Assessing biological aging: the origin of deficit accumulation arising from age associated increase in recovery time

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Inspiring Minds

Acknowledgements

- **Colleagues:**
  - Professor Kenneth Rockwood (Medicine)
  - Dr. Xiaowei Song (Medicine), Dr. Melissa Andrew, (Medicine)
  - Prof. Andrew Rutenberg (Physics), Dr. Swadhin Taneja (Physics)
- **Agencies:**
  - Canadian Institutes of Health Research, Institute of Aging
  - Mathematics, Information Technologies and Complex Systems (MITACS) program of the National Science Council
  - Alzheimer Society of Canada
  - National Natural Sciences Foundation of China
  - Dalhousie Medical Research Foundation
  - University Internal Medicine research Foundation
  - Nova Scotia Health Research Foundation

How do we age? and why…

- Can we find a metric accounting for aging better than just chronological age?
- Accumulation of deficits as a proxy measure of aging. Utility of the frailty index.
- Accumulation of deficits, environmental stresses and recovery time.
- Statistical mechanics of aging: networks dynamics model.

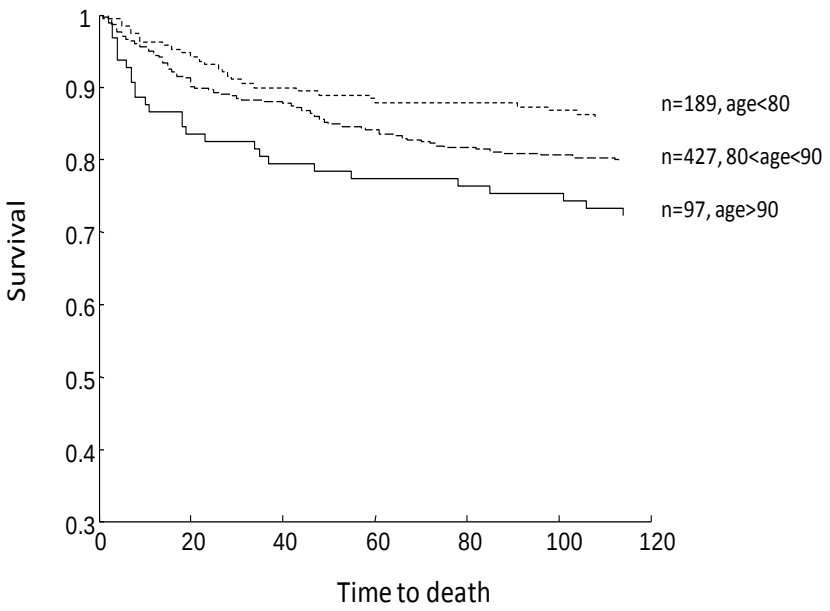
Background: quantifying health and aging: the number of deficits

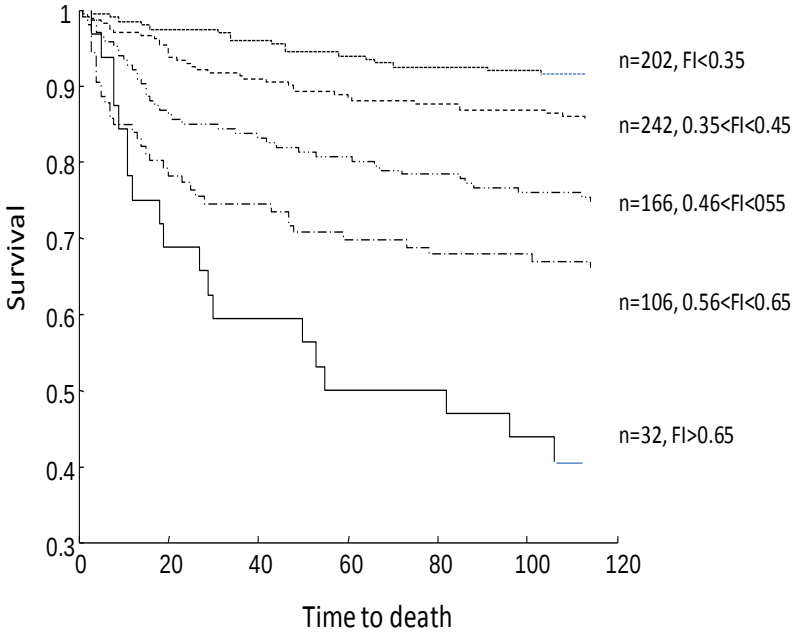
- Age related deficit accumulation is an important hallmark of aging.
- These deficits are health characteristics (symptoms, signs, laboratory abnormalities, illnesses, functional limitations, etc.).
- We characterize health of the individual by the number of such conditions.

Background: quantifying health and aging: the frailty index

- The fraction of the deficit present in individual is called the frailty index (cumulative deficit index).
- The frailty index is a useful health utility measure, an indicator of longevity. It has multiple applications in medicine and the other areas (Mitnitski et al., 2001; 2002; 2005, 2013; Rockwood & Mitnitski, 2004, 2007,2011; Yashin et al., 2007; 2008, Kulminski et al., 2007;2008; 2010; 2011) and many others.
- This approach has also been applied to animals (e.g. aging mice, Parks et al, 2012, Whitehead et a., 2013).

