Hazards and Plateaus

Kenneth W. Wachter

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Outline: 19 February 2020

1. Extremes of Longevity in Humans and Other Species
2. Gamma-Gompertz Fixed Frailty Hazards
3. Mutation Accumulation, Gompertz Hazards with Plateaus

References

Elisabetta Barbi *et al.* (2018) "The plateau of human mortality: Demography of Longevity Pioneers", *Science* 360:1459:1461.

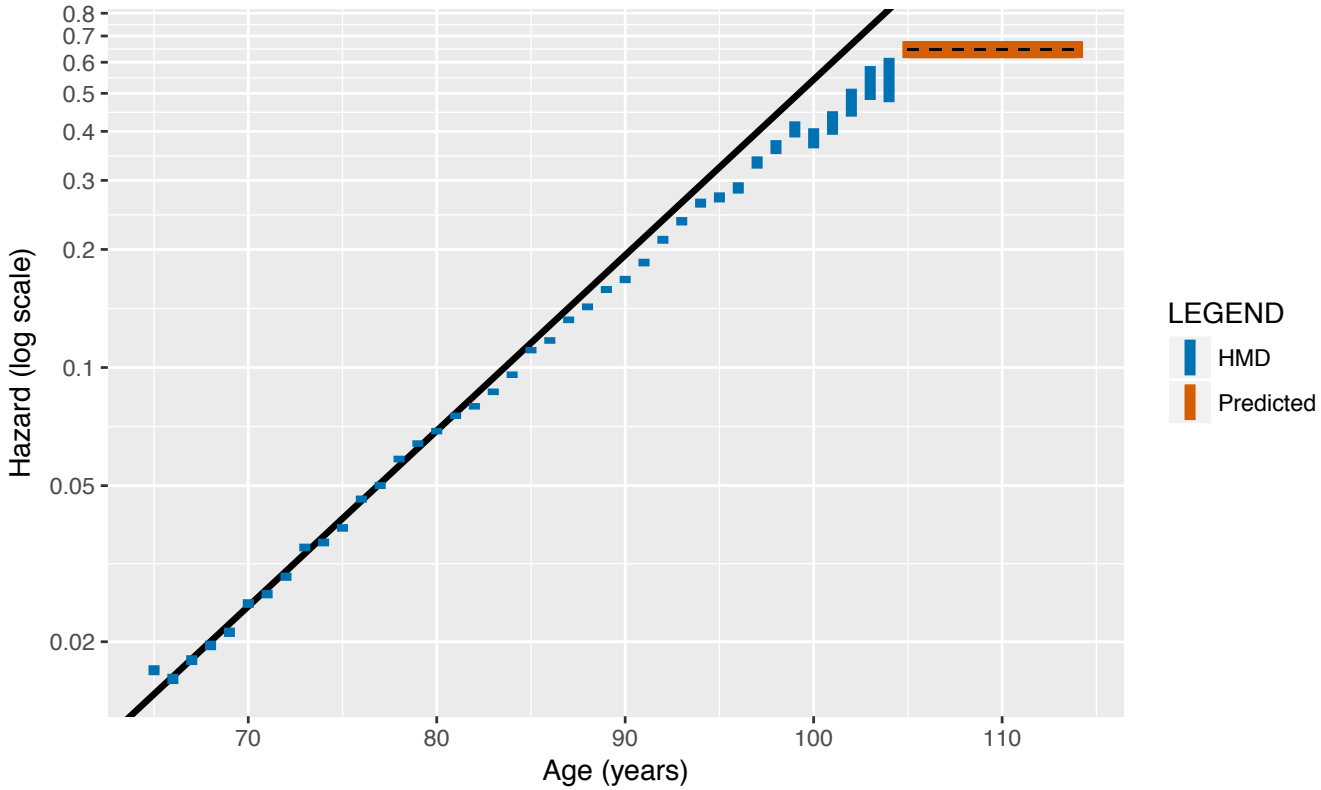
Kenneth W. Wachter (2020) "Genetic Evolutionary Demography" in *Human Evolutionary Demography*, edited by Oskar Burger, Ronald D. Lee, and Rebecca Sear, osf.io/p59eu.

