Damage accumulation, repair, and aging

David Steinsaltz

Dept. of Mathematics and Statistics

Queen's University

or, What's wrong with immortality?

"No, I don't want to live forever, but I damn sure don't want to be dead forever, either."

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Dept. of Mathematics and Statistics

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“Evolutionary biologists, since they’re interested in Why, can ignore the How”

-Michal Jazwinski

Santa Fe, 3/25/07

Wear and Tear theories

- "Things fall apart". Why should aging need further explanation?
- Can we use accumulation of damage to predict the details of aging?
- Reliability models of Gavrilovs, Koltover, many others -- Aim to reproduce Gompertz mortality
- These models have yielded few insights
- When they have, these have generally depended upon faulty or fake mathematics.

Begging the question: Why does damage accumulate at all, given that repair is possible?

It is indeed remarkable that after a seemingly miraculous feat of morphogenesis a complex metazoan should be unable to perform the much simpler task of merely maintaining what is already formed. -- G. Williams

Energy budget approach

- Popularized by Kirkwood and Holliday
- Developed in sophisticated forms by Mangel & Bonsall, Chu & Lee, Kaplan & Robson
- Total energy budget divided among repair, growth and reproduction.
- Assumes that more repair is always possible: Just need to “spend” more.
- Why reproduce? Under what circumstances is it favorable to replace a fully functioning organism with several immature (and

Repair models

"You fix it by buying a new one."

Inherent limitations of repair

DS and Goldwasser: "Aging and Total Quality Management: Extending the reliability metaphor for longevity". Evolutionary Ecology Research Dec. 2006.

- Reparability carries costs: Tradeoff between repair and reliability
- Overactive repair
- Loss of structural integrity
- Some damage cannot be repaired

Thermodynamically, these could all be line items on an energy budget, but... biology is not physics.

Costs of reparability

- Need a hierarchical model
- Engineering: “Total quality management”
- Are there engineering rules of thumb?

Overactive repair

Stem cells and cancer: Programmed senescence?

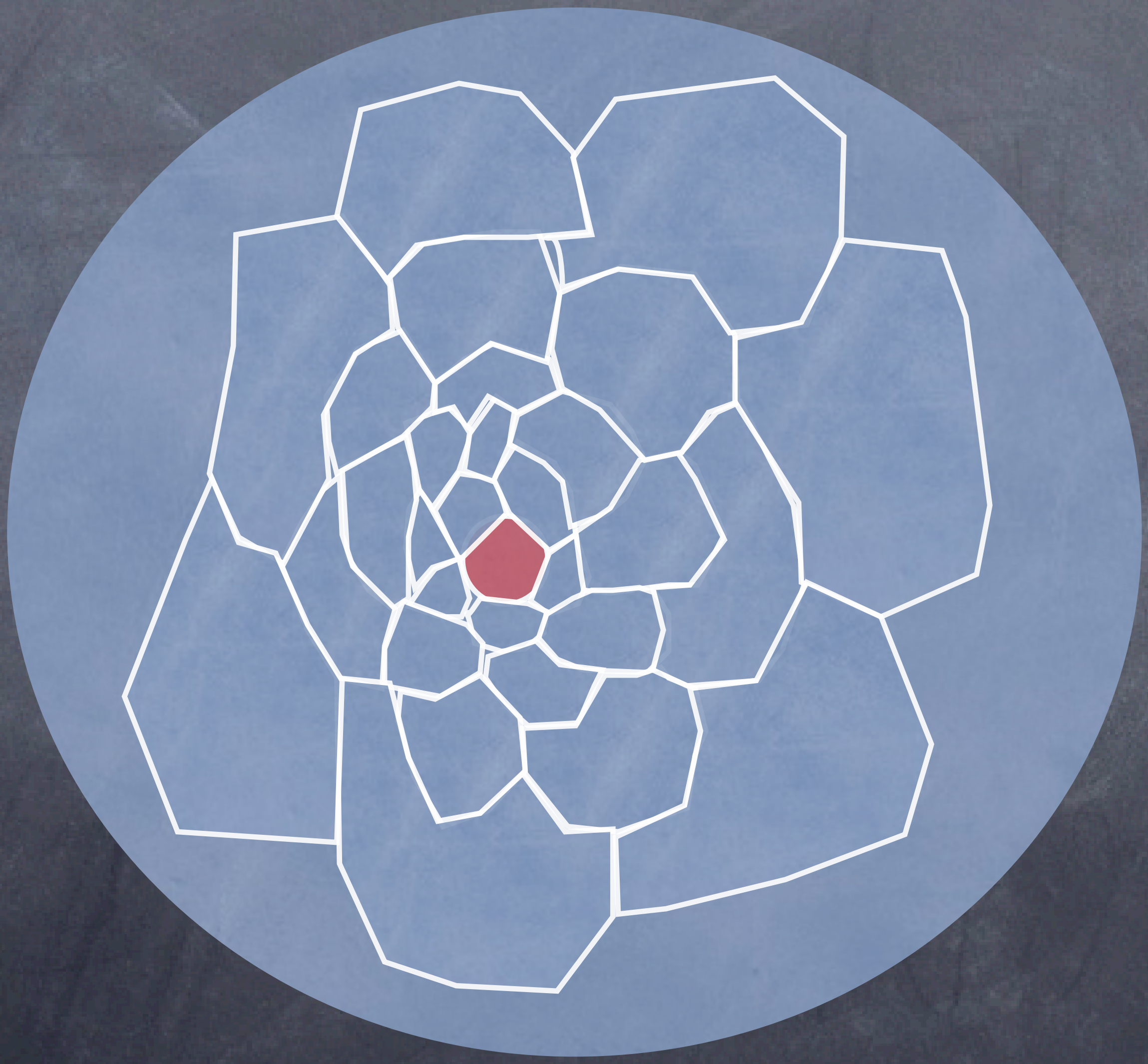
Stem-cell ageing modified by the cyclin-dependent kinase inhibitor $p16^{INK4a}$