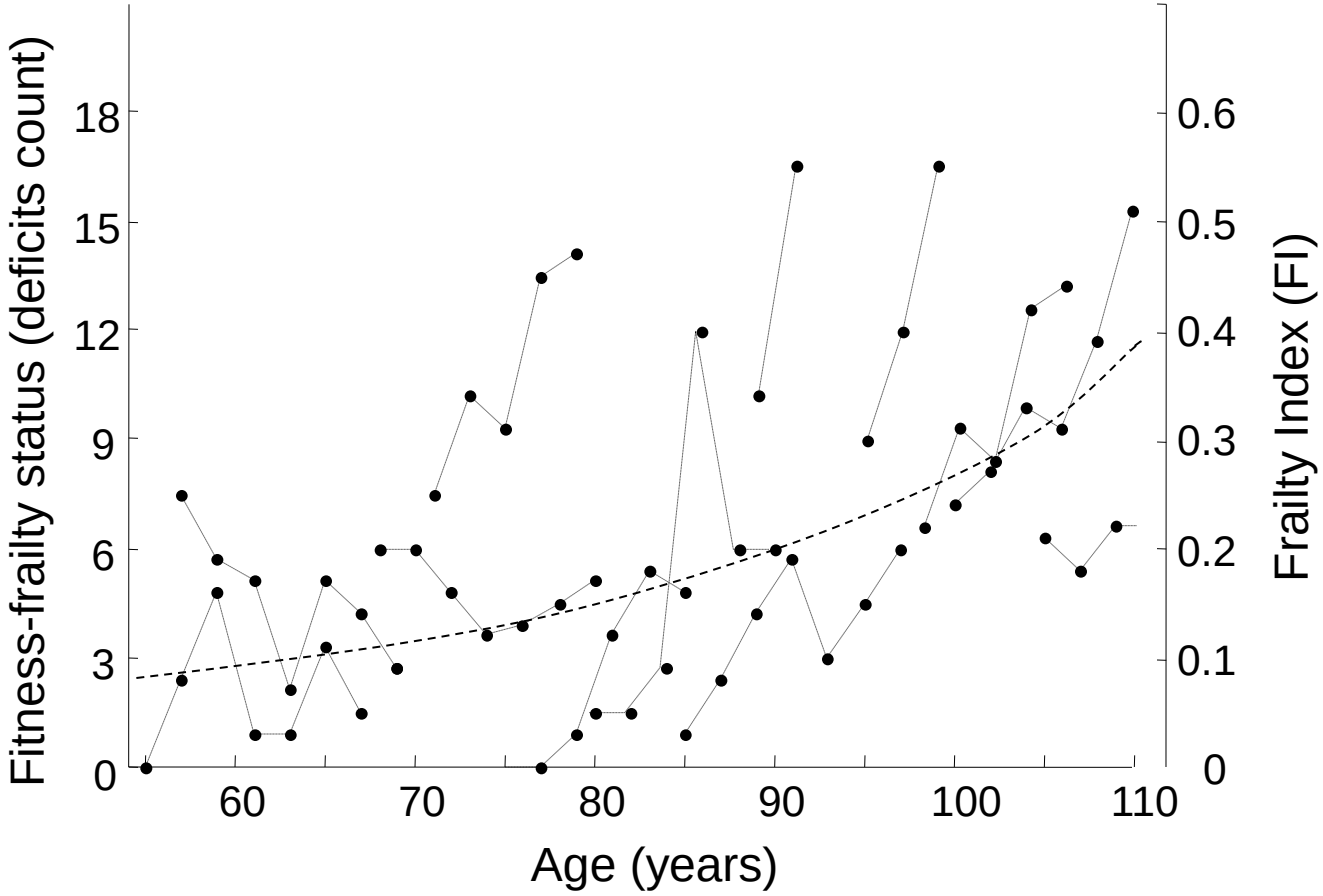
Background: Kaplan-Meier survival curves stratified by age (left) and FI (right)





Source: Evans et al., Age Ageing 2014

Background: Individual health trajectories show stochastic dynamics



Methods

- Mathematical modeling /
  / computer simulations.

- MODEL **MUST NOT** BE DETAILED.

Results: macro modeling

- The relationships between the number of accumulated deficits N, the intensity of environmental stresses λ and recovery time R can be modeled using an apparatus known in Operation Research area – the queuing model

- This yields a simple relationship between the number of accumulated deficit and average recovery time R:

$$N = \lambda \times R$$

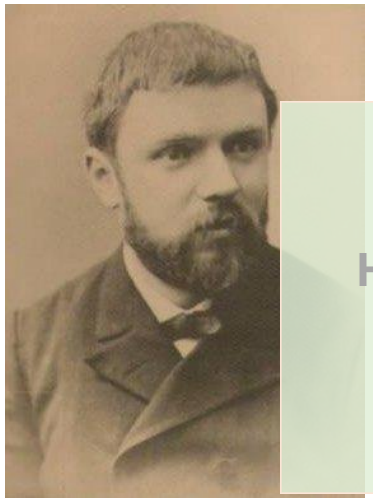
This result is not empirical!

- The average number of accumulated deficit *N*,
- The intensity of environmental stresses λ and
- The average recovery time *R*:

$$N = \lambda \times R$$

“Mathematics is the art of giving the same name to different things”

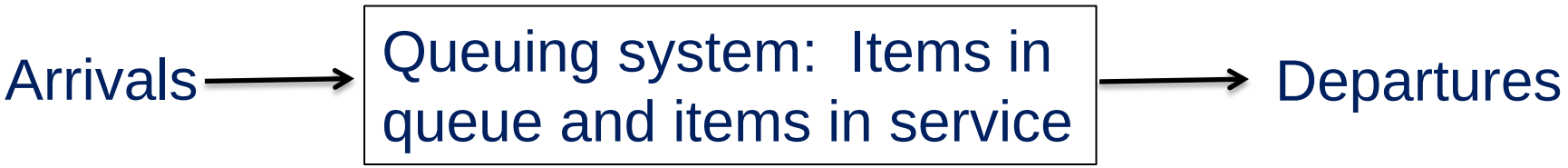
Mathematicians do not study objects, but relations between objects. Thus, they are free to replace some objects by others so long as the relations remain unchanged. Content to them is irrelevant: they are interested in form only.



Henri Poincare
(1854 – 1912)

