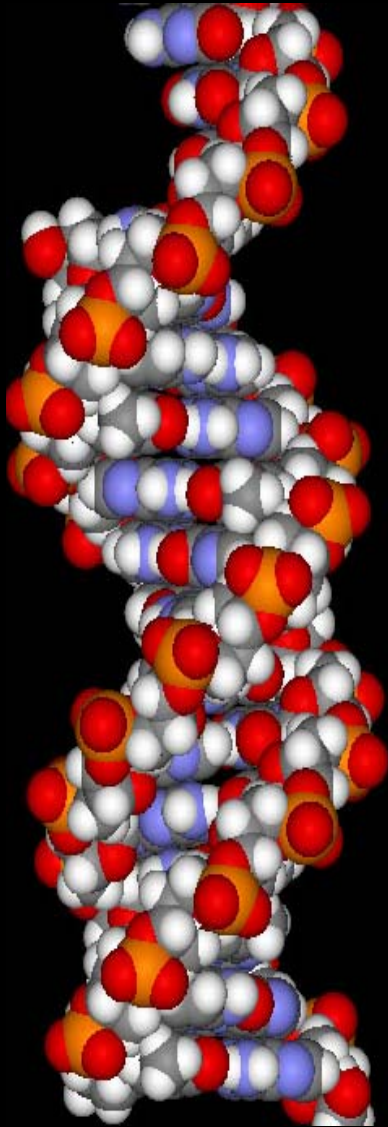# Genome-wide Estimates of the Mutation Rate Across the Tree of Life
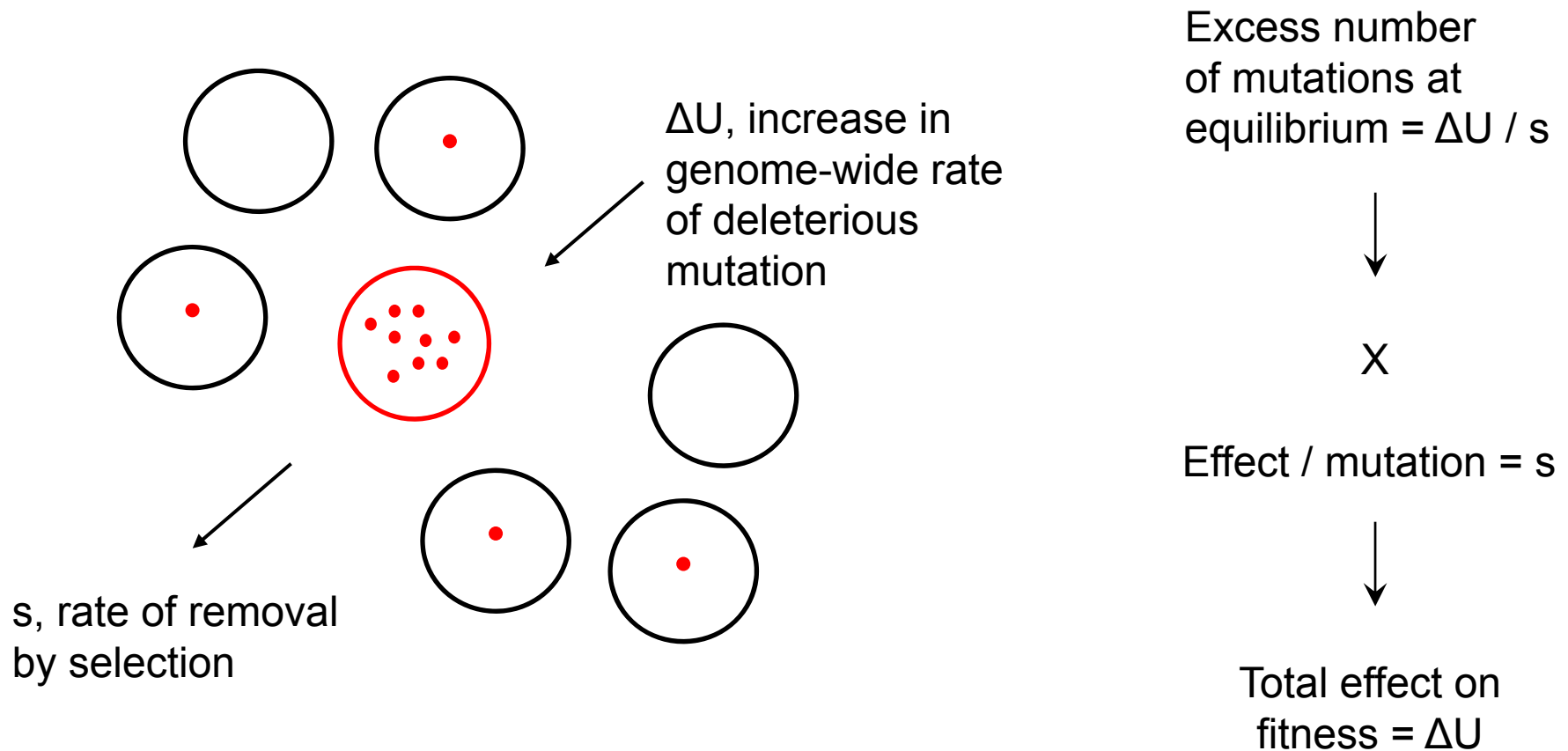
- Why this is centrally relevant to radioecology:

    – Critical to understanding the mechanisms by which radiation increases the mortality rate of individuals, the extinction risk of populations, and the collapse of ecosystems.

