f} = L/\tau, \qquad \tau = 4^k. \qquad \bar{f}_m^{\{\infty\}} = L_m^{\{\infty\}}/\tau_m$$

Shannon entropy (briefly)

- ***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 τ types of events: $\Sigma_i = \tau$. Then H has **maximum value** when every f_i is equal to N/τ:

$$H_{max} = \log \tau$$

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

$$H_{max} = 2k \log 2$$

Divergence in frequency distribution (*D*)

- Let *D* be coefficient of invariance (SD/mean) of distribution of frequency of occurrence of k-mers

$$D = (CV)^2 = \left(\frac{\sigma}{\bar{f}}\right)^2 = \frac{1}{\tau \bar{f}^2} \sum_{u \in \mathcal{G}_k} (f_u - \bar{f})^2$$

- Random sequence: $D \sim L^{-1/2}$
- Define l_{eff} for a genome to be the random sequence length having the genomic *D*
- Genomes have (almost) universal l_{eff}, *about* 150-600 bases long (for 2-mers)

Shannon information & relative spectral width

- **Shannon information**: information is *decrease* in *H*: define

$$R = \log \tau - H$$

Shannon called R/H_{max} redundancy; Gatlin (1972) called *R* divergence

- Relation to **relative spectral width** (for unimodal distribution)

$$\sigma = \Gamma/2\ \bar{f}$$

$$R = \sigma^2/2 + O(\sigma^3)$$

- Shannon information and relative spectral width ("fluctuation part" from Lecture 1) are equivalent measures

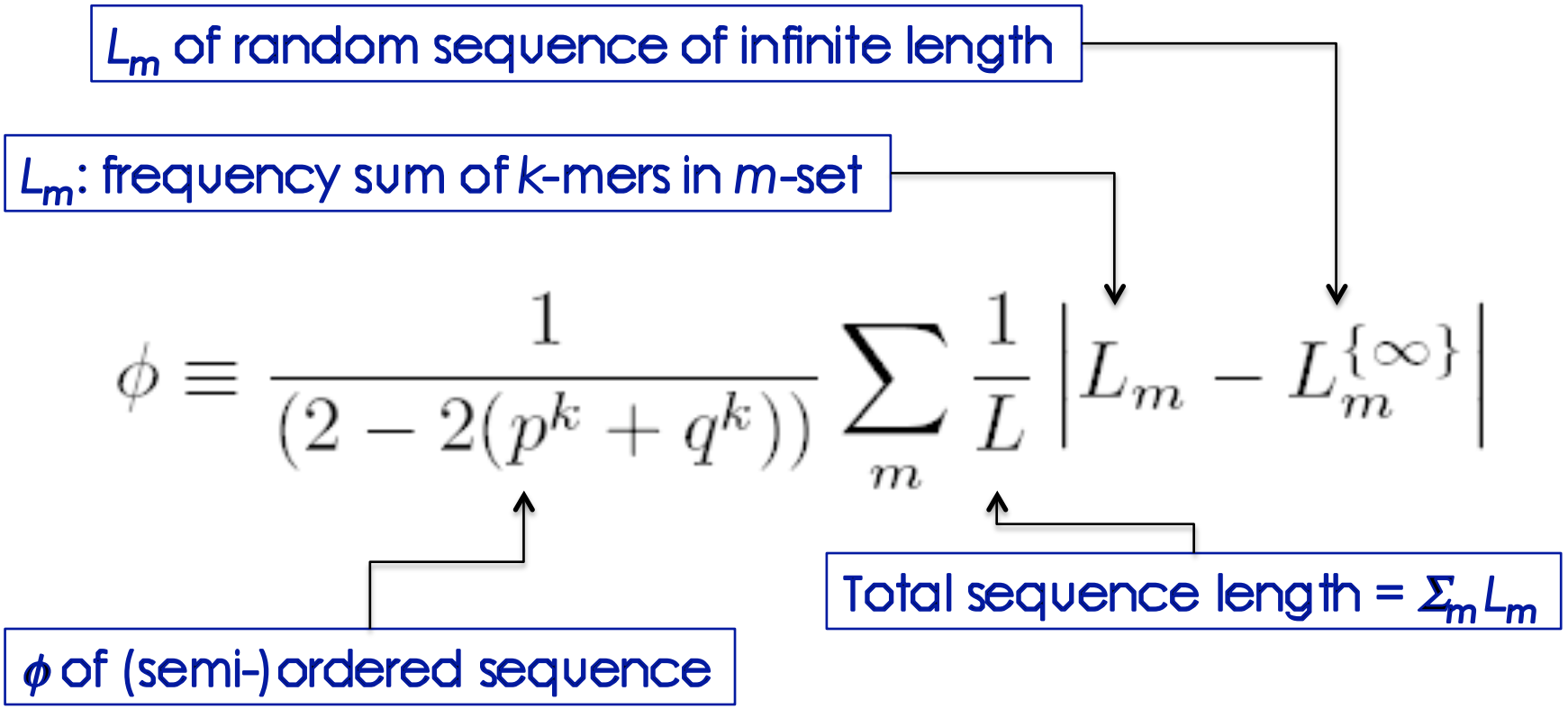
HD Chen, et al. Divergence and Shannon information in genomes. Phys. Rev. Lett. 94 (2005) 178103.
CH Chang, et al. Shannon Information in Complete Genomes. J. Bioinfo. & Comp. Biology 3 (2005) 587-608.

$R = log\ \tau - H$ 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**

	Random sequence			Genome sequence		
k	H	R	R_{ex}	H	R	R_{gen}/R_{ran}
2	3.9999	5.90 E-6	5.77 E-6	3.973	2.66 E-2	4500
3	5.9999	3.72 E-5	3.46 E-5	5.933	6.65 E-2	1922
4	7.9999	1.72 E-4	1.62 E-4	7.881	1.18 E-1	728
5	9.9993	7.26 E-4	7.53 E-4	9.821	1.79 E-1	246
6	11.999	2.94 E-3	2.90 E-3	11.75	2.74 E-1	94
7	13.988	1.18 E-3	1.17 E-3	13.66	3.35 E-1	29
8	15.955	4.78 E-2	4.71 E-2	15.53	4.69 E-1	10
9	17.798	2.02 E-1	1.88 E-1	17.26	7.33 E-1	3.0
10	19.xxx	x.xx E-1	5.24 E-1	19.xx	x.xx E-1	-

