Conceptual models of human aging and resilience

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The aging paradox

- Molecular turnover in cells is rapid
- Molecule are replaced according to digital information – no information loss
- Faulty molecules are quickly degraded
- Efficient information repair with high fidelity
- Apoptosis and Senescence as final backstops
- **Why do we age? Why are we not perfectly resilient?**

Models

- Naïve wear theories are not likely – rapid, high fidelity turnover of cell components, protein machines do not "wear out"
- Naïve ideas of "entropy increase" – organisms are open systems and thermodynamic cost of DNA repair is very low
- Evolutionary explanation – Programmed aging not likely; disposable soma theory presumes aging, does not explain it
- Cancer protection (senescence) – but this already presumes inevitable information loss in cells.

Physical models: Entropy

- Resources for repair
  - Note: Pure "thermodynamic" cost of repair is extremely low.
  - ~ $F = NK_BTln4$ for N mutations. N= 0.1%/cell $3x10^9$ base pairs* 10^{14} cells
  - Add in entropy production during repair: F ~ 7 J = 0.002 kcal
- Energy resources *should* be more than sufficient to repair all DNA all the time.
- **But**: Mitochondrial and DNA damage, as well as protein aggregation, cell senescence etc. are a well-known hallmarks of aging
- Clearly damage is increasing over time, despite "ease" of repair

Why can't our cells repair all damage?

Simple conceptual model:

$$\frac{dD}{dt} = kN - rN_r D = 0$$

Assume steady state

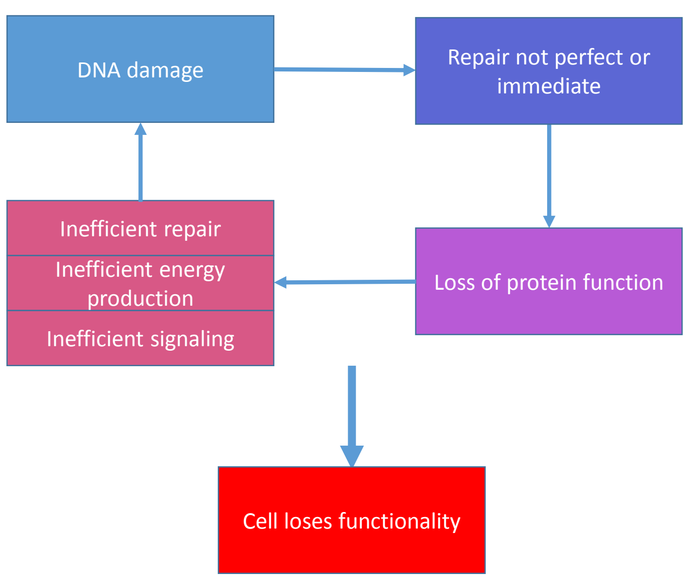
Rate of change in damage

Ongoing damage rate

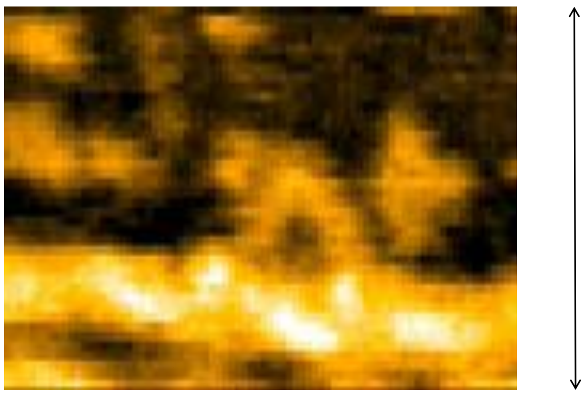
Repair rate: proportional to number of repair enzymes and amount of damage

$$\Rightarrow D = \frac{kN}{rN_r}$$

A damage level of zero would require infinitely fast and perfect repair at all times.

