Aging in individuals and populations: Mathematical modeling

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DALHOUSIE UNIVERSITY
Inspiring Minds

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Objectives:

- To introduce the state of the art of the current approaches to mathematical modeling of aging in populations and individuals
- To illustrate how mathematical models can be used not just for data fitting but also for building theoretical approaches, as common in Physics

A little bit of mathematics

The Ornstein-Uhlenbeck process

$$dY(t) = a(t)(Y(t) - f(t))dt + sdW(t)$$

Kolmogorov equations/ birth death process

$$\frac{dP(n,t)}{dt} = \lambda P(n-1,t) + \mu(n+1)P(n+1,t) + (\lambda + n\mu)P(n,t)$$

$$\frac{dP(0,t)}{dt} = \lambda P(0,t) + \mu P(1,t)$$

$$-\frac{1}{\varepsilon}\frac{d\mu}{dt} = \mu + \varphi(\lambda)$$

The Message from the Past…

Galileo Galilei (1564 – 1642)

"Measure what is measurable, and make measurable what is not so"

Introduction: What is aging?

- Aging is very complex involves each and every system
- Aging is difficult to study in general terms

- Aging makes us closer to death
  - The Gompertz Law: or acceleration of mortality

    (q –mortality rate, or hazard rate)

$$q = -\frac{1}{N}\frac{dN}{dt} = R \cdot \exp(\alpha \cdot t)$$

Theories of Ageing

Over 300 theories of ageing !

…

means

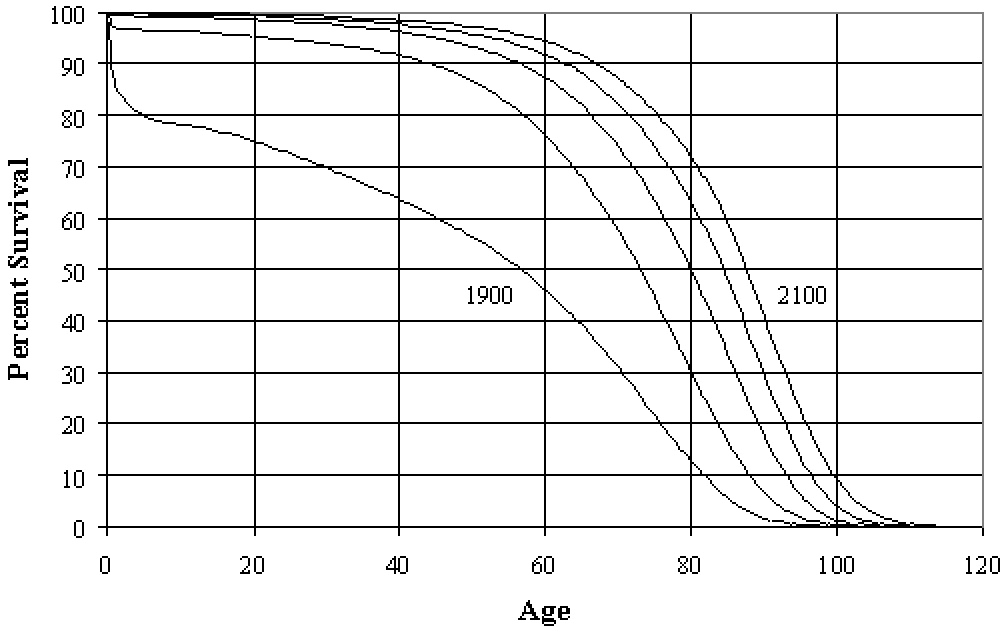
…

No Theory

Yet

abundance of empirical data instead

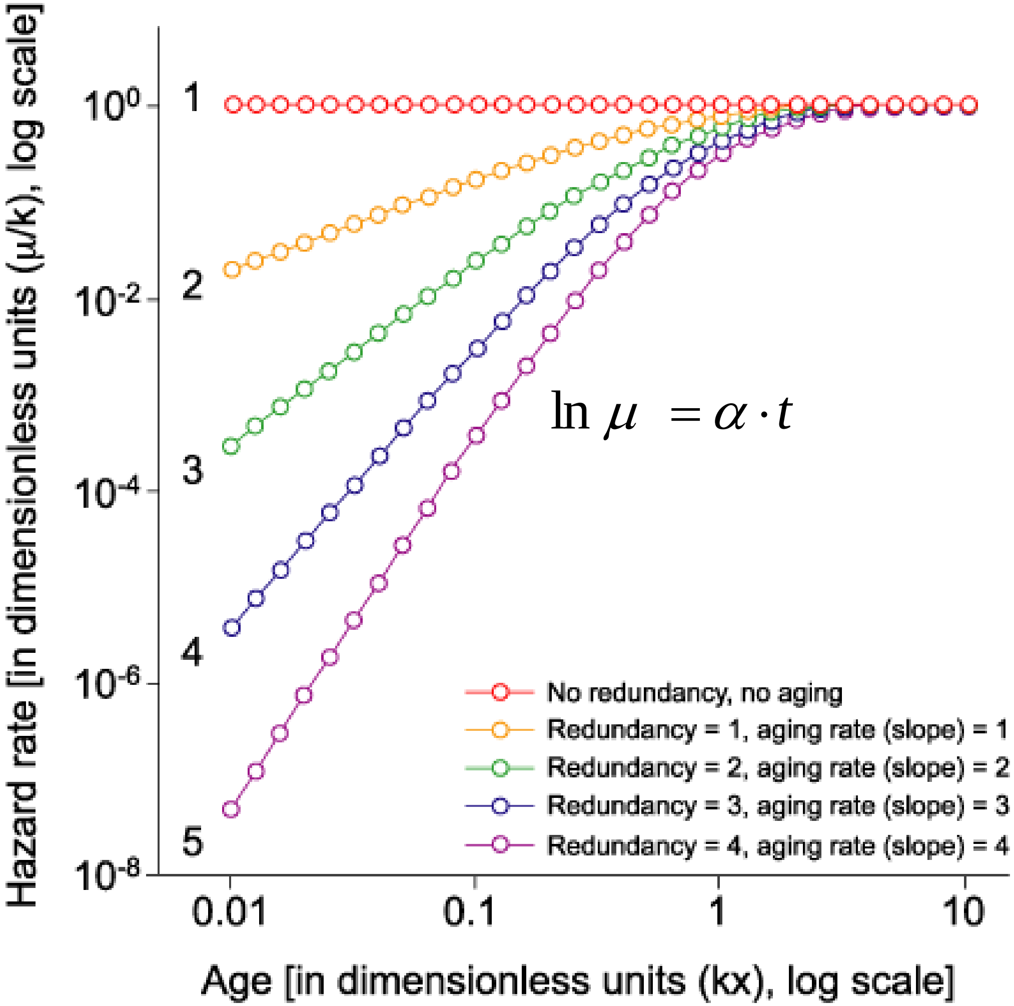
Survival Function



Survival Function for SSA Population
for Selected Calendar Years (1900, 1950, 2000, 2050, 2100)

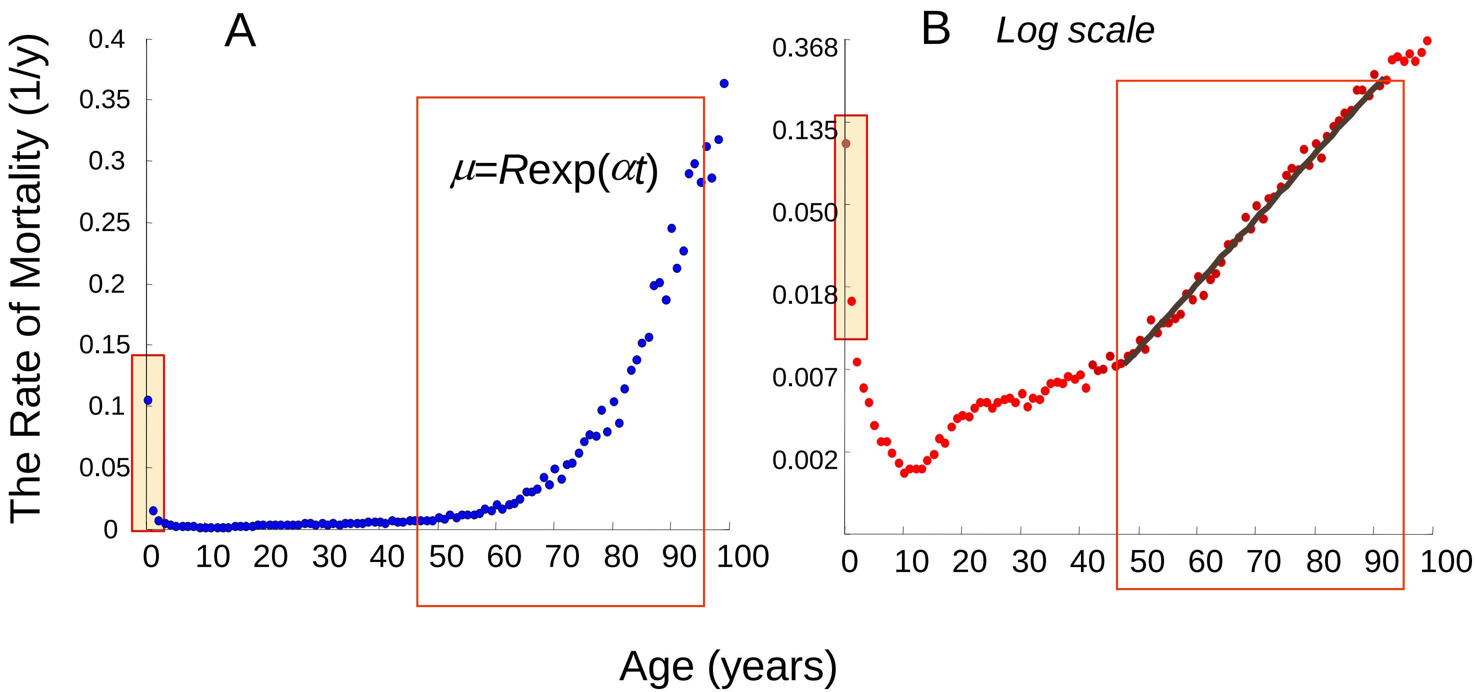
Reliability theory of aging:

Failure kinetics of systems with different levels of redundancy



From Gavrilov & Gavrilova *Sci Aging Knowledge Env*, 2003; 28:1-10

Chronological age is often used as a rough measure of the aging process

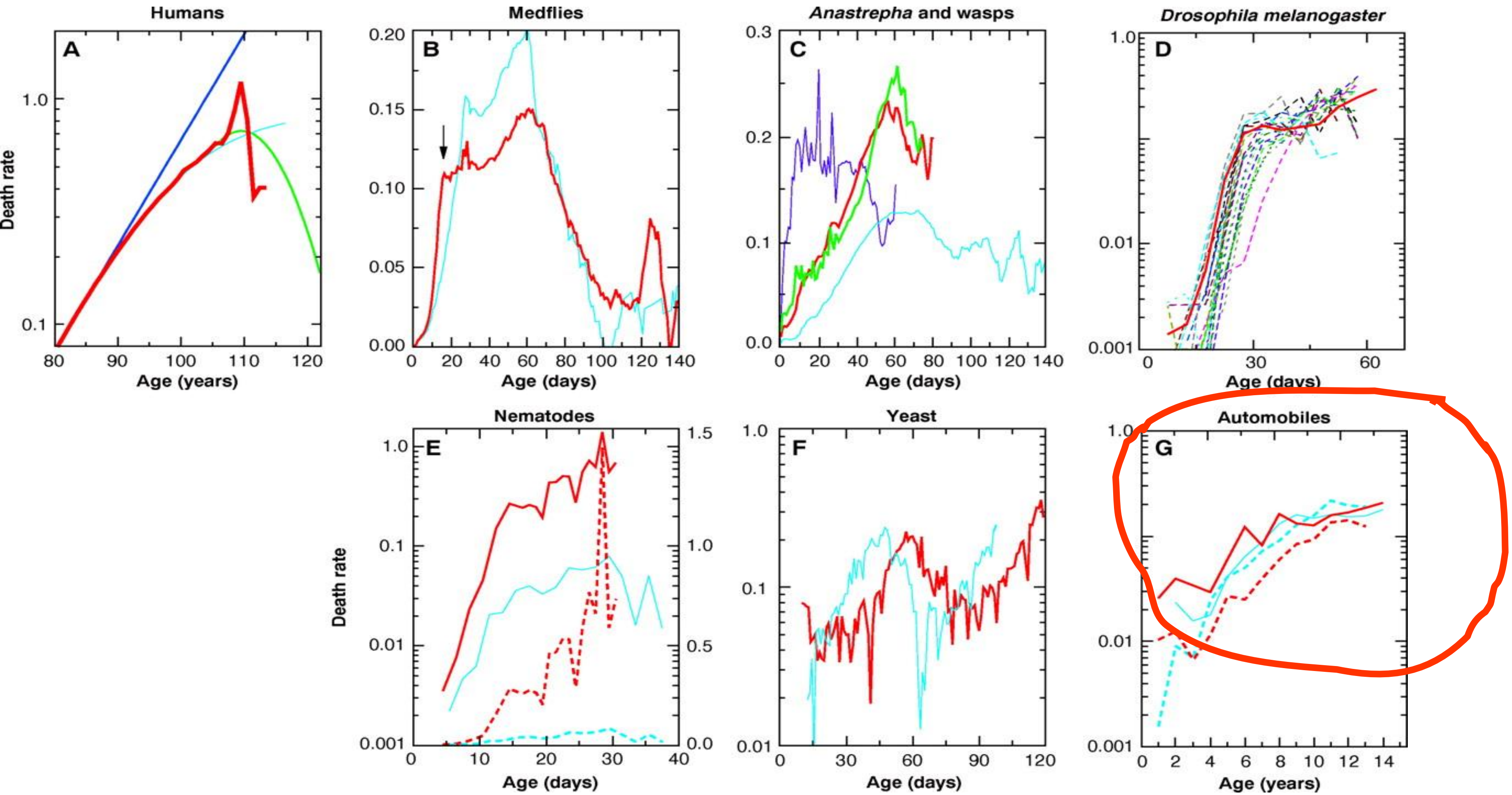


The rate of mortality as a function of chronological age (Canadian data, cohort 1900-1901).

