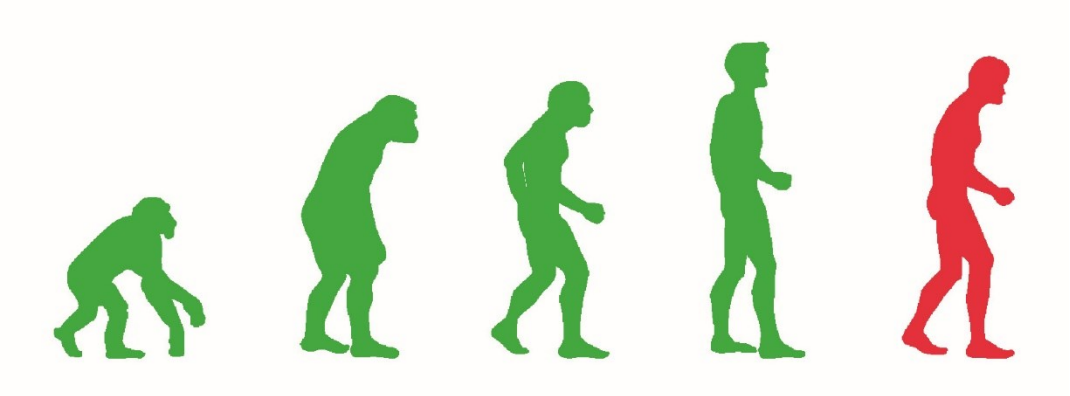
Theories of

Biological Aging



And

Implications for Public Health

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9/2009 Revised 10/2019

Theories of Biological Aging and Implications for Public Health

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September 2009 revised October 2019

doi:10.13140/RG.2.1.2832.4242

The current version of this presentation is kept at http://www.azinet.com/aging/Theories_Summary.pdf

Keywords: aging theories, senescence, gerontology, evolution, anti-aging medicine, biology

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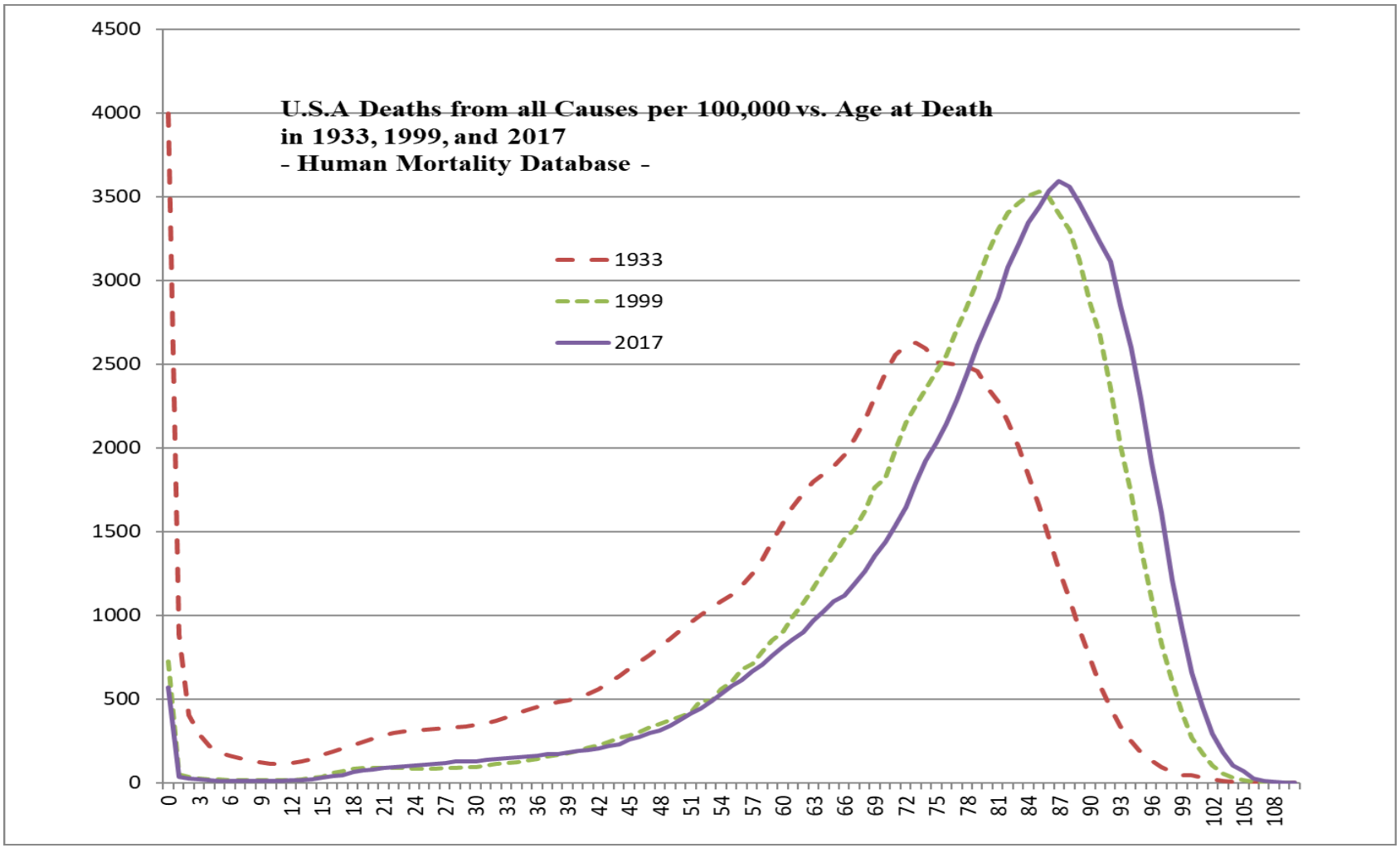
Aging Theory Overview

