The Medfly as a Frailty Model: Implications for Biodemographic Research

James R. Carey[1] *and Nikos Papadopoulos*[2]

Summary

Despite the economic, medical and demographic importance of understanding the determinants of chronic disability and frailty in particular and morbidity compression in general, the experimental method and model (animal) systems have not been brought to bear on questions related to these areas. Thus the purpose of this paper is to 1) briefly review the basic concepts of disability and impairment as they relate to both humans and non-human animals. 2) present the results of a study of medflies in which individuals can be classified as healthy or unhealthy based on whether they exhibit "supine behavior," and 3) introduce a general framework for research on morbidity that integrates experimental biology (manipulative experiments, model animals, hypothesis testing) into the current clinically based morbidity research paradigm on humans.

Introduction

Chronic disability in general and degenerative diseases in particular are considered by the biomedical and public health establishments to be the most important (and costly) issues in health care confronting developed countries such as the US and France in the 21st century. For example, chronic diseases with limitations on activity affect as much as 10% of the US population, primarily among the elderly (Lollar and Crews 2003). This percentage will continue to increase because the number of individuals in the US over age 65 is predicted to double from 35 million in 2000 to an estimated 70 million in 2030 (Mehrotra et al. 2002). With health care costs already accounting for 15% ($1.5 trillion) of the US economy (Mehrotra et al. 2002), this surge in the elderly population will increase this percentage even further, because health care costs for those over 65 average three times the costs for those aged 19 to 65.

---

[1] Department of Entomology, University of California, Davis, CA 95616; and Center for the Economics and Demography of Aging, University of California, Berkeley 94720 USA

[2] University Thessaly, Department of Agriculture Crop Production and Rural Environment, Laboratory of Entomology and Applied Zoology Phytokou St. N. 384 46 N. Ionia Magnisias, Volos, Greece

Carey et al.
Longevity and Frailty

Understanding chronic disability is important for several reasons (Manton et al. 1997). First, as life expectancy continues to increase, it is important to understand if and to what extent disabilities will increase. This information will shed important light on the period of life spent disabled, which, in turn, has profound implications regarding the cost of Social Security and the debate over retirement age. For example, a relative rate of improvement of 1.5% per annum in chronic disability could ensure the long-term fiscal solvency of the Medicare and Social Security programs (Singer and Manton 1998). Second, because chronic disability is a sensitive measure of age-related changes in the health and biological fitness of individuals, disability is a marker of whether life expectancy increases are associated with changes in the age rate of the loss of the average biological fitness of a population (i.e., marker of biological rate of aging). Third, increases in birth rates and in-migration cannot be counted upon to replaces losses to the stock of human capital available in the U S economy. Thus the only viable strategy is to adopt programs that will preserve human capital and keep it in the labor force for longer periods of time (Manton and Gu 2001).

Clearly, health and health care expenditures in developed countries for the 21st century must be based on a strategy designed to develop new conceptual and practical approaches for health and solid theoretical and empirical foundations for considering research policy on disablement. Despite the statement a decade ago by Verbrugge and Jette (1994) that "…there is great need for more theoretical work about how onset and duration affect the disablement experience," there has been little progress on either theory or empirical data. We believe a large reason for this lack of progress is the absence of an experimental research paradigm. For example, neither of the "bibles" on disability - the 850-page *Handbook of Disability Studies* (Albrecht et al. 2001) and the 300-page WHO-publication *International Classification of Functioning, Disability and Health* (WHO 2001) - contains any reference to the experimental biology literature.

There are several reasons why the experimental method has not been brought to bear on questions concerning frailty and disablement processes. First, no model system has been developed for studying the dynamics of impairment and disability. Aging research focuses on death as the endpoint rather than on the onset of impairment or chronic disease. Second, the same types of problems of ambiguity arise in characterizing disablement and morbidity in model systems as with humans. That is, unlike the (usually) unambiguous endpoint of death, in the vast majority of cases the endpoint of active life span (i.e., onset of chronic disease and/or impairment) is subjective and arbitrary, involving composite scores on a battery of Activities of Daily Living indices (ADLs). Third, just as actuarial studies of mortality require the use of large initial numbers to measure patterns at older ages, investigations on morbidity also require large numbers, particularly for studies concerned with the interrelationship of morbidity and mortality.

We have two main goals in this paper ; first, to describe the results of a study by Papadopoulos and co-workers (Papadopoulos et al. 2002, 2004) in which a new and unique behavior, referred to as "supine behavior" was discovered in older medfly males that serves as a biomarker for deteriorating health and impending death. We use this study as a foundation upon which more general concepts are built, including the development of a simple model to explore the effects of changes in hazard rates on life expectancy and morbidity compression; and second, to discuss the general implications for the use of insect models in particular and animal models more generally to research the dynamics of morbidity and mortality. We argue that the development of a broader and more basic paradigm that includes experimental methods and the use of model is critical for advancing an understanding of the biology and demography of morbidity.

