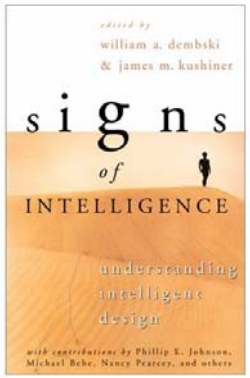
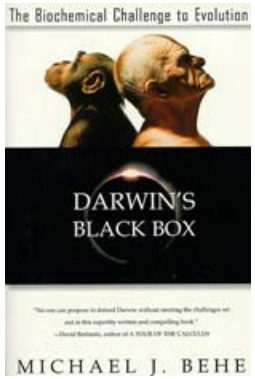
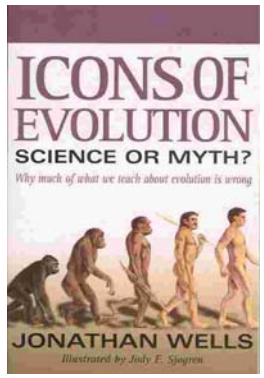
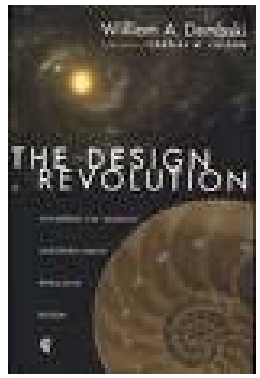
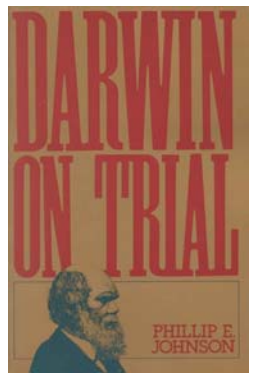
Evolutionary Mythology versus Evolutionary Science

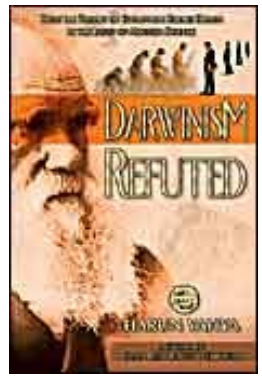


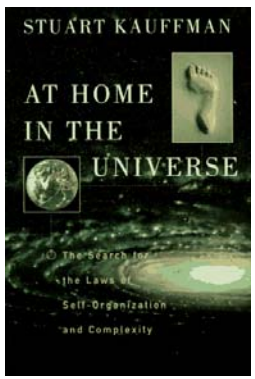


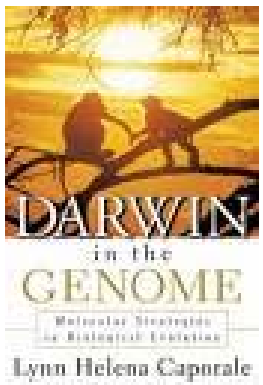


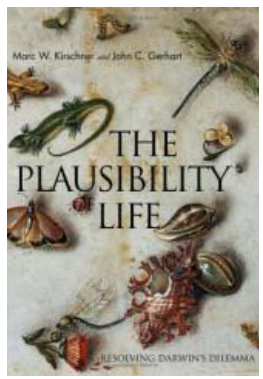


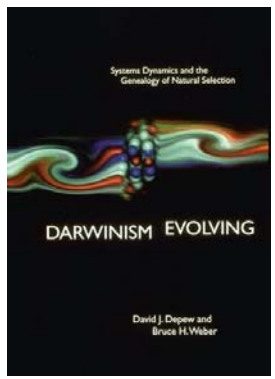


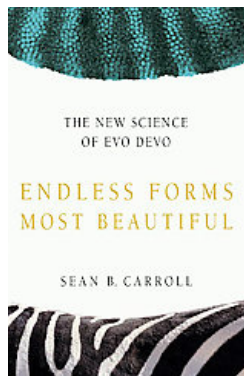


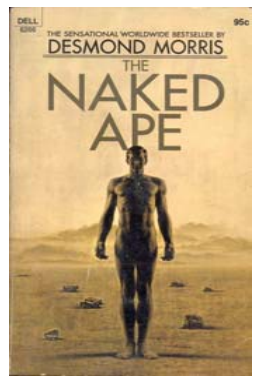


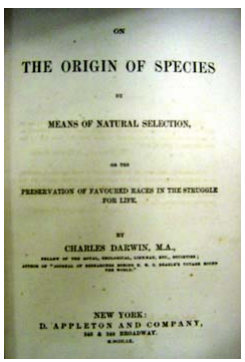


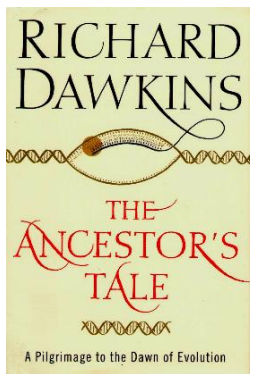


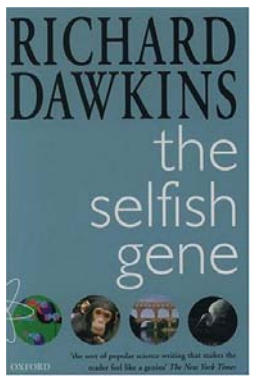


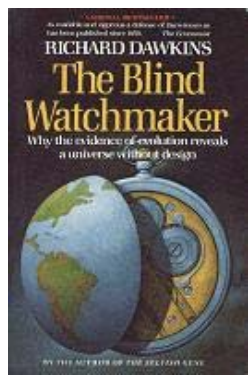


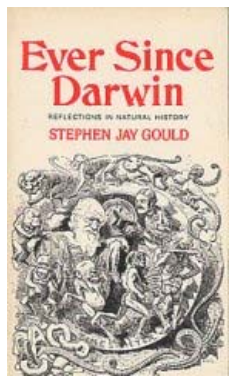


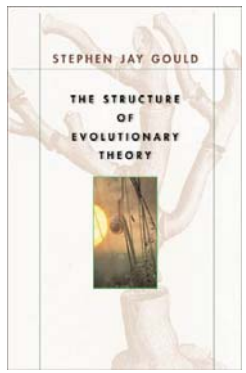












“Most expositions of the evolutionary process have focused on microevolutionary mechanisms. Millions of biology students have been taught the view (from population genetics) that ‘evolution is change in gene frequencies.’ Isn’t that an inspiring theme? This view forces the explanation towards mathematics and abstract descriptions of genes, and away from butterflies and zebras… The evolution of form is the main drama of life’s story, both as found in the fossil record and in the diversity of living species. So, let’s teach that story. Instead of ‘change in gene frequencies,’ let’s try ‘evolution of form is change in development’.”

Myth. Evolution is a story-telling exercise.

Reality. Evolutionary biologists are concerned with the mechanisms (population-genetic processes) that result in change, not just in documenting history.

Myth. Microevolutionary theory based on gene-frequency change is incapable of explaining the evolution of complex phenotypes.

Reality. Evolution reflects changes in genotype frequencies.

No principle of population genetics has been overturned by an observation in molecular, cellular, or developmental biology.

No novel “macroevolutionary” mechanism of evolution been revealed.

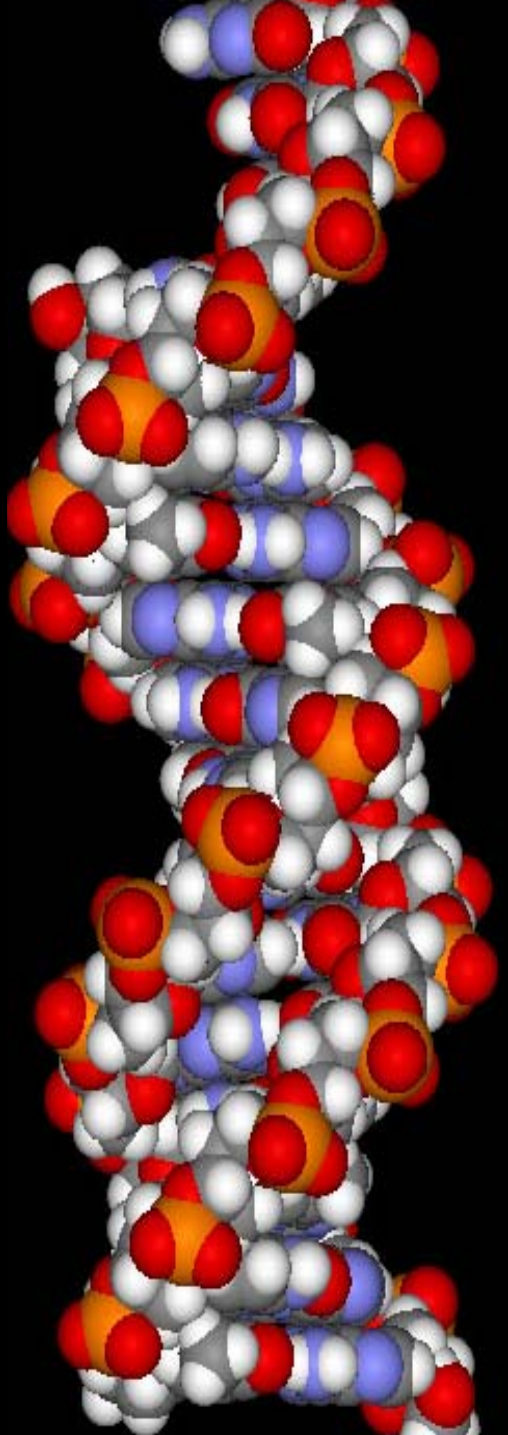
Myth. Population genetics is uninspiring.

Reality. The goal of population genetics is not to be inspiring, but to provide explanatory power. Population genetics grounds us in reality, whereas verbal adaptive arguments easily lead us astray.

Myth. Identification of interspecific differences at the molecular and/or cellular levels is tantamount to identifying the mechanisms of evolution.

Reality. The resources deployed in evolutionary change reside at the molecular level, and catalogs of interspecific differences identify the end products of evolution, but not the processes that promoted such change.

The identification of causal population-genetic processes distinguishes evolutionary biology from comparative biology.



Minimum requirements for a mechanistic understanding of evolution:

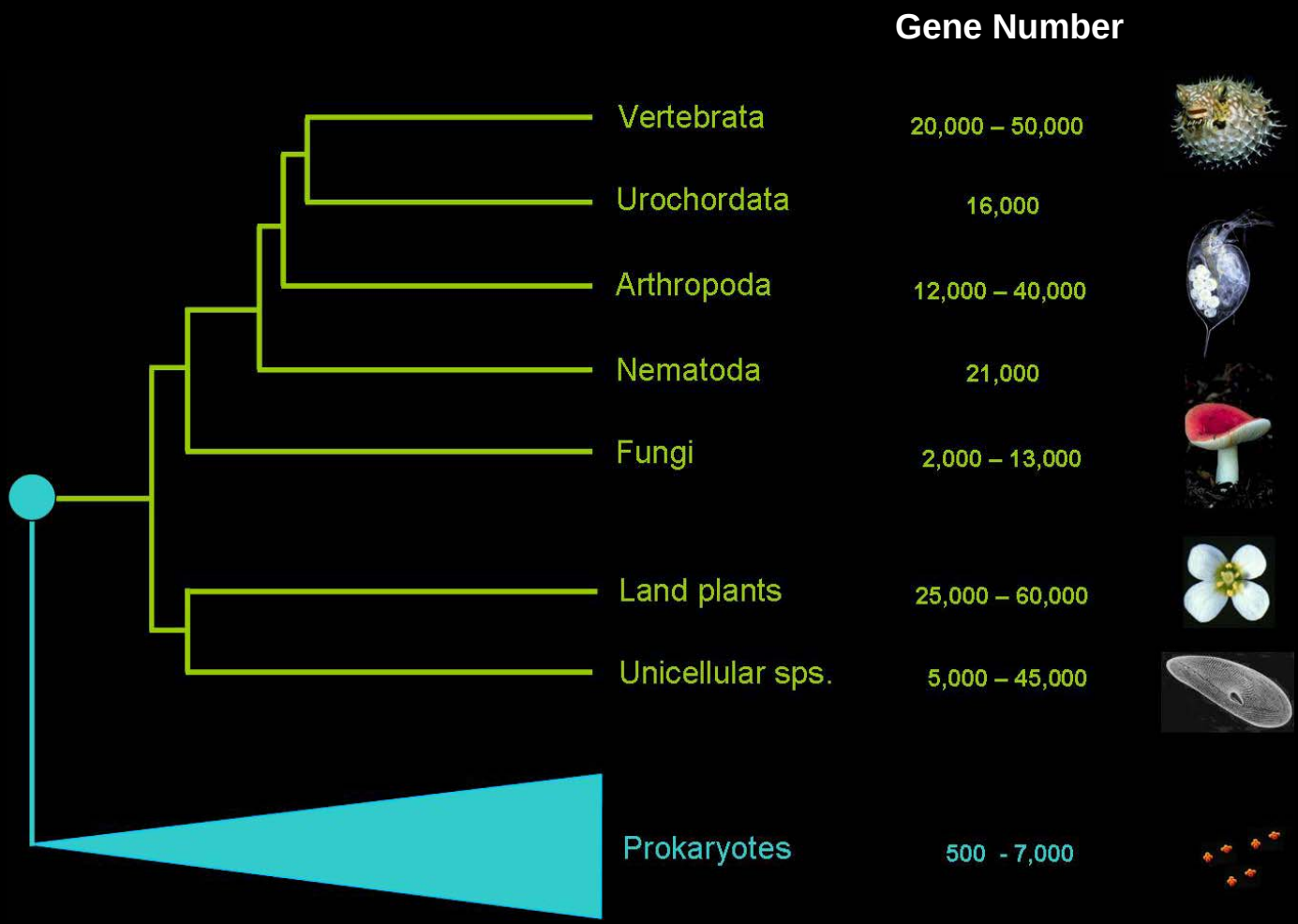
- **The population-genetic environment** – the relative power of the population-genetic forces that promote the proliferation vs. eradication of mutant alleles.

- **The intracellular environment** – a deep understanding of molecular and cellular biology; the natural history of various genetic elements and the cellular functions and localizations of their encoded products.

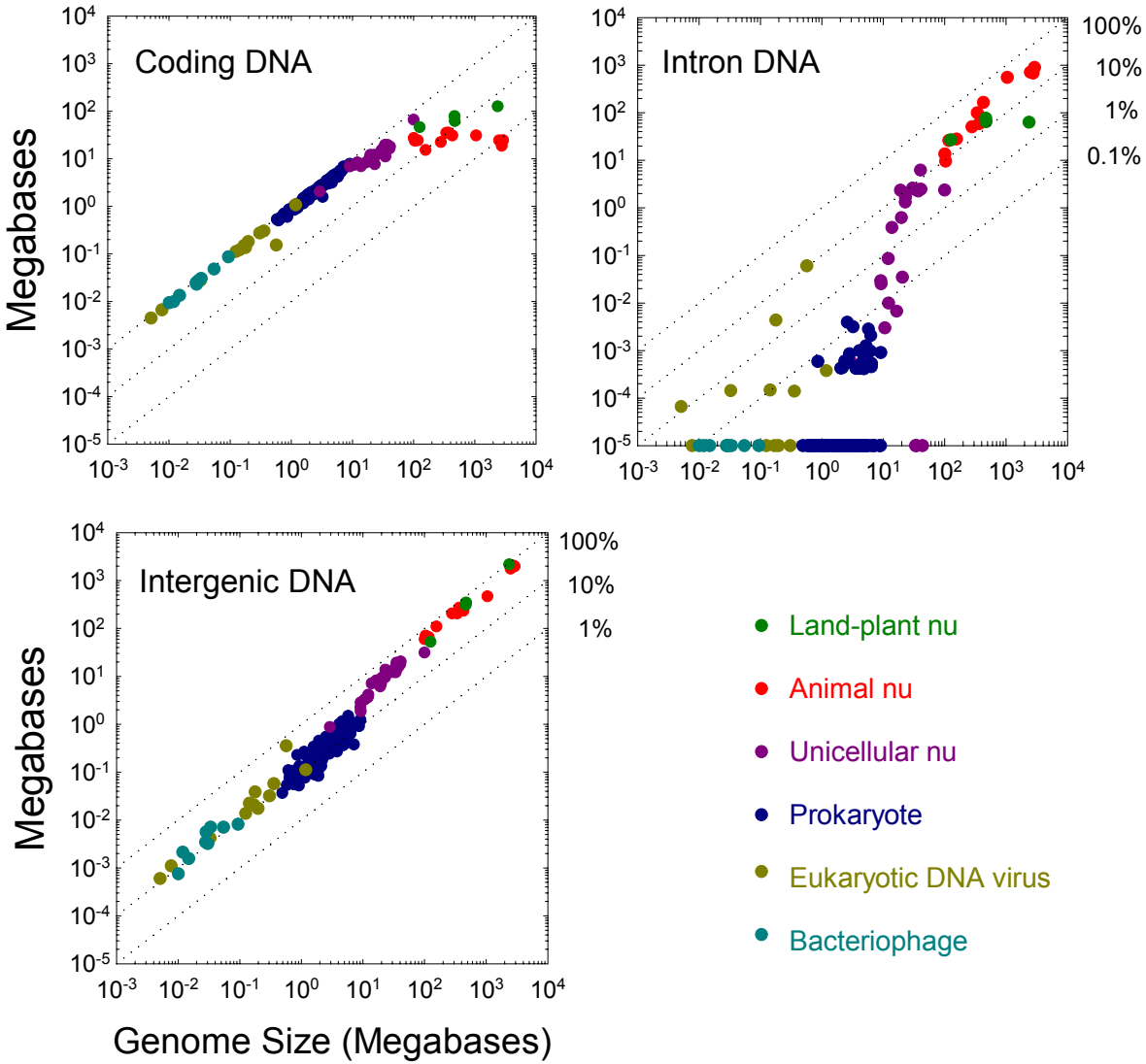
- **The external environment** – changes driven by ecological challenges.