$$\mu = R \cdot \exp(\alpha \cdot t)$$

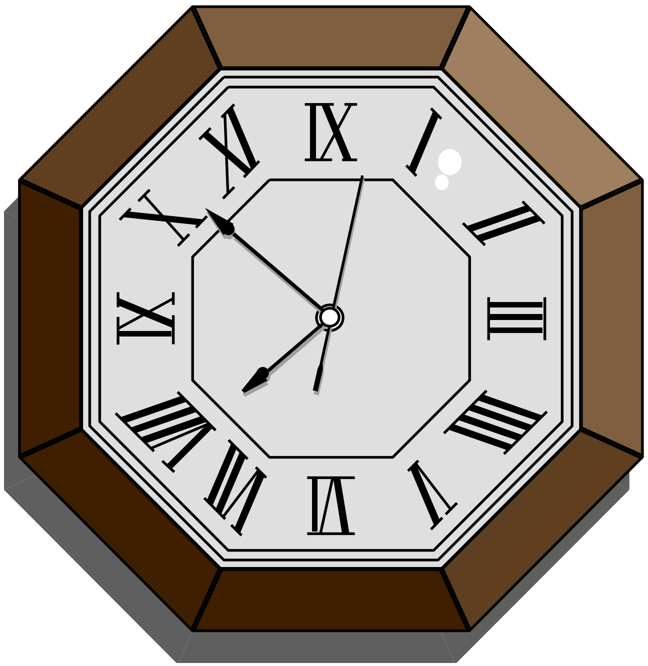
Biodemographic trajectories of mortality

Vaupel at al., *Science*, 1998



Heterogeneity of frailty hypothesis

Measuring aging in individuals

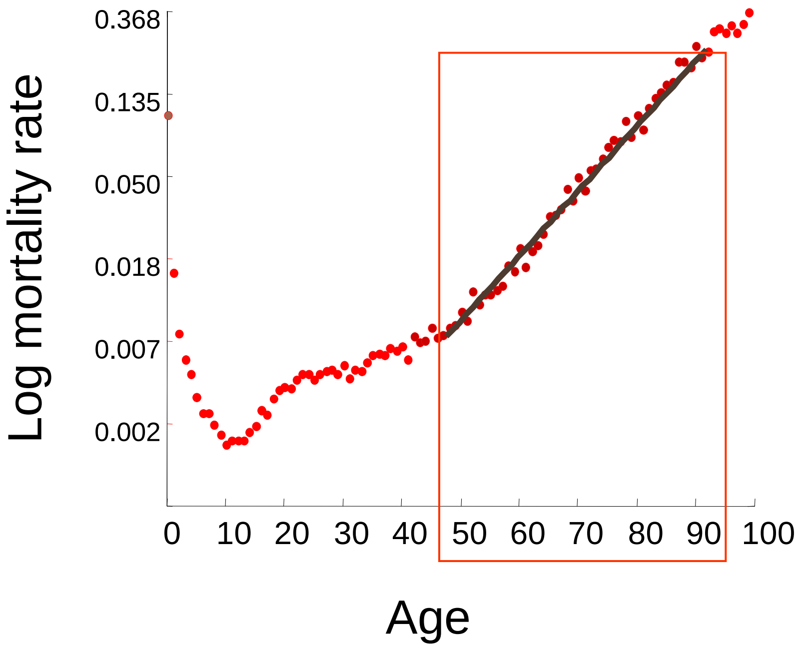


What is Biological Age?

- Chronological age is often used as a rough measure of the aging process
- Even so, for people of the same chronological age, their health status differs greatly.
- “Biological age” is intrinsically individual
- The major challenge is how to measure health status from readily available, health-related information

Aging is related to increasing vulnerability to stresses

- Actually, increasing vulnerability is an intrinsic part of aging



How can we assess vulnerability?

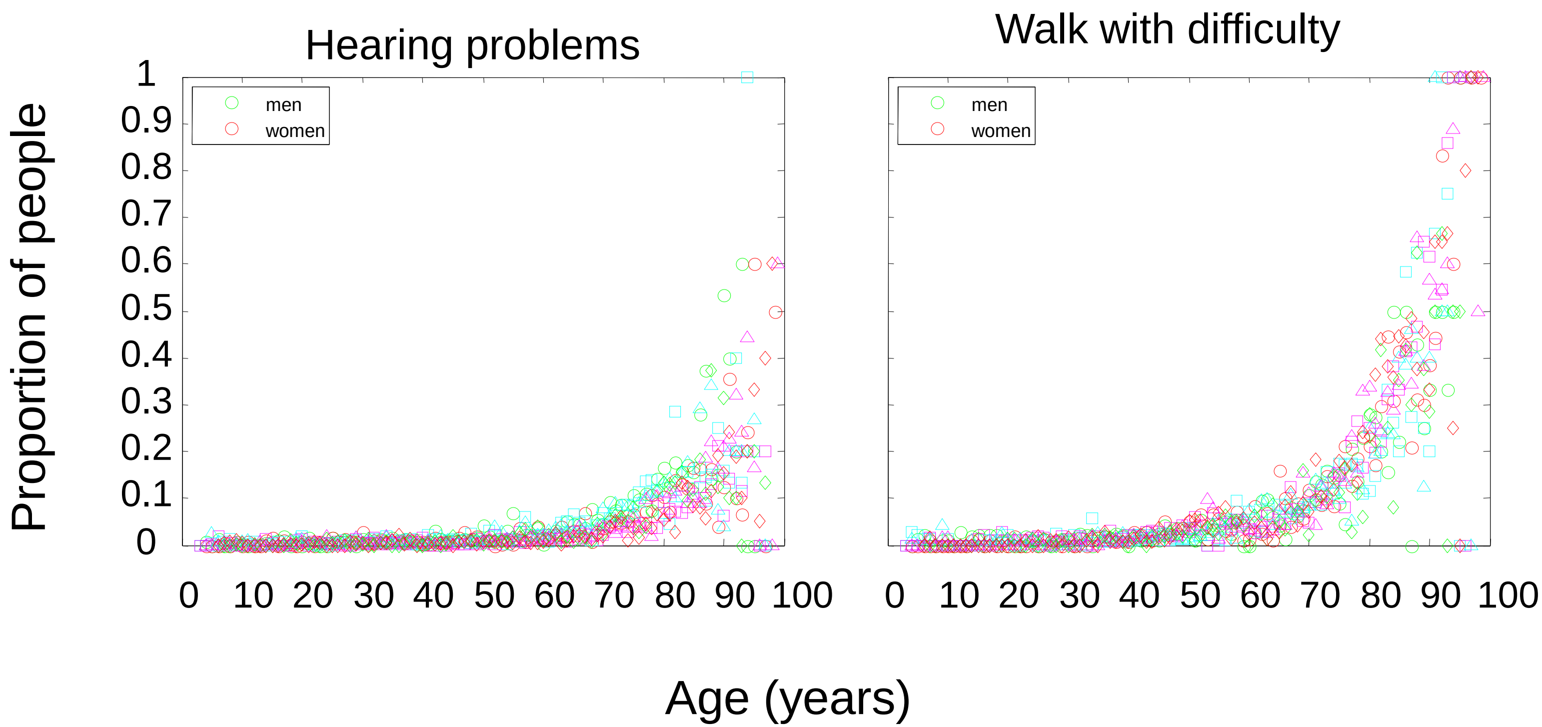
- For example, people with a history of heart attack or cancer are more vulnerable
- So are those with diabetes or hypertension
- So too those who need help for walking
- You can name more…

The concept of health deficits

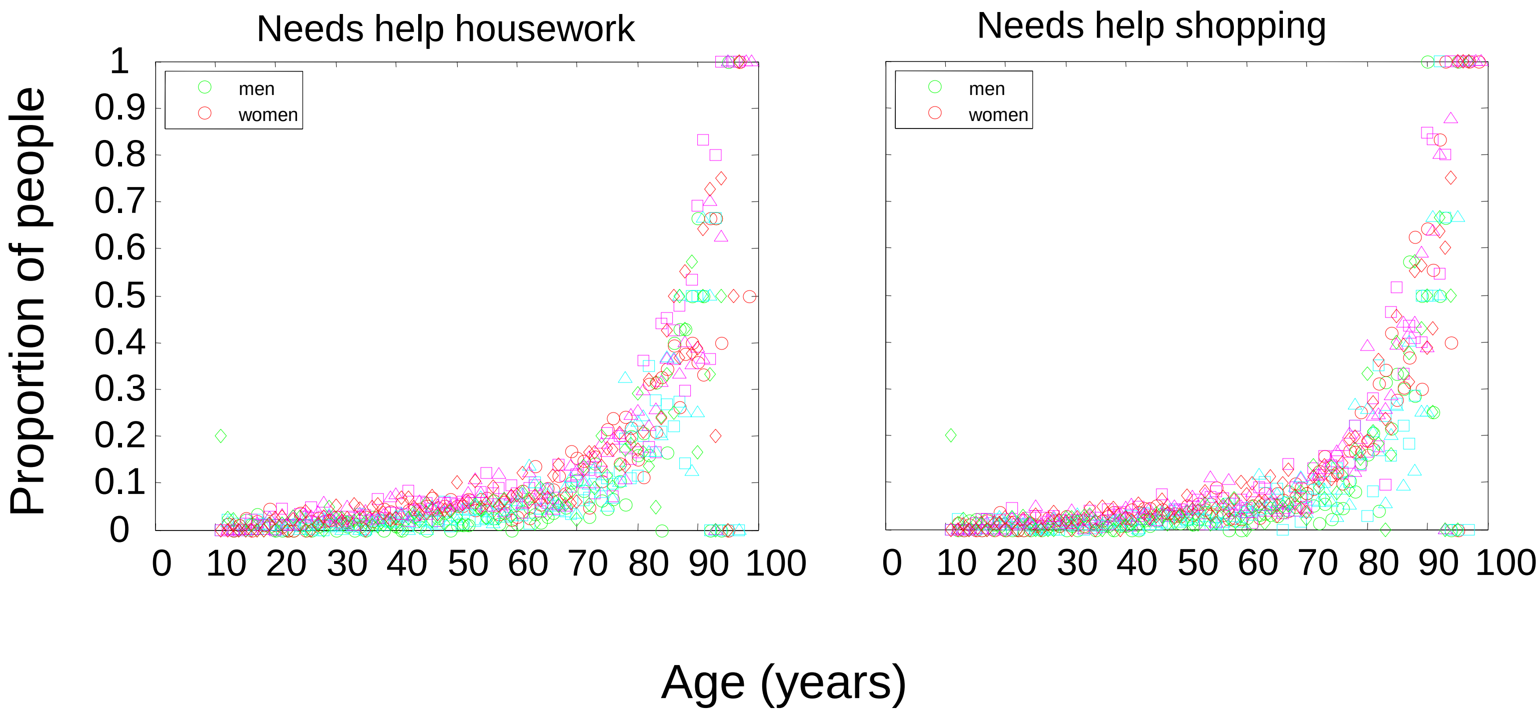
- No rigorous definition can include variety of "wrong" things with health
- Such things have different scales (e.g., interval measures, ordinal, etc.)
- Binary deficits (Yes/No)

People accumulate various deficits with age

from NPHS, Canada, n~17,000



Almost all acquired problems accumulate with age, especially after age 60



What is the Frailty Index?

