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Opinion article

A revolution for aging research

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Abstract

In the year 1992, two publications on age-specific mortality rates revealed a cessation of demographic aging at later ages in very large cohorts of two dipteran species reared under a variety of conditions. Despite some initial concerns about possible artifacts, these findings have now been amply corroborated in the experimental literature. The eventual cessation of aging undermines the credibility of simple Gompertzian aging models based on a protracted acceleration in age-specific mortality during adulthood. The first attempt to explain the apparent cessation of aging was extreme *lifelong heterogeneity* among groups with respect to frailty. This lifelong heterogeneity theory assumes an underlying Gompertzian aging affecting every member of an adult cohort, with a merely apparent cessation of aging explained in terms of the increasing domination of a slowly aging group among the survivors to late ages. This theory has received several experimental refutations. The second attempt to explain the cessation of aging applied *force of natural selection* theory. This explanation of the cessation of aging has been corroborated in several *Drosophila* experiments. In particular, this theory requires that *both* age-specific survival and age-specific fecundity cease declining in late life, which has now been experimentally established. This theory also predicts that the timing of the cessation of aging should depend on the last age of reproduction in a population's evolutionary history, a prediction that has been corroborated. While lifelong heterogeneity should reduce average age-specific mortality in late life whenever it is pronounced, the cessation of aging in late life can be explained by plateaus in the forces of natural selection whether lifelong heterogeneity is present or not. The discovery that aging ceases is one of the most significant discoveries in recent aging research, with potentially revolutionary scientific implications.

The revolution of 1992

Two papers from the journal Science

At the heart of any scientific revolution are observations that shake the foundations of conventional scientific beliefs. The October 16, 1992, issue of the journal *Science* included two papers on dipteran demography, one by Carey et al. (1992) and one by Curtsinger et al. (1992). The last author of both was James W. Vaupel, which was highly significant, for reasons we describe below. These articles reported the cessation of demographic aging at later ages in cohorts of medflies and laboratory fruit flies, respectively. The data can only be described as massive, involving millions of flies.

The initial reaction to these publications was mixed. Among others, two of the present authors (Rose and Mueller) had grave doubts about some of the experimental cohorts, because of the problem of density effects in cohorts with falling numbers kept in containers of fixed size (vid. Nusbaum et al. 1993). But even our skepticism was restrained by the fact that the same qualitative result was obtained using two fly species and a wide variety of culture conditions. There had to be something there, something important.

Everybody who read these two papers knew that.

Anticipations and artifact controversies

The 1992 results showing a cessation of aging late in adult life were not the first of their kind. Human demographic research had turned up hints of these effects for some time. Demographic analyses of European populations by Greenwood and Irwin (1939) and Gavrilov and Gavrilova (1991) revealed a detectable slowing in human mortality rates late in life. The gerontologist Alex Comfort re-published some of the data of Greenwood and Irwin (1939) in the 1964 edition of his classic book, *The Biology of Senescence* (Fig. 18, p. 90). In people over the age of 92, the rate of age-specific mortality appears to be roughly constant in this figure. While the papers in *Science* sparked the current interest in late-life mortality, there were earlier observations of the cessation of ageing in late life. For example, Economos (1979) had made similar observations in fruit flies and nematodes (see Olshansky [1998] for a review of this prior history). Thus a flattening of age-specific death rates late in adult life had been noticed long before 1992, especially in human data. But no one had made much of the earlier findings. One problem with the human data was people sometimes lie about their ages, with some older people inflating their chronological age. In addition, it is also normal for scientists to give up their favored theories only reluctantly in the face of apparent refutations (cf. Popper 1959).

Experimental biologists know full well that botched results are very common, particularly in the aging field. Studies of aging cohorts can be muddled by infection, changes in handling methods, inbreeding, and other artifacts and confounds (vid. Finch 1990; Rose 1991). Thus part of the hesitation of aging researchers to embrace the revolution of 1992 was the problem of artifacts. Even as late as 1999, the ostensible cessation of aging in very old humans was dismissed as a result of old people changing their behavior or being better looked after (e.g. Maynard Smith et al. 1999, p. 269). It was vital to the scientific credibility of aging cessation that experiments be done with laboratory cohorts. Only in the laboratory could we be sure that confounding age-specific changes had not artifactually lowered mortality rates late in life. Thus it was appropriate that the methodological criticisms offered by Nusbaum et al. (1993) as well as Graves and Mueller (1993), to give one example, were answered by the Curtsinger laboratory, which convincingly demonstrated that the cessation of aging late in life was not artifactual (e.g. Curtsinger 1995; Khazaeli et al. 1995, 1996).