- **A non-adaptational null hypothesis**.

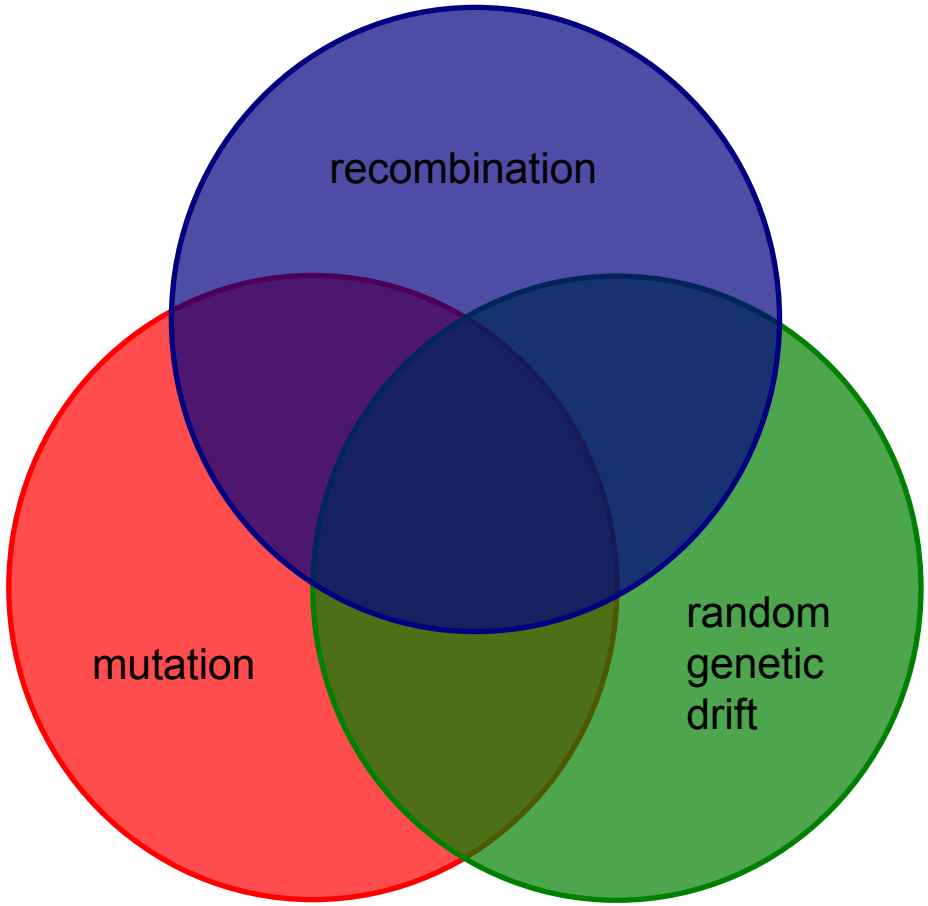
Expansion in Genome Complexity with the Evolution of Multicellularity: Cause or Effect?



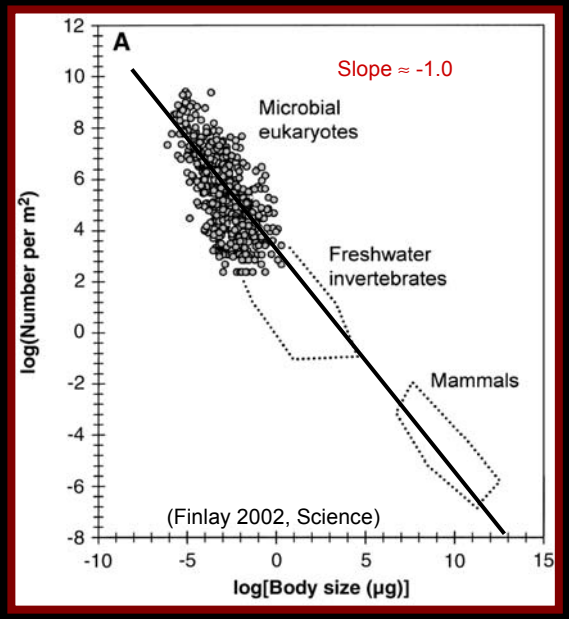
The Expansion of Noncoding DNA with Genome Size



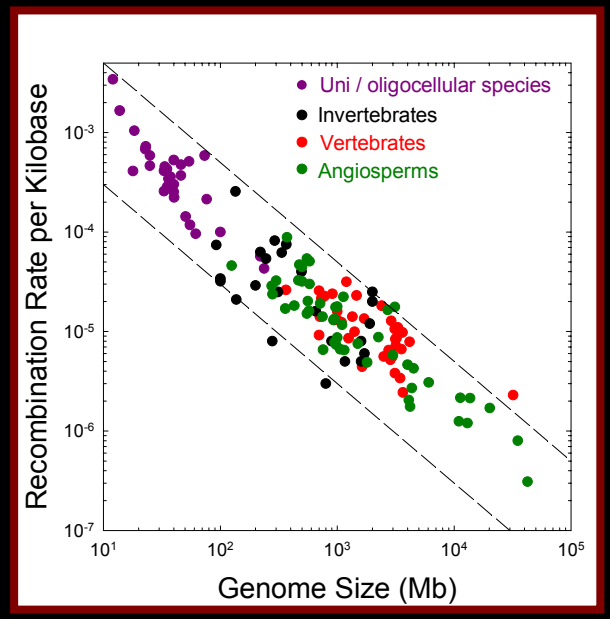
The Population-genetic Environment



Two Genetic Perils of Evolving Large Size



Reduction in absolute population size



Reduced recombination per physical distance

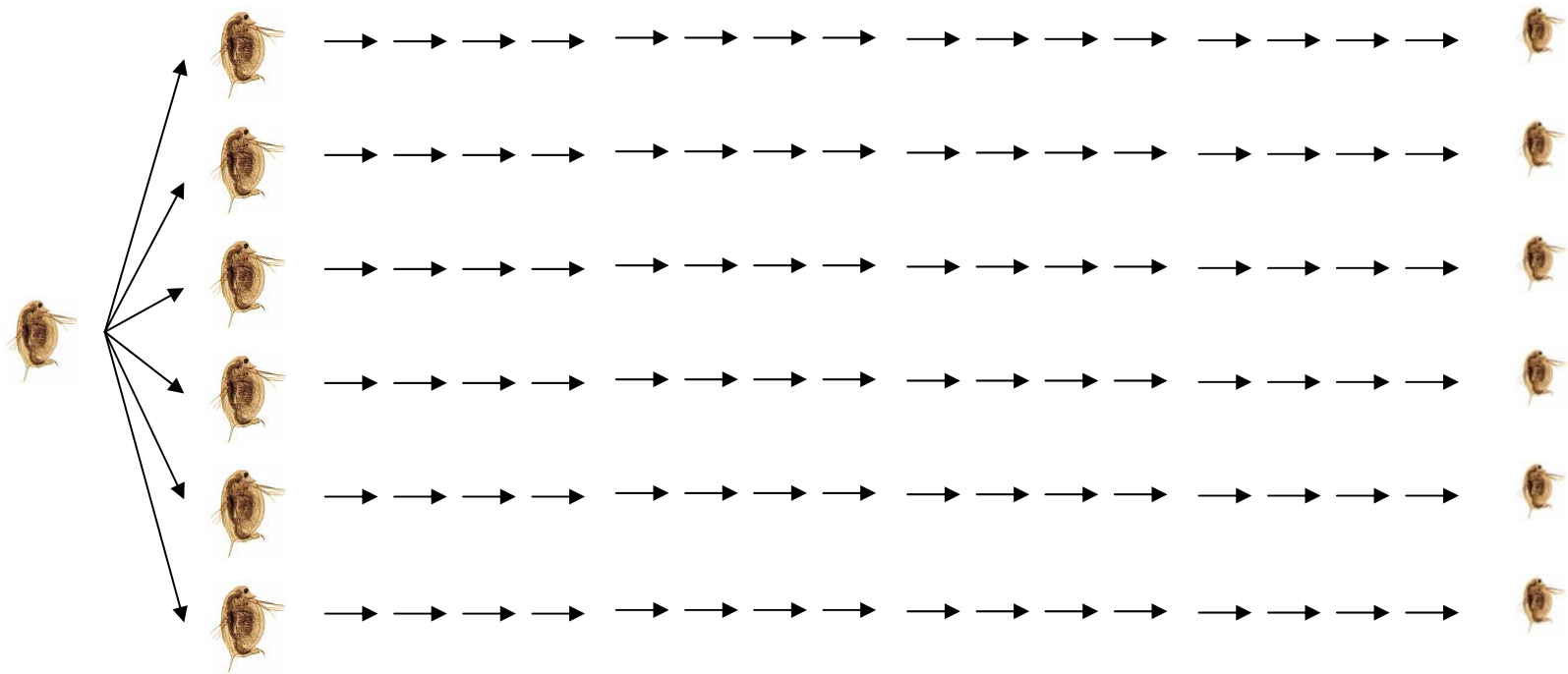
- What is the mutation rate; how and why does it scale across phylogenetic groups?

  - Like all traits, the mutation rate is subject to modification by mutation pressure (in this case, on the repair apparatus).

  - Because the magnitude of selection operating on the mutation rate is small, the mutation rate is bounded away from its physiological minimum by the power of random genetic drift.

  - The enhanced power of genetic drift in eukaryotes, and multicellular species in particular, encourages the emergence of aspects of gene structure that magnify mutational target sizes to defective alleles.

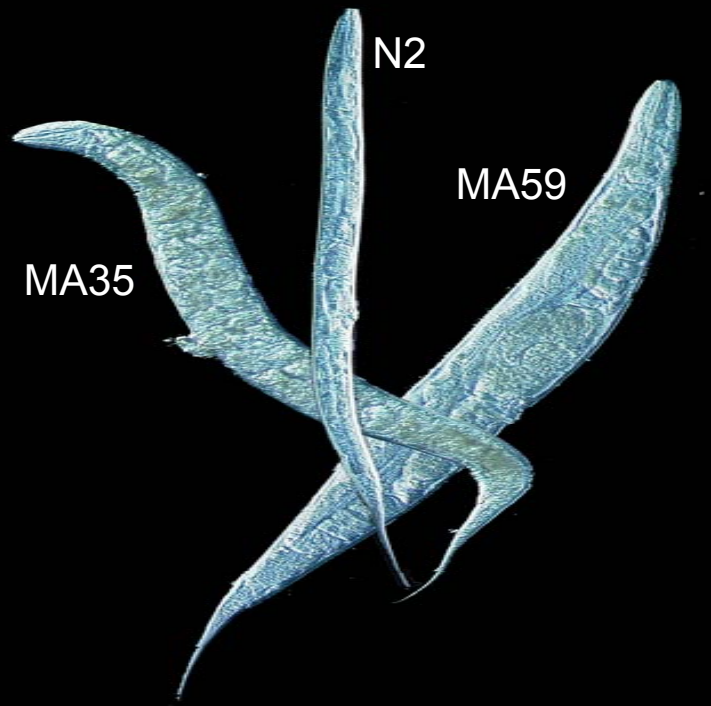
Mutation-accumulation (MA) experiment. Starting with a single stem mother, sublines are maintained by single-progeny descent, preventing selection from removing spontaneous mutations. This protocol is continued for hundreds of generations with dozens of lines.



Advantage – essentially no selection bias; allows a genome-wide perspective of the mutation profile.

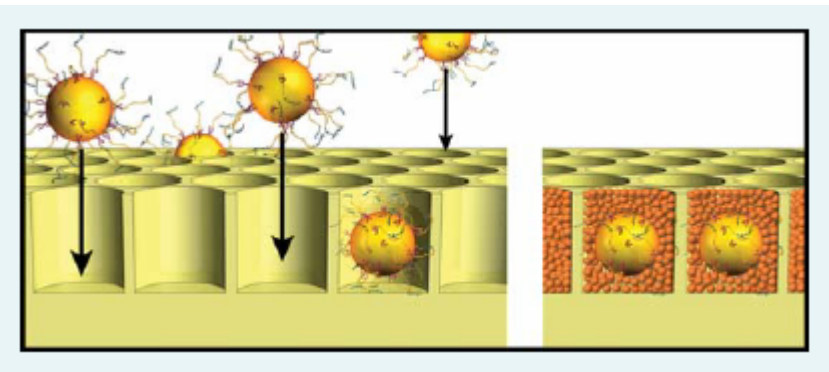
Disadvantage – labor intensive; line / investigator loss.

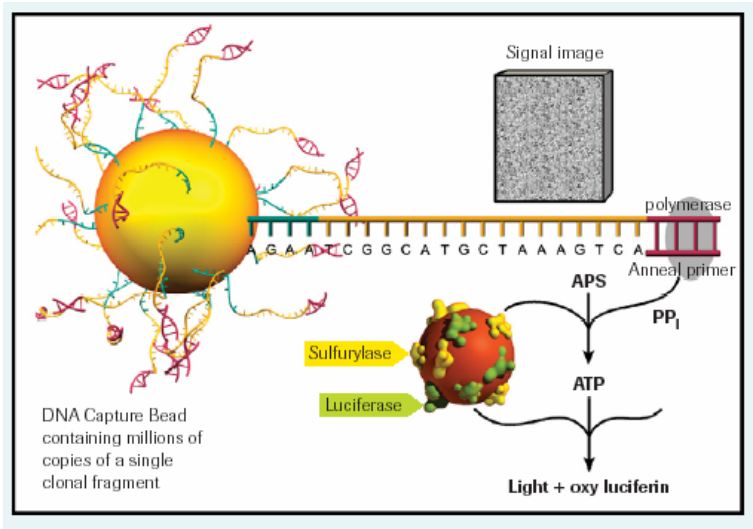
Extreme Morphological Divergence in MA lines of *C. elegans*



Whole-genome Mutational Screening by 454 Life Sciences Technology

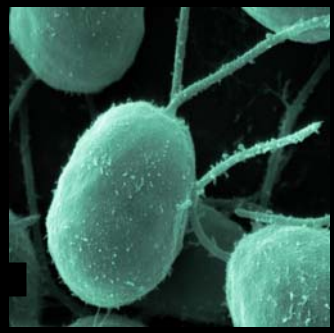
- Clonal amplification of random single-stranded DNA fragments on luciferase / sulfurylase-containing beads.
- Deposition of beads into a picotiter plate containing 250,000 wells.
- Sequential addition of nucleotides and detection by chemiluminescence.
- Generates hundreds of millions of bps of sequence in a few days, without cloning.
- Build contigs from the shot-gun sequences to a depth of 4 to 8x.
- Analyze the data in a maximum-likelihood framework to remove error contributions.



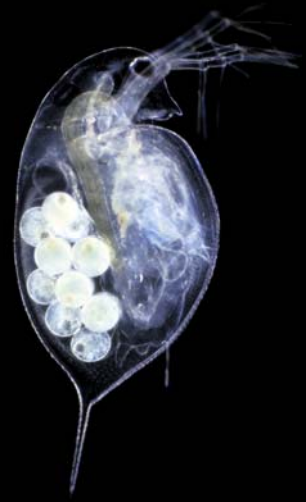


Recent and Current Targets of Study

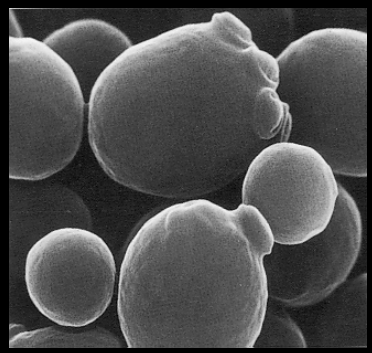
Arabidopsis



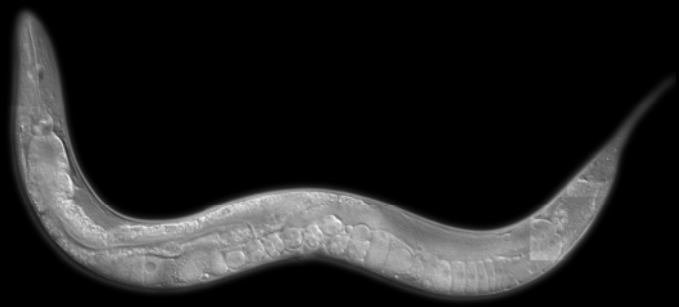
Chlamydomonas



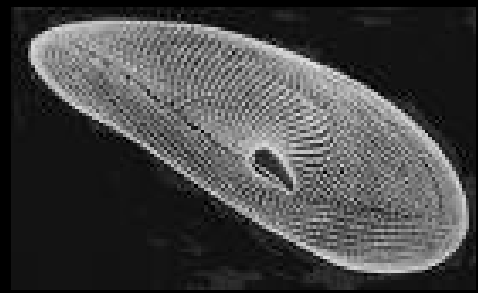
Daphnia



Saccharomyces



Caenorhabditis



Paramecium

Major contributors:

Indiana University: Jamie Choi, Nicole Coffey, Ignasi Lucas, Rohan Maddamsetti, Sam Miller, Sarah Schaack, Amanda Seyfert.