- We characterize health by the **NUMBER** of deficits
  - *Deficit are considered to be **EQUAL***
- The Frailty Index is the ratio of the number of health deficits to the total number of deficits considered
  - This is necessary for comparisons between different datasets
- Frailty index values are between 0 and 1
  - *In fact they rarely (<<1%) exceed 0.7*

Research Article
TheScientificWorld (2001) 1, 323–336
ISSN 1532-2246; DOI 10.1100/tsw.2001.58

Accumulation of Deficits as a Proxy Measure of Aging

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This paper develops a method for appraising health status in elderly people. A frailty index was defined as the proportion of accumulated deficits (symptoms, signs, functional impairments, and laboratory abnormalities). It serves as an individual state variable, reflecting severity of illness and proximity to death. In a representative database of elderly Canadians we found that deficits accumulated at 3% per year, and show a gamma distribution, typical for systems with redundant components that can be used in case of failure of a given subsystem. Of note, the slope of the index is insensitive to the individual nature of the deficits, and serves as an important prognostic factor for life expectancy. The formula for estimating an individual's life span given the frailty index value is presented. For different patterns of cognitive impairments the average withingroup index value increases with the severity of the cognitive impairment, and the relative variability of the index is significantly reduced. Finally, the statistical distribution of the frailty index sharply differs between well groups (gamma distribution) and morbid groups (normal distribution). This pattern reflects an increase in uncompensated deficits in impaired organisms, which would lead to illness of various etiologies, and ultimately to increased mortality. The accumulation of deficits is as an example of a *macroscopic variable,* i.e., one that reflects general properties of aging at the level of the whole organism rather than any given functional deficiency. In consequence, we propose that it may be used as a proxy measure of aging.

Age-specific trajectories of the frailty index

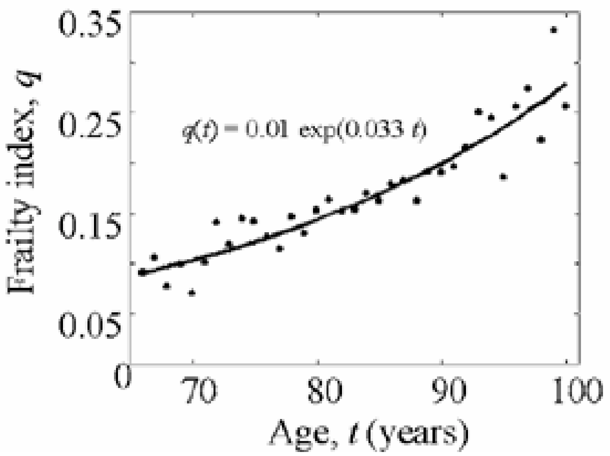
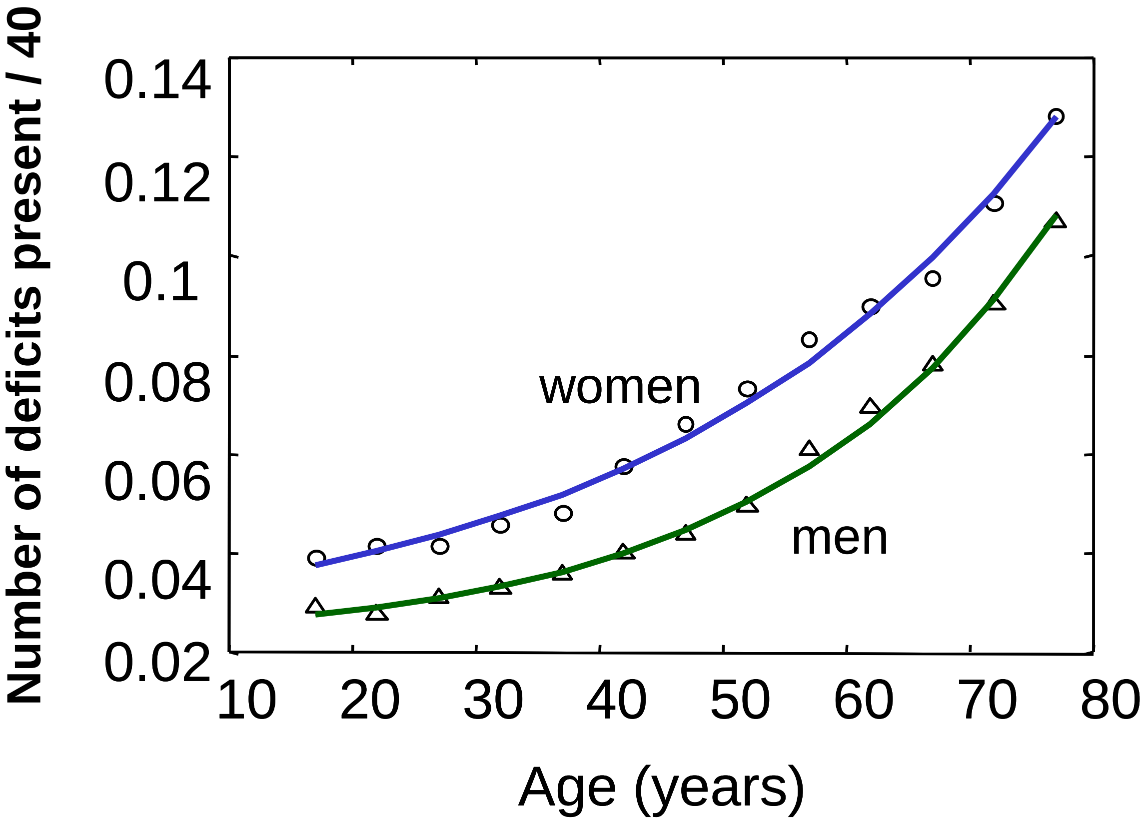
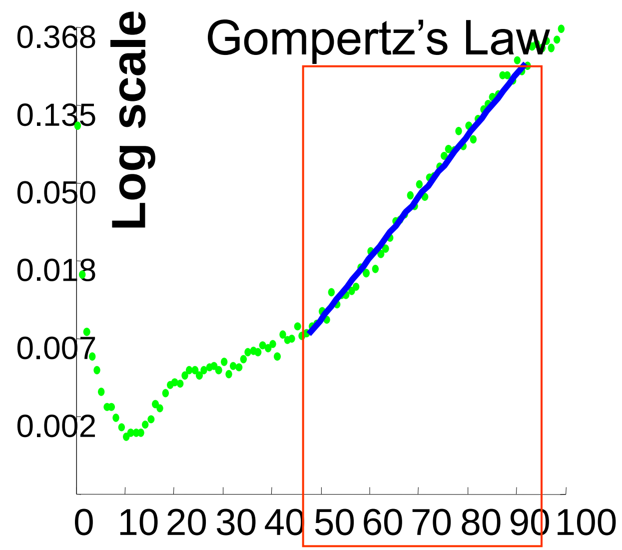


FIGURE 2. Accumulation of the frailty index with chronological age. Points represent the proportion of deficits averaged across the individuals with the same age. Solid lines represents exponential function obtained from to the least square regression, according to Equation (2).

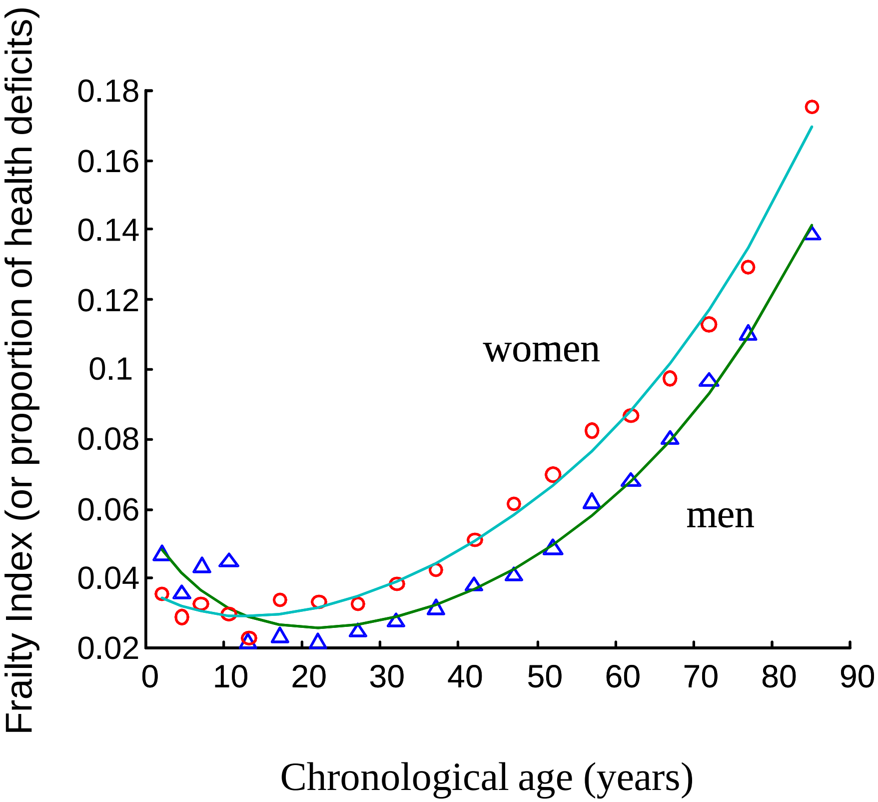
On average, the accumulation of deficits is exponential*