Schematic diagram of a queuing system

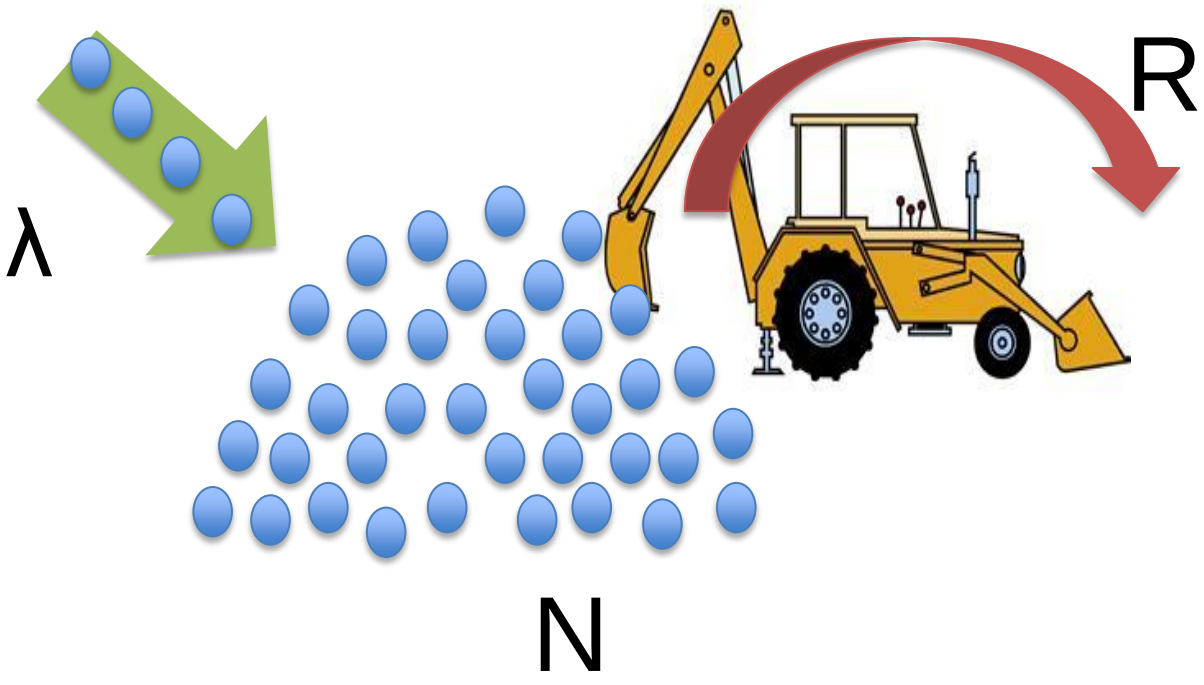
Flow of items through a queuing system



Little JDC, Little's law as viewed on its 50th anniversary. *Operation Research* 2011;59:536-549.

Little's Law: $N = \lambda R$

(# items in the system N is a function of intensity of arrival λ and service time R)



Little's Law (LL)

- LL in Operation Research (queuing theory)

- The average number of items in a queuing system *L* equals the average arrival rate λ times the average waiting time in service and in queue, *W*

$$L = \lambda \, x \, W$$

Little JDC, A proof for the queuing formula: L=lW. *Operation Research* 1961;9:383-387.

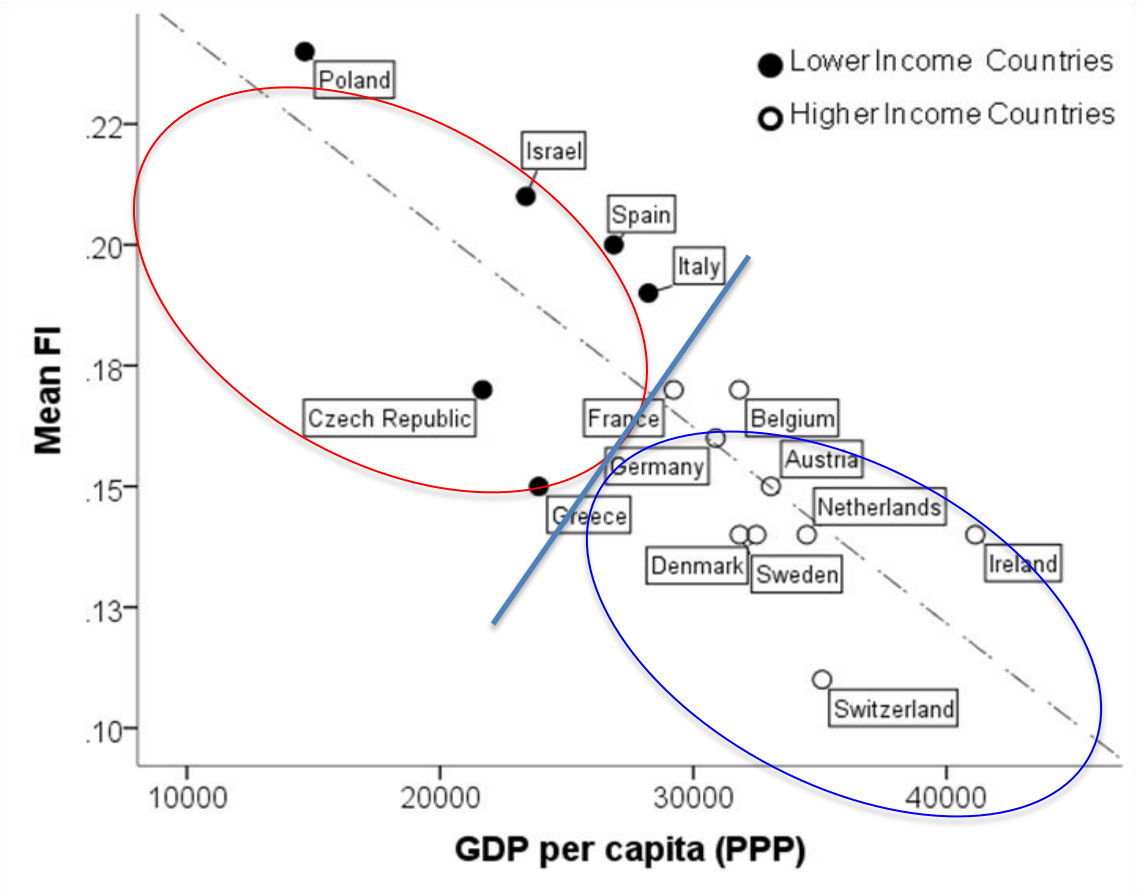
- Reformulation of the LL in terms of deficit accumulation

The average number of deficits in an individual *N* equals the average rate λ of environmental stresses multiplied by the average recovery time of a deficit, *R*

$$N = \lambda \, x \, R$$

Mitnitski A, Song X, Rockwood K. Assessing biological aging: the origin of deficit accumulation. *Biogerontology* 2013;14: 709-717.