University of New Hampshire: Kelley Thomas, Shilpa Kulkarni, Krystalynne Morris, Kazufusa Okamoto, Way Sung.

University of Utah: Joe Dickinson.

Max Planck Institute, Tubingen: Detlef Weigel, Korbinian Schneeberger, Stephan Ossowski, Norman Warthmann.

Harvard University: Daniel Hartl, Christian Landry, Eric Dopman.

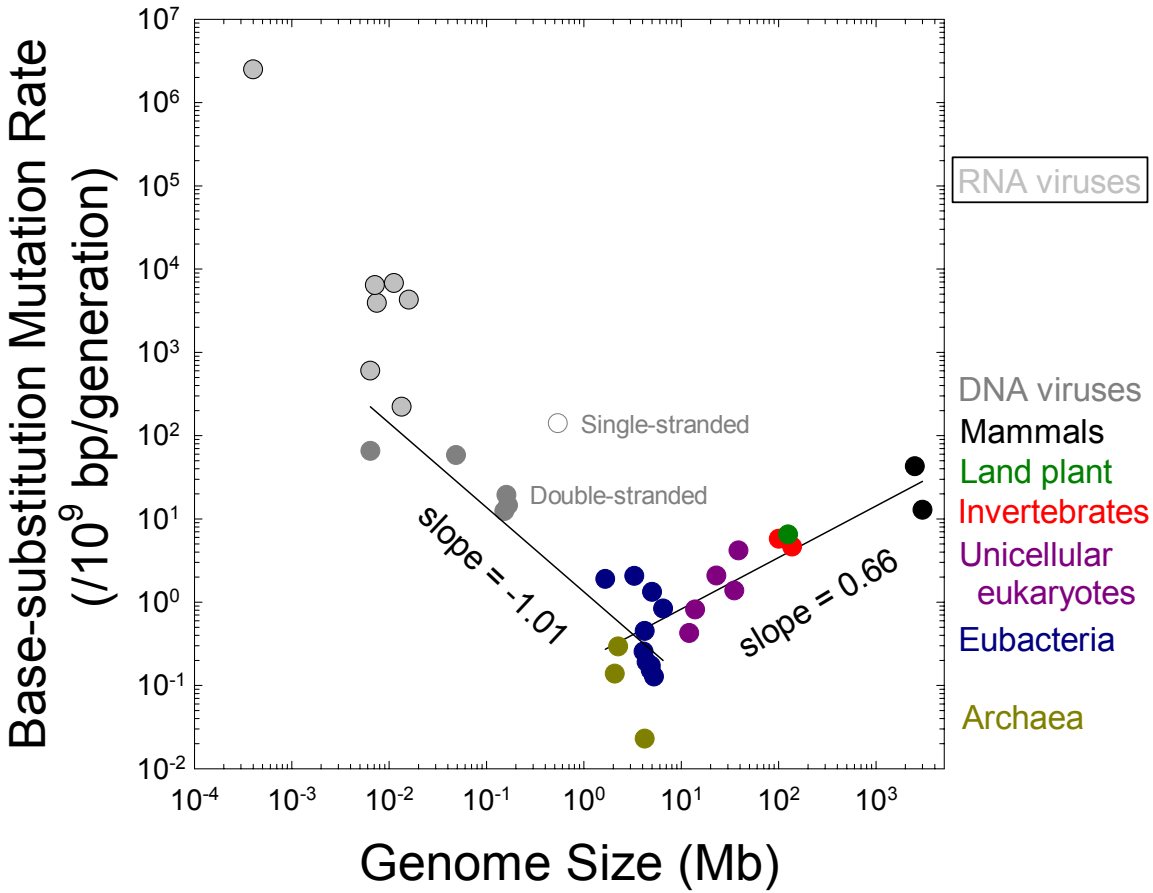
University of Florida: Charles Baer.

Oregon State University: Dee Denver.

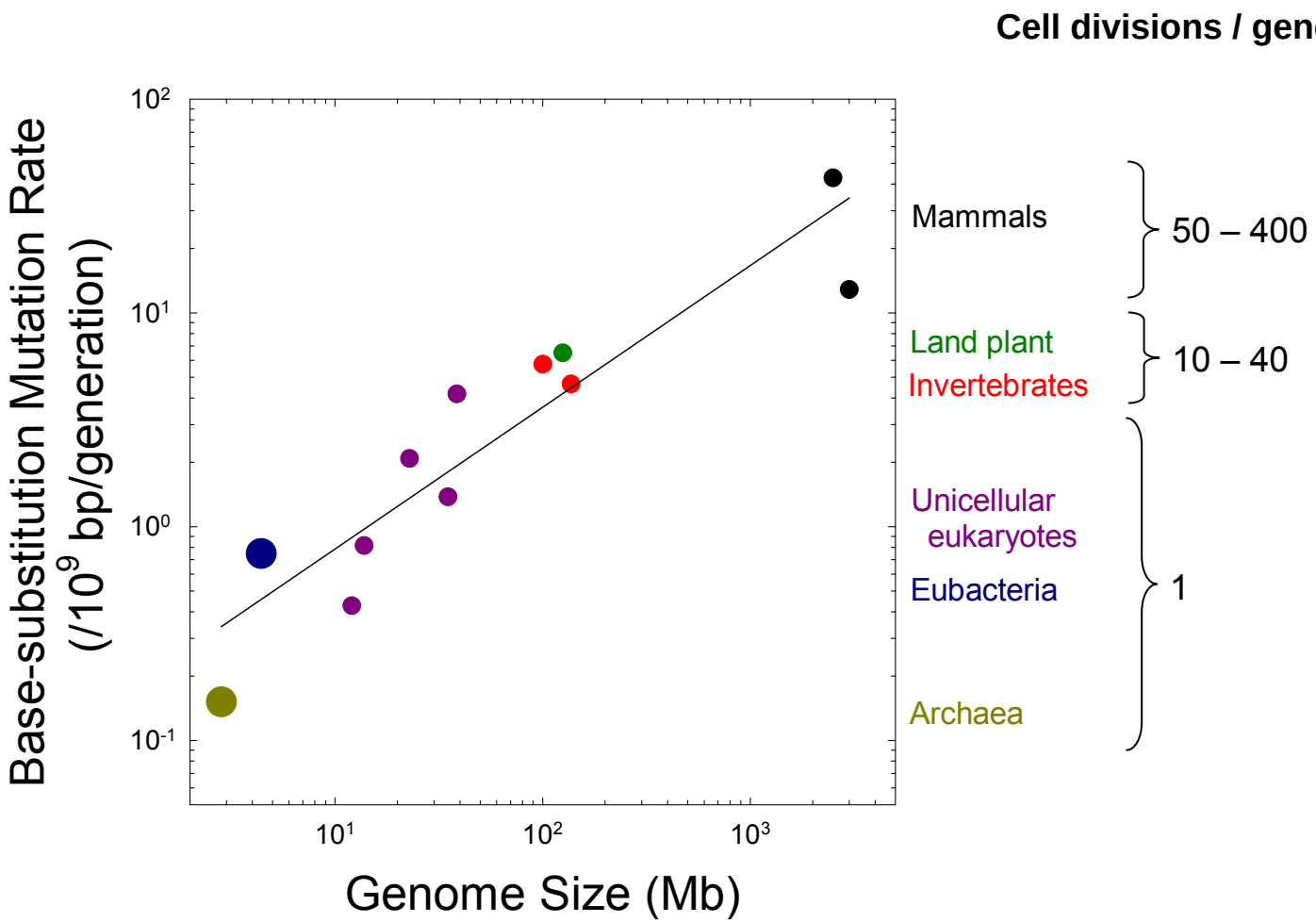
University of Minnesota: Ruth Shaw.

- The *average* number of mutations per genome is roughly constant in noneukaryotic microbes, in accordance with Drake.

- The mutation rate per nucleotide site increases with genome size in eukaryotes, yielding a dramatic increase in the genome-wide mutation rate per generation.

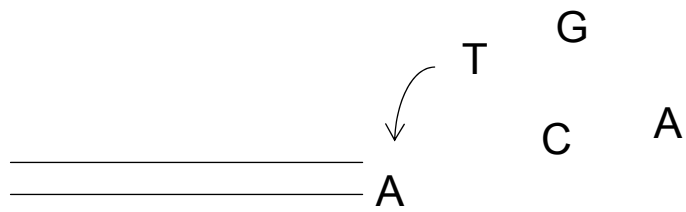


The Lower Bound to the Mutation Rate in Cellular Life is Dictated by the Power of Random Genetic Drift

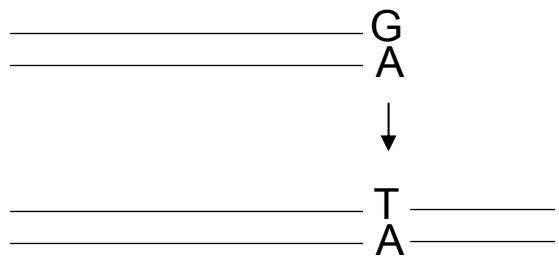


The Three Molecular Lines of Defense Against Mutation

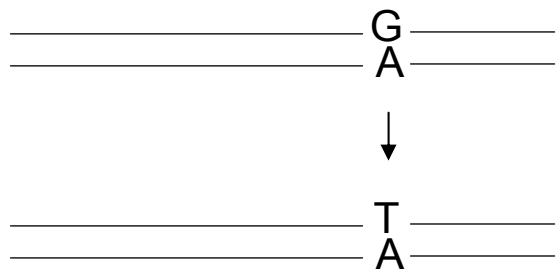
1) Polymerase base-incorporation fidelity:



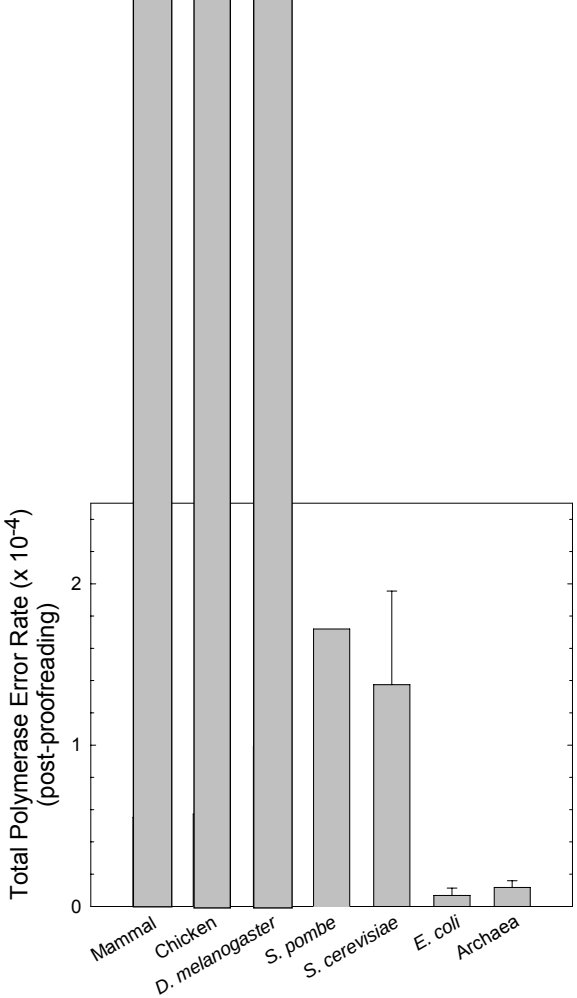
2) Polymerase proofreading:

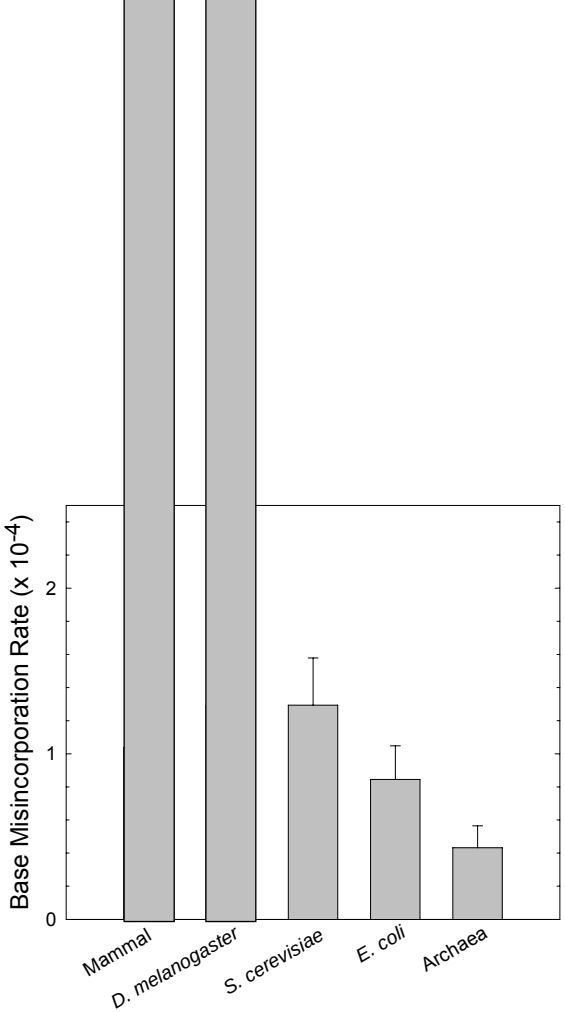


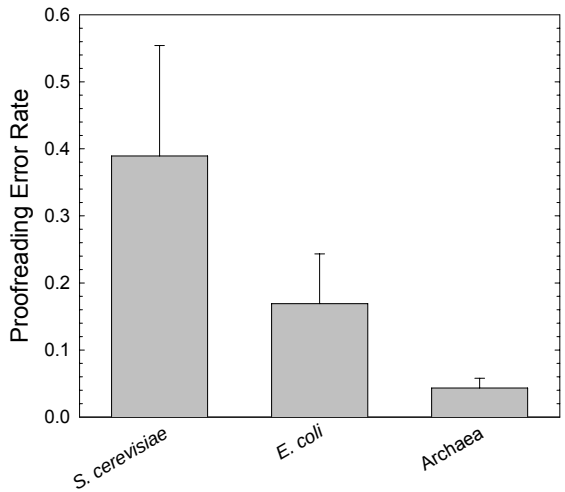
3) Post-replicative mismatch repair:



