Towards a Public Health Ecology: HIV/AIDS and HAART in New York City

by

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Abstract

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The three papers that comprise this dissertation explore the public health ecology of HIV/AIDS and HAART in New York City from a variety of angles.

In the first paper I report the population and spatial dynamics of a contraction in New York's AIDS epidemic, during which HAART combination therapies were first introduced. I address whether the decline in AIDS incidence was homogenous across two New York boroughs, Manhattan and the Bronx, at the zip code level. From 1993 to 1998, zip codes in Lower Manhattan, with large white and affluent populations, had declines as much as 55% more than the rest of Manhattan. Bronx zip codes underwent still lesser declines. The paper analyzes what combinations of socioeconomic and ecological cofactors defined possible differences in AIDS decline among zip codes. Such heterogeneous geographic and social distribution in the epidemic could provide HIV refugia, areas where the virus can weather the epidemic's ebb, a troubling possibility with the accelerating microbicidal failures of HAART and the emergence of MDR- HIV.

In the second paper I model the evolution of HIV's life history and reproductive strategy in response to the combination therapies. The time-invariant stage-classified Lefkovitch population matrix model developed explores the possibility HAART can select for a semelparous life history that can evolve and invade populations of 'wildtype' iteroparous HIV. The semelparous life history includes a precocious senescence that may

be embodied by an accelerated time to AIDS during the infection. In short, if such a virus evolved, HIV infections would be deadlier.

The third paper proposes a new method for analyzing and displaying epistatic change in spatial data. The method, using techniques from geometric morphometrics, is demonstrated with HIV/AIDS epidemiological data for 1990s New York. The approach captures the HIV/AIDS dynamics observed in the first paper; namely, the decline in Manhattan's epidemic was defined along a socioeconomic fault separating Lower Manhattan from Harlem, while the Bronx's decline was not so geographically distinct. The promises and problems of the technique are discussed.

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This is not my dissertation. This is *our* dissertation. No one works (or lives) in a vacuum, not even someone who spent countless hours alone in a lab over a hot computer. In the deepest nights I thought about you all and drew much strength.

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Chapter 1

Introduction: Studying Epidemics in a Socialized World

...in the face of misery and suffering on a monumental scale, epidemic theory for its own sake is a luxury mankind can ill afford.

Norman Bailey (1975)

The work presented in this dissertation applies principles and techniques from the fields of ecology and evolutionary biology to HIV/AIDS. Specifically it addresses the population dynamics of HIV/AIDS and highly active antiretroviral therapy (HAART) in New York City. The application is not unique. Biologists of various stripes have analyzed HIV/AIDS using population biology (e.g., Anderson and May 1991, Nesse and Williams 1994, Lipsitch and Nowak 1995, Levin et al. 1996, Frank 1996, Boily and Mâsse 1997, Stearns 1999, Nowak and May 2001).

Such methodology, however, is not without its critics. Grossman (2001) censures Nowak and May's within-host, prey-predator models of immune response as "superficial" and "potentially misleading" because the models eschew the real immune system. Grossman declares the models miss the immune system's refractory states and anergy, time delays and overshooting, multiple activation thresholds and tuning, dynamic competition between activation and tolerance, and self-recognition and homeostasis, among other characteristics. A key omission is HIV infects memory T-cells and undergoes localized bursts of replication.

Similar reproach has been directed at many among-host population models of HIV dynamics. For example, the social environment in which HIV is embedded is often defined solely by population density or transmission rate. At best, those infected are cross-sectioned by risk group and sex. Gould (1993, Chapter 12), focussing on the work of Anderson et al., castigates what he terms the "differential paradigm." These non-spatial models deploy differential equations to estimate rates of transmission, and little else. Of the consequences of the approach, Gould writes,

> The journals are flooded with one variation on the basic theme after another, all of them equally pretentious and unilluminating. We even have the

> ridiculous sight of anthropologists wandering around East Africa with their differential equations hoping to estimate transmission coefficients between sub-groups in the midst of a region where whole villages are being abandoned, hoping to "calibrate" their still purely temporal equations. The epitome, the ultimate folly of this approach came in a paper modeling the diffusion of HIV in the whole of New York City with 34 differential equations, churning out numbers down the time horizon. Geographically, of course, New York was homogenized and compressed to the head of a pin, simply because there was no need to consider any difference between the burnt-out Bronx and the trim lawn suburbs, or people in the packed tenement houses of a Harlem slum and the residents of apartments overlooking Central Park. After all, people are people, and since we are only playing computer games anyway, we can lump them together.
>
> As can be imagined, the conclusions were carefully couched in the language of "scenarios," but nothing could really cover up their devastating banality.

The banality stems in part from a failure or refusal to bridge conceptual and professional ravines that separate the natural and social sciences. Absent is any apparent effort to situate HIV epidemics within their real-world contexts. In an effort to better portray HIV/AIDS population dynamics, the work presented in this dissertation bridges multiple epistemologies with five general principles:

1. Human phenotypes, like those of other organisms, are derived from an interpenetration of genetics, development, and the environment (Levins and Lewontin 1985, Lewontin, 2000). In short, humans shape and are shaped by their environments.

2. Many human phenotypes instantiate culturally derived processes; that is, the human-environment interaction also includes cultural inputs and outputs (Cavelli-Sforza and Feldman 1981, Boyd and Richerson 1985, Findlay 1990, Durham 1991).

3. These environments are currently entrained by historically contingent trajectories: social conditions, ideologies and technologies exemplified by the subway, capitalism, the housing stock, racism, teen fads, "welfare reform," etc.

4. Human pathogens, particularly a behaviorally transmitted one such as HIV, also shape, are shaped by, and embody population-specific amalgams of "natural" and cultural environments (McKeown 1988, Montagnier 1996, Morse 1993, Ewald 1994, Rosner 1995).

5. Humans and their pathogens comprise populations that change in composition over sociogeographic space and ecological time, influencing evolutionary and health outcomes (Haining 1990, Smallman-Raynor et al. 1991, Wasserheit 1994, Tilman and Kareiva 1997, Porter and Ogden 1998, Keeling 2000). The populations interact at multiple scales and levels of organization that need not be entrained by the same causes (Levin 1992, Ives et al. 1993, D Wallace 1995).

How is such a hybrid epistemology operationalized? The best mode of explanation may be by example.

In a 1998 article for *Harper's Magazine*, JoAnn Wypijewski wrote about the national scorn (and jail time) to which a young black man with HIV was subjected for infecting a group of young women, many of them white, in an economically depressed upstate New York county. Wypijewski's ethnography included the interplay of the area's manufacturing collapse, the drug trade's recent colonization, the prison economy, a backdrop of racism, town rituals and myths, the greater pop culture, and how these together interact with social and personal psychologies. More specifically, Wypijewski traced how these forces exchange with the multiple roles sex can play: a source of pleasure; a means of procreation; an expression of love and affection; a port in an emotional storm; a weapon; release from boredom, anger or lonesomeness; a declaration

of independence; a plank in personal identity; a message to friends or family; for some a source of income; and, for the state, an intermittent rationale for intervention.

Gould (1993), R Wallace and D Wallace (1993) and R Wallace et al. (1999) provide literal road maps for Wypijewski's county-level landscape. The U.S. HIV epidemic is characterized by hierarchical diffusion. Over the first ten years of the epidemic HIV jumped from New York City, Los Angeles and Miami down the economic hierarchy into second cities, via air travel and interstate traffic. It also diffused into nearby suburbs, via the daily commute in and out of central cities. HIV eventually flowed into rural areas and smaller towns ravaged by industrial abandonment, in under social off-ramps and wrong sides of the tracks, like water flows through cracks in ice.

HIV quasispecies resistant to at least one antiretroviral now infect nearly 80% of those tested in the West (Susman 2002). As many as 50% of Western infections are multiple drug-resistant (MDR) (Schmidt et al. 1998, Dietrich et al. 1999, Loveday et al. 1999, Salomon et al. 2000, Susman 2002). We should not be surprised if MDR-HIV follows the same routes of diffusion its drug-naïve predecessors took. It is highly unlikely a ping-pong model of HIV dynamics that abstracts and atomizes the virus out of its socialized context would ever hypothesize such a possibility. Rhatigan et al. (1996) make similar criticisms of the clinical AIDS literature.

Simplified models *can* add much to our understanding about pathogens and their behaviors, but such models are often treated as ends unto themselves. Often unrecognized is that deciding what inputs to include in or exclude from a model is in itself a social act (Levins 1998). Be it as it may, in whatever way models are constructed the assumptions

presumed and conclusions derived should at some point be tested by data. They need to address the tumult of the real world.

To that end the work in this dissertation points towards a new public health ecology (see also Wallace 2002, Wallace, in press). Humans and pathogens—at multiple levels of organization—are treated as synergistic outgrowths of and inputs into dynamic and intensely socialized environments: a world of truck drivers and gender roles, trade tariffs and bowie knives, the Internet and neo-colonialism. Accounting for the greater totality of such causes and effects is, I argue, an act of practical prudence. Good public policy depends much on the validity and relevance of basic research.

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Chapter 2

AIDS in the HAART Era: New York's Heterogeneous Geography

Social Science and Medicine. In press.

During the first century of plague, magistrates of Europe's semi-autonomous towns either made no official response to an outbreak, or if required to do something, introduced controls of the type used when dealing with disease crises in general. The rationale behind this was simple. Even in the most advanced parts of the West—the trading cities of northern Italy and the Iberian peninsula—magistrates had only recently (in the 1290s) came to regard public health as a legitimate concern.

As part of their new interest in health as *publica utilitas*, urban Italian rulers had accepted recently reinterpreted medical teaching about the six Non-Naturals the Ancients (such as Hippocrates and Galen) had thought caused disease. For our purposes the most important of these was what medieval people called "climate," which translates into socio-physical surroundings, including air. Fourteenth-century experts thought that contaminated air in the form of a *miasma* (from the Greek word for "defiled") caused disease. Another Non-Natural was the category type "afflictions of the soul" which translates as mental depression or melancholia. Using a tool of logic (argument by analogy) which medieval schoolman often applied to the writings of the pagans (such as Aristotle and Plato) to bring them into line with Christian revelation, "afflictions of the soul" came to mean ill health caused by the contamination of the space of the *civitas* (city or city state). Using another tool of scholastic logic, it was held that the whole of a community might be targeted by the arrows of God (in the form of a miasma) to demonstrate His wrath against a defiling few.

Building on these learned understandings, before 1347 (and the coming of the plague) whenever an up-and-coming north Italian or Aragonese town was racked by influenza, strange fever or other disease crisis, authority trotted out the emergency rules. Following this sanitary regimes, the heaps of offal which butchers left rotting in front of their shops, the scraps and liquids that leather-workers pushed out into the streets, the human excrement that people tossed out their front doors, and all other smelly things were collected and bundled out of town. If the disease crisis was unusually serious (a subjective understanding which was not constant over time), prostitutes and other morally contaminating people would also be driven from the city.

Sheldon Watts (1997)

In short, if it remains true, as the record suggests, that the sections of [New York City] in which the poor people lived were also the sections with the highest death rates from disease and accident, the effort to achieve moral order in the city was somewhat easier because of the impact of these premature deaths fell heaviest on the class that was producing the greatest number of disorderly people in turbulent time...

Public sanitation, clean water, and government inspection of eating and health facilities have all played a part in the immense and heartening reversal in health statistics. At the same time they have not been without cost...

In a highly congested city, if health care has the effect of increasing the number—or changing the demographic pattern that formally decreased the number—of dangerously uncivil people in the population, the cost of trying to impose moral order on them must rise significantly.

No serious person can claim that in the past years, tuberculosis, with miraculous aim, wiped out the potential New York criminals and spared the poet and the philanthropist... Yet it would be equally nonsensical to overlook the fact that unconscious blind forces, by helping reduce the size of the potentially disruptive population, made easier the job that the city must now do consciously: imposing moral order.

Roger Starr (1985)
Former New York City
Housing Commissioner

Abstract

During the 1990s, the number of new AIDS cases in New York City declined precipitously. The declines, beginning before highly active antiretroviral therapy (HAART) was introduced, were geographically heterogeneous across two New York City boroughs analyzed. From 1993 to 1998, zip codes in Lower Manhattan, with large white and affluent populations, had declines as much as 55% more than the rest of Manhattan. Bronx zip codes underwent still lesser declines. Declines also differed within zip codes among subpopulations. White zip code populations tended to have greater declines than Latino populations, which in turn tended to have greater declines than black populations. According to bivariate and stepwise regressions, an array of socioeconomic and community stress variables acted in combination on the decline in New York AIDS. Manhattan's declines in total AIDS incidence were primarily defined by changes in AIDS incidence for whites and for men who have sex with men, racial segregation, and the proportions of households in upper income classes and under rent stress. Bronx declines in total AIDS are principally explained by a broader range of income classes, and social instability as marked by housing overcrowding and cirrhosis and drug mortalities. Whatever the combination of proximate causes for the decline in AIDS incidence in 1990s New York (educational campaigns, HAART, demographic stochasticity), the decline was shaped by the city's socioeconomic structure and political and ecological history. That structure and history generates the geographically defined aggregates of behaviors that promote or impede AIDS decline. Such spatial heterogeneity may provide for HIV refugia, areas where the virus can weather the epidemic's contraction, a troubling possibility with the accelerating microbicidal failures of combination therapies.

Key words: AIDS geography, HAART, community stress, HIV refugia

Introduction

New York City has been an epicenter for the human immunodeficiency virus (HIV) since the emergence of the virus in the West (Grmek 1990, Gould 1993). As of late 2000, 116,316 New York adult cases of acquired immune deficiency syndrome (AIDS) were diagnosed since 1980, about 17% of the U.S.'s total (Office of AIDS Surveillance 1999a, 1999b, 2000a).

From 1995 to 1997 New York City HIV/AIDS deaths declined by 63% (Chiasson et al. 1999). Annual AIDS incidence dropped from a high of 12,502 cases diagnosed in 1993 to 3886 cases in 1999 (Office of AIDS Surveillance 2000a). The number of pediatric AIDS cases and deaths also plummeted (Office of AIDS Surveillance 2000b). Incidences of opportunistic infections and HIV-associated malignancies similarly collapsed (Miller 1998, Sparano et al. 1999, Paul et al. 1999).

The contraction in New York's AIDS epidemic has been attributed to highly active antiretroviral therapies (HAART), introduced to the public in 1996 (Office of AIDS Surveillance 2000b, Wong et al. 2000). But no report has directly connected the geographic dynamics of New York's epidemic with access or adherence to HAART. The connection between New York AIDS declines and HAART availability has not been demonstrated at anything more than the clinic level or with small samples from city-level data. Sackoff et al. (2000) show HAART widely used in four New York HIV clinics across races, modes of infection, and CD4+ nadirs. Wong et al. (2000) show HAART prescriptions are associated with lesser mortality for 399 patients culled from citywide AIDS surveillance data.

A part of any small-area analysis of HAART use would involve addressing a second omission. Save periodic New York City Department of Health maps, a literature search found no work exploring the dynamics of the AIDS abatement within New York City. Fordyce et al. (1998) analyzed AIDS incidence in New York by zip code and income, but only through 1995, before the introduction of HAART.

This report attempts to address the second omission. *If* access to HAART has been virtually universal since its introduction, and *if* indeed HAART access is now a primary determinant of AIDS outcome in New York, then the rates of decrease among neighborhoods should approximate each other regardless of prevalent socioeconomic and public health characteristics. Whatever differences in rates of decline that exist under equal access to HAART may be due solely to a type of demographic floor effect in which areas with few AIDS cases to begin with undergo small declines. Because these areas have few initial cases their range of subsequent decline is severely truncated, particularly as the few cases that remain in any area are typically difficult to treat.

On the other hand, if declines in AIDS incidence are not at all similar among neighborhoods, HAART use may be heterogeneous. Residents of areas of lower socioeconomic rank often have lesser access to new treatments and/or suffer worse baseline health to start with (Link and Phelan 1996, Wilkinson 1996, Link et al. 1998). Moore et al. (1994), Solomon et al. (1998), Mocroft et al. (1999) and Sorvillo et al. (1999) have shown populations of intravenous drug users (IDUs) and blacks exhibited lesser use of protease inhibitor, reverse transcriptase and prophylaxis for opportunistic infections. Less access to or use of antiretrovirals may stem from several proximate causes. These include decisions made by clinicians, the lack of financial or social

resources necessary to obtain expensive drugs, or trouble in drug adherence due to drug side effects, unstable housing situations, chronic illness, mental illness, and/or weakened social networks (Mehta et al. 1997, Eldred et al. 1998, Wallace and Wallace 1998, Carr and Cooper 2000).

Phenomena other than HAART, including safe sex and other educational campaigns, may also help shape distributions of HIV/AIDS decline.

In this study I test the null hypothesis that declines in AIDS incidences across New York zip codes during the 1990s differed only by a floor effect.

Methods

Study area. Zip codes of Manhattan and the Bronx, two boroughs of New York City, comprised the study area (Figure 1). The US Census shows Manhattan with 1,487,536 persons in 1990, at the start of the study period. The Bronx had 1,203,789 persons. Both populations were near or above those of US cities like Indianapolis and San Antonio. Zip code populations 1990 used in this study range from 4958 to 107,197 persons, at an average of 45,789. Together the two boroughs totaled 64,039 accumulative AIDS cases or 55% of New York City's geographically identifiable cases as of first quarter 2000 (Office of AIDS Surveillance 2000a).

Figure 1b and c show greatly overlapping geographic distributions of race and class across the two boroughs. An apparent line runs through 96th Street in Manhattan separating populations of poor and minorities from affluent whites. Indeed, despite areas of interesting exception, New York City is one of the world's most residentially segregated cities.

AIDS data. Annual adult AIDS incidences per zip code for Manhattan and the Bronx for 1991-1998 were obtained from the Office of AIDS Surveillance (OAS), New York City Department of Health. These were collated by sex, race, age, and mode of infection. OAS collects these data from physicians, infection control practitioners, and other health care professionals in hospitals, clinics and private practices throughout New York City.

The total adult AIDS incidence for each zip code was determined by combining male and female incidences for each year and standardizing the total by 1990 zip code population.

A complication requires redress. OAS censors all data cells below five cases for use by outside investigators on the grounds of protecting patient confidentiality, a debatable justification (see Chapter 13 in Gould 1993). Data subjected to censorship include cells with zero cases. The data are not missing and we know their restricted range. Two possible solutions are to assign values by interpolating by regression on an independent variable of strong association or to assign values on the basis of the spatial distribution of uncensored data.

The first possibility is problematic because no single independent variable strongly regresses on AIDS incidence. The second is confounded by mode of transmission. The eight zip codes with censored data included in this study have their female incidences censored. These zip codes are situated in Lower Manhattan: Prince Street, Canal Street, Village, Grand Central, Midtown, FDR, Gracie, and Peck Slip (Figure 1). All, save Peck Slip, had substantially greater numbers of male incidence. Whether we assign more or fewer cases to the censored female cells may also depend on the prevalent mode of transmission in the zip code. For example, the first three zip codes listed above are

characterized by relatively large gay male populations. Do we assign fewer cases to these areas even with their large male incidences?

We avoid the problem altogether, as assigning any number proves satisfactory. First, larger male incidences, as in this case, minimize what effect the censorship of female incidence may have on measures of decline in total AIDS incidence. Second, to test for what, if any, bias is introduced by arbitrary assignments the analyses in this study were conducted with substitutions of 0 and 4, the extreme values of the censorship range. The general results, what we aim for here, proved little different in substance. In the interests of parsimony, a single number (3) was entered in all censored cells. Still, whatever method for assigning data used under the constraints imposed by the OAS exacerbates the small-numbers problem for some individual zip codes when changes in incidence are calculated, as done in this study.

Socioeconomic and health covariates. The socioeconomic and health covariates included in this study as independent variables were obtained from Infoshare, a computerized database developed and updated by Leonard Rodberg and John Seley of the Urban Studies Department at Queens College, CUNY (www.infoshare.org.). Infoshare aggregates federal, state, and city census and health data by various New York administrative districts including census tract, health area, zip code, and borough. All variables used here were collected for 1990 per zip code unless otherwise indicated.

The SES variables included the proportions of all individuals on Medicaid for 1991; of housing units that are governmentally subsidized (Section 8 rent-assisted or public housing); of adults with college degrees; of the total population black and white; and of

total households in each of four income classes for 1989 (<$10,000 [<$10K], $10-20,000, $20-35,000, and $35-50,000). Also used were unemployment rate, defined here as the proportion of all adults 18 years and older unemployed or not in the labor force; number of persons eligible for food stamps per 100,000 total population; and total immigration 1990-96 per 100,000 total population.

Markers of community stability and stress included in this study were mortalities due to tuberculosis, cirrhosis, drugs and homicide, as well as the decline in homicides, each variable 1990-1997 total per 100,000 population. Cirrhosis cases are markers for alcohol abuse (Kane 1981). Also used were percent change in total population 1980-1990; the proportion of households extremely overcrowded (1.5+ persons per room); and rent stress (the proportions of households of each of the four income classes listed above using 30%+ of their incomes to pay rent).

The public health indicators used included the decline in the numbers of new AIDS cases by mode of infection (men who have sex with men [MSM], intravenous drug use [IDU] and heterosexual transmission) (1993-1998), obtained from the Office of AIDS Surveillance. These mode data were not standardized by their population sizes because such populations are not known per zip code.

The decline in new sexually transmitted disease cases between average 1990-92 and 1994-96 per 100,000 adults was included in the analysis. STDs have been shown to be cofactors for HIV infection (Greenblatt et al. 1988, Latif et al. 1989, Schacker et al. 1998). STD incidence is an albeit problematic marker of HIV infection rates (Renton and Whitaker 1994, Grosskurth et al. 1995).

An additional variable included was the decline in the annual percent of newborns perinatally exposed to HIV (1989-1998). These data were obtained from New York State's Office of HIV Epidemiology. The newborn data for 1988-1996 were collected from the New York State Survey of Childbearing Women (Amy Storfer-Isser, State Department of Health, personal communication). Data for 1997 and 1998 were taken from the State's Comprehensive Newborn Screening Program.

Not all newborns with HIV antibodies are infected. All, however, have been perinatally exposed to the virus. The incidence of newborns exposed acts as a marker for HIV prevalence among mothers. Many of the mothers may have been infected years previous to giving birth, but because New York State did not maintain a registry of adult HIV infections during the 1990s these incidences of newborn exposure provide the best available citywide snapshots of prevailing HIV infection rates, albeit for a restricted population.

Analysis. Adult AIDS incidence per 100,000 population was mapped for Manhattan and Bronx zip codes using Atlas Graphics, a mapping application.

To test the null hypothesis that zip codes differed in AIDS decline only by a demographic floor effect, adult AIDS incidence for the epidemic's peak year (1993) was correlated against percent decline in incidence for 1993-1998. To explore what role, if any, race played in the declines, the percent decrease (1993-1998) for new black, white, and Latino AIDS cases were plotted against each other.

For both boroughs bivariate and stepwise multiple regressions were conducted for the declines in total AIDS incidence 1993-1998 and in average total AIDS incidence 1991-

1993 to 1996-1998. The average decline was included to better control for year-to-year stochasticity. The independent variables used in the regressions were the SES, public health and community stress indicators described above. The stepwise regression used was a maximum R^2 improvement procedure run in SAS (SAS Institute, 1999) that adds and subtracts independent variables in determining the best models (greatest R^2) of i variables. Declines in AIDS cases by race were not included in the stepwise regressions because these cases together comprise the dependent variable (decline in total cases). The bivariate regressions for race-specific case declines should be looked at with this caveat in mind. These race-specific bivariate regressions may still be informative. They show the relative contributions each population makes to the total decline in AIDS.