    – J. Environ. Radioactivity – no paper on the effects of radiation on the mutation rate.

    – A PubMed search of "dose response," "mutation rate," and "radiation" yields nothing but a few studies of reporter constructs and microsatellite loci.

Take-home Messages

- The baseline mutation rate / nucleotide site varies ~1000x among species.

  - ~0.003 mutations/genome/generation in bacteria; ~1 in invertebrates; ~100 in humans.

- Stress is an indirect mutagen.

- Mutation rates in somatic tissues are >10x those in the germline.

- Transcription error rates are >1000x higher than replication-error rates.
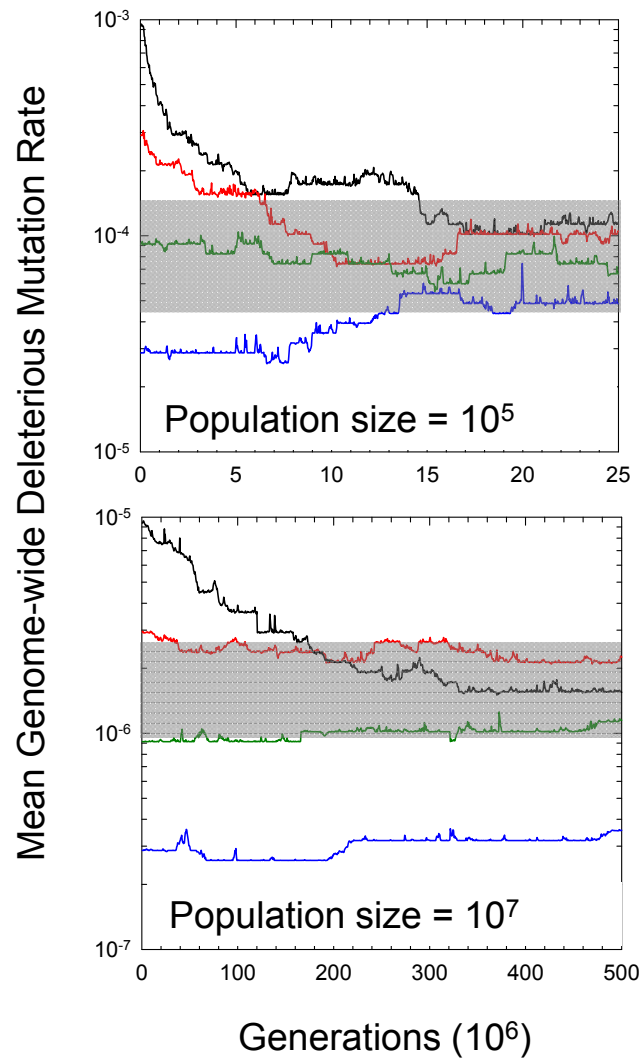
- Key areas for future research.

The Mutation Rate is the Only Trait for Which We Have a General Theory of Evolution

ΔU, increase in genome-wide rate of deleterious mutation

s, rate of removal by selection

Excess number of mutations at equilibrium = ΔU / s

↓

X

Effect / mutation = s

↓

Total effect on fitness = ΔU

- Selective disadvantage of a mutator in an asexual population = increase in genome-wide deleterious mutation rate
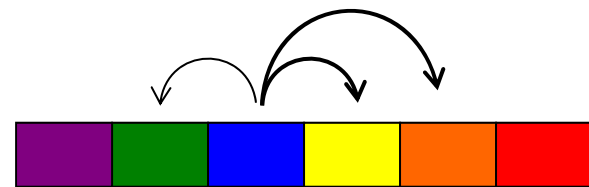
Mutation Rates Evolve to Levels Inversely Proportional to Population Size

