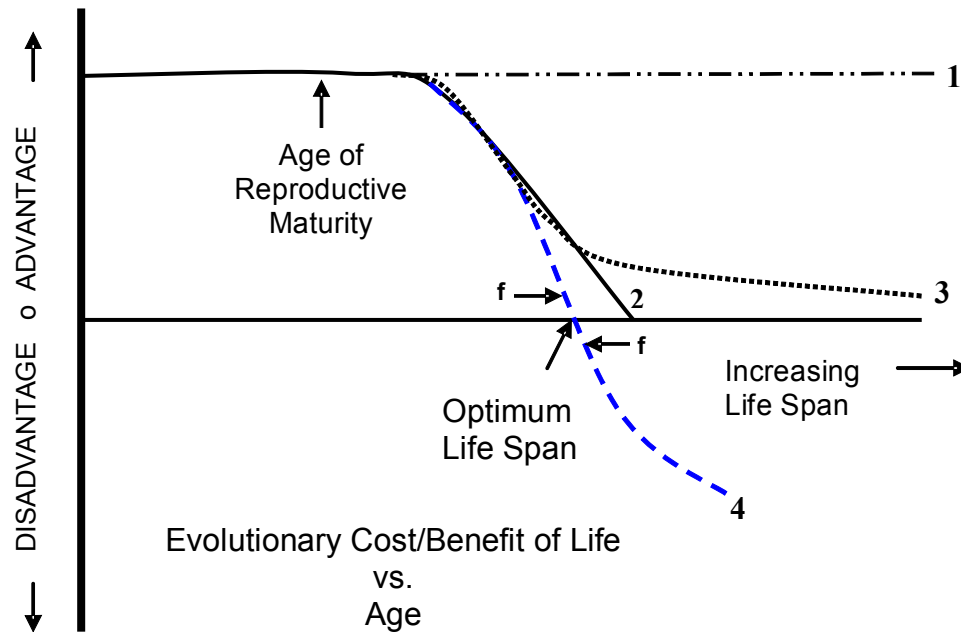


# Rationale for Complex Life Span Regulation in Mammals

Homo Sapiens Liberatus Workshop  
Moscow, May 2010

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# Incremental Evolutionary Value of Life vs. Reproductive Age - Four Concepts



# Evolutionary Value of Life

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- Issue: Incremental evolutionary value of life as a function of age relative to age of reproductive maturity. All four concepts agree there is value in an organism living long enough to reproduce and nurture immediate descendents (if applicable).
- Concept 1: Darwin 1859, incremental value of life continues indefinitely, therefore evolutionary force is toward developing immortality. Conflict with (non-immortal) observations was immediately criticized. Leads to generic degradation or “wear and tear” theories of aging.
- Concept 2: Medawar 1952, life value declines to zero; mutation accumulation theory
- Concept 3: Williams 1957, Kirkwood, others, value declines, but not to zero; antagonistic pleiotropy, disposable soma, other “unavoidable side-effect” theories of aging
- Concept 4: Life value negative beyond optimum life span; purposely programmed adaptive aging theories

# Value of Life - Status

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- All four concepts still have proponents and corresponding dependent theories of biological aging. This issue remains unresolved despite ~150 year history, an “unsolved problem of biology.”
- The four concepts span all of the possibilities re evolutionary value of life vs age relative to reproductive maturity.
- Aging theory is essentially dictated by the value of life issue.
- Although details are species-specific, the value of life concept appears generally applicable to complex organisms.
- This problem is analytically difficult. Distinguishing between concepts 2, 3, and 4, involves “comparing different values of zero.”
- The science-oriented general public is unaware of this issue and is trained to believe concept 1.