Biodemography of frailty in medflies

Background

A biomarker of aging is a behavioral or biological parameter of an organism that either alone or in some multivariate composite will better predict functional capacity and/or mortality risk at some late age than chronological age will (Markowska and Breckler 1999; Papadopoulos et al. 2002). Behavior biomarkers of aging are important because 1) behavior changes with aging and thus behavior itself can be used as an index of aging, and 2) any intervention to alter the chronological course of aging must be assessed behaviorally since quality of life as well as longevity must be considered in the evaluation of any intervention (Baker and Sprott 1988). Because of their rapid generation time and low cost relative to mammalian models such as rodents or primates, understanding behavioral biomarkers in fruit flies has important implications for research designed to understand morbidity dynamics, behavioral neuroethology and gerontology, and the interpretation of longevity extension in model organisms.

While monitoring the behavior of male Mediterranean fruit flies (*Ceratitis capitata*) throughout their lives, Papadopoulos and co-workers (2002) discovered a behavioral trait that is unique to older, geriatric flies in general but especially to individuals that are gradually approaching death. They used the term supine behavior to describe this behavior trait in accordance with the upside-down position of the temporarily immobile flies (Fig. 1). Supine males lie on their backs at the bottom of the cage, appearing dead or moribund. But these flies are very much alive and moderately robust, as becomes evident when they right themselves either spontaneously or after gentle prodding and initiate walking, eating, and wing-fanning behaviors, some of which are indistinguishable from those of normal flies.

Inasmuch as any upside-down adult insect is dysfunctional, it follows that the health of medfly males that we observed spending progressively greater amounts of time in the supine position was both poor and declining relative to the health of flies capable of remaining upright. Because virtually nothing is known about the nature of chronic conditions (illnesses, infirmity, dementia) in insects, as no viable animal model systems exist for studying morbidity dynamics (e.g., determinants, age of onset, persistence, association with mortality), and because of the importance of understanding morbidity incidence and prevalence in human populations, we initiated studies designed to address and test a number of questions regarding supine behavior in medfly males: When do flies first begin to exhibit supine behavior? Is it sporadic or progressive? What is the age and frequency

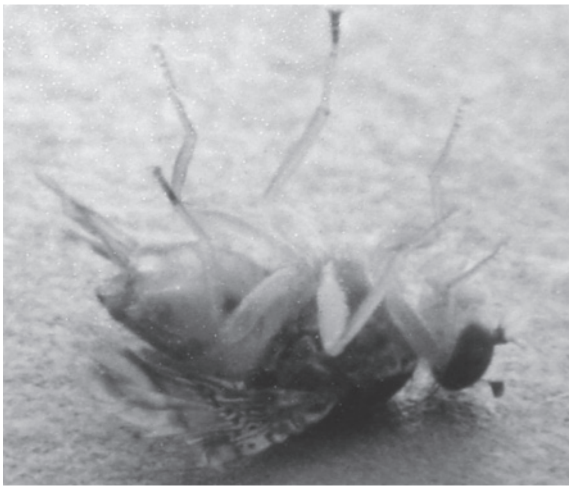

Fig. 1. Male Mediterranean fruit fly male in supine position. When supine flies are disturbed they begin moving their legs, use their wings and/or legs to become upright, and then begin walking slowly (their wings usually appear droopy when resting or walking). Their feeding behavior appears normal and in rare instances males exhibit sexual calling although it is much less intense than normal males.

distribution of this behavior for both cohorts and individuals? Is supine behavior "reversible" or is it a behavioral marker of impending death?

Age-specific Morbidity and Mortality Patterns

An event history chart (Carey et al. 1998) showing the age patterns of the supine behavior for each of the 203 males (Fig. 2) reveals a distinct association of individual life span and both the age of onset and the intensity of this behavior. The band depicting supine behavior shows that, in many flies, it begins to occur about 2-3 weeks prior to death; therefore, the period of its occurrence closely follows the cohort survival (lx) schedule. Supine behavior seldom occurred in very young flies (<25 days) but frequently occurred in flies that were over 50 days old - ages at which mortality rates began to increase substantially. The event history chart reveals four general properties of the medfly supine behavior:

1) *persistent* – occurs on subsequent days after onset;
2) *progressive* – intensity increases with age;
3) *predictive* – onset and intensity are strong indicators of impending death; and
4) *universal* – nearly all male medflies exhibit this behavior regardless of their age of death.