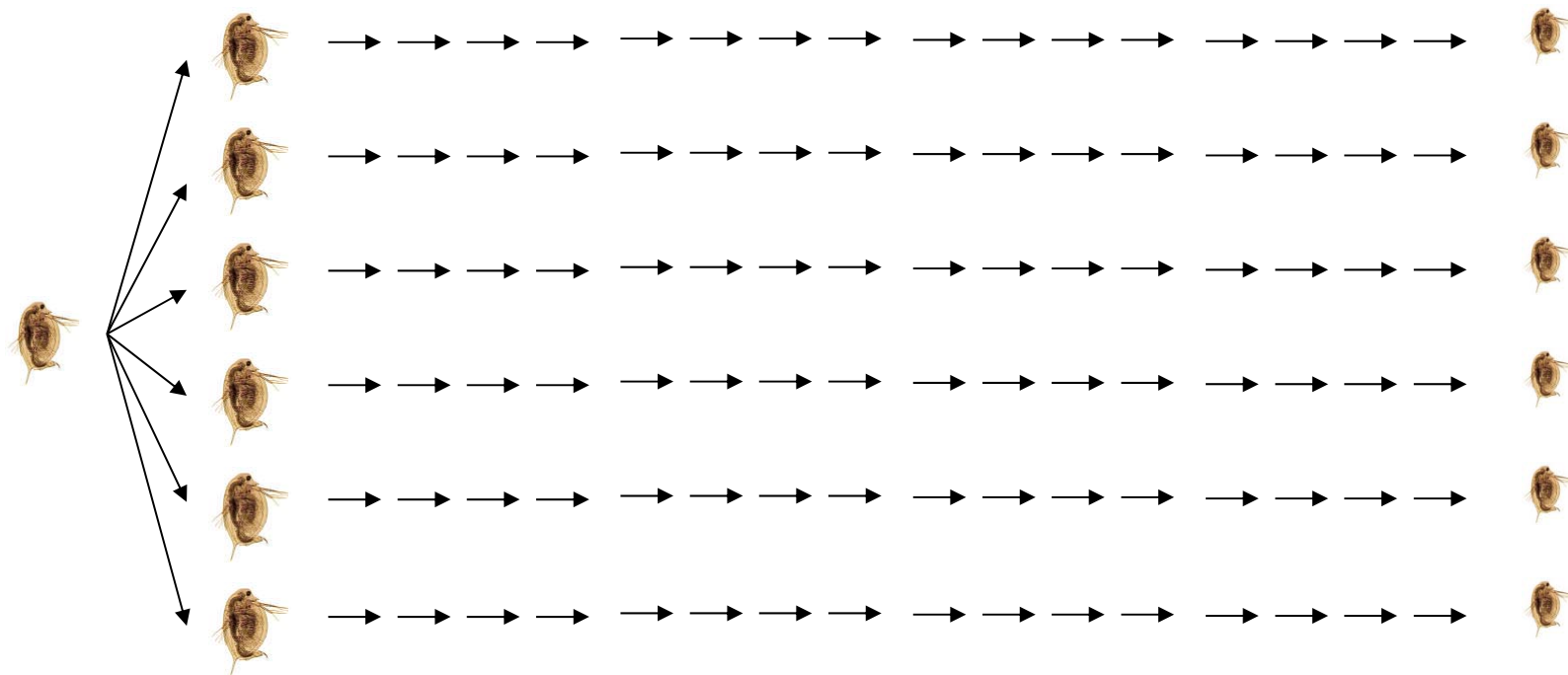Effective selection promoting antimutators

DRIFT BARRIER

Biased production of mutators

Population size = 10^5

Population size = 10^7

Mean Genome-wide Deleterious Mutation Rate

Generations (10^6)

Mutation-rate classes

Analysis of Genome Stability with a Mutation-accumulation Experiment:

Starting with a single stem mother, many dozens of sublines are maintained

by single-progeny descent, for hundreds to thousands of generations.

Advantage – essentially no selection bias; allows a genome-wide perspective of the entire molecular profile of mutations, from substitutions to large deletion/duplications.
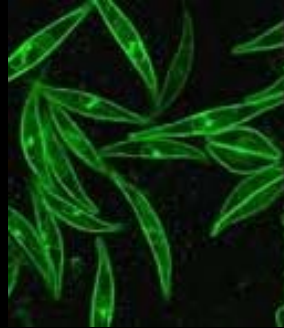
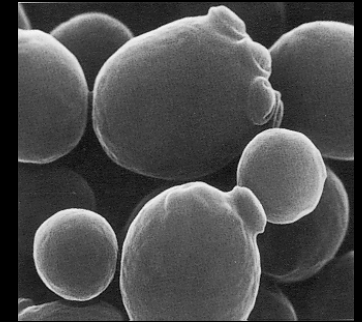Recent and Current Eukaryotic Targets of Study

Arabidopsis *Chlamydomonas* *Phaeodactylum* *Dictyostelium* *Saccharomyces*

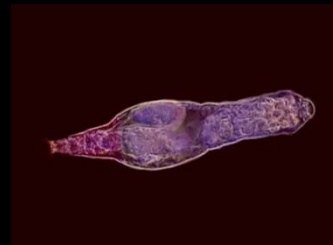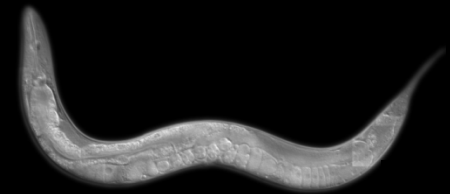*Rhodotorula* *Ichthyosporean* *Naegleria* *Paramecium*
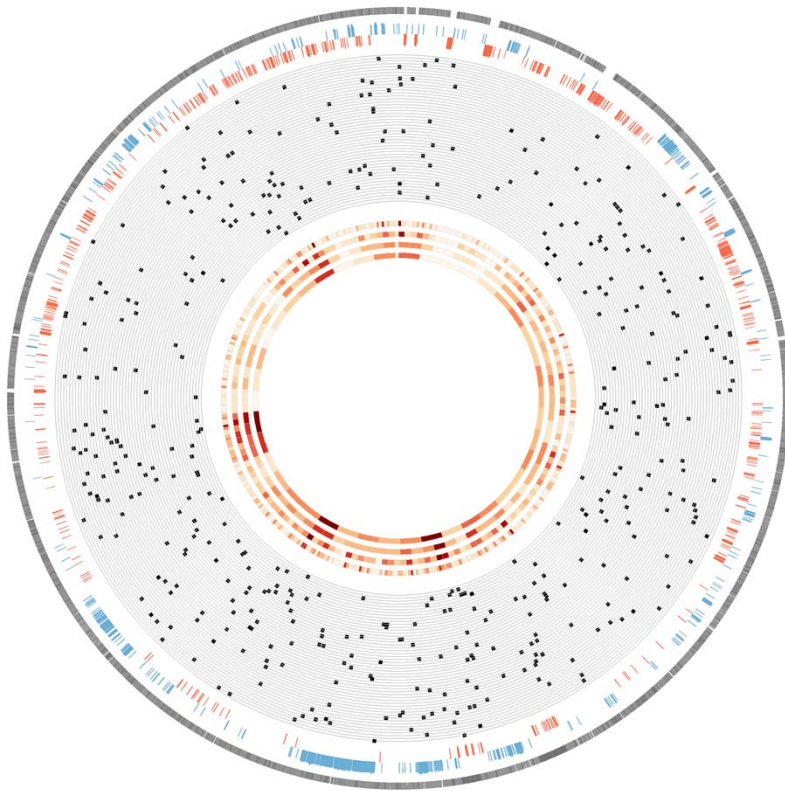
Daphnia *Drosophila* *Adineta* *Caenorhabditis*

