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Reflexion

Top-down and bottom-up research in biodemography

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Top-down and bottom up research in biodemography

Hillard Kaplan¹

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Abstract

The most efficient way to make scientific progress in biodemography is to encourage bi-directional exchange between ‘top-down’ and ‘bottom-up’ research. This will entail exchange along the continuum of research from microscopic intracellular processes to population-level consequences. In addition, our understanding of the biology of aging and its demographic consequences will be enriched by mutual influence between studies of mechanistic or ‘proximate’ causal processes and investigations of the evolutionary processes underlying the same phenomena. Researchers working at these different levels of explanation could be more productive if they were informed by research at other levels and interacted with scientists with complementary expertise. Such collaborations could be encouraged both through interdisciplinary workshops, research projects, program projects and training programs.

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1. Overview

The overarching theme of this essay is that given our current state of knowledge, the most efficient way to make scientific progress in biodemography is to encourage bi-directional exchange between 'top-down' and 'bottom-up' research. These terms are used in two senses here. First, they are used to refer to the continuum from microscopic intracellular processes to population-level consequences. In a second sense, 'bottom-up' is used to refer to mechanistic or 'proximate' explanations. 'Top-down' refers to 'ultimate,' or evolutionary explanations of phenomena, based on the action of natural selection working on genes and the phenotypic traits with which they are associated (Mayr 1961). Researchers working at these different levels of explanation could be more productive if they were informed by research at other levels and interacted with scientists with complementary expertise. Such collaborations could be encouraged both through interdisciplinary workshops, research projects, program projects and training programs.

We now know that the processes linking genes to fertility and mortality outcomes, and the impacts of those processes on gene distributions in populations over generational time are both tremendously complex and highly structured. The genetic system is in many respects comparable to the generative grammars of human languages, which are capable of an almost infinite number of meaningful utterances. With a relatively small number of genes, based on only four base pairs, an immensely large number of phenotypes can be generated through additive and interactive effects of genes, gene-environment interactions and epigenetic processes. The action of natural selection brings order to those processes, but a very complex and difficult order to understand.

Consider the immune system of higher organisms as an illuminating example. This type of immune system is generally thought to be composed of interacting components of innate and acquired cell-mediated responses (Rao 2005). The latter component is specifically designed to engage in life-long learning and to be capable of producing a very large distribution of lymphocyte cell types through processes of genetic recombination and differential cell reproduction due to the history of antigen exposure. This system is energetically expensive to build and produce, and competes directly with other processes affecting fitness, such as growth and reproduction. However, those large investments in the immune system evolved because they reduce mortality sufficiently over the life course in an ecological context of rapid reproductive rates of evolving populations of diverse pathogens. The overall effects on fitness of such expensive protection must be positive.

The ultimate goal in the biodemography of aging should be to understand the processes linking genes to phenotypes, phenotypes to mortality and fertility outcomes, and those outcomes to gene distributions over generational time. This will require both mechanistic physical models and specific theories of how natural selection acts to order those processes, both within populations of a single species and among species in evolving

ecosystems. 'Bottom-up' research investigates the mechanisms by which genes translate into their products, and how those products interact with environmental inputs to result in physiological and, ultimately, demographic outcomes. It is bottom-up in the sense that knowledge about how those processes work provides the empirical facts that evolutionary theories must explain. Evolutionary modeling is top-down in the sense that it provides the deductive logic and the organizing principles that bring order to organismal design. Any complete understanding of the aging process and its effects and implications will require both bottom-up and top-down approaches.

This essay outlines a vision of interdisciplinary research that combines top-down and bottom-up investigation, where the bi-directional dynamic of mutual influence is explicitly pursued. The next section provides a brief overview of the principle of allocation and life history theory from evolutionary biology and how it can inform research in the biodemography of aging. This is followed by an example of combined bottom-up research on biomarkers and aging, with top-down research on the evolution of the human lifespan.

Specific high priority research areas are then discussed. These areas include: 1) Species-typical commitments to a pace of life and flexible responses to environmental variation; 2) disease, development and aging in high burden populations; 3) Host-pathogen co-evolution; and its implications for gene-environment interaction, intra-population variation in rates of aging and mortality, and inter-population variation in gene frequencies; 4) physiological and behavioral adaptations to aging itself; and 5) responses to changed conditions in recent human history. This list of high priority research areas is not meant to be exclusive, but to provide a vision of how top-down and bottom-up research can contribute to our understanding of the aging process.