Most of the supine behavior began between 10 and 15 days prior to death, with the highest concentrations occurring five to seven days prior to death. Cox propor-

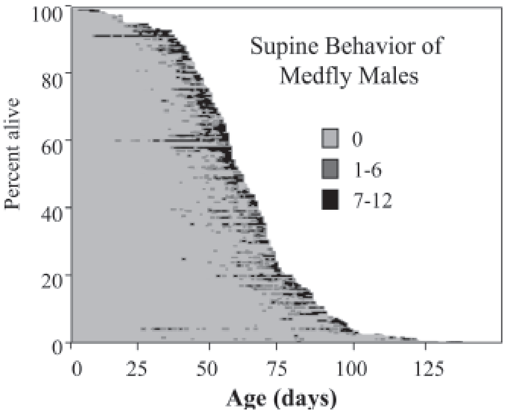

Fig. 2. Event history charts for supine behavior in 203 male medflies relative to cohort survival. Each individual is represented by a horizontal line proportional to his life span. Each day an individual that displays supine behavior, it is coded according to the number exhibited: dark gray indicates 1 to 6 supine observations and black indicates 7–12 supine observations.

tional hazards regression models with time-varying predictors were fitted to the data to test for the significance of both onset (pre-supine –to supine) and level of supine behavior with respect to mortality (hazard) rate. The onset of the supine behavior is a highly significant predictor of mortality ($P < 0.0001$) and increases mortality risk considerably more than the level of supine behavior. The model showed that a fly's mortality risk increased by nearly 40-fold once it began exhibiting supine behavior. The level of supine behavior is also a significant predictor of mortality and, for every increase in supine level by 1.0, the hazard rate increases by 26.3%. Fitting a model that has both the onset and level of supine behavior as predictors indicates that both are highly significant, with mortality risk ratios of 17.59 and 1.18 for onset and level of supine behavior, respectively.

Hazard Rates

Three hazard rates derived from the medfly data are presented in Figure 3, including:

1) *To supine.* This is the hazard rate for the transition from the pre-supine to the supine state, defined as the first observation of any supine behavior. Note the near-linear or Gompertz-like increase in hazard with age, which reveals the ever-increasing likelihood that a fly will experience supine as it ages.
2) *Supine – to death.* This is the supine age-specific death rate, where supine age refers to the number of days since a fly first exhibited supine behavior. This hazard function increases from an initial level of 0.04 at the time of the first supine behavior to a peak of nearly 0.08 at 20 days (supine age). This hazard rate then gradually decreases for the next 30 days to around 0.05 at 50 days (supine

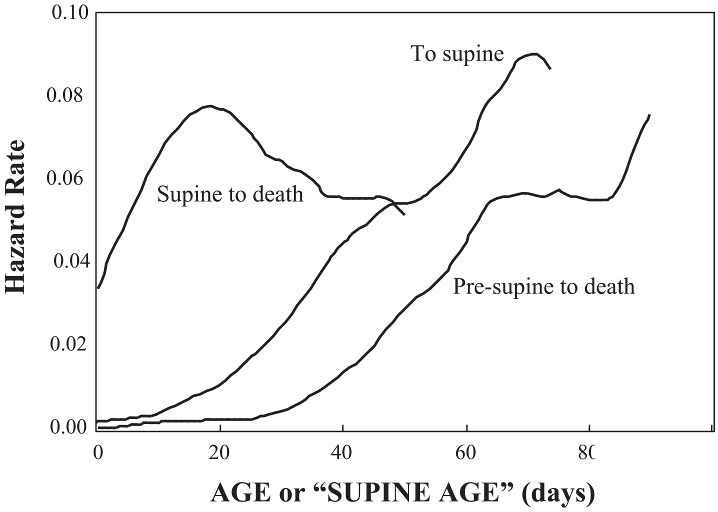

Fig. 3. Hazard rates for three transitions observed in male medflies including 'to supine', 'supine-to-death', and 'pre-supine-to-death' (see text).

age). Because the death rate of a pre-supine fly is substantially lower than the death rate of a supine fly, the rate at which pre-supine flies enter the supine state will determine the age pattern of death in the cohort; for a fly to be in the supine state is to be in the state of impending death.

3) *Birth – to death*. This hazard rate is the background age-specific death rate for pre-supine flies. The curve corresponding to this rate that is shown in Figure 3 reveals the reduced probability of a fly dying in the pre-supine state relative to dying in the supine state or of transitioning to the supine condition. In other words, the longer a pre-supine fly can remain in this state rather than transition to supine with higher hazard rates of death, the longer it will live. Note that the death rate of a pre-supine fly does not equal the death rate of a fly newly transitioned into the supine state (i.e., first day in supine state) until it is two months old.