Mutation-accumulation Studies in Prokaryotes

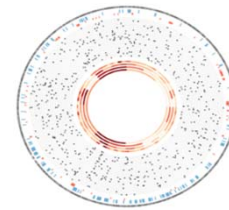| Group	Species	Genome Size (Mb)	G/C %
Bacteria:			
Acidobacteria	*Acidobacterium capsulatum*	4.1	61.0
Actinobacteria	*Kineococcus radiotolerans*	5.0	74.2
Actinobacteria	*Mycobacterium smegmatis*	7.2	65.2
Actinobacteria	*Mycobacterium* sp.	7.2	65.2
Alpha-proteobacteria	*Agrobacterium tumefaciens*	5.7	59.0
Alpha-proteobacteria	*Caulobacter crescentus*	4.0	67.2
Alpha-proteobacteria	*Rhodobacter sphaeroides*	4.5	68.2
Beta-proteobacteria	*Burkolderia cenocepacia*	7.8	66.8
Beta-proteobacteria	*Janthinobacterium* sp.	6.0	61.1
Gamma-proteobacteria	*Photorhabdus luminescens*	5.7	42.8
Gamma-proteobacteria	*Pseudomonas fluorescens**	7.1	63.3
Gamma-proteobacteria	*Shewanella putrefaciens*	4.7	44.5
Gamma-proteobacteria	*Teredinibacter turnerae*	5.2	50.9
Gamma-proteobacteria	*Vibrio cholerae**	4.1	47.5
Gamma-proteobacteria	*Vibrio fischeri**	4.3	38.3
Cyanobacteria	*Synechococcus elongatus*	2.7	55.5
Deino-Thermus	*Deinococcus radiodurans**	3.2	66.6
Firmicute	*Bacillus subtilis**	4.2	43.5
Firmicute	*Staphylococcus epidermidis*	2.6	32.0
Flavobacteria	*Flavobacterium* sp.	6.1	34.1
Lactobacillale	*Lactobacillus* sp.	2.9	46.4
Planctomycete	*Gemmata obscuriglobus*	9.2	67.2
Tenericute	*Mesoplasma florum*	0.8	27.0
Archaea:			
Euryarchaeota	*Haloferax volcanii*	4.0	65.5

Mutation in Small vs. Large Genomes

Bacillus subtilis 3610
  Genome size: 4,214,598 bp

  50 lines - 450 mutations - 5000 gens.

  Mutation Rate : 3.27 × 10^{-10}/site/gen.

Mesoplasma florum L1
  Genome size: 793,224 bp

  50 lines – 599 mutations - 2000 gens.

  Mutation Rate : 1.14 × 10^{-8}/site/gen.