The essay concludes with some suggestions for ways to stimulate such interdisciplinary research and training.

2. Evolutionary biology, trade-offs and the physiology of aging

The *principle of allocation* provides a fundamental theoretical foundation for the explanation of organismal design. The principle of allocation states that time and energy allocated to one function is generally not available for other functions. The basic concept is that the production of genetic descendants places competing demands on organisms. They may grow to more effectively produce energy, defend themselves from mortality threats, seek and compete for mates, or put effort into offspring production and care. These investment options each require time and energy, and produce fitness returns that are realized over time.

A fundamental constraint that all organisms face is that neither time nor energy is free, so budgets are limited. Given that the production of descendants requires investments in

more than one, and often all, the above functions, organismal design is the outcome of trade-off decisions shaped by natural selection that impact how much effort to allocate to each function. One fundamental trade-off is between present and future reproduction. Both the gains from growth and defense against mortality are realized in the form of future offspring production, as more energy is produced with greater body size, and the probability of being alive at older ages increases.

Incorporating the principle of allocation and trade-offs in investment among competing functions into the theory of evolution by natural selection has led to the development of life history theory (Stearns 1992; Roff 1992). The principal expectation of models derived from life history theory is that natural selection will tend to result in phenotypes that *optimize* quantitative investments in all competing functions affecting fitness over the life course. The application of life history theory to behavioral and demographic outcomes, such as age of first reproduction, adult body size, gestational length and size at birth, inter-birth intervals, and adult life expectancy, is well-developed with a very successful 50 year history (ibid; see Hill and Kaplan 1999 and Kaplan et al. 2003 for reviews of human applications).

While life history theory has illuminated some patterns underlying physiological processes, such as scaling rules governing basal metabolic rate, the direct application of life history to physiology is still in its infancy, and its impact on our understanding of physiological processes is still rather limited, especially among humans. To date, most research into physiology remains mechanistic, uninformed by the micro- and macro-level trade-offs governing physiological processes. The best examples of application of life history models to human physiology focus on growth and immunity (McDade 2003) and reproduction (Bentley 1999, Ellison 2003). With notable exceptions (e.g. Drenos and Kirkwood 2005; Kirkwood 2004; Kirkwood and Austad 2004) there is a vacuum of research into the physiology of human aging that specifically incorporates life history models in a predictive fashion.

3. Biomarkers and the human lifespan: An example case

The incorporation of biomarkers into demographic and aging research is a classic example of bottom-up research. There is a growing set of biomarkers (such as ApoE and IL-6 allelic variants, C-reactive protein, fibrinogen and other acute-phase proteins, glycosylated hemoglobin, serum lipids, telomere cap lengths) that are being increasingly measured in national and international longitudinal aging studies (e.g., HRS, Mexican Health and Aging Study, Indonesian, English Longitudinal Study of Aging, SHARE, Taiwan, McArthur, Health Aging and Body Composition Study). The markers are generally used as predictors of healthy function, morbidity and mortality among middle-aged and elderly popula-

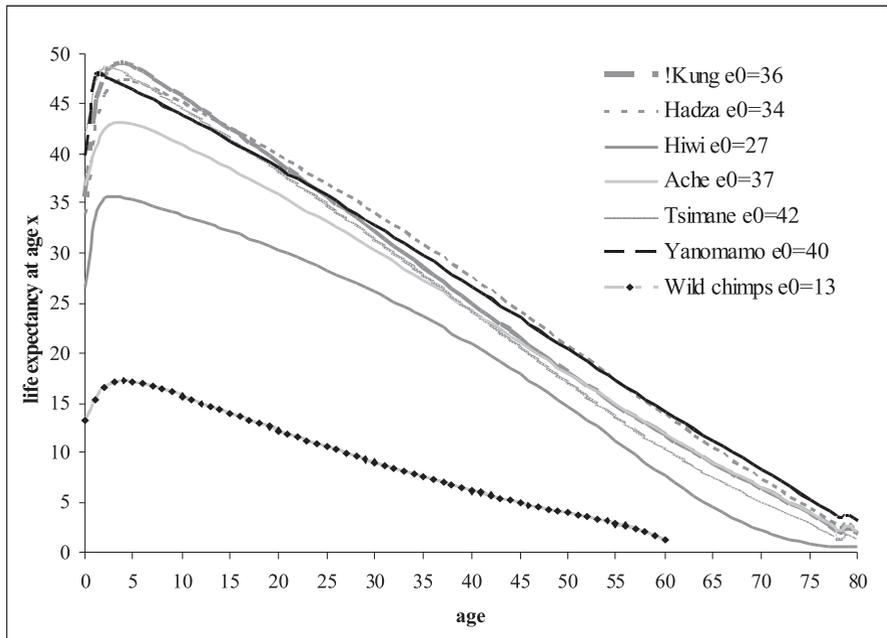
tions. For some markers, there are mechanistic causal theories about the link between the marker and the outcome. For example, C-reactive protein (CRP) is produced as part of an acute inflammatory response. It is thought that a secondary effect of CRP is to change the binding properties of lipoproteins, and that over time, such inflammatory processes can result in vascular obstruction and a cascade of secondary morbidity and mortality inducing effects (Finch 2005). Despite these causal effects, much of CRP research to date is essentially correlational whereby the risk factors for high levels of CRP and for outcomes associated with elevated levels are discovered on a mostly trial and error basis. There is now a vast literature on both what predicts CRP levels and its effects on cardiovascular disease, type II diabetes, cognitive and neurological disease, and mortality (ibid). Parallel literatures exist for the study of the effects of ApoE variants and their distributions in different populations (e.g. Ewbank 2002) as well as tumor suppression and telomere maintenance genes, such as p53, ATM and TRF2 (Gu et al. 2005).