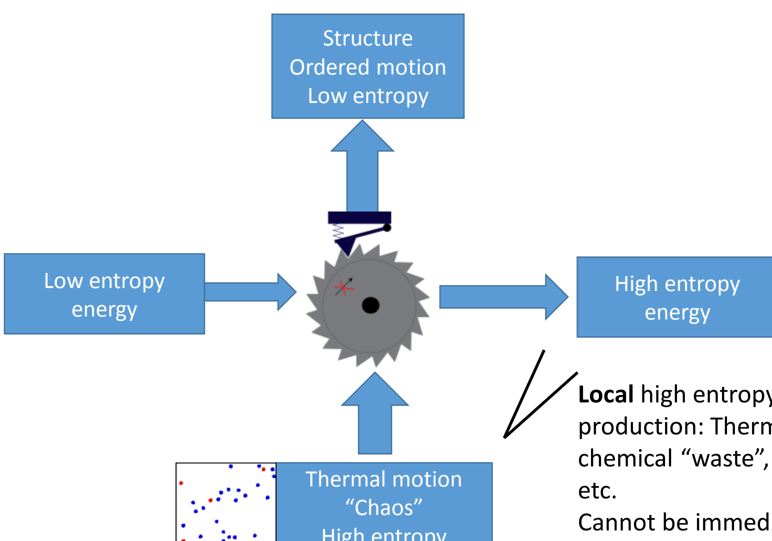


The machinery of life…



150 ms/frame

Life is a dynamics state: Ratcheting order from chaos



Local high entropy energy production: Thermal motion, chemical "waste", radicals etc.
Cannot be immediately exported

Entropy Production: Open systems (after Prigogine)

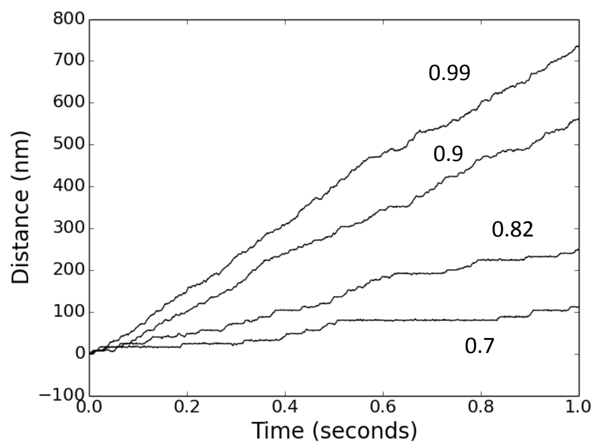
$$\frac{d_i S}{dt} = \sum_k F_k \frac{dX_k}{dt} > 0$$

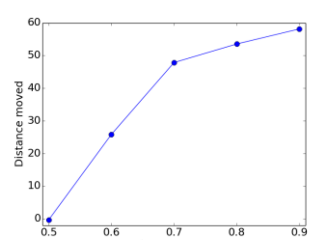
Entropy production

Thermodynamic forces:
- Chemical potential
- Concentration gradient
- Electrostatic potential
- Mechanical potential
- Thermal gradient
- Etc.

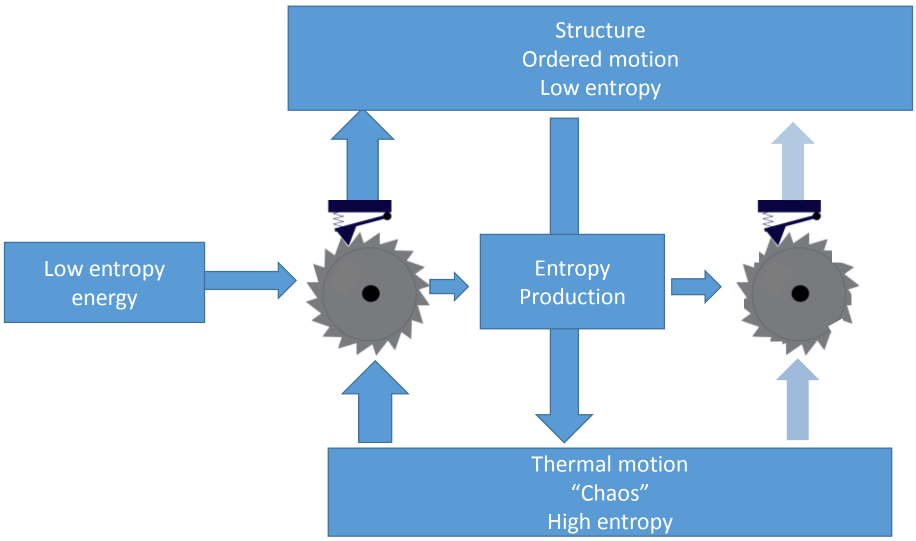
Thermodynamic currents:
- Chemical reaction
- Diffusion
- Electrical current
- Motion
- Heat flow
- Etc.