- ***Why do we age?*** This question has baffled scientists for millennia. There is still substantial scientific disagreement regarding even the basic nature of aging.
- There are three main classes of theories:
  - Legacy theories (wear and tear and fundamental limitation theories)
  - Evolutionary Non-Programmed Aging (non-adaptive aging)
  - Evolutionary Programmed Aging (adaptive aging)
- Aging theories are important: Most people in developed countries die of highly age-related diseases such as cancer and heart disease.
  - Understanding age-related diseases requires understanding aging.
  - Is anti-aging medicine (that generally delays aging) feasible or impossible?
  - Is anti-aging research foolish and wasteful or potentially vital to the future of medicine?
- Modern aging theories and theories regarding the mechanics of the evolution process are critically interrelated.

Aging Overview

- *Biological aging (senescence)* refers to gradual internally caused deterioration and death seen in multiparous organisms such as mammals. Symptoms of aging include many different *age-related* diseases and conditions that display incidence that drastically increases with age.
  - Diseases include cancer, heart disease, stroke, arthritis, cataracts, Alzheimer's disease.
  - Conditions (are more universal) include physical weakness, loss of sensory capacity (vision, hearing, smell, balance), appearance changes, loss of reproductive capacity.
- *Immediate causes* of the many different symptoms are known to be different and treatments directed at the different causes have been developed and applied.
- *Lifespan* refers to the lifetime a typical individual would obtain in the absence of external causes of mortality such as infectious diseases, predators, or lack of food or habitat.
- Different mammal species exhibit similar symptoms but on drastically different age-schedules resulting in vastly different lifespans.

Human Mortality



Human Mortality Notes

- Medical, safety, and other health advances have dramatically reduced infant, childhood, and other mortality in younger people due to non-age-related causes. In developed countries age-related diseases and conditions now cause most deaths.
- Beyond approx. age 30 probability of death increases exponentially doubling approx. every 10 years.