Life Expectancy Disaggregated by Supine Status

The impact on mortality risk of the onset of supine behavior is illustrated in Figure 4, which shows the remaining life expectancy at each age for all flies (middle curve) as well as flies disaggregated according to whether they had exhibited supine behavior (lower curve) or not (upper curve). Three aspects of this figure merit special comment. First, striking differences occurred in the remaining life of young flies (<20 days) that had not exhibited supine behavior and young flies that were exhibiting supine behavior: the former had over 50-60 days of life remaining (non-supine) but the latter had only 20 days or less left (supine). Sec-

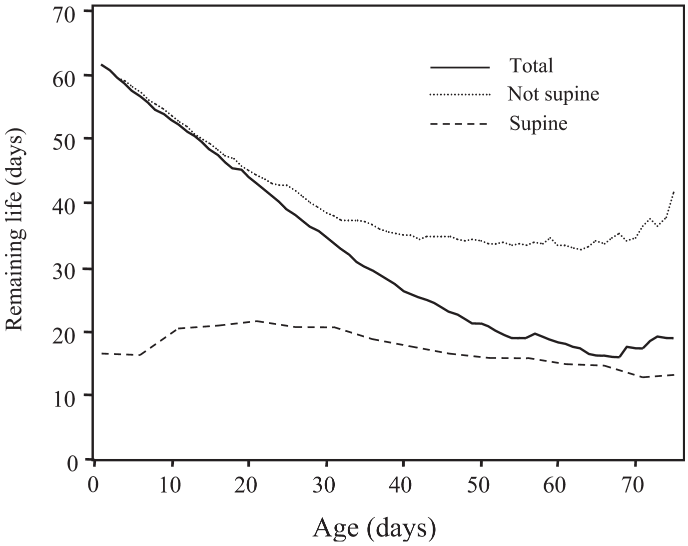

Fig. 4. Schedules of remaining life expectancy (days) for male medflies for the cohort as a whole (center line) as well for males both prior to (top line) and after (bottom line) the onset of supine behavior.

ond, the remaining life expectancy of a non-supine fly between 25 and 70 days of age remained constant at about 35 life-days. However, once it entered the supine state, its life expectancy immediately dropped by 20 days to approximately 15 days. Third, the remaining life of flies that initiated the supine behavior was also remarkably constant, ranging from slightly over 20 days for flies that were 10 to 30 days old to around 16-18 days for very young flies and flies older than 30 days.

"Active" and Total Life Expectancies

We used the age at which a male medfly first exhibited supine behavior to demarcate the end of the "active" period of a fly's life to construct a cohort schedule of "active life" (Katz et al. 1983; Manton and Land 2000). This schedule, combined with the conventional survival (l_x) schedule, was used to estimate the age distribution and prevalence of inactive life by taking the difference at each age between the inactive and total life schedules (Fig. 5). Total and active life expectancies were computed as 61.7 and 45.6 days, respectively (Carey 2001) and thus the average male experienced 16.1 days or 26.1% of its 61.7-day lifetime partially in the supine state. The distribution of inactive life for the cohort varied with age, with the greatest prevalence occurring between 30 and 50 days and the least occurring at the younger and older ages. This measure of inactive life provides information about the dimensions of health and morbidity for a fly, other than death, that can be used as a model system for actuarial analysis as a health-status measure.

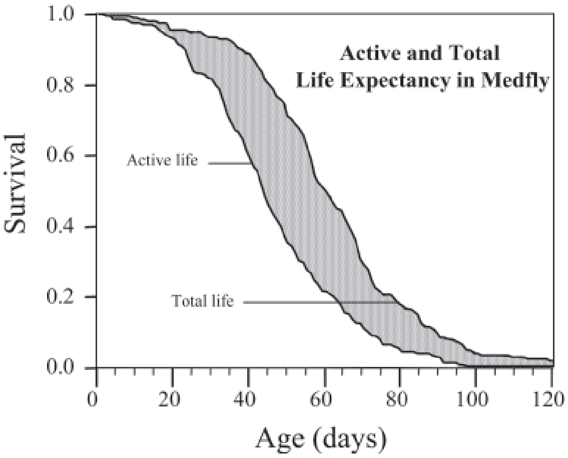

Fig. 5. Schedules of active life and total survival for the male medfly cohort. The age at which active life for an individual ended was defined as the age at which supine behavior was first observed. Inactive life was thus defined as all life-days beyond this onset age. This is a schematic example of how the discovery of disablement classification in the medfly can be used to study dynamics of disablement, morbidity and mortality. Nearly all flies become disabled (exhibit supine behavior) prior to death: the average fly spends nearly a quarter of its life in the unhealthy state and never returns to the healthy state. Once a fly is classified as 'unhealthy' (first supine), it has approximately two weeks more of life (Papadopoulos et al. 2002).