GDP per capita (PPP) characterizes the environment: health is related to wealth



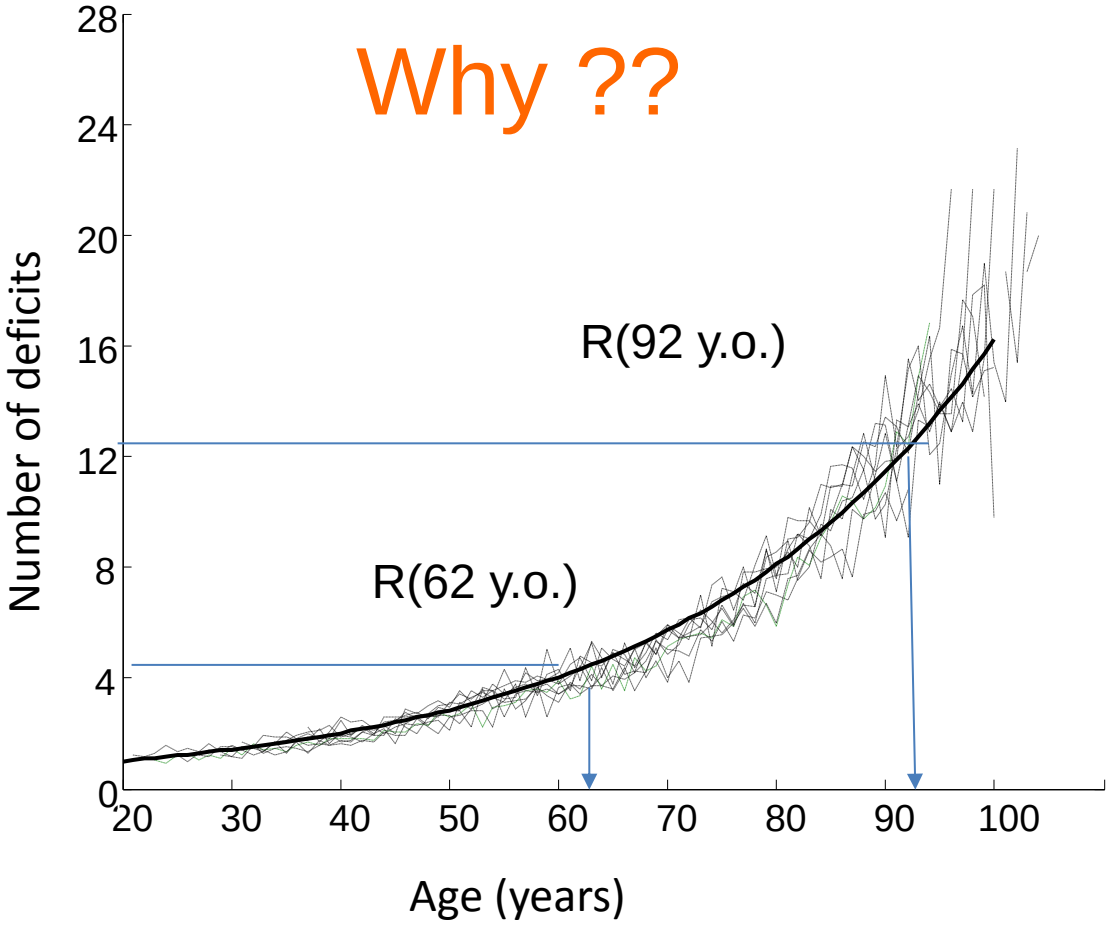
Theou O et al. *Age Ageing* 2013, Sep;42(5):614-9.

$$N = \lambda \times R$$

IMPLICATIONS

- Environment
  - Protective vs. harmful
  - Social circumstances
  - **But not a "cocoon"**
- Recovery control
  - **Immune system status**
  - Medications
  - Social circumstances
  - Healthcare expenditures

The number of deficits increases [exponentially]



Because recovery time Increases with age.

Mitnitski A, Song X, Rockwood K. Biogerontology, 2013

Why recovery time increases with age?

- Why deficits accumulate with age?
  - Because recovery time increases with age.
- Why recovery time increases with age?
  - ???
  - Because deficits accumulate….

- Statistical mechanics of aging: the network model of deficits accumulation.

Conclusions

- Age related deficit accumulation is an important hallmark of aging.
- Age related deficit accumulation is directly related to an increase in recovery time, due to widespread weakening of repair mechanisms.
- The impact of deficit accumulation can be mitigated by improving lifestyles, the environment and the health care system.

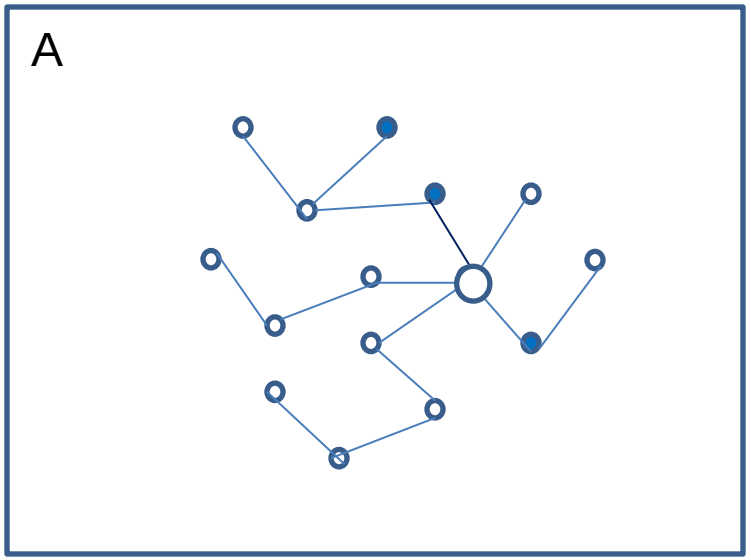
Statistical mechanics of aging

The network model
of deficits accumulation

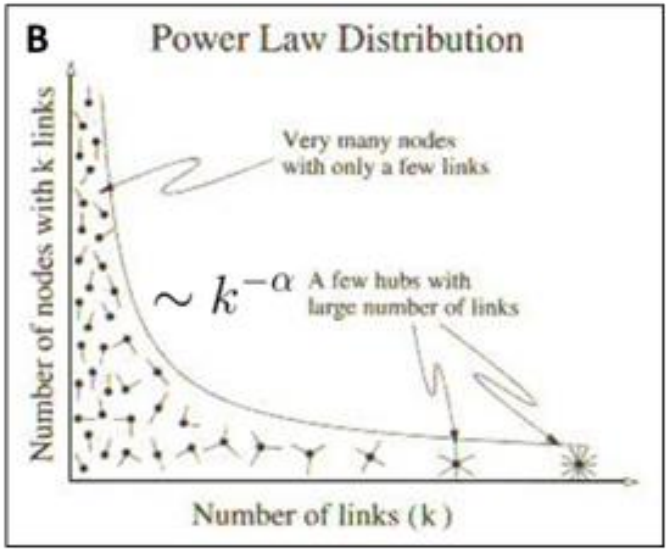
The sketch of the micro model

- A set of connected nodes: Taneja at al., Bulletin of the American Physical Society, 2014
  - The nodes are deficits, connections correspond to interdependent deficits