In addition to the artifact-barring of the Curtsinger laboratory, Vaupel et al. (1998) pulled together a wide range of data suggesting the cessation of aging in a variety of organisms. It was clear by the year 2000 that demographic or actuarial aging did indeed effectively cease late in life, in a variety of well-studied organisms. This phenomenon was no artifact.

The first interpretation: lifelong heterogeneity

Scientists hold on to their traditional theories

Even when artifacts have been precluded, scientists tend to cling to the conventional theories of their disciplines in the face of evidence against those theories. Historically, perhaps the most famous example of this is the addition of epicyclic modifications to the geocentric model of the solar system. The geocentric theory of the solar system had the advantages of both tradition and intuitive plausibility, since the Earth seems fixed beneath us. Thus Western physicists and astronomers steadfastly resisted abandoning the geocentric model in the face of a long sequence of observations inimical to their preferred theory, notably Galileo's observations of the moons of Jupiter.

In the first third of the 20th century, biometricians similarly resisted the idea that their theories of inheritance should be replaced by quantitative genetics (e.g. Provine 1971). Even Newton's prerelativistic cosmology had its adherents for some years after Einstein's revolution of 1905, a topic to which we shall return.

Vaupelian lifelong heterogeneity theories remain Gompertzian

The conventional theories of demography and gerontology characterize the aging of demographic

cohorts using exponential models for age-specific mortality rates that have most of the features of Benjamin Gompertz's original model:

$$\mu(x) = Ae^{\alpha x} \quad (1)$$

where x is age, μ (x) is the age-specific mortality rate, A is an age-independent parameter that gives the baseline mortality rate of the population, and α is an age-dependent parameter, or the rate of aging. This equation quantitatively summarizes the commonly observed, though not universal, exponential increase in mortality rates with age among adults in well-tended cohorts of both humans and laboratory animals (Finch 1990). While the Gompertz equation was produced by actuarially fitting human data, it does intuitively suggest that aging is an inevitable and accelerating process of deterioration, which fits some intuitions of how entropy should progressively degrade biological processes. We refer to all models of this type, regardless of their specific mathematical form, as 'Gompertzian.'

As already mentioned, James W. Vaupel was one of the key figures in the revolutionary observations of 1992. He was also the key proponent of the theory of lifelong heterogeneity (e.g. Vaupel 1988), though this part of demographic theory was first developed mathematically by Beard (1959). In this theory, heterogeneity in lifelong robustness within a population causes a slowing of mortality rates at late ages, because individuals that have greater lifelong frailty will be underrepresented at later ages in an experimental cohort. Most importantly, such lifelong heterogeneity is not the same as sporadic or intermittent heterogeneity that might affect several, but not all, adult age classes. In Vaupelian theory, lifelong differences between individuals arise early in life and remain fixed throughout the life span.

While the theory of Beard and Vaupel is both simple and testable, there are variants of this theory which permit heterogeneity to arise at any point in the life cycle and therefore are not lifelong heterogeneity theories (Weitz and Fraser 2001). The evolutionary theory for demography developed by e.g. Charlesworth (1994) is based on such 'variable' heterogeneity. We discuss this type of theory next.

It is a key feature of Vaupelian lifelong heterogeneity theory that the Gompertz model, or its congeners, is retained as the underlying model of the aging process. In the Gompertz case, for example, lifelong heterogeneity can be parametrically embodied by sub-groups that have different values of A or α, although many formulations are conceivable. Like the epicyclic modifications of the original geocentric theory, Vaupelian theory is a conservative accommodation to the observations of 1992. Demographers and gerontologists who accept Vaupelian theory are thereby able to retain their basic assumption that aging continues in a predictably progressive, indeed accelerating, manner for each and every organism. This retains a two-part scheme for life history, in which implacable aging follows development.