Lynch, 2008, Genetics

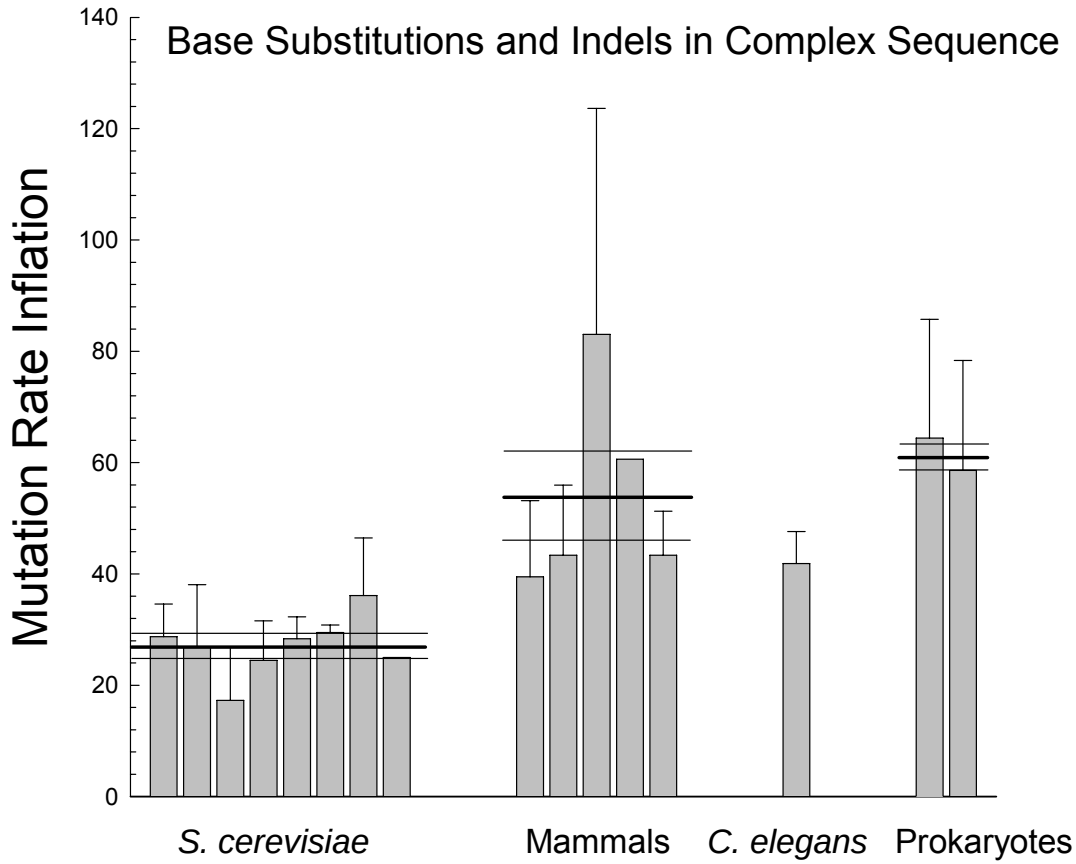






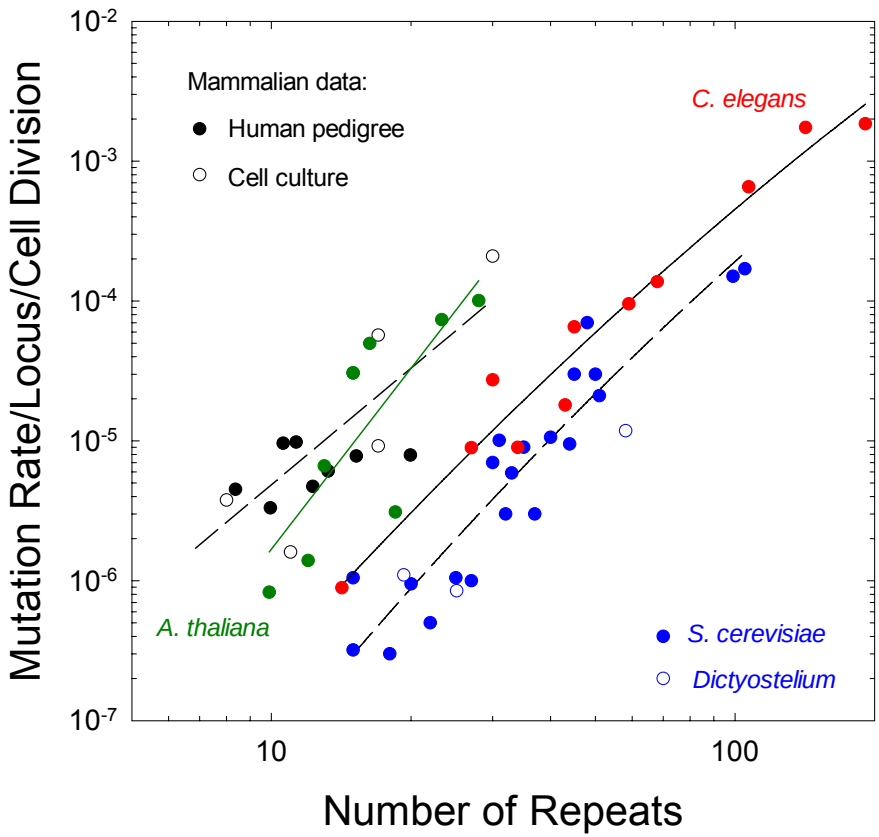
Polymerase Error Rates Are Magnified in Eukaryotes

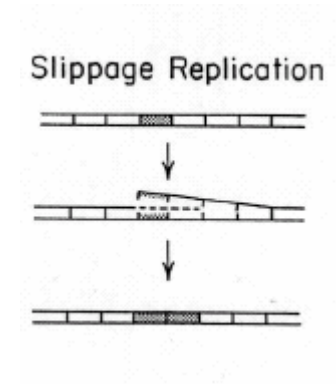
Mismatch Repair Efficiency is Reduced in Eukaryotes

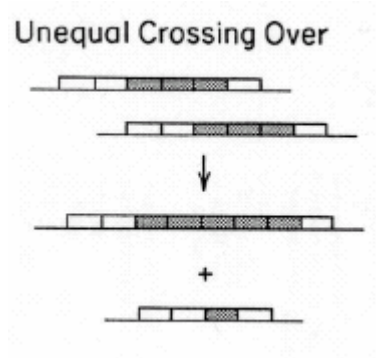


Lynch, 2008, Genetics

Microsatellite mutation rates in unicellular eukaryotes, *C. elegans*, and mammals / land plants scale 1 : 5 : 70 on a per-cell-division basis.







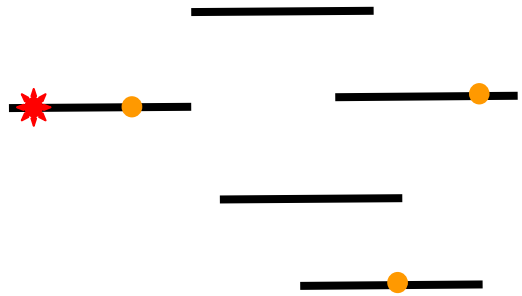
Seyfert et al., 2008, Genetics

The induced selection coefficient on a mutator allele from linked and unlinked mutations

≅ the excess genomic mutation rate to deleterious alleles
x the average deleterious effect of a heterozygous mutation
x 2 generations of association.

For multicellular species:

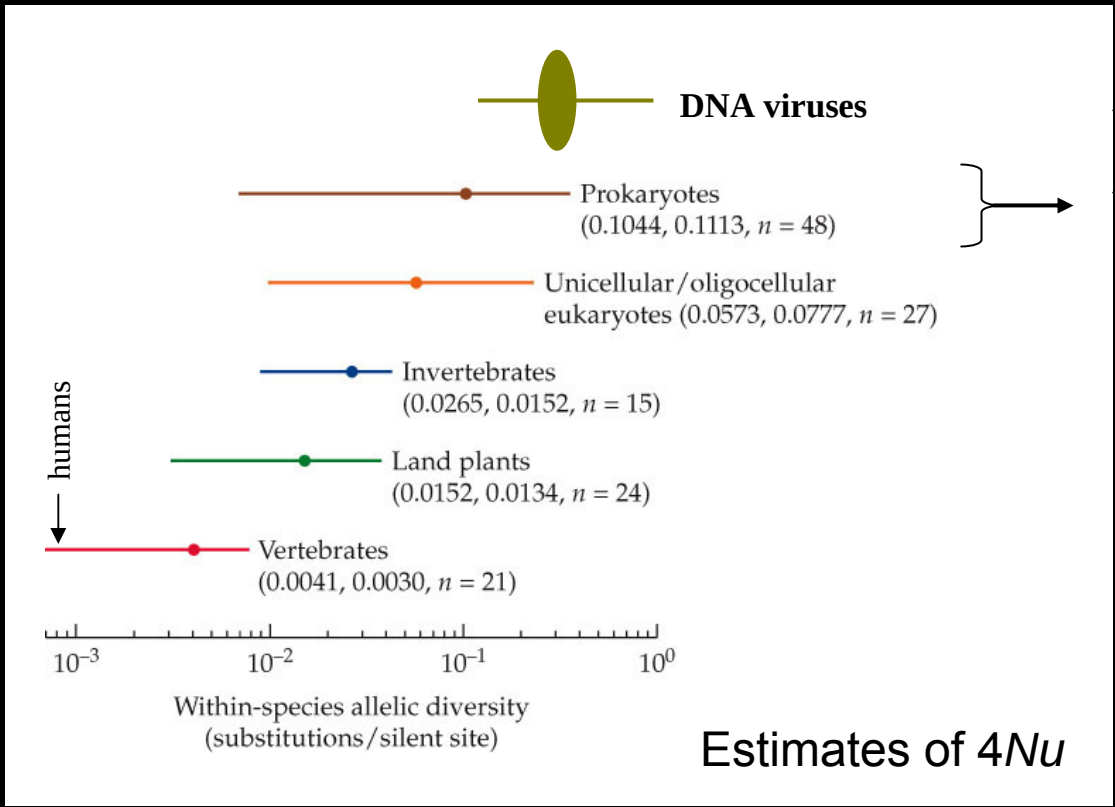
- the heterozygous effect of a deleterious mutation ≅ 0.01;
- the genomic mutation rate to deleterious alleles ≅ 1.0;
- small modifications to the mutation rate will be << 10^{-4};
- the selective disadvantage of a weak mutator allele will often be < 10^{-6}.



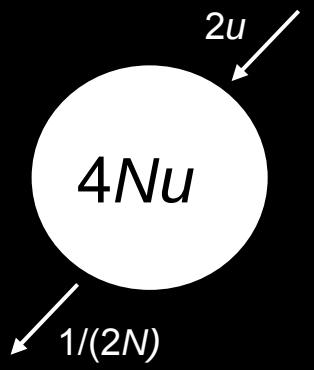
Transient Effects
of Induced Mutations

- Weak mutator alleles are subject to accumulation by random genetic drift.

Estimates of the ratio of the power of mutation ($2u$) to the power of random genetic drift ($1/2N$) obtained from standing population-level nucleotide heterozygosity at silent sites.



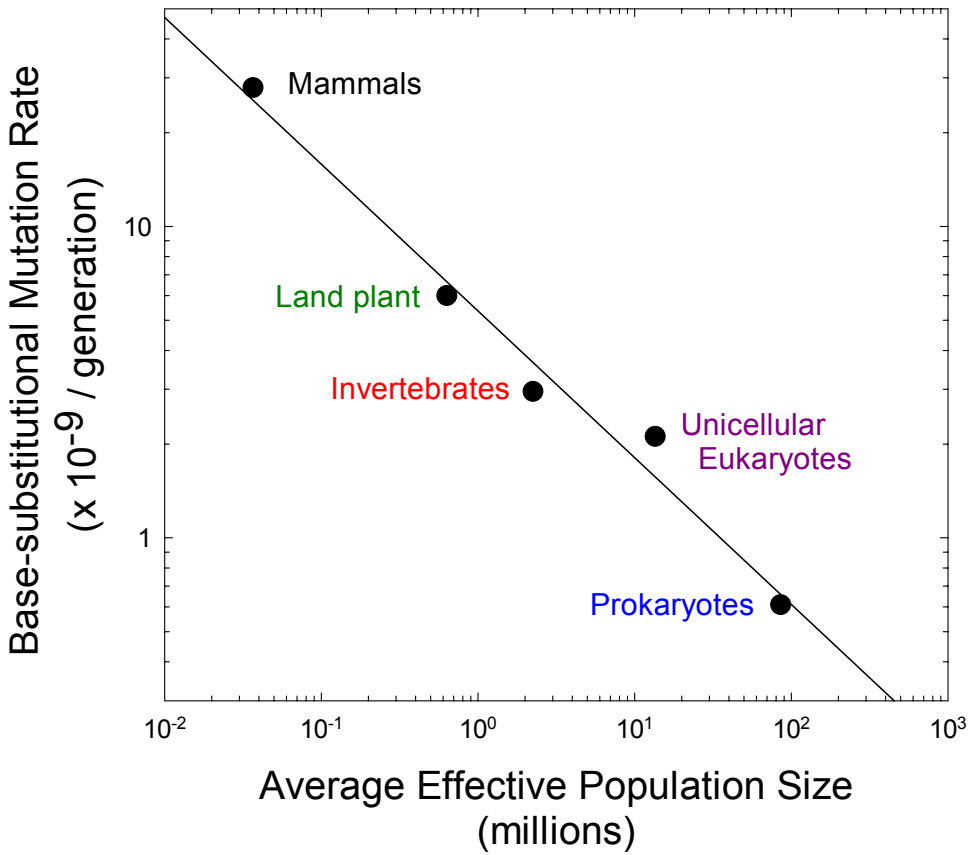
Estimates of $4Nu$



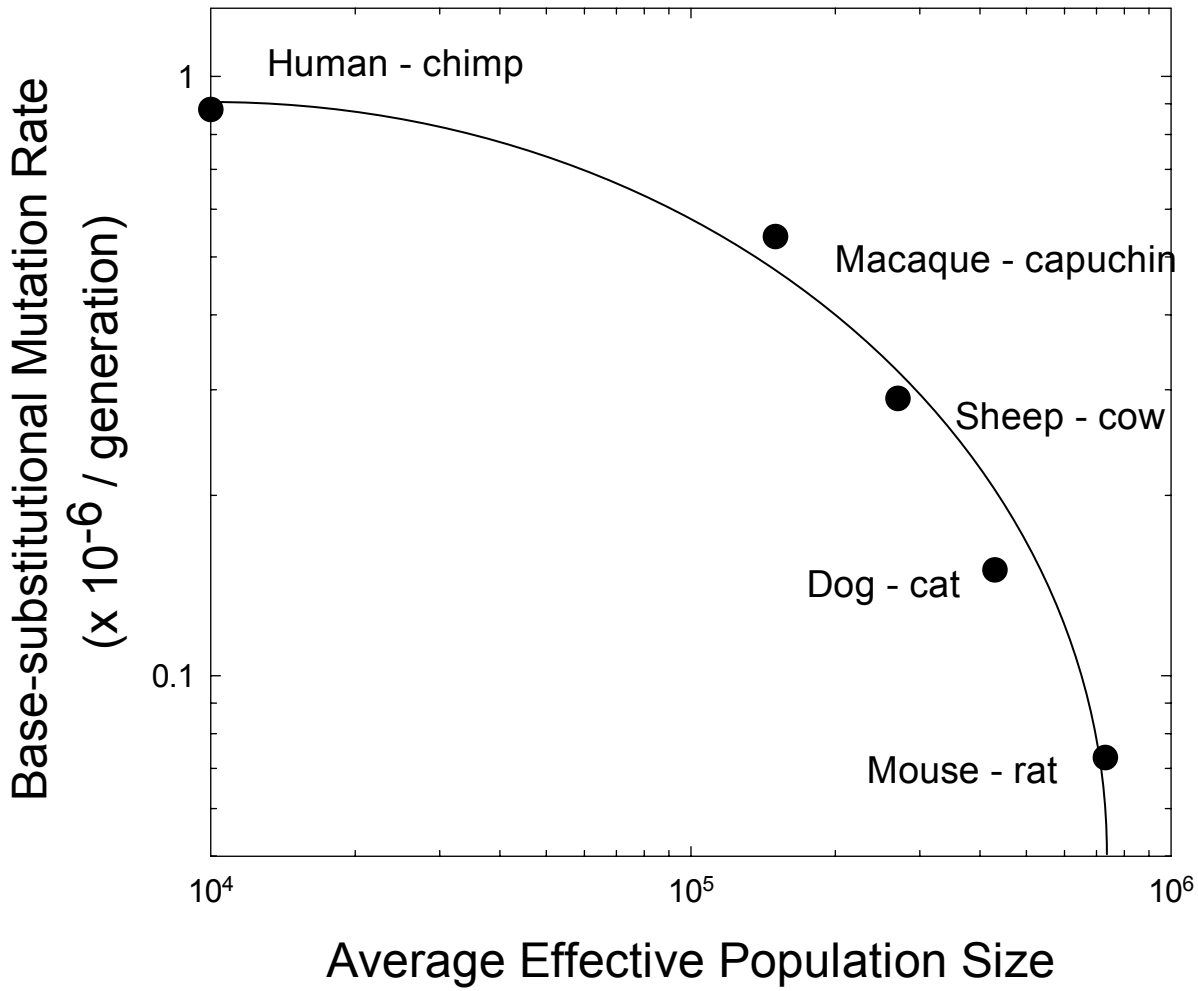
At equilibrium, average allelic divergence at neutral sites =

ratio of the power of mutation to the power of random genetic drift.

The Per-generation Mutation Rate Increases With the Power of Random Genetic Drift



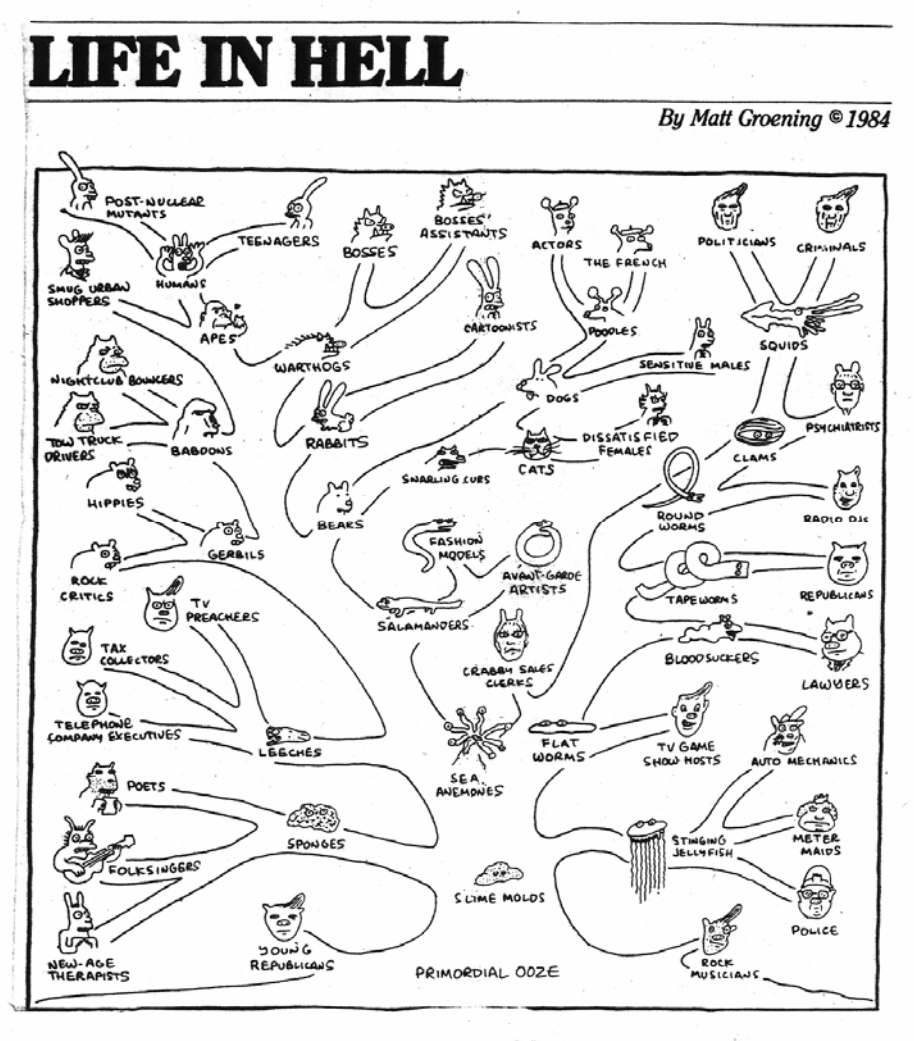
Mitochondrial Mutation Rates



From: Piganeau and Eyre-Walker. 2009. PLoS ONE 4: e4396.