Effects of Changes in Hazard Rates

The morbidity (supine) and mortality hazard rates computed from the medfly data provide useful baselines for use in modeling the impact of changes in these rates on active and total life expectancies and the prevalence of cohort supine behavior. The four patterns of change in morbidity-mortality relationships (Verbrugge and Jette 1994) for each of the hazard rates are presented in Figure 6 and include the following:

Case #1. Rising morbidity (supine hazard) and declining mortality. Both total and active life expectancies increase as does the number of fly-days in the supine state because greater numbers of flies survive to the ages at which the "to supine" hazard rates are highest and flies that enter the supine state live longer due to the reduced mortality. Analogous situations for human diseases include diabetes, diseases of the heart, arteriosclerosis, and nephritis.

Case #2. Rising morbidity and mortality. In the case shown in Figure 1b, total life expectancy was increased but active life expectancy was decreased, resulting in an increase in the prevalence of morbidity (supine). This is because flies enter the morbid (supine) state at younger ages but the rate of entry into the supine state is not offset by a concomitant increase in mortality. For this case the prevalence of morbidity is conditional on the improvement in morbidity relative to improvement in mortality. Examples of diseases in humans in which both incidence and

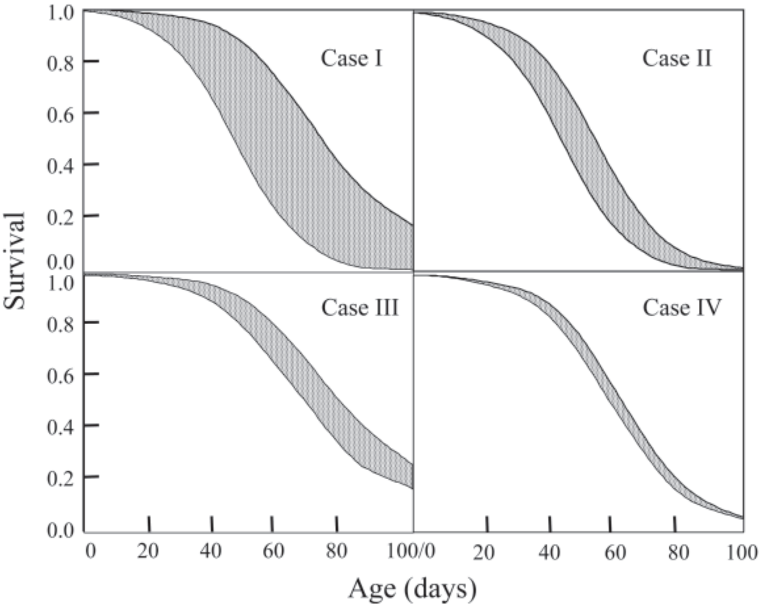

Fig. 6. Composite of four scenarios in morbidity and mortality with total and active life expectancies and prevalence of morbidity listed for each case in this respective order. Case I: 65.3, 41.7, and 23.6 days, respectively; Case II: 50.0, 40.6, and 9.4 days, respectively; Case III: 69.3, 61.2, and 8.1 days, respectively; Case IV: 57.6, 54.3, and 3.3 days, respectively.

mortality are increasingly malignant neoplasms, bronchitis, emphysema, and cirrhosis of the liver for individuals aged 45 to 64.

Case #3. Declining morbidity and mortality. In this case both active and total life expectancies will increase. Examples of diseases in humans in which both incidence and mortality are decreasing include hernias in men older than 65 and nephrosis for individuals aged 45 to 64.

Case #4. Declining morbidity but rising mortality. The prevalence of morbidity will decrease in this case because many flies die prior to the onset of morbidity and those that transition to the morbid (supine) state die more quickly. An example of a disease in humans in which the incidence is decreasing but mortality is increasing is cirrhosis of the liver for individuals aged 65 and older.

Modeling these four hypothetical cases of changes in morbidity and mortality is important for at least three reasons:

1) the process fosters a deeper understanding of the underlying demographic trade-offs necessary to generate different levels of life expectancy and morbidity prevalence;
2) the outcome provides a useful frame-of-reference for comparing the outcome of future experiments in which changes in morbidity and mortality are induced through environmental manipulations; and

3) the implicit assumption for the model is that morbidity and mortality are quasi-independent, that there is a dynamic equilibrium in the relationship between morbidity and mortality as life expectancy changes (Manton 1982).

