Sebastes aleutianus (rougheye rockfish) possibly born the same year as Darwin (maximum age of S. aleutianus ~205 yrs)

Shortraker rockfish (S. borealis) caught in March 2007; estimated 95-115 years old
Why We Age, What Causes Us To Age, And What Can Be Done About It

Synergy Lecture May 2007

Marc Mangel
Department of Applied Mathematics and Statistics
UCSC
• Mathematics in Biology ("How Extraordinary")
• Exactly What are We Talking About
• Why We Age
• What Causes Us to Age
• What Can Be Done About It
• Some Conclusions
“It is a widespread fallacy that what mathematics contributes to biology is quantification of an otherwise innumerate science. But experimental biologists have long been expert at measuring and quantifying.

The real contribution of mathematics lies in a precise qualitative framework of reasoning…

Experiment, however, is in no sense superior to theory, nor vice versa: both are necessary ingredients of a proper understanding of nature. An experiment done with no theoretical framework to analyze or interpret the results…is meaningless; theory in the absence of experiment remains mere theory.”

No new principle will declare itself from a heap of facts

The book of Nature is written in the language of mathematics
Three Definitions of Aging

Physiological: A decline in performance with age (more properly termed senescence)

Demographic: An increase in the chance of death with age; a decrease in the chance of reproduction with age

Evolutionary: A decline in the expectation of future genetic representation with age
We are familiar with the physiological definition...
The Demographic Definition Deals with Mean Life Span (Life Expectancy)
And Maximum Life Span

Mme. Jeanne Calment: World Record Holder For Human Life Span 122 years (born 1875)

Still rocking at 121. Frenchwoman Jeanne Calment, who died in 1997 at the age of 122, shows off a CD she released the year before.
The Survival Curve Underpins Demographic and Evolutionary Ideas
US Survival Curves in 1901, 1946 and that predicted in 1950 for 1975
The Demographic Ideal: Rectangularization of The Survival Curve
The Mortality Rate at Age, $M(a)$, Quantifies the Changes in the Survival Curve

1. Follow a cohort of individuals, all born in the same year

2. $N(a) =$ Number of individuals alive at age $a$

3. Find $M(a)$ from

$$
N(a + 1) = \frac{N(a)}{e^{M(a)}}
$$

$$
M(a) = -\ln \left[ \frac{N(a+1)}{N(a)} \right]
$$
Mortality Rates in Sweden

Estimating the mortality curve is a problem in statistics.
A discovery of the 1990s: The Emergence of Supercentenarians and Slower Aging

Mortality curves do not always rise: they may level off or even decline in the oldest of the old.
Predicting the shape of the mortality trajectory is a great challenge and has important policy implications.

A problem in applied mathematics.
Why We Age

The major question is not whether aging leads to debility, the inability to overcome disease, and then death, but why individuals age in the first place.

OUR ANCESTORS’ SHORT LIVES

Few of them made it to thirty,
Old age was the privilege of rocks and trees.
Childhood ended as fast as wolf cubs grow.
One had to hurry, to get on with life
before the sun went down, before the first snow.

…

There wasn’t a moment to lose,
no deferred questions, no belated revelations,
just those experienced in time.
Wisdom couldn’t wait for gray hair.
…

Life, however long, will always be short.
Too short for anything to be added

Harcourt Brace.
Peter Medawar (1952): There is no selection on mutations that express themselves after the reproductive lifespan. Mutations accumulate
Woody Guthrie (1912-1967) 
Died of Huntington's Chorea, a 
Recessive Genetic Disease

“This machine kills fascists”

Arlo Guthrie (b. 1947) 
Induced into the Long Island Music Hall of Fame 2007

“Alice’s Restaurant Massacre”
George Williams (1957): The news is even worse: Antagonistic pleiotropy

Natural selection will favor genes that increase survival or reproduction at young ages, even if they have adverse affects at post-reproductive ages

What if there is an advantage to keen eyesight at young age, even if it means glaucoma at older age?
Bill Hamilton (1966): The moulding of senescence by natural selection: Live now, pay later

\[ R_0 = \sum_{x=0} l_x m_x > R_a = \sum_{x=a} l_x m_x \]

In a stable or growing population, Medawar and Williams have to be correct

\[ \sum_x e^{-rx} l_x m_x = 1 \]
The Waning Power of Natural Selection: Fitness Consequence of a One Year Increase in Survival at Different Ages
Experiments Confirm These Ideas—That Aging Can Evolve Due to Selection

Graphs showing survival rates of male and female flies under different breeding conditions.
What Causes Us To Age

Oxidative Damage

Telomere shortening

The ultimate irony: The thing we need most to live—oxygen—is what’s killing us.