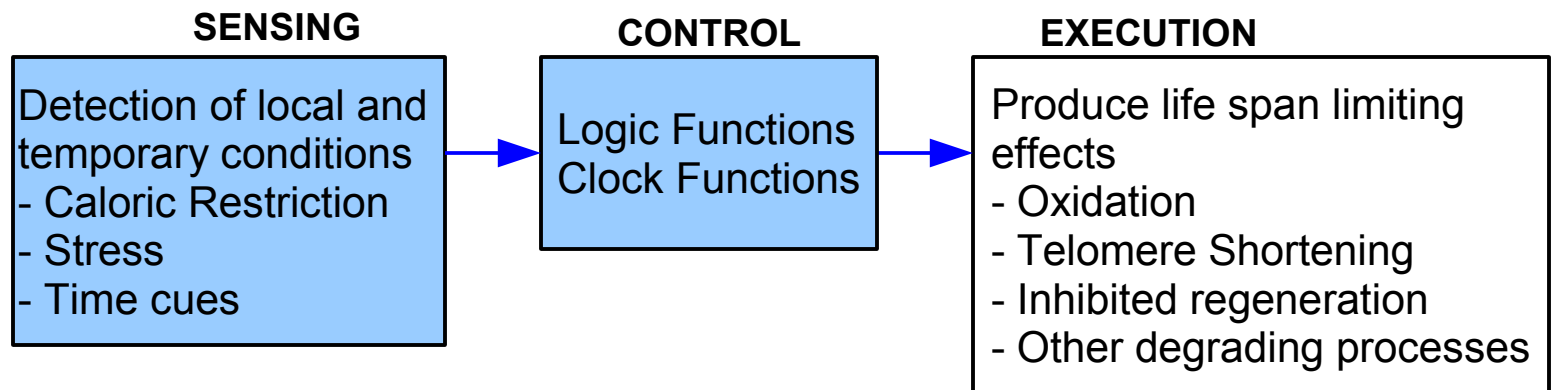
# Optimum Life Span Concept (curve 4) - Consequences

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- **Complex Mechanism:** Organisms have evolved myriad complex mechanisms involving genes, signaling, cooperation between tissues, etc. directed at achieving the optimum life span. If there is evolutionary force toward limiting life span we would expect similar complex mechanisms directed at limiting life span.
- **Regulation:** Many evolved mechanisms are equipped with means (including sensing, processing, signaling) for real-time self-adjustment (*regulation*) in response to external conditions. We could reasonably expect this to also apply to life span limiting mechanisms.
- Concepts 1, 2, 3, do not allow for existence of a complex mechanism whose purpose is to limit life because no evolutionary force to develop it exists. Concept 4 is incompatible with traditional (c. ~1950) evolutionary mechanics theory.

# Complex Life Span Regulation

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Intervention targets could exist in sensing, control, and signaling mechanisms in addition to execution mechanisms.

# Aging Theories vs. Observational Evidence

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- The non-programmed (concepts 2, 3) and adaptive theories (concept 4) both provide an explanation for the wide variation of mammal life spans between species by relating life span to reproductive maturity.
- Non-programmed theories have significant internal logical problems and compete with each other.
- Adaptive theories (complex life span regulation mechanism) provide a better fit to additional observations:
  - Caloric restriction effect
  - Stress effects
  - Progeria/ Werner syndrome
  - Aging genes
  - Negligible senescence
  - Observed life span regulation in simple organisms (Kenyon, et al)
  - Octopus suicide mechanism (Wodinsky 1977)
  - Similarity in aging symptoms between short and long lived species

# Aging and Evolutionary Mechanics

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- Theorists favoring non-programmed theories generally cite compatibility with traditional (c. ~1950) evolutionary mechanics as their *only* rationale. The following statement is typical: “*The way evolution works makes it impossible for us to possess genes that are specifically designed to cause physiological decline with age or to control how long we live.*” Olshansky, Hayflick, and Carnes, *Scientific American*, 2004.
- When declining value-of-life aging theories originated (1952), traditional mechanics theory was generally accepted.
- Since 1962, multiple (4+) alternative mechanics theories have been published (in response to observed conflicts *other than aging*) and our collective scientific certainty regarding traditional mechanics has clearly declined.
- Many of these developments have been driven by rapid and continuing genetics discoveries.
- Programmed aging theories based on group selection, kin selection, and evolvability have been published.

# Evolvability

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- Evolvability premise:
  - Organisms can acquire design characteristics that affect their capacity for further evolution (*evolvability*).
  - Characteristics that benefit evolvability can be selected.
  - Design characteristics that benefit evolvability are generally adverse or neutral to traditional fitness. Evolvability benefit can trade off against traditional fitness disadvantage.
  - Design characteristics benefit evolvability by increasing local variation in a population or by enhancing the sensitivity or effectiveness of the natural selection process.
  - Evolvability characteristics increase the *rate* at which a population under evolutionary pressure could adapt to changes in their external world – producing competitive advantage.
  - “Evolvability” in PubMed: Conrad (1989), Wagner (1995). Currently 315 articles.
  - Weismann's programmed death theory (1882) is essentially an evolvability theory of aging.