Results

AIDS geography. Figure 2 shows the geography of total annual adult AIDS incidence per 100,000 population for Manhattan and Bronx zip codes for 1991, 1993, 1995-1998.

The epidemic of new adult AIDS cases peaked in 1993 for Manhattan and the Bronx overall. More Manhattan zip codes than any year studied showed AIDS incidence of the top 1991 quintile, though this may be in part a function of the expansion of the AIDS definition in 1993 (Center for Disease Control and Prevention 1992). These top-quintile zip codes are situated across Lower Manhattan, characterized by large MSM populations, and in Harlem, with large poor, black and Latino populations (Figure 1). Much of the rest of 1993 Manhattan fits into the second highest incidence quintile. Exceptions include the Upper East Side, largely white and affluent, and Washington Heights, which has a large, relatively poor population of immigrants from the Dominican Republic.

In 1993, four proximal Bronx zip codes exhibited incidences of the top 1991 quintile (Figure 2). The Bronx epidemic orbited about this single epicenter, with its large poor and black and Latino populations. The geographic distribution of incidence appears more spatially gradated at the zip code level than in Manhattan, degrading from the epicenter.

By 1995 AIDS incidence had already begun to collapse in Manhattan on the Lower East Side and the Upper West Side. For 1996-98, the epidemic receded in Manhattan and the Bronx, leaving geographic pools of AIDS incidence in East Harlem, Times Square and South-Central Bronx.

Declines from peak year. Figure 3 shows the percent decline in total adult AIDS incidence per 100,000 zip code population between 1993 and 1998 against the total peak year 1993 adult AIDS incidence per 100,000. Manhattan zip codes display no relationship between peak year 1993 incidence and subsequent decline in incidence. From 1993 to 1998, 33 of 36 Manhattan zip codes, regardless of their peak-year incidence, show declines of 50% or more. About a third of Manhattan zip codes had declines of over 80%. Most Manhattan zip codes showed declines of 45-90%.

The Bronx, with a lesser range of peak-year incidence, also showed no clear relationship between 1993 zip code incidence and subsequent decline. Over the range of peak incidence the Bronx shares with Manhattan most Bronx zip codes underwent declines of some 20% less than Manhattan zip codes. Only half of Bronx zip codes underwent declines of over 50% and none over 80%. Bronx declines typically ranged 25-60%.

Figure 4 shows the geographic distribution of the declines in AIDS incidence between 1993 and 1998. Zip codes of Lower Manhattan and the West Side showed the greatest declines for both boroughs. The Upper East Side, with lesser peak incidences, still showed declines greater than those of Harlem zip codes. Only one Bronx zip code's decline approached those of Manhattan (Westchester, 75.75%). The zip codes of South-Central Bronx underwent lesser declines than Harlem, despite similar census and socioeconomic characteristics, including income and racial distributions.

AIDS and race. Minorities now bear the brunt of New York's AIDS epidemic. The AIDS epidemic for blacks in New York City was greatest in 1993, as for total cases, although 1991 shows the single greatest incidence at 3020 per 100,000 blacks (data not shown). The greatest incidences were concentrated in Lower Manhattan and up the West Side. The next highest quintile, throughout Manhattan and into the South and East Bronx, contains zip codes with per-100,000 incidence greater than the highest quintile for the population as a whole. In contrast, zip codes with relatively large black populations in the northeast and southeast Bronx had low black AIDS incidences.

By 1997, the epidemic for blacks had declined. However, several zip codes, particularly Times Square, hosted per-100,000 black incidences in 1998 near or above peak-year incidences for the total population. Westchester in the Bronx displayed a particularly sharp divide in AIDS incidence in the 1990s. While Westchester's total per-100,000 incidence never exceeded 72.27, black incidences ranged from 169.97 to 453.25.

Figure 5 shows serial contrasts between declines in black, white and Latino adult AIDS incidence 1993-1998 per Manhattan and Bronx zip code. Zip codes with no

declines for any one race typically had small populations of that race in the first place. Both black and white zip code populations tended to have greater declines in Manhattan than the Bronx (Figure 5a). The bulk of zip codes had greater declines in white AIDS incidence than black (see annotated zip codes for some especially egregious disparities).

Latino zip code populations also tended to have greater declines in Manhattan than in the Bronx (Figure 5b). Latino populations, like white populations, tended to have greater declines than black populations, though there were exceptions, including Hamilton Grange in Manhattan and Parkchester in the Bronx. The Latino populations of Times Square and Throgs Neck, like their white counterparts, exhibited similar disparities with black declines (Figure 5a).

White zip code populations tended to have greater declines than Latino populations (Figure 5c), also with exceptions, including Triborough and Williamsbridge. White AIDS declined much more than both black and Latino AIDS in Fordham and Morrisania in the Bronx.

AIDS, SES, and community stress. Table 1 shows bivariate regressions with r^2's greater than .30 for SES/community stress variables on the average decline in AIDS incidence. The bivariate contrasts are for the most part weak, as is the case with many ecological systems of strongly interacting variables.

The Manhattan SES/stress variables with the strongest positive relationships with AIDS decline included decline in white AIDS cases, two rent-stress classes ($20-35K and $35-50K, Figure 6a), and college education. The proportions of persons on Medicaid and adults unemployed had the strongest negative relationships with AIDS decline. The

proportions of the total population black and white had similar coefficients with AIDS declines, but with contrary signs. Homicide and change in homicide are markers of community stress.

For the Bronx, income class $35-50K and the proportion of the population that is white were positively associated with AIDS decline. All other variables with r^2s greater than .30 were negatively associated. Three of these were proximately related to housing and community stress (population change, overcrowding, and rent stress <$10K). Three others, including unemployment, were income-related.

Given how well income regressed with Bronx AIDS declines, does income have anything to do with how the AIDS epidemic peaked in the first place? In other words, does income shape the trajectory of AIDS incidence whether or not the epidemic expands or contracts? Bivariate regressions of the four income classes and peak year 1993 total AIDS incidence per 100,000 population for the Bronx showed <$10K, $10-20K, and $35-50K with strong relationships (Figure 6b). Manhattan showed no such relationships between income and peak-year incidence.

The maximum-R^2 stepwise regressions of SES and community stress indicators show the decline in the Bronx's ecology better defined by a multitude of interacting variables (Figure 7, see especially 7b), a result shown elsewhere (Wallace and Wallace 2000, Wallace 2002). With each additional variable included, the R^2s of Manhattan's models increase at a lesser slope.

As with the bivariate regressions, the stepwise regressions exhibited stronger relationships with the average AIDS declines than with the 1993-98 declines. What number-variable model for the average decline best explains AIDS decline for the two

boroughs? The more variables we include, the less parsimonious the model. On the other hand, ecosystems need not be parsimonious and are often marked by complex synergies. The rule of thumb adopted here is to choose the model for which the latest added variable greatly increases the R^2 for either borough's model. Because of the great increase in R^2 (.88) for the Bronx, the nine-variable models for both boroughs' average decline were chosen for further analysis (Figure 7).

The contractions in the Manhattan and Bronx AIDS epidemics were associated with somewhat similar factors (Table 2). Both boroughs' declines were in part defined by housing availability, income, peak-year incidence, and their interactions. Bronx declines were also related to two markers of social instability: cirrhosis and drug deaths, the latter also a marker of the IDU mode of transmission.

Discussion

What caused the decline in New York AIDS? McKinley and McKinley (1977) and McKeown (1979) showed the declines in infectious diseases that marked the first half of the 20th century in industrial countries were brought about primarily by public health interventions and improvements in personal health, and less so by medical advances. Can the same be said for the decline in AIDS that largely marked New York City's epidemic during the late 1990s? The question is problematic because AIDS is the end result of years-long infection by a pathogen, HIV. The population dynamics of pathogenic cause and effect can be disconnected. AIDS cases can decline even as the HIV epidemic continues unabated. It cannot be determined from the data presented in this paper whether the decline in AIDS in New York was brought about by a decline in HIV incidence, the

emergence of HAART (which suspends the HIV infection in its asymptomatic stages), or by some combination of the two.

The great declines in AIDS incidence registered in 1997 and 1998 after the introduction of HAART across Manhattan and Bronx zip codes (Figure 2) lend considerable support to the claim HAART had a prominent role in New York's AIDS abatement (Chiasson et al. 1999, Sackoff et al. 2000, Wong et al. 2000). But declarations about HAART's relationship with New York's declines rely on currently untested assumptions. Such declarations may be examples of the inverse of the ecological fallacy, what might be termed the clinical fallacy. That access to HAART can be shown at the individual and clinical levels does not necessarily mean such access exists across geographic areas.

A geography of HAART prescription would do much to tease apart the possible causes for the decline in New York AIDS. Prescription data are collected both by state AIDS Drug Assistance Programs (Doyle et al. 1999) and the federal Healthcare Finance Administration. The data, sectioned by small area, can tell us what proportions of patients have been prescribed 0-3+ antiretrovirals. Although New York State's data do not address adherence (Lanny Cross, New York HIV Uninsured Care Programs, personal communication), they would be, if made available, a good first step in testing hypotheses about drug access and regional disease prevalence. Perhaps the expected would emerge: New York City neighborhoods with greater HAART access had greater declines in AIDS incidence. But in all likelihood some areas with great HAART access will show low AIDS decline and vice versa. The causes for such unexpected results would be of considerable interest.

So what, then, have we shown? The data presented here indicate that the decline in AIDS incidence was not homogenous. Differences in decline between boroughs and among zip codes are apparent even as the epidemic's abatement was widespread (Figures 2-4). Nor were declines correlated solely with peak incidence as one might expect if zip codes differed only by a demographic floor effect as hypothesized by the null.

A geography of the decline in AIDS incidence indicates additional effects for which HAART alone is unlikely to account. For both Manhattan and the Bronx the AIDS epidemic began to ebb in 1994, before HAART was introduced (see 1995 in Figure 2). Law et al. (2000) show a similar collapse in Australian AIDS incidences, starting in 1995, not the second half of 1996, when HAART became available enough to begin to reduce population-level incidence. Law et al. conclude that although HAART is the primary reason for the recent rapid decline in new Australian cases, a plateau in new cases in 1994 and 1995 may have resulted from a decline in HIV incidence since the late 1980s.

The latter possibility may explain parts of New York's AIDS ecology. In 1989, perinatal exposures to HIV (a possible marker of heterosexual transmission rates) began to decline in Lower Manhattan (data not shown). By 1998, a standard incubation period, those zip codes had much lower adult AIDS incidences, save Times Square (Figure 2, Table 2).

Declines in HIV incidence can also arise from intrinsic demographic processes. If the pool of susceptibles available for infection decreases below a threshold community size at the peak of the HIV epidemic's cycle, the rate of infection may decrease regardless of whatever prevention programs may be in place (Koopman et al. 1997, Levin et al. 2001).

When the pool of susceptibles refills with younger cohorts, the epidemic can again lurch forward. Such age-structured negative density-dependent feedback is a staple of the population biology literature (e.g., Tilman and Kareiva 1997, Keeling and Grenfell 1997, Lundberg et al. 2000).

In sum, the declines in new AIDS cases in New York were likely caused by a complex combination of HAART use, education campaigns, and demographic effects. These proximate causes have geographic distributions (Figures 2, 4, 5) intimately related to the city's socioeconomic structure (Tables 1, 2 and Figure 6). The latter structure helps generate the geographic aggregates of behaviors that promote or impede AIDS incidence. Possible mechanisms for such aggregates are explored below.

Declines and race. AIDS declines differed within New York zip codes (Figure 5). In many zip codes, black, white and Latino declines differed greatly. White populations tended to have greater declines in AIDS incidences than Latino populations, which in turn had greater declines than black populations, with interesting exceptions.

Racial differences in HAART use have been documented. A survey of 700 AIDS patients conducted by the Columbia University School of Public Health in 1997 for New York City's HIV Health and Human Services Planning Council found 33% of white patients and 19 and 12% of Latino and black patients using HAART (Richardson 1997). Sorvillo et al. (1999) found for Los Angeles County that through a twelve-month period in 1996 and 1997, treatments that included the new protease inhibitor were prescribed more to whites and US-born Latinos than for blacks and foreign-born Latinos.

Fordyce et al. (1995) showed changes in increases in New York AIDS incidence in the early 1990s were infection mode-, age-, race- and gender-specific. Between 1989 and 1992, only white MSM born before 1960 and minority MSM born before 1940 showed declines in AIDS incidence. We should therefore not be surprised that population-specific differences in the epidemic remain, as such differences precluded HAART. Indeed, the recent contraction in New York's epidemic widened disparities.

A nest of cofactors. Race was not the only dynamic. An array of socioeconomic, health and community stress factors at the zip code level acted in combination on New York AIDS incidence.

Declines in MSM-contracted AIDS cases were the only mode-specific declines with bivariate regressions of any impact (r^2 = .22). White AIDS declines most strongly regressed with average total AIDS declines in Manhattan (Table 1). White MSMs were the first New York population affected by and the first to respond socially to the HIV epidemic. The white gay community had already been politically organizing against discrimination for over a decade (Cohen and Elder 1989). They are a comparatively affluent community (e.g., Phua and Kaufman 1999), which may in part account for income class $35-50K's place in the Manhattan stepwise model (Table 2). Fordyce et al. (1998) found more than half of cumulative white MSM AIDS cases through 1995 resided in zip codes of high median household income ($42,235 to $63,431).

Affluence permits a community faster and greater response to common crises because it is 1) associated with greater education and disposable income, 2) buys greater—if incomplete—protection from social marginalization, and 3) generates the neighborhood-

level stability requisite for social responses to communal crises (Wilkinson 1996). Comparative wealth also permits access to better-trained doctors better able to prescribe cutting-edge prophylaxis, even as government programs like CARE and AIDS Drug Assistance subsidize the cost of the drugs for poorer patients (Sorvillo et al. 1999). Indeed, federally funded Medicaid coverage was negatively associated with AIDS decline (Tables 1 and 2), indicating little impact on the epidemic at the zip code level.

In contrast, communities subjected to the physical and social destruction that arises from public policies such as benign neglect and the Rust Belt effect of factory flight suffer a disintegration of social networks and community institutions necessary for responding to epidemics, particularly for a behaviorally transmitted pathogen like HIV (Wallace 1990, Wallace and Fullilove 1991, Wilson 1996, Wallace et al. 1999). New York City's planned shrinkage policy of cutting city services such as firefighting and sanitation in minority neighborhoods led to the destruction of the community institutions (churches, block associations, supervised youth groups) needed to block the behaviors that spread HIV (Wallace and Wallace 1998). In the institutions' stead developed previously marginalized organizations (drug and youth gangs, prostitution rings) that promote unsafe behaviors. As a result, neighborhood-wide and cross-generation social support networks were truncated and HAART and other interventions to the HIV epidemic only weakly disseminated through sociogeographic space.

Extreme housing overcrowding, often a marker of grave social disruption, regressed with the average decline in AIDS (Tables 1 and 2). The Bronx in particular suffered massive housing destruction from planned shrinkage, in some areas losing as much as 80% of available housing. Overcrowding has since been compounded by a deficit in new

affordable housing (Willen 2000, Padgett 2001). Rent stress is another marker of housing famine and had comparatively strong bivariate and/or stepwise regressions with total declines in Manhattan AIDS (Tables 1 and 2). Surprisingly, many of these were positive associations. Zip codes with greater proportions of households paying 30%+ of their incomes to rent tended to have greater declines in AIDS incidence (for example, Figure 6a).

The latter result may seem peculiar as one might expect lesser declines in AIDS with more rent stress: less money is available to the individual households to pay for treatment. On the other hand, New York neighborhoods considered desirable have high rents, an outgrowth of a long-manipulated housing market (Blackmar 1995). Residents may be willing to pay more to live in safer, stable neighborhoods, even if risking more of their incomes. The residents may be willing to trade the stresses of high-homicide or drug-deluged neighborhoods for the personal stresses of a rent crunch.

Another possible explanation for such counterintuitive results is that populations and their conditions change from census to census over space and time. AIDS incidence represents the compounded, time-lagged ratio of several variables, including HIV infection rates and population size (Wallace 1990). New York City changed during the 1990s. Declines in the crack trade, violent crime and unemployment, while spatially heterogeneous, may have promoted the rebuilding of severed social networks and community institutions demolished in the planned shrinkage fire burnouts (even as such policies remain in effect). New social networks, in turn, spur and reflect a restructuring of the "choice matrix" individuals walk around with in their heads (Wallace et al. 1996). Even if some population-level variables have changed little, residents' expectations about

where they live and what their options are may have changed. Sex and drug behaviors that drive HIV susceptibility may shift accordingly.

How the Bronx compares. Despite similarities, the Bronx AIDS epidemic is more clearly black, Latino, and heterosexual in character than the Manhattan epidemic. Income seems to be driving the Bronx's epidemic in a different way as well. While in Manhattan relatively affluent communities of MSM were first struck with the epidemic, wealth "shielded" affluent zip codes in the Bronx (Figure 6b). A greater range of income classes contributed to explanations of the Bronx's total AIDS decline. The greatest bivariate regressions included negative associations with income classes <$10K and $10-20K, and a positive relationship with income class $35-50K. Income classes <$10K and $20-35K contributed to a stepwise regression for declines in AIDS incidence 1993-1998 (data not shown). In short, at the zip code level, the less affluent in the Bronx appear to have less access or adherence to HAART, if HAART is indeed driving AIDS dynamics at the small-areas level.

How, then, does Harlem in Manhattan and the South Bronx, differing little in their SES parameters and prevalent modes of infection, so differ in AIDS decline? One explanation involves differences in what Wallace and Wallace (2000) define as the areas' "ecological resilience." Resilient ecosystems—not to be confused with ergodic ecosystems—better absorb the effects of external perturbations (Holling 1973, Ives 1995). Such communities exhibit few outward signals they have been affected by population-level impacts or crises.

Wallace and Wallace (2000) analyzed how numerous health and SES factors correlated with homicide rates and low birth weights for 27 health areas in Upper Manhattan and 34 areas in the southwest Bronx. Despite hosting similar distributions in low-birth weights, youth mortality rates, housing overcrowding rates, and education and welfare assistance levels, the southwest Bronx displayed much looser associations among its economic, demographic, social and health variables than Upper Manhattan. In other words, changes in one variable in the Bronx do not amplify through other variables the way they do in Upper Manhattan. An upswing in Upper Manhattan's drug trade, for example, broadcasts throughout the entire social-health milieu. Upper Manhattan is less resilient to perturbations.

Wallace and Wallace hypothesize the differences in ecological resilience between the two areas may be due in part to path dependence. The boroughs differ in their recent social, economic and political histories, including the effects of planned shrinkage. Such histories shape how resident interpersonal ties and community structures evolve, interconnect, and respond in crises. The boroughs may differ in how crises, and perhaps interventions such as HAART (Figures 2-4), are amplified, even when health and SES variables appear superficially similar. Indeed, the very sociogeographic mechanisms that permitted greater HIV propagation in Manhattan than the Bronx may also be responsible for greater HAART use in Manhattan as well (Wallace 1991, Wallace et al. 1996).

HIV refugia. Time-series analyses of citywide incidence alone, even of specified populations (e.g., race, mode of infection), miss areas of apparent AIDS endemicity in Harlem and the South Bronx, and within zip codes. At the zip code level, hot spots of

infection and disease burned off and on during the 1990s, even as the AIDS conflagration retreated across the city.

If we accept that HAART has had a major impact on the U.S. epidemic (Center for Disease Control and Prevention, 1997), a reasonable but yet unmeasured supposition *at the small-area level*, HIV refugia, at both the among- and within-area scales, are dangerous. These refugia are potential sources for new outbreaks of HIV/AIDS, affecting the greater metropolitan region (Wallace and Wallace 1993). Indeed, New York City hosted an increase in AIDS incidence of 65%, from the end of 2000 to the end of 2001, an outbreak apparent throughout mid-Atlantic U.S. states (Center for Disease Control and Prevention, 2001). A follow-up study is needed to determine in what New York neighborhoods the AIDS rebound is located.

Such outbreaks may now be multiple-drug resistant (MDR). Nearly 80% of those infected with HIV carry quasispecies with mutations resistant to at least one antiretroviral (Susman 2002). The portion of new Western HIV infections that are MDR has reached 10%, but may be as much as 50% (Schmit et al. 1998, Dietrich et al. 1999, Loveday et al. 1999, Salomon et al. 2000, Susman 2002). Incomplete courses of HAART, another possible explanation for lesser AIDS declines in politically targeted refugia, can more sharply select for MDR-HIV. Areas with substantial HAART use and attendant lapses in safe behavioral practices can also act as sources of MDR-HIV.

In short, HAART appears a provisional public health intervention. The population-level gains that may have been won by the combination therapies seem reversible if HIV, a veritable evolution machine of a virus, is given the epidemiological room to develop its cures to HAART.

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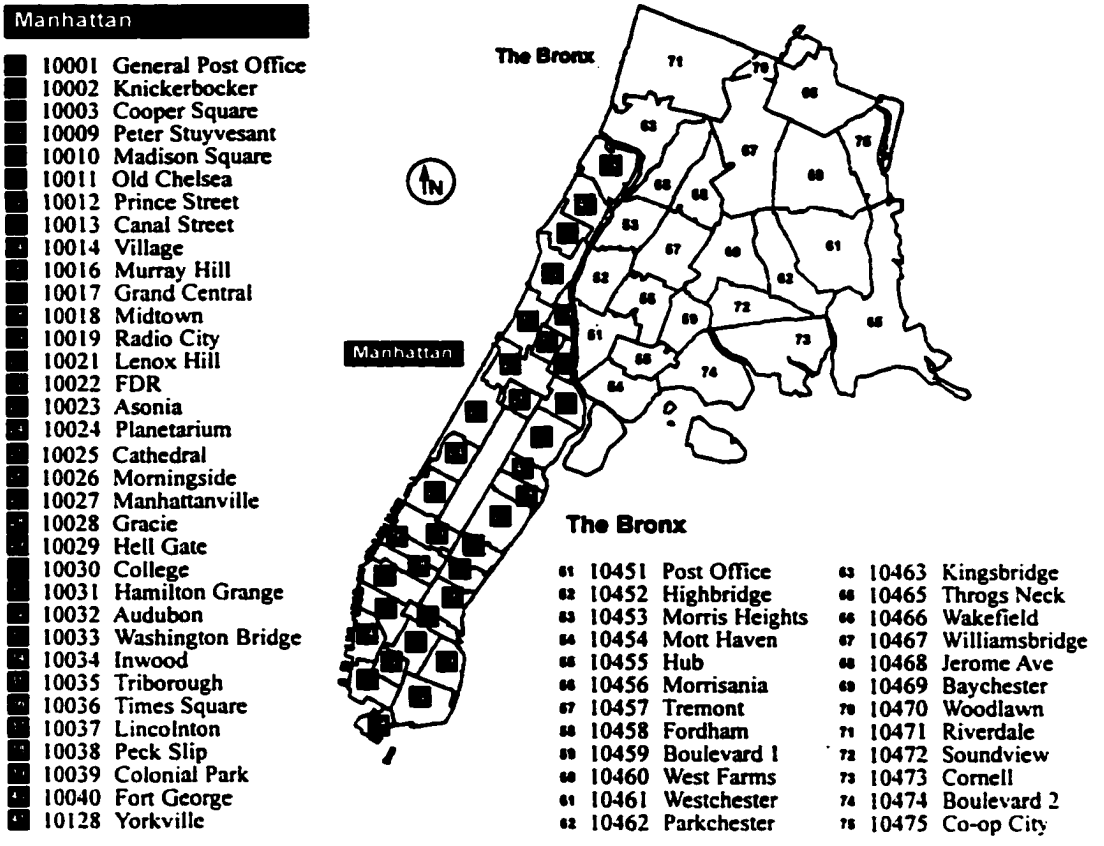


a

Figure 1. a) Manhattan and Bronx zip codes and their names. Zip codes assigned to single buildings or in areas with comparatively few residents and/or overly censored AIDS data (see text) are omitted. b) Proportion of households with annual incomes less than $10,000 per 1989 Manhattan and Bronx zip code. c) Proportion of total population black per 1990 Manhattan and Bronx zip code.

