Natural Selection does not always act effectively on a population. Several factors could limit the action of Natural Selection. Evolutionary Perfection is difficult to achieve because of constraints on Natural Selection.

Outline

1. What are Evolutionary Tradeoffs?
2. Example of a Life History Evolutionary Tradeoff: Ageing
3. Evolutionary causes of Ageing
   - Mutational Accumulation
   - Antagonistic Pleiotropy

A “tradeoff” is when you gain something, but lose something else in return. An “evolutionary tradeoff” is when a genetically based trait or set of traits increases performance (fitness) in one environment or condition, while decreasing performance (fitness) in another.

Last time we discussed examples of Antagonistic Pleiotropy leading to Evolutionary Tradeoffs. What is pleiotropy? What is Antagonistic Pleiotropy?
Conversely, a seemingly unbeneficial trait might get selected for because the gene that codes for it also enhances fitness.

Pleiotropy: when a gene affects many traits or functions
- Selection might not be able to act on trait if the gene that encodes the trait is Pleirotic, and also affects other traits. So, changing the gene could negatively affect the other traits.
- Conversely, a seemingly unbeneficial trait might get selected for because the gene that codes for it also enhances fitness.
- Pleiotropy could sometimes lead to evolutionary tradeoffs (you can have evolutionary tradeoffs that are not pleiotropic—between traits encoded by different genes).

Antagonistic Pleiotropy
- Antagonistic Pleiotropy: where a gene has a positive effect on one heritable trait but a negative effect on another trait (Example: a gene that increases heat tolerance but also reduces cold tolerance)
- Antagonistic Pleiotropy can lead to evolutionary tradeoffs. A gene that encodes one trait that increases fitness, and also encodes another trait that decreases fitness would lead to a tradeoff between the impacts of that one gene.

Example of Antagonist Pleiotropy leading to an evolutionary tradeoff between male vs. female fitness
- Selection can act simultaneously on male AND female traits, but in opposing directions.
- Any gene that affects estrogen/testosterone-receptor activity will lead to tradeoffs between male and female fitness.
- An alteration at a single locus, i.e. estrogens, estrogen receptor, expression of either, could simultaneously have opposing effects on male and female fitness.
- Such a locus has antagonistic pleotropic effects… having opposing effects on different traits (male vs. female fitness).

Examples of antagonistic pleiotropy leading to evolutionary tradeoffs
- Selection on HIV reverse transcription: Discussed in last lecture
- Sickle Cell Anemia: Discussed in last lecture
- High estrogen could increase fertility, but also increase cancer (estrogen has many targets in the body, and many consequences).
- The P53 gene encodes a protein that suppresses the formation of tumors (and cancer), but also suppresses the proliferation of stem cells → premature aging.
- Some genes (“Thrifty genes”) are thought to be helpful in famines but also lead to diabetes and obesity.

Evolutionary Tradeoffs could arise from different causes
- Evolutionary tradeoffs could result from antagonistic pleiotropy... but, antagonistic pleiotropy is not required for there to be a tradeoff.
- Evolutionary Tradeoffs could be caused by fitness tradeoffs between traits encoded by different loci (NOT pleiotropy).
- Evolutionary Tradeoffs could also arise from energetic constraints (energetic tradeoff)
  - An organism might not be both heat and cold tolerant because it is too expensive to maintain both traits.
  - Big brains might be useful for some organisms, but are really energetically costly (Big Brains and Small Guts: http://www.tgdaily.com/general-science/brief/68506-brainy-guppies-show-evolutionary-tradeoff).
  - Big brains vs. Reproduction (“Big Brains or Big Balls?” http://scienceblogs.com/grrlscientist/2006/01/24/evolutionary-question-big-bra/)
Examples of Evolutionary Trade-offs:

- **Life History Tradeoffs**: what might be beneficial early in life could be harmful later (Example: ageing)

- **Tradeoffs Across Environments**: what might be good in one environment could be bad in another:
  - Pale skin is helpful in Northern latitudes:
    - 6x rate of Vitamin D synthesis relative to darker skin
  - While, Pale skin is harmful in Southern latitudes:
    - 6x increase in skin cancer

Life History Tradeoffs: Example of Ageing

(Images of people showing aging)

Evolutionary Theories of Ageing

Images of Darwin and another scientist

Evolutionary Costs or Tradeoffs: Ageing is an example

- Adaptation is not perfect
- There is often a cost, and there are often tradeoffs
- One example of such a cost or tradeoff is Ageing