Darwin's Evolution Theory

- There is no current scientific disagreement with *most* aspects of Darwin's theory:
- Evolution is extremely incremental, accumulative, and has operated over a period spanning billions of years.
- Current species are descendants of earlier different species and ultimately descended from single-cell organisms.
- Organisms can *adapt* via natural selection to changes in their external world.
- Darwin's survival of the fittest concept: The evolution process causes organisms to acquire evolved inheritable design characteristics (*traits*) that cause *possessing individuals* to produce more adult descendants.
- Therefore: The force of evolution is toward developing *internal immortality* or the absence of any internal limitation on lifespan. Leads to the idea that aging results from fundamental limitations i.e. laws of physics or chemistry.

Evolution and Aging

- Following Darwin's publication (1859) it was soon apparent that:
  - Darwin's concept provided a plausible explanation for the vast majority of observed traits.
  - Aging closely resembled other traits that varied greatly between physically and biochemically similar species. Lifespans vary more than 200:1 in mammals, from <1 year to >200 years. Fish lifespans vary more than 1000:1.
  - Aging and internally limited lifespan could ***not*** be Darwinian traits because they ***reduced*** an individual's ability to reproduce.
- There is still no wide scientific agreement on a solution to this problem!
- Eventually other traits such as *animal altruism* appeared that also conflicted with Darwin's concept regarding the mechanics of evolution.
- Subsequent discoveries, especially in genetics, exposed issues with arcane details of evolutionary mechanics that affect aging.

Individual vs. Population Benefit

- Beginning in the1960s multiple theories appeared to the effect that a trait that benefitted the ability of a *population* to avoid extinction and grow could evolve and be retained despite causing an *individual* disadvantage. These theories resulted from observation of inherited animal behaviors that did not appear to make sense according Darwin's individual-oriented concept.
- Most traits that benefit populations also benefit individual members. Aging is one exception.
- There is no scientific disagreement with the idea that an extinction event affects the subsequent biosphere.
- However, there is still disagreement regarding the idea that a population benefit could override an individual disadvantage.
- The population vs. individual issue drives modern aging theories.

Evolvability and Aging

- Darwin's concept assumes the ability to evolve (evolvability) is an inherent property of life; all organisms are subject to mutations, natural variation, and natural selection.
- Subsequent discoveries show that in complex (diploid, sexually reproducing) organisms, evolvability is itself mainly the result of evolved traits.
- Evolvability theories propose that a trait that increases evolvability can exist even if individually adverse.
- Aging theories based on evolvability suggest many ways in which limiting individual lifespan increases evolvability such as by increasing variation between members of a population.
- Evolvability issues are relatively recent (1995+).

Legacy Aging Theories

- ***Damage theories*** suggest that the many age-synchronized symptoms are simply the result of some more general deteriorative process such as oxidation, free radicals, or mechanical wear and tear.
- ***Fundamental limitation theories*** suggest that aging is the result of a fundamental limitation such as one of the many laws of physics or chemistry. Entropy is often mentioned.
- Legacy theories fail to explain the gross lifespan differences in biochemically and physically similar species and have little current scientific credibility. Why does a parrot live six times longer than a crow? Damage theories fail to explain why the evolution process would not have evolved *repair* processes to reverse or prevent the damage. Myriad examples of repair processes exist. Wounds heal; cells are replaced; infections are combatted; worn toenails regrow.
- Legacy theories still appeal to those interested only in human aging and not concerned with evolution issues.