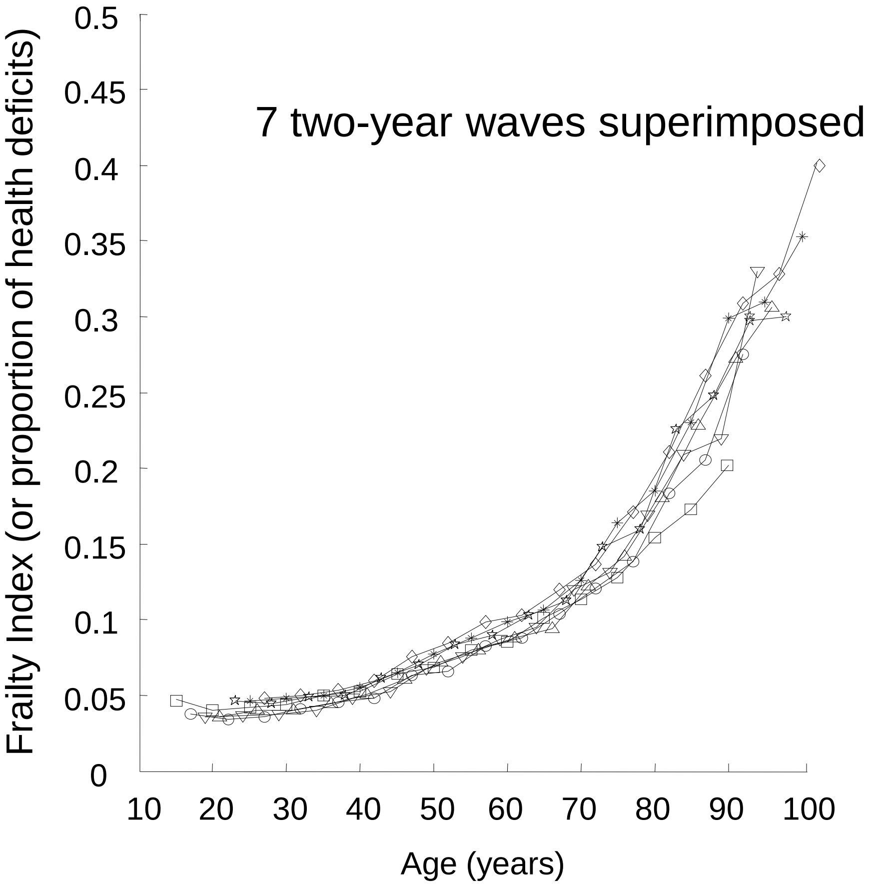




* Mitnitski et al., *Mech Ageing Dev*, 2003

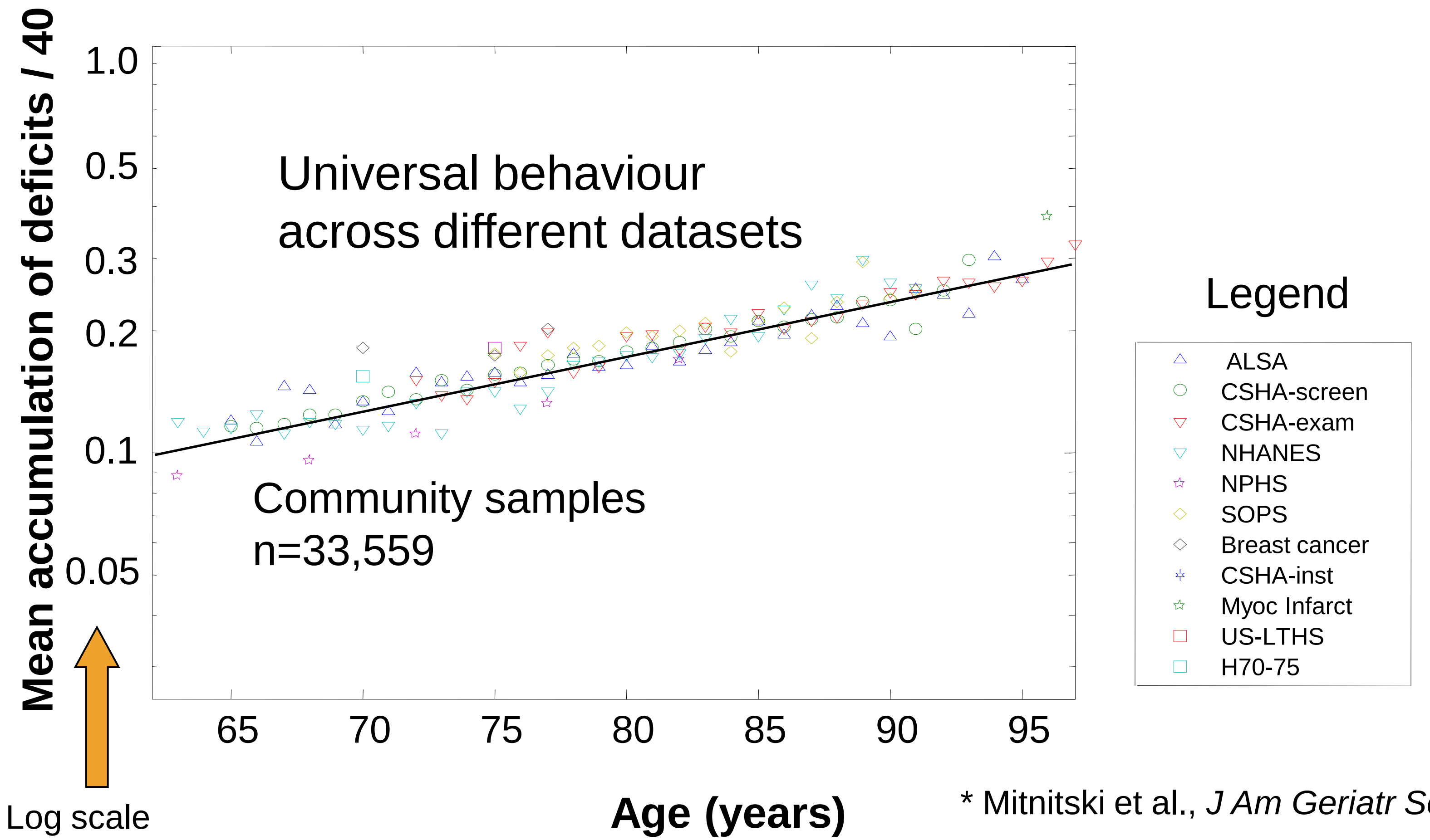
Age-specific trajectories of the frailty index* show a pattern similar to the Gompertz law





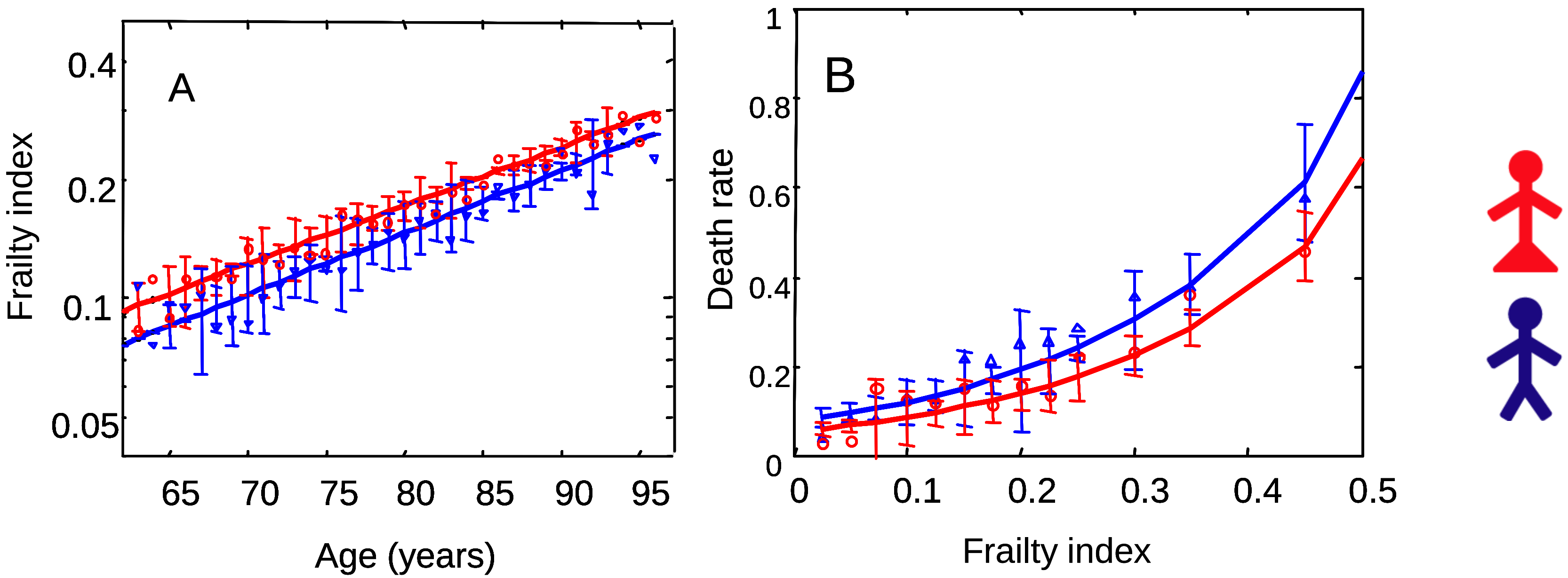
*Rockwood K, Song X, Mitnitski A. Changes in relative fitness and frailty across the adult lifespan. CMAJ. 2011 Apr 26

Deficits accumulate exponentially*



* Mitnitski et al., *J Am Geriatr Soc*, 2005

Gander related differences in the Frailty Index



Mitnitski et al. *J Am Geriatr Soc*, 2005;53:2184-9

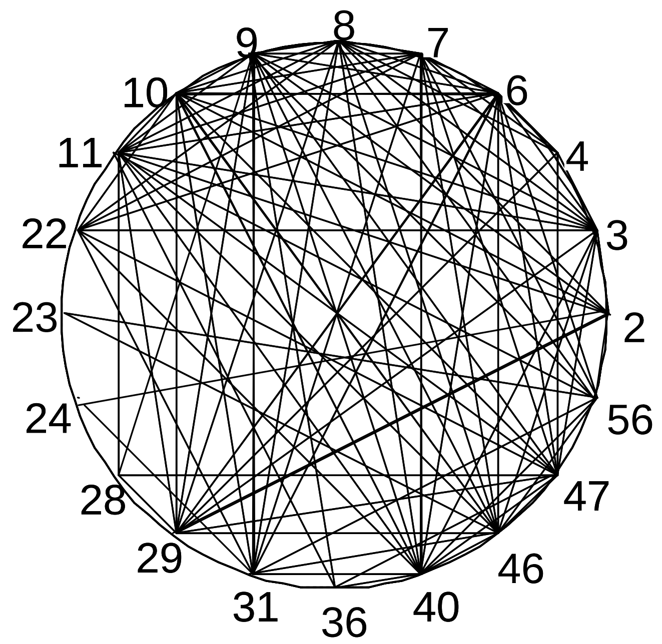
The concept of equality of health deficits.

- All statistical approaches are based on identification of relative importance of health related characteristics
- All predictive models are based on weighing variables (predictors, covariates…)
- This ensures a good performance of the model in the data used for its creation but not necessarily well generalizes

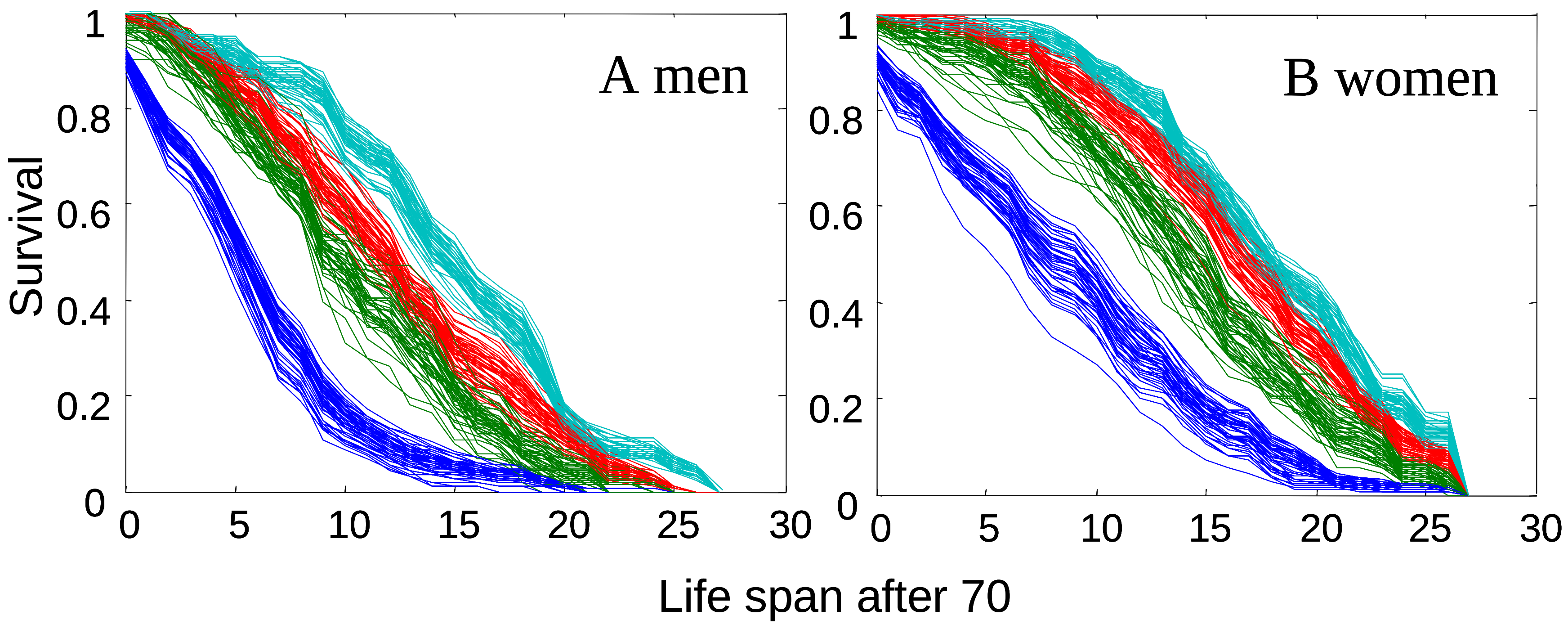
Why we do not need to weight variables?

Because they are inter-dependent!

2 SLEEPCH
3 MOBILITY
4 MEMORY
6 GOUOUT
7 COOKING
8 GETDRES
9 GROOM
10 BATH
11 TOILET
22 LOSSVISI
23 LOSSHEAR
24 ARTERIAL
28 GASTRO
29 URINARY
31 HXDM
36 VASCULAR
40 SKINCLIN
46 TONELIMB
47 TREMORRE
56 VIBRATION