A key important point here regarding how Natural Selection acts:

- Natural selection weakens with age… traits that are expressed later in life do not get selected out efficiently
- This phenomenon leads to Life History Tradeoffs… where traits that favor fitness at youth will be favored by selection, even if those traits are harmful later in life

Reading:

- Within Chapter 13, focus mainly on 13.1 and 13.2 on Ageing
- Review Evolutionary Tradeoffs in 10.6
A key important point here regards how Natural Selection acts:

- Selection is most effective prior to reproduction, as selection at this stage would affect which genes get passed on.
- Once an individual is done reproducing, selection becomes less effective, this becomes even more true after individuals are done caring for offspring.
- What happens to individuals after reproduction and childcare will not affect allele frequencies at the next generation.
- This phenomenon leads to Life History Tradeoffs.

• REMEMBER... Natural Selection can act ONLY when there is fitness.

Trade-offs during Aging

- If a trait is deleterious at a young age, the individual will die before reproducing.
- If it is harmful at an old age, it won’t get selected out of the population (no kids, nothing to select on).
- Example: sex hormones; high estrogen concentration at a young age could enhance fertility, but increase risk of cancer at an older age.

Questions:

Q: What are proposed evolutionary causes of ageing?

Q: Why do some organisms age, whereas others do not?

Q: How might selection act on a population to increase or decrease lifespan?


What is ageing?

Senescence: decline in performance and fitness with advancing age.

Ageing is not Universal

- Bacteria can suffer DNA damage, but they do not age the way we do.
- Multicellular organisms tend to age and die.
- Organisms that reproduce early in life are the ones that age faster.
Causes of Ageing

• There might be no adaptive reason for an individual to age
  – It could be a tragic by-product of natural selection weakening with age
  – Natural selection would act to reduce physiological damage, but not when there is no longer any fitness

• Cellular ageing and death might occur to prevent excessive cell proliferation in multicellular organisms

Evolutionary Causes:

Senescence occurs because the force of natural selection declines with age in populations that have age structure (individuals of different ages)

Selection acts differently on different age groups (more effective before reproduction, declines with age)

Why would the action of natural selection weaken with age?

Because natural selection acts deterministically: individuals die for a reason... selection acts when more adapted individuals have a greater probability of surviving and leaving offspring

Evolutionary Mechanisms

• There are many other theories on mechanisms of ageing: Disposable Soma, telomere shortening, and hundreds regarding physiological mechanisms...oxidative stress, etc... a lot of these are mechanisms of how aging happens

• But, I will focus on the fundamental evolutionary causes of aging (why aging evolved rather than how it happens) that have the most data to support the hypotheses.

General Model: The ultimate evolutionary cause of aging is extrinsic mortality (WD Hamilton, 1966) – (note that your book calls it “ecological mortality” but no one else does)

The hypothesized evolutionary genetic mechanisms by which ageing could evolve include:
  – Mutational Accumulation
  – Antagonistic Pleiotropy

Why would the action of natural selection weaken with increasing age?

With increasing age, extrinsic mortality increases, that is death from random causes (genetic drift, accidents, non-age specific diseases, predation, factors not having to do with selection, etc).

These random deaths weaken the efficiency of natural selection (as deaths need to be caused by nonrandom forces for selection to act)

Natural selection is less efficient when deaths are random, and not due to particular genetically-determined traits
So, as Natural Selection weakens with age (due to extrinsic mortality), traits that are harmful later in life do not get weeded out of the population…

Negative traits that are expressed later in life in a population accumulate, because selection does not act on traits expressed later in life

(most random mutations that affect function are deleterious)

The relative strength of selection weakens, whereas that of genetic drift becomes stronger later in life