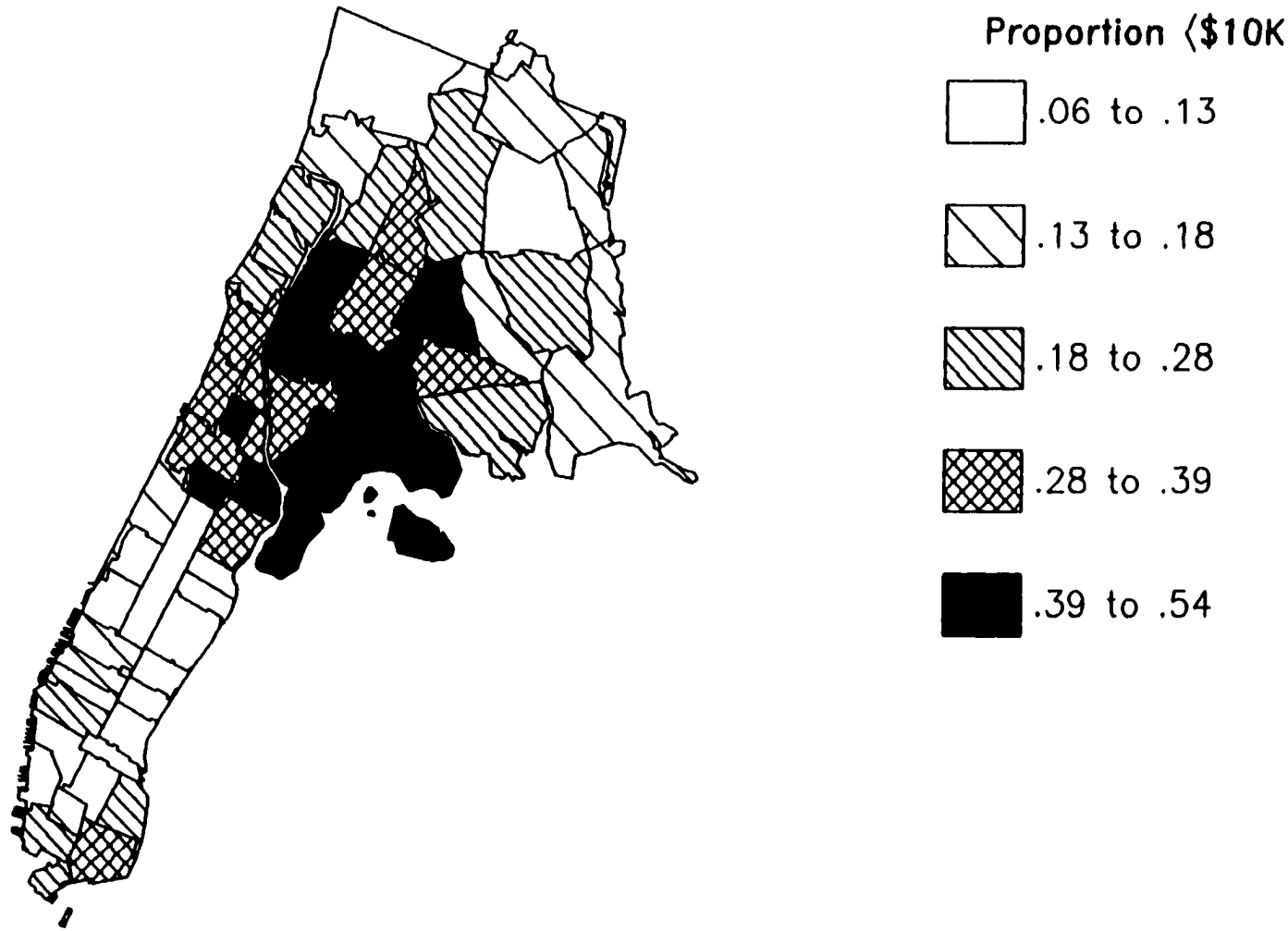


Figure 1 (continued). b) Proportion of households with annual incomes less than $10,000 per 1989 Manhattan and Bronx zip code.

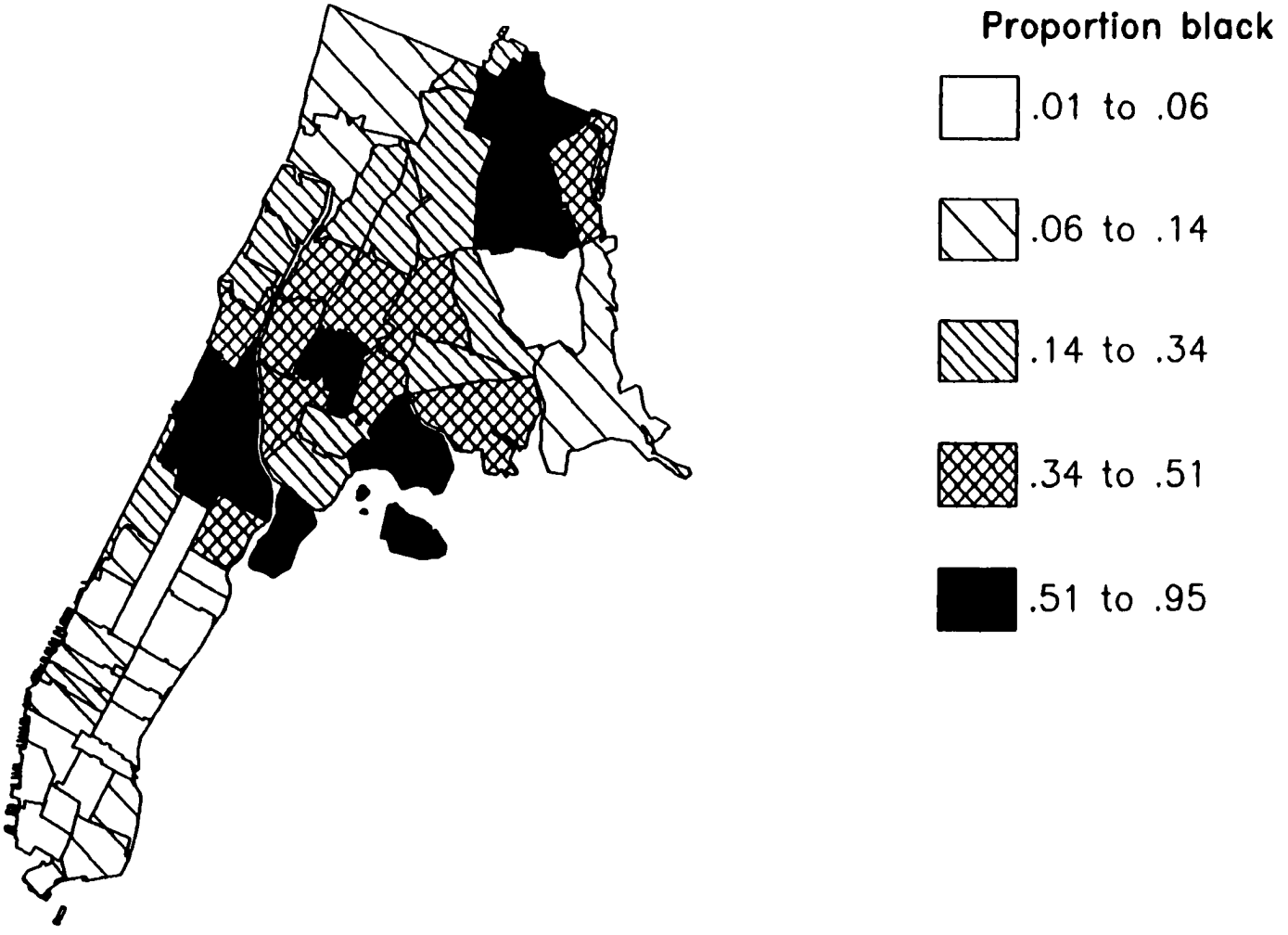


Figure 1 (continued). c) Proportion of total population black per 1990 Manhattan and Bronx zip code.

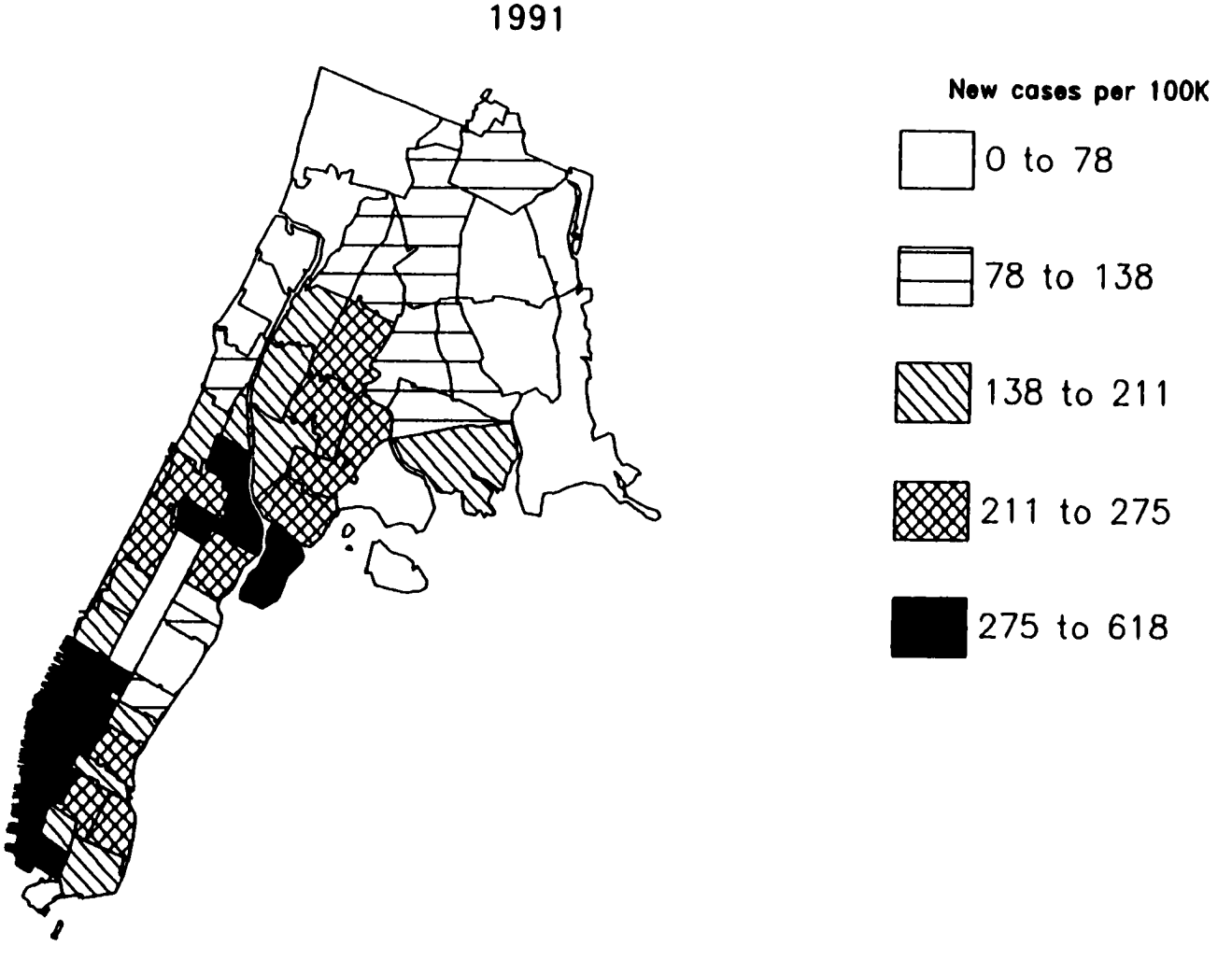
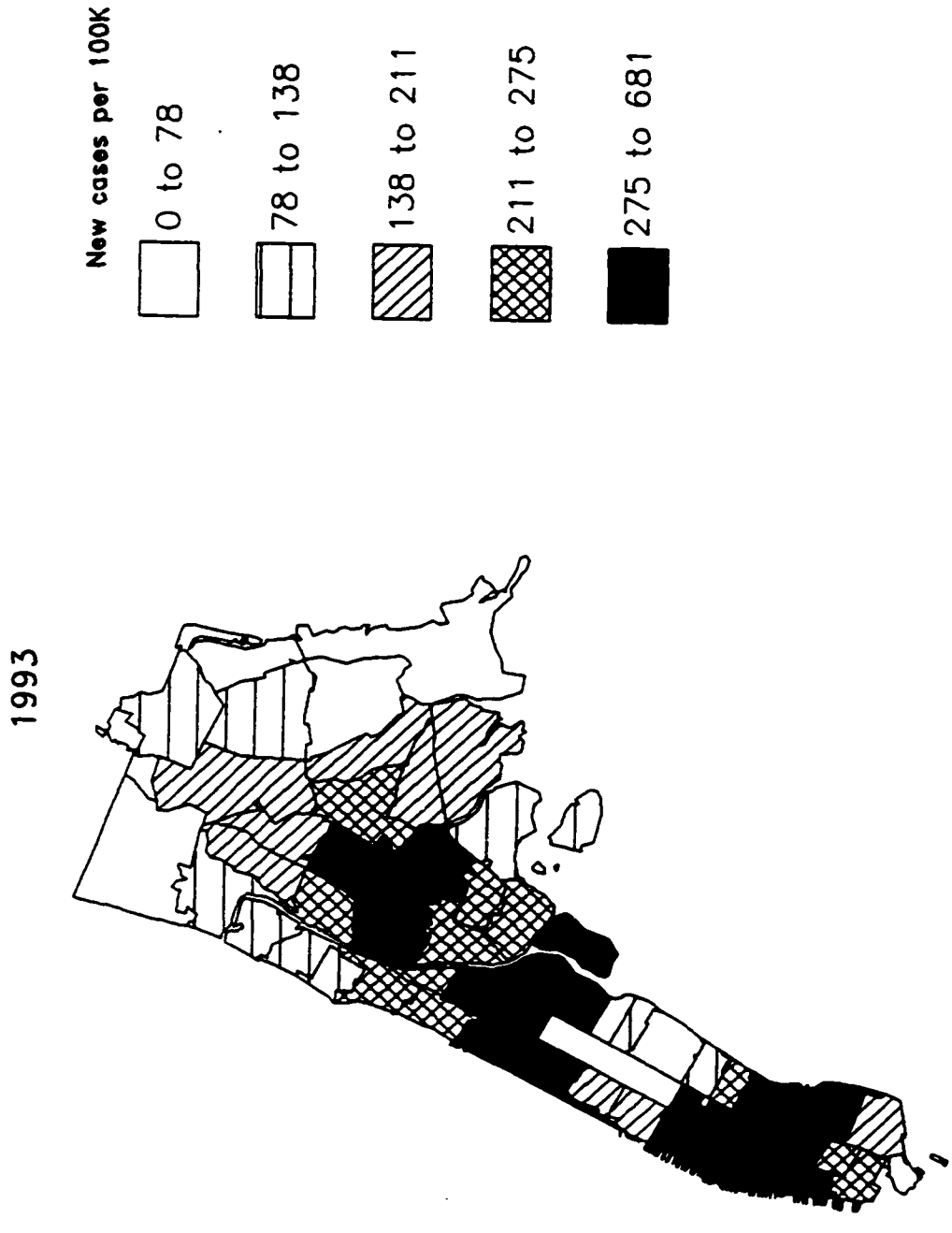


Figure 2. Adult AIDS incidences per 100,000 total population for 1991, 1993, 1995-1998 by Manhattan and Bronx zip codes. The data ranges for all years are defined by 1991 quintiles. Only the top quintile's range changes, depending on the greatest incidence per 100,000 for that year.



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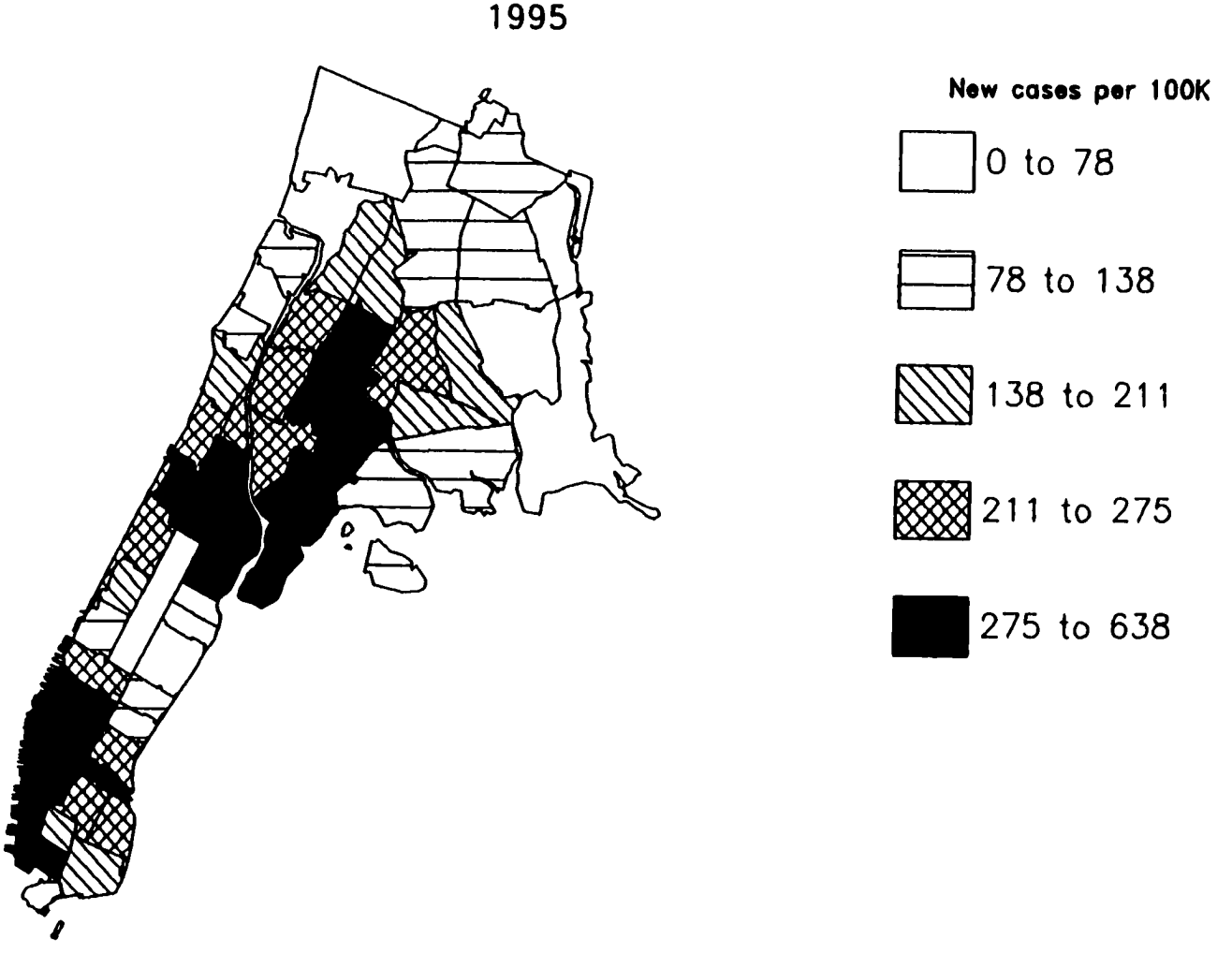

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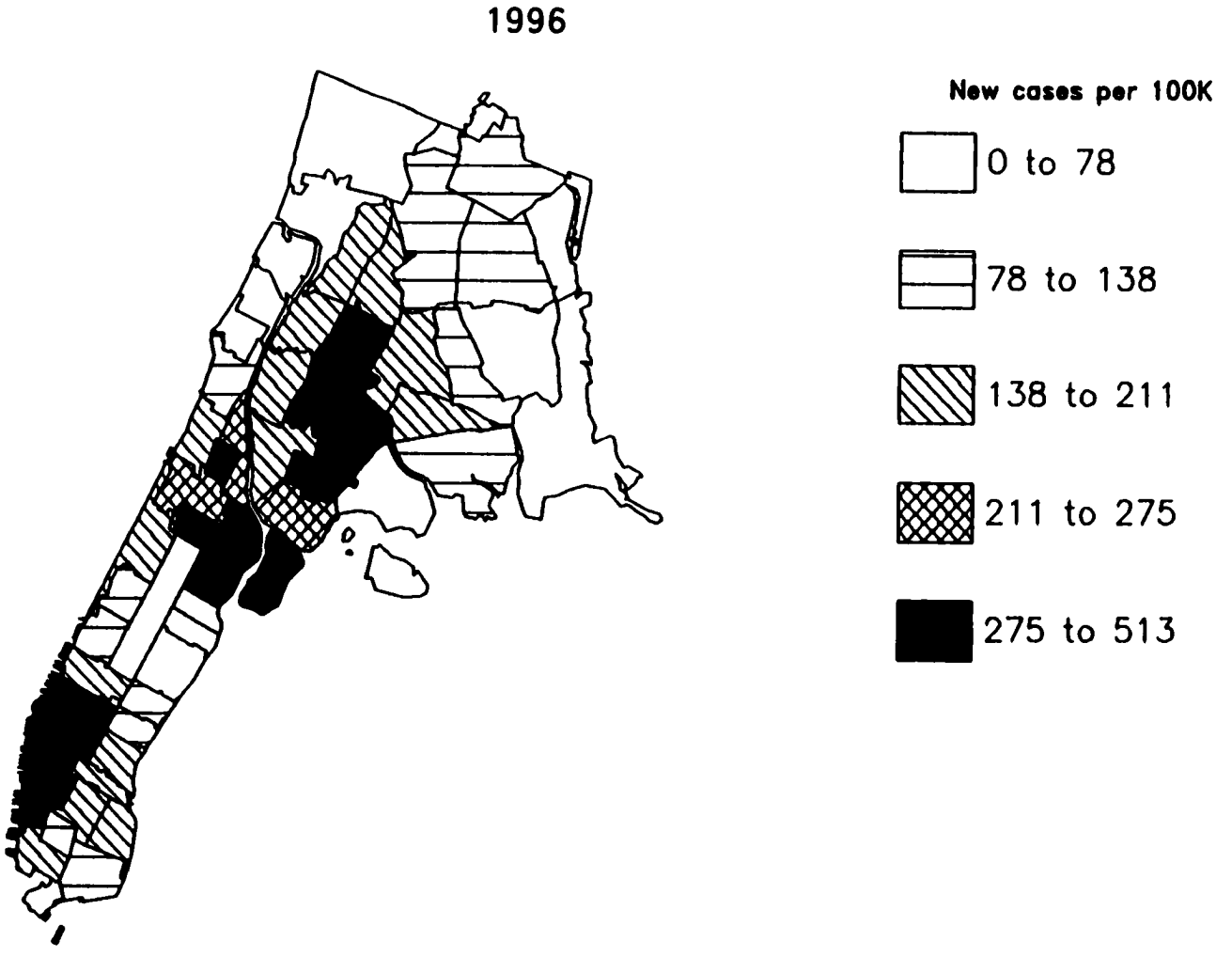