Shiro Horiuchi (2003) "Interspecies Differences in the Lifespan Distribution", in *Lifespan*, edited by James Carey and Shripad Tuljapurkar, *Supplement to Population and Development Review*, volume 29.

Kenneth W. Wachter and Caleb Finch, Editors (1997), *Between Zeus and the Salmon*, National Academies Press, Washington, DC.

Bryan Sykes (2001) *The Seven Daughters of Eve*, W.W. Norton and Company, New York.

1. Extremes of Longevity: Example of Human Hazards



Source: Barbi *et al.* (2018)

The Importance of Plateaus

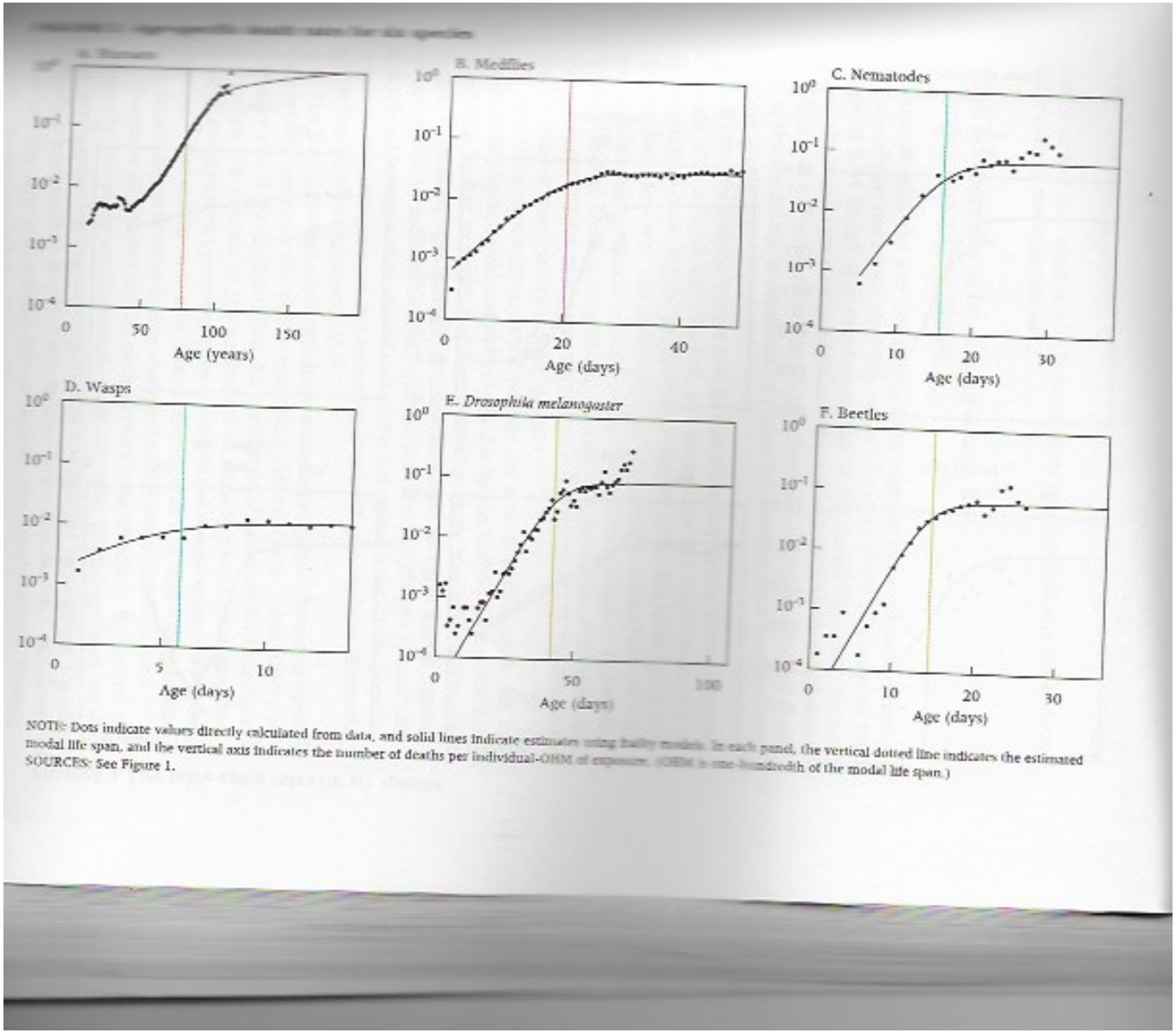
- They encourage optimism that future progress against old-age mortality is feasible.