An Order Index ϕ



Note: ϕ is a measure of differential in averages

ϕ is a measure of order in a sequence

- An (semi-)ordered sequence

  AT…TATTATATTAATATTTAGCCGGGGCGGCGC…GG

  or a checker-board sequence

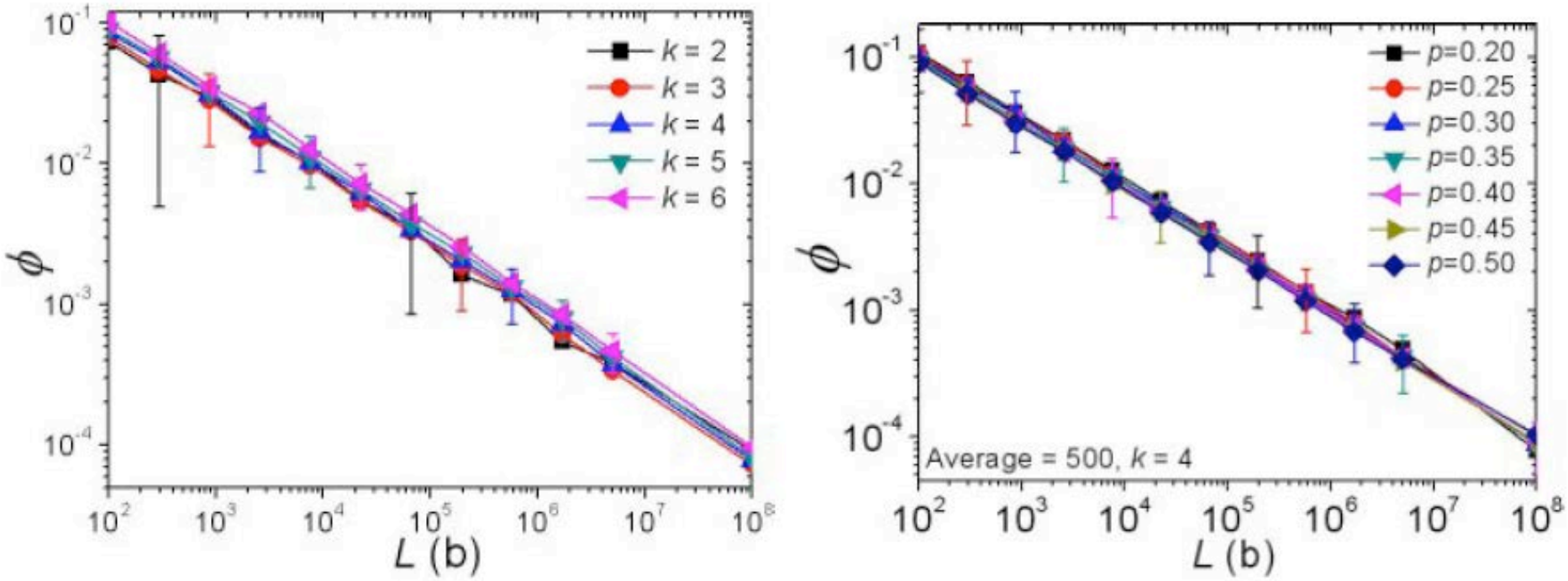
  …AGAGTGACAGTCTGTCTCACTG…

  have $\phi \sim 1$

- A random sequence has

  $\phi \sim L^{-1/2} \sim 0$ for large L

ϕ scales as $L^{-1/2}$ for random sequences



Depends only weakly on *k* or AT-content (*p*).
Averaged over *k* and *p*:

$$\phi^{\{ran\}}(k;p) = c_\phi L^{-\gamma_\phi}, \quad \gamma_\phi = 0.500 \pm 0.005, \quad c_\phi = 1.0 \pm 0.2$$

An equivalent length L_ϕ for order index

Use the relation

$$\phi^{\{ran\}} \approx L^{-1/2}$$

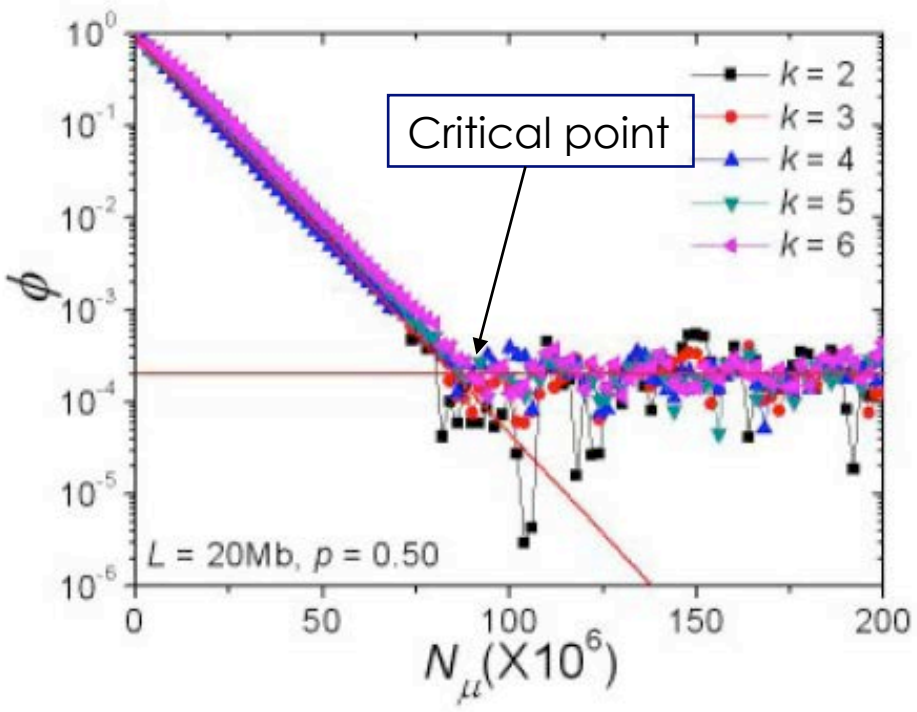
to define an (order-index) Equivalent Length for a ϕ-valued sequence:

$$L_\phi(\phi) = \phi^{-2} \ ,$$

the nominal length of a (non-random) sequence whose order index is ϕ.

(Note. Unlike the CV-defined and k-dependent L_e, L_ϕ is essentially independent of k.)

ϕ decreases exponentially with increasing number of point mutations



For an ordered sequence, ϕ drops exponentially from ϕ=1 as a function of N_μ, until it reaches a critical point when the sequence has become random.
N_μ : # of random mutations

$$\phi = \begin{cases} \exp\left(-2N_\mu/L\right), & N_\mu \lesssim N_{\mu c}; \\ \phi_c \approx L^{-1/2}, & N_\mu > N_{\mu c} \end{cases}$$

