Sex and Death

Major Issues in the Evolution of Meiosis

- Unique to eukaryotes, the establishment of meiosis required a minimum of two to four cytological changes.

- Meiosis creates variation via independent segregation and the recombinational exchange of sequence among homologous chromosomes, but it remains unclear that this was the driving force for the origin of meiosis.

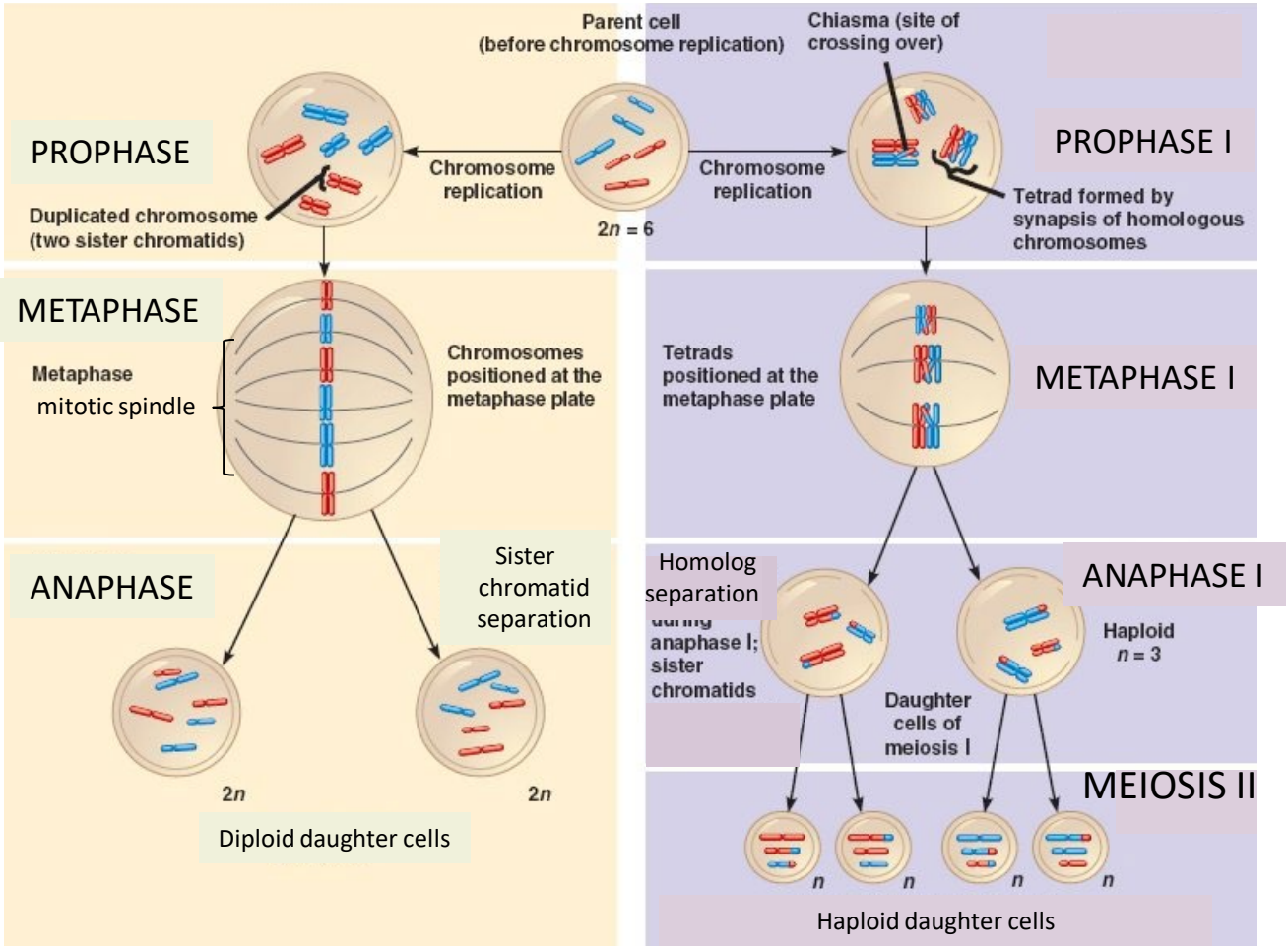
- As with mitosis, much of the machinery of meiosis appears to have arisen by gene duplication in the path from FECA to LECA, and a good deal of phylogenetic diversification of the underlying mechanisms has subsequently developed.

- Many of the proteins associated with meiosis appear to undergo relatively rapid sequence evolution.

- Because meiosis relies on the fusion of two haploid cells, sexual reproduction promoted the evolution of pheromone / receptor-based mating types to enhance the likelihood of mate acquisition.

MITOSIS

MEIOSIS



The Evolution of Meiotic Mechanisms: four novel modifications of steps in mitosis?

Mitotic stage	Result	Meiotic stage	Result
S phase	Chromatid duplication	S phase, I	Chromatid duplication; DNA breaks introduced
Prophase	Chromosome condensation	Prophase, I	Chromosome condensation; *homolog pairing, recombination*
Metaphase	Chromosome alignment in center of spindle body	Metaphase, I	Alignment of homologs in center of spindle body
Anaphase	Centromere splitting; chromatids separated	Anaphase, I	Separation of homologs with independent assortment; *centromere splitting suppressed*
Telophase	Chromatid decondensation; two daughter nuclei with mother-cell ploidy, single-chromatid chromosomes	Telophase, I	Partial or complete chromatid decondensation; two haploid nuclei with replicated chromatids
		Prophase, II	*No S phase*; chromosome condensation
		Metaphase, II	Alignment of replicated chromatids
		Anaphase, II	Centromere splitting; separation of chromatids
		Telophase, II	Chromatid decondensation; four haploid nuclei, single-chromatid chromosomes

← Transient homolog pairing is seen in some mitotically dividing cells.

← Absence of replication in second meiotic division might be regulated in the same way that further replication is prevented in the G2 phase of mitosis.

- Only fully novel features in the evolution of meiosis from mitosis are:

  1) insertion of a stable synapsis; and

  2) suppression of centromere splitting in the first division.

Wilkins and Holliday (2009, Genetics)

Was the Evolution of Meiosis Propelled by Selection for Increased Variation?

- Prokaryotes can recombine as much as eukaryotes.

- Typically, <5% of recombination events are crossovers, and just one crossover per chromosome arm.

- Alternative view: the DNA-repair hypothesis postulates that the selective benefit of meiosis is the **prevention of recombination-generated** damage.

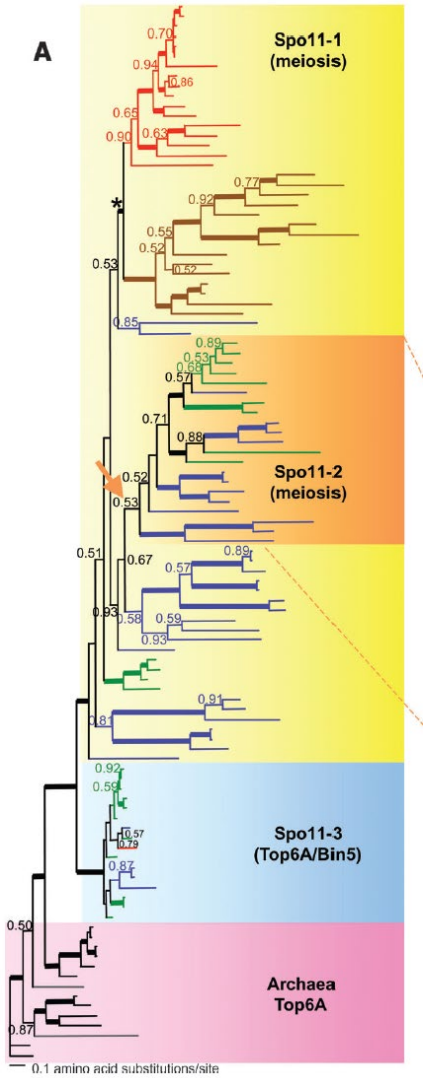
  - Homolog synapsis prevents nonhomologous exchange, mitigating aberrant chromosomes, gene deletions, and aneuploidy.

