Damage segregation in fissioning organisms increases population growth rates

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(with David Steinsaltz)

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•"Force of mortality" (hazard rate) increases with age

"Senescence of **multicellular** plants and animals is an almost universal phenomenon; it needs to be explained both in terms of cellular and physiological mechanisms, and of evolutionary forces."

Brian Charlesworth, 2001

Bacteria death reduces human hopes of immortality

- 05 February 2005
- From New Scientist Print Edition.

THE quest for immortality looks more than ever like an impossible dream. Even bacteria, long regarded as the masters of regeneration, eventually reach the twilight of their lives and die, just as we do.

Many microbiologists had assumed that bacteria effectively never die, as individuals simply split in two to make the next generation. Identical parents and offspring should be equally fit to carry on multiplying forever.

Researchers followed the fortunes of every descendant in nine generations, each grown from a single *Escherichia coli* in 94 separate cultures (that is over 35,000 cells), and have shown that this is not so. Early descendants become steadily wearier and less sprightly.

Each rod-shaped *E. coli* has two ends, or "poles". As the cell splits, each descendant inherits one "old" pole and builds one "new" one. But as a colony expands, the proportion carrying the original old poles gets smaller as waves of descendants with newly created poles take over.

By analysing microscope images of growing colonies, Eric Stewart and his colleagues at the René Descartes University in Paris, France, proved that direct descendants of old-pole cells grew 2 per cent more slowly, were 3 per cent smaller and were more likely to die (*PLoS Biology*, vol 3, e 45). Nature, does not seem to do immortality, Stewart says. "Never say never, but in natural organisms it seems unlikely."

Damage segregation in E. coli

◇ experiments in the lab of Francois Taddei track all the individuals in a population of *E. coli* through several generations and measure the amount of incorrectly folded proteins as evidence of *cellular damage*

◇ individuals sustain damage during their life span

◇ the degree of damage affects the splitting rate and the likelihood that individual will die rather than split

◇ when an individual splits, damage is not shared equally among the daughters – *segregated preferentially*

PLoS Biology: Slideshow

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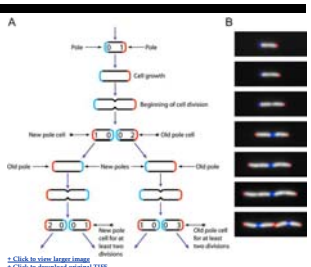

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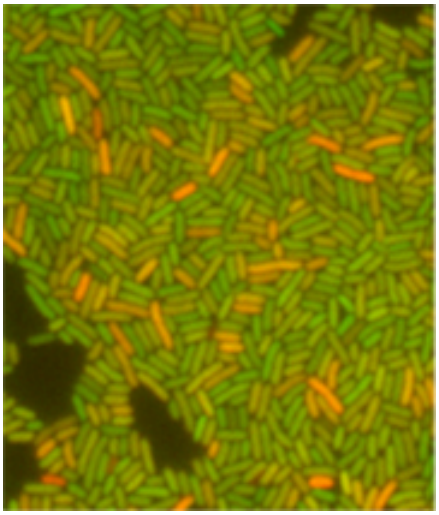
Figure 1.
The Life Cycle of *E. coli*

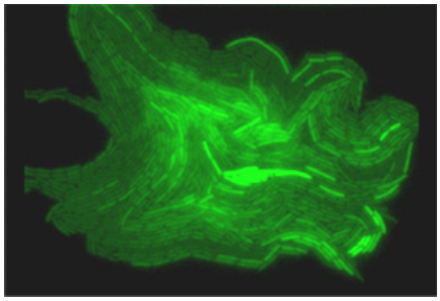
During cell division, two new poles are formed, one in each of the progeny cells (new poles, shown in blue). The other ends of those cells were formed during a previous division (old poles, shown in red).

(A) The number of divisions since each pole was formed is indicated by the number inside the pole. Using the number of divisions since the older pole of each cell was formed, it is possible to assign an age in divisions to that cell, as indicated. Similarly, cells that consecutively divided as a new pole are assigned a new pole age, based on the current, consecutive divisions as a new pole cell.

(B) Time-lapse images of growing cells corresponding to the stages in (A). False color has been added to identify the poles.