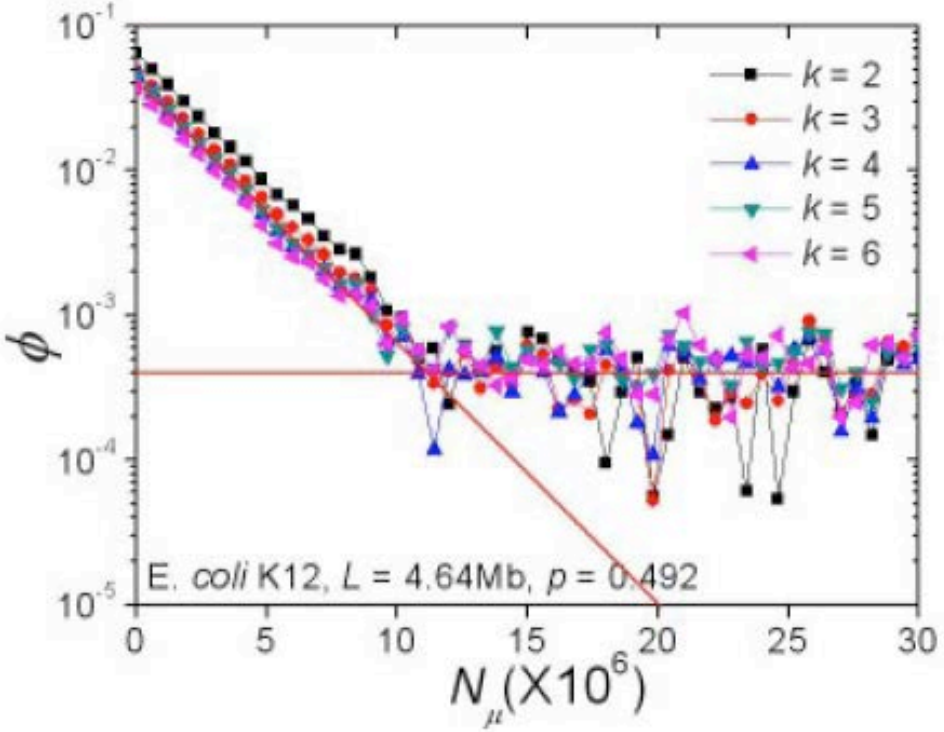
ϕ decreases exponentially with increasing number of point mutations

If sequence already has $\phi_0 < 1$, then as a function of $N\mu$

$$\phi = \phi_0 \exp(-2N_\mu/L),$$

until ϕ reaches its critical value $\phi_c \sim L^{-1/2}$.

Let $\mu = N_\mu/L$ be mutation density (mutation per site)



- Equivalent mutation density for a ϕ-valued sequence: $\mu_{eq}(\phi) \equiv \ln \phi^{-1/2}$, the nominal mutation density needed to bring an ordered sequence to a state of ϕ

The critical mutation density

Given

$$\phi = \begin{cases} \exp\left(-2N_\mu/L\right), & N_\mu \lesssim N_{\mu c}; \\ \phi_c \approx L^{-1/2}, & N_\mu > N_{\mu c} \end{cases}$$

The critical mutation density that will bring an ordered sequence to a state of randomness is given by

$$\phi_c = \exp(-2N_\mu/L) = \exp(-2\ \mu_c) = L^{-1/2}$$

That is:

$$\boxed{\mu_c = (1/4)\ \ln L}$$

(For $L = 10^6$ to 10^8, $\mu_c = 3.4$ to 4.6/site)

SG Kong, et al. Quantitative measure of randomness and order for complete genomes. Phys. Rev. E 79 (2009) 061911

Equivalent mutation density is a path-independent state quantity

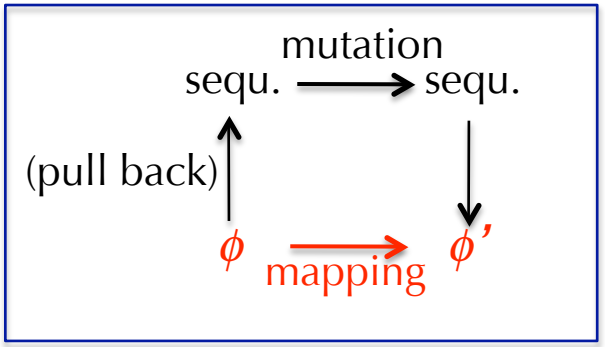
- Want to test whether ϕ (or equivalently, μ_{eq}) is akin to a potential energy, or a quantity that defines a state, but not how that state is arrived at.
  - The 4.6 Mb *E. coli* DID NOT arrive at its present state by random point mutation from an ordered sequence.
  - It is measured to have $\phi = 0.049$, or $\mu_{eq} = 1.5$/site.
  - The critical μ_{eq} for a 4.6 Mb sequence is $\mu_c = (1/4) \ln (4.6 \times 10^6) = 3.8$/site.
  - If we assume is ϕ a path-independent state quantity, then we predict it will take $(\mu_c - \mu_{eq}) \times L = 1.1 \times 10^7$ additional mutations to randomize *E. coli*
  - The actual number is found to be $1.1(+/-)0.1 \times 10^7$

State of randomness as a fixed point

Considered as a dynamical system driven by mutations, the state of randomness is a fixed point in ϕ space.

[Fixed point. Consider a function $f(x)$ mapping a point x in a space to another point x' in the same space. Then x_* is a fixed point of f if

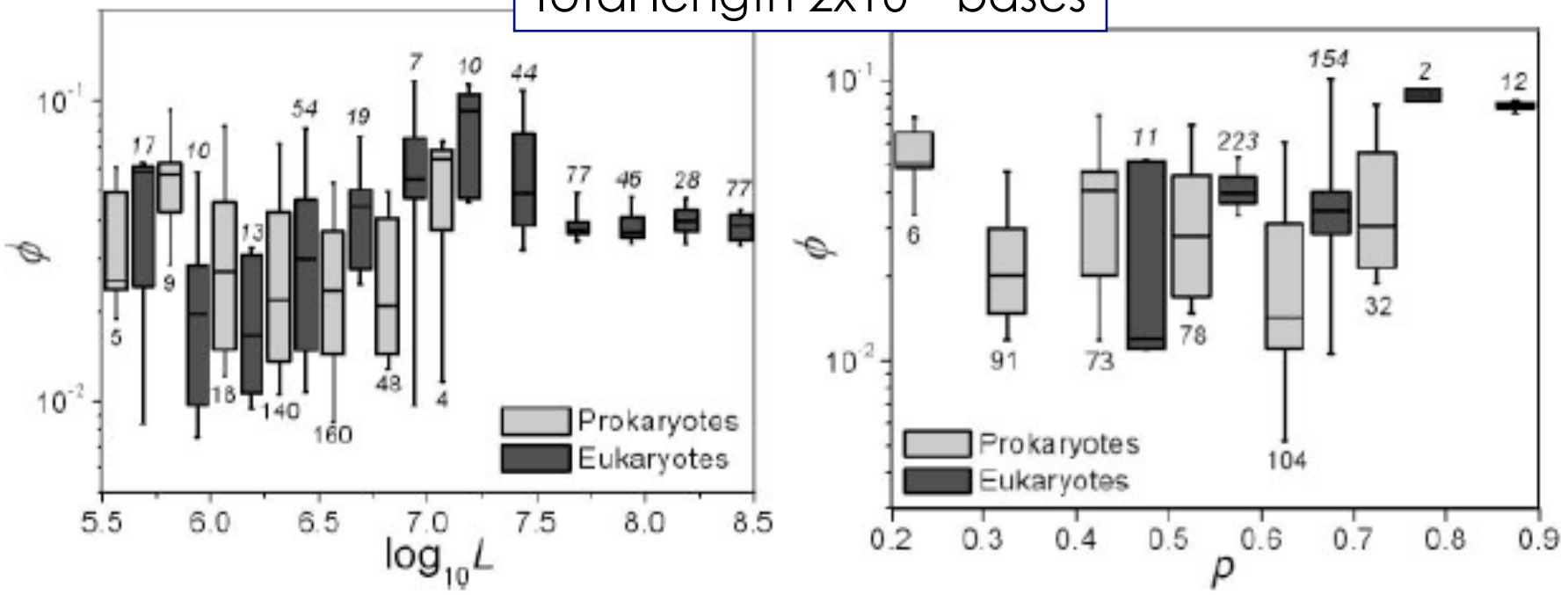
$$f(x_*) = x_*.]$$



Here the action causing the mapping is mutation, and the space is the ϕ-space. Mutation takes the sequence from one ϕ to another ϕ. When the sequence is random, mutation maps ϕ_c back to itself.