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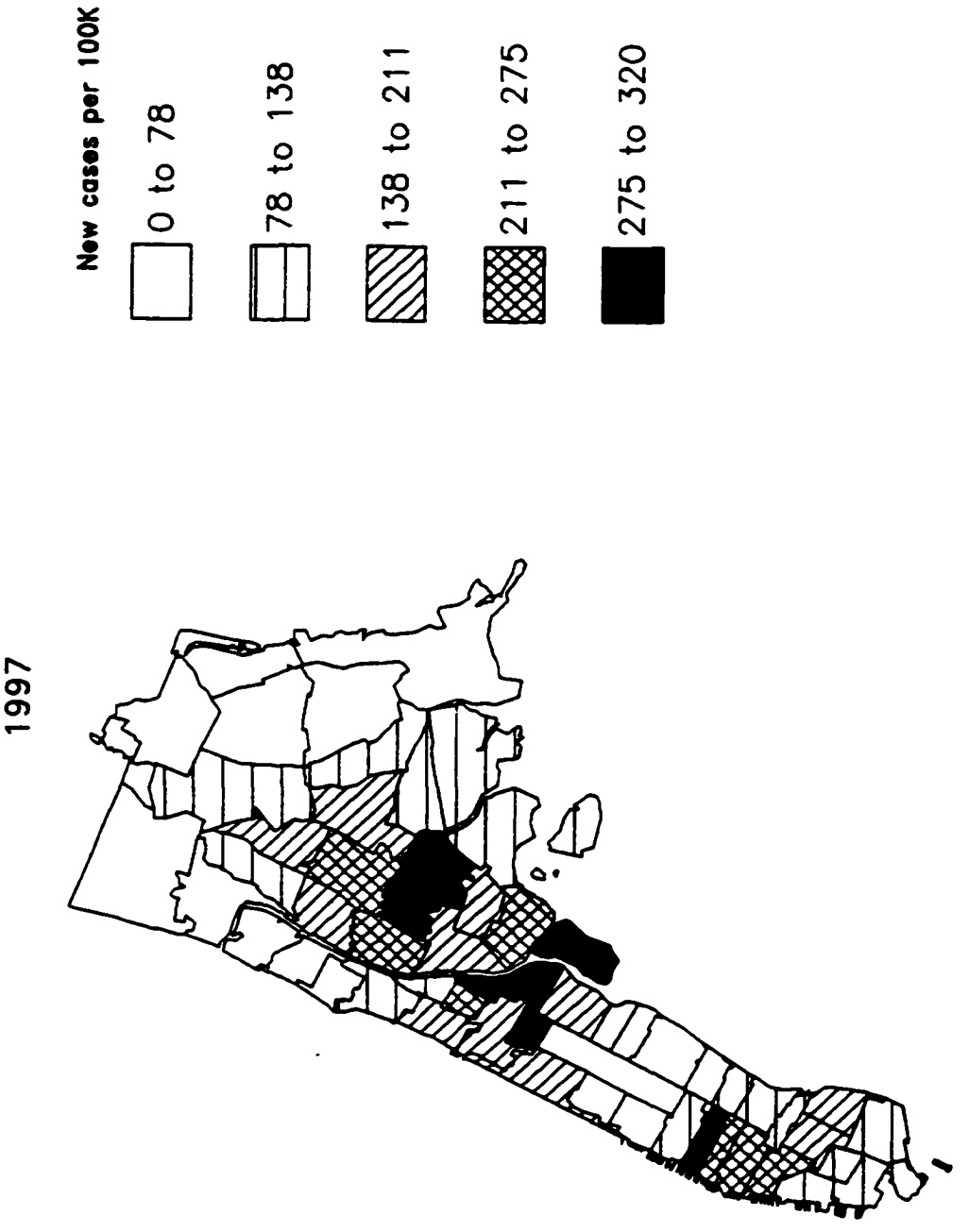

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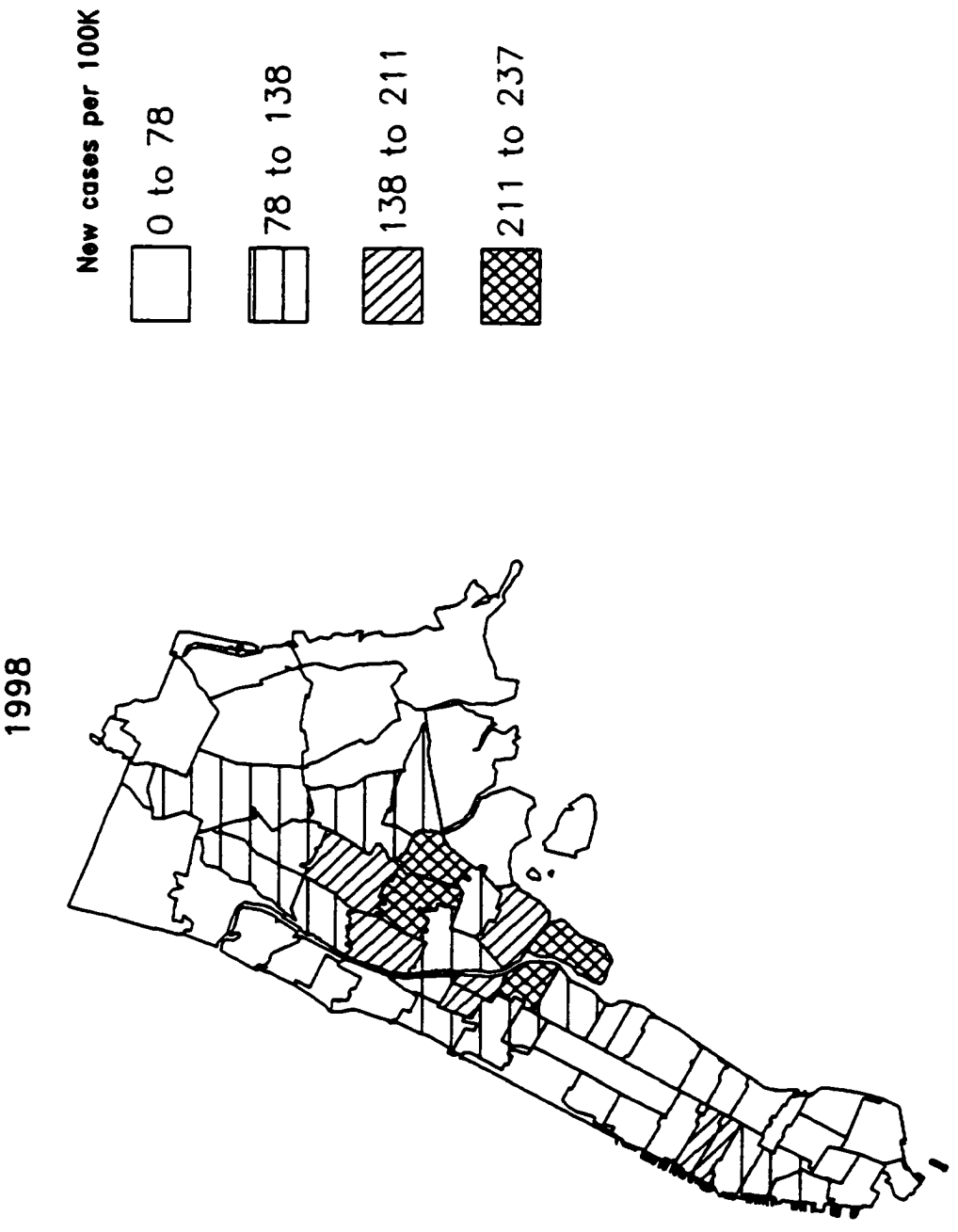

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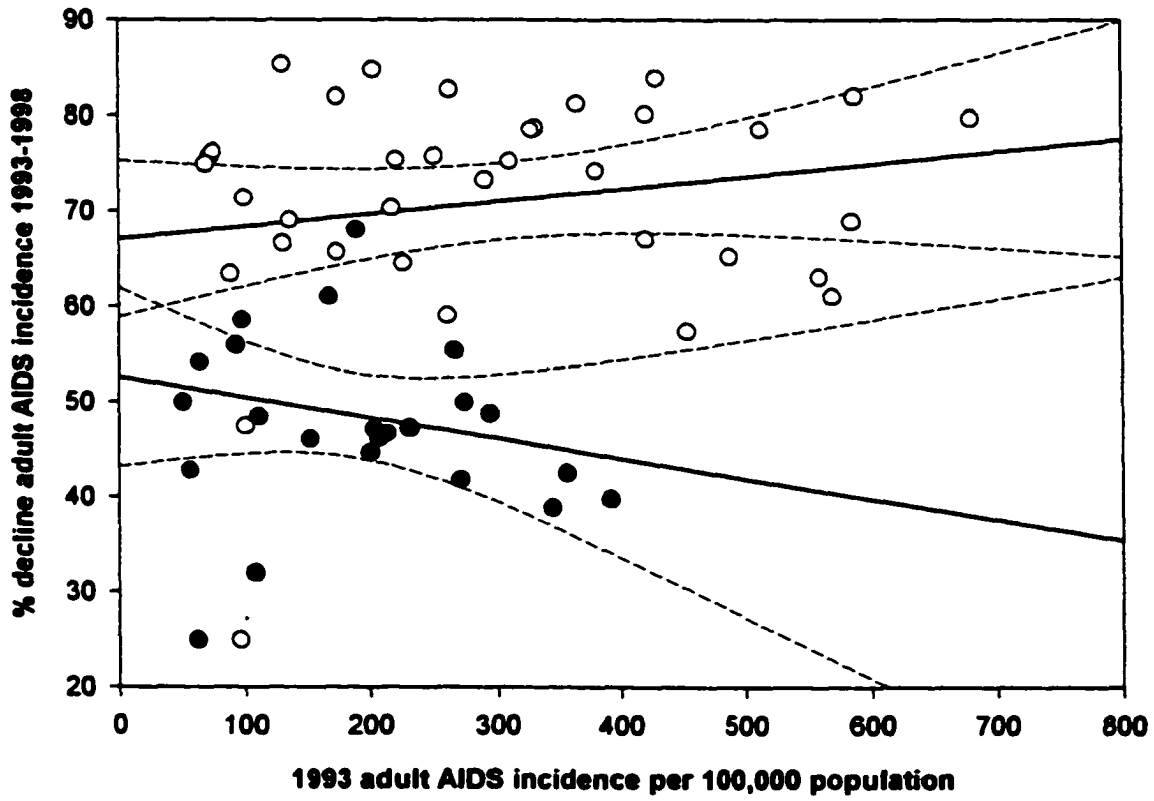


Figure 3. Percent decline in adult AIDS incidence per 100,000 population from 1993 to 1998 and peak year1993 adult AIDS incidence per 100,000 for Manhattan and Bronx zip codes. r^2 Manhattan =.036, r^2 Bronx = .041.

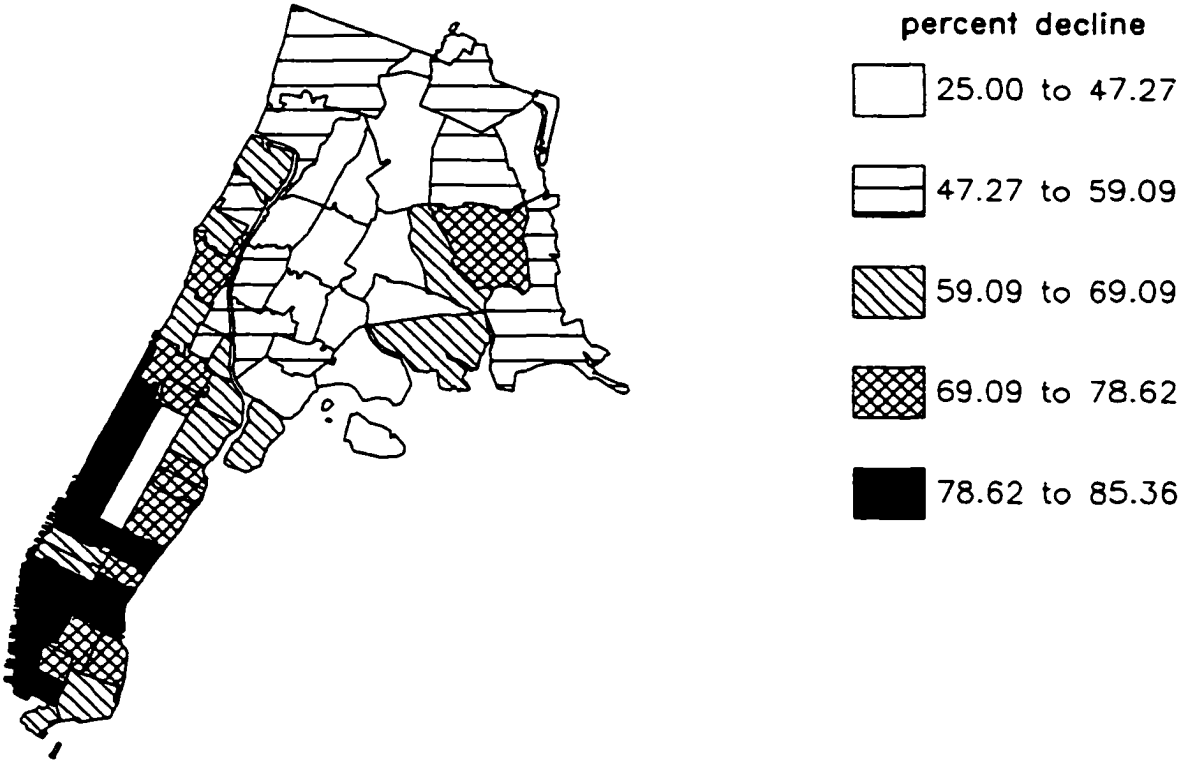
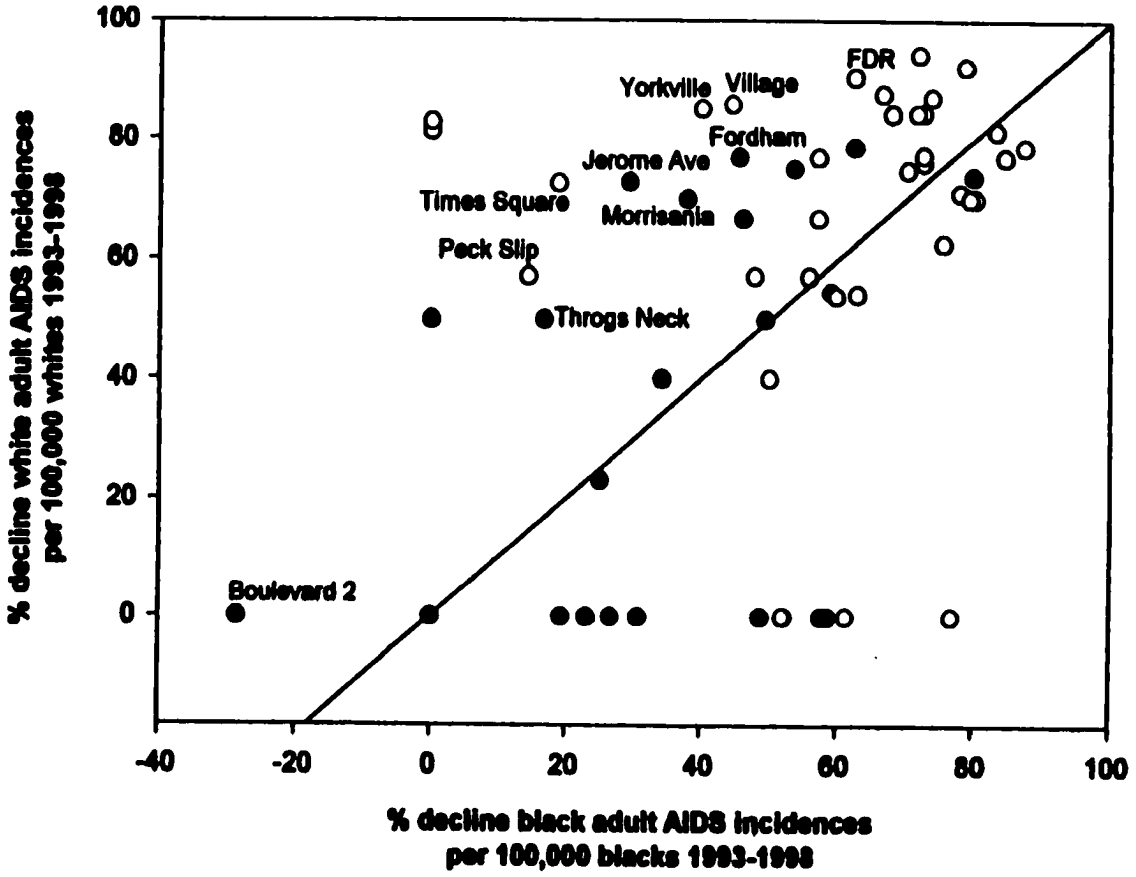
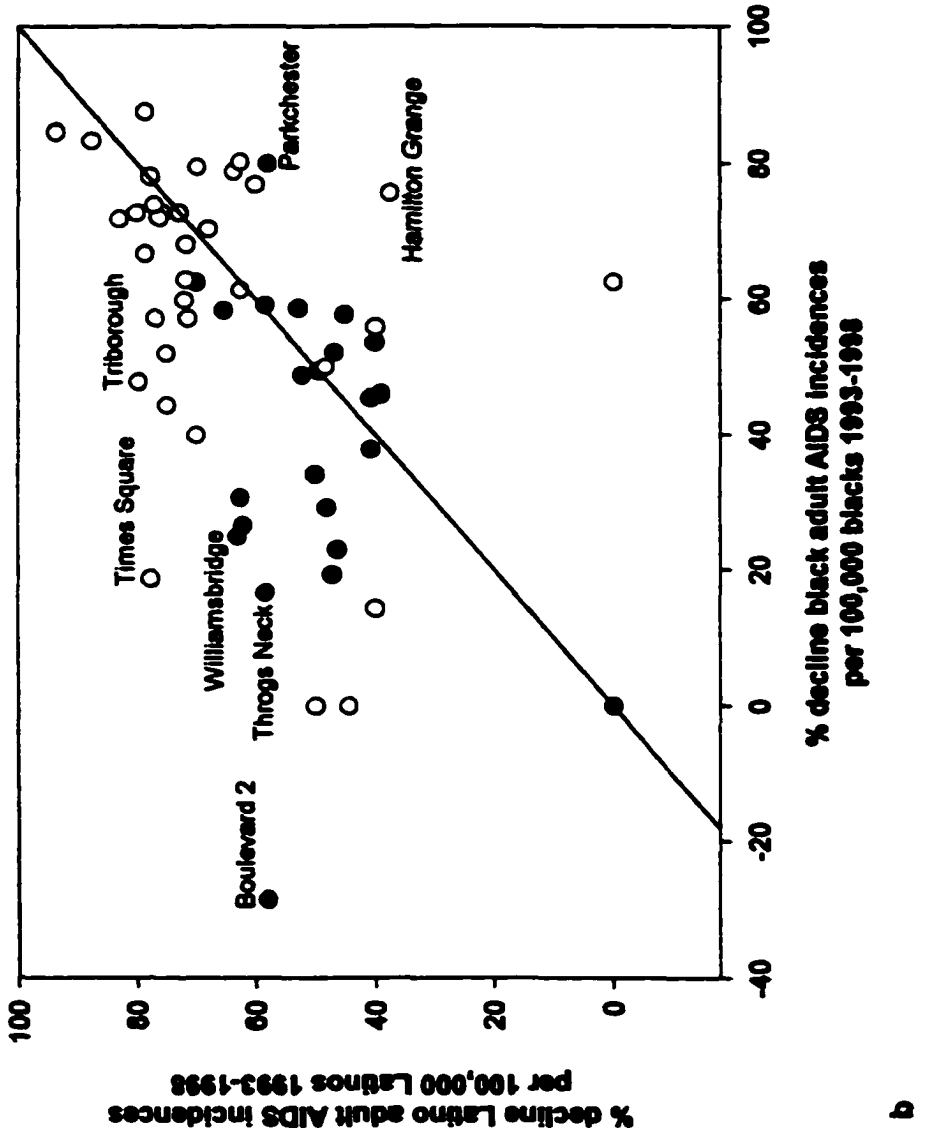


Figure 4. Decline in AIDS by Manhattan and Bronx zip code. Percent decline in total adult AIDS incidences per 100,000 population from peak year 1993 to 1998



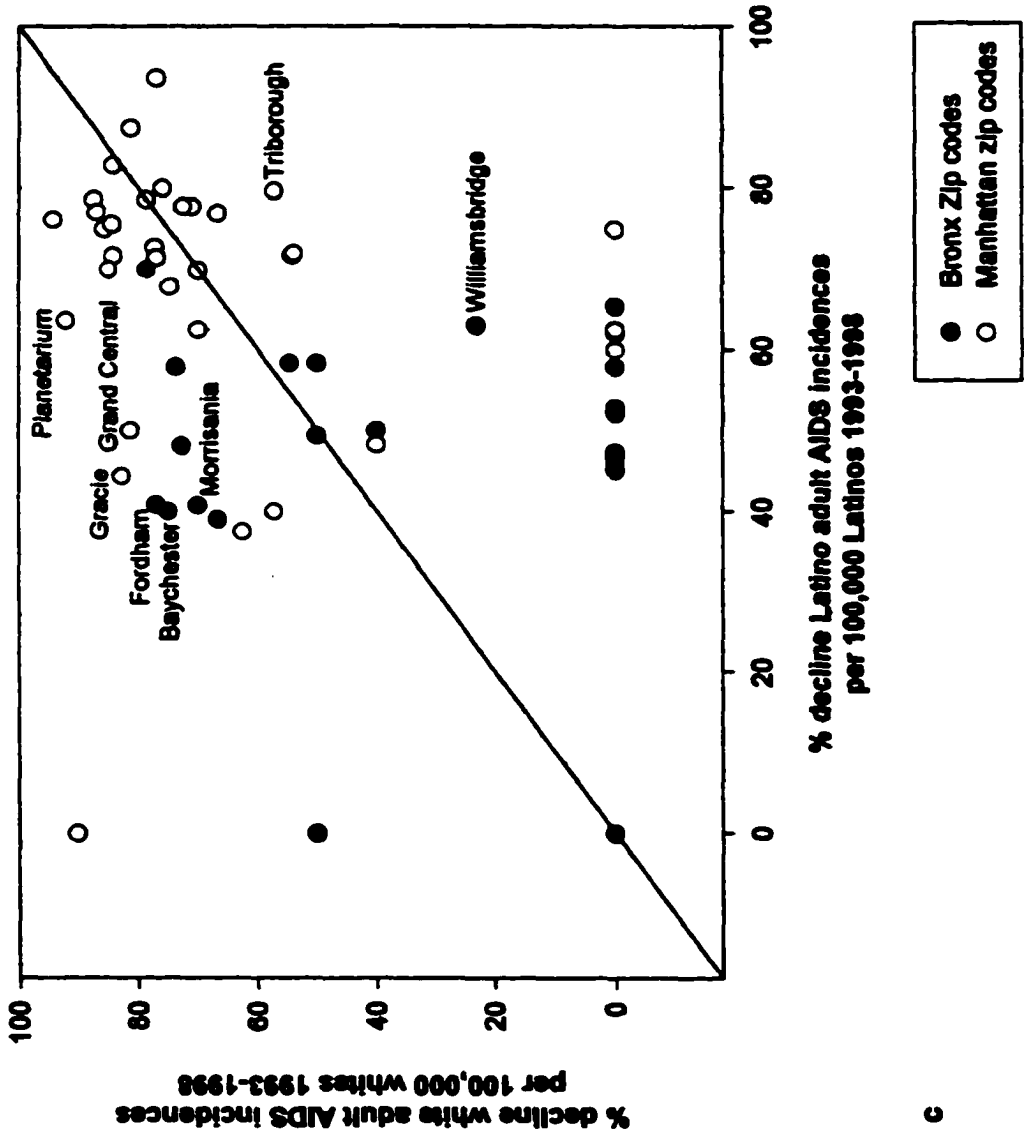
a

Figure 5. Serial contrasts of percent decline adult AIDS incidence per 100,000 per race 1993-1998 for black, white and Latino zip code populations in Manhattan and the Bronx. a) black and white, b) black and Latino, c) Latino and white. Line $y = x$ bisects the parameter spaces to aid identifying zip codes with disproportionate decline ratios. Zip codes with notable disparities in percent AIDS decline are annotated. Zip codes with no decline for any one race typically have small populations of that race to begin with. The contrasts are not strictly orthogonal in the sense that Latino is not officially defined by the U.S. Census as a race, but is instead considered an "origin." Origin is the heritage or national group of a person's parents ot ancestors. People who identify themselves as Latino, and come from Spanish-speaking nations of backgrounds, may be of any race.



b

Figure 5 (continued).



c

Figure 5 (continued).