  Our bodies are not facing an endlessly mounting set of things going wrong.

- They point to commonalities with the life-course demography of other species.

  The shared genetic heritage of advanced organisms is permissive.

Hazards from Other Species from Horiuchi (2003), page 129.



NOTE: Dots indicate values directly calculated from data, and solid lines indicate estimates using [illegible] models. In each panel, the vertical dotted line indicates the estimated modal life span, and the vertical axis indicates the number of deaths per individual-OHM of exposure. (OHM is one-hundredth of the modal life span.)
SOURCES: See Figure 1.

2. Gamma-Gompertz Fixed Frailty Hazards

- The Gamma-Gompertz model of Vaupel, Manton, and Stallard is familiar from this course and Chapter 8 of *Essential Demographic Methods*.
- Gamma Gompertz models are one way of generating plateaus for population hazards out of increasing individual hazards.
- We fit parameters to the data in Barbi *et al.* (2018) and look for a predicted plateau, starting from age 60 onwards.
- We need formulas for the individual hazard h_x, for the individual cumulative hazard H_x, and for the aggregate population hazard μ_x implied by Gamma-distributed frailty with shape parameter k and rate parameter $\theta = k$.
- Does the prediction show a plateau?
- Does the level of the plateau fit plateau observed in the Italian cohorts over age 105?

How does Gamma Gompertz Make a Plateau?

- Try alternative values for k and for β. Guess a formula for the level of the plateau.
- This formula can be proved by showing that h_x/H_x goes to β in a Gompertz model and plugging into the formula for Gamma Gompertz aggregate hazards.
- What happens to the mean frailty of survivors as x increases?
- What has to balance what in order for a plateau to appear?

Troubles with Gamma Gompertz

- Poor fits to observed cohort plateaus.
- Unrealistic mortality rates at younger ages for those who do survive out onto the plateau.
  (The frailty distribution reaches down to zero frailty).
- Individual centenarians still experience exponentially increasing hazards under the model.
- Why should frailty remain fixed across life?
- The model assumes rather than explains an underlying Gompertz.
- There is no full genetic or evolutionary story.

Optional: Mathematics of Frailty as a Gamma Random Variable

- Probability density $(\theta^k/\Gamma(k))\, z^{k-1}\, e^{-\theta z}$
- Mean k/θ
- Variance $k/(\theta^2)$.
- $\mathbb{E}\, e^{-ZH} = \left(\frac{\theta}{\theta+H}\right)^k$

Optional: Exponential and Gamma Random Variables

- When U has a uniform distribution on $[0, 1]$, then $Y = -\log(U)/\theta$ has an exponential probability distribution on $(0, \infty)$ with mean $1/\theta$ and variance $1/(\theta^2)$).
- The sum of k independent exponential random variables with the same mean $1/\theta$ has a gamma probability distribution with shape k, scale θ, rate $1/\theta$, mean k/θ and variance $k/(\theta^2)$.
- With an exponential variable Y, we have

$$E\, e^{-YH} = \int e^{-yH} p(y) dy = \frac{\theta}{\theta + H}$$

- Because expectation values of independent random variables multiply, with a gamma variable $Z = Y_1 + Y_2 + \cdots Y_k$, we have

$$E\, e^{-ZH} = \left(\frac{\theta}{\theta + H} \right)^k$$

Vaupel, Manton, and Stallard (1979)

- Lifelong Fixed Frailty Z.
- The Gamma distribution has

$$\mathbb{E}\, e^{-ZH} = \left(\frac{\theta}{\theta + H}\right)^k$$

.