For ~800 complete genomes extant in GenBank, ϕ is essentially length- and base-composition-indepentent

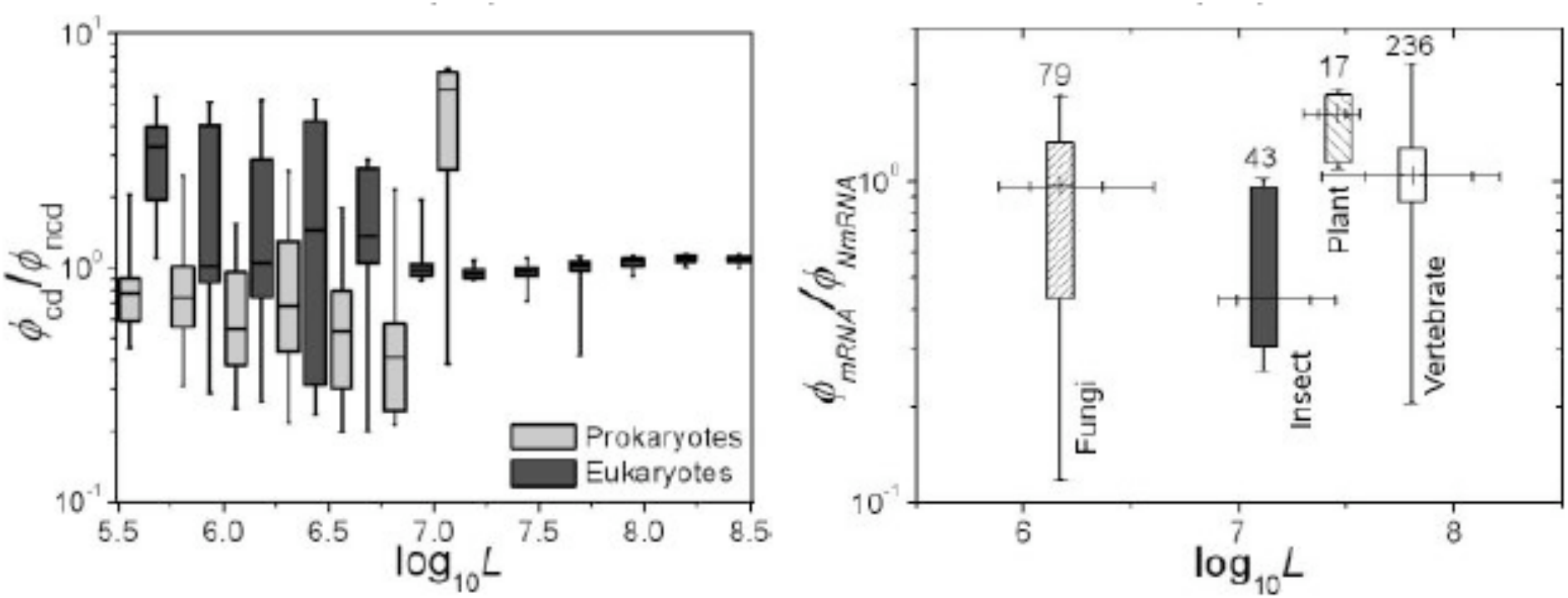
Total length 2×10^{10} bases



- Genomic ϕ congregates in a narrow range

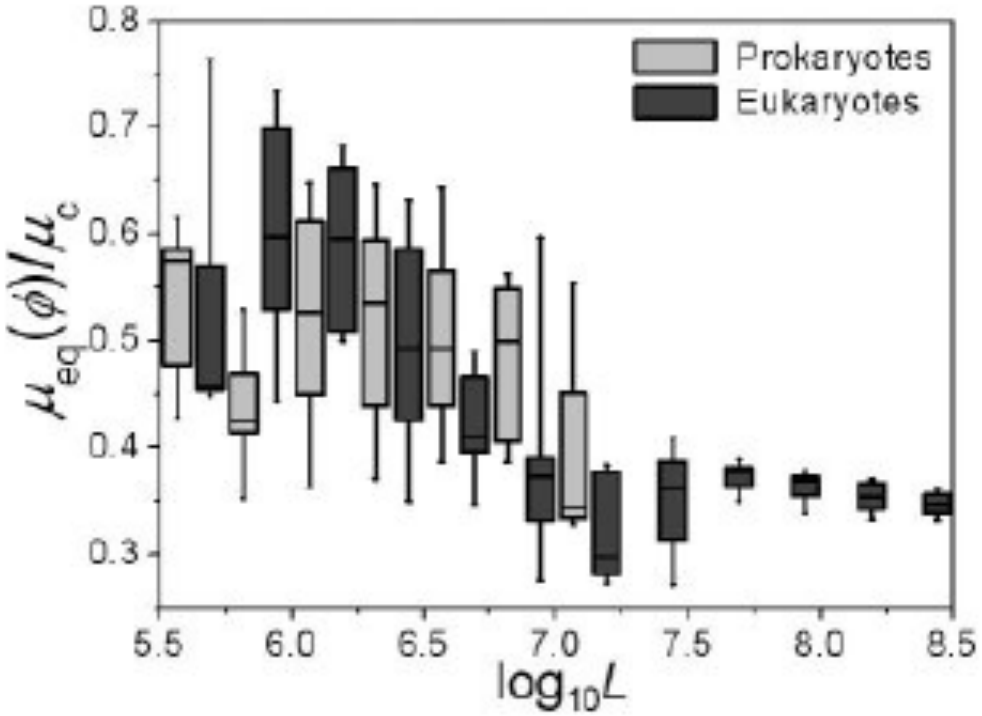
$$\phi_g \equiv 0.037 \pm 0.027$$

Coding (genic) and non-coding parts have similar ϕ



- Dynamics of genome evolution leading ϕ to ϕ_g is not under strong (genic) selection pressure
- Predominant characteristics is neutral