Table 1. Manhattan and Bronx socioeconomic and community stress variables with zip code-level r^2's greater than .30 on percent decline in total AIDS incidence per 100,000 population from average 1991-1993 to average 1996-1998. All data from 1990 except where noted.

% decline in total AIDS incidence average 1991-93 to average 1996-98

Manhattan

Variable	Variable description	r^2	Pr>F	Slope
Average white AIDS	Percent decline in average white AIDS cases 1991-93 to 1996-98	.57	<.0001	.49
Medicaid	Proportion of total persons on Medicaid 1991	.55	<.0001	-64.09
Unemployment	Proportion of adults unemployed or not in labor force (without single outlier)	.53	<.0001	-68.65
Homicide	Total homicides per 100,000 population 1991-97	.49	<.0001	-.05
Change in homicide	Change in total homicides per 100,000 population 1991-97	.47	<.0001	-.47
Proportion white	Proportion of total zip code population white	.46	<.0001	27.45
College degree	Proportion of adults with college degree	.46	<.0001	38.56
Income <$10K	Proportion of all 1989 households in zip code with annual incomes $10,000-20,000	.44	<.0001	-68.25
Rent stress $20-35K	Households with rent 30%+ of income $20,000-35,000 per total households of that income class	.44	<.0001	60.48
Proportion black		.41	<.0001	-26.97
Income $10-20K		.37	.0001	-158.10
Rent stress $35-50K		.37	.0001	81.34

Bronx

Population change	Percent change in zip-code population size 1980-1990 (without single outlier)	.42	.0007	-.75
Unemployment		.38	.0012	-55.26
Rent stress <$10K		.38	.0012	-81.88
Income $10-20K		.36	.0017	-215.84
Income $35-50K		.34	.0027	138.77
Extreme overcrowding	Proportion of total housing units with 1.5+ persons per room	.33	.0030	-160.50
Income <$10K		.32	.0037	-43.94
Proportion white		.30	.0054	22.91

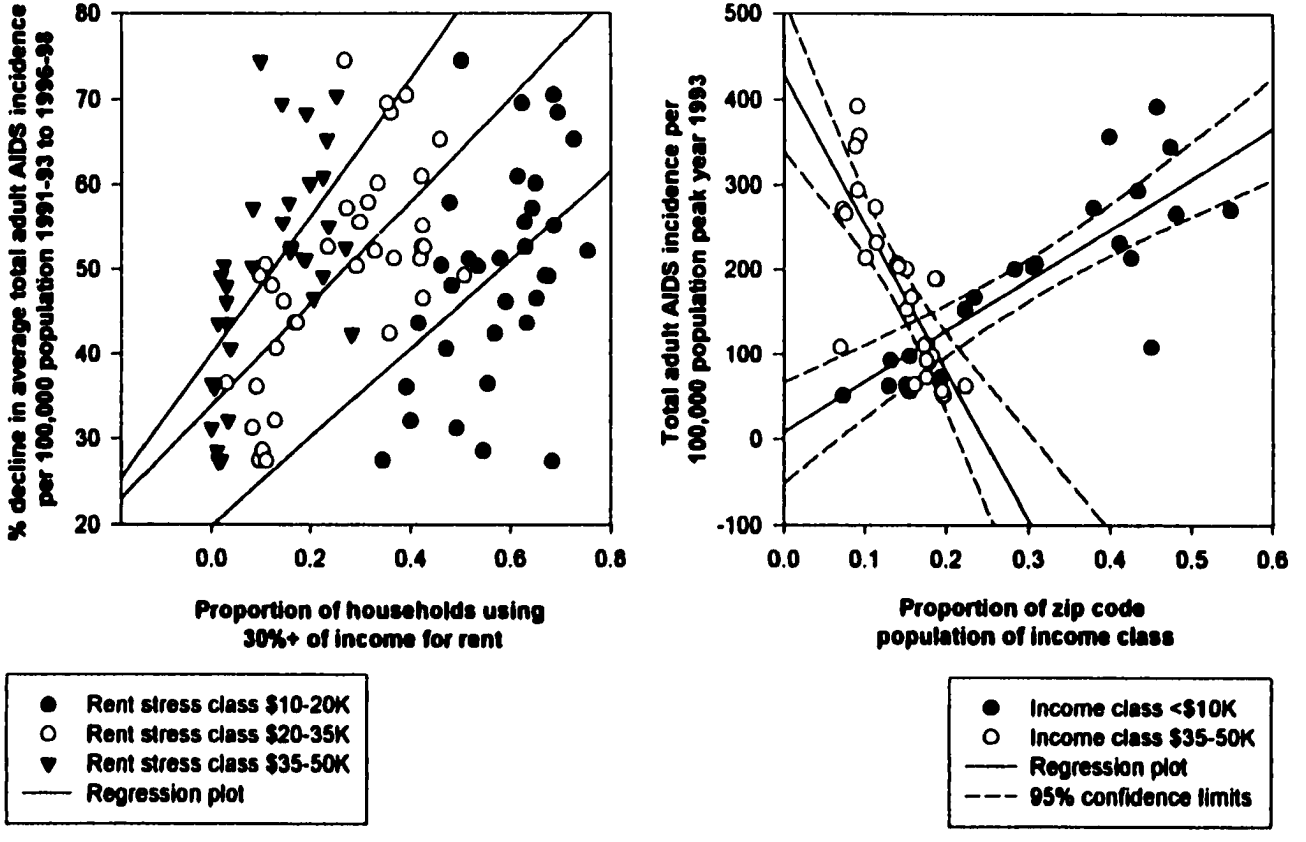


Figure 6. a) Decline in average total AIDS adult incidence per 100,000 population for Manhattan zip codes over three rent stress classes: $10-20K ($r^2$ = .20), $20-35K (.44), $35-50K (.37). Rent stress classes are defined by the proportion of households of each of four income classes (<$10,000 a year, $10-20,000, $20-35,000, $35-50,000) that use 30%+ of their income to pay rent. Confidence limits are omitted for graphical clarity. b) Peak year 1993 total adult AIDS incidence per 100,000 population for Bronx zip codes vs. proportion of zip code households with annual incomes <$10K ($r^2$ = .67) and $35-50K (.60). Income proportions are not independent. If most of a zip code's households are of the <$10K income class, fewer households are in the other income classes. Still, even with whatever proportion effects there may be, it is clear income had a relationship with peak incidence in the Bronx in ways not apparent in Manhattan.

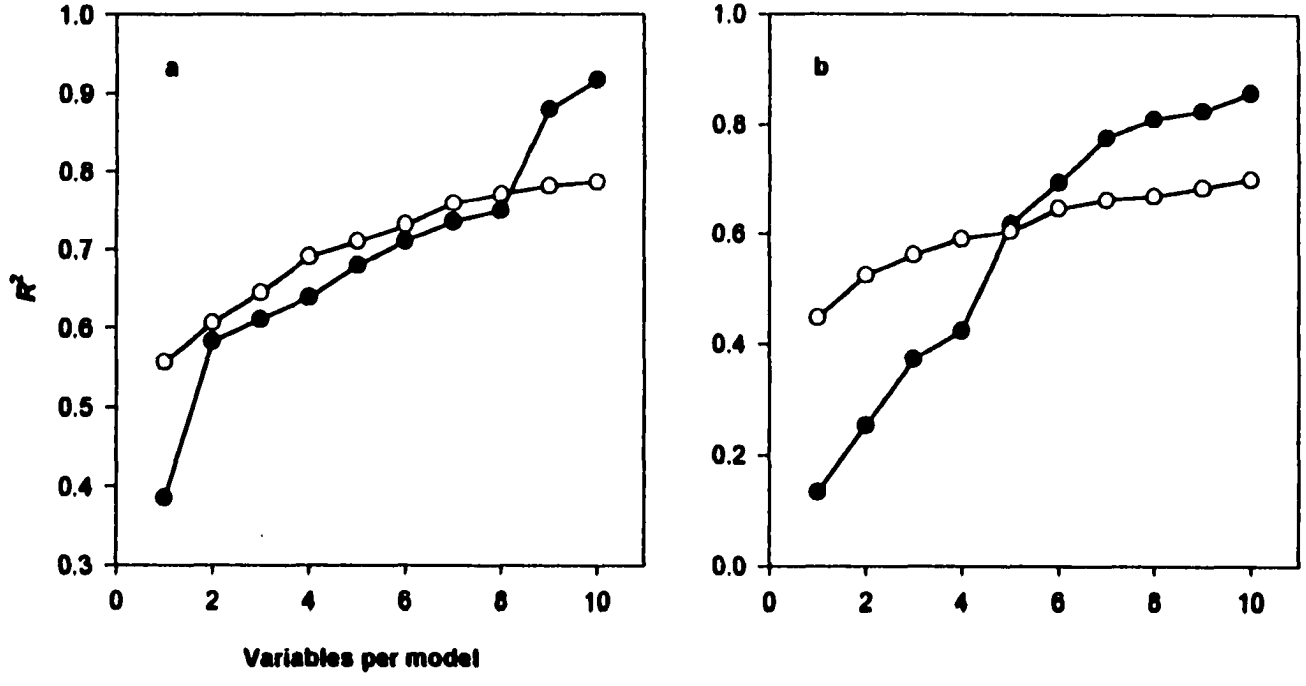


Figure 7. Best one to ten-variable models from maximum R^2 improvement stepwise regression on declines in Manhattan and Bronx zip-code AIDS incidence. Twenty-five zip code-level socio-economic and community stress variables were regressed against a) decline in average total adult AIDS incidence 1991-93 to 1996-98 and b) decline in total adult AIDS incidence 1993 to 1998. 1998. Declines in AIDS incidence by race per 100,000 population were not included in the models because these data are not independent of declines in total AIDS incidences. Also left out was change in population 1980-1990 because of missing data. (Manhattan's Yorkville zip code did not exist in 1980. Yorkville was made from a subdivision of Gracie, so, in addition, the Gracie zip code of 1990 is not the same as the Gracie of 1980.)

Table 2. Best nine-variable models from maximum R^2 improvement stepwise regression on average Manhattan and Bronx declines in zip code AIDS incidences 1991-93 to 1996-98.

Manhattan

$R^2 = .78$

Source	df	Sum of Squares	Mean Square	F Value	Pr>F
Model	9	4045.11	449.45	9.55	<.0001
Error	24	1129.21	47.05		
Corrected Total	33	5174.33			

Variable	Parameter Estimate	Standard Error	F-Value	Pr>F
Medicaid	-135.42	38.44	12.41	.0017
Income class $20-35K	-312.38	101.64	9.45	.0052
Rent stress class <$10K	79.65	31.22	6.51	.0175
AIDS incidence peak year 1993	.02	.00	6.41	.0183
Income class $35-50K	-226.95	96.16	5.57	.0267
Extreme overcrowding	169.00	76.38	4.89	.0367
College degree	-68.31	36.15	3.57	.0710
Decline in perinatal exposure to HIV	2.32	1.49	2.41	.1334
Rent stress class $20-35K	23.27	20.82	1.25	.2748
Intercept	100.97	29.95	11.36	.0025

Bronx

$R^2 = .88$

Source	df	Sum of Squares	Mean Square	F Value	Pr>F
Model	9	2390.56	265.61	11.46	<.0001
Error	14	324.41	23.17		
Corrected Total	23	2714.97			

Variable	Parameter Estimate	Standard Error	F-Value	Pr>F
Cirrhosis deaths	.33	.06	28.91	<.0001
Decline in perinatal exposure to HIV	12.21	2.72	20.13	.0005
Medicaid	-206.83	47.12	19.26	.0006
AIDS incidence peak year 1993	.13	.03	15.78	.0014
Rent stress class $20-35K	129.10	35.43	13.27	.0027
Drug deaths	-.19	.06	9.56	.0080
Extreme overcrowding	296.26	104.33	8.06	.0131
Rent stress class <$10K	-42.22	16.73	6.36	.0244
Change in STD incidence	.13	.07	3.66	.0763
Intercept	17.03	13.17	1.67	.2170

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Chapter 3

Making Mr. Hyde? HAART and the Evolution of HIV's Life History

The prospect of bacteriological explanations held promise not only that specific cures and preventive vaccines could be developed but also that focusing on specific disease-prevention programs could result in more efficient uses of public health resources. "A careless or ignorant expectorating consumptive can eliminate and distribute seven billions of bacilli in twenty-four hours," warned S. A. Knopf in the journal *Charities* in 1901. Hence, by encouraging the tuberculous to carry and use flasks to dispose of their spittle so that "it cannot dry and be blown about to be inhaled by others," journals declared responsible tuberculars could stem the disease. Public health policies that focused on the sources of specific infection rather than on the general sanitary conditions of the broader city had numerous attractions. Among them was the prospect of efficiently stemming infection without disrupting existing social relationships between tenant and landlord, employer and worker, political leaders and voters. Health and wealth could both be attained.

David Rosner (1995)

I must have stared upon [my hand] for near half a minute, sunk as I was in the mere stupidity of wonder, before terror woke up in my breast as sudden and startling as the crash of cymbals; and bounding from my bed, I rushed to the mirror. At the sight that met my eyes, my blood was changed into something exquisitely thin and icy. Yes, I had gone to bed Henry Jekyll, I had awakened Edward Hyde. How was this to be explained? I asked myself, and then, with another bound of terror—how was it to be remedied?

...This inexplicable incident, this reversal of my previous experience, seemed, like the Babylonian finger on the wall, to be spelling out letters of my judgement; and I began to reflect more seriously than ever before on the issues and possibilities of my double existence. That part of me which I had power of projecting, had lately been much exercised and nourished; it had seemed to me of late as though the body of Edward Hyde had grown in stature, as though (when I wore that form) I were conscious of a more generous tide of blood; and I began to spy a danger that, if this were much prolonged, the balance of my nature might be permanently overthrown, the power of voluntary change be forfeited, and the character of Edward Hyde become irrevocably mine. The power of the drug had not been always equally displayed. Once, very early in my career, it had finally failed me; since then I had been obliged on more than one occasion to double, and once, with infinite risk of death, to treble the amount; and these rare uncertainties had cast hitherto the sole shadow on my contentment. Now, however, and in the light of that morning's accident, I was led to remark that whereas, in the beginning, the difficulty had been to throw off the body of Jekyll, it had of late gradually but decidedly transferred itself to the other side. All things therefore seemed to point to this: that I was slowly losing hold of my original and better self, and becoming slowly incorporated with my second and worse.

Robert Louis Stevenson (1886)

Abstract. Alternative reproductive strategies are introduced to HIV population models. A time-invariant stage-classified Lefkovitch population matrix model hypothesizes antiretroviral innovations such as HAART may select for, among other possibilities, an HIV with a semelparous life history and a precocious senescence. The senescence may be embodied by an accelerated time to AIDS.

Key words: HIV, life history, HAART, reproductive strategy, senescence

Introduction. A growing body of work investigates the effects of variable infectivity on the HIV epidemic (May and Anderson 1990, Ahlgreen et al. 1990, Jacquez et al. 1994, Levin et al. 1996, Pinkerton and Abramson 1996, Koopman et al 1997, Hyman et al. 1999, Coutinho et al. 2001, among others). These models define reproductive success at the level of the individual infection, not that of the virion. Infections are characterized by an ontogeny, with stage-specific fecundity and survivorship. As individuals, HIV infections are typically defined by a three-stage life cycle: the initial infection and the first viremia collapsed together, a long-term asymptomatic stage, and AIDS (Figure 1). The final stage ends in the infection's—and host's—death. Reproduction occurs when the infection 'gives birth' to subsequent infections by transmission to susceptibles.

Infection 'births' and 'deaths' are tracked over time to account for the epidemic's population dynamics. For example, Levin et al. (1996) track the frequencies of individual infections in each stage by modifying the Euler-Lotka equation for continuous stage-structured population growth and partitioning the net reproductive rate (R_0) by infection stage. Levin et al. assume a stable stage distribution, fixed stage-specific fecundities, and survivorships that varied only over the asymptomatic stage. The major result of the model is that transmission from the first viremia provides the greatest contribution to infection

population growth, particularly for early-stage epidemics, a result reported by others (May and Anderson 1990, Jacquez et al. 1994, Pinkerton and Abramson 1996, Koopman et al 1997, Hyman et al. 1999). Viral concentration, as measured in blood, semen and vaginal fluid, appears correlated with the probability of infection (Simmonds 1990, Mellors et al. 1996, Leynaert et al. 1998) and may account in part for the first viremia's epidemiological prominence.

The result inspires questions. If most subsequent transmissions stem from the first viremia, why do HIV infections last so long afterwards? Why do HIV infections have the ability to evade within-host immune responses for years? HIV infections, for example, undergo a broadening of cell and tissue ranges (Pantaleo and Fauci 1996). HIV avoids clearance by infecting immune memory cells, hiding out in lymphatic refugia, and undertaking localized bursts of replication (Balter 1997, Wong et al. 1997, Finzi et al. 1997, Grossman et al. 1998). HIV infections undertake a switch from the M-tropic to the more virulent syncytium-forming T-tropic phenotype (Groenink et al. 1991, Schuitemaker et al. 1992), although the switch can occur in the other direction (McKnight et al. 1995).

In short, why do HIV infections avoid entering an immediate post-reproductive degeneration after the first viremia if subsequent transmission is the ultimate measure of reproductive success at the infection level? Why does HIV elude immunal clearance in ways other infections such as the common cold can not?

One explanation is the models above are mistaken and it is instead the asymptomatic stage that makes the greatest contribution of new cases to the HIV epidemic. Coutinho et al. (2001) show what infection stage drives the epidemic may depend upon the

relationship between infectivity and viral load. For example, if infectivity is proportional to the log of HIV RNA concentration rather than the absolute value (Quinn 2000, Vella et al. 2000), contrary to what the models above assume, the asymptomatic stage should epidemiologically predominate. Indeed, Gupta et al. (1997) show viral loads in semen, in contrast to peripheral blood loads, are rather low in early infection, increasing severalfold over the duration of the asymptomatic stage.

Another explanation evokes the concept of reproductive strategies, patterns of age-specific fecundities and survivorships intrinsic to the evolved life histories of organisms (Stearns 1976, 1992, Ebert and Weisser 1997, Villarreal et al. 2000). Such strategies evolve in response to ecological pressures in such a way as to generate optimal population reproductive rates.

HIV infections may maintain the capacities for immunal evasion because the infections embody an iteroparous reproductive strategy, reproducing in more than one bout, even as their reproductive values decline over time. In other words, even as most subsequent infections are derived from the initial life stage (during the first viremia), secondary bouts of transmission occur in the asymptomatic stage. Levin et al. (1996) show the intrinsic rate of infection population growth to be greater with joint transmission from the first viremia and asymptomatic stage than from the first stage alone or from the first and AIDS stages together.

In spite of lesser per-exposure transmission efficiencies, secondary 'births' may be possible because of the long duration of the asymptomatic stage. Without intervention, 70-90% of infections progress to AIDS in eight to ten years (Pantaleo et al. 1993, Pantaleo and Fauci 1996, Viscidi 1998). The lesser probabilities of infection, similar to

the decay in mammalian reproductive values, may prove evolutionarily more rewarding than no possibility of reproduction at all. An iteroparous reproductive strategy may be adaptive in HIV because sexual and parenteral exposures are relatively secure lines of transmission if practiced over a sufficient number of exposures (Holgate 1967, Murphy 1967).

HIV's iatrogenic selection? What happens when the secondary transmissions or 'births' that emanate from the asymptomatic stage are blocked by an extrinsic source?

In 1996, highly active antiretroviral therapy (HAART) was introduced. These 'cocktails' or combination therapies are comprised of two different nucleoside analogues and a protease inhibitor or, later developed, a non-nucleoside reverse transcriptase inhibitor. HAART dramatically arrests AIDS onset and death, including a 3-log reduction in viral burden, especially in treatment-naïve individuals (Hammer et al. 1996, Saravolatz et al. 1996, Collier et al. 1996, Weidle et al. 1999). To HAART has been ascribed dramatic abatements in AIDS epidemics where therapies are available (Center for Disease Control and Prevention 1997, Chiasson et al. 1999, Beck et al. 1999, Law et al. 2000, Wong et al. 2000).

HAART, however, is typically prescribed years after infection. Campsmith (2001) reports 40% of 18,150 U.S. HIV patients surveyed were diagnosed with HIV only within a year of developing AIDS. Therefore, even as AIDS incidences and mortalities have for the most part declined in industrial countries, HAART may contribute little to blocking first viremia, from which it is hypothesized most subsequent transmissions emanate. At best, HAART suppresses HIV replication in the asymptomatic and AIDS stages, blocking

secondary transmissions alone. In practice, then, a fully realized campaign dedicated to prescribing HAART earlier in the infection (Cates et al. 1997) would transform HIV from an iteroparous infection into a semelparous reproductive strategy. Such an iatrogenically shaped life history reproduces itself in a single bout alone, during the first viremia.

Increasingly isolating reproduction to the first viremia across the population of those infected could select among several possible evolutionary responses in HIV.

1. One possible response has already taken place. HIV can maintain iteroparity by developing resistance to the drugs, evolving out from underneath viral suppression. Nearly 80% of those infected in the West carry quasispecies resistant to at least one antiretroviral (Susman 2002). The proportion of HIV infections in the Western world that are multiple-drug resistant has reached 10% and may be as much as 50% (Schmit et al. 1998, Loveday et al. 1999, Dietrich et al. 1999, Salomon et al. 2000, Susman 2002). Resistant quasispecies arise even in individuals with complete adherence.

2. HIV can maintain iteroparity by evolving greater infectiousness in the asymptomatic stage. HIV may perhaps accomplish this by changing HIV's phenotype in such a way as to permit greater infectiousness at lower viral loads and/or by increasing the number of viremia in the asymptomatic stage. For example, Kovacs et al. (2001) show in some women a compartmentalization in HIV-1 replication under HAART treatment. Genital load remained high (10^4-10^5 copies/ml) despite successful therapy. Genital inflammation may be one explanation for the compartmentalization (Vernazza 2001). Genetic differences between genital and peripheral quasispecies have been shown as well (Zhu et al. 1996).

Depressed transmission efficiency can be ameliorated in the asymptomatic stage by increasing the number of competent exposures. Increased exposures can arise from relapses into unsafe behaviors brought about by HAART's success (Anderson et al. 1991). Another possibility involves changing viral dynamics. Gunthard et al. (1999), Ramratnam et al. (2000), and Havlir et al. (2001) describe unexplained intermittent viremia under HAART regimens, even in patients with viral nadirs below 50 HIV RNA copies/ml. These low-level "blips" are relatively frequent and associated with slower decay rates of latently infected cells. They are also associated with greater viral diversity. The viremia, however, do not appear to lead to virologic failure (>200 copies/ml) (Havlir et al. 2001).