A network of nodes

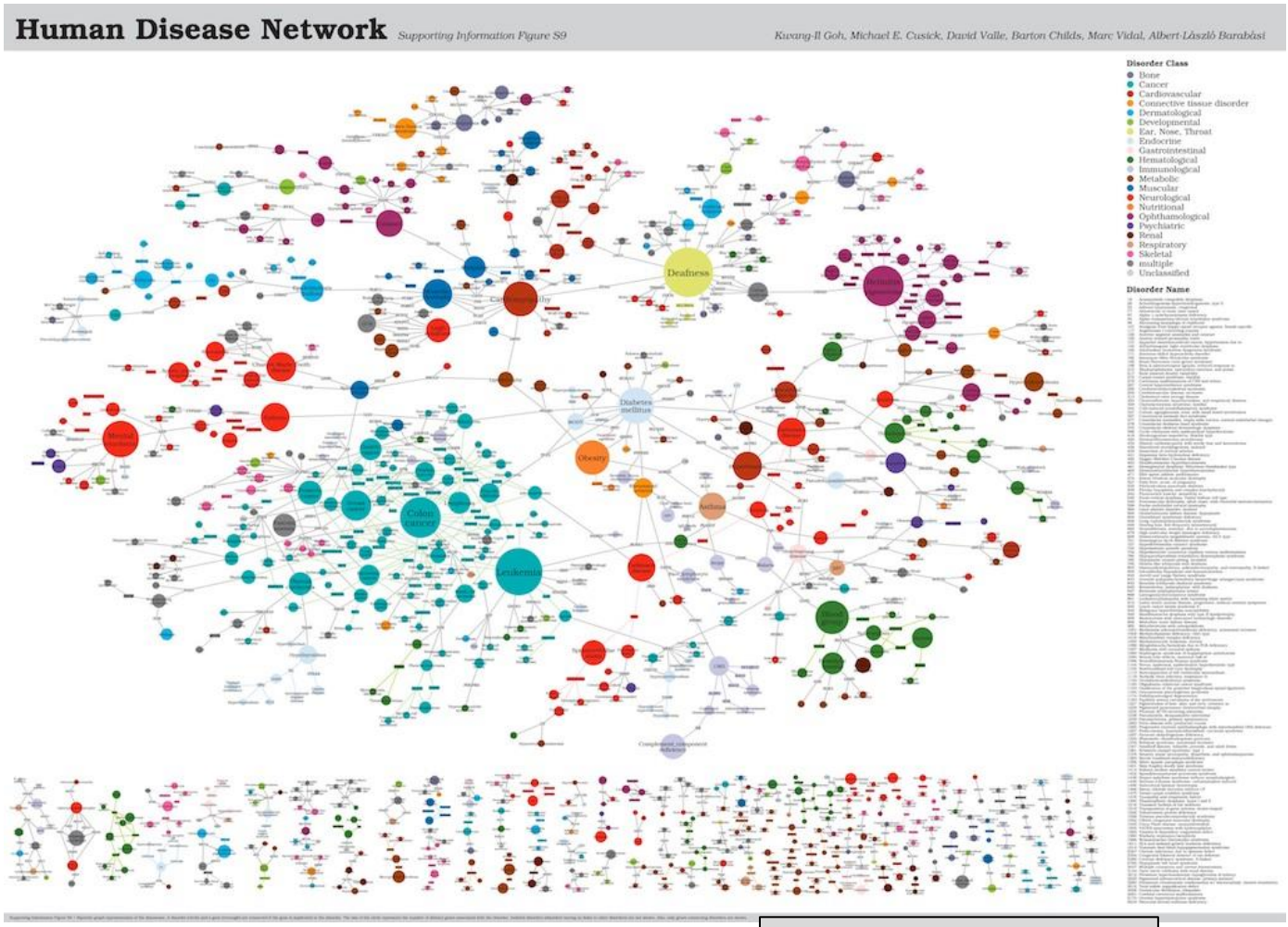


The power law distribution of links



  - Each node can be in two states ("healthy", "deficits")

Human Disease Network



Goh et al., PNAS,2007

To be continued…

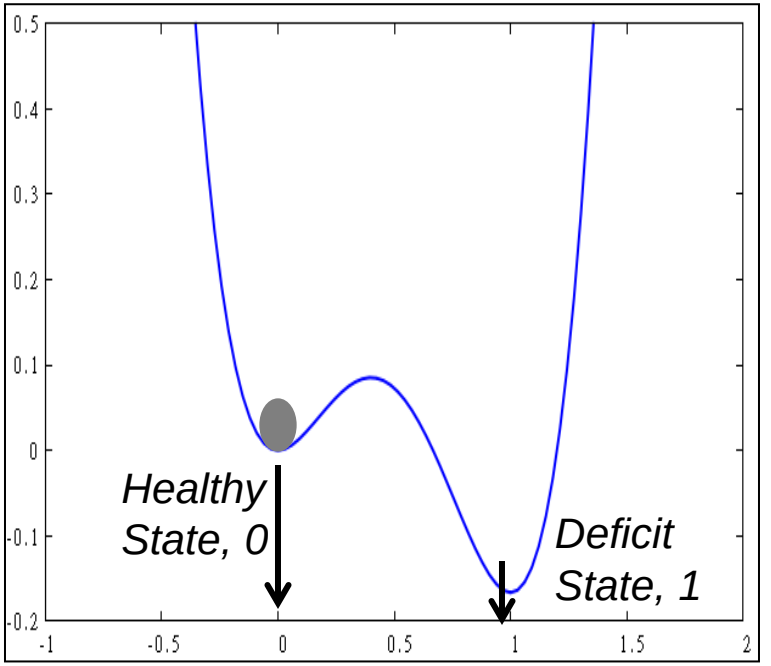
Transitions between the states depend on the random "force" (environment) and on the potential function (double well).