# Evolvability Benefits of Aging

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- Adult Death Rate
  - Evolution rate is nominally inversely proportional to life span.
  - Evolution of adult characteristics requires adults
  - An immortal population would have fewer adults than an aging population of the same size and would tend to be genetically dominated by relatively fewer individuals thus reducing variation.
- Evolution of characteristics that involve accumulative acquisition of non-genetic fitness factors
  - Evolution of intelligence and immunity would be difficult in an immortal population because acquired fitness advantage (e.g. knowledge and experience) would be competing with genetic fitness advantage (e.g. intelligence).
- Challenge effect
  - Skulachev and Goldsmith suggest gradual aging has an evolvability benefit over semelparity or sudden biological suicide by amplifying the functional difference between more and less fit individuals.

# Traditional Objections to Evolvability

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- There is little opposition to the idea that a design characteristic could benefit evolvability nor to specific proposed benefits. The objections center around mechanics of propagation and retention.
- Extensive analyses purporting to debunk group selection were performed in the 1960s (e.g. G. Williams 1966).
- A major objection to group selection concerns timing, sequence, and scenario for propagation and retention of an individually-adverse but group-benefiting trait. Group benefit is seen as longer-term, “slower”, and weaker than individual disadvantage. See some counter-arguments in appendix.
- Evolvability theories (~1990+) post-date these analyses.
- Critics *currently* suggest the earlier analyses also apply to evolvability. Evolvability benefits groups, species, even future species at expense of individual disadvantage and superficially seems to be an instance of long-term group selection.
- This assessment ignores major logical differences to be described.

# Evolvability Timing

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- Evolvability characteristics enable or enhance the natural selection process. Their “benefit” is to the evolution process. Evolvability characteristics produce *preconditions* (e.g. variation) needed for the operation of the natural selection mechanism.
- We can imagine a relationship like  $dF/dt = kEP$  where  $dF/dt$  is the rate at which population fitness would change in response to evolutionary pressure (P) given a population evolvability (E). If evolvability was zero, no adaptation could take place. A population of identical, perfectly adapted clones, would possess maximum fitness but zero evolvability. The above relationship is not dependent on the time period (dt) chosen.
- Therefore contend: Evolvability is not subject to the timing/sequence criticism attributed to group selection.

# Non-Science Factors

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- Many non-science factors influence aging theories and underlying evolutionary mechanics theory and generally favor non-programmed theories:
  - Counter-intuitive nature of programmed aging
  - Public ignorance of *scientific* evolutionary mechanics issues and consequent alternative mechanics theories
  - Religious opposition and pseudoscience proposals (intelligent design) in evolutionary mechanics act to discourage scientific disagreement with traditional mechanics
  - Public ignorance re value-of-life controversy
  - Ethical, moral, religious issues surrounding aging
  - Historical sequence
  - Specialization and relative lack of inter-discipline communication
- Efforts to resolve the programmed/non-programmed issue need to recognize and deal with the non-science factors.

# Conclusions

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- The programmed and non-programmed theories suggest that substantially different mechanisms are responsible for aging in humans. This could affect directions for medical research into treatment and prevention of age-related conditions.
- Traditional (c. ~1950) evolutionary mechanics concepts should no longer be an excuse for discounting empirical evidence.
- The importance of this issue deserves a serious and well-funded effort directed toward definitive resolution.
- Any serious analysis should consider:
  - Empirical evidence (including non-mammals)
  - **Current** state of evolutionary mechanics theory
  - Impact of non-science factors

# Programmed-Aging.org

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- Several theorists (T. Goldsmith, G. Libertini, J. Mitteldorf, and J. Bowles) maintain and edit a web site devoted to programmed (adaptive) aging and the programmed vs. non-programmed controversy.
- This site (<http://www.programmed-aging.org/>) provides extensive expansion and documentation of arguments for programmed aging.