  - Such pressure must have become increasingly strong as genomes increased in size, especially via the accumulation of mobile elements, which encourage nonhomologous recombination.

  - If correct, meiosis evolved not in response to challenges from the external environment, but from internal cellular limitations.

Protist Homologs of the Meiotic *Spo11* Gene and Topoisomerase VI reveal an Evolutionary History of Gene Duplication and Lineage-Specific Loss

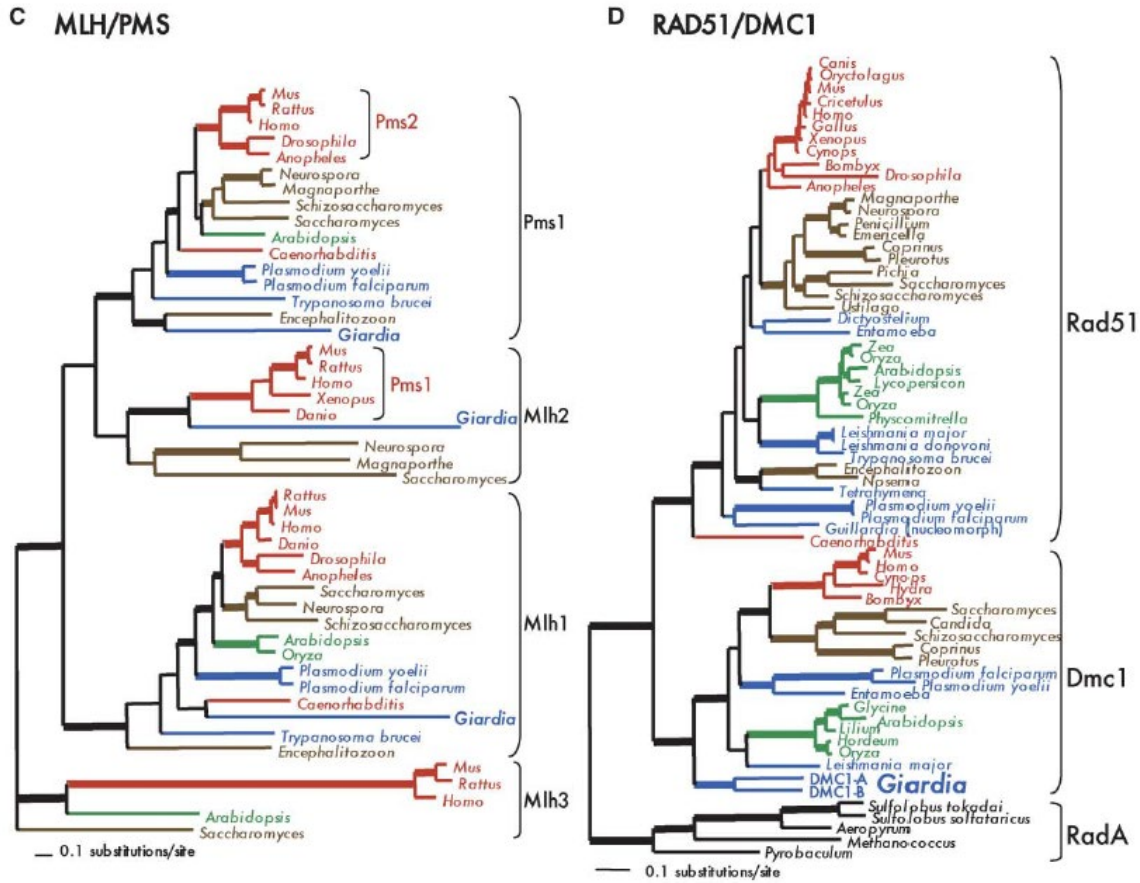
Malik et al. (2007, Mol. Biol. Evol.)



- A meiosis-specific protein that creates double-strand breaks, initiating recombination.
- Orthologous to archaeal topoisomerase VI, a heterotetramer involved in the separation of two chromosomes.
- Three eukaryotic orthologs evolved by gene duplication in the interval between FECA and LECA, although the functional differences are not well-understood.
- Some orthologs have been lost from some lineages.

Many Other Components of the Meiotic Machinery Originated Early (Prior to LECA) and Diversified by Gene Duplication

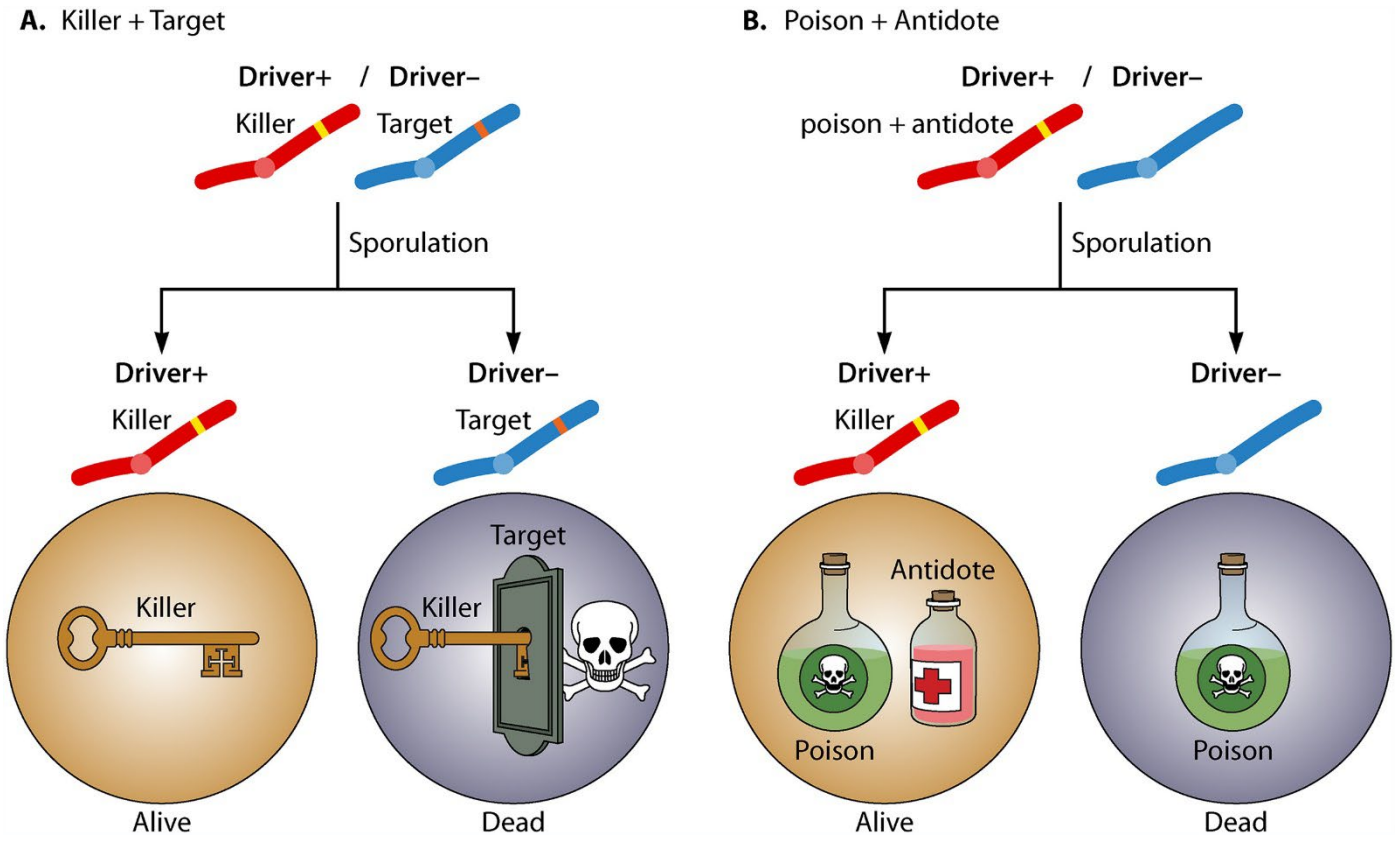
Involved in: mismatch repair double-strand break repair



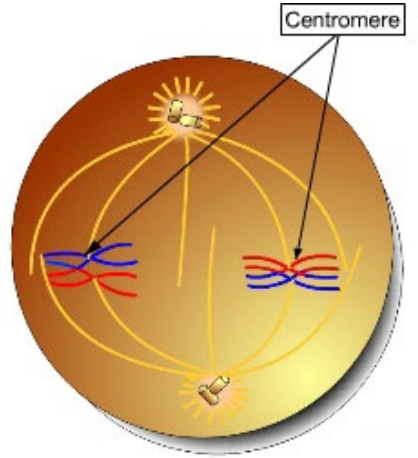
Ramesh et al. (2005, Curr. Biol.)