Random damage-repair

$$\dot{p}_i(t) = \xi_i(t) - V_i'(p_i)$$

white noise

drift

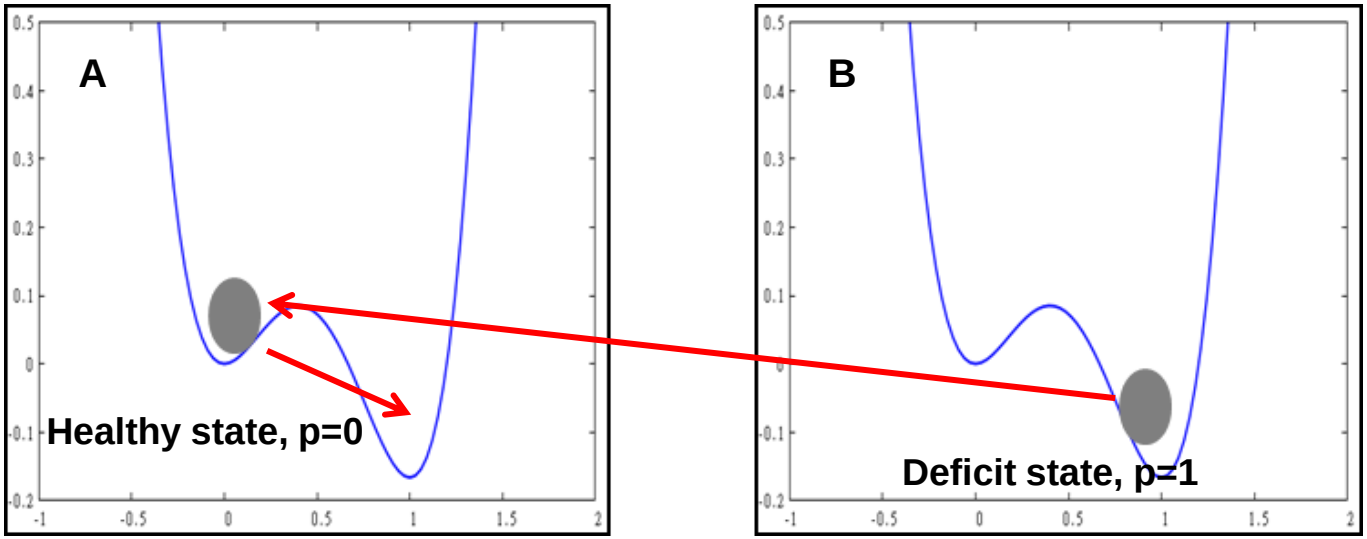


$$V(p) = V_0 \left[\frac{p^4}{4} - \frac{p^3}{3}(1+\theta) + \frac{p^2}{2}\theta \right]$$

Transitions between nodes also depend on the interactions between the nodes

Node, i

Node, j



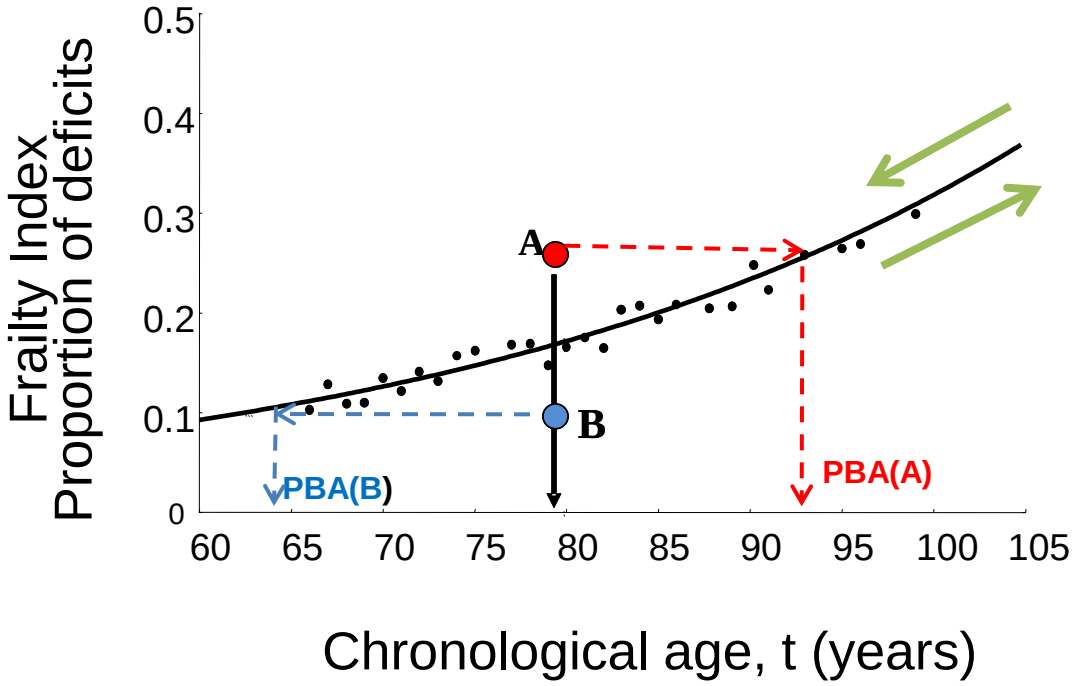
$$\dot{p}_i(t) = \xi_i(t) - V_i'(p_i) + \sigma \frac{\sum_j d_{ij}}{D_i}$$

$$V(p) = V_0 \left[\frac{p^4}{4} - \frac{p^3}{3}(1+\theta) + \frac{p^2}{2}\theta \right]$$

Taneja S, Mitnitski A, Rotenberg A, Rockwood K. *Bull Amer Phys Soci* 2014

All parameters of the model are time (age) independent!