There are proximate explanations for the intermittent viremia. Perhaps they represent the localized reproductive bursts characteristic of latently infected cells (Grossman et al. 1998, Grossman et al. 1999). That explanation may suffice. In the spirit of stimulating discussion I offer the additional hypothesis the blip viremia may represent, at the life-history level of causation, attempts on the part of the infections to increase the number of effective exposures.

3. HIV could endure a demographically defined semelparity because the intrinsic rate of growth of the infection population does not change enough to require an evolutionary response. This phenotype is "demographically defined" because the source of the reduced infectiousness in the asymptomatic stage is extrinsically imposed. If HAART treatment is discontinued, HIV infections would, in this scenario, rebound to iteroparous phenotypes. In evolution, though, extrinsically defined effects can select for intrinsically defined changes in life histories (Stearns 1992).

4. Such an intrinsically defined change could involve HIV embracing semelparity with a greater fecundity (greater infectiousness) in the first stage to maintain a viable intrinsic rate of growth. In other words, if those secondary infections emanating out of the asymptomatic stage are of epidemiological importance, even as their fecundities are comparatively truncated to begin with, perhaps HIV would compensate for their loss, and the resultant reproductive deficit, by making the first viremia more infectious.

5. Whether or not the first viremia become more infectious, an evolutionary side effect of such a semelparity seems possible. Concentrating reproduction to an early stage alone could select for an accelerated senescence in the infection. Senescence is the increase in the proportion of the age-specific mortality rate due to intrinsic changes in the organism (Stearns 1992). Senescence means, in a word, aging.

There are a number of theories for senescence (Medawar 1946, 1952, Williams 1957, Hamilton 1966, Rose 1991, Charlesworth 1994), but a general explanation involves the lack of selection against mutations and failing physiology. Once an organism reproduces, its semaphoront (the phenotype at a particular time in its life cycle) is—to put it crudely—evolutionary dead meat. By definition, any trait that permits post-reproductive organisms to succeed is not passed onto the next generation.

AIDS may represent the senescence of HIV infections. On the molecular level, HIV at this point infects cells that have nothing to do with subsequent transmission, including those of the central nervous system. Clinically, the immune system has collapsed and all the opportunistic infections that comprise AIDS, such as toxoplasmosis and *Pneumocystis carinii*, arise, threatening the life of the host and, it follows, that of the infection. Epidemiologically, people with AIDS are typically in less shape to engage in

behaviors needed to infect others. Many refrain from such behaviors as they become cognizant of their status, a culturally derived knowledge (Fox et al. 1987). People with AIDS also have visible disease-specific symptoms that could detract potential susceptibles.

By depressing reproduction in the asymptomatic and AIDS stages, HAART increasingly defines the first viremia stage as the only stage in which the infection reproduces itself. So, following our post-reproduction rule of thumb, senescence—AIDS—should be, by this hypothesis, accelerated to just after the first stage. In short, the first viremia should be followed by a precocious senescence as embodied by AIDS.

In this paper I explore the relationship between HIV's life history and its epidemiological dynamics and fitness. I also attempt to address the possible effects HAART may have on the evolution of reproductive strategy in HIV. I model under what conditions and with what life-table parameters a strictly semelparous HIV, with precocious senescence, can invade a population of HAART-treated iteroparous counterparts.

The model. To track what effects HAART may have on the population dynamics of HIV infections as well as the evolution of HIV's life history, I constructed a time-invariant stage-classified Lefkovitch population matrix model (Leslie 1945, Lefkovitch 1965, Crouse et al. 1987, Caswell 2001).

Figure 2 shows a life cycle graph and related growth equations for the three stages of the HIV infection (primary infection and first viremia together, asymptomatic stage, AIDS). By following the paths and loops we can see what contributions are made to each

stage in the next time class (t+1) as defined by stage-specific survivorships (s_i), fecundities (f_i), and transitions (or 'growth' changes, g_i). The population sizes for each stage in t+1 are defined by the difference equations near the life cycle graph.

The parameters of the life cycle graph and the stage-specific equations can be ordered into a population projection matrix and stage population vectors:

$$\mathbf{n}(t+1) = \mathbf{A}^*\mathbf{n}(t) \qquad (1)$$

or, in this case,

$$\begin{bmatrix} n_1 \\ n_2 \\ n_3 \end{bmatrix}(t+1) = \begin{bmatrix} f_1 & f_2 & f_3 \\ s_1g_1 & s_2(1-g_2) & s_3g_3 \\ s_1(1-g_1) & s_2g_2 & s_3(1-g_3) \end{bmatrix}\begin{bmatrix} n_1 \\ n_2 \\ n_3 \end{bmatrix}(t).$$

A fundamental assumption of a stage-based matrix model is that all individuals in each stage exhibit identical stage-specific fecundities, survivorships, and growth transitions. In actuality, individuals differ in their infectivities and survivorships within-stage for a multitude of reasons, including HIV subtype, HIV load, level of immune activation, and general health (Quinn et al. 1987, Phillips et al. 1991, Michael et al. 1992, Gao et al. 1994, Mellors et al. 1996, Nicholson et al. 1996, Montagnier 1996, Innocenti-Francillard et al. 1997). Stochasticity can be introduced to, in effect, generate within-population variation, but will be saved for another study.

The stage-specific parameters are also assumed to be time-invariant, meaning they do not change over the course of the simulation. The latter assumption, however, is not a prerequisite for the discrete matrix models I run here the way it is for the type of continuous Euler-Lotka analyses Levin et al. (1996) conduct (Rockwell et al. 1983). Periodic temporal variation in the projection matrix is a blossoming subfield (Skellam

1966, Caswell and Trevisan 1994, Caswell 2001: Chapter 13), including epidemiological applications (Sandberg et al. 1992).

Parameter estimates and time interval. The stage-specific values introduced into the projection matrix are taken largely from published cohort studies of the HIV infection and other models (Table 1). The studies chosen are of specific populations and modes of infection, which often differ in their infectivities and survivorships (Eyster et al. 1987, Munoz et al. 1989, Ward et al. 1989, Vlahov et al. 1998). But as few studies have segregated vital rates by infection stage, we are left to stitch together a Frankenstein life history, culling the literature for available variates for equation (1). The chimera seems a better start than filling in with guesses. Table 1 shows the estimates and, where appropriate, their citations. Clearly these parameters change *within* stages of many years (Enger et al. 1996), as well as across populations, but we will have to account for such changes in another study.

I contrasted the population dynamics of three life histories. The first is a wildtype iteroparous HIV infection derived from the survivorship studies of either the early HIV epidemic, before pharmaceutical interventions were available, or in non-industrial countries, where antiretrovirals are effectively unavailable (Tables 1 and 2). The second life history is a HAART-treated iteroparous HIV infection. The infection is defined by three stages, but the fecundities of the asymptomatic and AIDS stages are greatly reduced by HAART. The third life history analyzed is a hypothetical HAART-selected semelparous HIV. For the latter, HAART is assumed to have selected for a precocious senescence, reducing HIV to a two-stage infection.

With a time interval of two months, the average duration of the first stage (g_1) is set to 1. All 'wildtype' infections move out of the first stage at each interval, either into the asymptomatic stage or, less likely, death. All estimates obtained from the literature were calibrated for two-month intervals.

Fecundity here is a compound variable. Modifying Hyman et al. (1999),

$$f_i = 1 - (1 - z_i)^{r_i c_i}, \quad (2)$$

where f is the fecundity for stage i = 1 to 3, z_i the stage-specific transmission per contact, r_i the number of partners per interval, and c_i the number of contacts per interval.

The numbers of partners and contacts tends to decline over time, even in healthy individuals (Konings et al. 1994, Koopman et al. 1997). On the other hand, Rotheram-Borus et al. (2001) show greater average number of partners for youth with AIDS than asymptomatic youth, although more youth with AIDS were abstinent and more used condoms 100% of the time.

HAART's effects on actual infection rates are still under investigation. Musicco et al. (1994) showed AZT cut transmissions in half, all other things equal, while Quinn (2000) showed no transmission events for discordant couples in which the infected partner has an undetectable viral load. In this model we set the asymptomatic- and AIDS-stage fecundities (f_2 and f_3) to what a fully pursued public health campaign would ideally aim: effectively zero.

In practice, however, Gange et al. (2002) show HAART use of up to 60% for populations of those infected and with CD4+ counts of 200-500 at baseline led to negligent changes in median CD4+ counts. Indeed, lymphocytes continued to *decline* under HAART albeit at a lesser rate. Zhang et al. (1998) found replication-competent

HIV in seminal cells of men taking HAART and with undetectable HIV RNA in their blood plasma. The HAART era has also been marked by an attendant increase in the number of unsafe sexual episodes (Scheer et al. 2001, Dukers et al. 2001, Katz et al. 2002) that may discount any reductions in transmissibility brought about by deflated viral set points (Anderson et al. 1991, Blower et al. 2000).

Certainly HAART has ameliorated survivorships for the later two stages since its introduction [increasing s_2 and s_3 in equation (1)], particularly for people with AIDS. It also pushes most HIV infections into remission. In other words, HAART makes HIV infections 'younger' by returning AIDS-stage infections to the asymptomatic stage (making $g_3 > 0$ and decreasing g_2).

For the hypothetical semelparous HIV, all infections grow from the first stage to the AIDS stage ($g_1 = 0$). The survivorship and fecundity of the AIDS stage is the same as that of the HAART-treated iteroparous infection, but with no regression to an earlier stage. The fecundity of the first stage is set at a level that makes the semelparous infection evolutionarily competitive with its HAART-treated iteroparous counterpart ($f_1 = 1.5$ times that of the HAART-iteroparous strategy).

How do these vital rates affect HIV's population dynamics? I follow much of Caswell's (2001) prescription for the full study of a matrix population model. I first conduct asymptotic analyses on the three life histories to determine their population growth rates, stable stage distributions, and reproductive values. I next conduct transient analysis of the three projection matrices, looking at the effect of changing the initial stage distributions and generating damping ratios. I then conduct a perturbation analysis to measure the effects on the intrinsic rate of growth brought about by changing per-stage

survivorships and fecundities in factorial fashion. Lastly I calculate the relative rate of change of the relative abundance of the HAART-iteroparous and semelparous HIV. The latter is a measure of selection, to test whether the semelparous life history can invade a population of HAART-treated iteroparous infections.

Asymptotic behavior. An eigen decomposition of the projection matrix produces a set of eigenvalues associated with the right eigenvector, the largest of which is, in this discrete system, the population's finite rate of increase (λ_1) (Caswell 2001, Gotelli 1995). Cushing and Yicang (1994) show R_o, the net reproductive rate, is equivalent to λ_1. Caswell (2001, pp 128, 295), however, points out that R_o does not stipulate how fast a population grows per time interval. Perturbations in R_o—a per-generation measure—need not affect λ the same way.

Figure 3 shows the eigenvalue spectra for the three life histories. All eigenvalues here are real and positive, with each life history's dominant eigenvalue (λ_1) near 1 (1.04, 1.01, .999). That is, each generation replaces itself, although eventually the semelparous should go extinct ($\lambda_1 < 1$), all other things remaining the same. As the subdominant eigenvalues (λ_2, λ_3) are not complex, the populations should not oscillate.

Figure 4 shows the separate, deterministic density-independent growth of the number of infecteds for the three life histories. Density-independent growth here involves an infinite supply of susceptibles, unlikely to be the case in real populations. We do, however, observe that the wildtype has the greatest potential growth, but still not a very great rate. Despite its lower finite rate of increase, semelparous HIV has a greater population size than HAART-iteroparous HIV over the five years shown.

In the long run, regardless of population size, each population should converge upon its own stable stage distribution, a set proportioning of infections in the three stages as shown in Figure 5. The wildtype and HAART-iteroparous strategies have great majorities of their infections in the asymptomatic stage at the stable stage distribution. Almost all semelparous infections, on the other hand, are AIDS cases. Changes in a population's AIDS incidence may arise from a number of causes, including antiretroviral availability and HIV transmission rates, which, in the real world, are molded by the socioeconomic and historical factors that underlie the population (Wallace, in press). Figure 5 indicates changes in reproductive strategy, if they do indeed come to pass, can also change AIDS incidences. HAART can cause a decline in AIDS cases if only by redistributing the proportions of infections at the stable stage distributions. If a semelparous strategy is selected for, a sharp increase in AIDS cases may only reflect a change in HIV's vital rates.

The reproductive values of all three strategies are defined by a greater relative contribution by the first stage (Figure 6). For HAART-treated HIV, the third stage makes as significant contributions as the asymptomatic stage. The AIDS stage may provide a greater relative contribution because of its greater survivorship and its contributions to the pool of asymptomatics. The evolutionary implications are interesting. Because of the AIDS stage's greater relative reproductive value, HAART may select for a less virulent AIDS beyond the drugs' pharmokinetic effects. The virus itself may evolve less intrinsic virulence during AIDS. Or, perhaps HIV would evolve no such reduction in virulence as HAART acts as a cultural crutch for the virus, pushing the infection back into the

asymptomatic stage. The latter would imply a cultural virology or an extended phenotype for HIV (Ewald 1994).

Transient behavior. Each population above was seeded with ten individuals in the first stage. Alternative initial populations (10 in stage 2 alone, 10 in stage 3 alone) show in the long term, ergodic behavior. That is, regardless how the population is seeded, it converges on the same population growth rate and stable stage distribution. However, within the five-year limit shown in Figure 7 alternative initial populations displayed disparate transient behavior. For example, a population of susceptibles seeded with wildtype AIDS cases will have a more truncated five-year growth rate than if infected first by a group of first or second stage infections. The differences are not at all great, but could be if the finite rates of increase were greater than they are here.

By way of explanation, we can rewrite equation (1) (Caswell 2001) as

$$\mathbf{n}(t) = \sum_i c_i \lambda_i{}^t \mathbf{w}_i \ , \qquad (3)$$

where the population size $\mathbf{n}$ at any time t is defined by the eigenvalues associated with each right eigenvector $\mathbf{w}_i$ and c_i is a scalar derived from $\mathbf{v}_i \times n_0$, the left eigenvector ($\mathbf{v}_i$) and the initial population. Changing the initial populations (or the left eignevectors, which are related to the reproductive values) changes c_i and, it follows, the resultant population size.

As t increases, the subdominant eigenvalues (<1) approach zero and the population growth becomes defined solely by the dominant eigenvalue. In other words, in the long run, the population growth rate for the wildtype population seeded by AIDS cases will approximate those of the other initial populations.

A measure of the rate of convergence upon the stable stage distribution is the damping ratio (Caswell 2001):

$$\rho = \lambda_1 / |\lambda_2| . \quad (4)$$

The difference between the dominant and first subdominant eigenvalues determines the rate of convergence. The damping ratios for wildtype, HAART-iteroparous and semelparous HIV are 1.12, 1.93 and 3.93 respectively. Coale (1972) showed, all other things equal, the more symmetric the distribution of reproductive output is among age classes, the more rapidly a population will converge on the stable age distribution. This holds true for the two iteroparous strategies (see Figure 6), but semelparous HIV, with two eigenvalues only and greater differences among its stages' reproductive values, proved fastest.

Perturbation analysis. To what HIV stage should public health interventions be directed? To see which variables are most sensitive to change, each entry in the life histories' projection matrices was reduced 10% in factorial fashion. Figure 8 shows growth trajectories for total population size for each of the three reproductive strategies. For wildtype and HAART-treated iteroparous, $s_2(1-g_2)$ is by far the most sensitive entry. A change of only 10% sends both populations plummeting.

The implications are startling. In the deterministic world created here, the best way to force populations of HIV infections toward extinction appears to be either 1) reducing the survivorship of those in the second stage or 2) increasing the transition rate from the asymptomatic stage to the AIDS stage. Neither is socially acceptable for obvious reasons. Indeed we are pursuing a strategy with contrary goals: With HAART we are increasing

the survivorship of asymptomatics and decreasing the transition between the asymptomatic stage and AIDS, which, in this simple deterministic system, induces the greatest increase in infection population size.

The result hammers home two important points. First, what may be best for individual patients may be worse for population-level dynamics. Populations interact at multiple scales and levels of organization that need not be entrained by the same causes (Levin 1992). Second, fighting human pathogens is not quite like fighting pests such as a plague of rats or snow geese (e.g., Cooke et al. 1995). Decreasing the number of female adults may be the intervention with the greatest impact on snow geese populations, but such an action in and of itself exists outside the welfare of the other organisms in the ecosystem. Reducing the survivorship of HIV's asymptomatic stage, even if it would have the greatest impact, is not an option. The infections are inside living people whose welfare must be of prime importance.

Selection and invasion. In what ways, if any, could semelparous HIV invade a population of HAART-iteroparous infections? Or, is HAART-iterparous an evolutionarily stable strategy, outcompeting semelparous HIV under all conditions? An optimality analysis finding the combination of proportions of the two reproductive classes that maximizes the overall population growth under HAART would show us the answer. If HAART-iteroparous is evolutionarily stable then the greatest population growth should occur with no semelparous present. I will try such an approach in a subsequent study.

Here, I calculate the asymptotic rate of change of the relative abundance of the two strategies (Caswell 2001):

$$r = \lim_{t \to \infty} (1/t) \log \left[\frac{N(\text{HAART-iteroparous})}{N(\text{semelparous})} \right], \quad (5)$$

where

$N(\text{HAART-iteroparous}) = \mathbf{e}^{\mathrm{T}}\mathbf{n}\,(\text{HAART-iteroparous})$,

$N(\text{semelparous}) = \mathbf{e}^{\mathrm{T}}\mathbf{n}\,(\text{semelparous})$,

and $\mathbf{e}$ is a vector of ones. We can restate the rate of change:

$r = \log \lambda_1(\text{HAART-iteroparous}) - \log \lambda_1(\text{semelparous})$.

That is, invasion of a resident strategy is dependent upon long-term relative population growth.

For these populations r is .0012 and the semelparous is unable to invade. But clearly the more the fecundities of the asymptomatic and AIDS stages are deflated by HAART, as recommended (Cates et al. 1997), the less increase in first-stage fecundity semelparous infections require to invade the HAART-treated strategy. Indeed, demographic stochasticities and spatial structure may permit the semelparous HIV devised here the population-level refugia needed to invade. Models by Ranta et al. (2000) show spatial structure facilitates the invasion of one reproductive strategy into a population of another. Such spatial structure appears to exist in the real world. Wallace (in press) shows geographic heterogeneity in AIDS decline in two boroughs of New York City, indicating sociogeographic disparities in HAART use there.

Discussion. HIV is pandemic, infecting humans in the Arctic and in the deepest tropical rainforests (Gould 1993). Along with its direct attack on the immune system and its transmission via pleasure-inducing behaviors, HIV's epidemiological success may stem from a dual life-history identity. In an epidemic phase, HIV acts much like a precocious

semelparous organism, using its first viremia to rapidly infect the large pool of available susceptibles. In an endemic phase, when available susceptibles are relatively rare, HIV uses its iteroparous nature, with multiple exposures during the long asymptomatic stage, to wait out for a new cohort of potential hosts. The asymptomatic stage's contributions to infection population growth appear decisive in the deterministic model developed here (Figure 8), even as its per-interval fecundity is small.

Higgens et al. (1997) simulated the population dynamics of a variety of life histories. They found precocious iteroparous populations, reproducing early and often like HIV infections appear to, to be the most evolutionarily stable. Neubert and Caswell (2000), on the other hand, found delayed semelparous life histories most stable. The latter live relatively long life spans before detecting the proper conditions for a single burst of offspring.

The first and second stages' contributions to the infection population growth may provide an epidemiological explanation for their relative physiological stealth. The AIDS stage's limited contribution to infection population growth may explain AIDS, the syndrome. AIDS may represent HIV infections' senescence, when, post-infectious, the infections physiologically fall apart, as expected under life history theory. As HIV is an STD, its declining reproductive value over the course of the long-term infection (Figure 5) may reflect the declining reproductive values of its hosts, who have declining numbers of both contacts and partners.

Labile reproductive strategies? HAART is a pharmaceutical attack on HIV's insidious nature. But HAART's miraculous effects at the individual level, literally bringing thousands off their death beds, appear to be increasingly saddled with population-level

overhead. The development of MDR-HIV and HAART's side effects are the most immediate examples, but there are others. For example, it has been argued that HAART can help control the epidemic by reducing viral loads and infectiousness per contact (Musicco et al. 1994, Gilliam et al. 1997). Some models, however, show ways HAART can worsen the HIV/AIDS epidemic by extending the infectious period and enlarging the pool of those infected who are able to infect susceptibles (Anderson et al. 1991, Garnett and Anderson 1996, Royce et al. 1997).

In this paper I propose still another complication. HIV's life history may be labile. By acting with the immune system in squelching viral densities in the asymptomatic phase, HAART, if widely distributed and adhered to, could turn HIV infections into semelparous life histories.

More specifically, in response to HAART HIV could evolve one of several counteradaptations to maintain the same reproductive output. First, HIV can maintain its iteroparous strategy by evolving resistance to HAART and reverting to its standard viral densities and dynamics. Second, HIV may lower the viral level at which HIV can infect susceptibles during the second stage; that is, make the second stage more infectious per contact. Viral characteristics involved in determining infectivity other than innoculum density, such as compartmentalization, may be subjected to more intensive selection pressure. In a third possibility HIV can embrace its new, iatrogenically produced reproductive strategy by evolving even greater infectivity during the first stage, particularly under epidemic conditions. The latter appears to be a competitive strategy with an increase of less than twice the iteroparous HIV's first-stage fecundity (Figures 4 and 8).

Even if HIV evolves none of the counteradaptations so far described, another disturbing possibility remains. If HAART eliminates any and all infectivity in the asymptomatic stage, the impetus for avoiding the immune system's defenses may be removed. The long asymptomatic stage becomes evolutionarily moot. In short, without the selection pressures of a reproductive stage, the senescence that characterizes the infection during the AIDS stage may be accelerated to soon after the first viremia.

What such a precocious senescence might involve is speculative. An AIDS as deadly as its current incarnation would imply the secondary reproduction of the wildtype's asymptomatic period provides individual HIV patients up to ten years of relative health before AIDS. On the other hand, because the HIV's cell range may be more limited by the shorter reproductive period, an earlier infection senescence could involve a less serious syndrome. I do not suggest HIV will evolve into a relatively harmless virus. I only offer the possibility a precocious AIDS may be different in character.

Still another option is that HIV does nothing, evolving no new life history phenotype. HAART may deflate f_2, but f_1 may be sufficient enough to maintain $R_o > 1$. The reduced force of infection may even prove adaptive for an epidemic with a declining pool of susceptibles available (Lipsitch and Nowak et al. 1995). Another explanation for non-response is that organisms are often blocked from exploring their evolutionary phenospaces by phylogenetic and developmental constraints as well as by quirks in their genetic architecture, including antagonistic pleiotropy and linkage disequilibrium (Stearns 1984).

But HIV has earned a well-deserved reputation for evolutionary plasticity and disparate life histories among related species are apparent elsewhere. Organisms as

disparate as mites, ants, worms, marine invertebrates, salmon and rice have exhibited markedly varied life histories across sister taxa (Sano and Morishima 1982, Finch 1994, Golding and Yuwono 1994, Bonato and Gutierrez 1996, Bekkevold and Boomsma 2000, Conti et al. 2000). Such variation exists even within single populations (Linhart 1974, Grosberg 1988).

What this model does and does not do. Engineers typically start a project asking, What function would we like performed? For example, they might be interested in getting scientific equipment to Mars. Engineers then attempt to design a machine—a space ship—that accomplishes the proposed task. Biologists often do the opposite: what can be called 'reverse engineering' (Tooby and Cosmides 1992, p. 61). Biologists work to determine the functions of discovered forms. The model presented here upends standard biological practice. Confronted with an emerging ecology (expanding use of HAART), I devise a form (semelparous HIV) that satisfies the postulates of basic theory (evolution of reproductive strategies and senescence) and an evolutionary criterion (greater relative fitness).