Survival in relation to frailty (h-70) in men and women



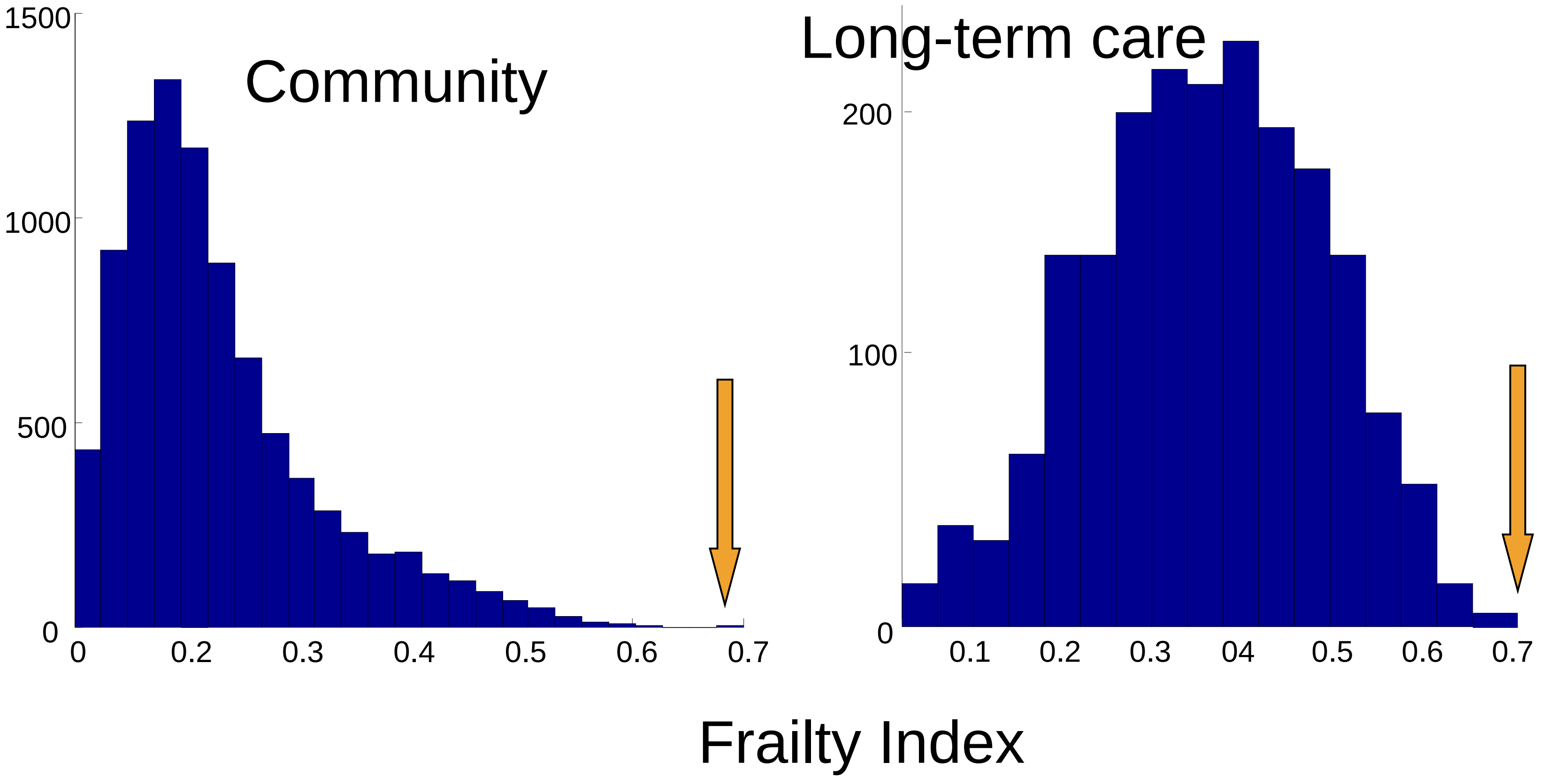
KM curves for each quartile (**blue-highest**, **cyan-lowest**)
4 curves (each for quartile) repeated 50 times

Rockwood et al., J Am Geriatr Soci, 2007

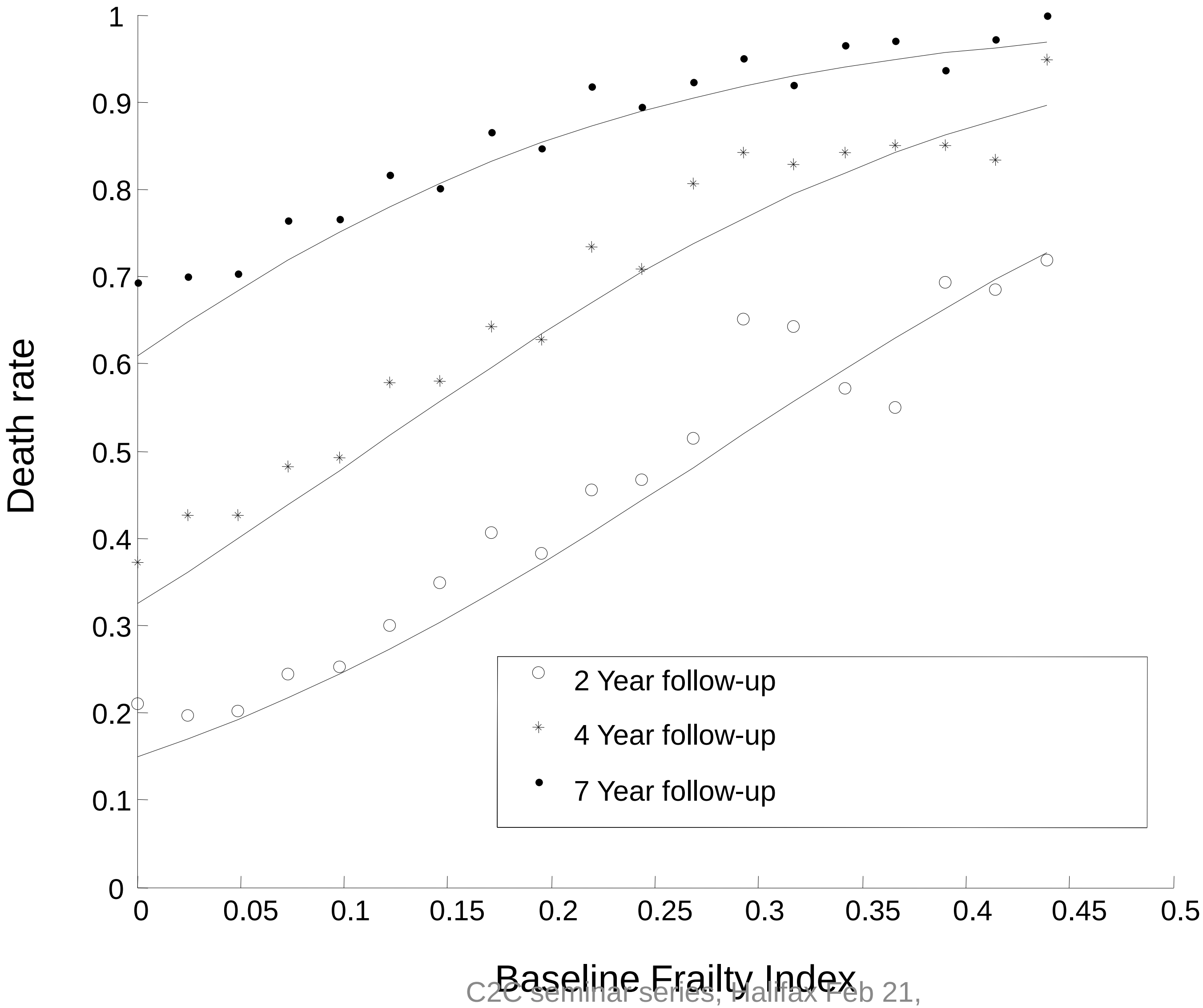
Phenomenological invariants of aging

- aging rates
    - 3%/year on the logarithmic scale
- sex-related differences
    - Women have more deficits than men do but survive better
- limit in the deficits accumulation
    - ~2/3 rule after that survival virtually impossible
- compensation laws of mortality and deficits accumulation
    - Life span is limited at about 120-130 years (that is for the current available data)

The Frailty Index distribution is typical and consistent and **does not have a ceiling effect**



The rate of death as a function of the Frailty Index in China

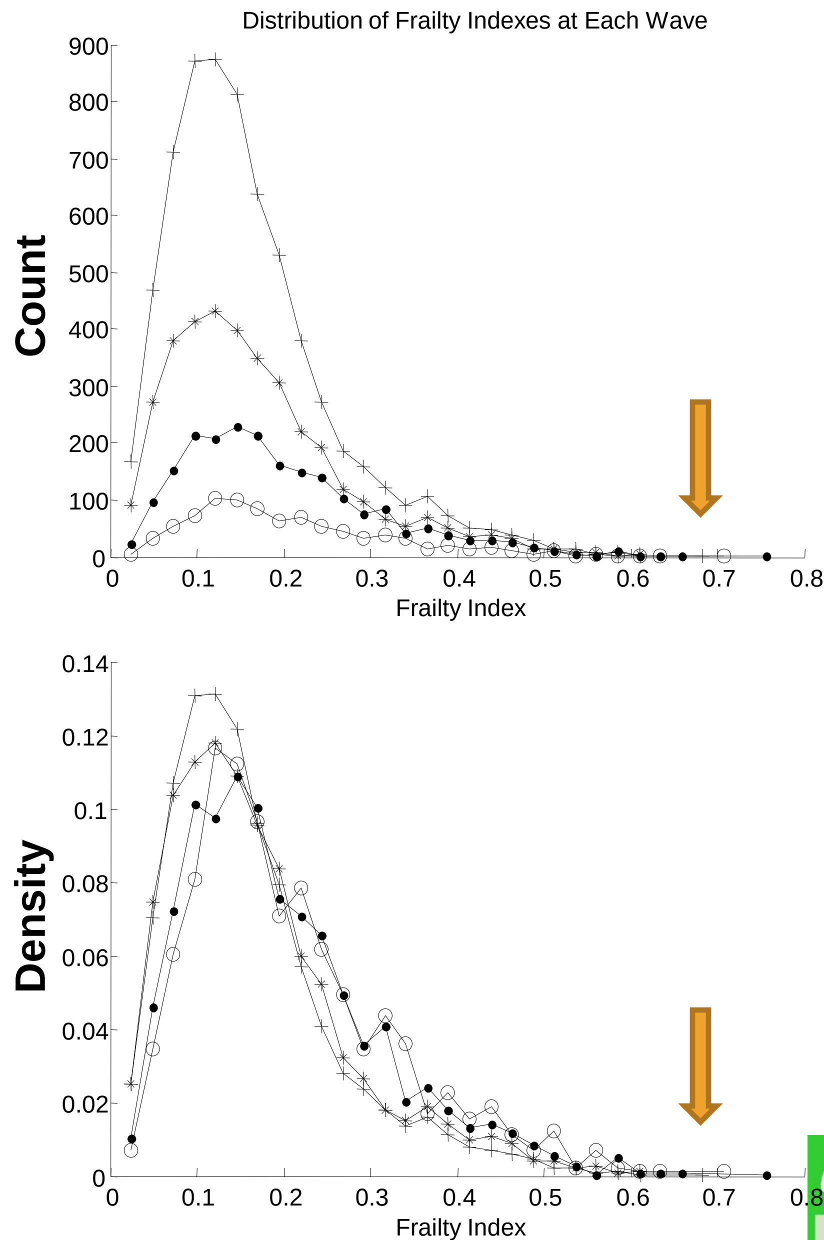


Distribution of the Frailty Index

in 4 successive waves of the Chinese Longitudinal Health and Longevity Study;

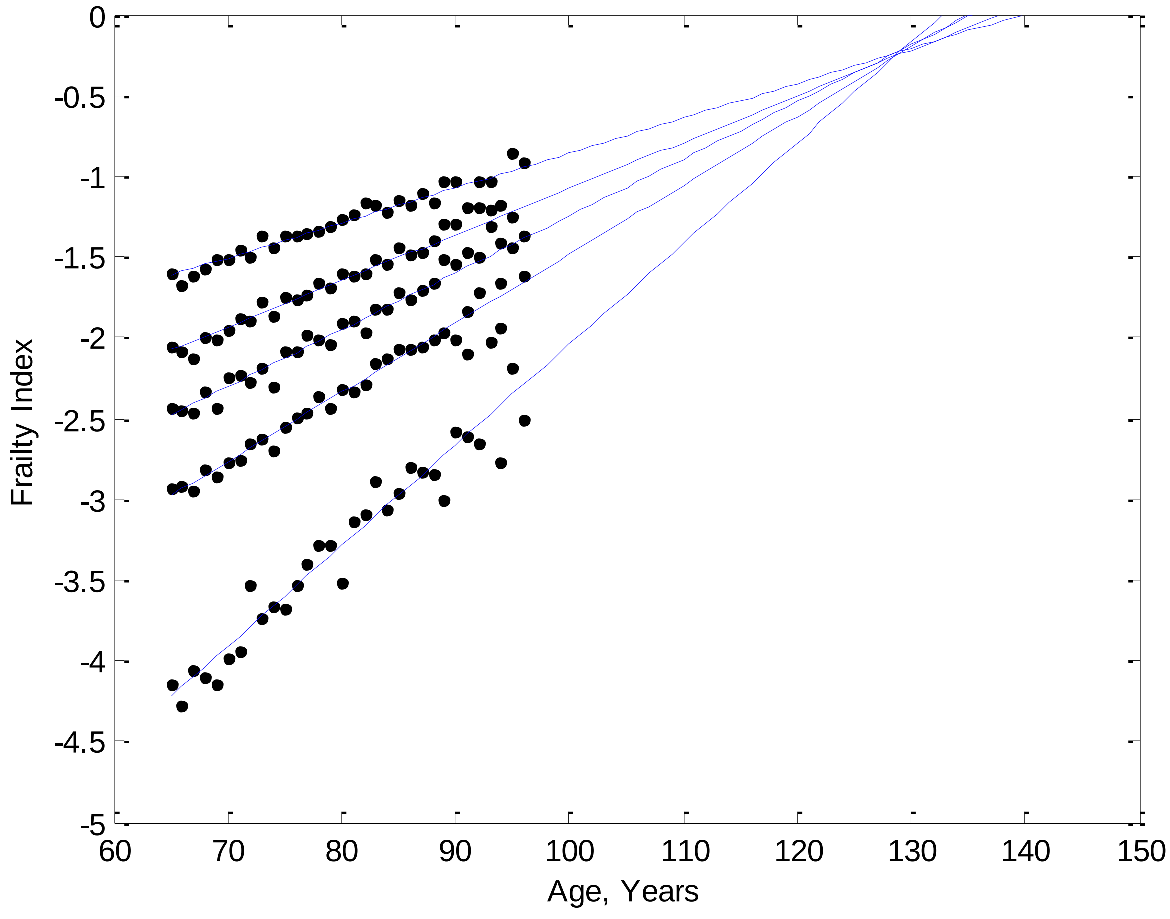
n= 6,664, 80-99 y.o.