“Extrinsic mortality” is a term used in demography, and refers to deaths that are imposed by external forces… accidents that have nothing to do with the genetic properties of the individual. So, extrinsic mortality would interfere with the action of natural selection. In contrast, “intrinsic mortality” refers to deaths that happen because of properties of the individual, and could result in natural selection. So then, as a cohort in a population ages, more and more people would have died by accident. When you get to age 90, a lot of people have died by accident, and what you have left is not representative of the original cohort. So, selection will be a lot less efficient. Lets say that in this cohort, originally 50% had brown eyes and 50% had blue eyes, and that the blue eyed individuals should go blind and then die due to cataracts. But then, lets say a lot of the brown eyed individuals already died by accident (just by chance), so selection cannot favor the brown eyed individuals because they are already dead. So, as you get older, the accidental deaths increasingly interfere with the ability of selection to favor the genotypes that they would have favored because the accidents randomly killed off a bunch of genotypes, sometimes randomly the ones that should have been favored. So, the action of selection to favor the fitter genotypes becomes increasingly difficult. Incidentally, this is a really interesting article on the evolution of aging rates of human populations in Europe:

http://evmedreview.com/?p=147

Extrinsic mortality

Evolutionary Mechanisms

General Model: The ultimate evolutionary cause of aging is extrinsic mortality (WD Hamilton, 1966) – (note that your book calls it “ecological mortality” but no one else does)

The hypothesized evolutionary genetic mechanisms by which ageing could evolve include:

- Mutational Accumulation
- Antagonistic Pleiotropy

Evolutionary Mechanisms

Lower efficacy of Natural Selection (due to extrinsic mortality) would result in accumulation of deleterious mutations expressed later in life due to:

- Mutational Accumulation
  - Due to ineffective selection later in life, deleterious mutations accumulate
- Antagonistic Pleiotropy
  - Mutations that are favored by selection early in life, might be harmful later, but selection is ineffective later in life

That is, ineffective selection later in life might lead to senescence (aging) due to one of the mechanisms above.

Tests of Hypotheses

Effect of extrinsic mortality

Prediction: if extrinsic mortality is reduced and natural selection could act on a population, the rate of aging should go down

Evidence:

- Organisms in low-risk environments with lower random deaths would age more slowly
- Artificial experiments that selectively bred older individuals, allowing natural selection to act at later life stages, increased life span (cited in Hughes p. 426)
When comparing mainland and island populations, the mainland population suffers much higher extrinsic mortality rates due to predation. The opossums live on both Sapelo Island and the mainland, but predators are absent from Sapelo Island.

(1) Mutational Accumulation
Medawar (1952)

- Deleterious mutations expressed at a young age are severely selected against, due to their high negative impact on fitness (number of offspring produced).
- On the other hand, deleterious mutations expressed only later in life are neutral to selection (genetic drift predominates), and not selected out of the population, because their bearers have already transmitted their genes to the next generation (little or no selection).
- Selection is weaker later in life, and thus deleterious mutations expressed later in life accumulate (fixation due to genetic drift), and the negative effects are manifested as ageing.

Tests of Hypothesis

- Role of Mutation Accumulation
  - Prediction: because of the accumulation of deleterious mutations (most of which will be recessive), inbreeding depression (due to homozygous recessive alleles coming together) should increase with age. Genetic variance and dominance variance should also increase (because of the new recessive mutations).
  - Evidence: A few studies support this prediction.

(2) Antagonistic Pleiotropy
Williams (1957)

- Pleiotropy: phenomenon where a gene affects several different traits
- Antagonistic Pleiotropy: where a gene has a positive effect on one trait but a negative effect on another trait (example: a gene that increases heat tolerance but reduces cold tolerance)
- Antagonistic Pleiotropy Theory of Aging: Mutations that are beneficial early in life (before reproduction), but are deleterious later in life do not get selected out of a population because selection is less efficient later in life.
- Antagonistic pleiotropy could lead to evolutionary "trade-offs" (sometimes between fecundity and longevity)
Selection might favor alleles that benefit early life stages even if they are deleterious later in life.

Thus, deleterious mutations that affect traits expressed after reproduction accumulate.

Williams 1957: antagonistic pleiotropy theory of aging

• Antagonistic Pleiotropy Theory of Aging: Mutations that are beneficial early in life (before reproduction) will be selected for even if they are deleterious later in life

Birth Juvenile Adult reproduction Post reproduction Death

• Genes that affect reproduction early in life might have negative health effects later in life

Example: high estrogen -> high fecundity when young, but increased chance of breast cancer, ovarian cancer, etc. later in life; tradeoffs between fecundity and ageing

Examples

• There is often a tradeoff between reproductive success and longevity

  – Example: Sex hormones; high estrogen concentration at a young age could enhance fertility, but increase risk of cancer at an older age

  – Methuselah gene in Drosophila (Fig. 13.15 in book)

• There is also often a tradeoff between early versus late life reproduction

Tradeoffs during Aging

• If a trait is deleterious at a young age, the individual will die before reproducing