Advantages and problems of Vaupelian theory

Survival probabilities vary within populations (reviewed in Finch 1990; Rose 1991; Roff 1992; Stearns 1992), which might be construed as evidence that the lifelong heterogeneity model is well-founded. However, such variation is also part of the evidential basis for the evolutionary theory of age-structured populations (e.g. Charlesworth 1994); it is not a warrant for Vaupelian theory, specifically. For the Vaupelian explanation of late life to work there must be strong positive correlations between survival probability among adult ages; there is evidence that this particular assumption is *not* true, some of which is reviewed in Rose (1991), Rose and Finch (1994), and Curtsinger (1995). However, it cannot be said that our knowledge of the correlations among survival probabilities at different ages is sufficient to preclude the existence of lifelong heterogeneity entirely.

One of the major tactical advantages of lifelong heterogeneity theory is that it is based on an underlying robustness (or, conversely, frailty) character that is unspecified. Attempts have been made to associate particular measurable characters with such robustness (e.g. Khaezeli et al. 1995; Drapeau et al. 2000), but such experiments can always be criticized on the grounds that they have not identified the '*true*' robustness character that determines lifelong heterogeneity. With such an invisible and unmeasured variable, Vaupelian theoreticians can avoid experimental refutation by inventing new *post hoc* variants of their theory.

Heterogeneity comes in two basic forms: environmental and genetic. Both forms may contribute to mortality plateaus under the Vaupelian model. Experiments with highly inbred lines have shown that mortality plateaus persist in the absence of genetic variation (Curtsinger et al. 1992; Fukui et al. 1993). These results suggest that if a heterogeneity theory of mortality plateaus is to be taken seriously, it must be possible to generate sufficient heterogeneity entirely from environmental effects.

Environmental heterogeneity in principle may affect either of the two parameters of the Gompertz Equation (1), A or α, to consider a simple case (Pletcher and Curtsinger 1998; Service 2000, 2004). (Different parameters would have to be used with other Gompertzian models, but the issues that we adduce here are general to this entire class of models.) Large-scale changes in the environment, like dietary restriction or the addition of urea to adult food, have been shown to change survival by altering the parameter A of the Gompertz equation; they typically have no consistent effect on α (Joshi et al. 1996; Nusbaum et al. 1996). However, numerical analysis of such environmental effects shows that they are unlikely to generate enough environmental heterogeneity to explain mortality plateaus (Mueller et al. 2003).

Despite the lack of empirical evidence that environmental variation can change α it is still possible to use regression techniques to get a least-squares estimate of the level of possible variability in α from *Drosophila* survival data (Mueller et al. 2003). Gompertz model parameters were chosen by Mueller et al. (2003) to give the best possible fit to an extensive collection of *Drosophila* data. Despite this, the best-fitting Vaupelian model failed to predict the actual survival trajectories observed at very late ages.

Another test of heterogeneity theory uses the age-specific pattern of variance in mortality rates. Models with lifelong heterogeneity predict a unimodal peak in the variance of the log of mortality rates vs. age (Service 2000). However, variance estimates obtained from *Drosophila* laboratory cohorts do not show such peaks (Mueller et al. 2003).

Despite these experimental refutations of lifelong heterogeneity theory based on Gompertz models, there is a large collection of alternative demographic models that could be combined with the lifelong heterogeneity hypothesis to fit extant experimental data for mortality rates. In principle, there are infinitely many such alternative models. Thus the tests of the Gompertz version of lifelong heterogeneity theory by Mueller et al. (2003) are only a first step. One approach has been to experimentally manipulate environmental heterogeneity (Khazaeli et al. 1998). The authors concluded that reducing environmental heterogeneity in larval and pupal stages of fruit flies had negligible effects on mortality deceleration. Some suggest that rejecting any particular heterogeneity model is pointless, given the existence of many conceivable lifelong-heterogeneity models having different functional forms. Unfortunately, there is often no way to test the heterogeneity hypothesis using mortality data without a specific model. Thus it is not surprising that it has proven difficult to devise experimental tests of the heterogeneity theory (Curtsinger et al. 2005).