Invariant distribution?



Bennett et al., Abstract, CGS Annual Meeting, Vancouver 2011

Frailty kinetics: Loss of redundancy in shown by changing slope of deficit accumulation with age



Searle et al., CSHA data, unpublished.

Statistical mechanics of aging: dynamics of age trajectories

The Ornstein-Uhlenbeck-like process

Y (t) - Physiological state at age *t*

$$dY(t) = a(t)\big(Y(t) - f_1(t)\big)dt + \sigma dW(t)$$

$a(t)$ - measure of stress resistance

$f_1(t)$ – allostatic trajectory (effect of allostatic adaptation)

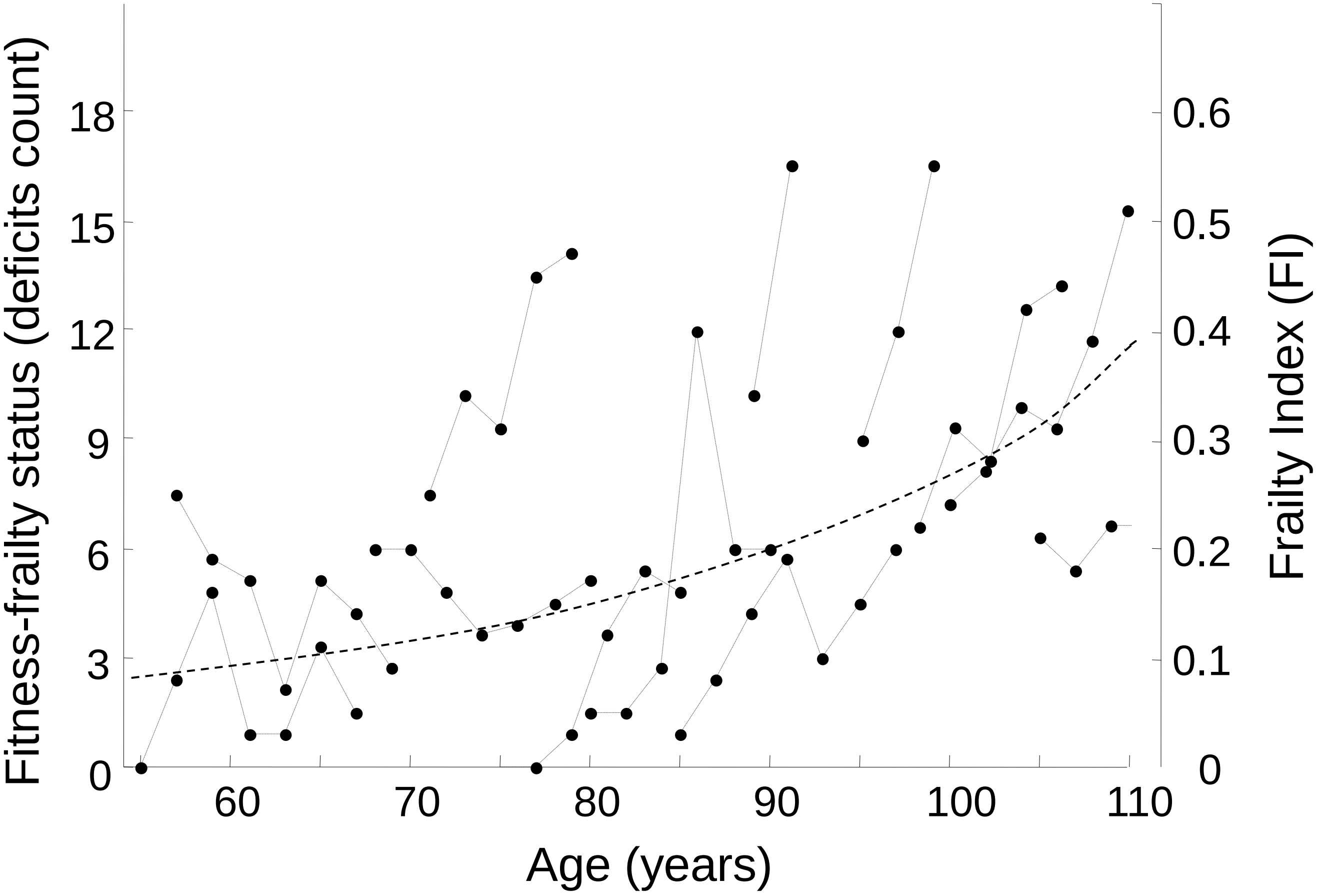
Quadratic hazard function

$$\mu(t,Y) = \mu_0(t) + \mu_1(t)\big(Y(t) - f(t)\big)^2$$

$f(t)$ - optimal age trajectory

Yashin et al., 2007; 2009; 2010; 2011; 2012

Frailty trajectories in the NPHS

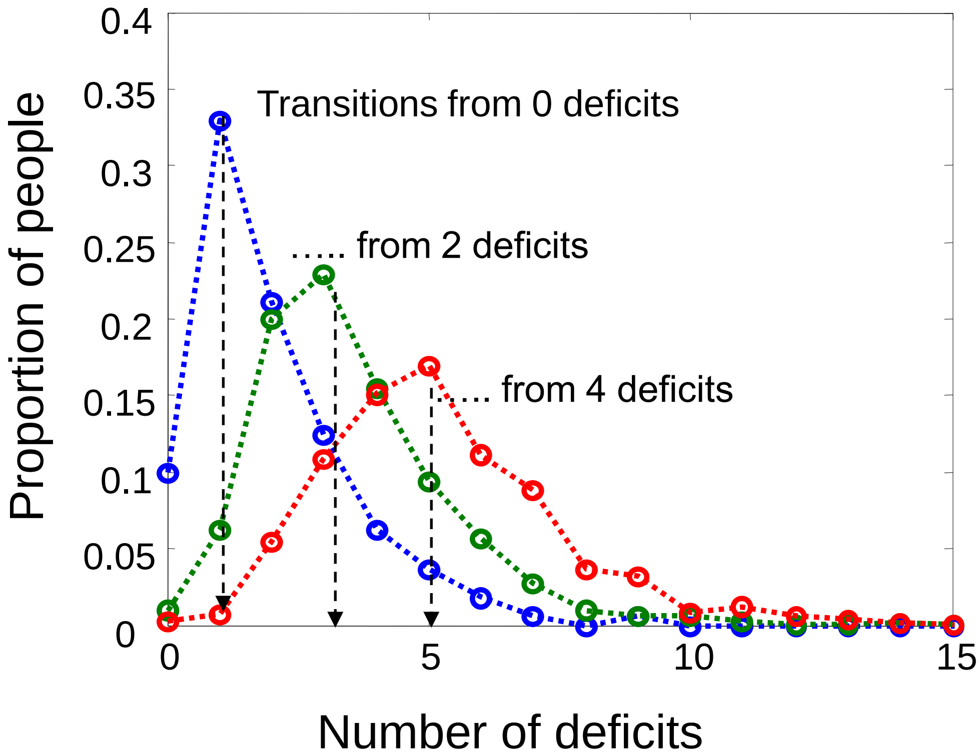


Transitions over a fixed time interval

- Observations
- Mathematical formulation

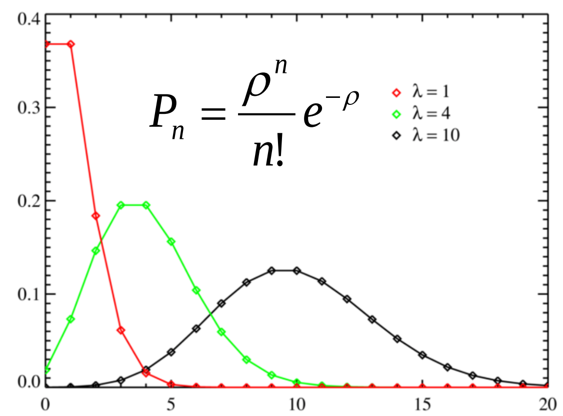
Frailty trajectories are summarizable

Empirical (NPHS)



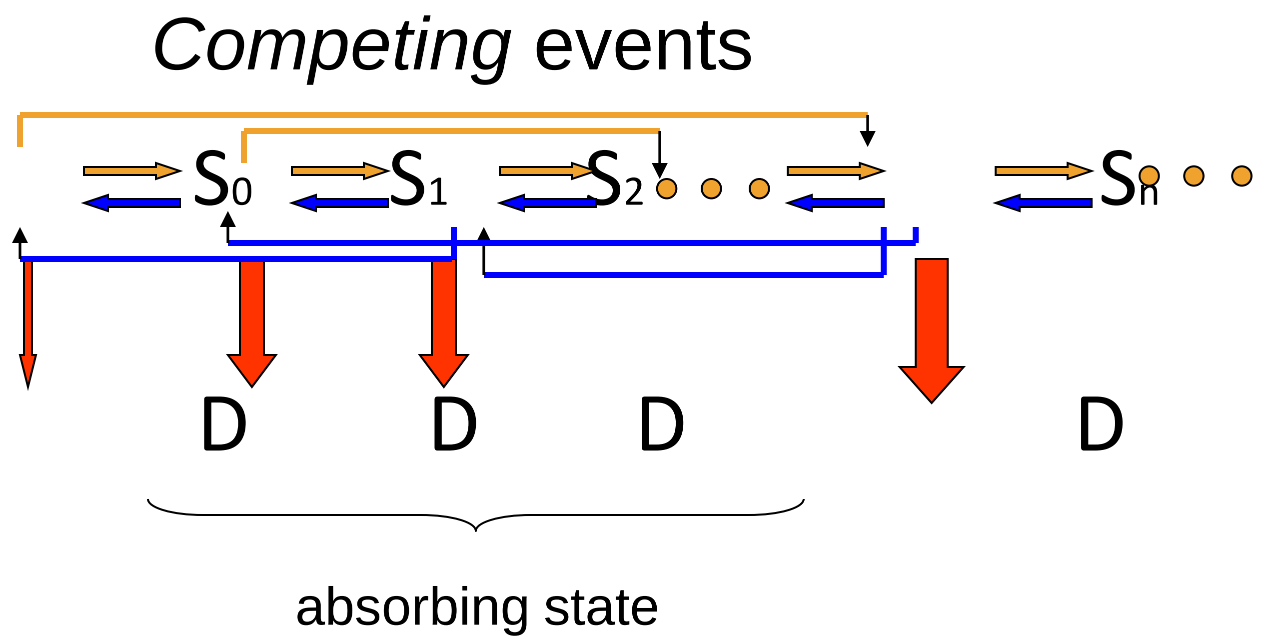
Theoretical

The Poisson Distribution



Schematic representation of transitions

as a Markov Chain* **(that is not a model, just a cartoon...)**



*Mitnitski , Bao, Rockwood, *Mech Ageing Dev* 2006;127:490-3
Mitnitski, Bao, Skoog, Rockwood, *Exp Geront* 2007:42:241-6
Mitnitski, Song, Rockwood, *Exp Geront* 2007;42:1109-15
Mitnitski & Rockwood, *BMC Geriatrics* 2008; 3