We age not because our cells die but because they stop dividing.
The processes of life require oxygen in many forms

- Molecular oxygen to bind with hemoglobin
- Reactive oxygen species (ROS) and reactive nitrogen species (RNS), the Free Radicals (chemical species with unpaired electrons), that are essential for signalling and defense
Some roles for ROS/RNS in normal cellular function

• Development: cell growth and division, fusion of egg and sperm

• Neurotransmitters

• Immune defense: destroy cancer and virus-infected cells, kill pathogens

• Energy metabolism and membrane function

• Regulation of cell death

• Recovery from hypoxia

• Insulin release
But some of these free radicals end up in the wrong places, causing damage. It is this damage, due to oxidative stress, that gets expressed as aging and mortality.
Free Radicals Are Associated with a Variety of Diseases

- Artherosclerosis
- Cancer
- Alzheimer’s disease
- Parkinson’s disease
- Hypertension
- Cataracts
- Fanconi’s anemia
- Huntington’s disease
- Chronic renal failure
- Diabetes
- HIV/AIDS
- Chagas disease
- Rejection of transplants
Sources of Free Radicals Are All Around Us
The same thing that makes you live can kill you in the end.

- Peroxidation of unsaturated fatty acids in membranes
- Oxidation of SH-containing groups, protein-misfolding, enzyme inactivation
- DNA strand breaks, cross-links, base excision
- Inhibition of synthesis of proteins, nucleotides and fatty acids
Damage to Protein Accumulates As we age

![Graph showing the accumulation of damage to protein over lifespan](image)

Fig. 1. Carbonyl content of protein from different tissues. One observes a dramatic increase in oxidized protein during the last third of the lifespan. The line is the semi-logarithmic fit to all the data points. The data points were taken from published reports: ■, human dermal fibroblasts in tissue culture (Oliver et al., 1987); ★, human lens (Garland, 1990); □, human brain obtained at autopsy (Smith et al., 1991); ◆, rat liver (Starke-Reed and Oliver, 1989); and ◆, whole fly (Sohal et al., 1993).
High Levels of Damage are Associated with Reduced Motor Performance

Figure 2. Inverse relationship between motor coordination and oxidative damage to brain mitochondrial DNA in mice. (From Pallardó et al. [110]). Points are average for $n = 3$–$4$ values. The vertical scale indicates the percentage of the score for motor coordination in old mice compared with the score for 12-month-old mice.
Higher Levels of Damage are Associated with Higher Mortality Rates

Figure 2. Relationship between mean 8-oxo-dG in lymphocyte DNA and early deaths from CHD in men (■) and women (○) in the five countries (each country is identified by its first letter).
Longer life is associated with low levels of Damage

Fig. 3. Steady-state levels of 8-oxoG in heart mitochondrial DNA correlate negatively with the maximum longevity of mammals (equation: \( y = a \cdot x^b \)). Modified from [49].

Fig. 9. 8-Hydroxydeoxyguanosine content in liver DNA as a function of life span in mammals. 8-OHdG was determined in purified DNA sample hydrolyzed to nucleosides by enzymatic digestion. Nucleoside preparations were analyzed by HPLC using an electrochemical detector at 600 mv.
Longer life is associated with higher levels of DNA repair.
We have cellular defenses against free radicals

- Catalase and Mn-Superoxide dismutase (mitochondria matrix)
- Membrane bound vitamin E (mitochondrial inner membrane)
- Cu-Zn Superoxide dismutase (mitochondrial inner membrane, matrix space and cytoplasm)
- Glutathione peroxidase and catalase (cytoplasm)
- Other antioxidant molecules (vitamin C, quinon) (blood plasma, serum, and cytoplasm)
Organisms with More Lifetime Energy Production have More ROS Defense
The Dynamics of Damage are Complex

Original Contribution

Obesity increases the risk of UV radiation-induced oxidative stress and activation of MAPK and NF-κB signaling

Santosh K. Katiyar a,b,*, Syed M. Meeran a
The Dynamics of Damage are Complex

Available online at www.sciencedirect.com

ScienceDirect


Original Contribution

Obesity increases the risk of UV radiation-induced oxidative stress and activation of MAPK and NF-κB signaling

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Mathematical models can help sort this out
Telomeres are an internal cellular clock telling our cells when their time has come

\[ [TTAGGGG]_n \]
Longer telomeres are associated with greater survival.