Meiosis Opens Up Vulnerability to Gamete Competition by Meiotic-Drive Mechanisms

- Spore killers in fungi.



Centromere Function and Evolution



- Assembly sites for kinetochores, which attach to the spindle microtubules, along which sister chromatids are dragged to opposite poles of dividing cells.

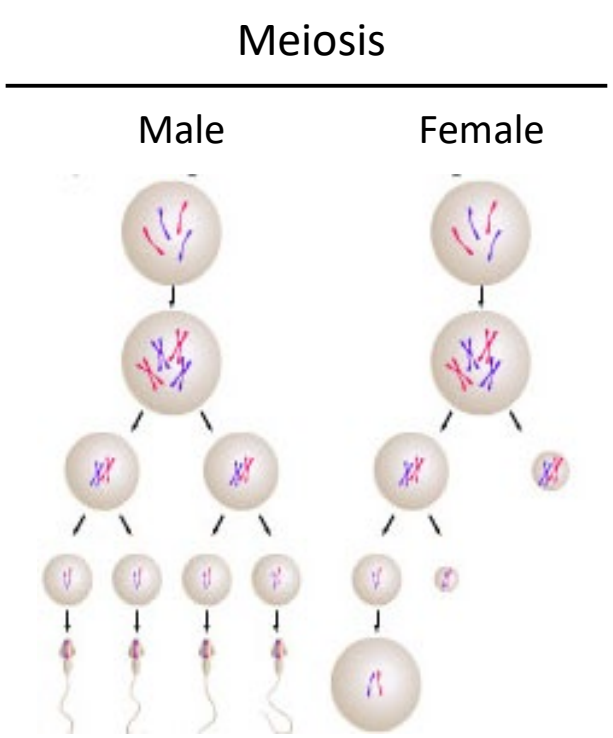
- The core set of proteins that carry out replication-associated functions of centromeres are highly conserved across eukaryotes, suggesting that the centromere was present in the stem eukaryote.

- Centromere lengths and complexity increase dramatically in multicellular species:
  - *S. cerevisiae* centromeres consist of a specific 125-bp signature.
  - Those of fission yeast *S. pombe* are 35-110 kb in length, with a central core that is just ~50% identical across chromosomes.

- Still larger are the 0.3 to 5.0-Mb long centromeres in multicellular species, which contain thousands of copies of repetitive DNAs and incapacitated mobile elements.

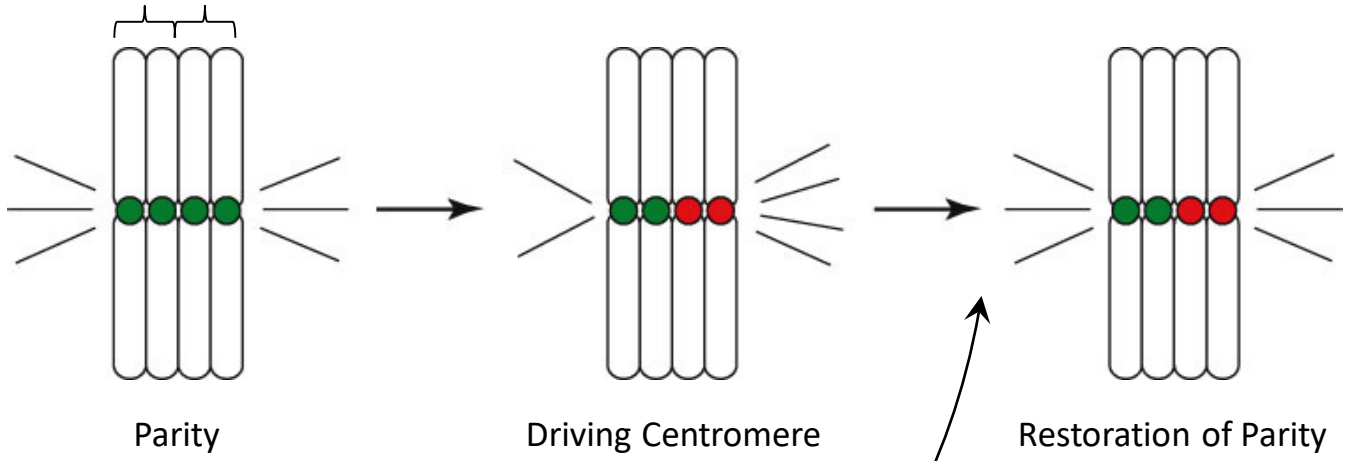
- Centromeric sequences and centromeric histones often evolve at exceptionally high rates.

The Centromeric-Drive Hypothesis (Henikoff et al. 2001)



- Postulates that meiosis sets up opportunities for centromeres to evolve so as to enhance their probability of appearing in haploid products.

The challenge of female meiosis:



Imposes selection for mechanisms that suppress the drive process, owing to negative side effects in mitosis or male meiosis

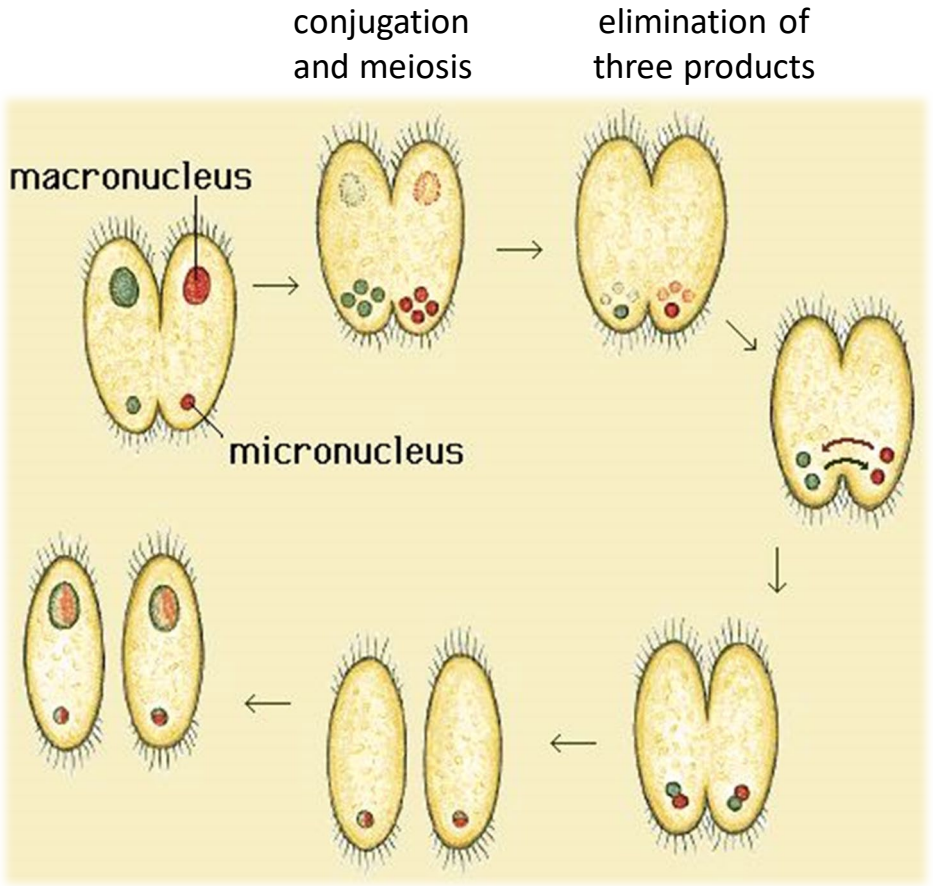
Unresolved Issues With the Centromeric-drive Hypothesis

- The drive process must be sufficiently slow to provide time to enable suppressor proteins to respond coevolutionarily.
  - A highly aggressive centromere will rapidly achieve high frequency, thwarting the selective promotion of modifier mutations because homozygotes for driving centromeres are not subject to differential spindle-binding strength.