The model: Modified Poisson

The probability of transitions from state “n” to state “k”

$$P_{nk} = \frac{\bar{k}_n^{\,k}}{k!} \exp(-\bar{k}_n) \cdot (1 - P_{nd}),$$

The Poisson parameter is state (“n”) dependent

$$\bar{k}_n = a_1 + b_1 n$$

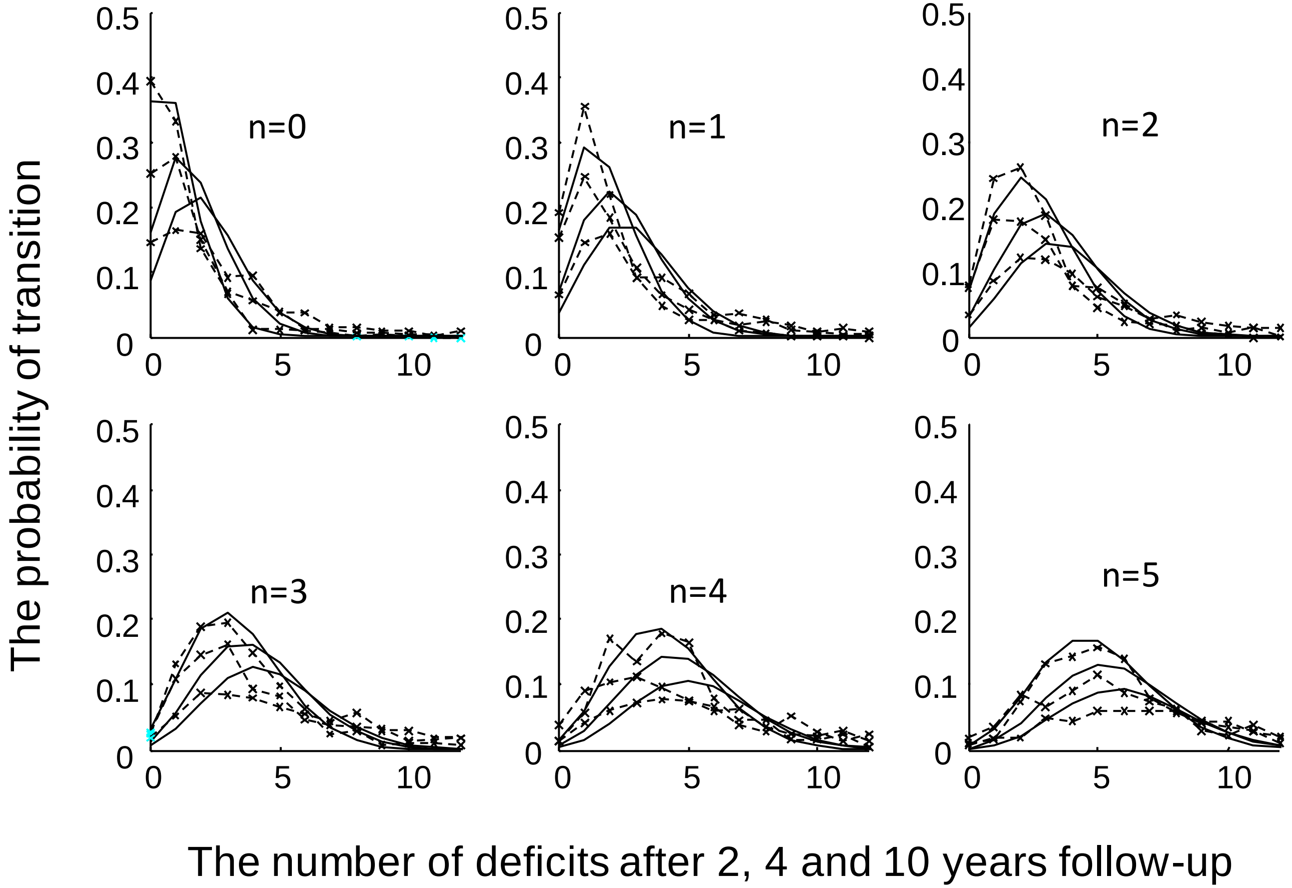
The probability of transitions from state “n” to death (absorption)

$$\operatorname{logit}(P_{nd}) = a_2 + b_2 n$$

Time dependent transitions

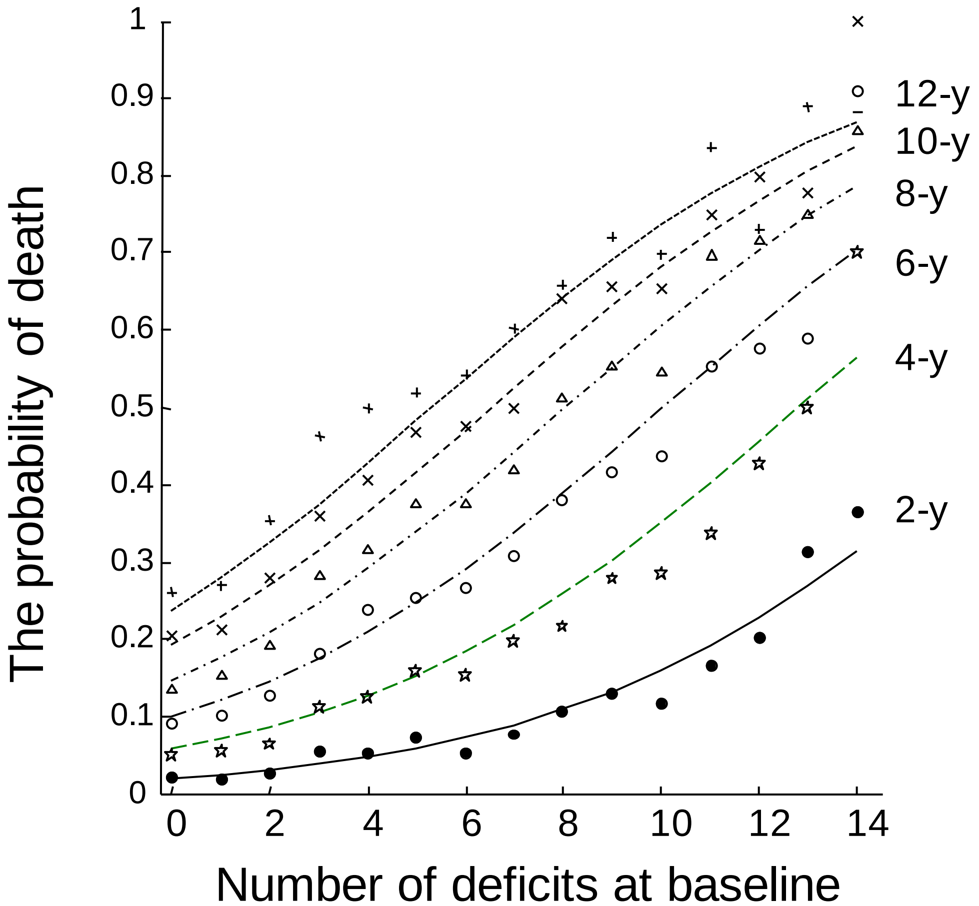
- Observations, NPHS, 12 years follow-up, every 2 years
- Mathematical formulation

Time dependent transitions



Mitnitski et al., submitted

The probability of death as a function of time and baseline state



Mitnitski et al., submitted

Time dependent transitions: fit of empirical data

Time non-homogeneous Poisson, the square-root-of-time rule

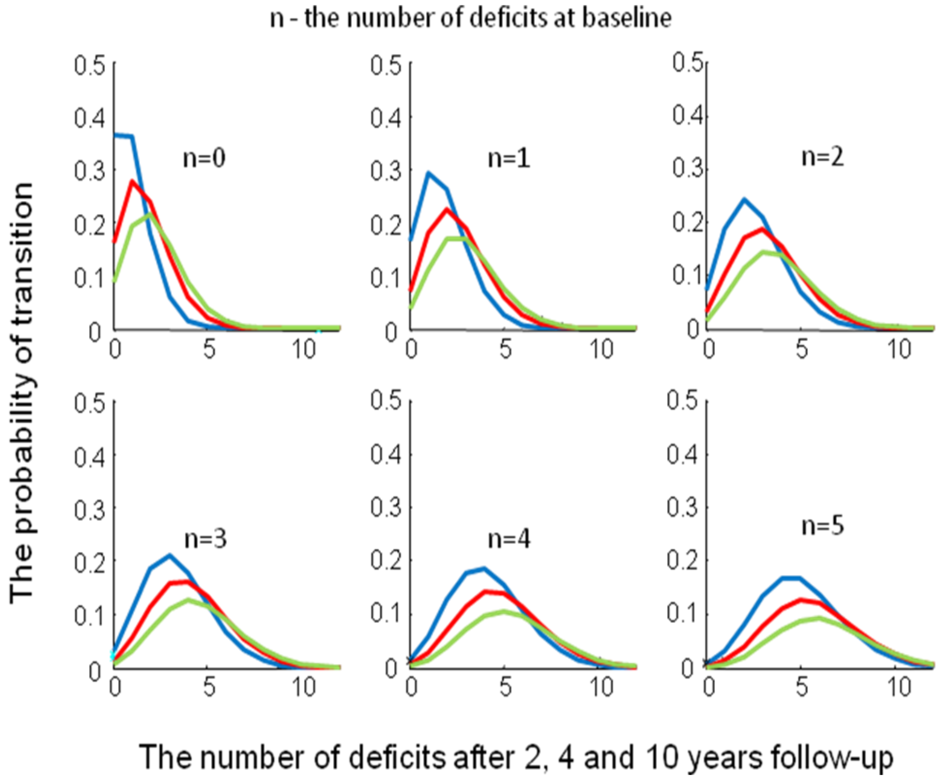
$$P(n,k,t) = \frac{(\alpha\sqrt{t} + an)^k}{k!} \exp(-\alpha\sqrt{t} + an)$$

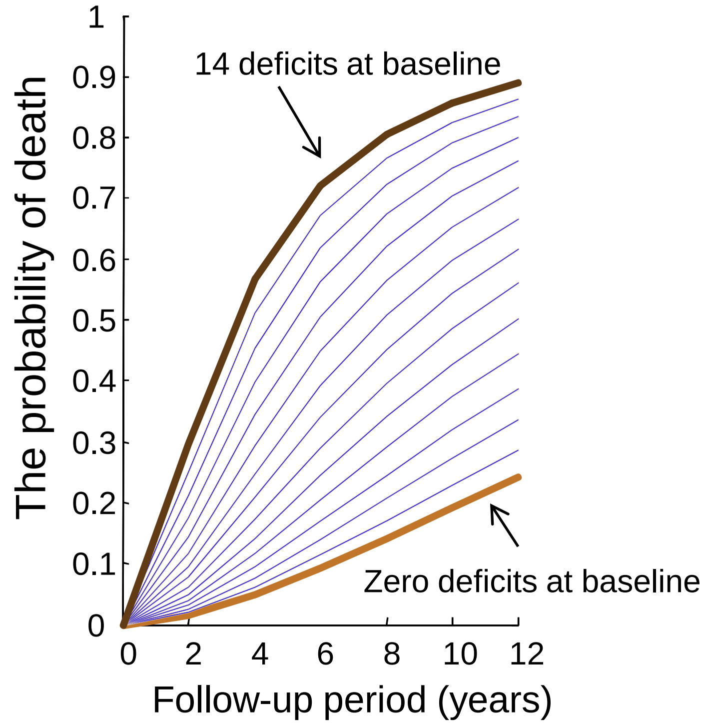
Time dependent logistic function

$$P(n,d,t) = \frac{\exp(\beta_1(\exp(\beta_2 t) - 1) + bn)}{1 + \exp(\beta_1(\exp(\beta_2 t) - 1) + bn)}$$

Mitnitski et al., submitted

The probability of transition (left) and mortality (right) during 12 years follow-up





Mitnitski et al., submitted

The origin of the Frailty Index

A sketch of the future theory

Queuing theory approach, overview

- Queuing theory
- Scheduling algorithms
    - Fist In, First Out (FIFO)
    - Last In, First Out (LIFO)
- Birth-death equations
- Toy model
- Perspectives

The origin of the Frailty Index
the “lambda/mu” model

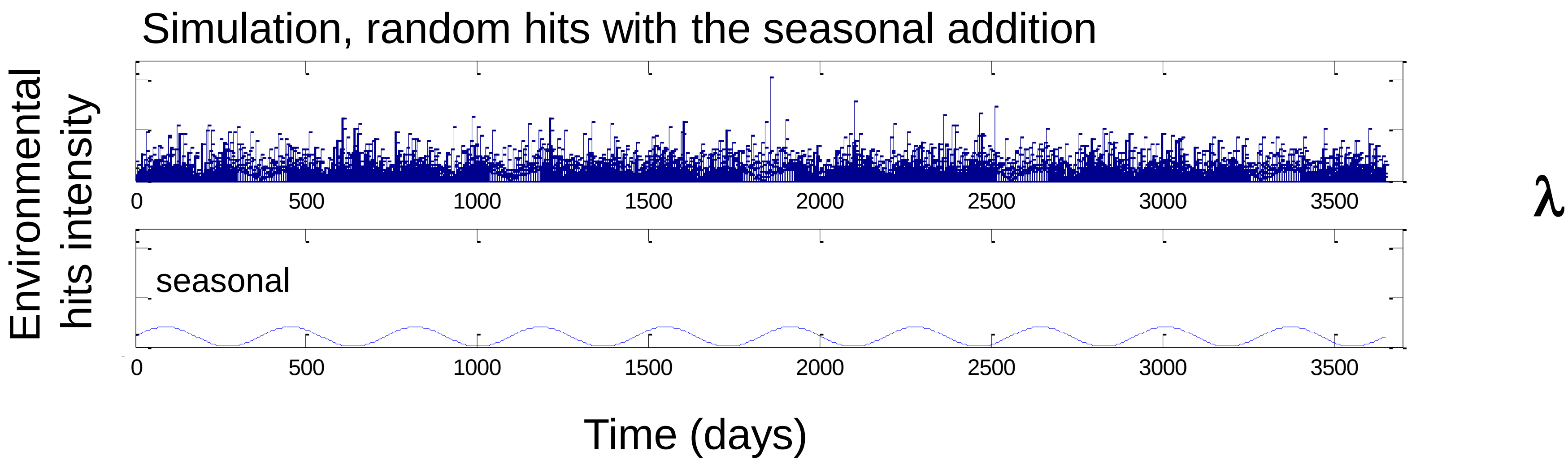
The number of accumulated deficits (at age *t*) is the product of the Intensity of environmental challenges (insults), λ by the mean recovery time *W*