Immune system: De Boer 1993 tradeoff between selectivity and efficiency.

Loss of integrity

- Model: Life is a high-dimensional diffusion
- Homeostasis: Drift is inward toward optimal point
- Problem: Which way? Based on evolutionary experience. Organism looks at times when its ancestor was close to the same state, and goes the same way. “Self-reinforcing diffusion”
- Homeostasis becomes increasingly vague with age.

Loss of integrity



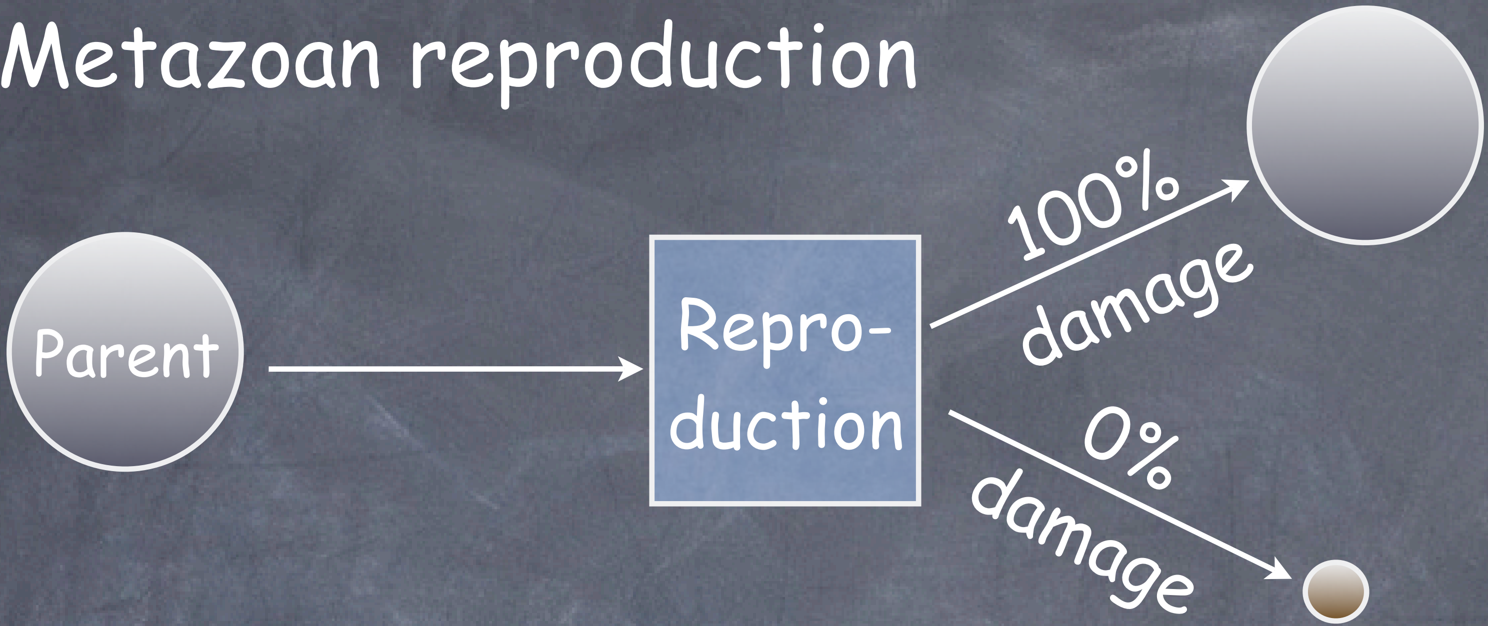
Irreparable damage

- No repair system is perfect
- Repair must be done “on the fly” (not true
- Substitution mutations in DNA are irreparable in principle, because information is lost

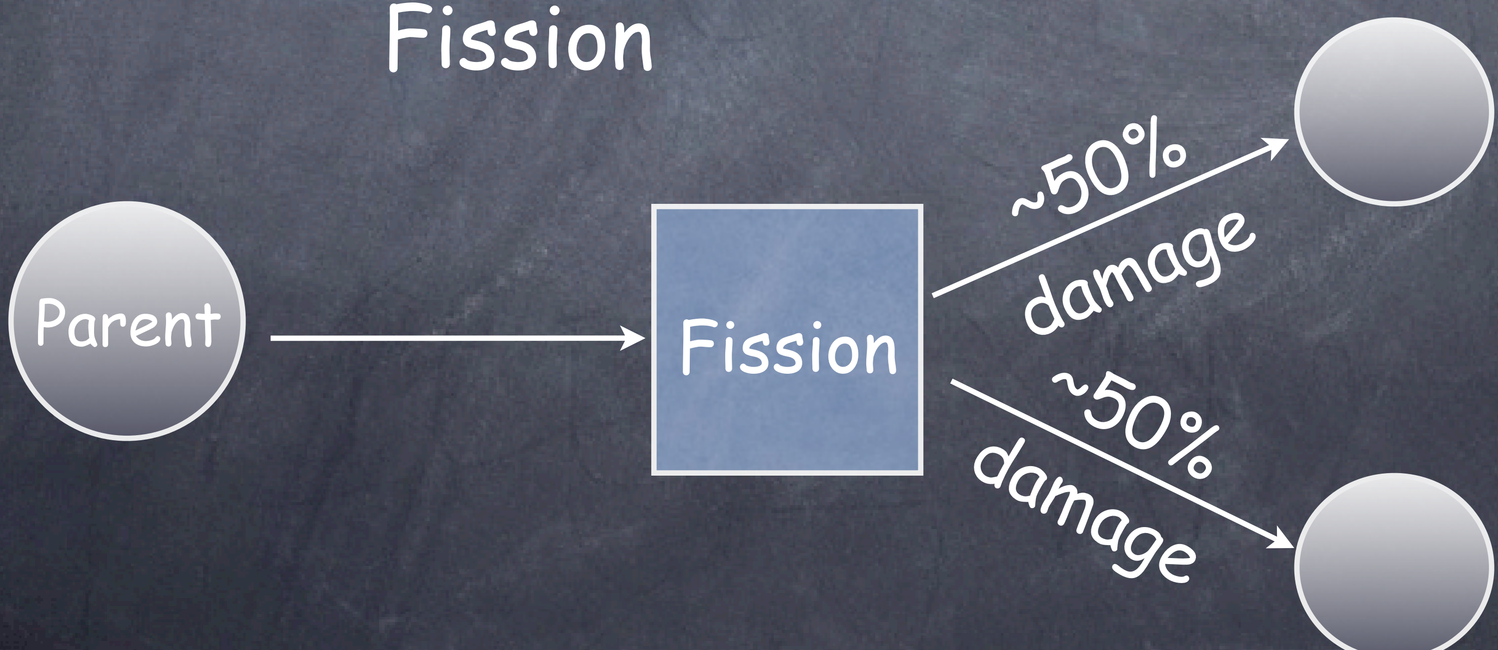
How is the irreparable damage repaired?