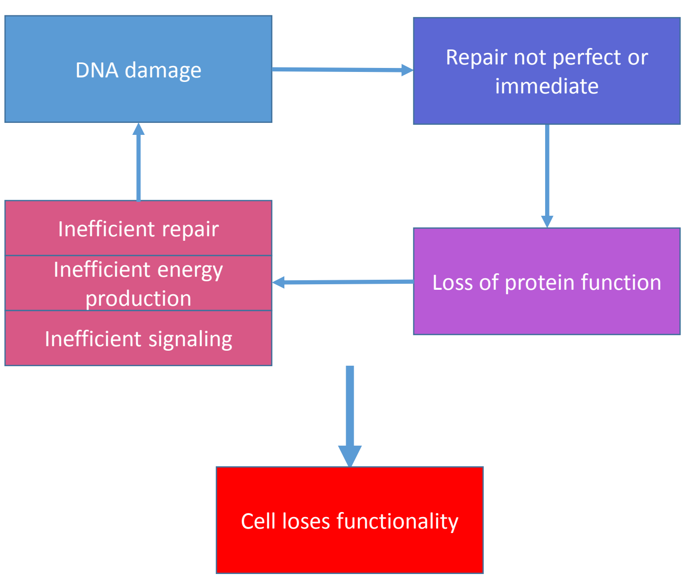
As a molecular ratchet loses structural fidelity....





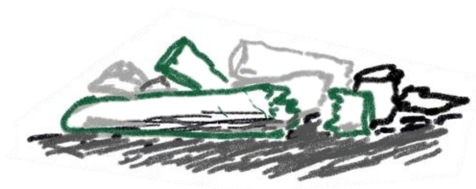
"Ratcheting" order from chaos requires intact structures and efficient energy flow



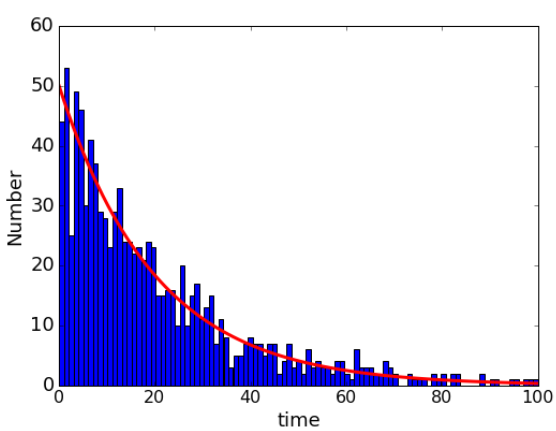


Reliability theory:
Medawar's test tubes – Chance failure

- Imagine 1000 test tubes
- On any given day, any test tube can break with a probability p.
- If a test tube breaks, it is replaced by a new one.
- After some time, what is the steady-state age distribution of the population of test tubes?