This basic relationship suggests that, if incidence is unchanged, mortality reductions leading to increases in life expectancy can only occur by increasing the duration of the disease and, consequently, its prevalence. However, as Manton noted, for chronic diseases it is useful to consider the way in which duration is increased:

1) by eliminating lethal sequelae such as pneumonia and not affecting the basic rate of progression of the disease process; and
2) by changing the rate of progression of the primary disease process (i.e., reducing disease severity).

In the Morbidity Compression model, the concept of equilibrium is rejected by arguing that mortality and morbidity are at least partly independent. Equilibrium as a demographic concept is important in human demography because it has serious policy implications: mortality reductions are directly linked with the long-term management of chronic diseases that, in turn, are components of primary health services that are likely to increase greatly (Manton 1982). Concerns about the validity of the assumptions underlying the Morbidity Compression model bring to the surface the inherent problems with hypothesis testing based on the results of clinical research: it is not possible to conduct manipulative frailty experiments on humans. These experiments can only be done with animal models.

Towards a general research framework

Importance of Animal Models

Research on impairment using model systems (non-human animals) in both the laboratory and the wild are important because

1) the results of comparative studies will identify common threads in the disablement process across species as well as at different biological levels (molecular, physiological, whole-organism);
2) studies may shed new and important light on the identification of preclinical signals of disablement in non-human species and identify valid methods to determine if these same signals occur in humans and are related to aging;
3) investigations will encourage development of novel concepts and approaches for understanding fundamental aspects of the disablement process rather than characteristics that are idiosyncratic to humans;
4) aging research on the determinants of endpoints other than death (e.g., onset of impairment, disabling or chronic conditions) will provide context and perspectives on mechanisms underlying aging as well as deeper insights into the manifestations of aging including co-morbidity and the sequence of onset, duration of conditions, and the relationship to mortality; and

5) the focus on general properties will foster the creation of a set of general principles of disablement that are as relevant to insects and other invertebrates as they are to humans and other vertebrates and, in turn, encourage the creation of a new research paradigm for manipulating environmental conditions and for hypothesis testing.

This last point is important because of bioethical issues that arise in manipulative research on human subjects as well as the time and cost constraints of longitudinal studies.

Ecology of Impairment

The vast majority of animals in the wild live on the razor's edge of physical and cognitive fitness. The onset of any physical impairment that would be a nuisance in a protected environment (laboratory or zoo) is virtually a death sentence in the wild. Any animal that no longer possesses the speed, strength and agility to forage for food to escape danger is at great risk in nature; arthritic lions that have difficulty quelling and killing large prey; wildebeests exhibiting even the slightest limp that are quickly targeted by sharp-eyed predators. Indeed, locomotor movement is one of the defining characteristics of animals (Biewener 2003), whether the animal is single-celled or has appendages. The specific mechanisms of movement across species are extraordinarily diverse: darting, (hummingbirds), soaring (petrels) and flapping (songbirds) flight in various bird species; lumbering (elephants), prancing (antelope), scurrying (lizards), racing (cheetahs) and running (cockroaches) gaits in terrestrial animals; swimming (otters), paddling (ducks), diving (seals) and flipper-propelled (whales) motion in aquatic animals. Despite the diversity of mechanisms and types of movement, there are a relatively small number of common principles and biological components that underlie these mechanisms, regardless of the medium through which the animals move. It follows that there will be a small number of principles that underlie the loss of function and the acquisition of impairments through physiological, morphological and/or neurological degeneration with age.

Morbidity Compression in Biodemographic Context

A useful frame of reference for developing a research program in disablement processes in particular is the well-known Compression of Morbidity hypothesis, which was first introduced in 1980 (Fries 1980) and has become the dominant paradigm underlying health improvement programs and policies directed at more successful aging (Fries 1983; Kannisto 2000) Most morbidity results from chronic processes and is concentrated in the years prior to death. The goal is the compression of morbidity between its time of onset (around 55 years) and the age of death (around 75 years). If mortality decreases predominate, there may be more morbidity in a typical life (so-called "failure of success") if the age of onset of chronic disease does not change. However, if the age of onset of chronic disease is increased, then (according to the model) morbidity is compressed, the period of adult vigor is prolonged, life quality is improved, and the need for medical care and associated costs may be reduced (Fries 2000). One of the central issues of medical discoveries of the future is whether they may add health or add illness to the average life. If morbidity is compressed by a new advance, then the advantage is clear; however, if the process of dying is prolonged, then major ethical issues arise (Fries 2000).