Rauser et al. (2003, 2006a) have recently found that age-specific fecundity in *Drosophila melanogaster* also undergoes a pronounced deceleration at late ages. It is conceivable that this deceleration could be due to interactions between lifelong propensities to reproduce and lifelong propensities to survive, both instances of lifelong heterogeneity. This bare possibility has been explicitly simulated (Rauser et al. 2005). In the case of fecundity plateaus, however, it is possible to measure the propensity to reproduce on a daily basis, allowing a more direct test of lifelong heterogeneity theory for at least one character that shows late-life deceleration of aging. Such an experiment was performed using *D. melanogaster*, and the results provided strong evidence against the explanation of late-life fecundity plateaus using any type of lifelong heterogeneity for fecundity (Rauser et al. 2005), regardless of the specific form of the theory.

There are now a number of published experiments that give results which either ostensibly refute Vaupelian theory or else do not support it. There are no critical, strong-inference experiments that directly corroborate Vaupelian theory. There remain *post hoc* uses of Vaupelian theory to explain particular findings (e.g. Kowald and Kirkwood 1993). One of the advantages of

Vaupelian theory is that it offers many opportunities for theoretical 'wiggling.' In addition, it remains indubitably true that whenever lifelong heterogeneity for robustness arises, there will be an eventual deceleration in the decline of survival rates very late in life. Nonetheless, this does not show that the late-life cessation of aging found by Carey et al. (1992) and Curtsinger et al. (1992) can be explained using lifelong heterogeneity theory.

Vaupelian theory refurbishes the Gompertzian paradigm

Perhaps the chief merit of Vaupelian theories of late-life is that they do not require any radical re-formulation of the conventional theories of aging and demography. Most demographers or gerontologists would no doubt prefer to retain the Gompertzian kind of model of aging, with its key assumption of an unending acceleration in the process of organismal deterioration. Vaupelian theory props up such long-standing preconceptions about aging by offering an explanation of late-life mortality plateaus given extreme lifelong heterogeneity in Gompertzian models that incorporate an unmeasured robustness variable. This is the central attraction of Vaupelian theory, for it has had no direct experimental corroboration.

The second interpretation: plateaus in the forces of natural selection

Hamiltonian forces of natural selection have been used to explain aging

Though the evolution of age-structured populations is studied theoretically and experimentally using many of the same parameters as those used by demographers (e.g. Charlesworth 1980; Luckinbill et al. 1984; Rose 1984), it is not based on the kind of *post hoc* curve-fitting that is used by demographers. Instead, the central theory for the evolution of aging is the *a priori* analysis of Hamilton (1966), particularly as elaborated and refined by Charlesworth (e.g. 1980, 1994).

Hamilton (1966) derived the result that the force of natural selection acting on mortality is given by $s(x)/T$, where x is chronological age and T is a measure of generation length. The function s at age x is given by

$$s(x) = \sum_{y=x+1} e^{-ry} l(y) m(y) \tag{2}$$

where r is the Malthusian parameter, or the growth rate of the population, associated with the specified $l(y)$ survivorship and $m(y)$ fecundity functions. The $s(x)$ function represents the fitness impact of an individual's future reproduction, after age x. Note that, before the first age of reproduction s is always equal to 1 (one), once reproduction has ended s is equal to zero, and during the reproductive period $s(x)$ progressively falls.

There is a similar equation for the force of natural selection acting on age-specific fecundity:

$$s'(x) = e^{-rx} l(x). \tag{3}$$

All the variables in Equation (3) have the same definitions as those in Equation (2).

These two scaling functions for the forces of natural selection have been used since Hamilton (1966) to explain and to manipulate the evolution of aging (e.g. Charlesworth 1980; Rose et al. 2004). [See Baudisch (2005) for some recent emendations of this theory.] In addition, Equation (2) has been used as a crude explanation of the form of the Gompertz equation and its congeners (Rose 1991, pp. 170–171).

It is important to note that Hamiltonian theory and the experiments based on it are not *ad hoc* or *post hoc*. Unlike the theories of Gompertz, Vaupel, and other demographers, Hamiltonian theory is based on first principles of inheritance and natural selection. It does not require *post-hoc* curve fitting.

Hamiltonian theory also explains late life

Hamiltonian theory can explain late-life plateaus in mortality. The key to this is that s is equal to zero for all ages after reproduction has ceased. This plateau in the force of natural selection implies that natural selection will no longer discriminate among genetic effects that act at ages so late that they have had no impact on fitness during the evolutionary history of a population

(see Figure 1). Even in organisms that reproduce at all ages, the force of natural selection is eventually overwhelmed by drift at late life. This result was obtained in explicit numerical simulations by Mueller and Rose (1996). Charlesworth (2001) supplied analytical solutions of this kind for special cases. Wachter (1999) has suggested that the plateaus observed by Mueller and Rose are only transient states under their assumed mutation model. While we believe that the simulations in Mueller and Rose (1996) have captured much of the short to medium-term effect of natural selection, more theoretical work in this area is clearly needed.