On the other hand, there is a paucity of research, both theoretical and empirical, on the evolutionary forces shaping the design of the inflammatory response system and the distribution of apolipoprotein genes. With respect to CRP, there are short term benefits of this response, and what appear to be long term costs - the grist for life history theory. An optimizing approach to the cascade of physiological responses that organize the inflammatory response system would have to take into account the costs and benefits of its reactivity as they are distributed over the whole life course.

There is good reason to believe that this system evolved under conditions in which our ancestors experienced a much higher burden of disease and physical trauma than do people in developed nations today. For example, results from research with Tsimane Amerindians in the tropical forests of Bolivia, who live in remote villages and who engage in subsistence foraging and horticulture, reveal a much higher prevalence of elevated CRP, parasitic disease, and diarrheal and respiratory infections than Americans (Gurven et al. 2008; McDade et al. 2006). Physical injury is also much more common.

At the same time, we now know with some degree of certainty that the human lifespan evolved to more than double that of chimpanzees, our closest genetic relatives. For example, life expectancy at age 15 is only about 13 additional years among wild chimpanzees, whereas it is close to 40 years among human hunter-gatherers for which we have reliable data (see Figure 1; see also Finch and Stanford [2004] for a discussion of how ApoE genes affecting lifespan may have changed with dietary changes in the course of human evolution). Moreover, cross-cultural variation in mortality rates among hunter-gatherers is greatest at young ages, but converges across groups at later ages, revealing a distinctly human stamp. Among the seven foraging groups, located in South America, Africa, Australia, for which reliable adult mortality data exist, the modal adult age at death is 71 years, with a standard deviation of only 2.3 years; among wild chimpanzees, the modal age at death is less than half that among foragers (Gurven and Kaplan 2007).

Figure 1: Age-specific years of remaining life (e_x): Hunter-gatherers and Wild Chimpanzees (adapted from Gurven and Kaplan 2007)



So far, virtually all evolutionary hypotheses regarding lifespan extension have focused on the benefit side of living longer, especially via intergenerational transfers from parents to children and from grandparents to grandchildren (Kaplan and Robson 2002; Hawkes et al 1998; Lee 2003). The cost side has yet to be addressed, but if we want to know why the human lifespan is traditionally about 70 years, and not 50, 80 or 100 years, both costs and benefits must be considered. Here is where a meeting between bottom-up and top-down research can generate significant gains in both arenas. The human immune and repair complex, broadly defined, appears to generate a lifespan in which many cells, organs and physiological processes show significant life-threatening changes in the seventh decade of life. Cancers, heart disease, decreased ability to work, cognitive decline, and impaired immune function greatly increase in frequency at this age as do mortality rates. Yet, these outcomes are the result of processes that were set in motion at the beginning of life, and potentially altered throughout early and late development.

The hypothesis suggested by life history theory is that apolipoprotein genes and the inflammatory response have been shaped by natural selection due to their short- and long-term effects on mortality and performance in the context of the human adaptive niche. This hypothesis generates important new research directions and can provide order to the trial and error correlation process, since it directs attention to quantifying those costs and benefits over different time scales. At the same time, the bottom-up research is critical to building a rich understanding of the human life course, because it reveals the mechanistic processes that shape the costs and benefits of different organismal designs. Currently, correlates of aging and mortality risk, such as elevated levels of CRP and LDL ('bad cholesterol'), are treated as risk factors to be reduced. The integration of top-down and bottom-up research can replace the risk factor approach with one based on organismal design and organized responses to environmental inputs.