As the proposed virus does not exist, the model's results are less definitive predictions about HIV's evolutionary trajectory and more a heuristic for new ways of thinking and asking questions about viral evolution, something simplified models *can* do (Pielou 1977). This is not to say the hypotheses are untestable. They are. Either HIV will evolve semelparity and precocious senescence or it will not. But we would not know what to look for otherwise. At their best, models inspire new avenues of empirical study. After all, we cannot measure the circumference of the world if we still think the Earth flat.

The model *is* simplistic. It is deterministic, making no test of the effects of demographic or environmental stochasticity. It excludes density-dependent population growth. There are no density-dependent vital rates, no periodic variation in the projection matrix, and no age variation over the course of the two long-term stages.

There is no stratification by host modes of transmission (Goedert et al. 1987), genetics, sex, age (Hirsch et al. 1992, Schoenbaum and Webber 1993, Fauci 1996, Delams et al. 1997 Liu et al. 1997, Cohen et al. 1997, Delams et al. 1997), socioeconomic status (Curtis and Patrick 1993, Hogg et al. 1994, Chaisson et al. 1995, Chaisson et al. 1998), or antiretroviral access/use (Easterbrook et al. 1991, Moore et al. 1994, Eldred et al 1998). There is no history and community structure (Wallace 1988, 1990, 1993, Wallace and Wallace 1998, 2000, Wallace, in press) or spatial structure (Gould 1993, Morand et al. 1996, Gandon et al. 1997, Thrall and Burdon 1997, Gandon and Van Zandt 1998).

These additions seem good points of departure for subsequent studies, particularly as such stratification often generates the ecological heterogeneity necessary for coexisting phenotypes.

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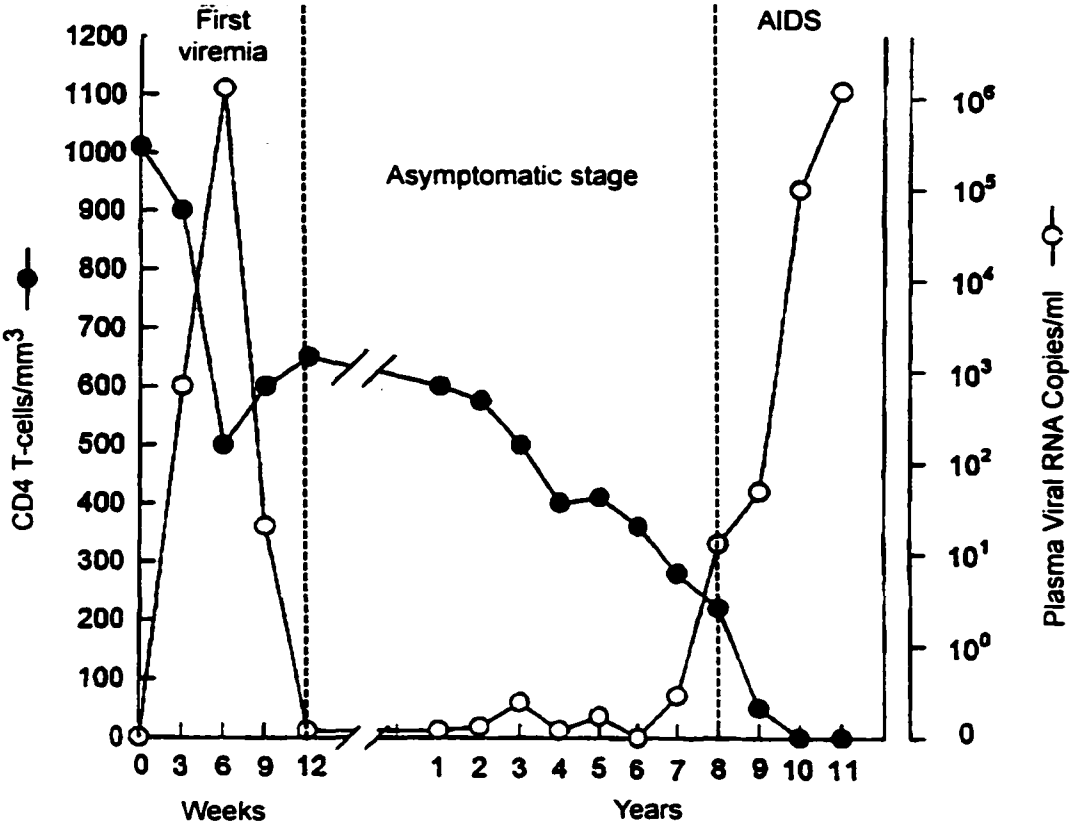


Figure 1. Typical course of HIV infection defined by three stages: first viremia, asymptomatic stage and AIDS. Adapted from Pantaleo et al. (1993) and Viscidi (1998). The primary HIV infection is characterized by a spike viremia and a migration into lymphatic tissue. The first viremia is characterized by an array of month-long clinical symptoms including fever, diarrhea, rash, headache and lethargy, all oft-confused for other illnesses. The immune response reduces HIV replication to a set-point equilibrium that for the most part lasts during the asymptomatic stage until a second viremia induces the onset of AIDS.

Figure 2. Life cycle graph for HIV infections. Graph shows how the three stages of the HIV infection contribute to each other from one interval to the next. Each stage has its own fecundity rate, the proportion of new infections produced per interval. All the fecundities lead to the first stage because all new infections in the next time interval are by definition newborn infections. Each stage has a survivorship rate (s), the proportion of individuals in each stage that survive to the next time interval. Each stage has a growth rate (g), the proportion of individuals in each stage that will develop into the next stage. For example, $s_1g_1n_1$ represents those individual infections in first viremia at time t that survive and progress into the asymptomatic stage at time $t+1$. If the individuals survive but do not develop into the next stage then they remain in their stage. For example, $s_2(1-g_2)n_2$ represents those infections that survive and remain in the asymptomatic stage. Loop $s_1(1-g_1)$ implies stage 1 can develop right into AIDS. In 'wildtype' HIV that is not the case ($s_1(1-g_1) = 0$), but a change in reproductive strategy can conceivably change that. ⟶

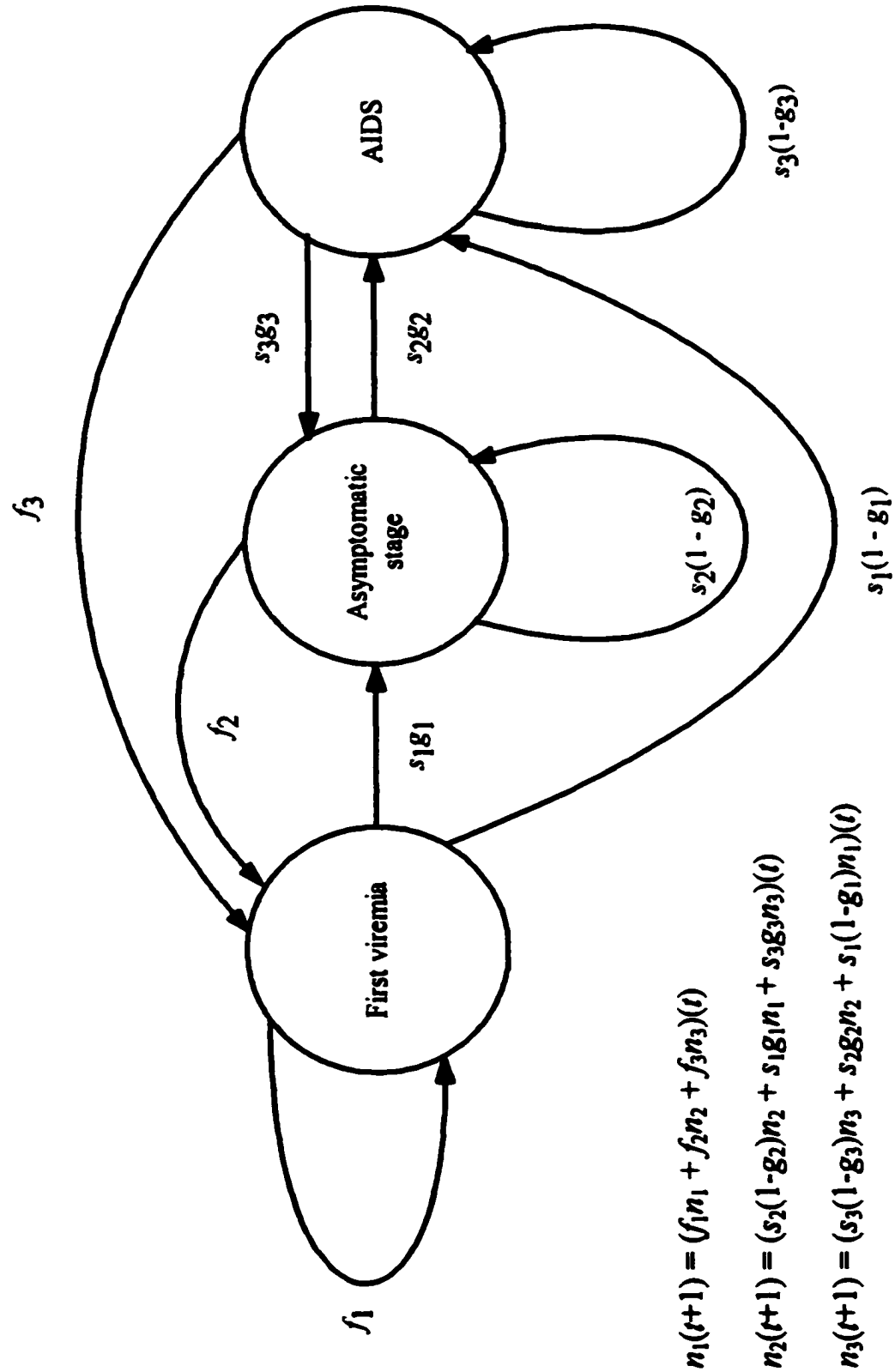


Table 1. Estimates for parameters in equations (1) and (2). The estimates are culled from a variety of cohort studies and models in the literature and calibrated for two-month intervals.

Fecundity (*f*)

$$f_i = 1 - (1 - z_i)^{r_i c_i}$$

wildtype

z (the average transmission per sexual contact for stage i)		
Stage 1	**Stage 2**	**Stage 3**
.007154	.0002	.0049
Source/comment		
Leynaert et al. (1998) model assumes stage 1 infectivity 1.46 times that of stage 3.	Gray et al. (2001) <1700 HIV-RNA copies.	Gray et al. (2001) >38,500 HIV-RNA copies.
Population		
	174 monogamous Ugandan couples.	
r (number of partners per interval)		
1.24	1.24	.62
Konings et al. (1994). Weighted average for men and women.		Stage 1 and 2 partner rates halved to reflect decline in partner rate.
Rural population northeast Tanzania. 400 men and 498 women 15-49 years of age Konings et al. studied general partnership rates by age and cohort, not in regards to HIV infection.		
c (number of contacts per interval)		
21	21	16
Partnership rate assumed the same as stage 2.	Gray et al. (2001)	Gray et al. (2001)

Table 1 (continued)

Fecundity (*f*)

$f_i = 1 - (1 - z_i)^{r_i c_i}$

HAART-iteroparous

z (the average transmission per sexual contact for stage i)		
Stage 1	**Stage 2**	**Stage 3**
.007154	effectively 0	effectively 0
Source/comment		
Assumed the same as wildtype because HAART at best prescribed in stage 2 (Campsmith 2001).	Fecundities for stages 2 and 3 set near 0 (see projection matrices in Table 2), assuming maximally effective public health campaign prescribing HAART and promoting safe sex and drug use.	

Population

r (number of partners per interval)		
1.24	see above	see above
c (number of contacts per interval)		
21	see above	see above

Table 1 (continued)

wildtype

Survivorship (*s*)

Stage 1	Stage 2	Stage 3
.99865	.99402	.940013

Source/comment

Enger et al. (1996). Weighted averages of CD4+ cell count classes combined to approximate CDC-defined HIV infection stages. For example, survivorships for CD4+ groups 0-100 and 101-200 were combined to make 0-200 class. Two-month survivorships interpolated from study's 2.5-year duration. Changes in survivorship are assumed here to be linear over stages of long duration (stages 2 and 3), an unlikely assumption but estimates give magnitude of difference in survivorship across stages.

Population

1683 gay males before treatment with monotheraputic antiretrovirals.

Growth (*g*)

g_1	g_2	g_3
1	.0185	0

Pantaleo et al. (1993), Pantaleo and Fauci (1996), Viscidi (1998). Typical first viremia lasts two months, so g_1 is by definition 1 (all infections progress into second stage in next time interval). Asymptomatic stage typically lasts 8-10 years. Stage 2 set here at 9 years or 54 time intervals. 1/54 = .0185 chance at each time interval infection will progress into AIDS stage, assuming, unrealistically, that likelihood of progression linear during stage. No wildtype infections rebound from AIDS, making $g_3 = 0$.

Table 1 (continued)

HAART-iteroparous

Survivorship (*s*)

Stage 1	**Stage 2**	**Stage 3**
.99865	.99997	99854
Source/comment		
Stage 1 survivorship assumed the same as no HAART yet prescribed.	Ledergerber et al. (1999). Stage 2 survivorship greater than stage 1, but greater than stage 3 survivorship, as we might expect.	Palella et al. (1998)
Population		
	2674 Swiss outpatients on HAART 1995-98 (27.3% women).	1255 patients from 8 US cities with CD4 counts <100.

Growth (*g*)

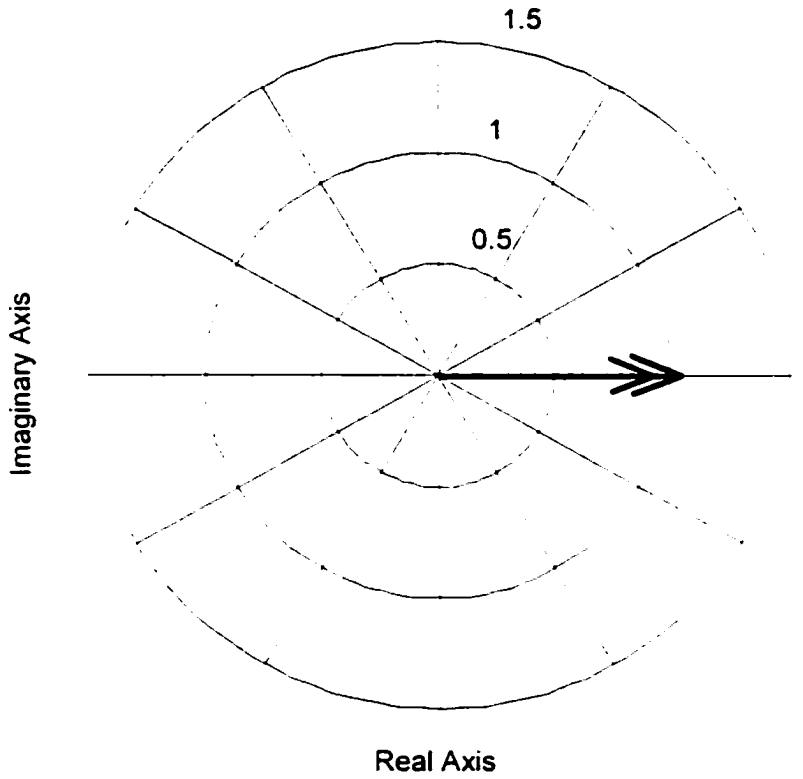
g_1	g_2	g_3
1	.006092	.1457

Ledergerber et al. (1999). Progression to AIDS slowed by HAART. g_2 estimated from proportion of studied population taking HAART and with undetectable viral loads who progress to AIDS event. Weighted average of patients with undetectable loads, undetectable loads but with viral rebound, and who never achieved undetectable loads. g_3 is a measure of the proportion of AIDS infections that get 'younger' (i.e., regress to the asymptomatic stage). g_3 is a weighted average of the proportion of treatment-naïve and pretreated patients given three new drugs who reach undetectable viral loads in 12 months. The proportions are calibrated for two-month intervals, assuming a monotonic rate of regression.

Swiss HIV cohort study. For g_2, n = 1799 for patients with undetectable loads, n = 433 with undetectable loads but viral rebound, and n = 422 for those who never achieved undetectable loads. For g_3, n = 1157 for treatment-naïve patients, n = 433 for pretreated given three new drugs.

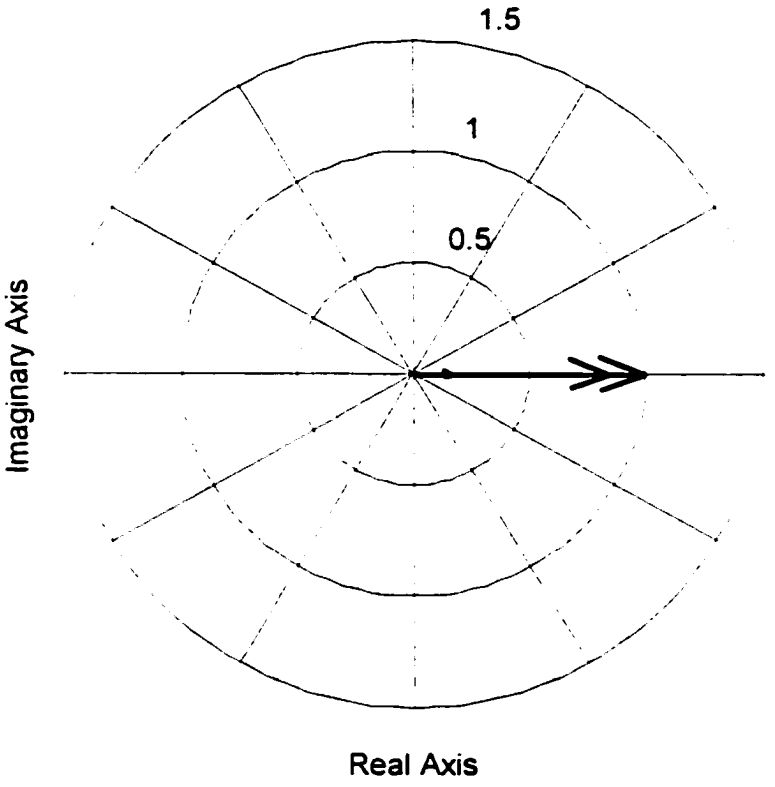
Table 2. Projection matrices for three HIV life histories: 'wildtype', HAART-treated iteroparous and semelparous. Entries derived from estimates found in the literature (Table 1) and, for fecundities, equation (2). For the HAART-iteroparous reproductive strategy f_2 and f_3 are made effectively null (.001) as expected under a wholly effective public health campaign of HAART access/adherence and safe sex promotion. For the semelparous strategy, stage 2 is eliminated by precocious senescence, f_1 is amplified 1.5 times, and g_3, the proportion that regress from AIDS to the asymptomatic stage, is made zero.

'Wildtype' HIV			HAART-iteroparous			Semelparous		
.17053	.0508	.04756	.17053	.001	.001	.25579	0	.001
.99865	.97563	0	.99865	.99388	.14548	0	0	0
0	.01838	.94001	0	.00609	.85305	.99865	0	.99854



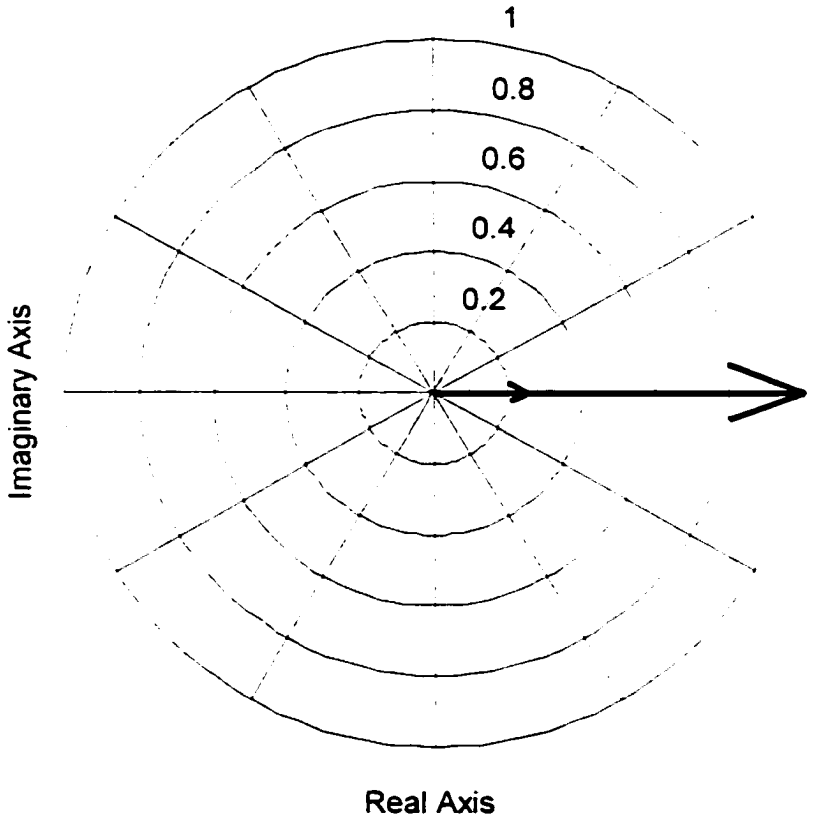
a

Figure 3. Eigenvalue spectra for three HIV infection life histories: a) wildtype. b) HAART-treated iteroparous, c) semelparous.



b

Figure 3 (continued).



c

Figure 3 (continued).

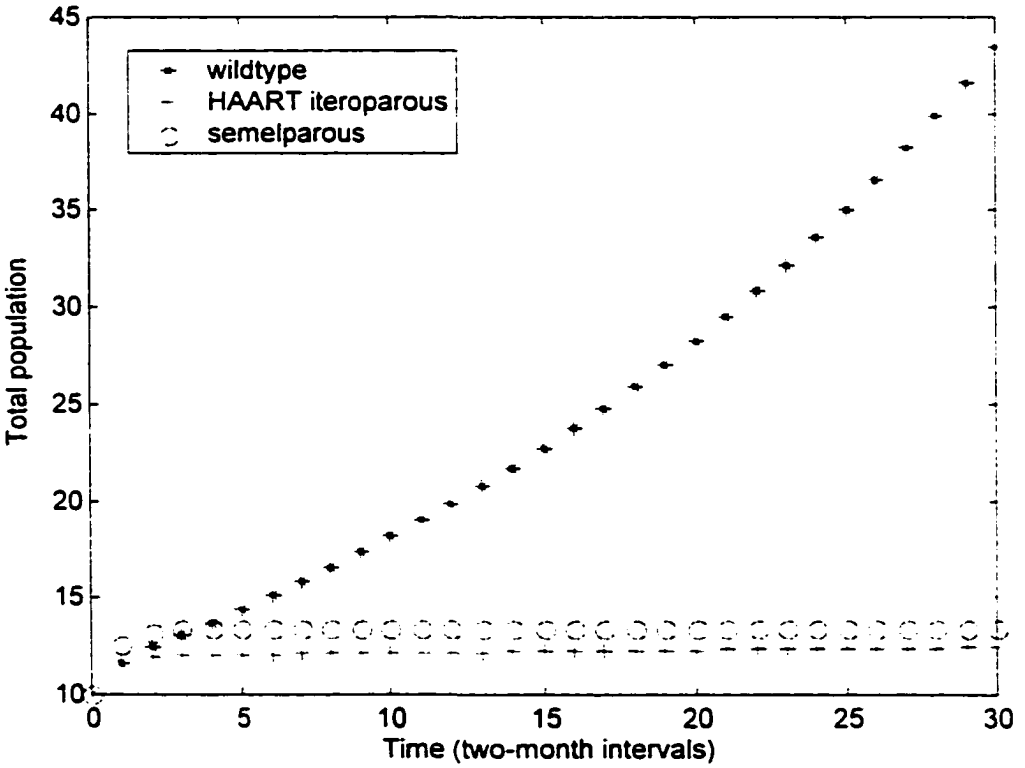


Figure 4. Simulated population sizes for three HIV life histories (wildtype, HAART-iteroparous, semelparous) over time, given projection matrices shown in Table 2.