- If the deleterious effects of a driving centromere on male meiosis or mitosis exceed the power of the drive process, the driving centromere will be eliminated from the population prior to the arrival of compensatory mutations.

- Centromeric proteins must recognize the full set of centromeric sequences across all chromosomes.
  - A successful modifier protein would have to restore parity at the problematical chromosome without generating new difficulties elsewhere.

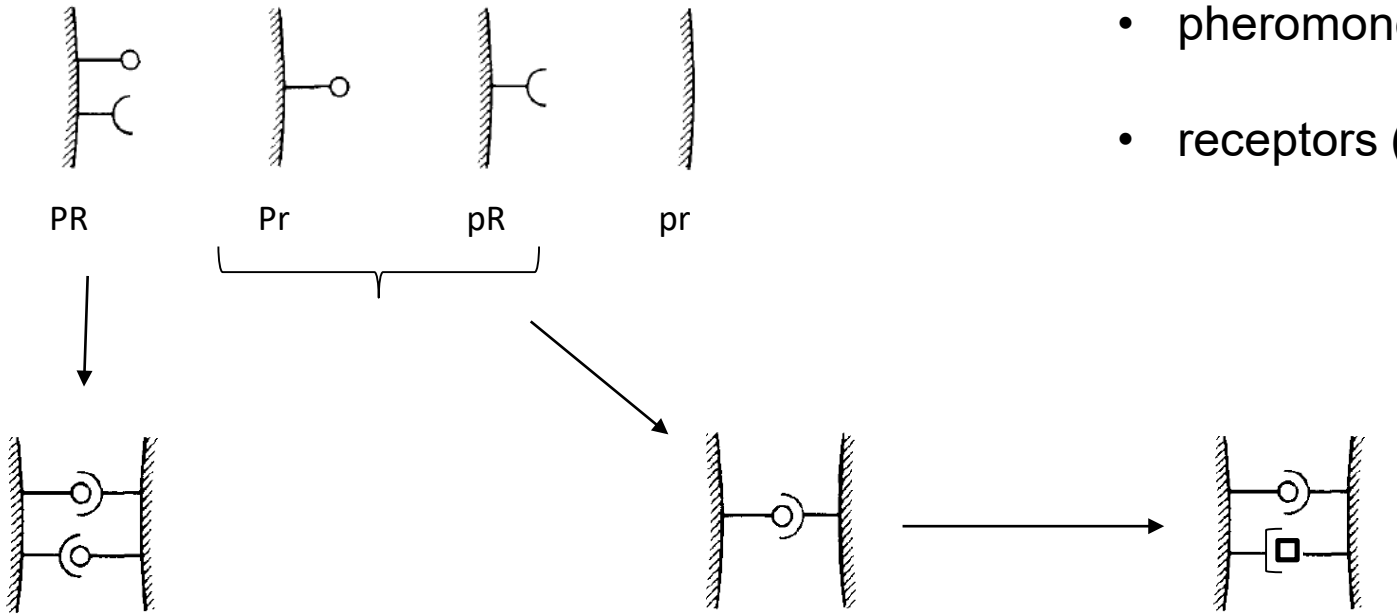
The Ciliate Life Cycle: no “male” meiosis



- With no conflict from male meiosis, the centromeric-drive hypothesis predicts an absence of accelerated evolution of compensatory changes in centromeric histones.
- No positive selection on the centromeric histone (Elde et al. (2011, J. Mol. Evol.)

- Potentially suggests that defects in male meiosis, and not mitosis, are the primary mechanisms encouraging the evolution of centromeric-drive suppression (assuming the hypothesis is actually correct).

Evolution of Mating Types



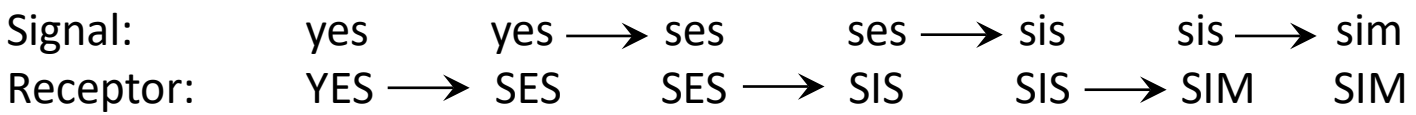
- pheromones (P, p)
- receptors (R, r)

- importance of recombination suppression

- Because it relies on the fusion of two haploid cells to produce the diploid substrate necessary for meiosis, sexual reproduction promotes the evolution of pheromone / receptor-based mating types to enhance the likelihood of mate acquisition.

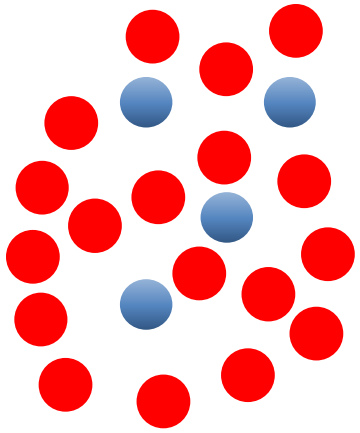
- Most species have two mating types, presumably because a single bipolar mating type leads to inefficient tracking of mates, as a cell's own plume of pheromone would overwhelm the gradient from foreign cells.

Coevolutionary Drift of Mate Recognition Systems

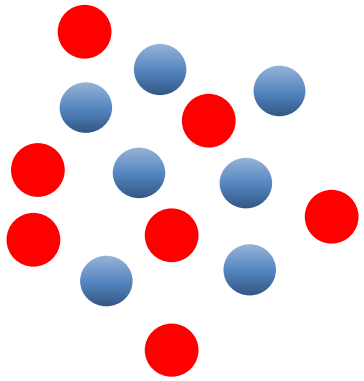


- Over long evolutionary time scales, coevolutionary drift of one-to-one signal-receptor interactions can lead to the passive emergence of reproductively isolated lineages.

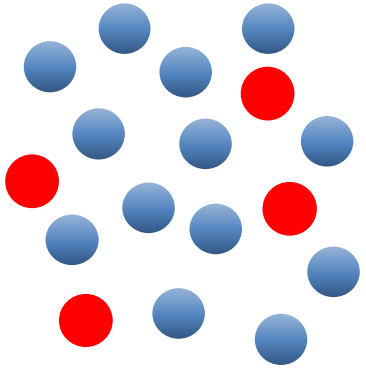
Frequency-Dependent Selection for Equal Mating-Type Frequencies



blue favored



stable equilibrium

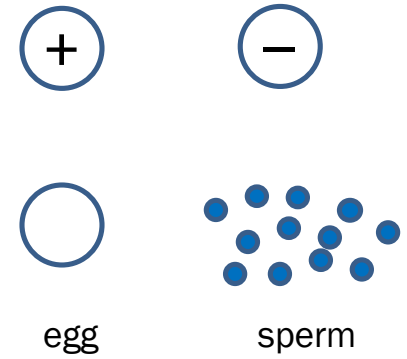


red favored

- Virtually all multicellular species have two mating types.
- Unicellular species often have more, and sometimes Many more (still with approximately equal frequencies).