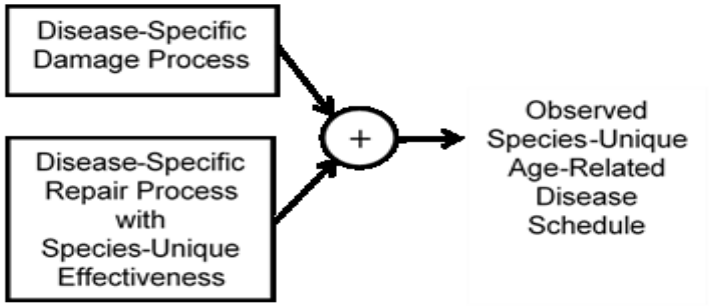
Evolutionary Aging Theories

- Beginning in1952 theories appeared to the effect that aging and lifespan ***were*** evolved traits. These theories were based on modifications to Darwin's *individual-oriented* concepts that were more *population-oriented,* and provided a much better fit to multi-species symptom and lifespan observations. There are two classes:
  - ***Non-programmed theories*** – The force of evolution is toward obtaining a particular species and population-specific ***minimum*** lifespan. The internal ability to live longer does not produce an evolutionary advantage or disadvantage.
  - ***Programmed aging theories*** – The force of evolution is toward obtaining a species and population-specific ***optimum*** lifespan. The internal ability to live longer creates a population disadvantage. This led to the evolution of biological mechanisms that ***purposely limit lifespan.***

Non-Programmed Aging Theories

- In 1952 P. Medawar suggested that a *wild population* is little affected by aging because of attrition due to *external causes* such as predators, infectious diseases, or lack of habitat or food supply. Example, if virtually no wild mice would be expected to survive more than 3 years because of external mortality (even if internally immortal) there would be little evolutionary force toward developing the internal capacity for living longer.
- In 1957 G. Williams suggested that the adverse fitness effects of mammal aging such as weakness occurred at too early an age to have zero effect on a population and that therefore aging must create at least a small evolutionary benefit to offset its disadvantage. Evolutionary aging theories attempt to accommodate the Medawar and Williams concepts.
- Non-Programmed theories include:
  - Mutation Accumulation theory
  - Antagonistic Pleiotropy theory
  - Disposable Soma theory (although some suggest this is actually a programmed theory).

Non-Programmed Aging Mechanisms

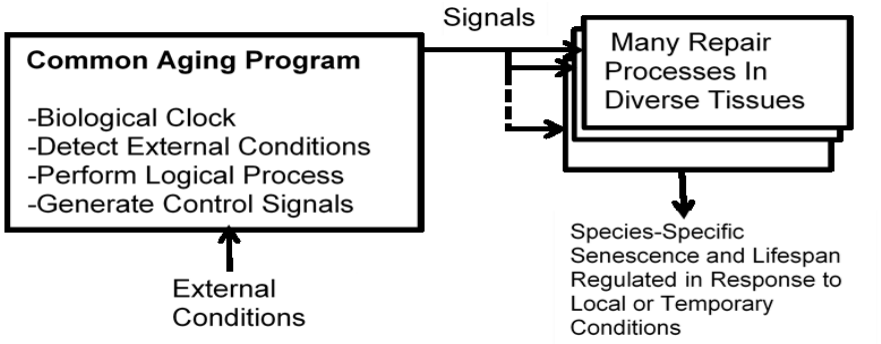


- Each of many different disease processes is counteracted by a different disease and species-specific repair process.
- Each population only evolved and retained repair processes effective enough to deliver the lifespan needed by that population.
- Explains the multi-species observations: similar symptoms occurring on a species-specific schedule, drastically different lifespans.
- Suggests the many different damage and repair processes are independent of each other. There is ***no potentially treatable common cause*** of the many different symptoms.

Programmed Aging Theories

- Based on more recent evolutionary mechanics theories to the effect that evolution can produce traits that aid growth and survival of a *population* despite being adverse for individual members.
- Population-oriented concepts include group selection (1962-), kin selection (1975), and evolvability theories (1995-).
- Many population benefits of senescence have been proposed:
  - Increases speed and precision of evolutionary adaptation
  - Reduces tendency toward overpopulation and consequent population crashes
  - Aids evolution of organism features like intelligence and immunity that involve acquisition of organism properties during lifetime
  - Limits ability of a few individuals to dominate the gene pool – increases variation

Programmed Aging Mechanisms



- Senescence is controlled by a ***biological program*** similar to those that control other life-cycle events such as growth, reproductive maturity, mating seasons, and metamorphosis. Such program might detect temporary or local external conditions that affect optimum lifespan and adjust genetically specified lifespan to compensate by regulating repair processes.
- Explains the multi-species lifespan observations.
- Also explains many other observations.
- Suggests that interfering with the common mechanisms or associated signaling could ***generally delay aging***.