- Metazoans "reset" somatic damage through reproduction
- What about protozoans? What about damage accumulated in the germ line? What about aging (non-aging) of tumours?
- Paradigmatic aging is simply the extreme version of a continuum of strategies

Metazoan reproduction



Fission



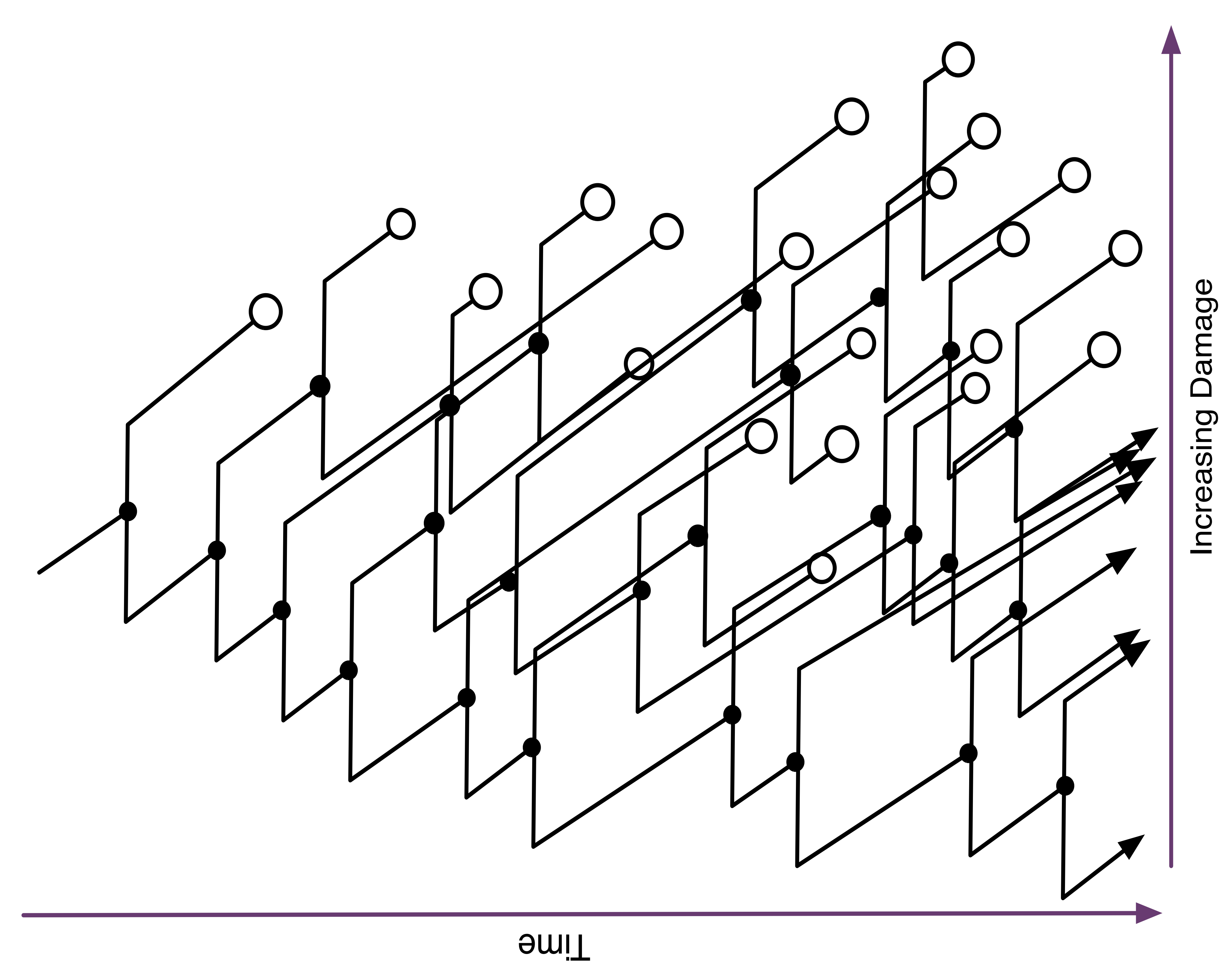
Graham Bell:
“Sex and Death in Protozoans”

- Empirical observations: Protozoan lines run down within 20 generations or so.
- They recover immediately after a round of genetic conjugation.
- Exogenous repair: No external prototype for correction
- Use overproduction + selection as repair mechanism

- Generalization: Exogenous repair doesn't depend on conjugation.
- Can the organism gain a selective advantage by accumulating more damage, but segregating more often?
- Evans and DS: "Damage segregation at fissioning may increase growth rates: A superprocess model" (to appear in TPB)

Branching model

- At any given time there is a collection of cells, identified with their damage states.
- The damage moves up or down at random, with an upward bias. The randomness for a cell with damage x is $\sigma(x)$; the bias is $b(x)$.
- A cell with damage x dies at rate $\kappa(x)$.
- A cell with damage x fissions at rate $\lambda(x)$.
- Damage segregation: Parent's damage divided unequally between daughters. A cell with damage x has daughters with damage states $x+y$ and $x-y$. (y may be random.)