- For starting mean frailty equal to 1, we have $k = \theta$.
- The aggregate population hazard is minus the slope of the logarithm of survivorship:

$$\mu_x = -\frac{d}{dx}\left(k \log(\theta) - k \log(\theta + H_x)\right) = (k/(\theta + H_x))h_x$$

- For the Gamma Gompertz, we insert Gompertz individual hazards h_x and individual cumulative hazards H_x into the formula.

3. Mutation Accumulation, Gompertz Hazards with Plateaus

- An alternative is to contemplate plateaus in individual hazards, not just in aggregate population hazards.
- The genetic evolutionary theory of "mutation accumulation" suggest a story to account both for Gompertzian increases over a stretch of adult ages and for plateaus beyond them.
- We each inherit genetic variants or "alleles" in our DNA originating in mutations thousands of generations in the past.
- Picture, say, the time of the cave painters, 40,000 B.C., when people died in their 30s and 40s and 50s rather than their 70s, 80s, and 90s, losing some of their chance to bear and raise offspring.

Mutation-Selection Equilibrium

- Go back to basic stable (stationary) population theory. Write $\rho(a)$ for size of the group of individuals (e.g. women) who carry a certain mutant allele indexed by the letter a.
- The NRR for members of the group is assumed to be $1 - S(a)$ for some small "selective cost" $S(a)$ due to effects of the "deleterious" allele.
- In the next generation, there are $\rho(a)(1 - S(a))$ daughters.
- There are also $\nu(a)$ new arrivals due to new mutations.
- The group keeps growing until it reaches equilibrium, when losses are balanced by new arrivals, and $\rho(a) = \rho(a)(1 - S(a)) + \nu(a)$.
- What is $\rho(a)$ as a function of $S(a)$?

Deleterious Alleles with Age-Specific Effects

- In our setting, many deaths come from external threats regardless of age, a background level of "extrinsic mortality" with constant hazard λ.
- To keep the story as simple as possible, picture a mutant allele that has a small bad effect on survival only at an "age of onset" a. It raises the hazard of the individual who carries it by an amount δ in the age interval a to $a+1$.
- Picture a constant level of fertility from age 20 onward, set to make the NRR equal to 1 for women who carry no mutant alleles.
- Take, for example, $\lambda = 0.080$, $\delta = 0.002$, and $\nu(a) = 0.020/50$ for any $a \geq 20$. For each separate choice of age of onset a, find and plot the equilibrium size $\rho(a)$ as a function of a.

Allele Counts and Individual Hazards

- Suppose that the alleles carried by an individual are a random sample of the alleles present in the population, so that $\rho(a)$ can be reinterpreted as the mean number of alleles of type a.
- Then the hazard for an individual at age a will look on average like the curve $\lambda + \rho(a) * \delta$.
- Does this curve resemble a Gompertz hazard? What about a Makeham hazard, that is, a Gompertz hazard plus a constant?
- The background intrinsic mortality λ comes from the environment, not from the DNA. What might happen to λ as we move from the time of the cave painters to the time of the moon landings?

Plateaus in Allele Counts

- Suppose, now, that each mutant allele raises the hazard by another small amount $\epsilon = 0.0005$ at all ages beyond 20, along with its special effect on raising the hazard by δ at age a.
- Find and plot the size $\rho(a)$ of the carriers of a at equilibrium under this new form of action.
- Is there an appearance of a plateau at high ages?
- Is it plausible to expect some fixed cost along with an age-specific effect from mildly deleterious mutant alleles?

Questions for Further Study

- What about the effect of each allele on the selective cost of all the other alleles?
- Looking across species, under this account would we expect some relationship between the level of extrinsic background mortality and the steepness of the slope of a Gompertz increase in mortality with age?
- In our calculation we let mortality over the age of 50 continue to reduce the "NRR". Why might survival beyond ages of childbearing have an effect on generational replacement?
- We carry in our DNA a load of mutant alleles shaped by natural selection over hundreds and thousands of generations. Why might it be that effects of those alleles that were once lethal in mid-adult life could now be influencing rates of mortality late in life for us?

Zeus and the Salmon