Evidence Favoring Programmed Aging Mechanisms

- A number of observations favor programmed aging mechanisms. Some of them involve non-mammal evidence that is typically ignored by non-programmed mammal aging theories.
- **Non-Aging Species** Some *negligibly senescent (NS)* species apparently do not age (do not exhibit reductions in survival or reproductive fitness with age) e.g. Rougheye Rockfish. Programmed theories suggest these species have *lost* the ability to age and are more likely to become extinct. Non-programmed theories have difficulty explaining NS.
- **Progeria** Hutchinson-Guilford progeria and Werner syndrome are human genetic diseases that accelerate many or most symptoms of aging – suggests defects in a common controlling mechanism.
- **Hormones** Multiple human hormones increase or decrease with age as predicted by programmed aging mechanisms that involve signaling.

Evidence Favoring Programmed Aging Mechanisms

- **Stress Effects -** Various forms of stress (caloric restriction, exercise, etc.) appear to ***increase*** lifespan suggesting a ***regulative response*** to local or temporary conditions such as famines, changes in predation, etc. that affect optimum lifespan.
- Experiments with genetically engineered roundworms (C. elegans) have increased lifespan by ***a factor of ten!***
- **Octopus Suicide** – Octopuses exhibit an explicit suicide mechanism in which individuals stop eating after reproducing. Removing optical organs inhibits this behavior. Suggests a complex mechanism involving connections to the nervous system in both detection and implementation of the suicide function.

Genetics Discoveries and Aging Theories

- Biological inheritance is crucial to the evolution process.
- Essentially the entire science of genetics post-dates Darwin. Genetics discoveries (some quite recent) have exposed issues with details of Darwin's concept regarding the evolution process that suggest that evolution is more population-oriented.
- In addition to having complex phenotypic designs, complex organisms have complex genomic designs, many details of which plausibly affect the evolution process in ways that support population-oriented evolutionary mechanics.

Implications for Medicine

- We cannot really understand cancer or other massively age-dependent disease without understanding aging.
- The major medical question is whether there exist potentially treatable (medically alterable) factors that are common to multiple manifestations of aging.
- Simple deterioration and non-programmed theories suggest there is no treatable common factor – continues existing main-line medical thinking.
- Programmed theories suggest existence of controlling mechanisms (biological clock, signaling, sensing, etc.) that are common to multiple symptoms and therefore existence of treatable common factors.
- Direct observational evidence supports this (progeria, caloric restriction, aging genes, etc.)
- The theories point in very different research directions: disease-specific damage mechanisms vs. common lifespan regulation mechanism.
- Continued non-resolution of the programmed/ non-programmed issue damages the credibility (and funding level) of age-related medical research efforts.

Programmed / Non-Programmed Controversy

- Programmed aging was originally proposed in 1882.
- However, as recently as 2002 programmed aging was widely considered *theoretically impossible* because of the very direct conflict with Darwin's individual-oriented evolutionary mechanics concept.
- Genetics discoveries favoring population-benefit evolution, and other discoveries suggesting programmed aging have resulted in a re-emergence of programmed aging theories.
- Substantial investment in medical research based on programmed aging has begun.

Potential Anti-Aging Agents and Protocols

- Some agents or behaviors appear to beneficially affect two or more major manifestations of aging:
  - Statins are useful in heart disease and also appear to have an anti-cancer effect.
  - Aspirin appears to beneficially affect several symptoms of aging.
  - Caloric restriction delays aging especially in short-lived mammals.
  - Exercise apparently delays incidence of many aging symptoms. Some studies suggest exercise is more important to lifespan than even obesity.
  - Resveratrol, a constituent of red wine and grape skins has been found to extend lifespan in animal studies and may beneficially affect heart disease, cancer, and diabetes. A fish experiment (Valenzano et al 2006) increased lifespan 56 percent.