The next section discusses some specific high priority areas for research based on this framework.

4. Specific productive research directions

4.1 The pace of life and response to environmental variation

While there is general consensus that aging occurs as a set of quasi-independent processes in different tissue and organ systems across the body (Wood et al. 1994), there also appear to be some overarching schedules of development and aging at the whole organism level (see Frank 2004, for illustration of similarities and differences in age-schedules of alternative mortality risks in the U.S.). We need a better understanding of both the proximate cellular and extra-cellular mechanisms responsible for such age-profiles and a causal theory of the evolutionary forces shaping those mechanisms. Several different questions merit serious attention in this regard. Are there commitments to rates of repair at the cellular level that result in a species-typical age pattern of senescence? Are the mechanisms governing cell repair, apoptosis, and the elimination of dysplastic cells by the immune system responsible for species differences in rates of aging and in mortality schedule? In what ways do such processes in humans differ from those among chimpanzees? For example, to what extent do species differences in telomere length shortening explain rather than simply describe differences in aging rates? How are the rates of aging in different bodily systems determined, such that at the population level, the process of aging appears to have a consistent shape? Why, on the other hand, do we find that certain functions, such as muscular strength, decline more rapidly than others, such as memory and cognition?

Additional evidence suggests that life experiences can significantly impact rates of aging. To what extent do early life experiences during fetal development and infancy affect rates of aging? (e.g. Bateson et al. 2004, Gluckman et al. 2007, Kuzawa and Pike

2005). Do rates of cell repair and does the development of the immune system respond to early life experiences in such a way as to affect rates of aging at the organismal level? Are such effects produced through epigenetic processes and are they adaptive (Burdge et al. 2007)? To what extent is epigenetic programming adaptive, and in what environmental contexts? Why does oxidative and psychosocial stress experienced over the life course further accelerate the rate of aging? (see Epel et al. 2004).

Thus, one high priority research goal is to explain the schedule of investments in tissue, organ and organismal integrity and how this schedule interacts with many environmental inputs to produce a rate of aging and its associated mortality schedule.

4.2 Disease, development and aging in high burden populations

The study of development and aging in high burden populations may help us understand the design features of the physiological mechanisms underlying the aging process. It is almost certainly the case that those mechanisms governing rates of cell repair, other senescent processes and effort at mortality prevention evolved in the context of greater disease burden than experienced in developed nations today (Black 1975; CIBA 1979). Although prehistoric foraging peoples may have suffered a lower disease burden than people living in high density, sedentary agricultural societies, there is a good deal of evidence indicating high rates of infectious disease in preindustrial societies that are mobile (Scott and Duncan 1998; Gribble and Preston 1993; Gurven et al. 2008). Co-morbidity among viral, bacterial and parasitic disease appears to have been quite common, and usually associated with diminished immune responsiveness, and other negative health outcomes such as anemia and fatigue. Moreover, disease burdens are likely to be correlated with malnutrition, both at the population- and individual- levels. At the population level risk factors for high disease burden, such as lack of clean water and inadequate sewage treatment, are likely to be associated with inadequate food supply, sedentism and high population density (ibid). At the individual level, inadequate nutrition decreases immune function, and high disease burden can lead to malnutrition. This raises several important questions with respect to development and aging.

First, how has the selective history of high-disease burden affected the current distribution of genes in populations, both over the long run in hunting and gathering populations and more recently over the past 10,000 years as agriculturalists with reportedly even higher disease burdens? As discussed above, one possible effect is that genes increasing the ability to mount short-term defenses against diseases (such as those governing inflammatory cytokines and lipoproteins) were favored over those which slowed the pace of aging. In populations with high disease burdens and high rates of infant and childhood mortality, it might be possible to track the effects of selection by examining allele distributions in newborns, teens and young adults, and elderly. Presumably, if genes have

pleiotropic effects, such that they promote survival at younger ages but decrease it at older ages, their frequency should be highest in teens and young adults, and relatively lower among newborns and aged.