A similar result applies to the function *s'* after the last age to which any individual survived in the evolutionary history of a population. The Hamiltonian expectation is that age-specific fecundity in protected cohorts can also plateau, as Rauser et al. (2006b) showed numerically.

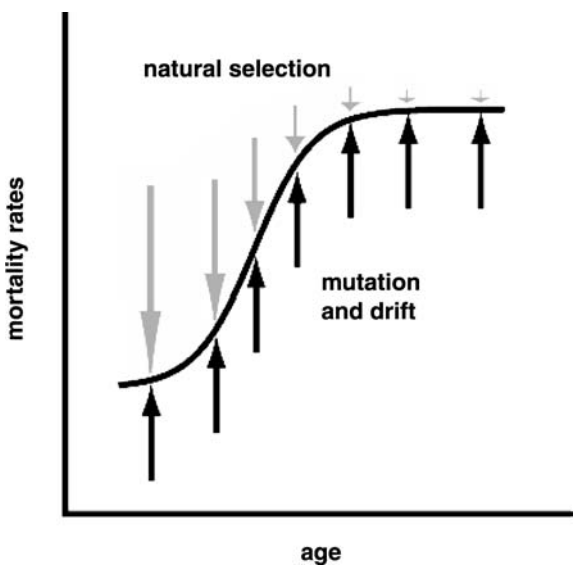

Figure 1. The evolution of mortality plateaus. Mutations and genetic drift increase the frequency of deleterious genes with more or less the same magnitude at all ages. This effect is symbolized by the black arrows pushing upwards on the mortality curve. Meanwhile, natural selection opposes these deleterious mutations by pushing in the opposite direction (grey arrows), keeping mortality rates low. The strength of natural selection decreases with the age of genetic effect, which weakens the force of natural selection. At very advanced ages, natural selection stabilizes at a low level. This leads to an end in the deterioration of the balance between selection and other evolutionary forces, and thus a plateau in mortality.

While it is possible that these late-life plateaus will be at the zero-survival or zero-fecundity levels in some species (cf. Pletcher and Curtsinger 1998), when there are enough alleles that have age-*independent* beneficial effects it is possible to have positive-valued average survival and average fecundity values during late life (vid. Charlesworth 2001). Any such age-independent genetic benefits will be favored by natural selection acting at early ages and will have positive pleiotropic benefits at all later ages.

Crucial predictions of Hamiltonian theory have been corroborated

Unlike the lack of corroboration of Vaupelian theories for late life (e.g. Khazaeli et al. 1998; Drapeau et al. 2000; Mueller et al. 2003; Rauser et al. 2005), there have been several substantial corroborations of the predictions of the Hamiltonian explanation of late life. Rose et al. (2002) have shown experimentally that the start of late-life mortality plateaus evolves according to the last age of reproduction in the history of *D. melanogaster* populations undergoing long-term experimental evolution, as predicted by Hamiltonian theory. This particular finding involved three different independent experimental tests, using a total of 30 large cohorts. Rauser et al. (2006a) similarly found that the start of late-life fecundity plateaus evolves according to the last age of survival in the history of *D. melanogaster* populations, as predicted by Hamiltonian theory. Two independent statistical tests were used in this study, with 18 large experimental cohorts. It would be desirable to have more tests of the Hamiltonian theory of late life, because these are the only major corroborations for *any* substantive theory of late life.

There are three contrasting phases of life

A major corollary of Hamiltonian theory is the existence of a late-life phase of life that is as distinct in its fundamental properties as aging is from development. Thus, on the Hamiltonian view, there are three phases of life: development; aging; and late life.