Increasing Damage
Time

Superprocess model

- Number of initial cells becomes large, splitting rate increases, segregation jump shrinks.
- Limit “superprocess”: Continuous mass of particles evolving randomly in time.
- Three state (damage)-dependent parameters.
- Two motion parameters: bias b and randomness parameter σ. Effect of damage segregation is to increase σ.
- Net birth rate $\beta=\lambda-\kappa$. κ=killing rate, λ=splitting rate.
- Assume β decreasing. More damage, slower growth.

What's the advantage of the superprocess picture?

- Instead of simulating, we can compute the long-term behavior.
- We can use differential equations instead of discrete math.
- That's good?

Warning: Equation coming up

Define ϕ_r to be the unique solution to

$$\frac{1}{2}\left[\sigma^2(x)\phi_r(x)\right]'' - \left[b(x)\phi_r(x)\right]' + \beta(x)\phi_r(x) = r\phi_r(x)$$

with $\phi_r'(0) = 2b(0)\phi_r(0).$

Let R be the smallest such that ϕ_R is positive.

Theorem (Evans & S. 2006) - If R>0, then the population distribution converges to a random multiple of ϕ_R.

The long-term growth rate of the total mass is R.

What does this say about the advantage of damage segregation?

Suppose we hold other parameters fixed, and consider different values of σ (corresponding to different imbalances in damage segregation).

Theorem: If drift b is bounded below, away from 0, then the maximum R is attained for a nonzero finite value of σ. In particular, if inherent damage accumulation is deterministic, then unequal segregation of damage increases the long-term growth rate.

Note: Increasing turnover of the generations effectively amplifies the inequality.

Unstructured demographic models are indifferent to the rate of generational turnover: Only affected by the growth rate per time unit.

Structuring by <u>heritable</u> damage produces an asymmetry, and so an optimal “length of life”

Example

$$\beta(x) = \beta_0 - \beta_1 x \quad \sigma(x) = \sigma x \quad b(x) = bx$$

R may be computed explicitly in terms of Bessel functions.