# Appendix

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- Table summarizing biological aging theories - 17
- Arguments in favor of group selection - 18
- Observations that apparently conflict with traditional (c. ~1950) evolutionary mechanics theory - 24
- Evolvability explanations for apparently conflicting observations - 25

# Aging Theories Summary

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Principal theories of biological aging by controlling evolutionary mechanics theory (traditional or alternative), controlling evolutionary value of life concept, and degree to which they fit multi-species observations and other empirical evidence.

<b>Evol. Mech.</b>	<b>Evolutionary Value of Life Concept</b>	<b>Dependent Aging Theories</b>	<b>Empirical Fit</b>
Trad.	1) Value of life does not vary with age	- Generic damage theories, wear and tear theories	Poor
Trad.	2) Value of life declines to zero	- Mutation accumulation theory, Medawar, 1952	Better
Trad.	3) Value of life declines, not to zero	- Antagonistic pleiotropy theory, Williams, 1957 - Disposable soma theory, Kirkwood, et al, 1975 - Other theories in which aging is an unavoidable adverse side-effect rigidly linked to some individually beneficial property	Better
Alt.	4) Value of life becomes negative beyond species-specific optimum age	- Purposely programmed adaptive aging theories	Best

# Traditional Objections to Group Selection

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- There is little objection to the idea that an organism design characteristic could benefit groups or to specific proposed group benefits. Objections primarily concern mechanics of propagation and retention of an individually disadvantageous trait.
- Extensive analyses purporting to debunk group selection were performed in the 1960s (e.g. G. Williams 1964).
- A major objection concerns timing of group benefit vs. individual benefit: Analyses suggested that short-term individual disadvantage would override longer-term group benefit. Group benefit would be “too slow” and “too late” to compensate for an individual disadvantage. Timing problem is worse for larger groups, still worse for “species-level” group selection.
- Difference between individual and group benefit is concerned with timing and details of associated propagation/ retention scenario. End result (extinction or non-extinction) is the same.

# Group Selection and Genetics

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- Genetics discoveries increasingly suggest that the evolution process is actually comprised of many sub-processes that operate over very different time scales. In addition to the antagonistic pleiotropy concept, the gene-oriented theories and evolvability theories are substantially based on these discoveries.
- The functional evolutionary difference between individual benefit and group benefit depends on one's assumptions regarding the overall pace of the evolution process. If, as suggested by genetics discoveries, the overall process is slower and more complex, then the functional difference (“slower”, “later”) between a group benefit and an individual benefit is also relatively less. This advances the case for group selection.

# Rigidity, Robustness, Pleiotropy

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- It is increasingly understood that the rate at which a particular *phenotypic* evolutionary change can occur depends on what sort of *genomic* change is required:

Required Genomic Change	Time Scale
Recombination of existing alleles e.g. selective breeding	Very rapid
New mutation to one gene	Slower
Coordinated changes to many genes	Very slow
New functionally different gene	Slower still

# Pleiotropy and Robustness

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- ***Pleiotropy*** refers to the fact that a single gene often controls several phenotypic properties and therefore changing that gene alters multiple properties. Those properties are therefore linked to each other. This linkage may not be perfectly rigid (forever and for all time) because complementary changes to many genes may allow changing one property without changing the others. Further, eventually, new genes could be created allowing yet more comprehensive changes. The rigidity of a pleiotropic linkage is therefore limited in duration.
- ***Robustness*** refers to the idea that genomic design can affect the rate at which specific phenotypic evolutionary changes can occur. One example: Multiple copies of essentially the same gene could make the controlled properties less susceptible to alteration.

# Evolutionary Processes

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Short-Term  
Less Conservation  
Less Rigid



Natural selection  
Recombination  
  
Gene modification  
  
Genome reorganization  
  
Species  
  
Gene formation  
  
  
Multiploidy  
  
  
Codons  
  
Basic Genetic Structure

Long-Term  
More Conservation  
More rigid

Evolutionary Processes  
vs.  
Time Scale

# Antagonistic Pleiotropy (AP) and Group Selection

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- Williams used genetics discoveries (pleiotropy) to justify the idea that an individually adverse characteristic (e.g. aging) could happen to be rigidly linked to an unspecified individually beneficial characteristic. The rigid linkage would prevent aging from being selected out (assuming a declining value of life).
- The same concept and assumptions would allow a group benefiting but individually adverse trait (e.g. aging) to be retained and would overcome the argument that group benefits are slower than individual disadvantage.
- Aging, per se, is apparently individually adverse for any complex organism and presumably has been so for billions of years. Pleiotropy can not be indefinitely rigid – eventually new genes would be produced and massive reorganization of old genes would occur. Why wouldn't aging select out over such a long period?
- In the group selection case, a pleiotropic linkage developed in the primordial past would tend to be retained because, in the long-term, the group benefit would offset the individual disadvantage. Therefore contend AP provides a better fit to group selection theories of programmed aging!