Medawar's test tubes – Chance failure

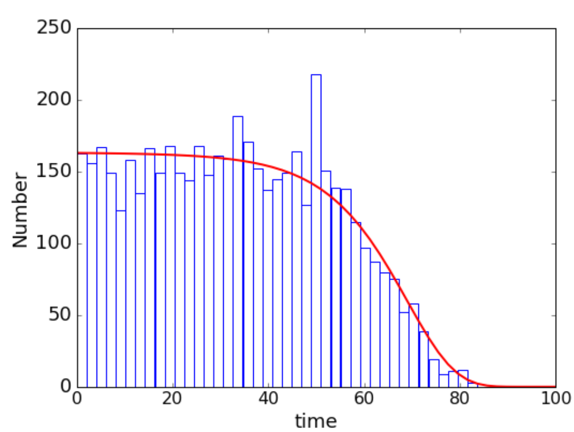


$N(T) \sim e^{-kT}$

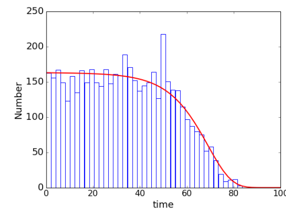
Medawar's test tubes – Chance failure and wear

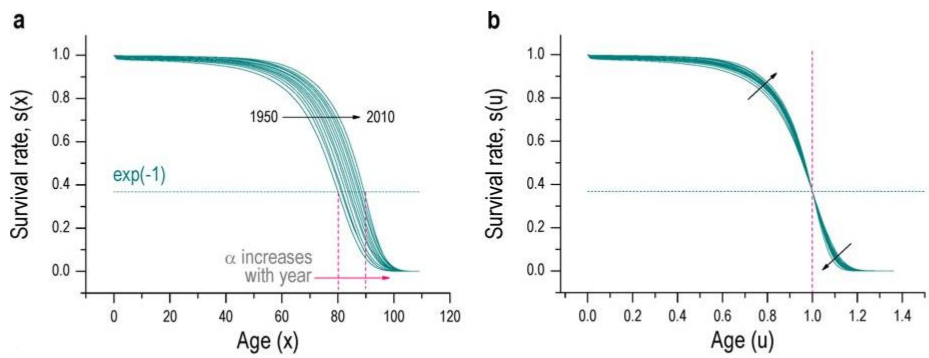
- Now assume that in addition to breaking by accident, test tubes accumulate hairline fractures that make them more vulnerable to breakage.
- Assume damage accumulates exponentially (when test tubes are already damaged, they are more likely to sustain further damage).
- What does the age distribution look like now?

Medawar's test tubes – Chance failure and wear



Human survival curves

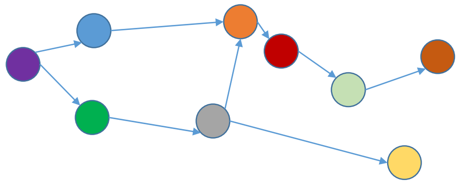




Trends in scale and shape of survival curves, Byung Mook Weon & Jung Ho Je, Scientific Reports volume 2, Article number: 504 (2012)

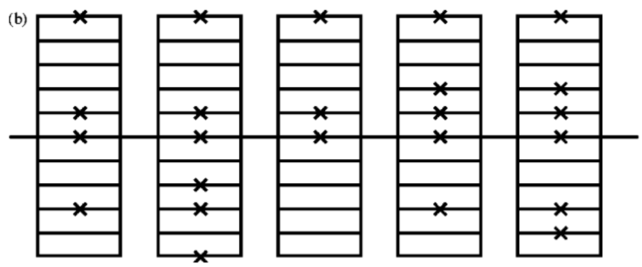
Reliability theory

- From engineering: deals with reliability & wear-out of machines
- Chance failure & wear (Medawar model)
- Can take into account:
  - Repair
  - Redundancy (Components in "parallel")
  - Co-Dependency of components (Components in "series")



Reliability theory (Gavrilov & Gavrilova)

- Critical systems with high redundancy (parallel) systems placed in series.
- Failures do not lead to death, but to aging, until redundancy is exhausted.
- Without redundancy, "aging" stops (mortality plateau)