Example

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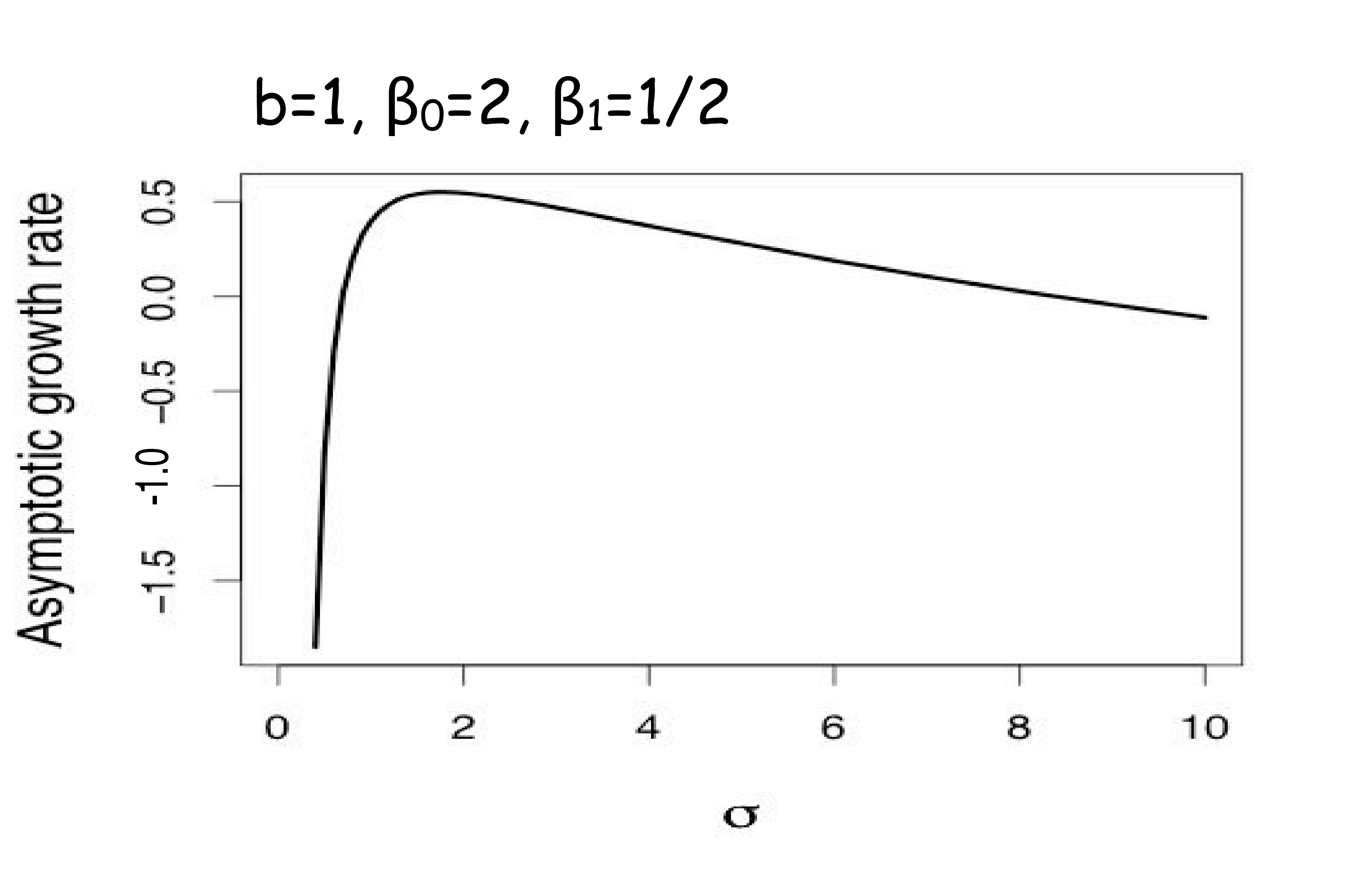
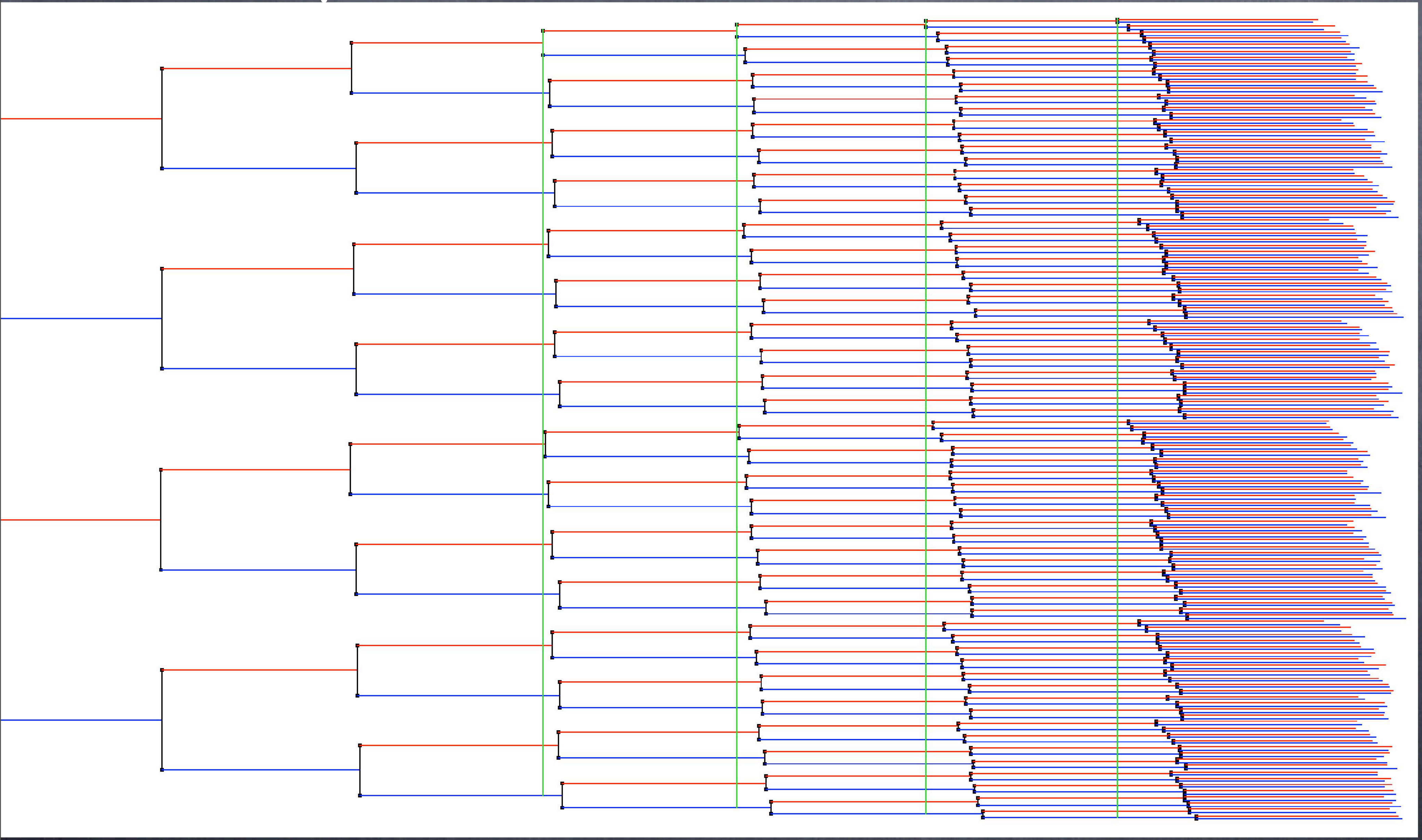