Sexual reproductive systems of unicellular species are substantially different from those in animals and plants.

- Unicellular species generally have isogamous (equal investment) gamete types.
- Multicellular species are generally anisogamous (females invest more heavily in gametes).



- Simple consequence of differences of cellular and population-genetic environments?
  - No opportunity for a tradeoff between gamete number and size in unicellular species with binary fission.
  - Stabilizing selection will operate on both mating types throughout prolonged phases of asexual reproduction, reducing the opportunity for sexual selection.

Sexual reproductive systems of unicellular species are substantially different from those in animals and plants.

- Unicellular species generally have short chromosomal segments involved in mating-type determination.
- Multicellular species generally have extensive chromosomal regions dedicated to sex determination, often with fully differentiated sex chromosomes, and one containing just a few genes dedicated to the heterogametic sex (e.g., Y).

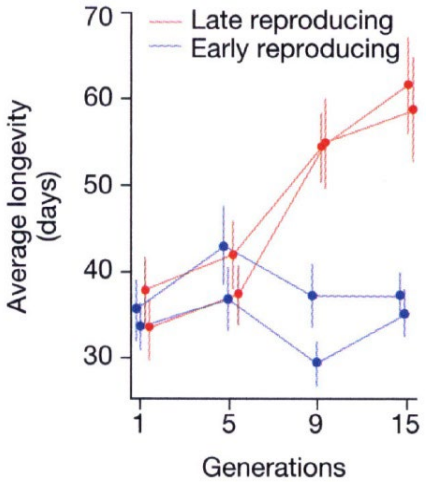
- Outcomes of the altered cellular and population-genetic environments of unicellular species?
  - The evolution of fully differentiated sex chromosomes may be a pathological response to relatively low rates of recombination and high rates of genetic drift enabling the location accumulation of deleterious mutations.
  - Does isogamy mitigate the opportunities for sex-chromosome evolution, or vice versa?

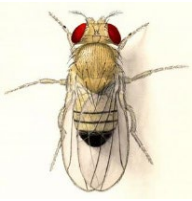
Senescence: Deterioration of Fitness-Related Traits With Age

- Proximate mechanisms:
    - Cumulative and/or asymmetric transmission of cellular damage.

- Ultimate evolutionary causes:
    - Antagonistic pleiotropy.
    - Mutation accumulation associated with relaxed selection.
    - All hypotheses imply that senescence is an inevitable genetic phenomenon, applying to all genetic loci, and not restricted to any specific set of genes.

- Successful selection for increased/ decreased longevity demonstrates the existence of natural variation for life span in multicellular species.





Antagonistic Pleiotropy Hypothesis (Williams 1957)

- A bioenergetic / structural constraint hypothesis: tradeoff (antagonism) between fitness components early and later in life –

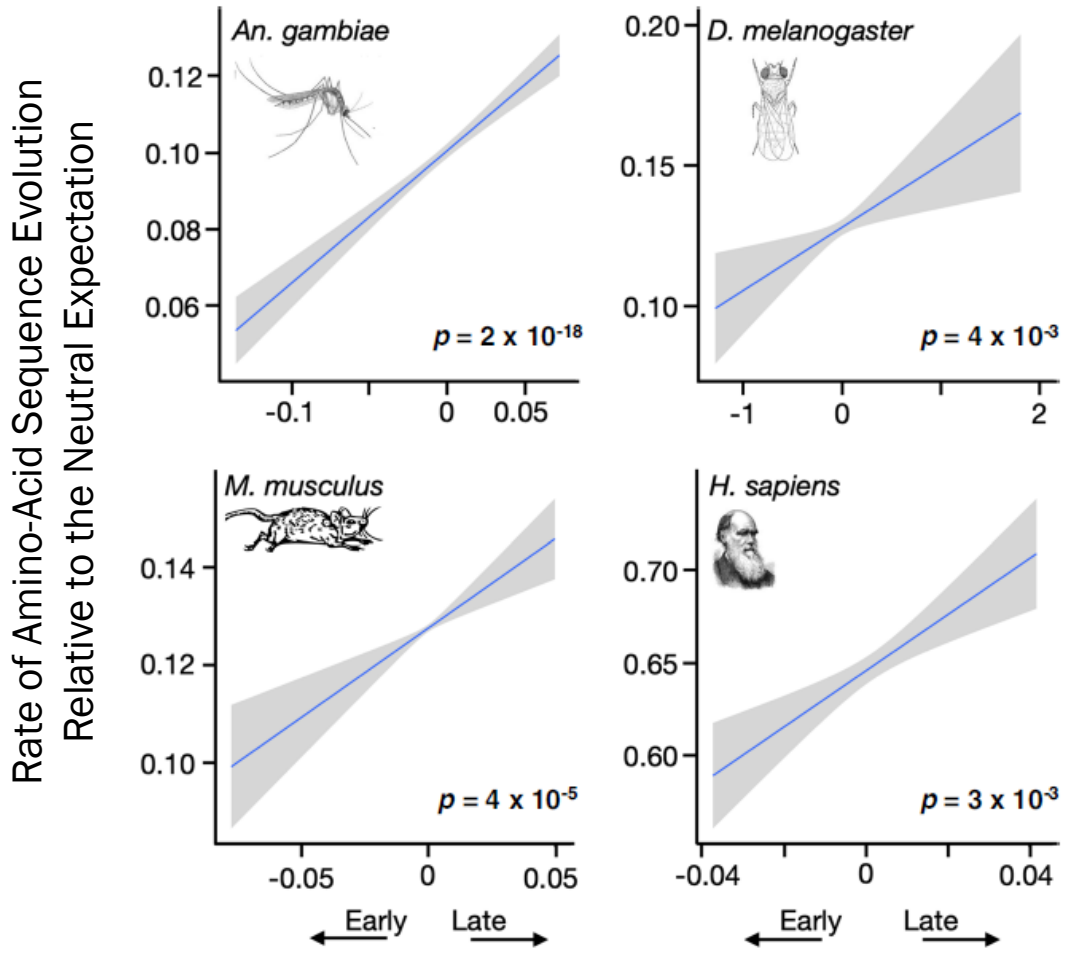
  Selection for alleles that enhance early survivorship and/or reproductive rate may concomitantly lower them at later ages.

Reduced Efficiency of Selection Operating on Late-Acting Genes (Medawar 1952)

A drift-barrier hypothesis: "… the forces of natural selection *weaken* with increasing age …. If a genetical disaster happens late enough in individual life, its consequences may be completely unimportant. Even in such a crude and unqualified form, this dispensation may have a real bearing on the origin of innate deterioration with increasing age."

- Because selection operates more strongly on early-acting genes, deleterious mutations whose effects are confined to late age are more liable to accumulate by random genetic drift.