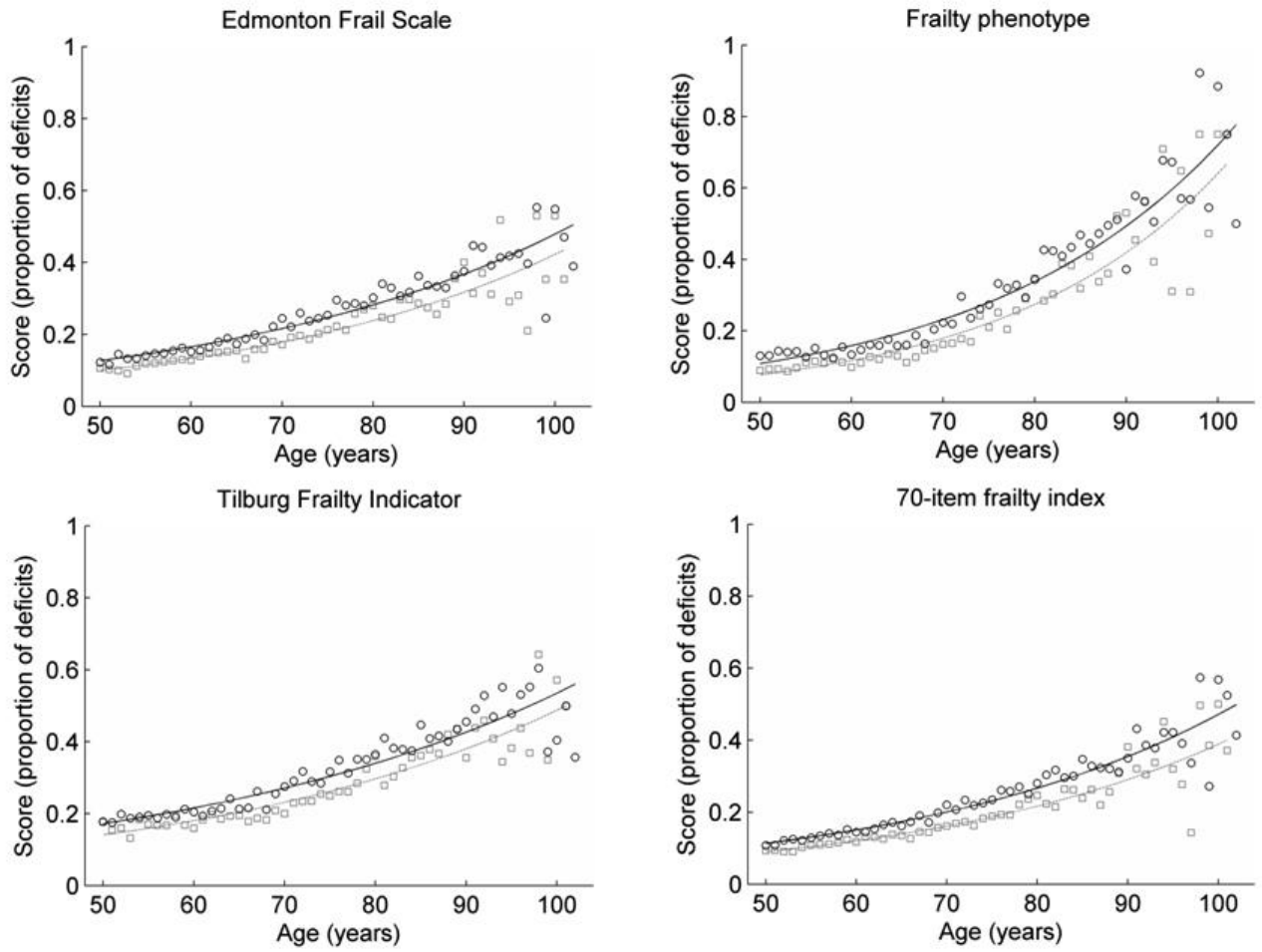
Frailty Index is a basis for estimation of Biological Age



Biological age can be modifiable!

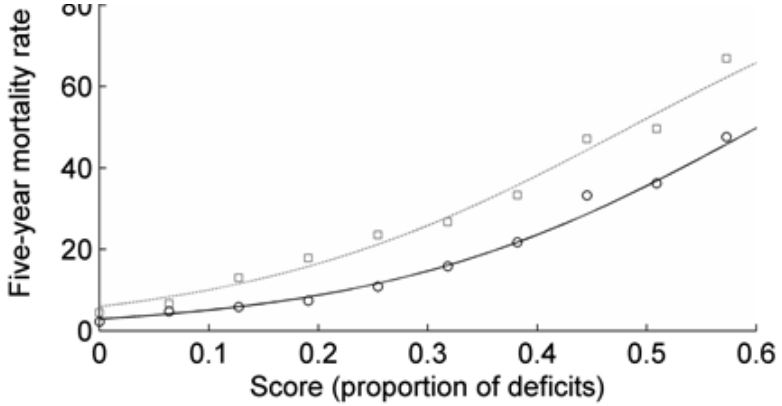
- Mitnitski et al. *BMC Geriatrics* 2002

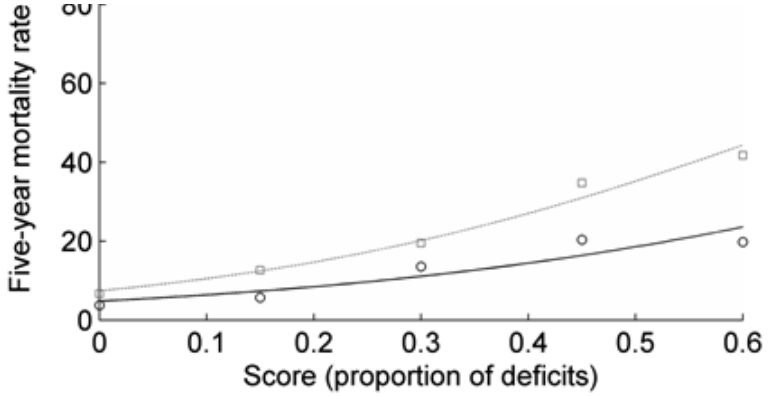
Different frailty measures show similar patterns of age specific increase