Connections to Experiments

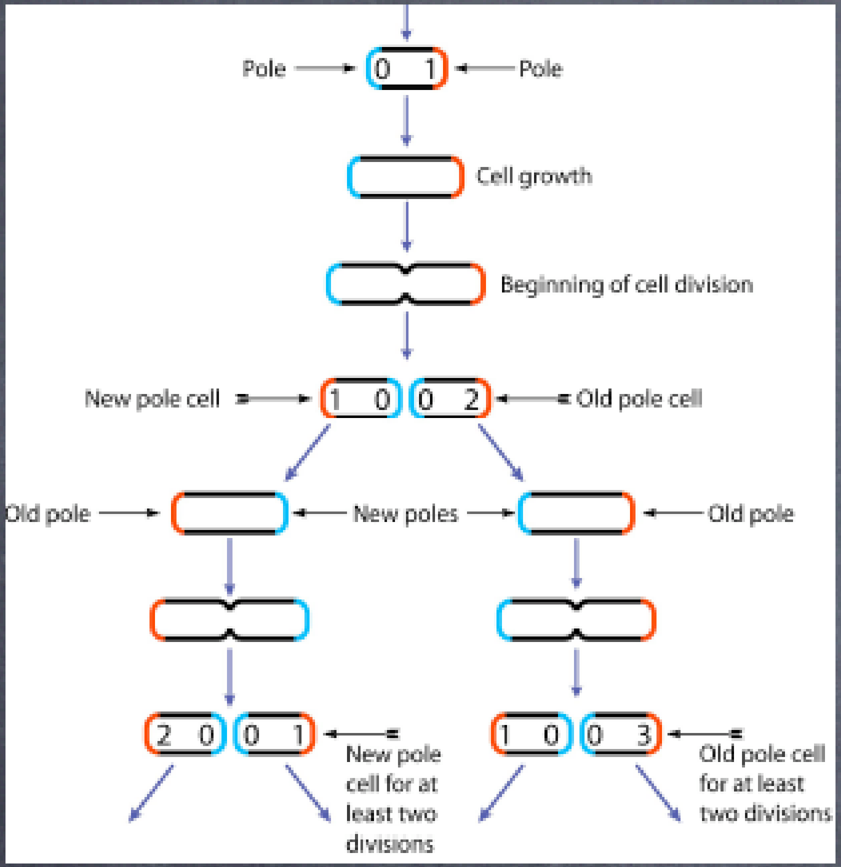
Budding yeast (S. cerevisiae)