- Years beyond age 60
- Beyond age 75
In Mice, at Least, Short Telomere and Telomerase Deficiency Means More Cancer and Shorter Lives
What Can Be Done About It
Prediction is difficult, especially about the future
Prediction is difficult, especially about the future
Avoiding Premature Aging and Death
• Genetic Counseling
• Caloric/Dietary Restriction
• Antioxidant Supplementation
• Telomerase Therapy
• A Manhattan Project For Aging: Engineering Negligible Senescence
Many Sources of Premature Aging Death Are Behavioral--We Can Easily do Something About Them
Genetic counseling may be most effective for age-related diseases that are recessive and have simple genetics

- Huntingdon chorea (post maturity)
- Werner’s syndrome (early aging)
- Bloom’s syndrome (increased susceptibility to cancer and infections; males usually infertile, females have fertility problems)
- Various cancers
In Small Mammals, Caloric Restriction Extends Lifespan

Fig. 1. A negative linear relationship can be demonstrated between the intensity of calorie-restricted feeding and the increase in maximum life-span recorded, within the limits tolerated by the species. The data is taken from 24 published studies using the CR model of retarded ageing in rodent species. In each study, increase in maximum life-span is normalised to that of the non-restricted animals in order to control for differences in husbandry practices, health status of animals, species, strain of rodent and feeding regime employed. An index of 1.0 represents survival in the control, non-restricted animals (100% energy intake).
When males of two long-lived mouse strains were put on calorically restricted diets at 12 months of age and given nutrient supplements, their life spans increased by 20 percent.
Some Consistent Effects of Caloric Restriction

- Extension of lifespan/dealy of aging
- Reduction in fecundity of females
- Increase in mass-specific metabolic rate
- Delay in accumulation of oxidative damage to macromolecules
- Increase in resistance to various forms of stress

----- BUT
In Longer-lived Species the Effects of Caloric Restriction are Less
2006: The Votes Are In

Biogerontology (2006) 7: 123–125

EDITORIAL

Can dietary restriction increase longevity in all species, particularly in human beings? Introduction to a debate among experts

Éric Le Bourg · Suresh I. S. Rattan

Category 1: Too early to decide (1 vote)

Category 2: DR can work for human beings (5 votes)

Category 3: DR cannot work for human beings (6 votes)
Antioxidant Supplementation

Curcumin

Krill oil

Fig. 3. Effect of curcumin on superoxide radical generation by HG. Values are means ± SE (n = 6). Differences between # and * are significant (P < 0.05).
Halliwell and Gutteride (1998)

Any expanding field attracts the charlatans, such as those who make money out of proposing that consuming radical scavengers will make you live forever or that taking tablets containing superoxide dismutase will enhance your sex life. In evaluating these and other less obviously silly claims, it is useful to understand the basic chemical of radical reactions.
Mortality due to heart disease

Blood levels of alpha-tocopherol

Epidemiology of Heart Disease and Vitamin E

Decreasing incidence of heart disease mortality
We already have exceptionally high levels of antioxidant defenses.

Superoxide Dismutase
Vitamin E

Carotenoids
The Antioxidant Story is also Complex

Antioxidants may become pro-oxidants ----->
Or suppress natural production

Life-long vitamin C supplementation in combination with cold exposure does not affect oxidative damage or lifespan in mice, but decreases expression of antioxidant protection genes

Colin Selman a,1,6, Jane S. McLaren a,1, Claus Meyer b, Jackie S. Duncan c, Paula Redman a, Andrew R. Collins d,2, Garry G. Duthie d, John R. Speakman a
**Nutrient Interactions and Toxicity**

Exposing Ferrets to Cigarette Smoke and a Pharmacological Dose of β-Carotene Supplementation Enhance In Vitro Retinoic Acid Catabolism in Lungs via Induction of Cytochrome P450 Enzymes

Chun Liu, Robert M. Russell and Xiang-Dong Wang
Nutrition and Cancer Biology Laboratory, Jean Mayer U.S. Department of Agriculture Human Nutrition Research Center on Aging at Tufts University, Boston, MA 02111

**Functions and Actions of Retinoids and Carotenoids: Building on the Vision of James Allen Olson**

The Enigma of β-Carotene in Carcinogenesis: What Can Be Learned from Animal Studies

Robert M. Russell
Jean Mayer U.S. Department of Agriculture Human Nutrition Research Center on Aging, Tufts University, Boston, MA 02111

**Original Research Communication**

β-Carotene and Cigarette Smoke Condensate Regulate Heme Oxygenase-1 and Its Repressor Factor Bach1: Relationship with Cell Growth

Paola Palozza, Simona Serini, Diego Curro, Gabriella Calviello, Kazuhiko Igarashi, and Cesare Mancuso
Advice of Halliwell and Gutteridge (2007) for minimizing oxidative damage:

• Maintain a good intake of fruits and vegetables
• Eat fish periodically
• Avoid too much red meat
• Exercise moderately
• Treat hypertension and hypercholesterol
• Take a daily multivitamin/mineral with the RDA
• Smokers should avoid high doses of beta carotene and take more vitamin B and C
• Drink alcohol in moderation
Telomerase therapy: Tricking Our Cells into Continuing On
The Telomerase Balance