Myth. Natural selection promotes the evolution of organismal complexity.

Reality. There is no evidence at any level of biological organization that natural selection encourages complexity. In contrast, substantial evidence exists that a reduction in the efficiency of selection promotes the evolution of genomic complexity.



Myth. Natural selection promotes the evolution of organismal complexity.

Reality. Larger organisms with more complex morphologies have higher historical extinction rates.

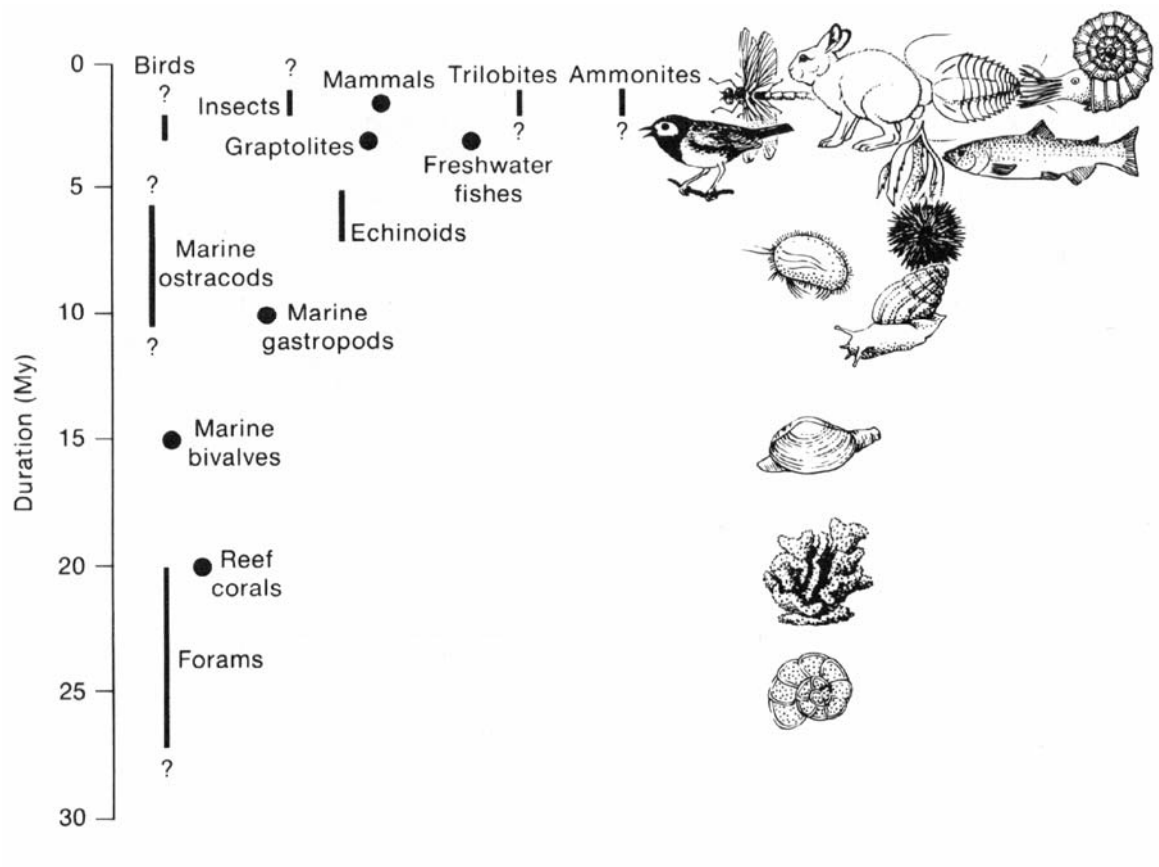
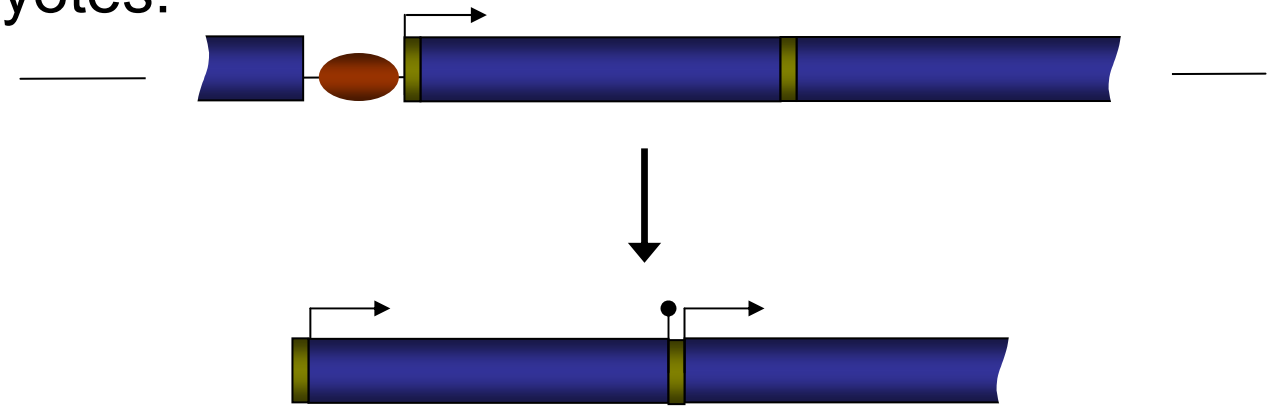


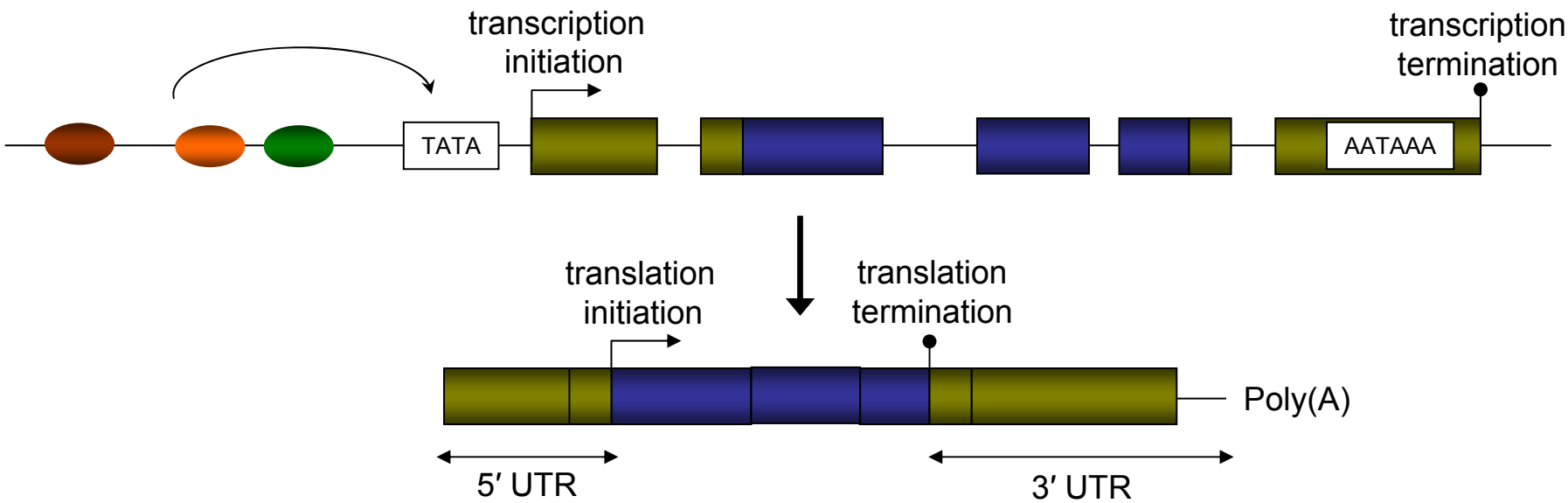
FIGURE 9-2
Hierarchy of average species durations estimated for major taxa.

From: Stanley (1985).

Prokaryotes:



Eukaryotes:



The Mutational Cost of Genomic Embellishments

- **The selective disadvantage of a mutational hazard** – alleles with increased structural complexity involving *n* key nucleotide sites have elevated mutation rates to defective alleles (*nu*),where *u* = mutation rate per nucleotide site.

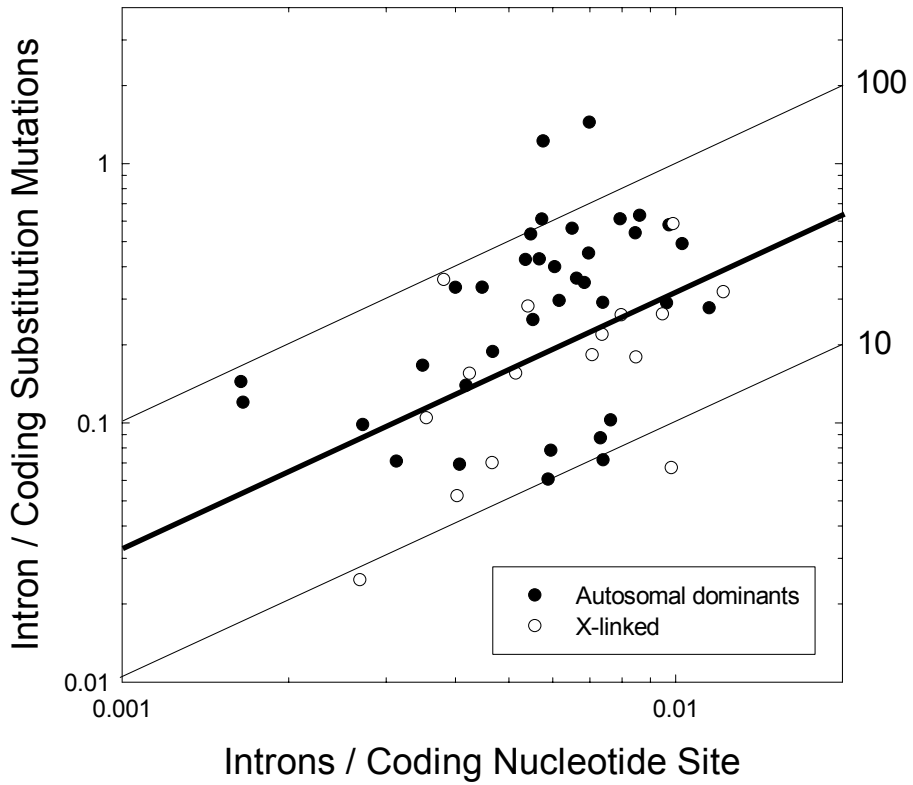
n ≈ 30 for introns

10 for transcription factor binding sites

4 for 5′ UTRs

?? nonfunctional DNA

The Cost of an Intron – equivalent to adding 10 to 100 nucleotides to a gene.



Results from large sequencing surveys of defective alleles for monogenic human genetic disorders.

• About 8% of human deaths are caused by introns – exceeds the total from accidents and war.

Lynch, 2010, PNAS

The Passive Emergence of Gene Structural Complexity by Nonadaptive Mechanisms

- **The power of random genetic drift** – the effective number of gene copies per locus in a species (N) dictates the efficiency of natural selection – the power of random drift ~$1/N$.

- If $nu << 1/N$, a mutationally harmful embellishment can establish by drift.

  If $nu >> 1/N$, emergence of the embellishment is inhibited by selection.

A key determinant in genomic evolution is the ratio of these opposing forces:

$$nu / (1/N) = Nu \cdot n$$

Nu ← Estimated from molecular biology

n ← Estimated from population surveys

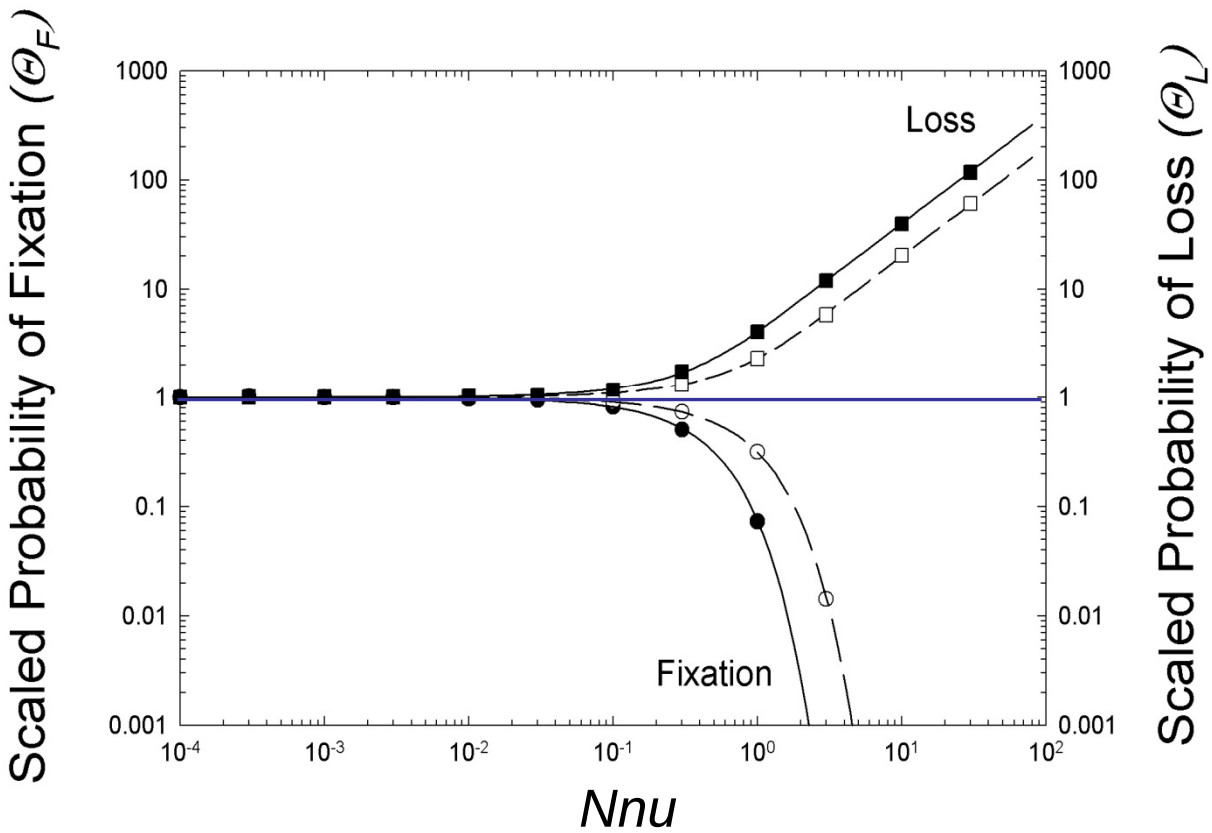
The probability of fixation of a mutationally harmful gene-structural embellishment declines with increasing population size.