Genomes are half as random as random sequences



$$\mu_{eq}(\phi)/\mu_c \sim 0.45 \pm 0.11$$

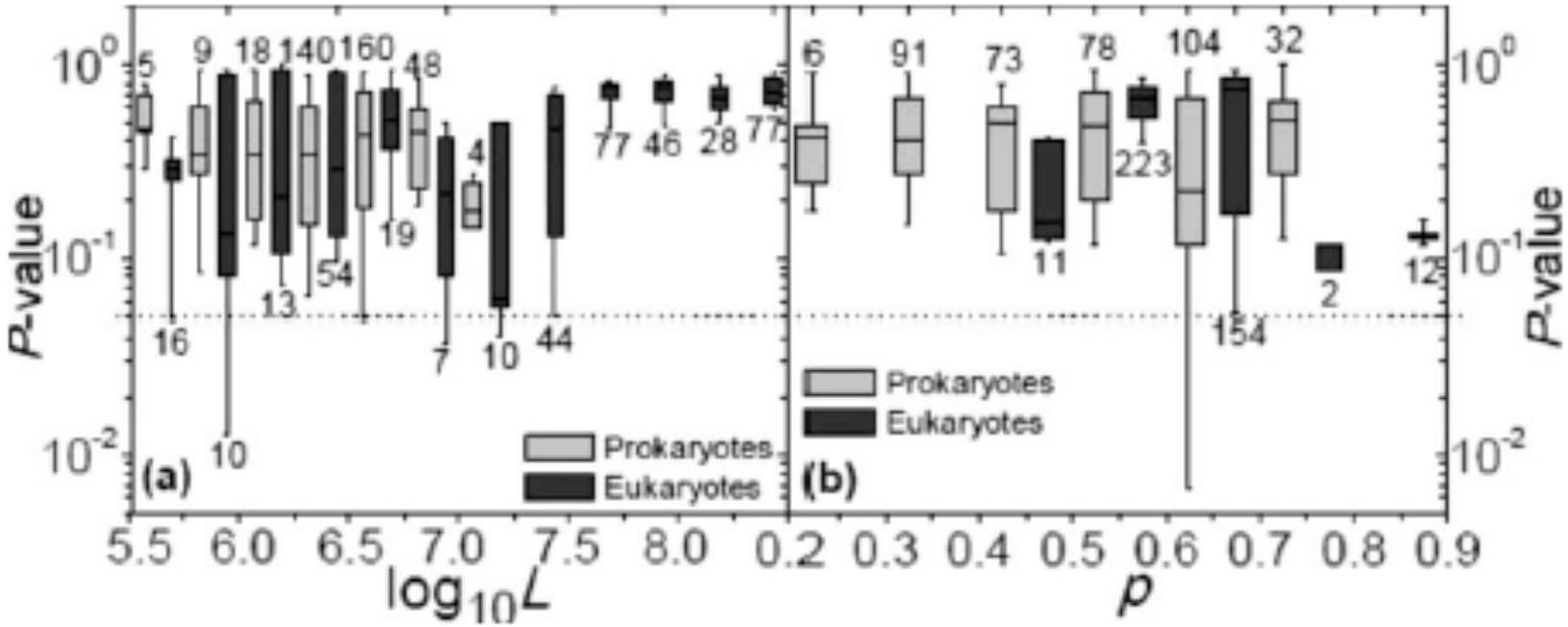
- μ_{eq} ~ 1.8 b^{-1} implies a genome is as random as an ordered sequence becomes after each site has on average been mutated 1.8 times.
- Genome is at the Edge of Chaos

Genomes form a universality class in ϕ

Vast majority of genomes have

$$\ln \phi_g = -3.49 \pm 0.65 \quad \text{, or} \quad \phi_g = 0.031^{+0.028}_{-0.015}$$

P-value of genomes belonging to the universality class define by ϕ_g



37 (out of ~800) chromosomes belong to universality class in ϕ with $P < 0.05$

TABLE II. Chromosomes belonging to the universal set defined by Eq. (8) with $P < 0.05$.

Name	Accession no.[a]	$\bar{\phi}$ [b]	P value[b]	Name	Accession no.[a]	$\bar{\phi}$ [b]	P value[b]
S. aureus	9 strains[c]	~4.4(−3)	~3.0(−3)	*A. marginale*	4842	4.45(−3)	3.15(−3)
S. epidermidis	4461	4.87(−3)	4.89(−3)	*C. felis*	7899	5.20(−3)	6.66(−3)
L. johnsonii	5362	5.58(−3)	9.18(−3)	*S. hemolyticus*	7168	5.79(−3)	1.08(−2)
S. epidermidis	2976	6.49(−3)	1.77(−2)	*M. mobile 163 K*	6908	6.80(−3)	2.14(−2)
T. denitrificans	7404	7.12(−3)	2.58(−2)	*L. acidophilus*	6814	7.34(−3)	2.90(−2)
G. sulfurreducens	2939	7.40(−3)	2.99(−2)	*F. tularensis*	7880	7.50(−3)	3.15(−2)
W. succinogenes	5090	7.51(−3)	3.17(−2)	*C. hydrogenoformans*	7503	1.23(−1)	3.20(−2)
M. hungatei	7796	7.75(−3)	3.57(−2)	*F. tularensis*	6570	7.90(−3)	3.84(−2)
C. caviae	3361	7.94(−3)	3.91(−2)	*M. succiniciproducens*	6300	1.15(−1)	4.04(−2)
C. abortus	4552	8.06(−3)	4.14(−2)	*X. fastidiosa 9a5c*	2488	8.12(−3)	4.25(−2)
P. marinus	7335	8.19(−3)	4.37(−2)	*S. tokodaii*	3106	8.47(−3)	4.96(−2)
S. cerevisiae	Chr V	6.00(−3)	1.26(−2)	*S. cerevisiae*	Chrs XV, III	~7.7(−3)	~3.5(−2)
S. cerevisiae	Chr VI	8.43(−3)	4.87(−2)	*A. mellifera*	8 chrs.[d]	~1.1(−1)	~4.8(−2)