From: Stewart EJ, Madden R, Paul G, Taddei F (2005) Aging and Death in an Organism That Reproduces by Morphologically Symmetric Division. PLoS Biol 3(2): e45



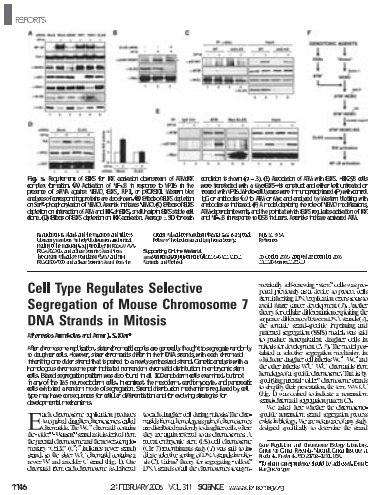


ALSO We were going to work with S. Michal Jazwinski in Biochemistry and Molecular Biology and Center on Aging at LSU on similar data for yeast BUT

"Hurricane Katrina wreaked billions of dollars in damage and claimed hundreds, maybe thousands of lives. For many researchers at universities affected by the storm, it also destroyed or menaced their lives' work.

Katrina destroyed thousands of animals – including fruit flies, mice, rabbits, dogs, and primates – and materials ranging from tissue samples to cell lines to micro-organisms like yeast and bacteria."

Lila Guterman
The Chronicle of Higher Education
September 30, 2005



REPORTS

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

Veronika Armakolas and Anne J. Klar*

Is there an evolutionary explanation for segregation?

$\Longleftrightarrow$

Does some degree of segregation increase the long-term growth rate?

Is there an optimal level of segregation?

BUT: Beware of "Just So Stories" - not everything we see in nature is an optimum.

Branching diffusion + jumps model

◇ each individual has a position in $\mathbb{R}_+$

◇ position = amount of *damage*

◇ during their lifetimes, individuals *accumulate and repair damage* – described by a diffusion (independent from individual to individual) with generator $\frac{1}{2}\sigma_{\text{acc}}^2(x)\phi''(x) + b(x)\phi'(x)$

◇ individuals *die* at a rate increasing in damage

◇ individuals *split* at a rate decreasing in damage

◇ at a split, two daughters *jump* by $\pm$ a random amount (i.e. a mother's damage is *divided* randomly between the daughters) – not the usual branching diffusion model

Rescaling the branching diffusion model

◇ sequence of models $\mathbb{X}^N$ with same damage + repair diffusion

◇ start with $\approx KN$ individuals, K constant

◇ encode the state of the population by placing mass N^{-1} at the position of each individual

◇ splitting rate + death rate at position x is $\approx N\rho(x)$

◇ splitting rate - death rate at x is $\approx \beta(x)$, $\beta \downarrow$

◇ individual splitting at x has offspring at $x \pm U_x^N$, with $N\mathbb{E}[(U_x^N)^2] \approx \sigma^2_{\text{seg}}(x)$

Rescaling limit

◇ if $\mathbb{X}_0^N$ converges in distribution to a finite random measure, then $\mathbb{X}^N$ converges in distribution to a *Dawson-Watanabe superprocess* $\mathbb{X}$ (continuous process with values in finite measures on $\mathbb{R}_+$) associated with the spatial motion that has semigroup generated by

$$\frac{1}{2}\sigma^2(x)\phi''(x) + b(x)\phi'(x),$$

where

$$\sigma^2 = \sigma^2_{\text{acc}} + \sigma^2_{\text{seg}},$$

and branching mechanism

$$h \mapsto \beta(x)h + \frac{1}{2}\rho(x)h^2.$$

Dawson-Watanabe as a stochastic PDE

◇ $\mathbb{X}_t(dx) = \xi(t,x)\,dx$ for $t \geq 0$, where ξ is a solution of the *stochastic partial differential equation*

$$\frac{\partial \xi}{\partial t} = \mathcal{L}^*\xi + \sqrt{\rho \cdot \xi}\frac{\partial^2}{\partial t \partial x}W,$$

with $\mathcal{L}^*$ the *adjoint* of

$$\mathcal{L}\phi(x) = \frac{1}{2}\sigma^2(x)\phi''(x) + b(x)\phi'(x) + \beta(x)\phi(x),$$

$\sigma^2 = \sigma^2_{\text{acc}} + \sigma^2_{\text{seg}}$, and $\frac{\partial^2}{\partial t \partial x}W$ is *time–space white noise*