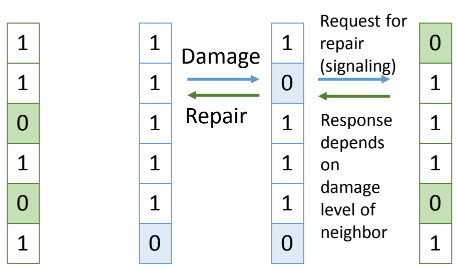
A simple model

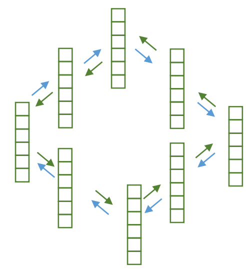
- Assumptions:
  - Systems are in parallel (genes, proteins, cells) & in series (cell assemblies, tissues, organs) ⇒redundancy and interdependence.
  - Model incorporates repair.
  - Damage happens locally, but repair requires systems response.
  - Probability and speed of signaling and repair depend on already existing damage.

A simple model

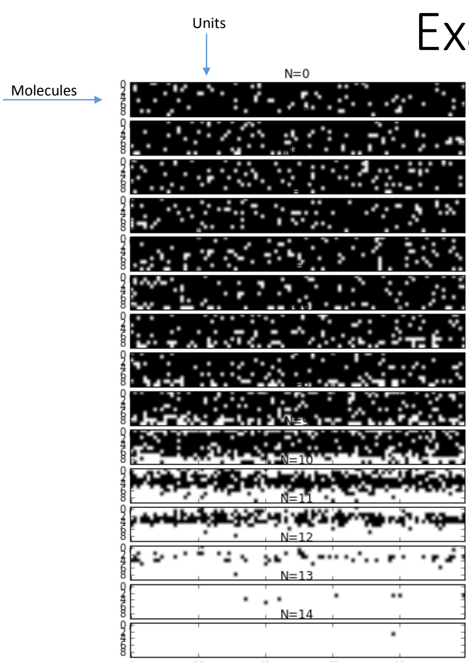
- M biomolecules (DNA) with N monomers each: 1 = correct monomer, 0 = incorrect monomer
- Random chance of getting damaged (1 to 0), number of damage chances = entropy production rate
- Entropy production rate increases with damage, decreases with repair
- Random chance of repair (0 to 1), probability of repair depends on state of "neighboring" molecules

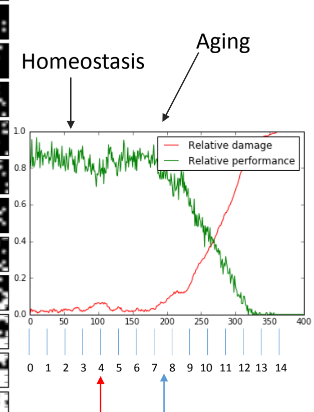
Random chance of repair (0 to 1), number of repair chances = energy supply