Second, the exposure to greater disease burdens and/or energetic stress early in life is likely to be associated with differential developmental patterns, with respect to growth and the organization of the immune system. With multiple disease exposure, there will be at least three important trade-offs affecting the developing individual: 1) growth vs. immunity; 2) maintenance and repair vs. defense against disease; and 3) defense against one pathogen vs. defense against another. For example, Long and Nanthkumar (2004) review evidence suggesting that the humoral ('Th-2') and cell-mediated (Th-1) arms of the immune system exert negative feedback with one another, such that activation of one arm suppresses activity in the other arm (Mosmann et al., 1986). They also report that nutritional stress and parasitic infection produce a developmental bias towards humoral as opposed to cell-mediated defenses. Chevalier et al (1998) show that malnourished infants can exhibit massive reductions ('involutions') in thymus size (two thirds reduction in volume compared to controls), which can be reversed with intensive hospital care and food supplementation.

Given the allocation trade-offs experienced by human infants and children during our evolutionary history, it is not surprising that the immune system is designed to respond to the antigens to which it is exposed. Both lack of exposure and high levels of exposure are likely to have life-long effects. High disease burdens may increase the rate of aging, due to both the direct damage caused by the diseases and the endogenous reallocation of energy to immediate defense over long term maintenance and repair. Since lack of exposure may have been rare in our evolutionary past, proper development of the immune system may depend on such exposures, producing unexpected and untoward consequences in novel environments, such as allergies and asthma (Leonardo-bee, Pritchard and Britton 2006). The comparison of immune system development and rates of aging in high and low burden populations will help us understand rates and the diseases of aging in both contexts.

4.3 Host parasite co-evolution

Given that selection between host and pathogens is bi-directional in that each forms part of the selective environment of the other, the disease environment of ancestral humans is likely to have been a dynamically evolving mosaic, both within populations over time and across populations over space. Models of host-pathogen co-evolution suggest that host populations will exhibit genetic polymorphisms, because selection on hosts proceeds more slowly than selection on pathogens (Clayton and Moore 1997). This means that at any one time, some phenotypes will be better adapted to previous disease environments than the current environment, whereas for others, it will be the reverse. Various mechanisms

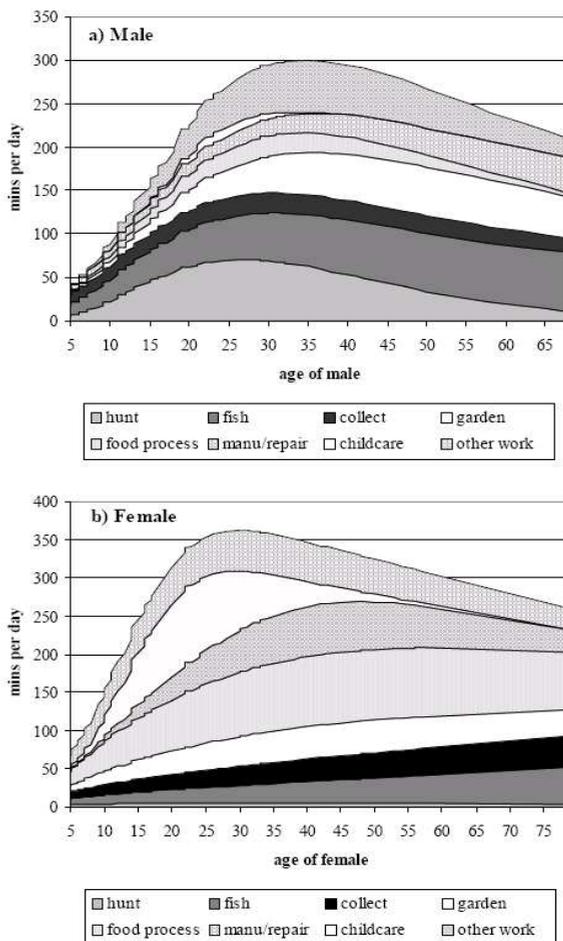
such as fetal exposure in utero and breastfeeding may forward-predict immune system development in growing infants to specific antigens in both current and recent conditions (Worthman and Kuzawa 2005). Such effects may explain individual variation in rates of aging. If some individuals are more susceptible to disease during childhood and/or throughout their life, they may age more quickly and exhibit higher rates of morbidity and mortality. Pathogen evolution is likely to be changing in character, as globalization is changing transmission rates and processes. Research into host-pathogen co-evolution, in high and low burden populations is likely to produce important results regarding genetic polymorphisms within and across populations and differential rates of aging at the individual level.