Probability of intron fixation = $2s / (e^{4Ns} - 1)$
Probability of intron loss = $2s / (1 - e^{-4Ns})$

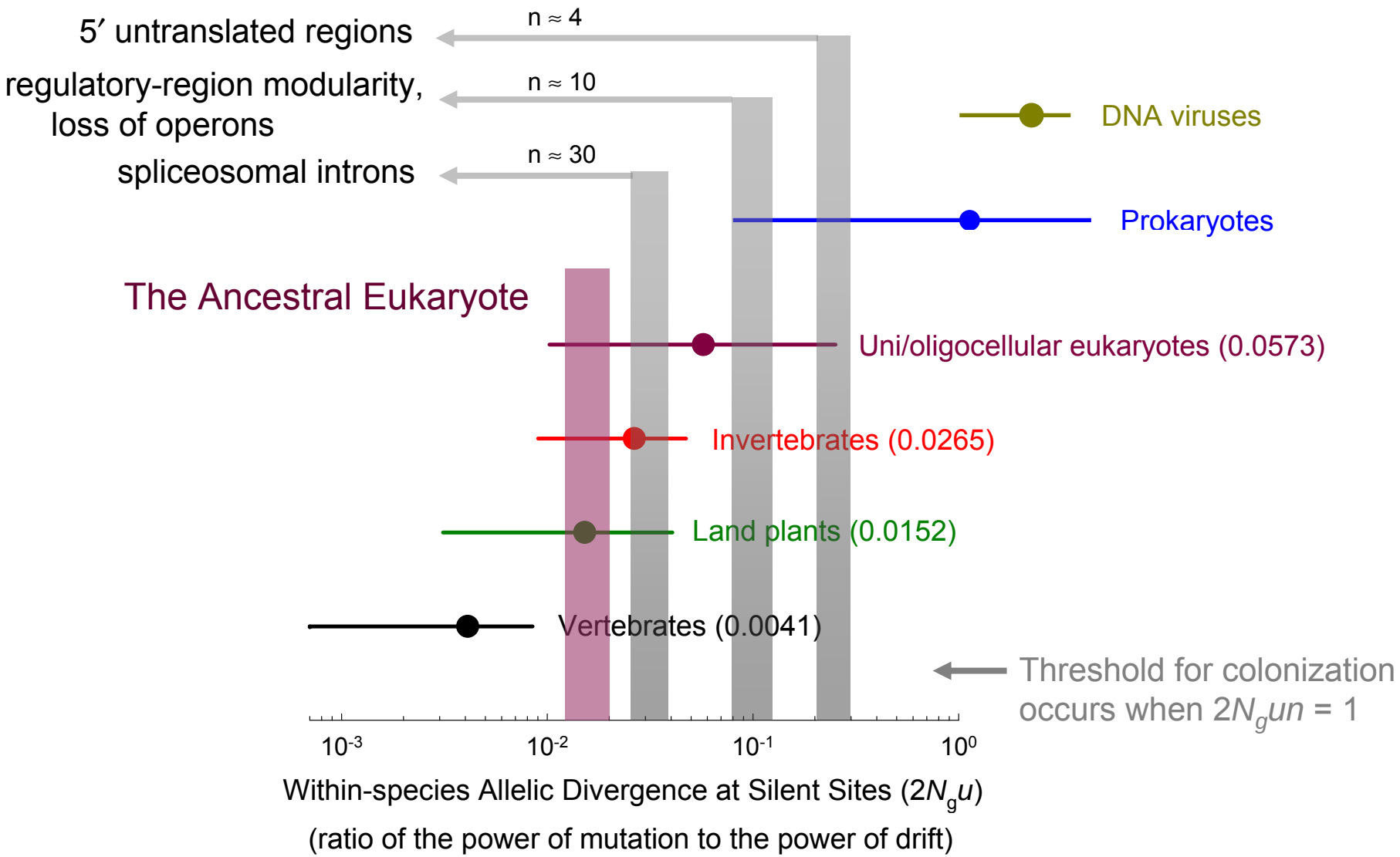
s = *nu* = excess mutation rate to defective alleles

Effective Neutrality:

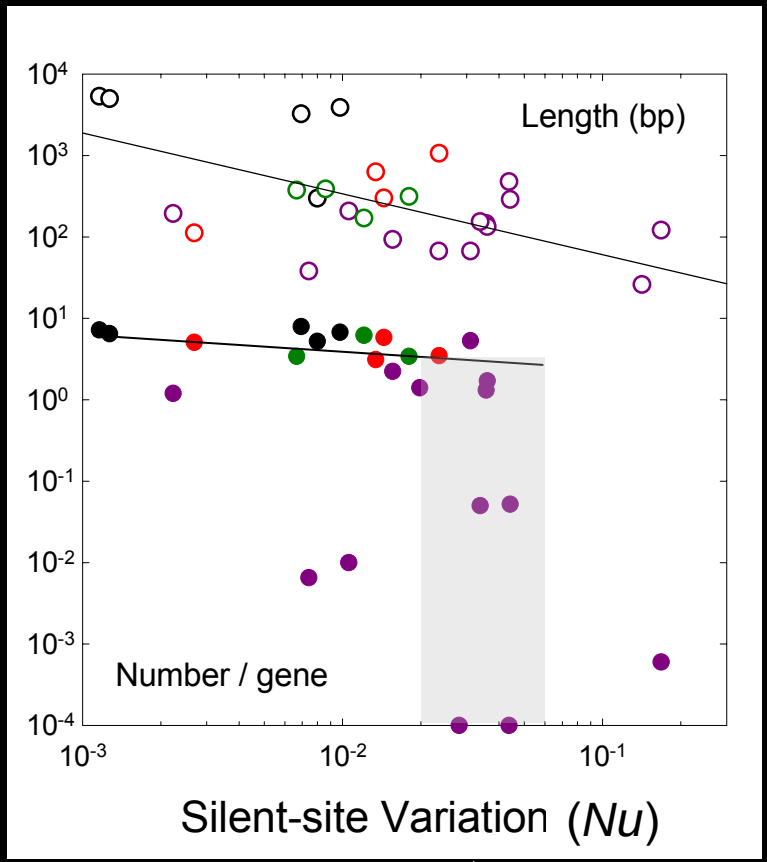
Probability = 1/(2*N*) →



- **The population-genetic environment of multicellular species provides a setting that is conducive to the evolution of gene features that magnify the mutation rate to defective alleles.**



Threshold Population Size for Intron Colonization

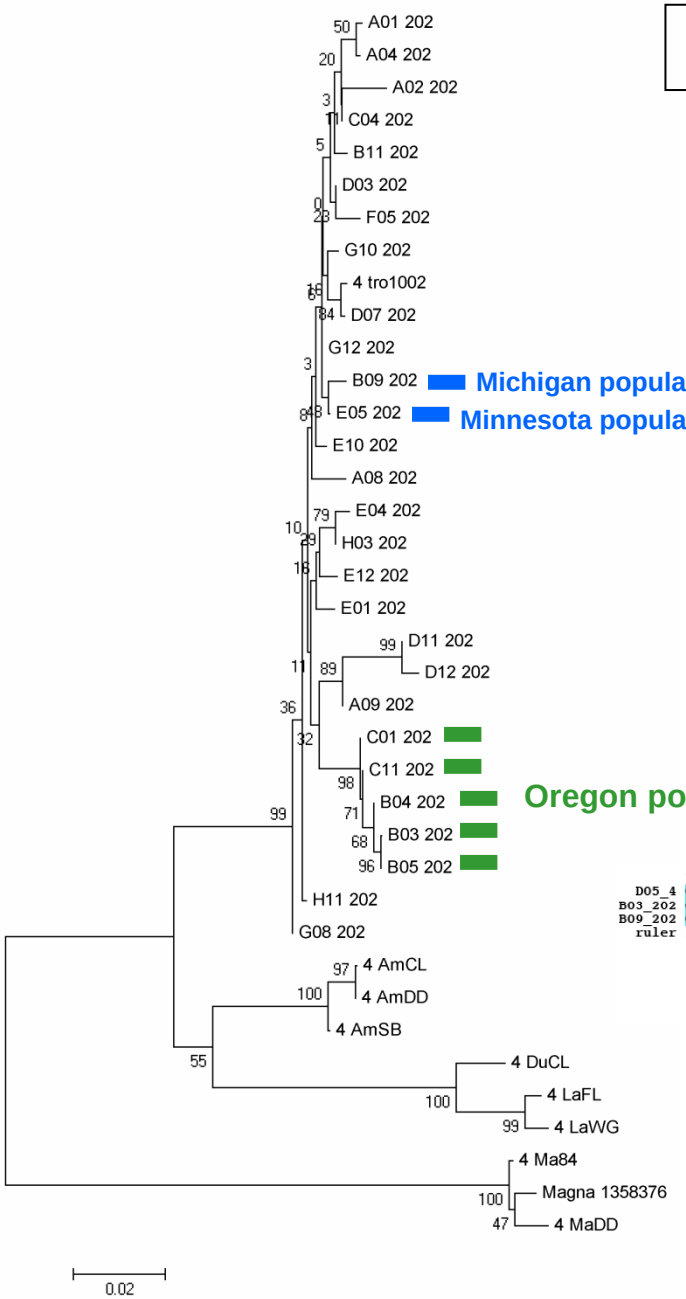


Intron size decreases with population size.

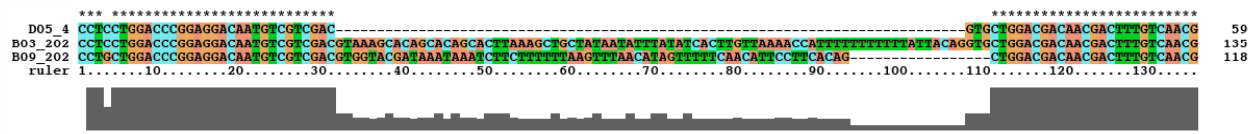
Intron number per gene approaches an asymptotic limit (~*B/D*) at small *N*.

Threshold *Nu* ≈ 0.03 ⟶ Theory predicts 1/*n* ≈ 1/30

Intron gain/loss in *Daphnia pulex*



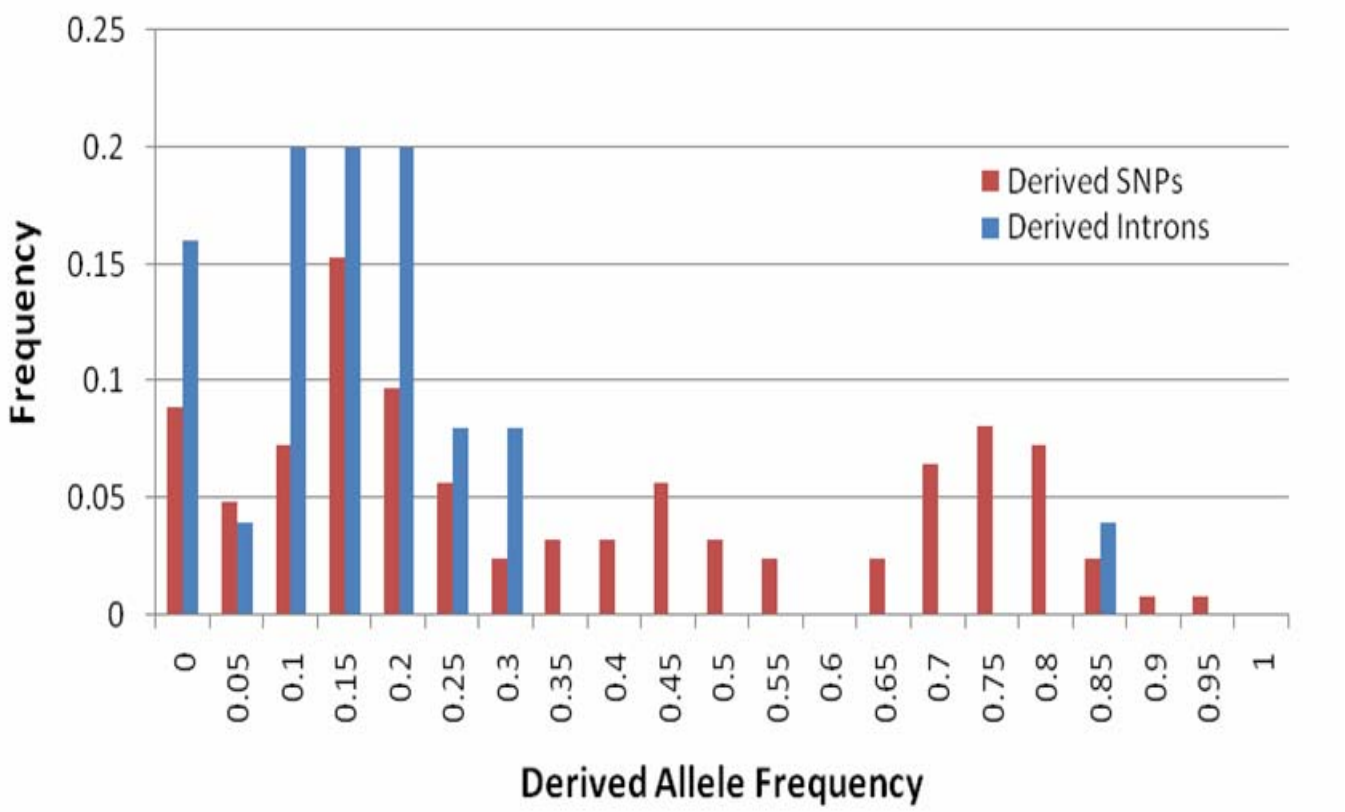
- 23 cases of intron gain.
- Five cases of parallel gains at the same site.
- Three cases of intron loss.
- Most of the newly gained introns are in a set of isolated Oregon populations that have been through a prolonged population bottleneck.



Bootstrap tree of a locus showing two newly gained introns at nearly identical sites.

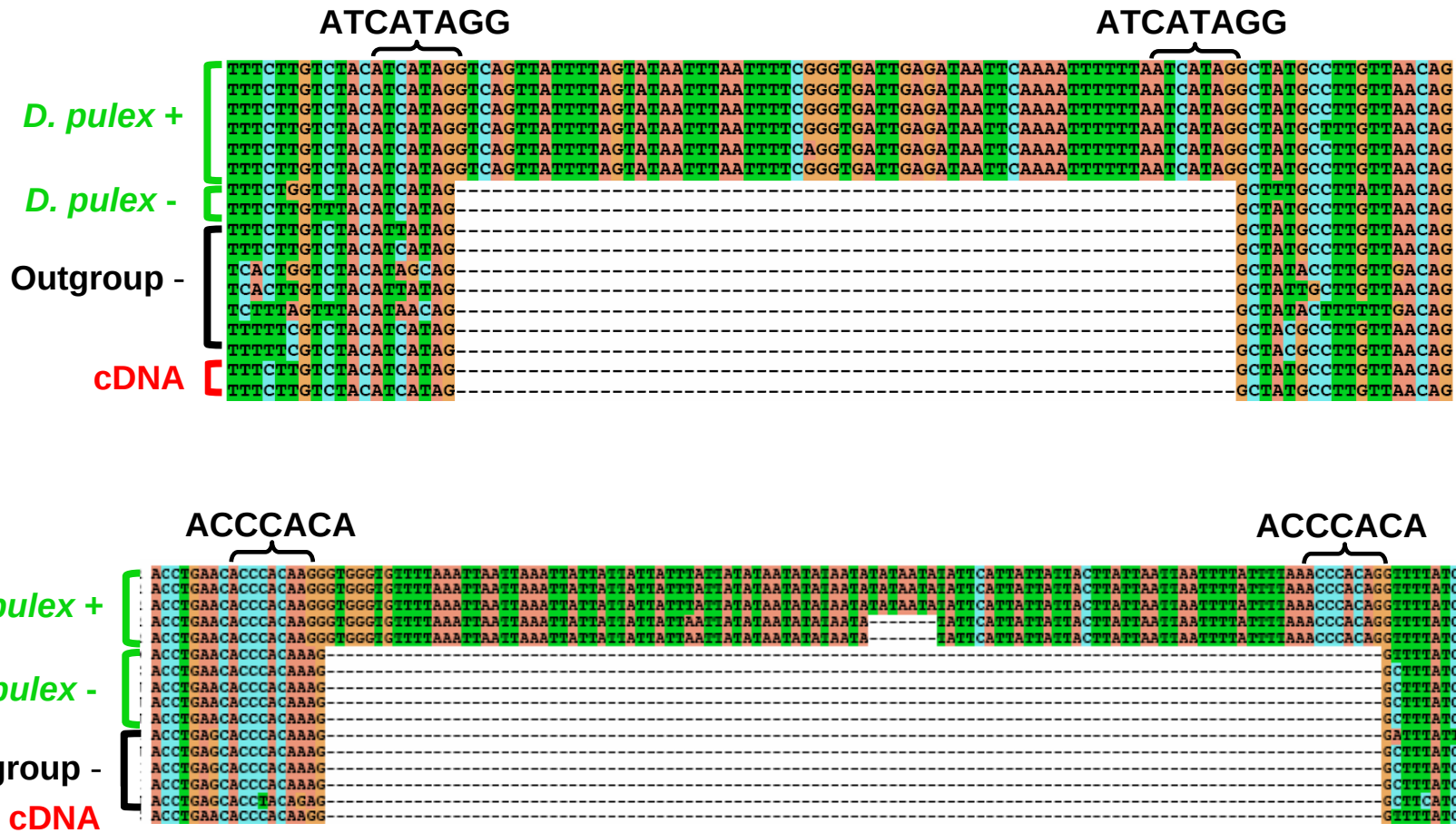
Li et al., 2009, Science

Intron-gain Alleles Are Weakly Deleterious



Li et al., 2009, Science

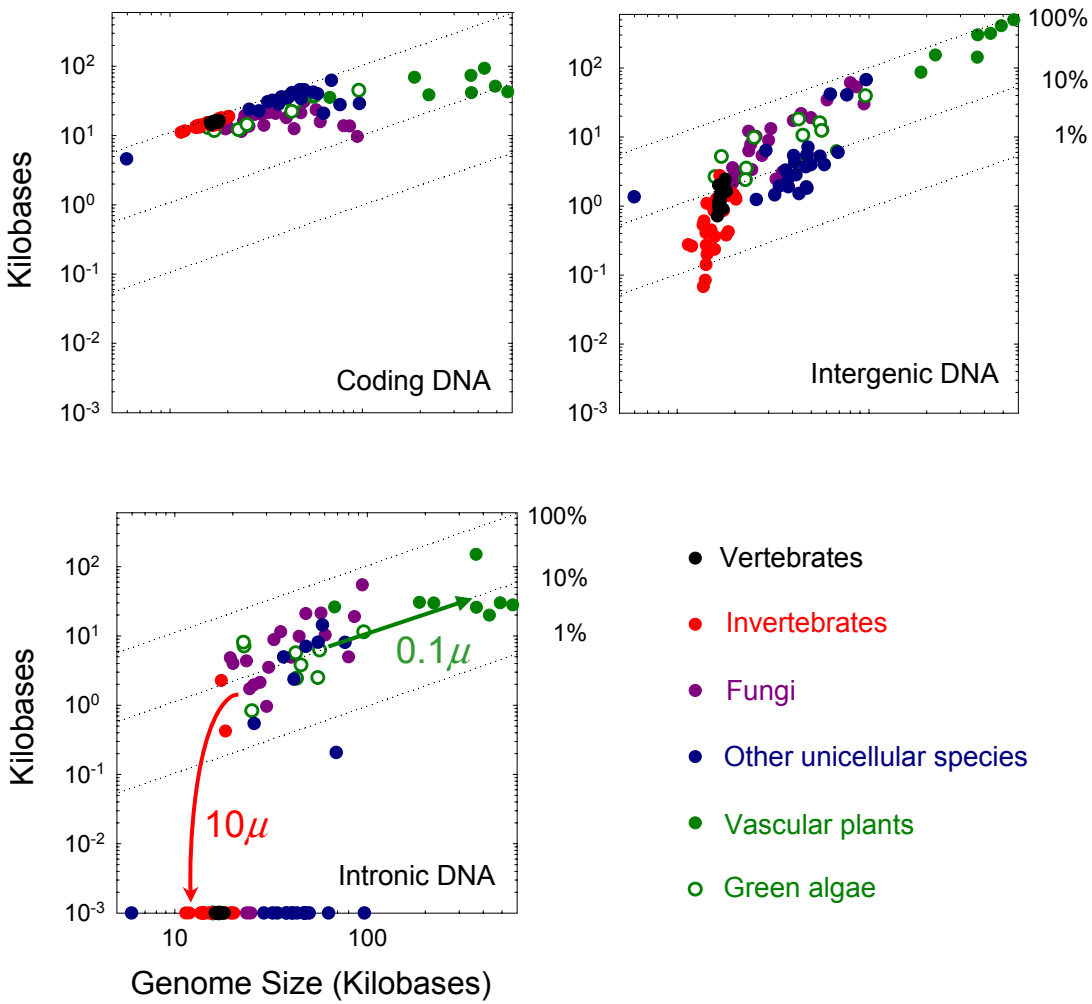
A Staggered Double-strand Break Model for Intron Origin