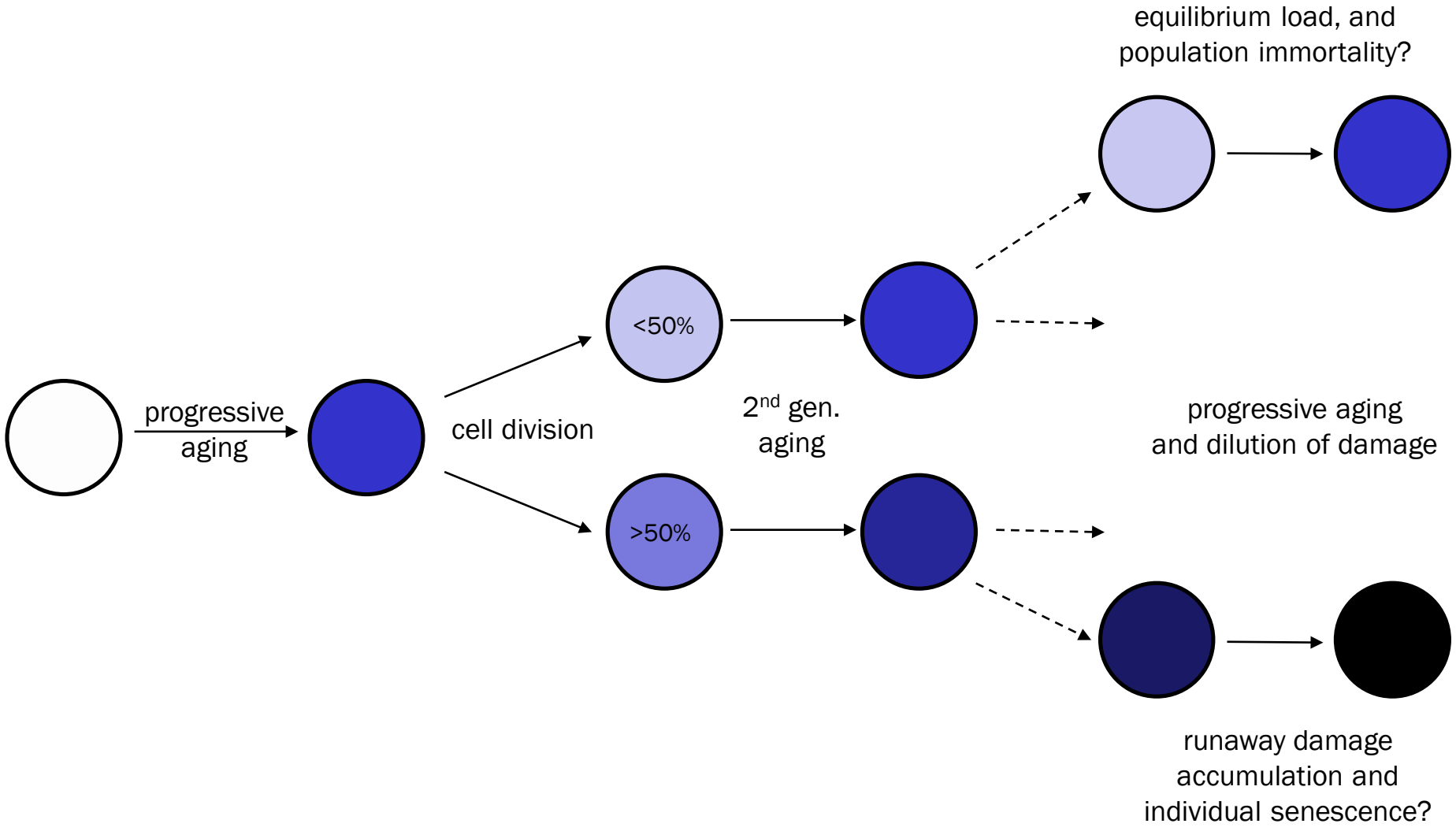
Genes with Relatively Late-Age Expression Accumulate Amino-Acid Alterations at Higher Rates



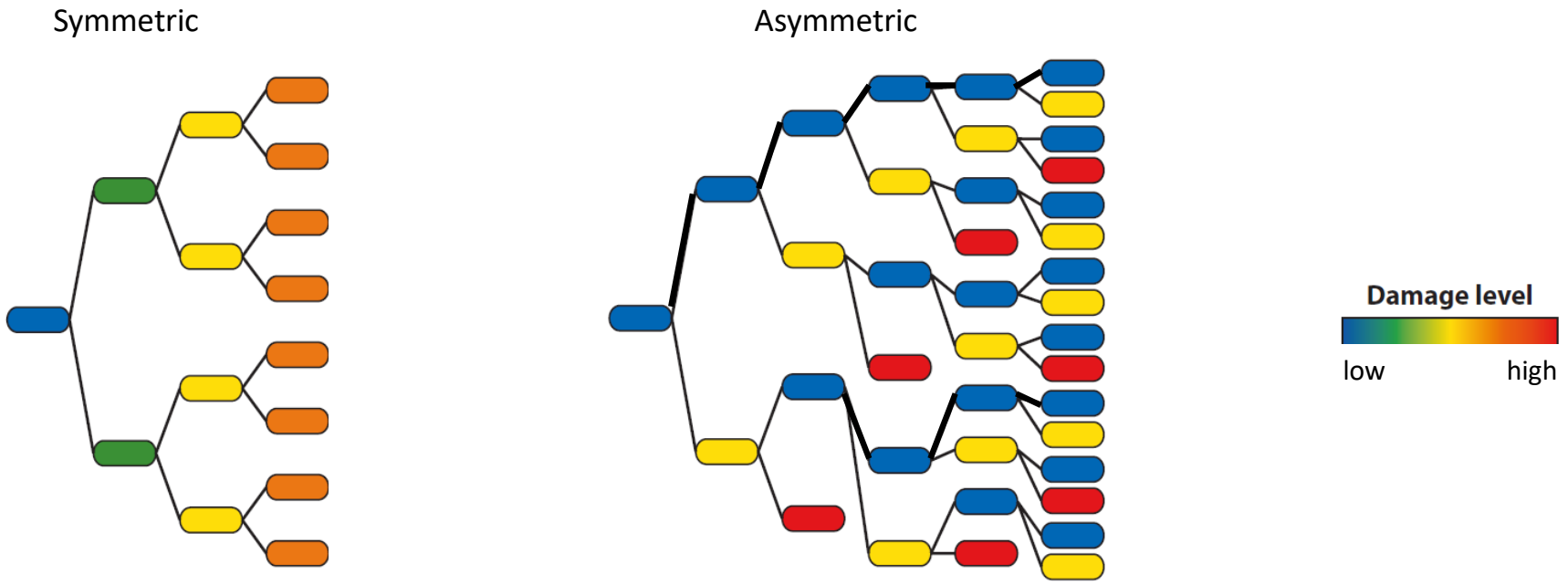
Cheng and Kirkpatrick (2021, Nature Comm.)

Individual Senescence vs. Population Immortality in Unicellular Species

- A balance between recurrent input and dilution via cell division?



Damage Segregation



- The molecular constituents of cells naturally deteriorate over time, raising the possibility of cellular senescence analogous to aging in multicellular species.

- However, the asymmetric inheritance of damage by daughter cells, whether programmed or simply stochastic, can lead to the rejuvenation of one member of the pair at the expense of the other.