• If it is harmful at an old age, it won’t get selected out of the population (no kids, nothing to select on)

Antagonistic Pleiotropy Theory of Aging:
Mutations that are beneficial early in life (before reproduction) will be selected for even if they are deleterious later in life

Birth Juvenile Adult reproduction Post reproduction Death

Genes that affect reproduction early in life might have negative health effects later in life

• Example: high estrogen -> high fecundity when young, but increased chance of breast cancer, ovarian cancer, etc. later in life; tradeoffs between fecundity and ageing

Examples

• There is often a tradeoff between reproductive success and longevity

  – Example: Sex hormones; high estrogen concentration at a young age could enhance fertility, but increase risk of cancer at an older age

  – Methuselah gene in Drosophila (Fig. 13.15 in book)

• There is also often a tradeoff between early versus late life reproduction

Tradeoff between reproductive success and longevity + stress resistance

Methuselah mutants live longer, but have fewer offspring

Females, reared at 29°C: Homozygous methuselah mutants Homozygous normal flies

Survivability (%) Cumulative fertility (Adult progeny per female)
Figure 13.15 In collared flycatchers (*Ficedula albicollis*), natural variation and experimental manipulations demonstrate a trade-off between reproduction early in life versus reproduction late in life.

### Tradeoff between early versus late life reproduction

- **Tradeoff between early versus late life reproduction**

![Graph showing tradeoff between early and late life reproduction](image)

**Legend:**
- (a) 
  - Breed sooner: 2, 4, 6, 8
  - Breed later: 8, 12, 12, 12

**Figure 13.15**

### Tests of Hypothesis

- **Role of Antagonistic Pleiotropy**
  - **Prediction:** selection on enhanced late life reproduction should select against early-life reproduction
  - **Evidence:** Several studies support this prediction

### BUT...

- **Why do women senesce more slowly than men?** (by ~10 years)
- **If so, why do they stop reproducing at an earlier age than men?**

### The “Grandmother Hypothesis:”

1. **Women live longer than men because they contribute to the fitness of their grandchildren**
2. **Menopause in older women reduces risk of cancer (estrogen), and removes responsibility of caring for their own children, so that they contribute to the fitness of their grandchildren**

**The Data:**
- [http://www.nature.com/nature/journal/v428/n6979/full/428128a.html](http://www.nature.com/nature/journal/v428/n6979/full/428128a.html)
- [http://www.pnas.org/content/95/3/1336.full](http://www.pnas.org/content/95/3/1336.full)

Maternal grandmother increases survival of their grandchildren.
Mechanistic Causes of Ageing:

- How does ageing occur (physiologically)?
  - We talked about deleterious mutations accumulating—and not getting selected out (via MA and AP); what mutations are accumulating? Which traits are affected by mutations? Which traits are experiencing tradeoffs?
  - These mutations could affect many physiological functions that manifest in ageing

- Oxidative Stress
- Other types of Stress
- Signal transduction pathways

So what are these deleterious mutations doing?

- The ones that are accumulating that are expressed later in life and not getting selected out?

  - Example: Cancer is considered a Disease of Ageing

What is Cancer?

A problem of multicellular organisms

Multicellularity requires social cohesion of cells:
- All cells must die at some point in multicellular organisms (apoptosis, programmed cell death)

Cancer cells revert to unicellular selfishness, and are immortal, and fail to die → tumor

Ageing and Cancer

- Cancer Cells
  - Cancer is considered a disease of ageing because the somatic mutations that accumulate during ageing can sometimes disrupt normal genetic control of cell proliferation and cell death (apoptosis)
  - Ironically, these mutations make cancer cells immortal, such that they fail to age and die (but they make the organism age and die)
  - Repair mechanisms (DNA repair and somatic repair) decline with age, as selection to maintain these functions weakens with age

The Irony of Cancer

Mutations that by chance occur at genes that affect cell growth, proliferation, DNA repair... Especially those that occur later in life

Cancer (immortal) cells that fail to age and die will proliferate... And the irony is that selection in the tumor will favor those immortal cells

Questions

- What types of selection scenarios would lead to evolution of longer life span?
- What types of selection scenarios would lead to evolution of shorter life span?
Basic Evolutionary Concepts

Natural Selection vs Genetic Drift
Evolutionary Tradeoffs
Pleiotropy
Antagonistic Pleiotropy