Moments of $\mathbb{X}$

◇ $\mathcal{L}\phi = \frac{1}{2}\sigma^2\phi'' + b\phi' + \beta\phi$ generates a *semigroup* $(P_t)_{t\geq 0}$ (*not necessarily sub-Markovian*, i.e. $P_t 1(x) > 1$ can occur)

◇ $\mathbb{E}^\mu[\langle \mathbb{X}_t, f\rangle] = \mu P_t f := \langle \mu, P_t f\rangle$

◇ $\mathbb{E}^\mu[\langle \mathbb{X}_t, f\rangle^2] = \{\mu P_t f\}^2 + \int_0^t \mu P_s \left\{\rho \cdot (P_{t-s}f)^2\right\} ds$

◇ similar formulae for *higher moments*

Long term behaviour of $\mathbb{X}$

◇ suppose $\lim_{t\to\infty} \delta(t)^{-1} P_t f(x) = \alpha(x)\langle \nu, f\rangle$ for some function δ, function $\alpha \geq 0$ and measure ν

◇ then $\lim_{t\to\infty} \mathbb{E}^\mu[\langle \delta(t)^{-1}\mathbb{X}_t, f\rangle] = \langle \mu, \alpha\rangle\langle \nu, f\rangle$

◇ suppose further that $\lim_{t\to\infty} \delta(t+u)/\delta(t) = e^{\eta u}$ for some $\eta > 0$, similar calculations for 2^{nd} moments show $\delta(t)^{-1}\mathbb{X}_t$ *converges in probability* as $t \to \infty$ to a *random multiple* of ν (related results by Engländer & Turaev, Engländer & Winter)

Showing $\delta(t)^{-1}P_t f(x) \to \alpha(x)\langle \nu, f\rangle$

◇ recall $(P_t)_{t\geq 0}$ has *generator* $\frac{1}{2}\sigma^2\phi'' + b\phi' + \beta\phi$

◇ suppose $\sup_x \beta(x) = \beta^*$, then $(e^{-\beta^* t}P_t)_{t\geq 0}$ is *sub-Markovian* and has generator $\frac{1}{2}\sigma^2\phi'' + b\phi' + (\beta - \beta^*)\phi$

◇ $(e^{-\beta^* t}P_t)_{t\geq 0}$ is the semigroup of the *diffusion* with generator $\frac{1}{2}\sigma^2\phi'' + b\phi'$ *killed* at rate $\beta^* - \beta(x)$ in state x

◇ Write ζ for the death time of the killed diffusion X, then

$$\frac{P_t f(x)}{P_t 1(x)} = \mathbb{E}^x[f(X_t) \,|\, \zeta > t]$$

Quasistationary notions

◇ consider a general Markov process X killed at time ζ (e.g. first time hit some set of states)

◇ say that X has *asymptotic killing rate* θ when started from the probability distribution χ if $\lim_{t\to\infty} \mathbb{P}^\chi\{\zeta > t+s \,|\, \zeta > t\} = e^{-\theta s}$ for all $s \geq 0$

◇ say that X *converges from the initial distribution* χ *to the quasistationary distribution* ν if

$$\lim_{t\to\infty} \mathbb{P}^\chi\{X_t \in A \,|\, \zeta > t\} = \nu(A)$$

◇ not equivalent to $\mathbb{P}^\chi\{X_t \in A\} \sim c_\chi e^{-\theta t}\nu(A)$

Quasistationarity for one-dimensional diffusions

◇ Suppose X is a killed diffusion on $\mathbb{R}_+$ with generator $\mathcal{G}\phi = \frac{1}{2}\sigma^2\phi'' + b\phi' + \kappa\phi$ having adjoint $\mathcal{G}^*$

◇ Suppose ϕ_λ solves

$$\mathcal{G}^*\phi_\lambda = \lambda\phi_\lambda, \quad \phi_\lambda(0) = 1, \quad \phi'(0) - 2b(0)\phi(0) = 0.$$

◇ Set $\underline{\lambda} = \inf\{\lambda : \phi_\lambda \geq 0\}$. If $\underline{\lambda} > \inf_x \kappa(x)$, then X has asymptotic killing rate $-\underline{\lambda}$ and converges to the quasistationary distribution

$$\frac{\phi_{\underline{\lambda}}(x)\,dx}{\int \phi_{\underline{\lambda}}(y)\,dy}$$

(Steinsaltz and Evans, to appear in *Trans. Amer. Math. Soc.*)

Example

◇ consider the diffusion on $(1,\infty)$ with generator $\frac{\sigma^2}{2}x^2 f''(x) + bxf'(x)$ reflected at 1 and killed at rate kx in state x – assume that $b > \sigma^2/2$ (so unkilled process goes to $+\infty$).