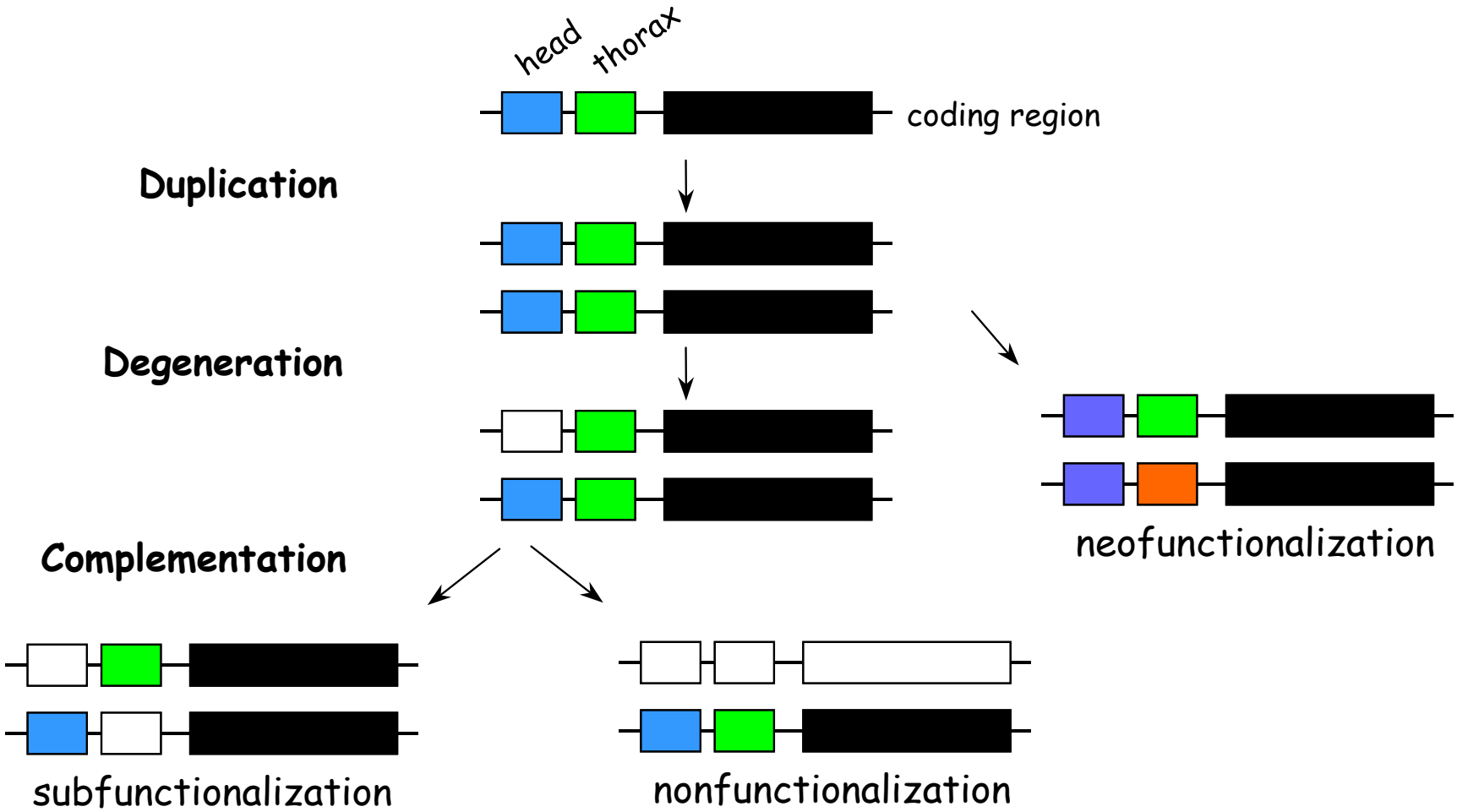
- 57% of the newly gained introns have short repeats.
- These short repeats are 5 to 22 bp long.
- Each intron gain has a unique repeat.

Li et al., 2009, Science

Scaling of Genome Size in the Mitochondrion



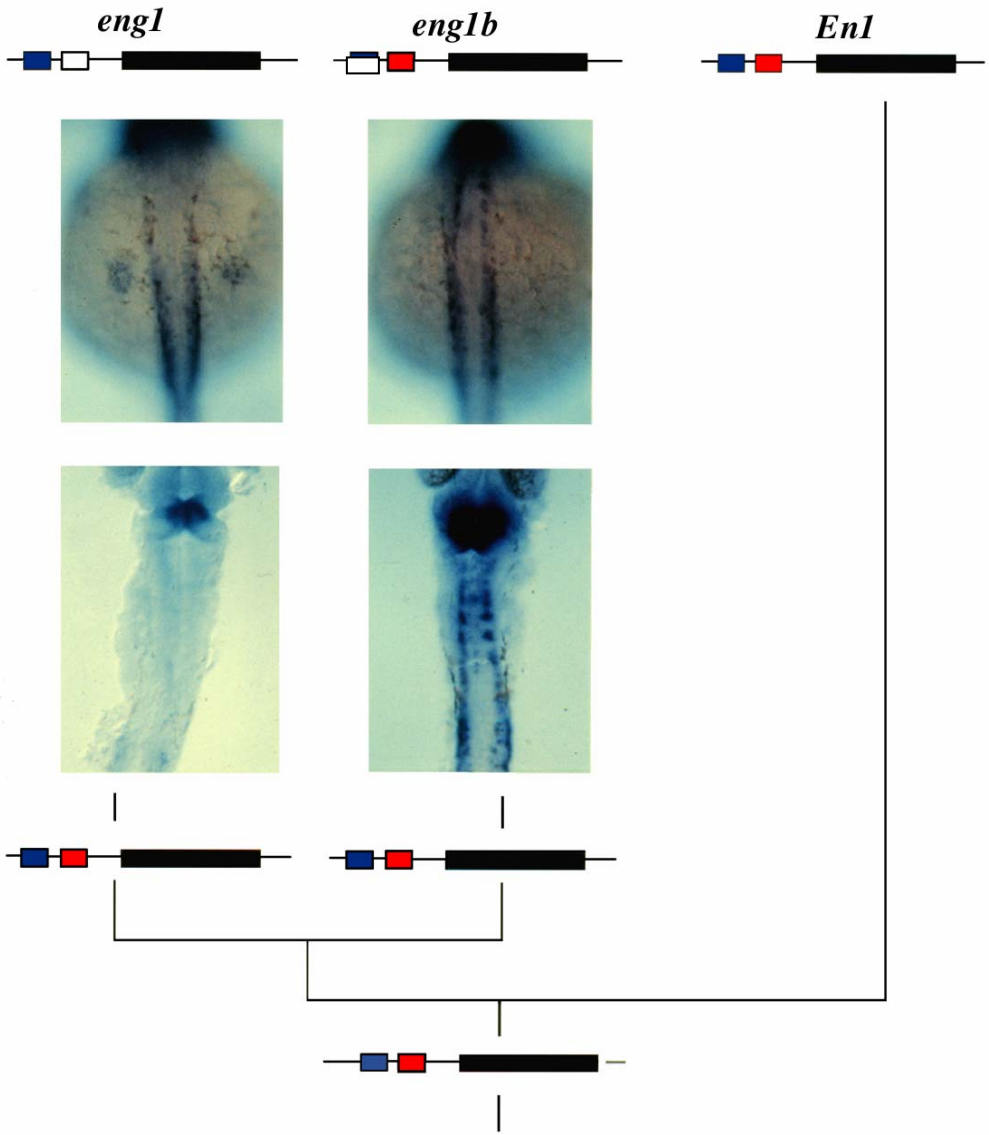
The DDC Model



Subfunctionalization of Modularized Duplicate Genes Can Eliminate Pleiotropic Constraints, Opening Up Novel Evolutionary Pathways

Duplicate *engrailed* genes in zebrafish

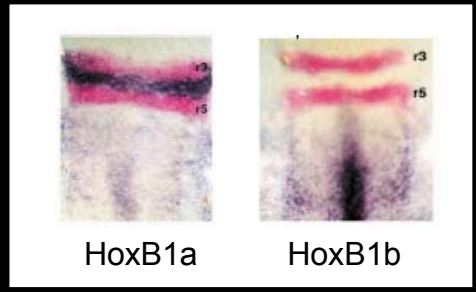
Single copy in tetrapods



Subfunctionalization is a Common Fate of Duplicate Genes in Animals and Land Plants

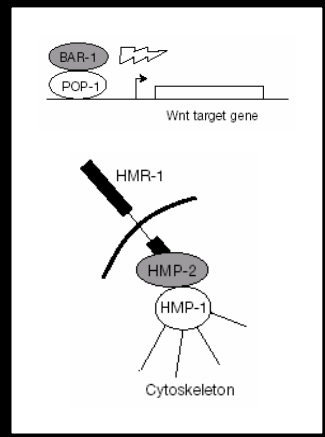
Complementary loss of regulatory elements:

Partitioned expression of HoXB1 duplicates in zebrafish embryo hindbrains recapitulates the expression pattern of the single gene in mouse embryos (McClintock et al. 2002)



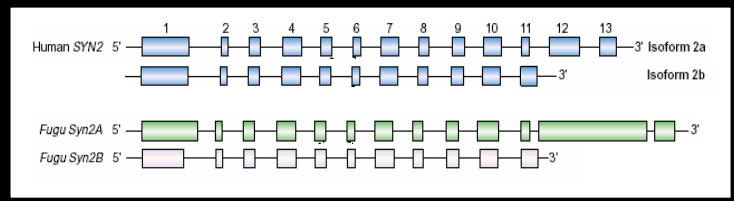
Coding-region modifications:

Duplicated β-catenin genes in *C. elegans* partition cell-signalling and cell-adhesion functions carried out by single gene in flies and vertebrates (Korswagen et al. 2000)



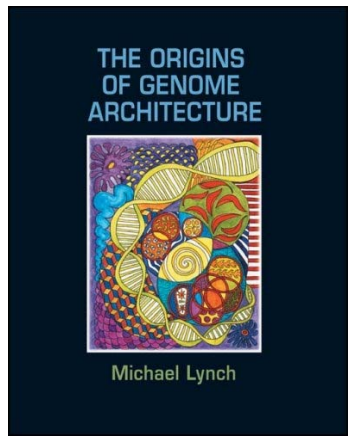
Loss of alternative splice sites:

Duplicated synapsin genes in *Fugu* adopted alternative-splice site variants of single-copy gene in tetrapods (Yu et al. 2003)



The mutational-hazard hypothesis provides a potentially unifying explanation for numerous other, disconnected observations on genomic diversity:

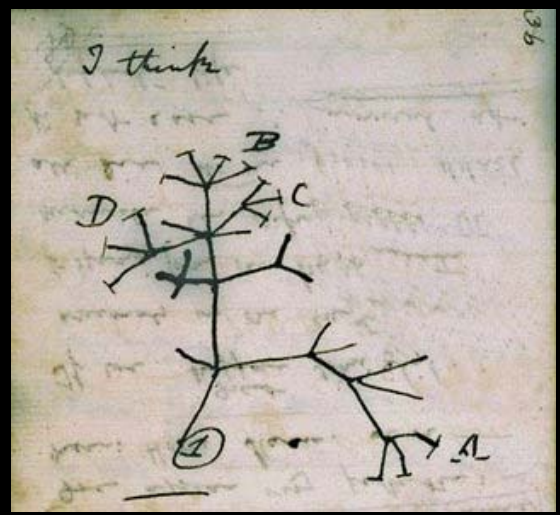
- Entry into the DNA world.
- Gene number – preservation of duplicate genes by subfunctionalization.
- Degradation of sex chromosomes.
- Restriction of sex chromosomes to multicellular species.
- Emergence of mRNA editing in land-plant organelles.
- Emergence of modular regulatory region complexity and network architecture.
- Differential proliferation of mobile genetic elements.



Genome Complexity and Organismal Complexity

- The population-genetic environment of multicellular species provides a setting that is conducive to the evolution of gene and genomic features that are essentially unattainable in unicellular species.

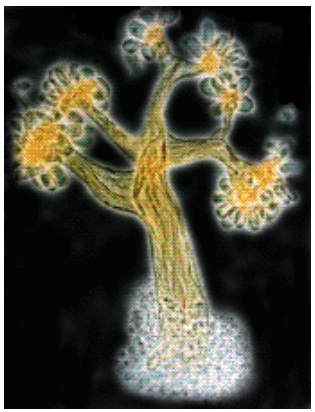
- The *nonadaptive* forces that initially allowed the establishment of new and reliable forms of genomic resources in multicellular species provided the substrate for natural selection to grow organismal complexity in novel ways.



C. Darwin, 1832

No statistical grounds for an association between multicellularity and eukaryotes

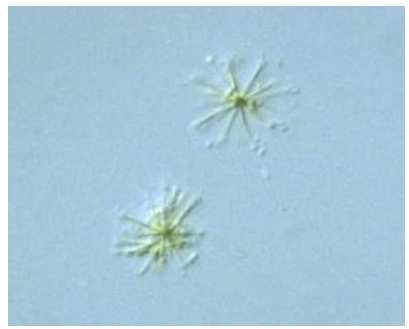
- oligocellularity has evolved many times in eukaryotes and prokaryotes.
- mega-multicellularity has evolved just twice (maybe three times).



Myxobacteria

Merismopedia

Anabaena



Planctomyces

Can the mutational-hazard theory be extended to understand the evolution of cellular features?

Some general questions:

1) Did the nuclear envelope evolve as a mechanism to isolate prespliced mRNAs from the ribosome, or vice versa (the presence of a nuclear membrane provided a physical barrier conducive to intron colonization)?

2) Did nonsense-mediated decay evolve as a means for dealing with erroneous transcripts?

3) What are the conditions that foster the origin and coordinated evolution of complex heterodimeric molecules – intrinsic adaptive advantage or necessity promoted by the growing incapacities of individual proteins?

4) Does increased internal cell structure promote the evolution of complex assemblages of proteins by providing an enriched environment for concentrated protein-protein interactions (necessary for coevolution)?

Nothing in evolution makes sense except
in the light of population genetics.