4.4 Adaptations to aging

As people age, deterioration in condition is likely to affect the fitness costs and benefits of alternative physiological and behavioral responses. Features of human behavior, culture and physiology may be endogenous responses to aging rather than direct effects of deterioration, *per se*. In the behavioral realm, it appears that people adjust their activities in relation to their condition. For example, Figure 2 shows the profiles of work effort by men and women in two groups of forager-horticulturalists. Work effort peaks at about 30-35 and declines thereafter. If people worked as hard in their sixties as they did in their thirties, they would likely age faster and die earlier. In the cultural realm, older people may differ in the size and composition of kinship and other social networks available to them, and the extent to which others in these networks act as a possible safety net or buffer during critical periods of disease or dysfunction.

The possibility that selection has acted on physiology in similar fashion suggests new research directions. Some age-related changes in hormone profiles, lean body mass, lipoproteins, and other biomarkers may be adaptive responses to aging itself. Consider the production of estrogens and androgens over the life course. One view is that aging renders men incapable of sustaining androgen production at previous levels, and therefore men reduce androgen production from middle age onwards (Ellison et al. 2002). Similarly, menopause renders women incapable of sustaining estrogen production at early adult levels. Another view is that the effects of androgens and estrogens on physiological functions become increasingly expensive or less beneficial with age, and that selection has acted on hormone production over the lifespan in ways that is sensitive to those changing costs and benefits. For example, two of the physiological effects of testosterone are increased muscle mass and decreased allocation to immune function. As men age, it may be increasingly expensive to maintain the muscle mass and decreasingly beneficial, as eyesight, hearing and cardiovascular function have deteriorated. A relatively greater allocation of available resources to immune function may be more beneficial, especially given

Figure 2: Total cumulative daily time allocation for work activities by age for Machiguenga and Piro a) males and b) females. Time spent in activities are stacked, starting with hunting, then adding fishing, collecting, gardening, food processing, manufacturing and repair, childcare, and other work activities. The average work day is 5 hrs for men, and 6 hrs for women at their peak (adapted from Gurven and Kaplan 2006)



its declining effectiveness. The changing effects of estrogens over the life course could be examined in a similar fashion.

At present, biomarkers of aging are used as predictor variables in population research. It is often not well understood, either in terms of mechanism or functional design, why such markers correlate with risk factors, morbidity and mortality. Aging and other forms of morbidity produce changes in phenotypic condition. Disentangling the direct deleterious effects of aging from endogenous, and possibly adaptive, responses to the aging process is a challenging task, but should lead the way to a more profound understanding of the aging process and its population-level manifestations.

4.5 Adaptive and non-adaptive responses to changed conditions

Implicit in the above discussion is that natural selection on human physiological control systems occurred within a range of environmental variation that is very different from contemporary developed nations. While food availability relative to energetic demands no doubt fluctuated a great deal in our evolutionary past, the abundance of low cost calories, low demands on physical work and low fertility that characterize many contemporary societies is unprecedented. The modeling of adaptive and non-adaptive responses to conditions outside the range of variation experienced in the past is likely to be an important tool in understanding diseases of aging, especially noncommunicable chronic diseases.

5. Conclusions

There are a growing number of scientists with strong interdisciplinary interests and the desire to learn enough about other disciplines to engage in productive scientific discussions and collaborative research. In our experience, the key to successful interdisciplinary workshops and research collaborations is the combination of complementary knowledge and skills with sufficient convergence in research interests and goals among participants.

Proposals to conduct interdisciplinary workshops that combine bottom-up and top-down approaches should be encouraged. For example, there are a growing number of population scientists introducing and analyzing biomarkers in representative samples in the developed and developing world. Interdisciplinary workshops with specialists in genetics, cell physiology, biogerontology, evolutionary biology and demography may be particularly productive in organizing these new research directions.

Both individual research and program projects should be supported that attempt to integrate knowledge gained at each of these levels. It would be best if such projects were not just a collection of independent research projects focusing on 'bottom-up' and 'top-down' aspects of the problem. 'Top-down' research should organize the questions

and theoretical expectations motivating the 'bottom-up' research. The 'bottom-up' research should produce results that confirm, modify, and/or further expand evolutionary and population-level models.

Training programs should be encouraged that give students and post-doctoral fellows exposure to expert researchers working on different levels in the biodemography of aging. Programs that bridge medical schools, departments of biology, sociology, economics and anthropology should be especially encouraged.

Specialization is a necessary feature of the scientific enterprise, but at this juncture, progress in our understanding of the biodemography of aging will be greatly facilitated by scholarly exchange and research that bridge different levels of inquiry.

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