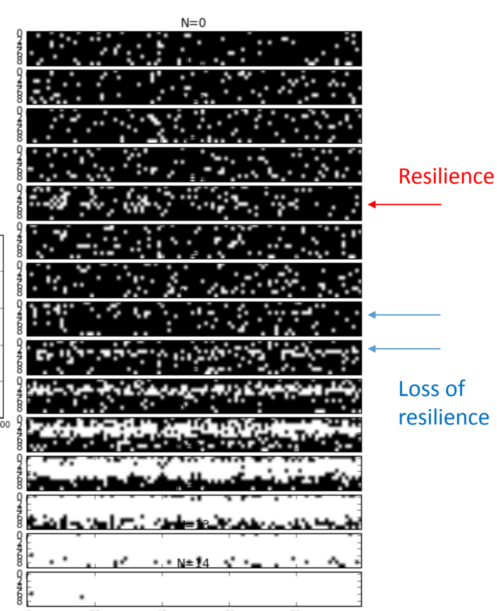


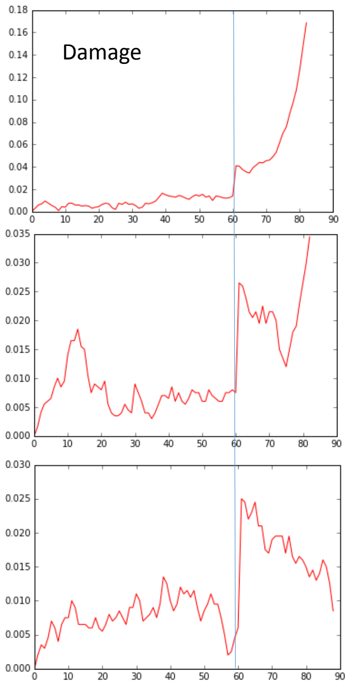


Examples of results

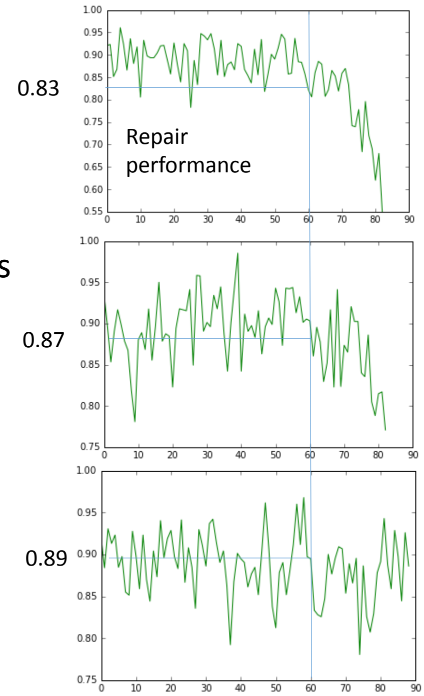


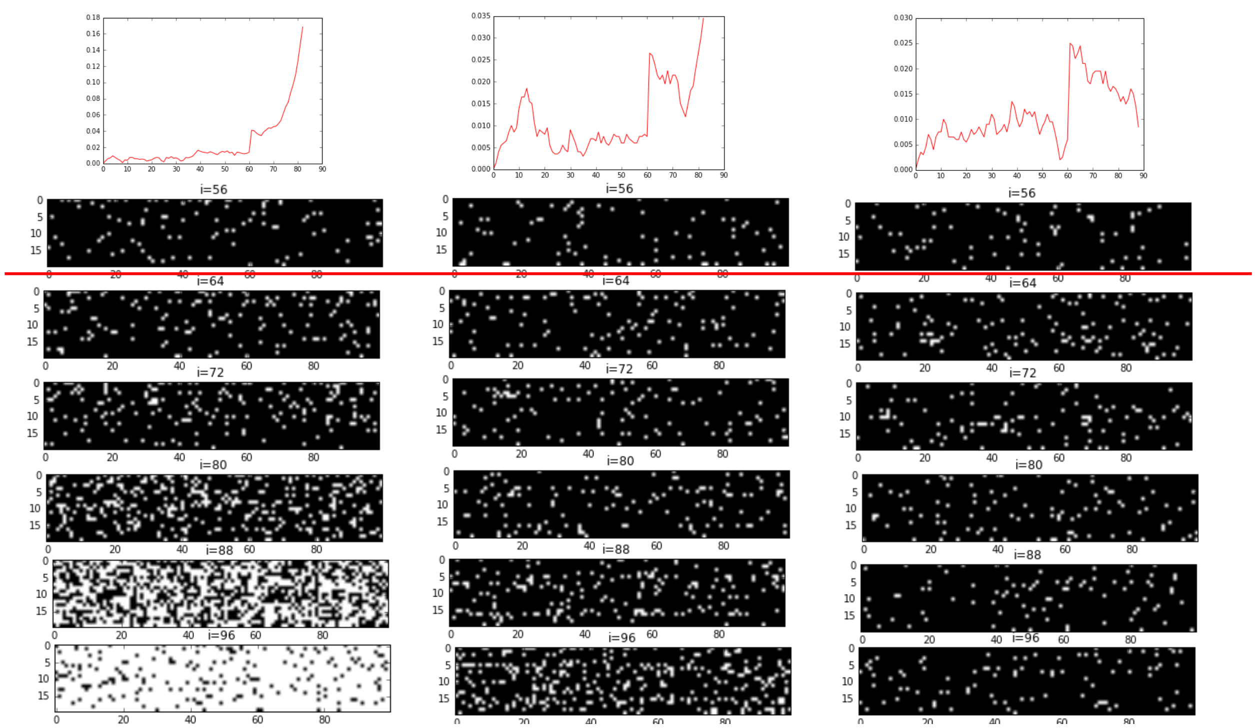






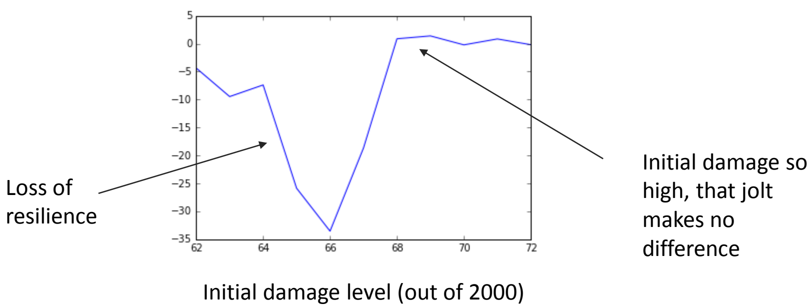
Same initial conditions
Same jolt at “age” 60
Three totally different outcomes…

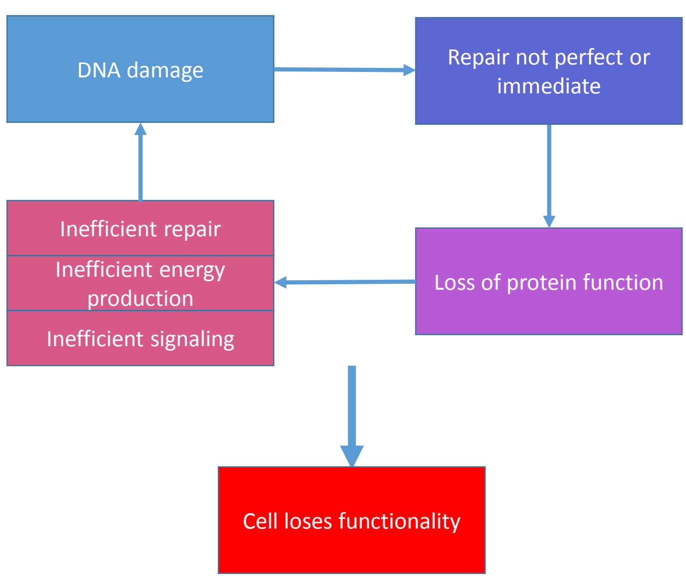




Resilience

- Start with individuals at different initial damage levels
- Give a "jolt" of additional damage (35/2000 sites)
- Look at average age reduction





Hierarchy of aging

- Local entropy production
- DNA damage
- Proteome damage
- Cell damage and loss
- Tissue damage and loss
- Organ failure

Conclusions

- Entropy production produces damage that can be repaired only up to a point.
- Over time, damage accumulates and causes further damage (positive feedback).
- Positive feedback due to loss of “repair kinetics” (dynamics of repair)
- Aging is the result of accumulating damage on complex system with high initial redundancy.
- Once redundancy is highly reduced, there is low resilience and avalanche failures become more likely.
- Simple models can reproduce some possibly realistic features:
  - Overall aging dynamics
  - Stochastic response to insults: Superficially similar states can show very different resilience, difference in resilience can be very subtle
  - Critical window where small insults can have a large effect.
- Next steps:
  - How to connect to reality (complexity of organisms, actual observables)