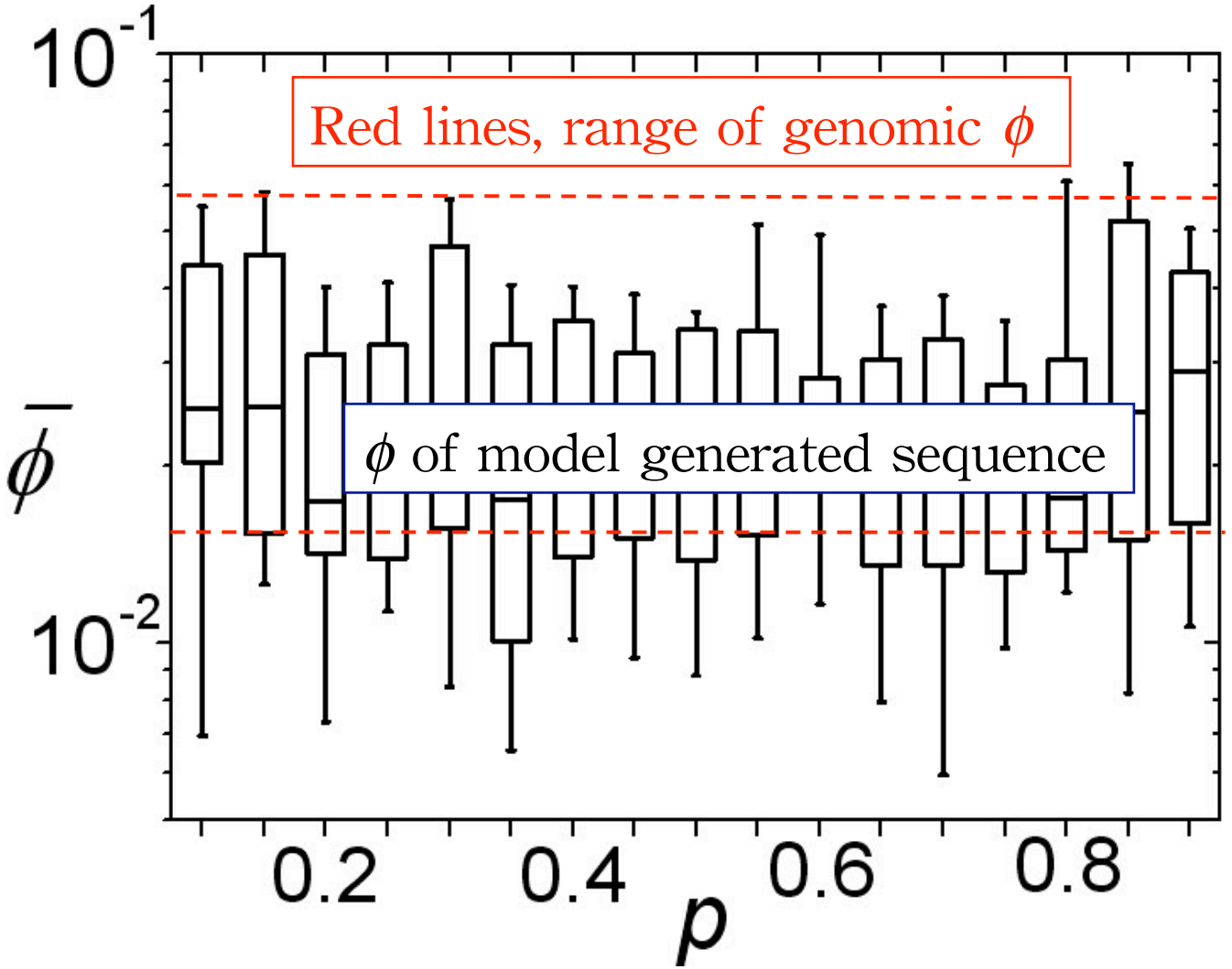
[a] 4842 indicates the accession no. NC_004842.

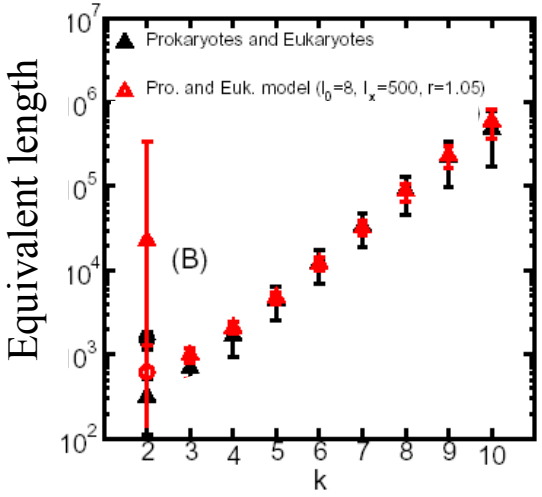
[b] The value 4.4(−3) means 4.4×10^{-3}.

[c] The nine strains, in order of increasing P value, are 3923, 2953, 7793, 7795, 2952, 7622, 2951, 2758, and 2745.

[d] The eight chromosomes, in order of increasing P value, are XV, X, XII, II, IV, V, I, and XI.

Artificial sequence with genomic L_e generated in RSD model has genomic ϕ





An empirical function of information capacitance

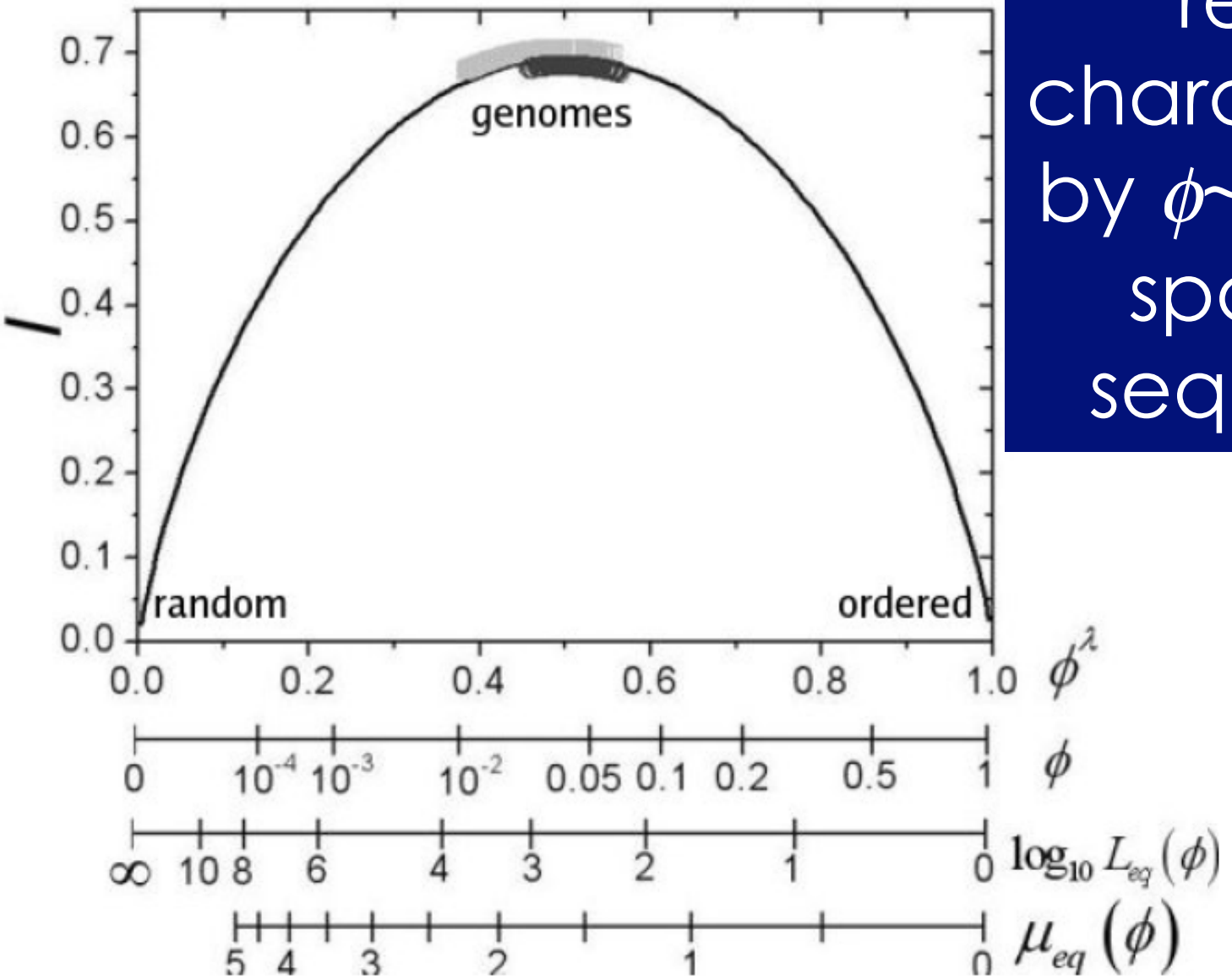
Define an "information capacity" function