◇ the process has asymptotic killing rate $\frac{\sigma^2}{8}\left[\left(\frac{2b}{\sigma^2} - 1\right)^2 + \tilde{y}^2\right]$, where $\tilde{y}$ is the largest zero of $y \mapsto K'_{iy}(\sqrt{8k}/\sigma)$

◇ the process converges to the quasistationary distribution const. $\times\, x^{\frac{b}{\sigma^2}-\frac{3}{2}} K_{i\tilde{y}}\left(\sqrt{\frac{8kx}{\sigma^2}}\right), \quad x > 1$

Does segregation confer any advantage?

Recall $\sigma^2(x) = \sigma^2_{\text{acc}}(x) + \sigma^2_{\text{seg}}(x)$, $b(x)$ = expected rate of damage accumulation, β = net birth rate, $\rho(x)$ = splitting rate. Suppose $b > 0$.

* A small variance gives greater growth rate than no segregation.

* Too much variance is counterproductive.

* There is a unique optimal amount of variance in models for which explicit calculations are possible.

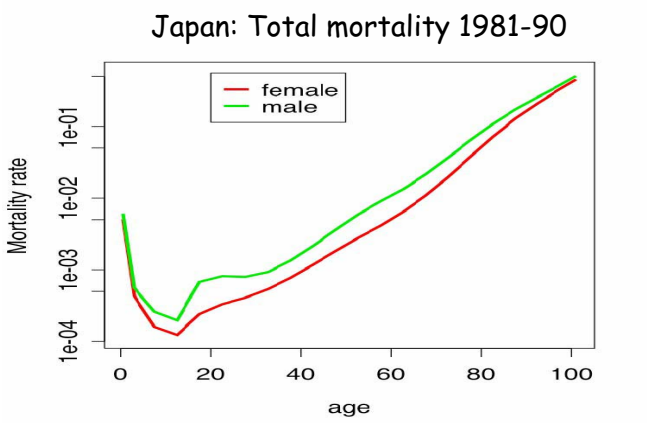
(Steinsaltz and Evans, in preparation)

Tail piece: Mortality plateaus and quasistationarity

mortality rate at age $t = \mathbb{P}\{\text{die in } [t, t+dt] \,|\, \text{live to } t\}/dt$

Gompertz (1837): Mortality for humans is an exponential function of age.

True for many multi-cellular organisms.



Gompertz doesn't hold in extreme old age

◇ mortality rates seem to flatten out to an asymptotic value at very advanced ages

◇ hard to observe in human populations - very small denominators, need to pool data from several countries

◇ observed in *Drosophila* experiments

Mortality plateaus

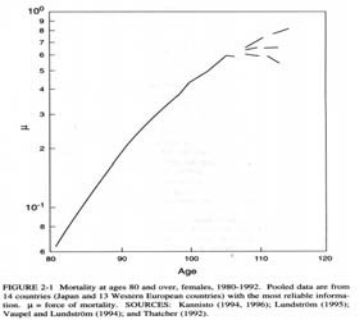


FIGURE 2-1 Mortality at ages 80 and over, females, 1980-1992. Pooled data are from 14 countries (Japan and 13 Western European countries) with the most reliable information. μ = force of mortality. SOURCES: Kannisto (1994, 1996); Landström (1995); Vaupel and Lundström (1994); and Thatcher (1992).

Why the plateau?

◇ several papers produce a mortality plateau from models in which individuals have a *vitality* that evolves according to some Markov process: when the process hits some set of states the individual dies

◇ followed by explicit or implicit reverse engineering: "Our model produces the plateau, therefore this must be how aging and mortality works."

◇ in fact, a plateau is almost unavoidable in ANY Markovian vitality model

FACT: Killed Markov processes on arbitrary state spaces have asymptotic killing rates and quasistationary distributions under quite general conditions.

$\Longrightarrow$ Mortality plateaus will appear in just about any vitality model – their presence doesn't provide much support for the model, but it is interesting to understand how features of the model influence the height of the plateau

NOTE: Can even produce Gompertz-like distributions for the life-time by very specific choices of the Markov process and by randomizing the initial conditions.

(Steinsaltz & Evans, *Theoret. Popul. Biol.*, 2004)