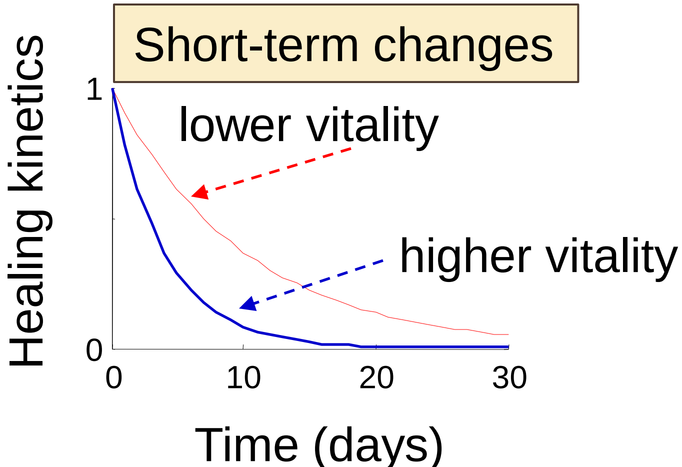
The Little’s law*, $E = \lambda W$ $W = 1/\mu$

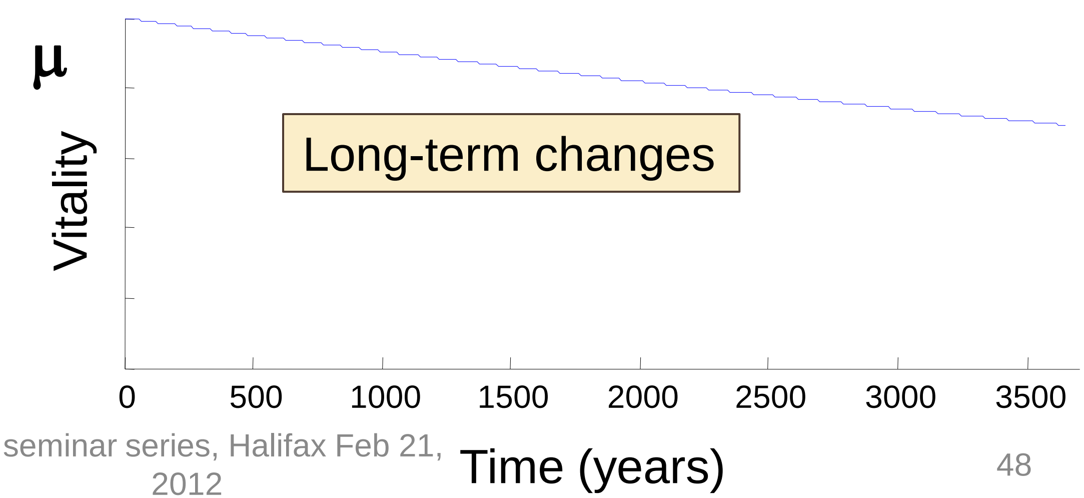
$$E = \lambda/\mu$$

*Little JDC, 1961, "A Proof of the Queuing Formula: L=λW". *Operations Research* **9** (3): 383–387

Schematic representation of the environmental hits/insults and the organism's vitality







Division of variables and quasi-stationary solutions

fast

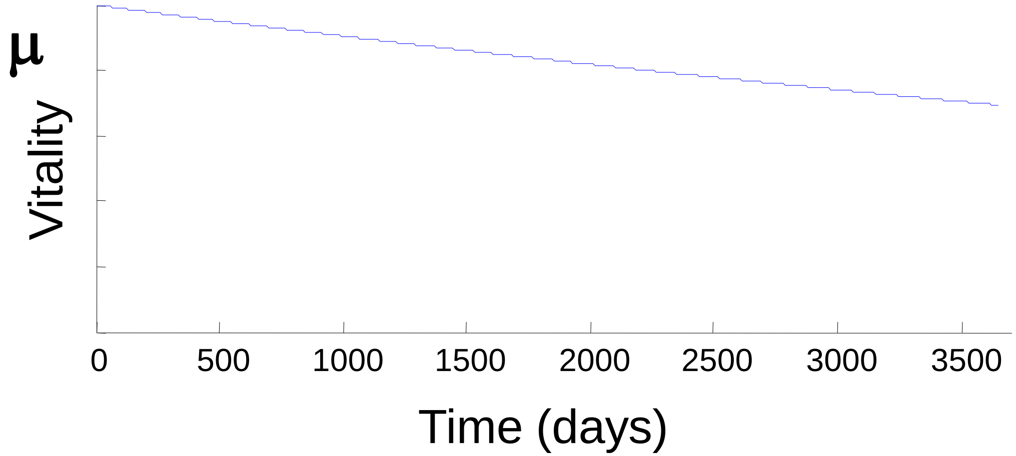
$$\frac{dP(n,t)}{dt} = \lambda P(n-1,t) + \mu(n+1)P(n+1,t) + (\lambda + n\mu)P(n,t)$$

$$\frac{dP(0,t)}{dt} = \lambda P(0,t) + \mu P(1,t)$$

slow

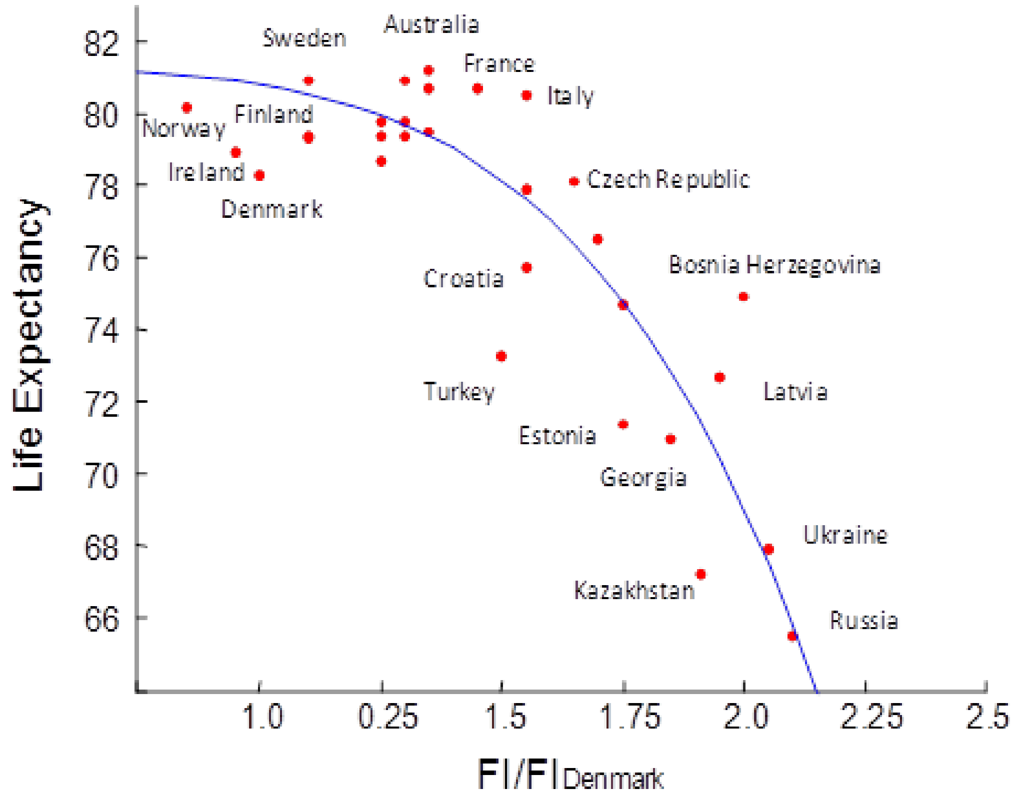
$$-\frac{1}{\varepsilon}\frac{d\mu}{dt} = \mu + \varphi(\lambda)$$

$$\varphi(\lambda) = 0$$

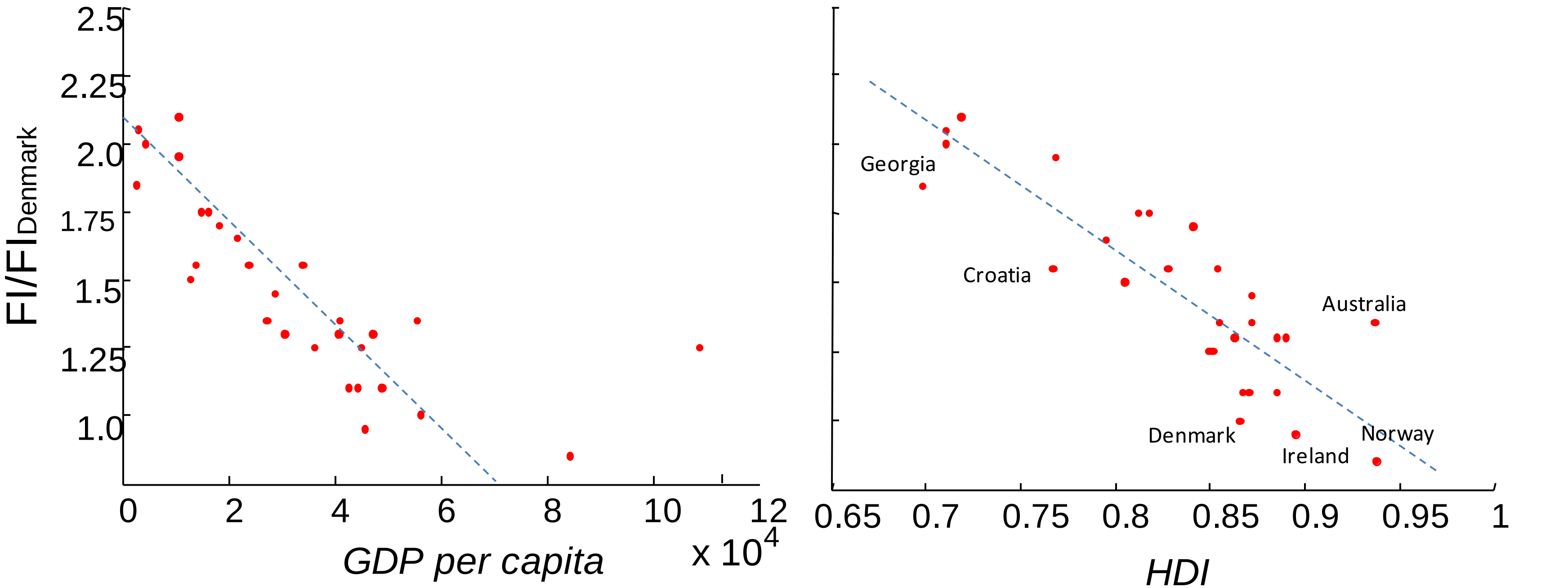


See for example,
Prigogine, 1977
Strehler & Mildvan, 1960

Frailty Index and International Health : Life Expectancy at birth, by country



FI and GDP per capita and between the FI and human development index (HDI)



Perspectives (some)

- Monte-Carlo simulations of the different environments and different stochastic mechanisms of dealing with deficits (FIFO, FILO)
- Non-Poisson models of the environmental load
- Random walk models with killing fields
- Applications to the World Wide Health

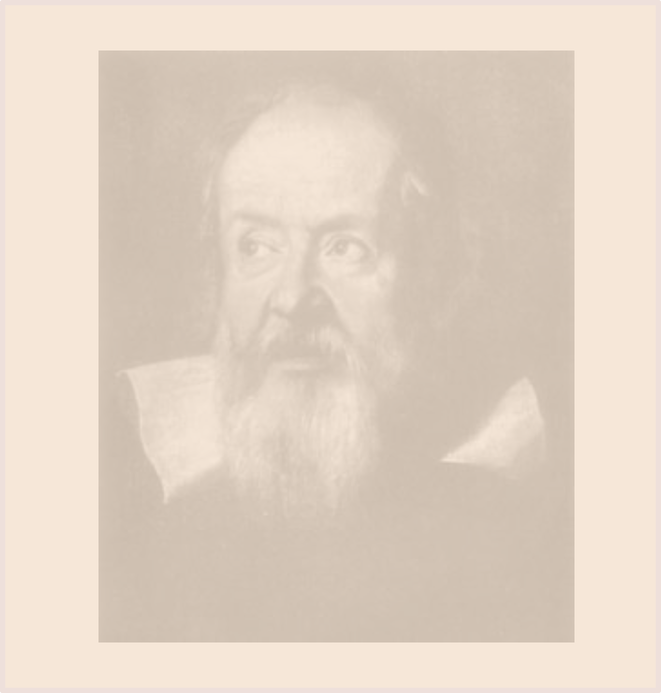
Conclusions

- There are no conclusions
  - For further advances increasing collaboration between different disciplines is expected
  - Mathematics gives a common language to facilitate such collaboration
  - Huge perspectives in both mathematical development and applications is anticipated

Conclusions, cont’d

“All truths are easy to understand once they are discovered; the point is to discover them.”

Galileo Galilei



THANK YOU for your attention