$I(z)$ such that: the variable z is a scaling function of ϕ with $z|_{\phi=0}=0$ and $z|_{\phi=1}=1$, and I has two minima at $I(0)=I(1)=0$ and a maximum at $z|_{\phi=\phi_g}=0.5$. The simplest solution is

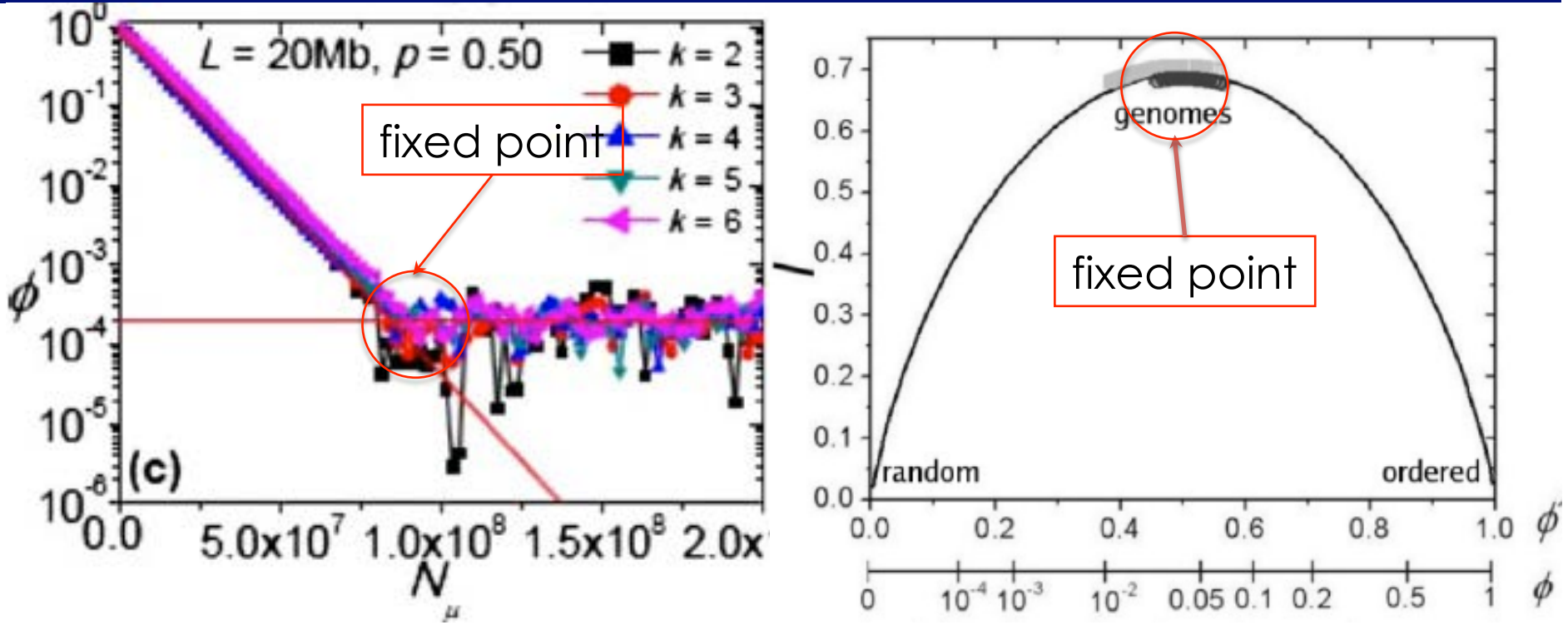
$$I(z) = -z \ln z - (1-z)\ln(1-z); \quad z = \phi^{0.21}. \qquad (10)$$

Say "information capacitance", not "information", because ϕ_g is universal but sequence length is not; not "information density", because not every sequence with ϕ_g has information.

Genomes reside in a small distinct region characterized by $\phi \sim \phi_g$ in the space of sequences



Genomes at a fixed point

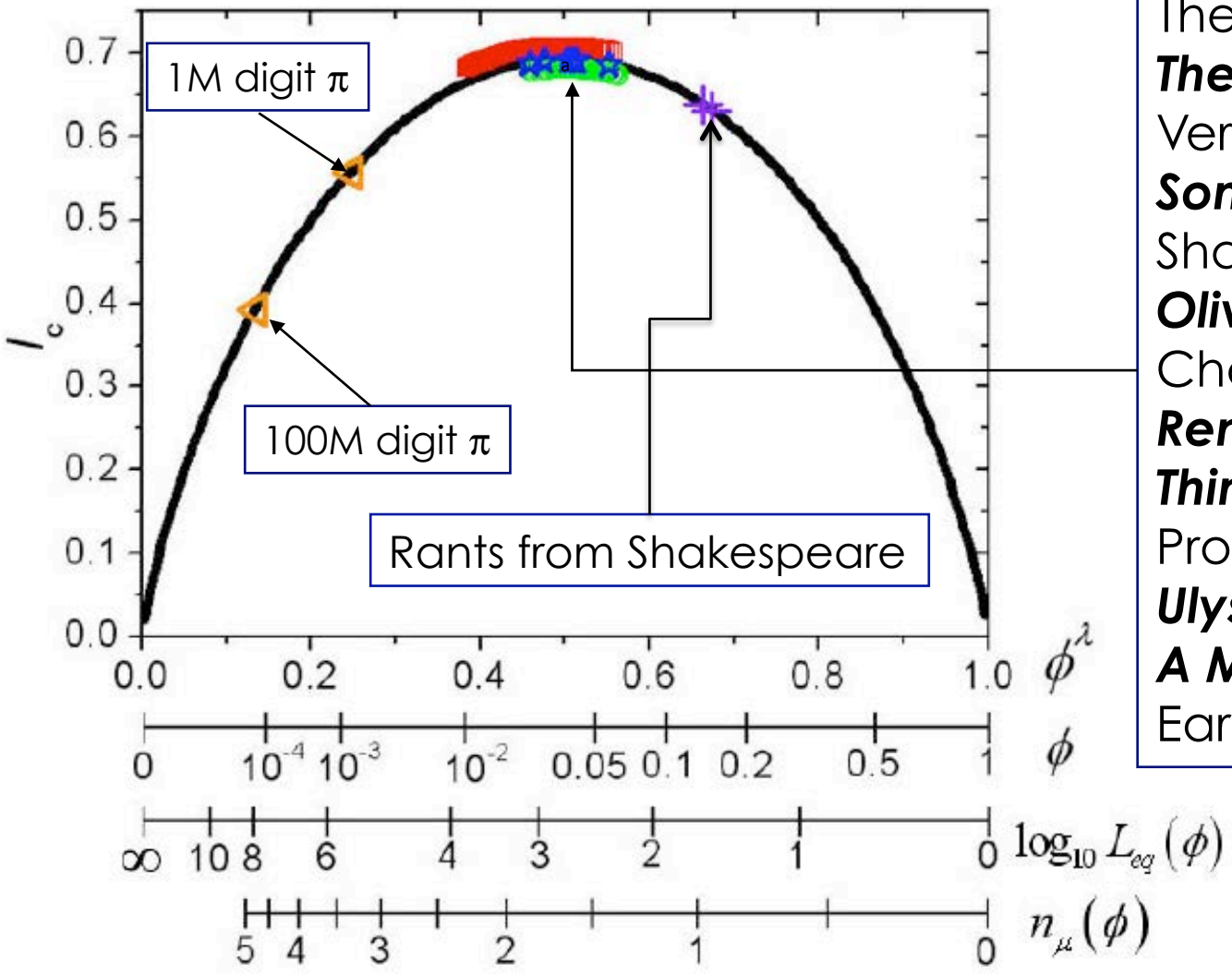


Recall: Sequences are driven by random mutations to a state-of-randomness fixed point. Similarly, genomes are driven by the dynamics of a robust evolutionary process (yet to be identified) to a fixed-point ϕ_g.