# Traditional Mechanics vs. Observations

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- The following apparent conflicts between traditional (c. ~1950) evolutionary mechanics and observations have been identified:
  - Animal altruism
  - Gross life span variations between similar species (~100:1 in mammals)
  - Apparently unnecessary delays in reproductive maturity of many species (especially males)
  - Sexual reproduction (massively individually adverse)
  - Some mating behaviors that generally delay reproduction
  - Some semelparity and biological suicide
  - Various genetics discoveries
- Apparent conflicts (especially altruism) resulted in development of alternative mechanics theories beginning in ~1962:
  - Group selection (~1962)
  - Kin selection (~1964)
  - Gene-oriented theories (e.g. selfish gene theory 1975)
  - Evolvability theories (~1995)

# Evolvability vs. Apparently Conflicting Observations

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- Sexual reproduction increases variation at expense of traditional fitness.
- An evolved trait that encourages animals to avoid mating with close relatives improves variation at expense of traditional fitness.
- Altruism is consistent: If it is logical to mate with non-relatives it is also logical to protect non-relatives. They might be future mates, have descendents that are future mates, or etc.
- Characteristics that restrict reproduction (e.g. unnecessarily late reproductive maturity, mating behaviors that delay reproduction) act to increase adult death rate.

# Evolvability vs. Evolution of Inheritance Mechanisms

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- Many obviously very complex evolved (genomic) mechanisms associated with inheritance do not have any first-order effect on traditional fitness design (expressed phenotypic characteristics that plausibly affect survival or reproductive capability):
  - Multiple paired chromosomes, meiosis, unequal crossover, etc.
  - An asexually reproducing, haploid, single chromosome organism can be envisioned that had identical fitness design as a sexually reproducing, diploid, multi-chromosome organism.
  - Problem: What is the origin of the evolutionary force that caused genomic evolution?
  - Evolvability (creation of local variation) provides an explanation.

# Genomic Design vs. Evolutionary Mechanics

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- Many aspects of genomic design have no apparent phenotypic effect but do have plausible effects on evolutionary mechanics by influencing subsequent genomic changes:
  - Genetic redundancy, “robustness”
  - Sex-linked propagation
  - Genetic linkage associates nearby alleles
  - Repeat patterns in introns or other “junk” DNA encourage copying of specific data segments
  - Genetic “modules”, “reusable code”
  - “Digital genetics”, constraints common to all digital information systems
  - “Inheritable epigenetics”

# Definitions

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- ***Programmed Aging*** – Theory proposing that deterioration and consequent life span limitation due to aging is an adaptation and purposely the result of mechanisms that evolved and were retained because life span limitation produces direct evolutionary benefit.
- ***Traditional Evolutionary Mechanics*** – Mechanisms that control the evolution process as generally accepted in 1950, i.e. *neo-Darwinism* or *The Modern Synthesis*.
- ***Alternative Evolutionary Mechanics*** – Modifications to traditional mechanics proposed (post 1962) in efforts to explain apparent observed discrepancies with traditional mechanics such as altruism, i.e. group selection, kin selection, gene-centered theories, and evolvability theory.

# Programmed vs. Non-Programmed Aging - Summary

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- Programmed aging provides a better match to observations.
- Criticism of programmed aging is nearly exclusively based on evolutionary mechanics issues. Specifically: programmed aging is incompatible with traditional (c. ~1950) evolutionary mechanics theory.
- Since 1962 multiple alternative evolutionary mechanics theories have been developed in response to observed conflicts *other than aging*. Programmed aging theories based on three of the alternatives have been developed.
- Scientific confidence in traditional mechanics theory has declined (witness all of the proposed alternatives) suggesting more weight should be given to empirical evidence. Logical arguments based on modern genetics increasingly support alternative theories.
- This issue is important to medicine and should be resolved.