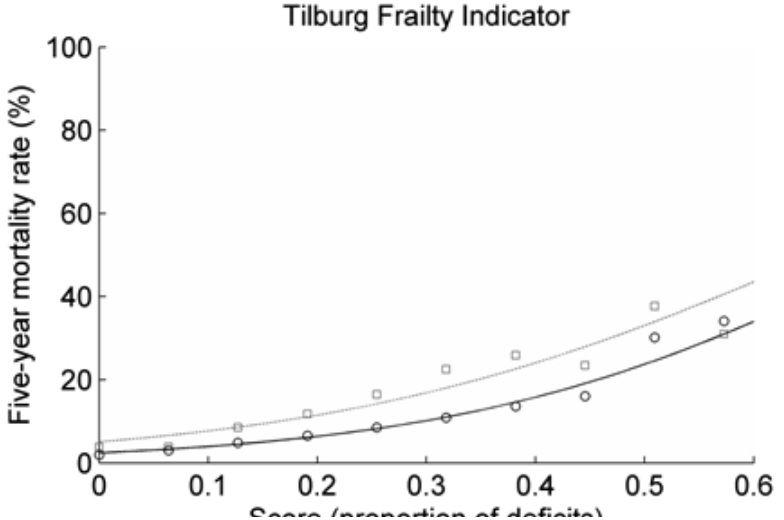


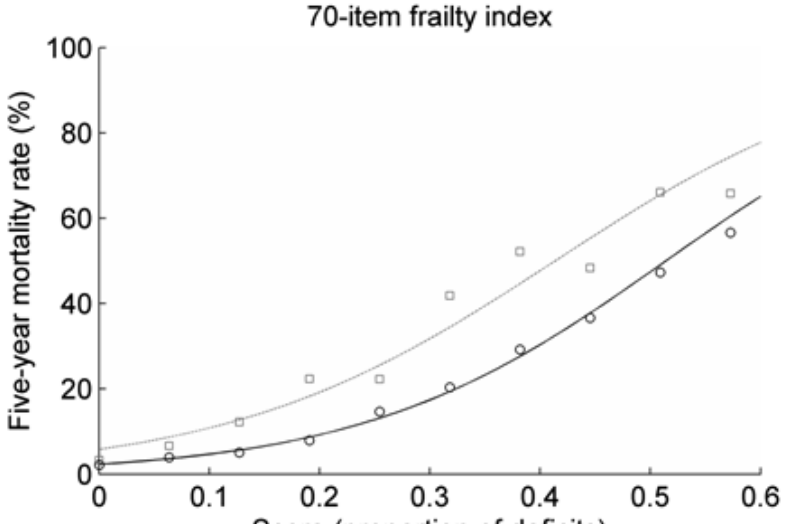
Theou et al, in revision

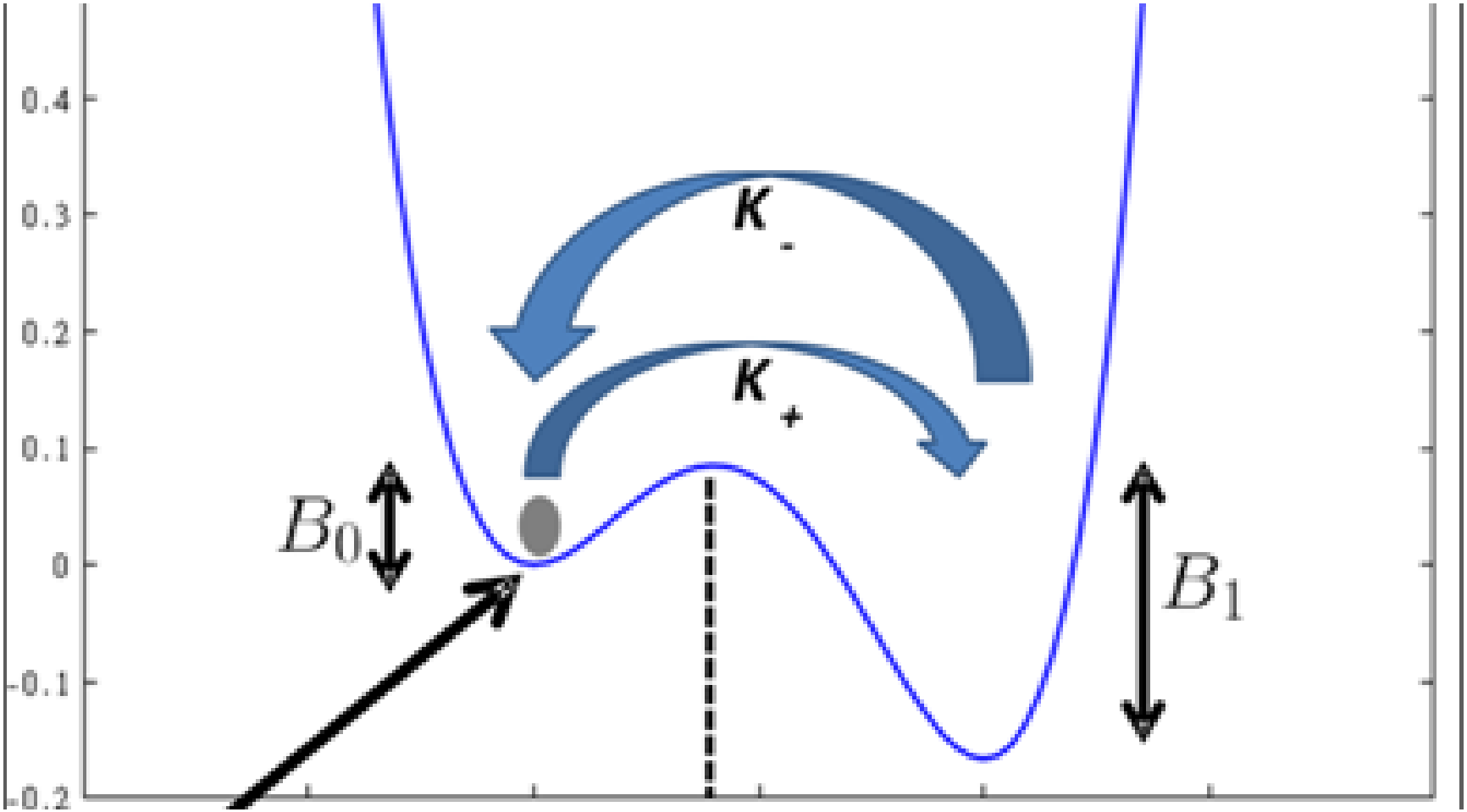
And similar associations with mortality







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