Gene Duplication:

John Conery
Allan Force
Vaishali Katju
Casey McGrath
Martin O'Hely
Bruce Walsh

UTRs:

Xin Hong
Doug Scofield

Modularity:

Allan Force

Endocytobionts:

Tom Doak

Introns and Intervening Excised Sequences:

Francesco Catania
Jim Forney
Xiang Gao
Xin Hong
Avinash Kewalramani
Wenli Li
Aaron Richardson
Doug Scofield
Abe Tucker

Organelles:

Britt Koskella
Sarah Schaack

Mobile elements:

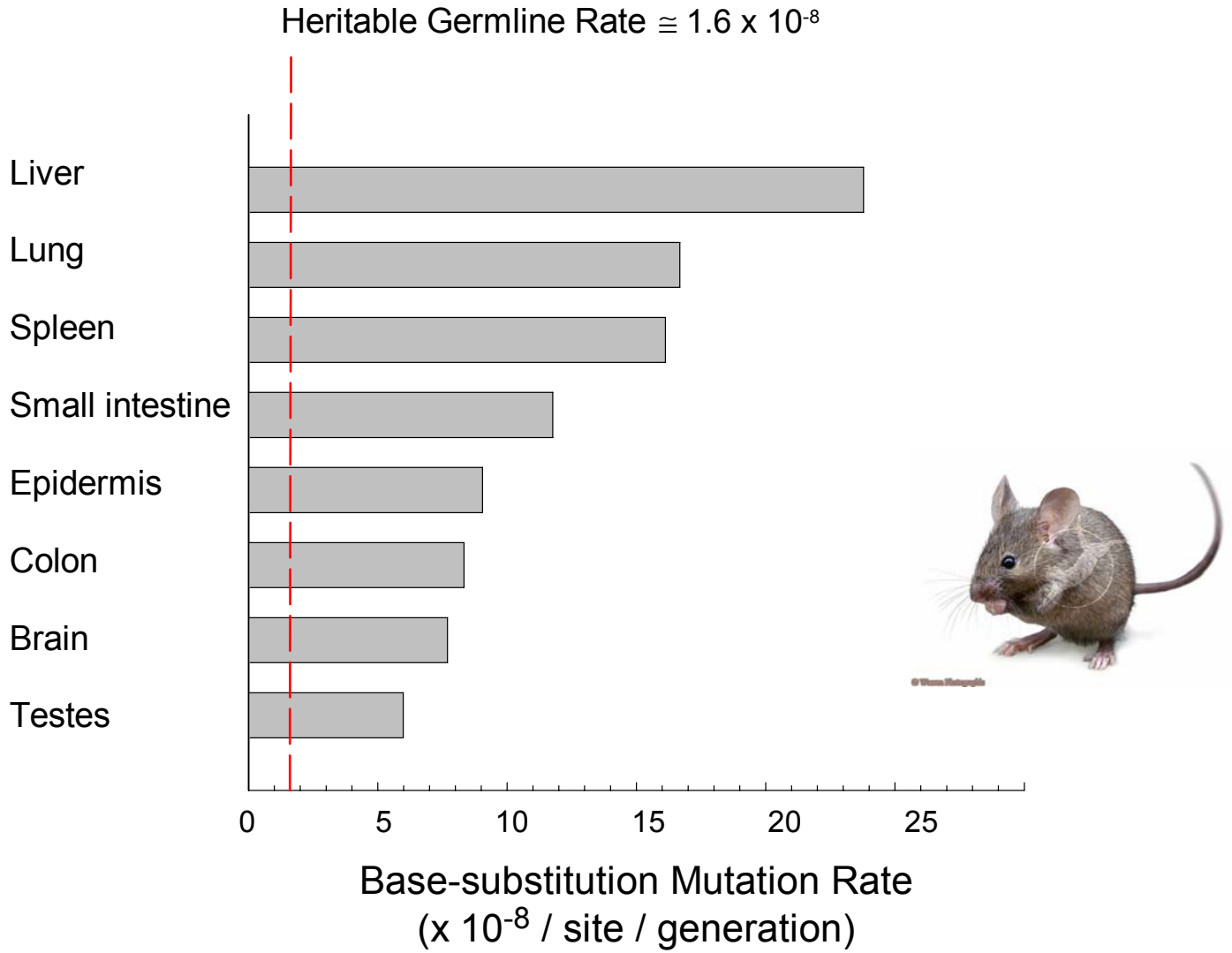
Xiang Gao
Mina Rho
Sarah Schaack
Haixu Tang

The Indirect Consequences of Eukaryogenesis and Multicellularity for Genome Evolution

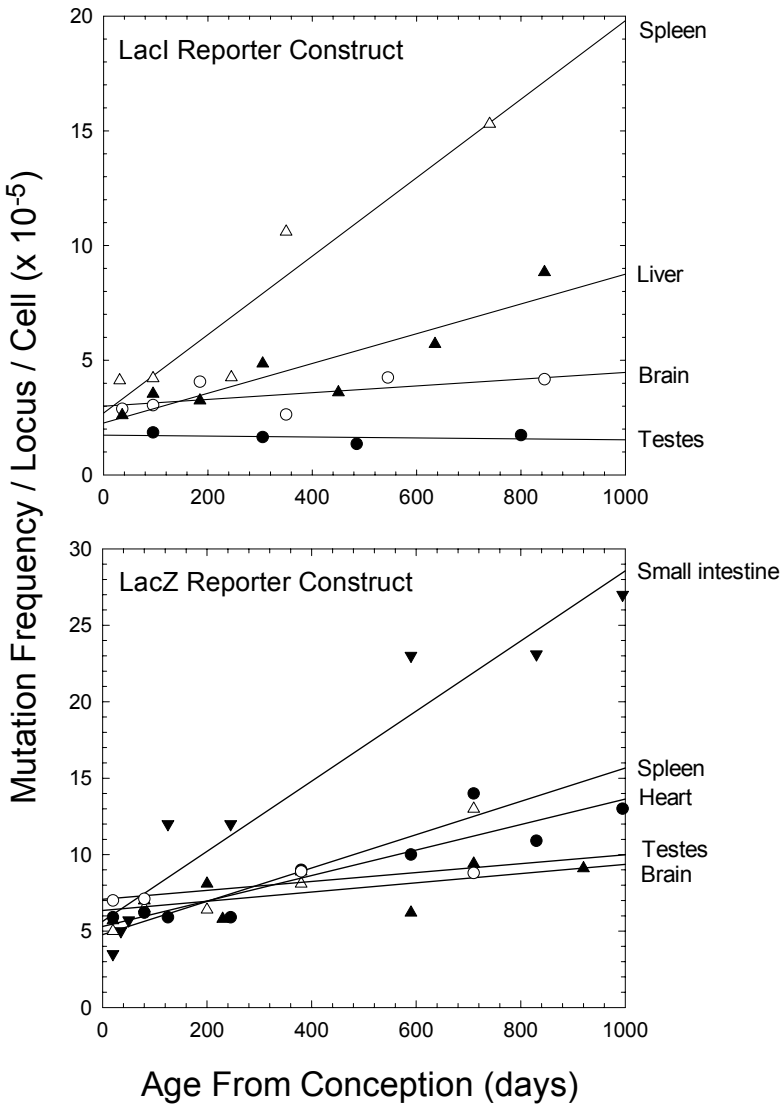
Relatively low population sizes and recombination rates diminish the efficiency of selection against mildly deleterious genomic modifications, leading to:

- A reduction in the efficiency of the DNA-replication machinery.
- An accumulation of genomic and gene-structural changes that further magnify the susceptibility of alleles to degenerative mutation.
- An enhanced vulnerability to somatic genetic disorders.

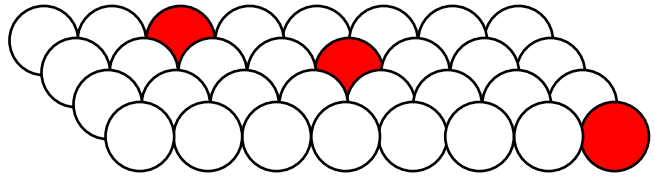
Mutation Rates in Somatic Tissues Are Up to 15x Those in the Germline

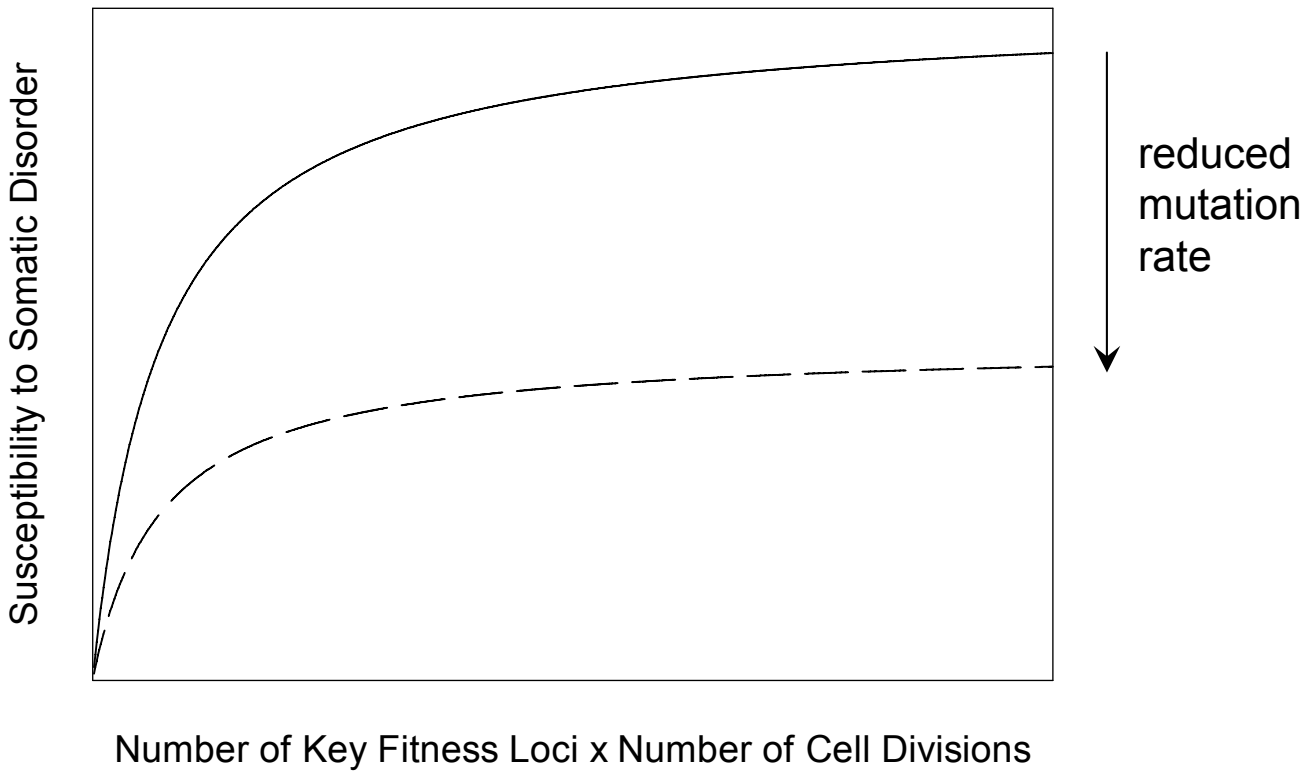


Somatic Mutations Accumulate With Age, But Only Weakly in the Germline

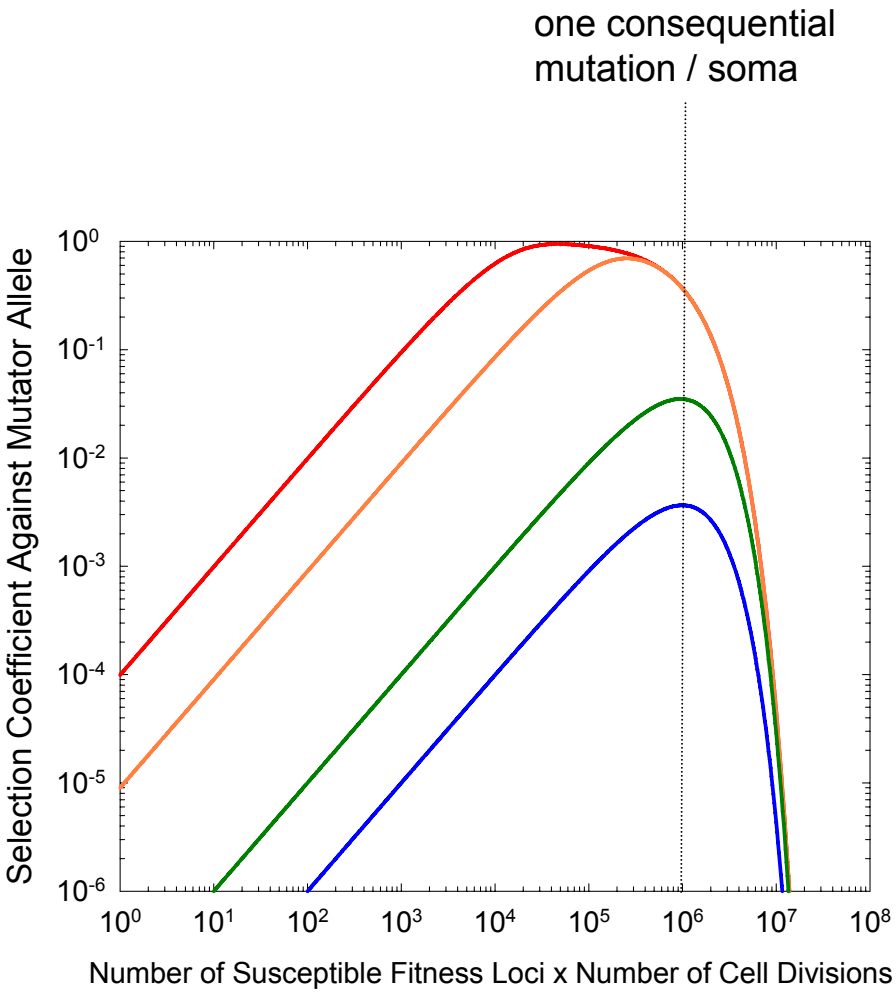


Multicellularity indirectly imposes selection pressure for a reduced mutation rate.





Although the absolute magnitude of somatic mutation increases with the level of multicellularity, the relative selective disadvantage of a mutator allele decreases above a critical number of cell divisions.



MM = nonmutator

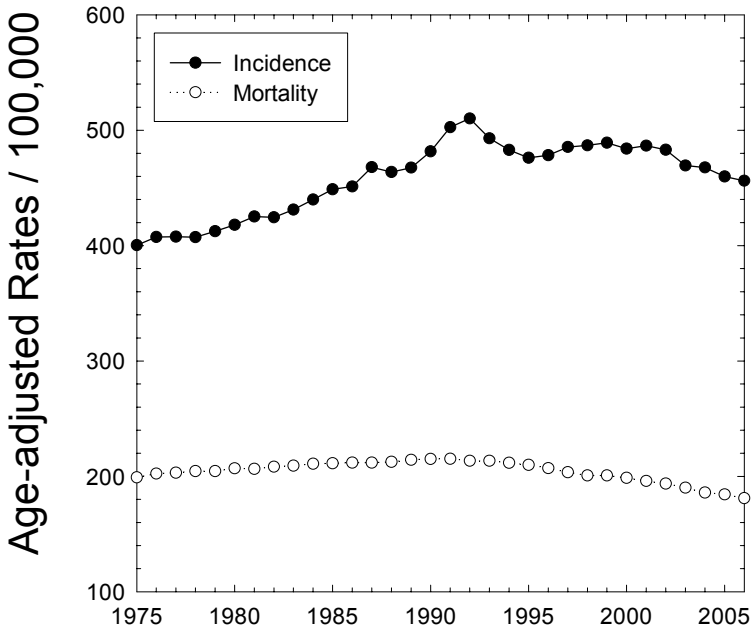
Mm = mutator heterozygote

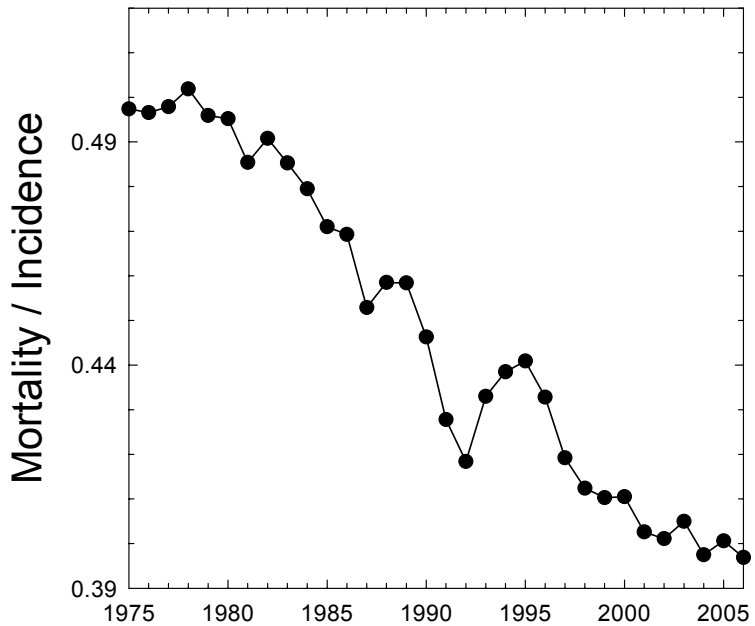
Mutation rates:

$u_{MM} = 10^{-6}$ / allele / cell division

- $u_{Mm} = 100u_{MM}$
- $u_{Mm} = 10u_{MM}$
- $u_{Mm} = 1.1u_{MM}$
- $u_{Mm} = 1.01u_{MM}$

All Cancers in the US Population





National Cancer Institute, Statistics Review, 2009

The Paradox of Universal Health Care / Personalized Medicine

- The human imperative is to magnify the probability of survival and reproduction regardless of the level of genetic affliction.

- At least one to two deleterious mutations arise per human genome per generation.

- The average deleterious effect of such mutations is very mild, ~1 to 2.5% per event.

- With a complete relaxation of selection, the decline in fitness per generation is 1 to 5% per generation, or 3 to 15% per century.

- The rate of decline in human fitness is operating on a time scale comparable to global warming.