The two types of fixed points are driven by different dynamics

- Random sequence fixed point
  - $\phi_C \sim L^{-1/2}$, depends on sequence length
  - Driven by random point mutation
- Genome fixed point
  - ϕ_C = 0.016-0.059 is universal (and independent on length)
  - Driven by "robust evolution process"
  - Our guess: random (+plus tandem) segmental duplication + plus point mutation

The $\phi \sim \phi_g$ "fixed point" shared by literature classics

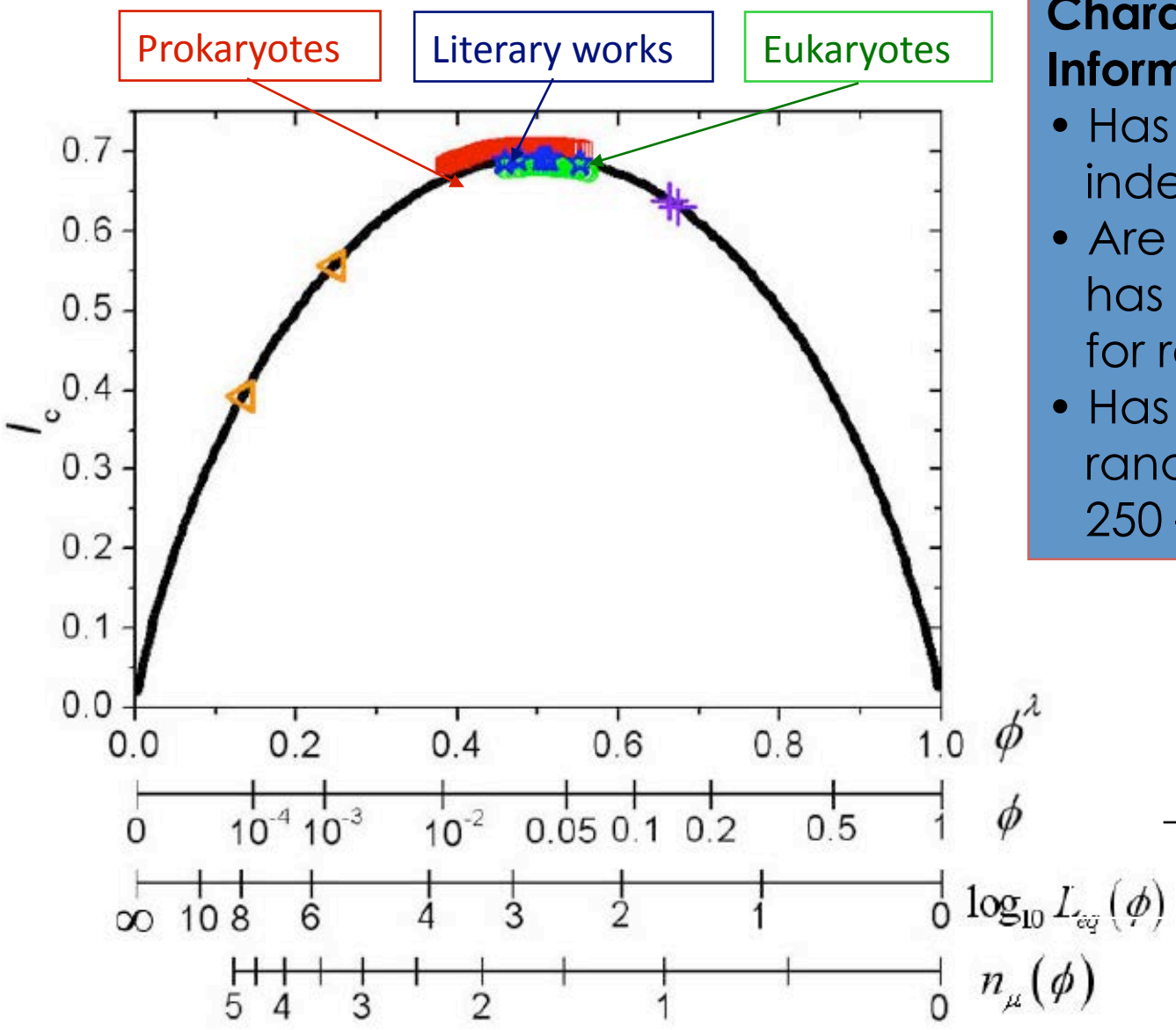


The six classics:
The Bible, King James Version;
Sonnets, William Shakespeare;
Oliver Twist, Charles Dickens;
Remembrance of Things Past, Marcel Proust;
Ulysses, James Joyce;
A Moveable Feast, Earnest Hemingway

Classics, rants, and π

- Making pseudogenomes of classics
  - (adjlsy) to A; （chiopq) to C; (efgnvxc) to G; (bkmrtuw) to T
  - All six classics have $p_A \sim p_C \sim p_G \sim p_T = 0.250 +/- 0.007$, or $p \sim 0.50 +/- 0.02$.
- The rants (repeated 1M times)
  - "Though this be madness, yet there is method in't" (Hamlet)
  - "All the perfumes in Arabia will not sweeten this hand" (MacBeth)
- π: equivalent length close to true length
  - Highly complex sequence, yet low information content.

Information capacitance



Characteristics of Information carriers:

- Has "maximum" I_C independent of length
- Are quasi-random – has ½ mut'ns needed for randomization
- Has ϕ equivalent to random sequence 250 – 10000 b

Order index

Equivalent length

Equivalent Mutation density

Conjectural Inferences

- $\phi \sim \phi_g$ are high information capacitance states
- The observed shortness of L_ϕ suggests that the neutral process is dominated by (fixed, hence non-deleterious) segmental duplications
- No difference in coding and non-coding part suggest process is random/neutral
  - Random: low free-energy, easy access
- Random process can only built infrastructure, not information; actual information is acquired in mostly fitness driven point mutation events
  - Selective: difficult to access

A two-step genome growth

- Genome growth by a two-step process:
  - One neutral, robust, infrastructure-building and universal
  - The other selective, fine-tuning, information-gathering and diverse
  - Example: paradigm of accidental gene duplication followed by mutation driven subfunctionalization
- The twin-processes acted in a ratchet-like, complementary manner, driving the genome, in successive stages, to a state of maximum information capacity, and helping it to acquire, at each stage, near-maximum information content.

End of Lecture Two