Another example of fitness tradeoffs

- Study suggests that a gene(s) that increases female fitness might also cause homosexuality in male offspring in humans.
- So, the gene(s) has an effect on more than one phenotype (it has pleiotropic effects)
- Female relatives on mother’s side of homosexual males had higher fecundity than those of heterosexual males.
- In this case, homosexuality would not get selected out, even if it reduced fitness of the homosexual individual, because the gene also increases fitness in his relatives (Selection would depend on the balance between the + and - effects on fitness)

1. Which of the following is NOT an example of an Evolutionary Trade-off?

(A) HIV, the virus that causes AIDS, normally has a reverse transcriptase that is prone to producing replication errors during rapid DNA synthesis, but undergoes selection for a reverse transcriptase that is less error prone, but slower, in the presence of AZT
(B) Mutation rate increases exponentially in the male germ line, but recombination, or the shuffling of alleles, allows sexual species to hide the deleterious effects of such mutations through dominance.
(C) Lighter skin (lower melanin) allows greater synthesis of vitamin D, but has a higher incidence of skin cancer, while darker skin protects against UV radiation but has lower vitamin D synthesis.
(D) Tahitians are islanders that traveled on long journeys on boats. They have high fat retention that is thought to enable survival on long trips. But in the modern day, they have high incidence of obesity and diabetes.

2. Which of the following is NOT an example of an Evolutionary Tradeoff?

(A) The heterozygote for the HbS gene encodes hemoglobin with reduced oxygen carrying capacity, but this hemoglobin also reduces infection in the presence of malaria.
(B) In some species of mammals, large males are favored by sexual selection, but the large males also have reduced immune systems
(C) HIV with high fidelity (careful) reverse transcriptase will make fewer errors during genome replication, but will have slower genome replication and will grow more slowly
(D) Natural selection favors big billed (beaked) birds where there are large seeds, and small billed birds where there are small seeds

3. Which of the following is an example of antagonistic pleiotropy?

(a) A gene that encodes for long life is correlated with another gene that encodes for lower fitness, leading to fitness (and evolutionary) tradeoffs
(b) A gene that encodes for long life also encodes for lower fitness early in life, leading to fitness (and evolutionary) tradeoffs
(c) A gene that encodes for long life also encodes for high survival
(d) Natural Selection is inefficient in smaller populations
(e) All of the above

4. Which of the following experimental results would provide support for Antagonistic Pleiotropy as an evolutionary mechanism of ageing?

a) Overexpression of SOD and CAT genes resulted in increased lifespan
b) Selection for increased reproduction late in life in a population of fruit flies resulted in lowered reproduction early in life
(c) A population of worms showed evidence of increases in inbreeding depression with increasing age
d) Selection for late life reproduction in a fruit fly population resulted in increased resistance to oxidative stress
e) Selection favoring reproduction of older individuals resulted in longer lifespan
5. Which of the following does NOT describe an evolutionary cause of aging?
   (a) The reduction in natural selection later in life results in aging
   (b) Life history structure, where selection acts before reproduction but not after reproduction, results in accumulation of deleterious traits after reproduction (either through mutation accumulation or antagonistic pleiotropy)
   (c) The decline in metabolic rate later in life due to oxidative stress promotes the onset of aging
   (d) Death due to random causes late in life reduces the effect of natural selection and the ability to select against deleterious traits

6. Dr. Robert Wilson advocated for hormone replacement therapy in his book "Feminine Forever.” He argued that as women age, estrogen levels decline, and that levels should be restored to those that are normal for younger women. What might he have neglected to take into account?
   (a) Mutational accumulation
   (b) Oxidative stress
   (c) Antagonist pleiotropy
   (d) That lowering estrogen levels in all women would increase lifespan
   (e) Gene regulation (Histone deacetylases)

7. Which scenario is most likely to select for the longer lifespan in a population?
   (a) A population where medicine technology has advanced such that people do not die of age-related diseases but only of accidents
   (b) A population where women are encouraged to bear many children
   (c) A population where males have offspring with many different women
   (d) A population where males bear offspring using sperm frozen from when they were 18 years old (to avoid mutations associated with replication error)
   (e) A population where women delay reproduction until after they have finished graduate school

Answers:
1B
2D
3B
4B
5C
6C
7E – If individuals reproduce at an older age, selection can act on phenotypes expressed late in life, and remove deleterious traits expressed later in life (reducing some of the negative effects of aging)