This means that we have an entirely new phase of life to explore, because late life has hardly

been studied at all. This situation is both exciting and troubling for practicing scientists. The excitement is obvious: there is a wealth of hypotheses about life-history, both physiological and evolutionary, that need to be tested. During development, organismal and cell biology are studied among ages when natural selection is extremely strong. This type of research fits the *organism as virtually perfect machine* model of life. During aging, natural selection is collapsing rapidly, and the effects of this are dramatic. For aging, the appropriate research paradigm is the study of the *organism as disintegrating machine*. As to late life, we have no intuitive concept of how the organism works. That is the problem facing late-life research; it is novel terrain.

This is a Kuhnian scientific revolution

Thomas Kuhn contrasted 'normal' science with 'revolutionary' science

Perhaps the single most influential work of science historiography is Kuhn's (1962) *The Structure of Scientific Revolutions*. Previous analyses of natural science, such as that of Popper (e.g. 1959), focused on the great transitions of physics as if they were characteristic of everyday science. Like Kuhn, most working scientists know that much of their work involves operating *within* established paradigms, not overthrowing or even deliberately challenging them.

A scientific revolution transforms the basic principles of a scientific field, even altering the very meaning of the entities that a field studies. For example, Darwin's theory of evolution by natural selection led biologists to radically different views of such basic features of life as adaptation, species, and the like. There is a huge difference between the biology of species created by God and the biology of species that have evolved on their own in response to environmental contingencies.

The phenomenon of late life and the Hamiltonian theory that explains it give an entirely different perspective on central features of life history. For example, Gompertzian patterns of mortality during aging are easily generated from first principles using Hamiltonian theory (vid. Mueller and Rose 1996), but this same analysis also shows that the Gompertzian period of mortality acceleration comes to an end. More profoundly, the phenomenon of late life shows that aging is not an advancing, inevitable 'wall of death.' It is instead a 'ramp of death,' which can come to an end fairly early, as shown by the results of Carey et al. (1992) for medflies. More surprisingly, it turns out that late life can evolve with great rapidity (e.g. Rose et al. 2002; Rauser et al. 2006a). Within just the first 15 years of focused laboratory research on late life, we already have a banquet of peculiar findings.

This scientific revolution is more like that of Einstein

Late life has revolutionary implications for our basic understanding of life history, and thus for the foundations of biology. But it has few of the intuitive satisfactions supplied by theories like Darwinian evolution or Newtonian mechanics. How to make sense of late life? Intuition doesn't work well for late life, or help with the design of late-life experiments. The failure of evolutionary gerontologists to anticipate the 1992 findings amply illustrates this, as do the experimental failures of the theories that explain the plateau of age-specific mortality using lifelong heterogeneity.

These properties remind us of Einstein's Special and General Theories of Relativity. The oddities of late life emerge at very late ages, just as the constraints of relativistic space-time become experimentally obvious only at very high velocities. Yet Einstein arrived at his Special theory by turning an observation – that light had a constant speed independent of one's velocity – into a general principle in itself. The late life plateau is puzzling for Gompertzian views, which has led us to suppose a completely new phase of life, which in turn undermines our very conception of aging as unrelenting during adult life. Einstein's General Theory of Relativity supplies a natural explanation of gravitational force as the curvature of space-time by mass. Newton's Universal Law of Gravitation was essentially *post hoc* action at a distance. Further, Newton had to suppose that God had set the stars in just the right orbits to avoid gravitational collapse into

one single mass. General Relativity did away with Newton's force law and the former's equations gave a fully solvable way to model the entire universe, particularly its spatial distribution of mass, while including its time-evolution from non-special conditions. It is notable Einstein did not see that his preferred static solution was unstable, and the universe would inevitably expand or contract. His equations knew more than he did.

Likewise, the empirical regularities of the Gompertz Law arise naturally for the aging period in calculations depending directly on Hamilton's first force of natural selection (vid. Mueller and Rose 1996). Equally naturally, the Gompertz pattern breaks down during late life in Hamiltonian theory. The failure of the Gompertzian models, even in their lifelong heterogeneity form, implies a fundamental change in our view of aging. Aging is not inherent for all adult ages.

Hamiltonian theory elegantly integrates natural selection over all ages and all age-structured components of fitness – a universal analysis of life-history. It supplies the undergirding for the multifold adaptive features of development and explains the accelerating deterioration of aging. In hindsight, its explanation of late life affords a culminating instance of its manifest scientific power. The Hamiltonian equations know more than we do, and they challenge us to tease out their implications in theory, and then to test each of these implications by experiment.

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