Drake's (1991) Conjecture: A Constant Rate of Mutation per Genome per Cell Division in Microbes
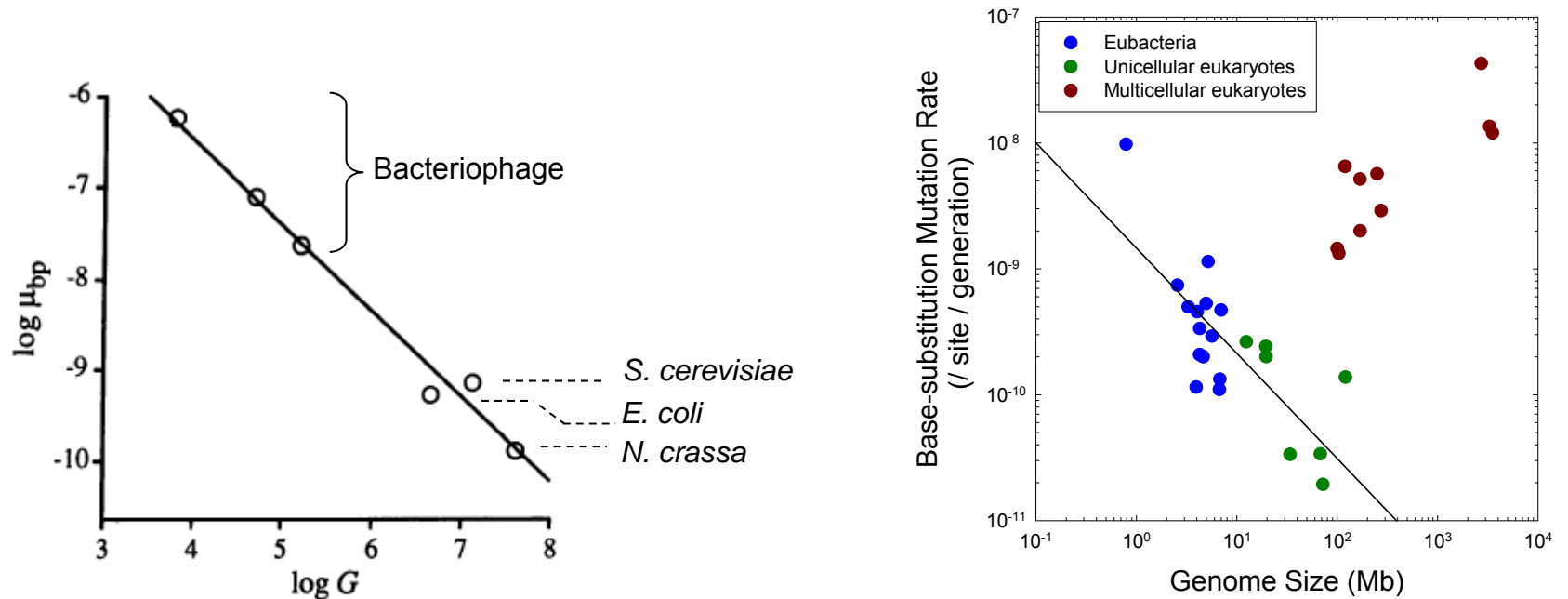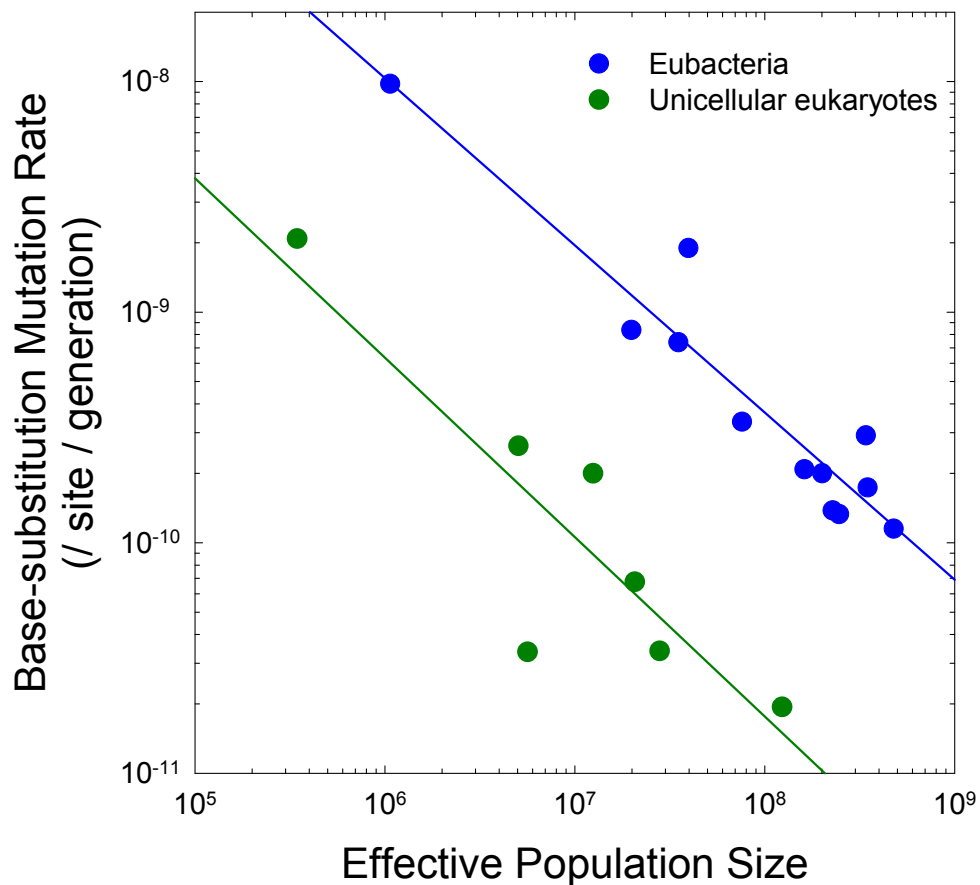