Senescence Reflected in Age-Specific Survivorship

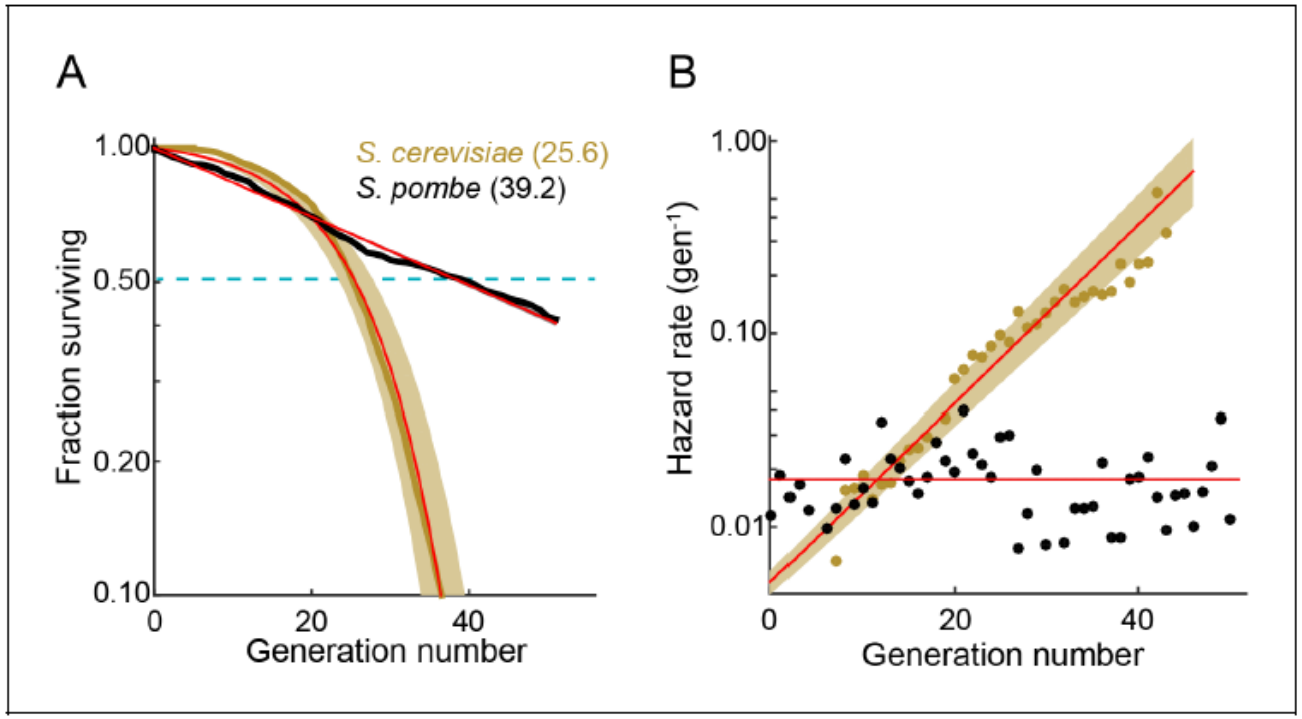
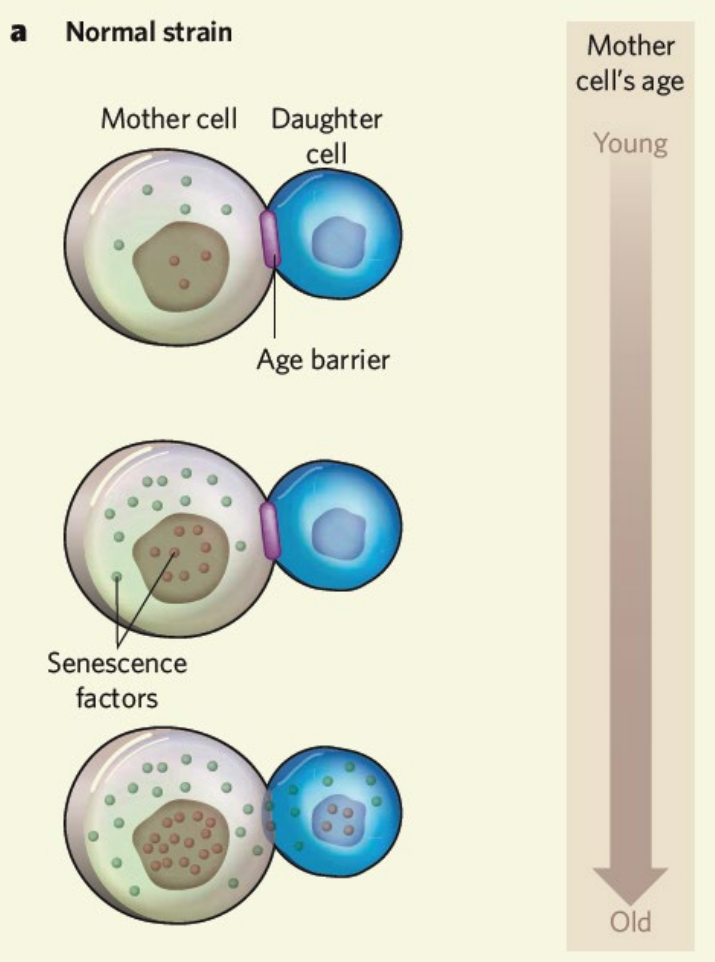


Figure 2. The fission yeast replicative lifespan (RLS). (**A**) Survival curves for wild-type *S. pombe* (black) and wild-type *S. cerevisiae* (brown, data from ***Jo et al., 2015***); both were grown in microfluidic microdissection devices. Numbers indicate the average lifespan. Red lines are a fit to a Gompertz (*S. cerevisiae*) and exponential decay (*S. pombe*) survival models. Shading indicates 95% confidence interval (C.I.). Dashed blue line: 50% survival. (**B**) Hazard rate curves for the data shown in (**A**). The hazard rate increases dramatically with increased replicative age for *S. cerevisiae* but not for *S. pombe*.

- Age-dependent mortality in *Saccharomyces pombe* (budding yeast).
- Age-independent mortality in *Schizosaccharomyces pombe* (fission yeast).

Spivey et al., 2017, eLife

In *S. cerevisiae*, There Exists an Age-Dependent Barrier to Damage Transmission



- In budding yeast, there is a clear distinction between mother and daughter, and aging occurs – mother cells have finite life spans.
- Known sources of damage include extrachromosomal circles of ribosomal DNA, oxidatively damaged proteins, dysfunctional mitochondria.
- Absence of senescence in *Schizosaccharomyces pombe* (fission yeast), where cell division and perhaps damage transmission is more symmetrical

Kaeberlein, 2008, Nature

In *E. coli*, Protein Aggregates (Inclusion Bodies) Are Differentially Segregated to Old Poles

- A natural consequence of midpoint division and static position of aggregates.
- Damage progressively locates to old poles through cycles of cell division.
- Cells progressively decline in division rates with increasing pole age.

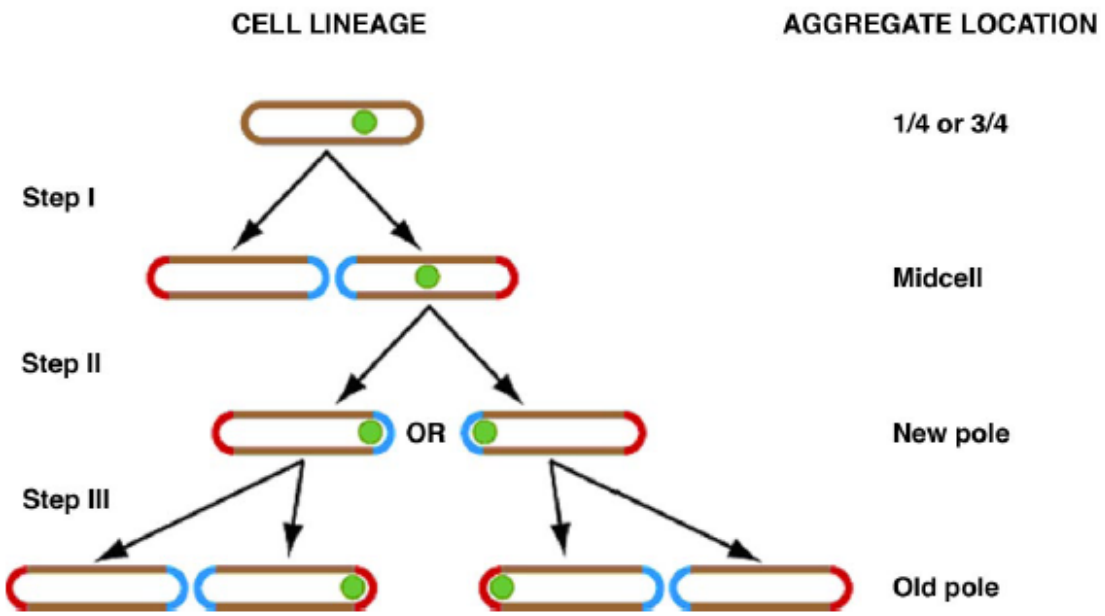
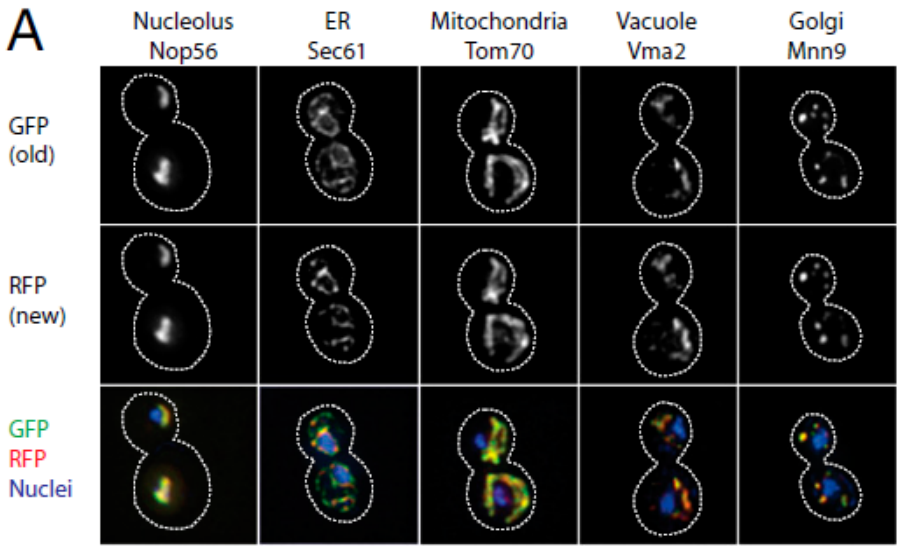