High levels of telomerase

- Growth promoting effects
- Tumor formation
  - Higher mortality due to cancer

- Tissue protective effects
- Reduction in age-related diseases
  - Enhanced tissue fitness
  - Increased life span

Antagonistic effects on survival
A Manhattan Project for Aging:
Strategies for Engineered Negligible Senescence (SENS)

Interventions at three levels:

• Metabolism (restrict)
• Damage (repair/remove)
• Pathology (replenish)

January 8, 2003

An Engineer's Approach to the Development of Real Anti-Aging Medicine

Aubrey D. N. J. de Grey
The author is in the Department of Genetics, University of Cambridge, Downing Street, Cambridge CB2 3EH, UK. E-mail: ag24@gen.cam.ac.uk

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SENS interventions:

• Using nanotechnology to clear damage

• Using stem-cell therapy to replenish tissues that experience cell loss or cells worn out by high mutation load

Goal -- Expected lifespan is 115 for those born in 2030
The Shape of Things To Come
Comparison of present and future life spans.

Extending maximum life span will stretch out the young-adult and middle-aged periods, probably with less extension of the period of decline. Longer youth period and later menopause will allow greater leeway in family planning. The diseases of old age will be delayed, and exposure to them will cover proportionately fewer years of the life span than they now do.
Why We Age:

• Because our ancestors lives were short

OR

• The strength of natural selection decreases as opportunities for future reproduction decline
What Causes Us to Age:

• The accumulation of damage due to a variety of sources, at the molecular, cellular and tissue level but expressed as mortality rate at the organismal level
What Can Be Done About It?

• Avoid sources of premature aging and death
  • Exercise and eat properly

• Antioxidant supplements
  • Caloric restriction

• Telomerase therapy

• Nanobiotechnology and stem cell therapy
But in the end, for all of us
It’s not dark yet, but it’s getting there

La vieillesse nuit gravement à la santé

Mayle, P. 1999. Encore Provence
(Roughly: Old age is hazardous to your health)
Possible origin of the gerontological fact:

“When men began to increase on earth and daughters were born to them…The Lord said ‘My breath shall not abide in man forever, since he too is flesh; let the days allowed him be one hundred and twenty years’”

Genesis 6:1-3

“Moses was a hundred and twenty years old when he died; his eyes were undimmed and his vigor unbated”

Deuteronomy 34:7

Is the gerontological “fact” of maximum life span 120 years a relic of the Western Canon?
<table>
<thead>
<tr>
<th>Individual</th>
<th>First Offspring</th>
<th>Death</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abraham</td>
<td>86</td>
<td>175</td>
</tr>
<tr>
<td>Sarah</td>
<td>90</td>
<td>127</td>
</tr>
<tr>
<td>Ishmael</td>
<td>NA</td>
<td>137</td>
</tr>
<tr>
<td>Isaac</td>
<td>60</td>
<td>180</td>
</tr>
<tr>
<td>Esau</td>
<td>&gt;40</td>
<td>NA</td>
</tr>
<tr>
<td>Jacob</td>
<td>&gt;47</td>
<td>147</td>
</tr>
<tr>
<td>Joseph</td>
<td>36</td>
<td>110</td>
</tr>
<tr>
<td>Moses</td>
<td>NA</td>
<td>120</td>
</tr>
<tr>
<td>Joshua</td>
<td>NA</td>
<td>110</td>
</tr>
</tbody>
</table>
Rosenzweig argues convincingly that the life history data from Abraham to Joshua are accurate IF

where life history data is concerned, we should read ‘year’ as ‘half-year’

- Even at the time of slavery in Egypt, Israelites celebrated two festivals a year, tied to growing seasons

- Hebrew word for year is Shanah, coming from the Semitic root for “two”. Other examples: second (sheynee), repeat (shoneh)

- To this day, Zuni tribe of Pueblo Indians uses a six month calendar

- Back calculations put Joseph in Egypt at the time of Pharaoh Ikhnaton, the monotheistic revolutionary and centralizer of the Egyptian economy
Implications:

Abraham is 37 when he relocated to Canaan, not 75

Sarah gives up on having her own children at 38, not 75; she conceives her first child at 45, not 90

(Would it even be worth mentioning that a 90 year old woman is beyond her child bearing years?)

Ishmael is 7 when he is upset about Isaac’s birth, not 13

Joseph is 8 when he becomes assistant shepherd, not 17

Moses leads the Israelites out of Egypt at 40, not 80 and dies at 60 not 120.
Likely Conclusion

Maximum Record Life Span has increased from about 60 years to about 120 years in the last 3500 years.

Question:

What are the prospects for longevity extension in the next 10, 20, 100, 1000 years?