FIG. 1. Average mutation rate μ_{bp} per base pair as a function of genome size G in bp. The logs of the rates for each organism were averaged and all 13 values are included. Phages T2 and T4 were treated as a single organism.
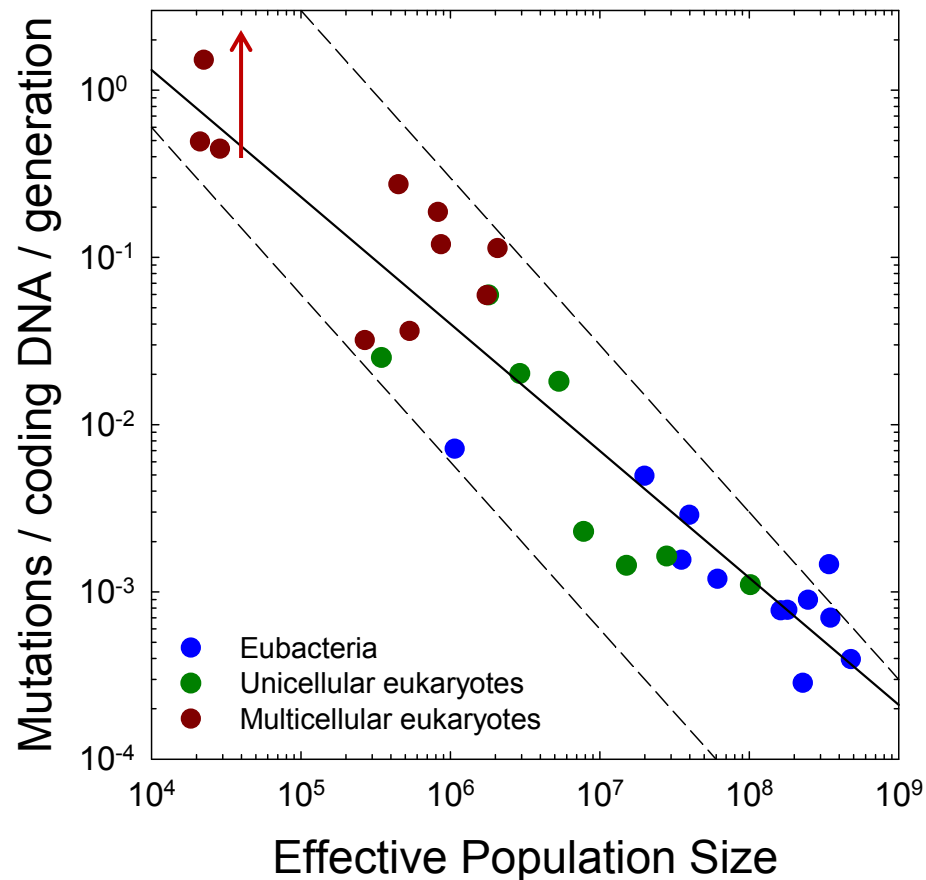
"Because this rate is uniform in such diverse organisms, it is likely to be determined by deep general forces."

The Mutation Rate / Nucleotide Site Is Inversely Proportional to the Average Effective Population Size of a Species

For a given magnitude of genetic drift, selection is capable of driving the mutation rate down further in eukaryotes than prokaryotes.

A Universal Inverse Scaling Between the Genome-wide Deleterious Mutation Rate and Effective Population Size Across the Tree of Life

- The mutation rate per nucleotide site scales inversely with both the effective population size and the amount of functional DNA in the genome (the total target size for deleterious mutations).

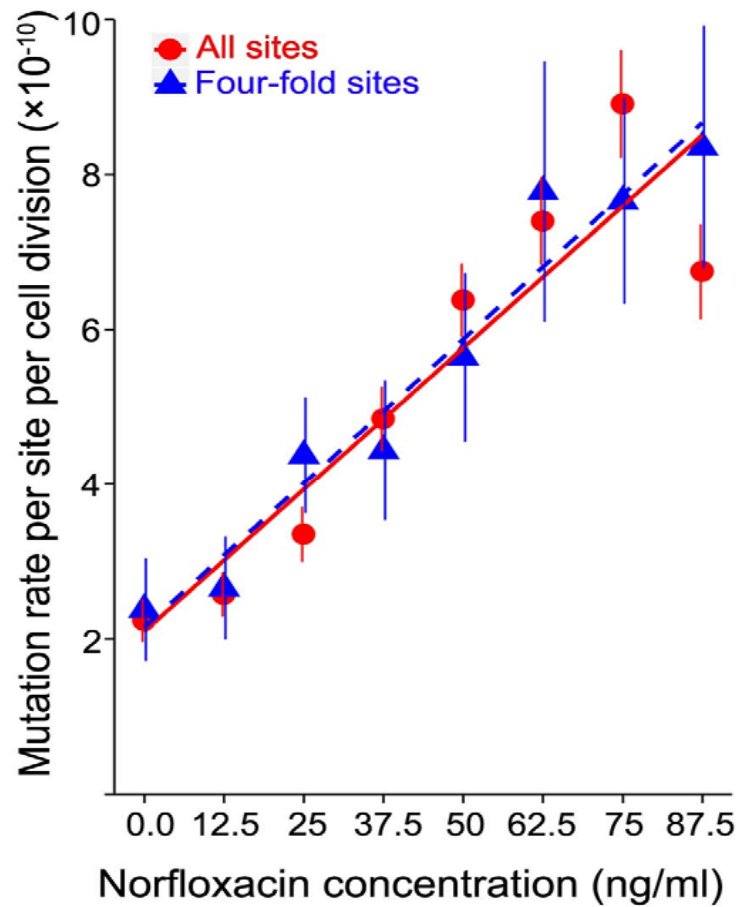$$uG_e \sim 1 / N_e \quad \rightarrow \quad u \sim 1 / (G_e \cdot N_e)$$

u = mutation rate / site / generation

G_e = amount of functional DNA (sites)