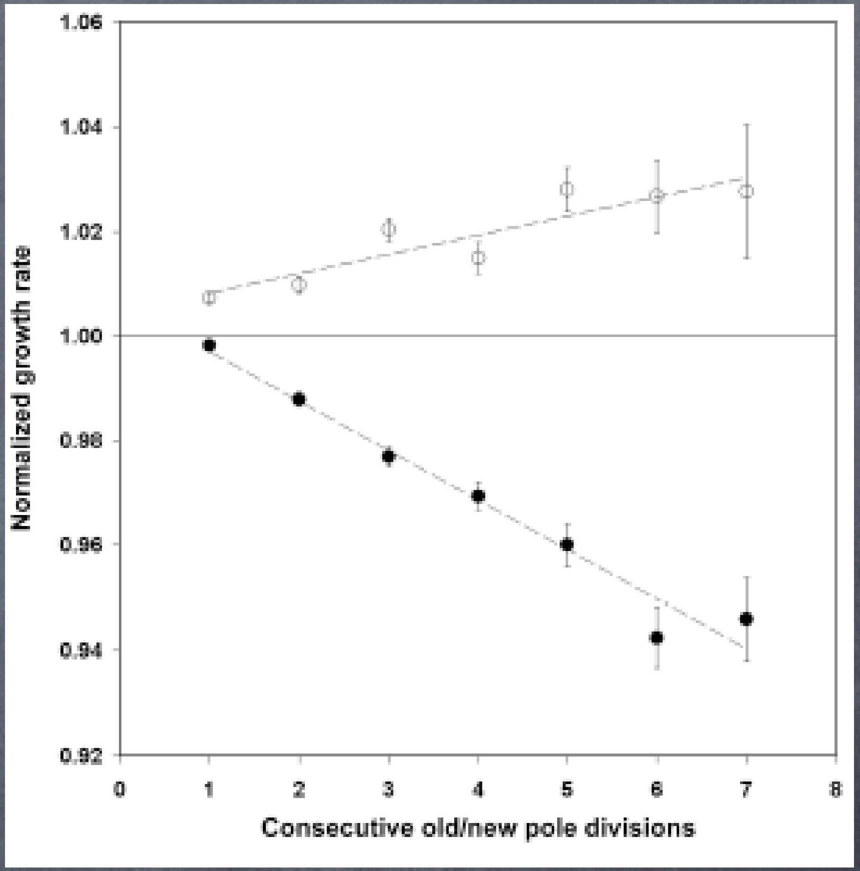
- Obvious morphological asymmetry between mother and daughter
- Mother ages (Hartwell & Johnston 1959)
- Heritable aging factor
- Asymmetry in damage level between mother and daughter actively maintained (Lai et al. 2002). Maybe connected with segregation of damaged mitochondria (Aguilaniu et al. 2003).

Population Senescence in E. coli



Stewart, Madden, Paul, Taddei (PLoS 2005)





Diagrams from Stewart, Madden, Paul, Taddei (2005).

Fission Yeast: S. Pombe

- Fission products look the same
- There is heritable asymmetry in number of fission scars (Calleja and Zuker 1980) and size (Barker and Walmsley 1999)
- Carbonylated proteins accumulate in a relatively quiescent subset of cells (Minois et al. 2006)
- Caveat: Are the cells quiescent because they've accumulated damaged proteins, or do they accumulate the proteins because they're inactive?

Cell Type Regulates Selective Segregation of Mouse Chromosome 7 DNA Strands in Mitosis

Athanasios Armakolas and Amar J. S. Klar*

After chromosome replication, sister chromatid copies are generally thought to segregate randomly to daughter cells. However, sister chromatids differ in their DNA strands, with each chromatid inheriting one older strand that is paired to a newly synthesized strand. Genetic analysis with a homologous chromosome pair indicated nonrandom chromatid distribution in embryonic stem cells. Biased segregation pattern was also found in all 100 endoderm cells examined, but not in any of the 165 neuroectoderm cells. In contrast, the mesoderm, cardiomyocyte, and pancreatic cells exhibited a random mode of segregation. Strand distribution mechanisms regulated by cell type may have consequences for cellular differentiation and for evolving strategies for developmental mechanisms.

Science 2/24/06

Two levels of experimental test

- Measure population growth rate as function of damage segregation. Can we measure damage? Can we manipulate inheritance?
- Evolutionary: Can we find mechanisms for manipulating the inheritance of damage?

Speculative extension: Intergenerational transfers

- Mathematical rule: Negative negative is positive
- Inheriting less damage is equivalent to inheriting more of something good.
- When offspring inherit important resources from parents, the parents may have an interest in dividing the resources unequally