Fig. 3. Individual aggregates are located to the old pole through cycles of cell divisions. Because movement of foci is rarely observed, the location of an aggregate within the cell after division is determined by its location in the mother cell. Those that were at the one- or three-quarter positions are found concentrated around the mid-cell point after division (Step I). Aggregates at the mid-cell are subsequently located in the new pole, with equal probability to be in either of the two cells (Step II). Those that are found in the new-pole end of the cell immediately before division remain in the same pole; however, that pole, having been formed in the previous division event, is now an old pole in the offspring cell (Step III). Note that aggregates can be initially detected at polar, mid-cell, or quarter-cell positions but are eventually located to an old pole. Once there, they are consistently inherited by the old-pole cell after division. Aggregates are indicated by green dots. Red cell ends are old poles, and blue cell ends are new poles.

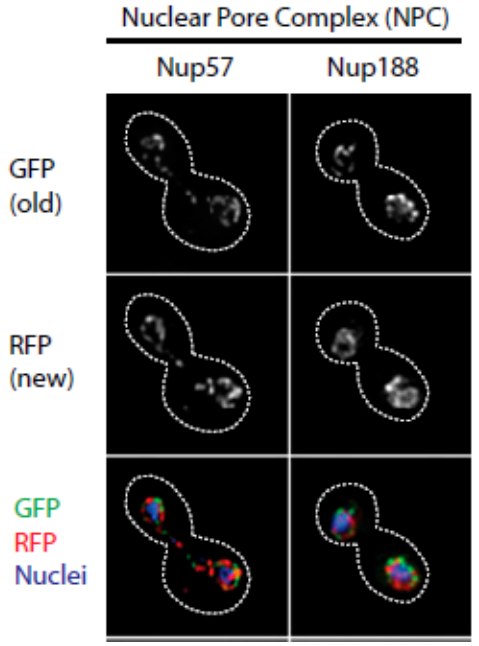
Lindner et al., 2008, PNAS

Partitioning of Cellular Contents at Cell Division: Differential Distribution of New vs. Old Parts?

In most yeast organelles, preexisting proteins are symmetrically partitioned, followed by addition of newly synthesized proteins to “divided” organelles.



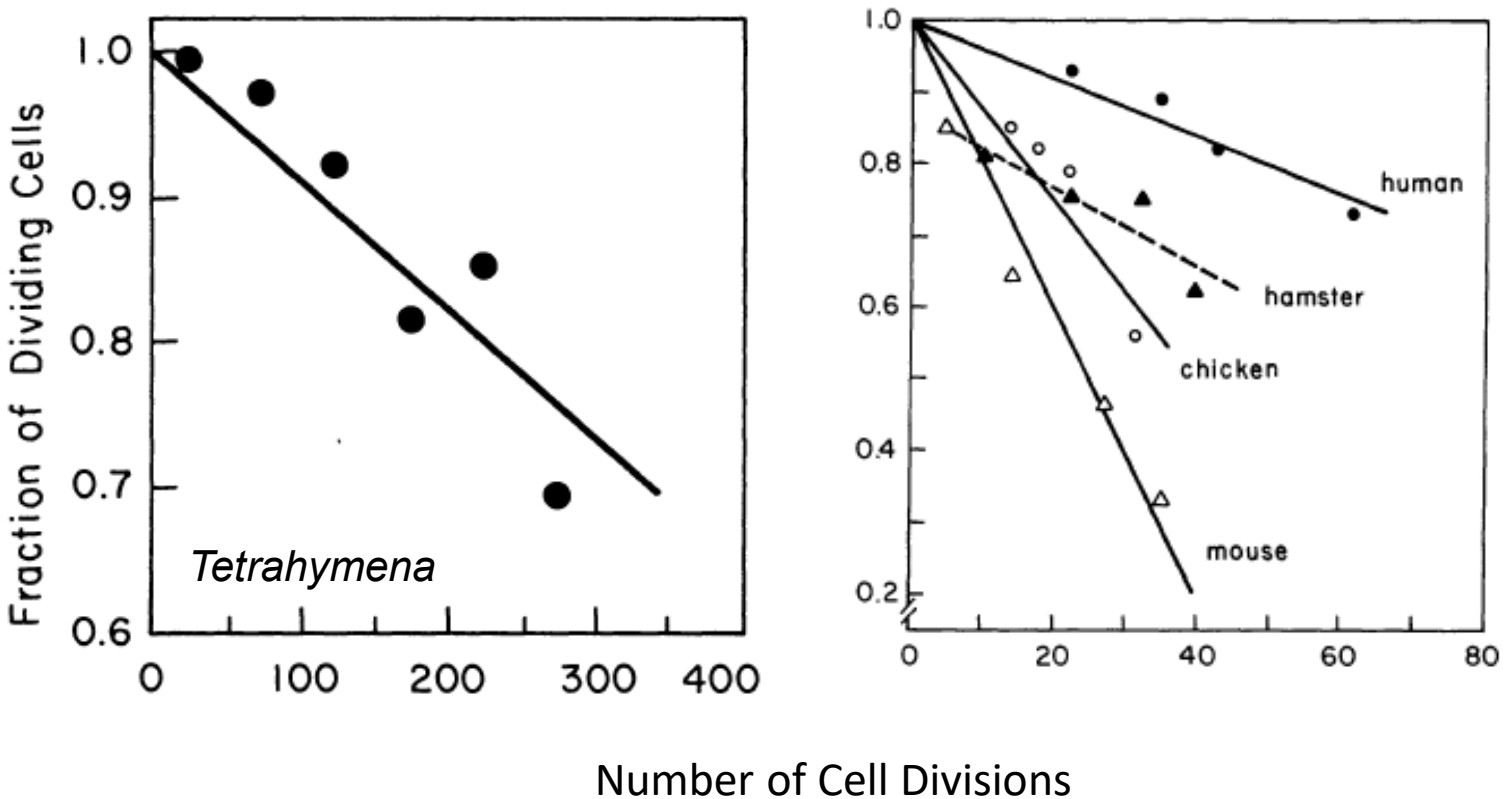
The nuclear pore complex is an exception -- old NPCs are stably inherited in complex, and new ones are produced *de novo*.



- The spindle pole body displays asymmetrical partitioning, with the old parts being primarily inherited by daughter cells, and new proteins being equally partitioned.

Menendez-Benito et al. (2013, PNAS)

Predictable Finite Lifespans of Cell Cultures



- Gradual deterioration of cell-division potential.

- The mechanisms likely involve large-scale problems with chromosomal integrity and imbalance, such as telomere and/or chromosome loss, rather than the accumulation of point mutations. Rejuvenation can be accomplished by sexual outcrossing and/or inactivation of genes involved in telomere erosion.