Biodemography of Disability Processes: Generalizing Frailty Concepts

The *International Classification of Functioning, Disability and Health*, known as ICF (WHO 2001), provides a unified and standard language and framework for the description of health and health-related states. It defines components of well-being and domains including 1) body functions and structures and 2) activities and participation. “Functioning” is an umbrella term encompassing all body functions, activities and participation; “disability” serves as an umbrella term for impairments, activity limitations or participation restrictions. “Pathology” refers to biochemical and physiological abnormalities that are detected and medically labeled as disease, injury or developmental condition. “Impairments” are dysfunctions and significant structural abnormalities in specific body systems. They involve the loss or limitation of physical, mental or sensory function on a long term or permanent basis. “Functional limitations” are restrictions on performing fundamental physical and mental actions used in daily life by one’s age/sex group. They indicate overall abilities of body and mind to do purposeful work (or make a living in the wild). “Disability” is experienced difficulty doing activities in any domain of life (humans or animals) due to a health or physical problem. Two features of disability are important. First, chronic conditions can affect any activity domain, which, for humans, can include personal care, household management, or employment. For non-human species, this activity domain includes grooming and other hygienic behaviors, food and mate foraging and, for social species, social communication as well as establishment and maintenance of social relationships. Second, the basic feature of disability is difficulty in doing activities in one’s regular milieu. Thus visual impairment (short-sightedness) does not become a (very minor) disability until reading is required. The injured leg in a zoo animal does not become a major disability unless the animal is released into the wild. The ICF framework can be used as a preliminary model for disablement studies on non-human species, examples of which are given in Table 1.

Conclusions

Although the importance of understanding how the behaviors of individuals change with age has long been recognized in honeybees (Frisch 1953) and other social insects (Bourke and Franks 1995; Choe and Crespi 1997) in the context of age polyethism (Seeley 1995; Wilson 1971), the study in which supine behavior in

Table 1. Disablement concepts with examples for humans and for the different model systems (possible scenarios).

Species	Scenario
Humans (Example 1)	A woman age 74 with osteoarthritis in both hands (pathology) has weak grip and restricted finger flexion (impairments). This causes difficulty in grasping and rotating fixed objects (functional limitations), and she has trouble opening jars or doors (disability). She purchases kitchen devices and special door handles (interventions) to overcome the difficulty (Verbrugge and Jette 1994).
Humans (Example 2)	A woman age 90 has no specific diagnoses (pathology), but her sight, hearing, and senses of taste and smell have diminished significantly in recent years and she is forgetful and feels confused (impairments). Gradually she stops socializing (disability) and becomes deeply depressed (quality-of-life outcome). She spends most of the time tearful and seated (functional limitations; feedback effects from disability). Her physical frailty steadily increases (impairment; feedback effect from functional limitation). One night she dies while sleeping (Verbrugge and Jette 1994).
Nematodes	A 23-day-old, post-reproductive (pathology) nematode rarely moves (impairment) because it has released all of its eggs and thus has no need to forage for the food (bacteria) required to produce more eggs. With no motivation for feeding (disability) but because it is a long-lived DAF-2 mutant, it lives for another month in a quasi-suspended state before it eventually wastes away and dies at 53 days.
Medflies	A 68-day-old medfly female has a damaged wing (pathology) and thus has difficulty flying (impairment). This causes difficulty in reaching the food located in a small container suspended from the cage top (functional limitation) and thus increases the risk of becoming weak or of dying due to inability to reach food (disability). Thus food is placed on the cage floor within easy reach (intervention).
Honeybee	A 25-day-old worker bee is weakened due to a parasite infection (pathology) and thus suffers from restricted mobility (impairment), including within-hive movement needed for brood care and pollen foraging outside the colony (functional limitation). This increases the risk of death due to its rejection by other workers within the hive and because of its reduced ability to navigate and avoid predation while foraging (Rueppell et al. 2004).
Mouse	A 17-month-old female mouse that, when younger, regularly used the treadmill, now suffers from progressive renal failure (pathology). She is listless and weak (impairment) and thus seldom feeds or uses the treadmill (disability). She spends much time curled up in a corner of the cage chewing on her tail (feedback from impairment) until she eventually dies.
Macaque	A 22-year-old male macaque is injured (pathology) in a fight with a younger male and suffers partial paralysis in one arm (impairment). This causes difficulty in both climbing and self-defense (functional limitation), which, in turn, reduces his social status, heightens stress levels and reduces access to food (disability). He spends most of the time in isolation (functional limitations; feedback effects from disability), receives little grooming and shows loss of condition (quality-of-life outcome). One day, he is attacked at feeding time by other males and dies of his injuries.