N_e = effective population size

● Eubacteria
● Unicellular eukaryotes
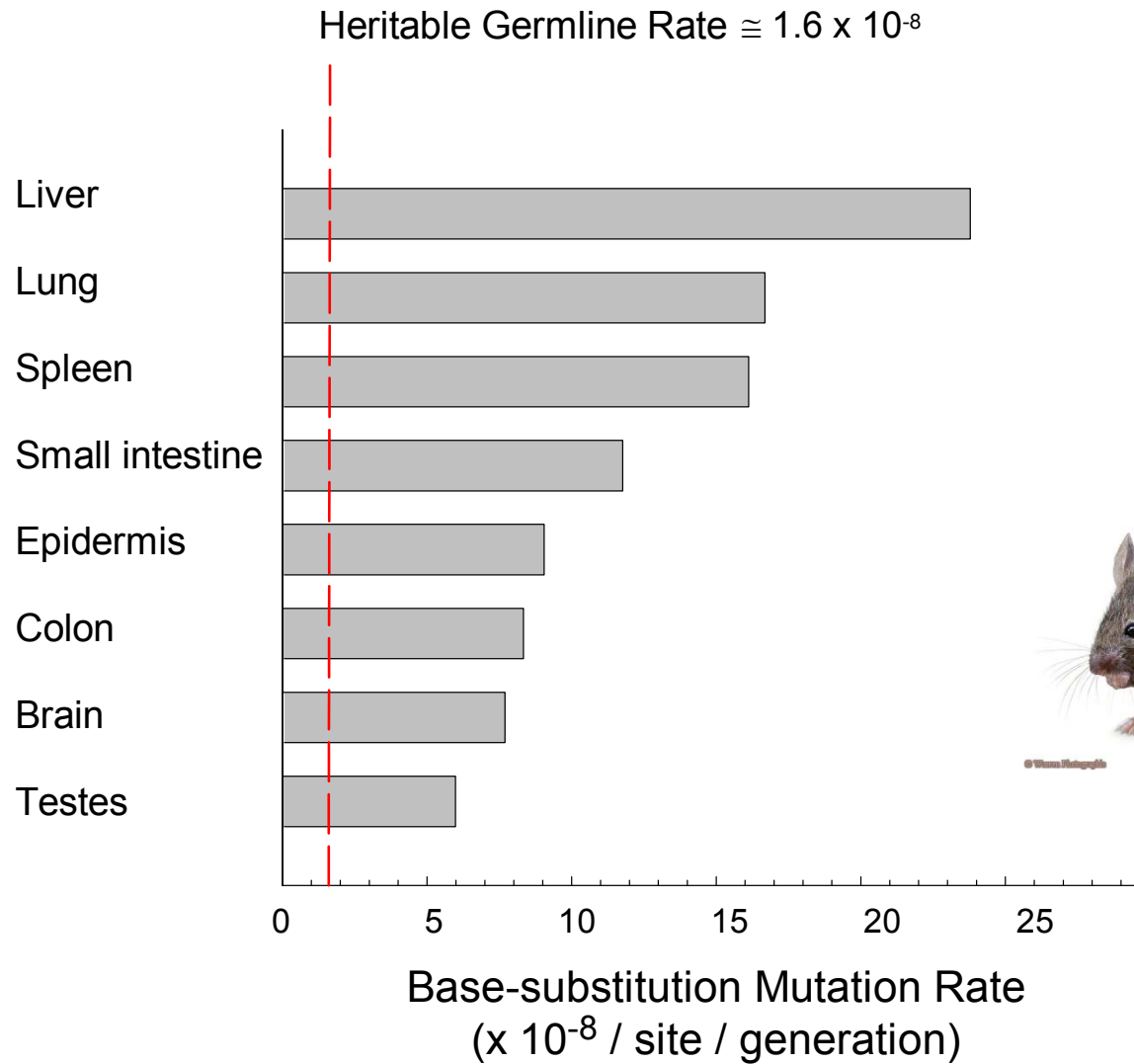● Multicellular eukaryotes
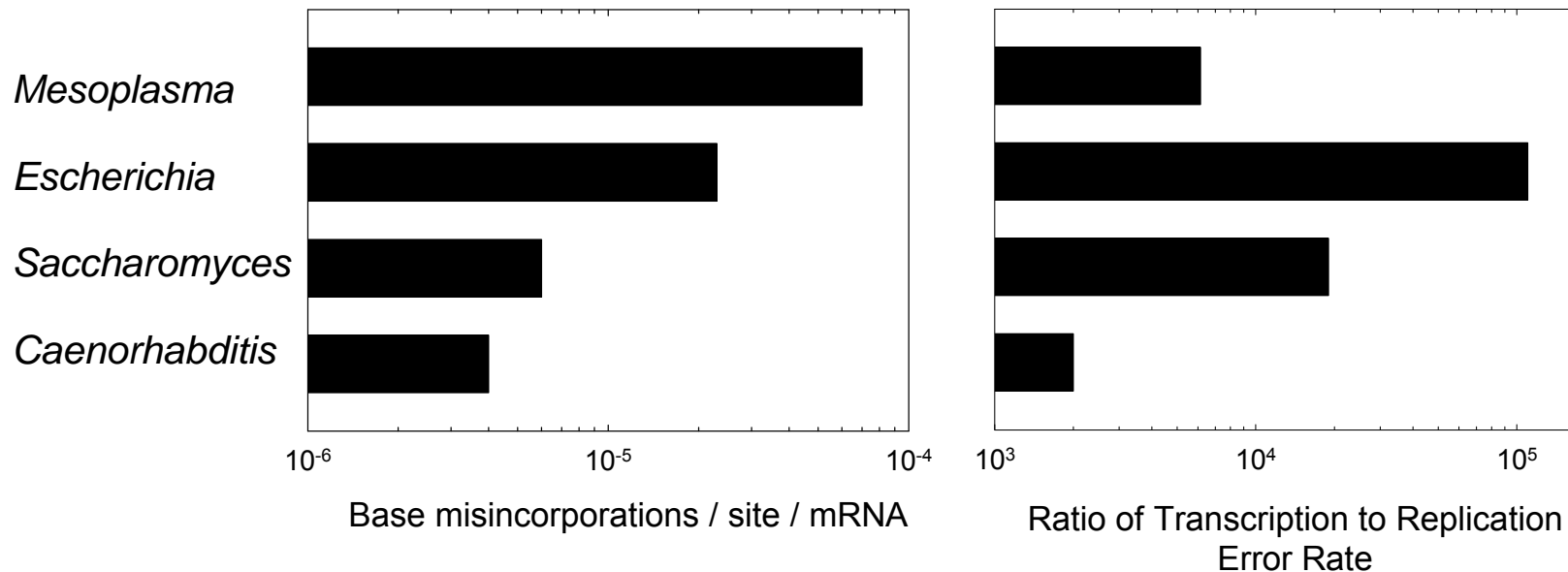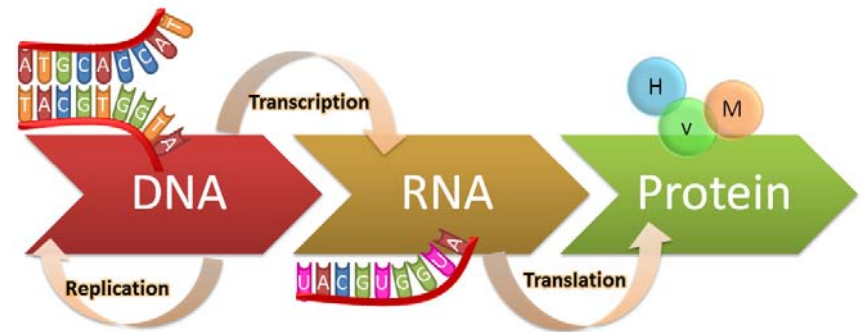
Minor Levels of Stress Elevate the Mutation Rate