Aging Research

- ***Google*** has started an ***anti-aging research company*** called ***Calico*** as part of their R & D program that attempts game-changing technological advances outside their core industry.
  - Calico is following a programmed aging path. Vice President for Aging Research is leading programmed aging experimentalist Cynthia Kenyon.
  - Calico and pharmaceutical company ***AbbVie*** have invested up to $1.5 billion in a joint effort to develop anti-aging "interventions."
- The U.S. National Institutes of Health (NIH/NIA) is conducting a *search for anti-aging agents* called the *Interventions Testing Program (ITP).*
  - Researchers can nominate proposed oral anti-aging agents for testing on mice in triple redundant geographically separate facilities.

Anti-Aging Medicine

- The ***American Academy of Anti-Aging Medicine (A4M)*** has 26,000 members (85% physicians, 12% scientists, researchers, and health practitioners). A4M provides certification, training, and continuing medical education in this specialty.
- A4M supports 3 interpretations of "Anti-Aging Medicine:"
  - ***Cosmetic*** – Delays appearance of aging
  - ***Healthy Life*** – Prolongs active and useful lifetime
  - ***Lifespan Extension*** – Generally delay aging and increase lifespan
- Many A4M physician members have added anti-aging medicine to an existing practice in another discipline.

Conclusions

- Scientific opposition to programmed aging is declining. Empirical evidence increasingly favors programmed aging.
- Substantial funds are now being invested in programmed aging research by Calico, the NIH/NIA Interventions Testing Program, and others.
- Programmed aging and anti-aging medicine add an important new approach to the ways in which we attempt to treat and prevent age-related diseases and conditions. We can reasonably hope for “low hanging fruit” and rapid advances.

Further Reading

- Book: ***The Evolution of Aging 3rd Edition***, May 2014, 200 pages **E-book version PDF (Free)** **Paperback Version** ISBN: 0978870956
- ***An Introduction to Biological Aging Theory 2nd Edition*** Overview in book format.
- **http://www.programmed-aging.org/** Comprehensive information on aging theories.
- **http://www.azinet.com/aging/** Additional detail and links to many online resources on aging.
- ***New Truth to the Fountain of Youth: The Emerging Reality of Anti-Aging Medicine***, ISBN0978870948, Short ebook discusses approaches to finding anti-aging agents. 2014
- Journal article: *Aging, Evolvability, and the Individual Benefit Requirement; Medical Implications of Theory Controversies*, Journal of Theoretical Biology DOI:10.1016/j/jtbi.2008.02.035 2008
- ***Encyclopedia of Gerontology and Population Aging*** Springer International Online: ISBN 978-3-319-69892-2 2019 Print version ISBN 978-3-030-22010-5 in-publication.

Further Reading

-- About the Programmed/ Non-Programmed Controversy --

- ***On the programmed/ non-programmed nature of ageing***…, T. Kirkwood and S. Melov, *Current Biology* 21-18 2011. The case for non-programmed aging.
- ***On the programmed/ non-programmed aging controversy***, T. Goldsmith, *Biochemistry (Moscow) Phenoptosis* 77-7 2012 The case for programmed aging.
- ***Aging as a particular case of phenoptosis, the programmed death of an organism (A response to Kirkwood and Melov "On the programmed/non-programmed …"),*** V. Skulachev, *Aging* 3-11
- ***Arguments against non-programmed aging theories***, T. Goldsmith, *Biochemistry (Moscow) Phenoptosis* 78-9 DOI: 10.1134/S0006297913090022
- ***Aging Theories and the Zero-Sum Game***, T, Goldsmith, *Guest Editorial, Rejuvenation Research* 17:1 Health policy issues with the continuing controversy. 2014
- Journal Article: *Biological Aging: Active and Passive Mechanisms Compared*, Journal of Bioscience Hypotheses 12/2008 DOI: 10.1016/j.bihy.2008.12.002