medflies was first discovered appears to be the first to systematically record and analyze data on the age patterns of behavior from birth to death for a non-social insect. Indeed, we could not find any other relatively large-scale study in which age-specific behavior was recorded over the lifetime of individuals. Not only was a new (supine) behavior discovered in the medfly investigation but the frequency of occurrence of supine was found to be a biomarker of aging and a predictor of impending death. Thus the study opens up new possibilities for experimental studies of frailty in model systems and with this, the opportunity to both re-visit and extend existing paradigms in disability studies and the demography of frailty. In particular, the hypothesis that morbidity and mortality are quasi or partially independent needs to be rigorously tested in model systems. We believe that it will not be possible to develop principles that are truly basic until experimental methods, animal models, and hypothesis testing are integrated into the existing, clinically based paradigm of frailty and disability studies. And without these basic concepts and principles, research on frailty will lack a coherency and a theoretical foundation that are essential for advancing the field.

References

Albrecht GL, Seelman, KD, Bury, M (2001) Handbook of disability studies. SAGE Pub., Thousand Oaks, California.
Baker GT, Sprott, RL (1988) Biomarkers of aging. Expl Gerontol 23: 223-239
Biewener AA (2003) Animal locomotion, Oxford University Press, Oxford
Bourke AFG, Franks NR (1995) Social Evolution in Ants. Princeton University Press, Princeton
Carey JR (2001) Insect biodemography Annu Rev Entomol 46: 79-110
Carey JR, Liedo P, Muller HG, Wang JL, Vaupel JW (1998) A simple graphical technique for displaying individual fertility data and cohort survival: case study of 1000 Mediterranean fruit fly females. Func Ecol 12: 359-363
Choe JC, Crespi BJ (1997) Social behavior in insects and arachnids. Cambridge University Press, Cambridge
Fries JF (1980) Aging, natural death, and the compression of morbidity. New Engl J Med 303:130-135
Fries JF (1983) The compression of morbidity. Milbank Mem Fund Quart /Hlth Soc 61: 397-419
Fries J F (2000) Compression of morbidity in the elderly. Vaccine 18: 1584-1589.
Frisch KV (1953) The dancing bees: an account of the life and Senses of the honey bee. Harvest Book, New York
Kannisto V (2000) Measuring the compression of mortality. Demog Res 3: 1-24
Katz S, Branch LG, Branson MH, Papsidero JA, Beck JC, Greer DS (1983) Active life expectancy. New Engl J Med 309: 1218-1224
Lollar DJ, Crews JE (2003) Redefining the role of public health in disability. Annu Rev Pub Hlth 24: 195-208
Manton KG (1982) Changing concepts of morbidity and mortality in the elderly population. Milbank Mem Fund Quart/Hlth Soc 60: 183-244
Manton KG, Land KC (2000) Active life expectancy estimates for the US elderly population: a multidimensional continuous-mixture model of functional change applied to completed cohorts, 1982-1996. Demography 37: 253-265

Manton KG, Gu, X (2001) Changes in the prevalence of chronic disability in the United States black and non black population above age 65 from 1982 to 1999. Proc Natl Acad Sci 98: 6354-6359

Manton KG, Corder L, Stallard E (1997) Chronic disability trends in elderly United States populations: 1982-1994. Proc Natl Acad Sci 94: 2593-2598

Markowska AL, Breckler SJ (1999) Behavioural biomarkers of aging: illustration of a multivariate approach for detecting age-related behavioural changes. J Geron Biol Sci 12: B549-B566

Mehrotra A, Dudley RA, Luft, HS (2002) What's behind the health expenditure trends? Annu Rev Pub Hlth 24: 385-412

Papadopoulos NT, Carey JR, Katsoyannos BI, Kouloussis NA, Müller HG, Liu X (2002) Supine behaviour predicts time-to-death in male Mediterranean fruit flies Proc Roy Soc London: Biol Sci 269: 1633-1637

Papadopoulos NT, Katsoyannos BI, Kouloussis NA, Carey JR, Müller HG, Zhang Y (2004) High sexual calling rates predict extended life span in male Mediterranean fruit flies. Oecologia 138: 127-134

Rueppell O, Amdam GV, Page RE Jr, Carey JR (2004) From genes to societies. Science Aging Knowledge Environment 5: pe5

Seeley TD (1995) The wisdom of the hive: The social physiology of honey bee colonies. Harvard University Press, London

Singer BH, Manton KG (1998) The effects of health changes on projections of health service needs for the elderly population of the United States. Proc Natl Acad Sci USA: 15618-15622

Verbrugge LM, Jette AM (1994) The disablement process. Soc Sci Med 38: 1-14

WHO (2001) International classification of functioning, disability and health. World Health Organization, Geneva

Wilson EO (1971) The insect societies, The Belknap Press of Harvard University Press, Cambridge, MA