Clinical Dose: ~750 ng/ml

Somatic Mutation Rates Are Up to 15x Those in the Germline

Heritable Germline Rate $\cong 1.6 \times 10^{-8}$

Liver

Lung

Spleen

Small intestine

Epidermis

Colon

Brain

Testes

0   5   10   15   20   25

Base-substitution Mutation Rate
$(\times 10^{-8}$ / site / generation$)$

Transcription-error Rates: Orders of Magnitude Higher Than Replication-error Rates
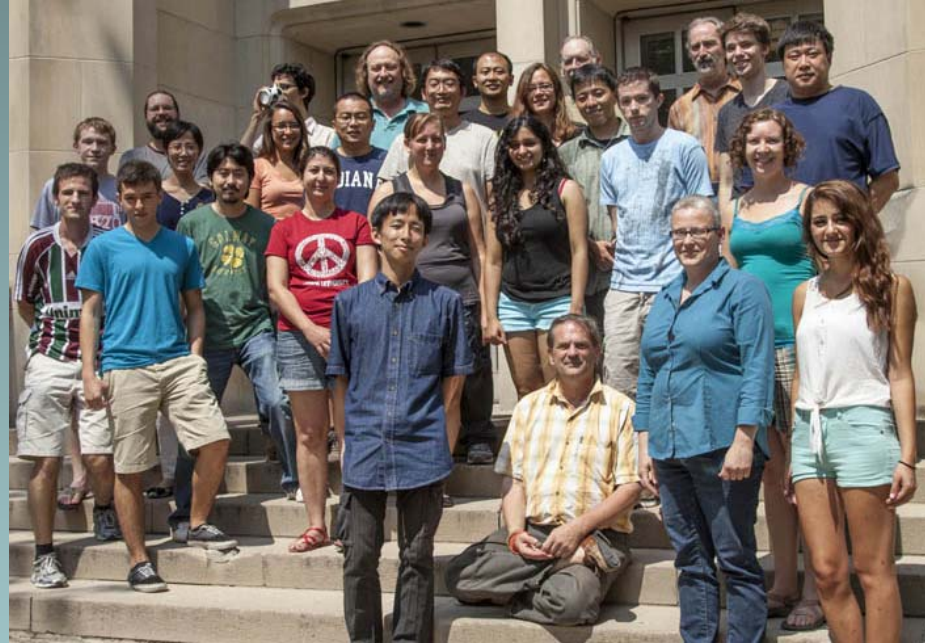
- ~1 to 5% of transcripts contain errors

Future Work:

- How do various types of genomic error rates scale with radiation dose?

- How do these responses vary across phylogenetic groups?

- How does chronic exposure to radiation lead to physiological and/or evolutionary changes in the mutation rate?

  - Physiological stress response can magnify the mutation rate by ~100x.

  - Adaptive evolution of radiation resistance or mutational meltdown?

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