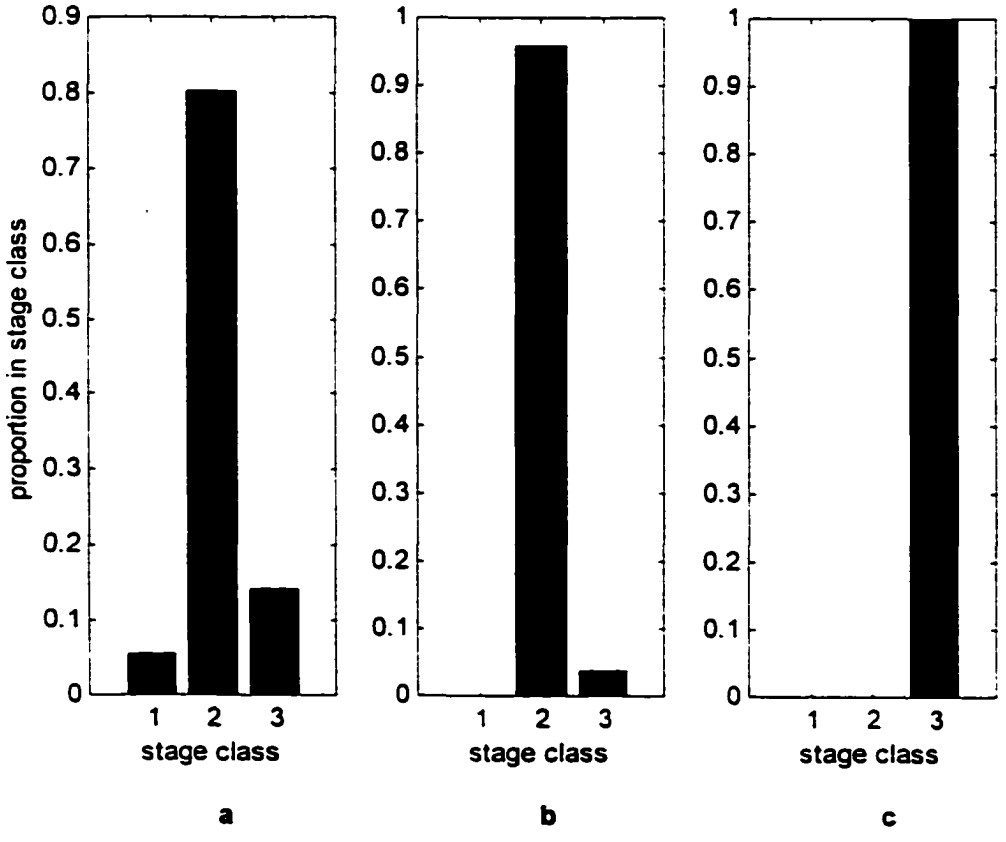


Figure 5. Standard stage distributions for three HIV life histories: a) wildtype, b) HAART-iteroparous, c) semelparous.

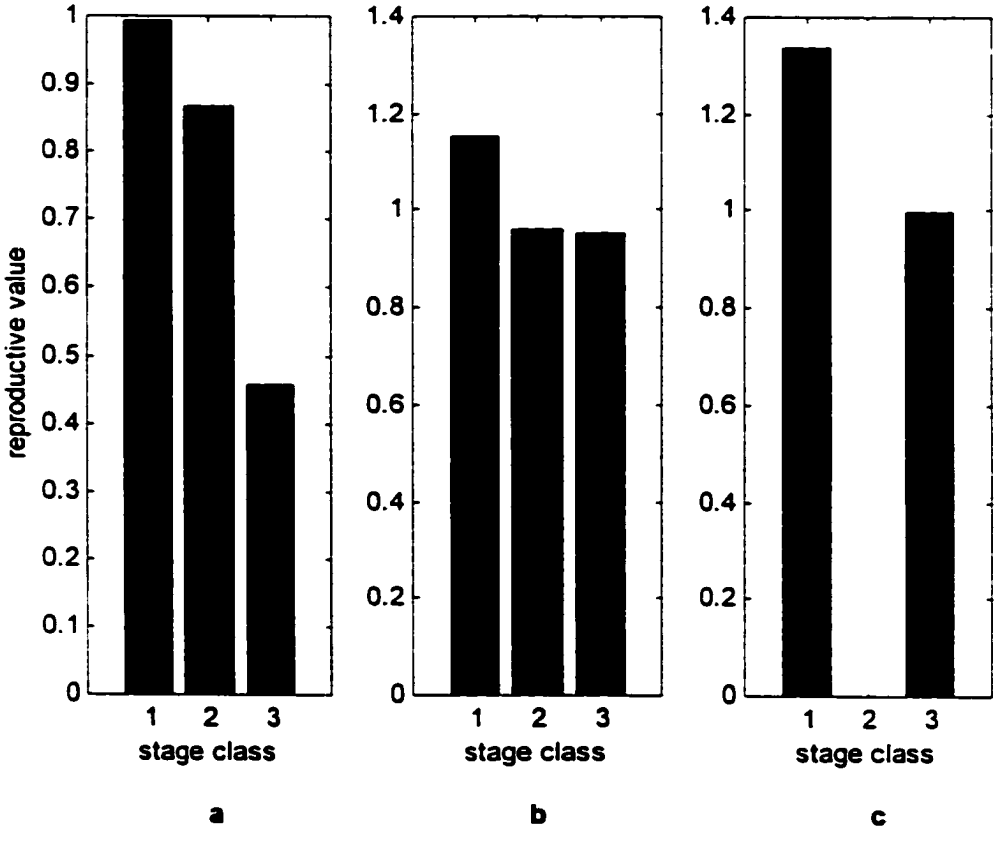
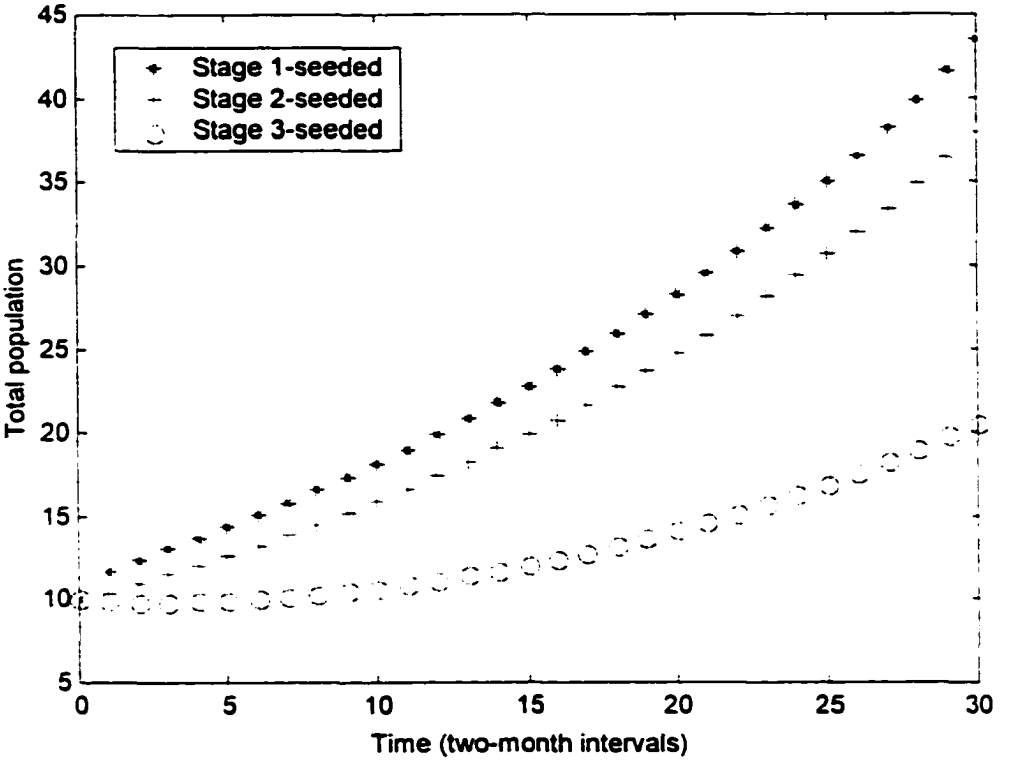
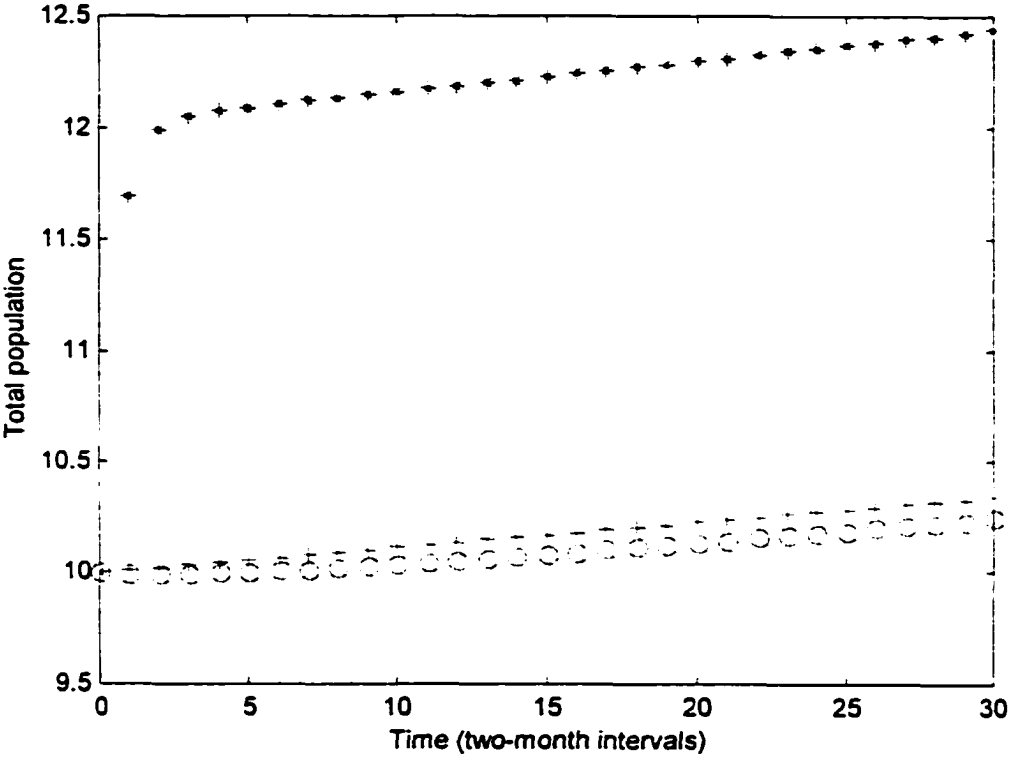


Figure 6. Reproductive values for three HIV life histories: a) wildtype, b) HAART-iteroparous, c) semelparous.



a

Figure 7. Effects of initial stage distributions for three HIV infection life histories: a) wildtype, b) HAART-treated iteroparous, c) semelparous. Three simulations are run for each life history with [n1, n2, n3] = [10, 0, 0], [0, 10, 0], [0, 0, 10].



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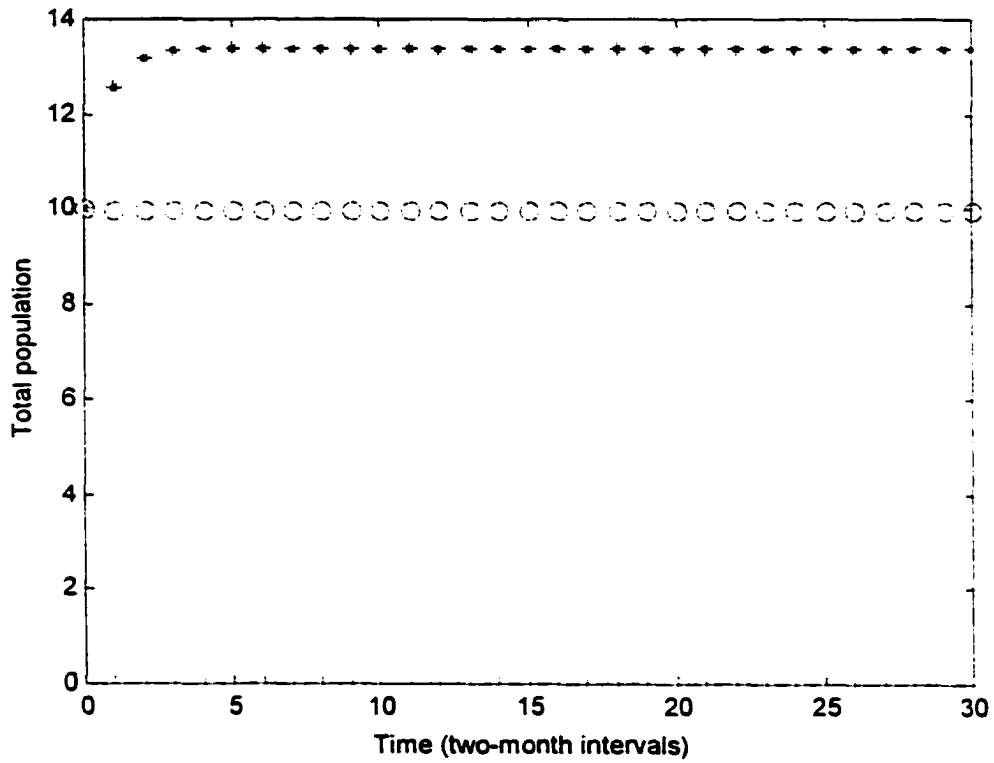

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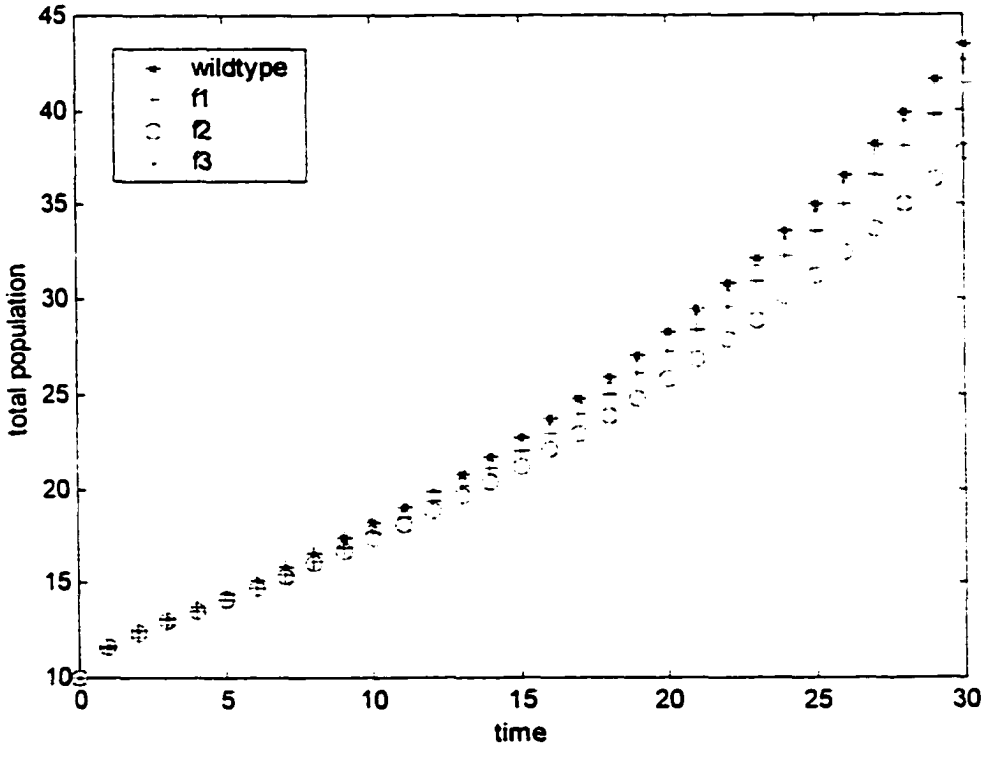
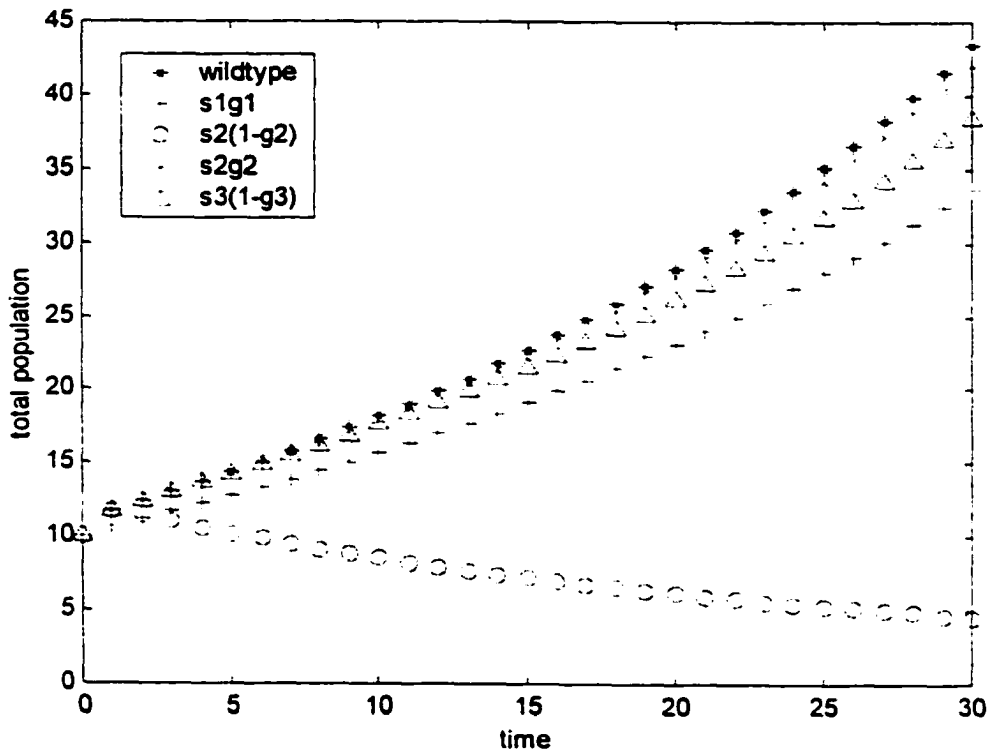
Figure 7 (continued).



a

Figure 8. For perturbation analysis entries in projection matrices for three HIV life histories are reduced 10% in factorial fashion. Population projections for a) perturbated wildtype fecundities and b) survivorships and transitions, c) and d) HAART-iteroparous, and e) and f) semelparous HIV.



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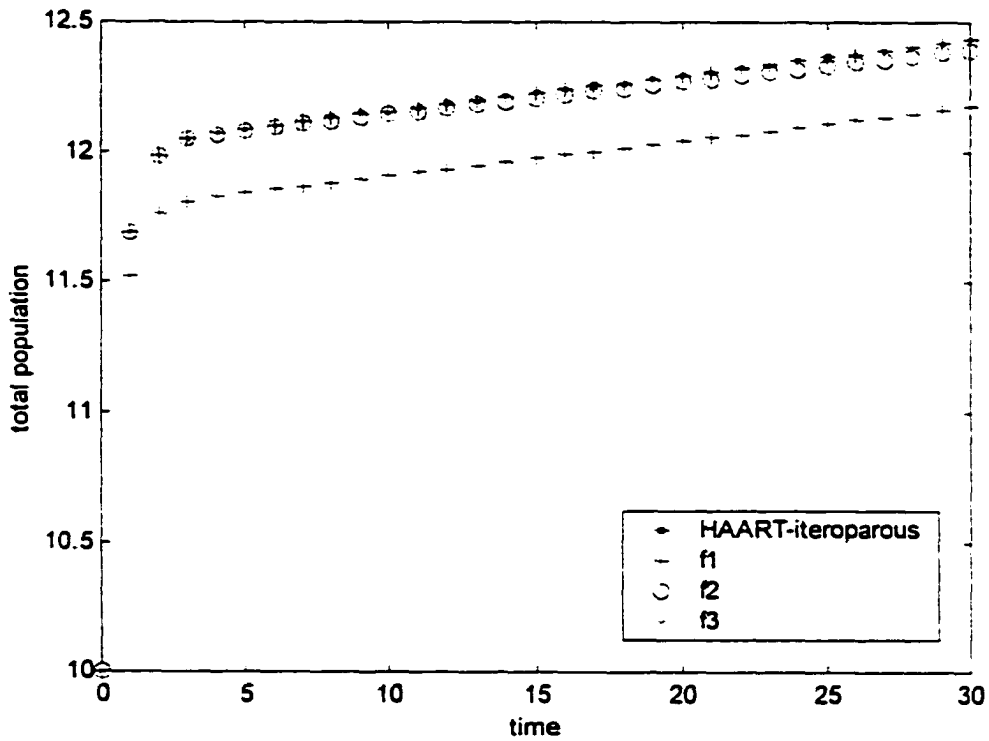

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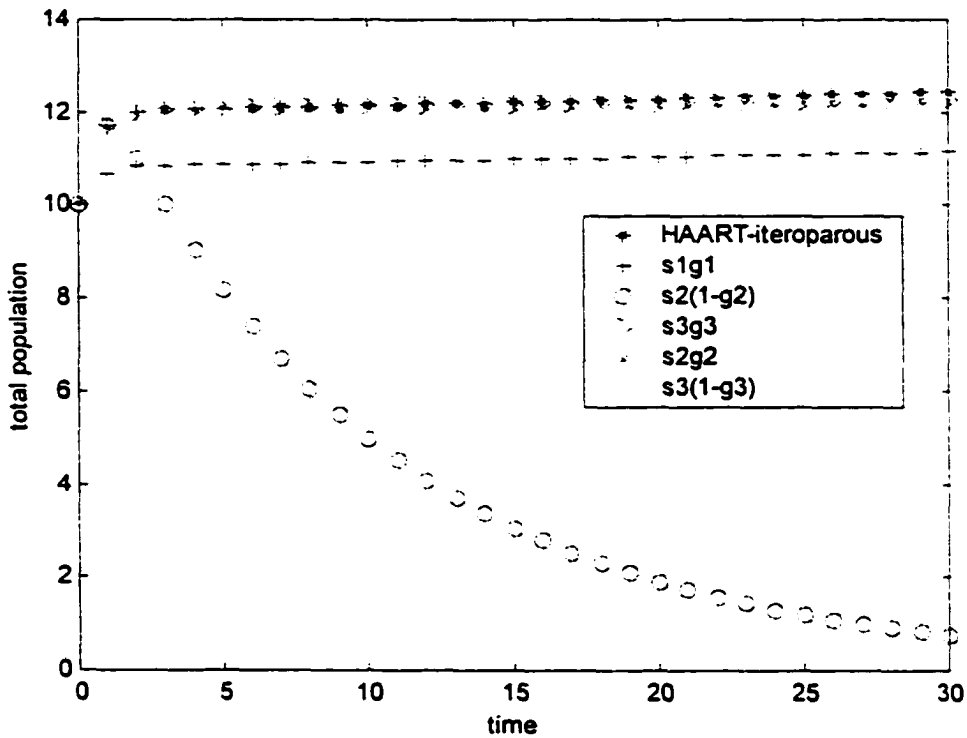

d

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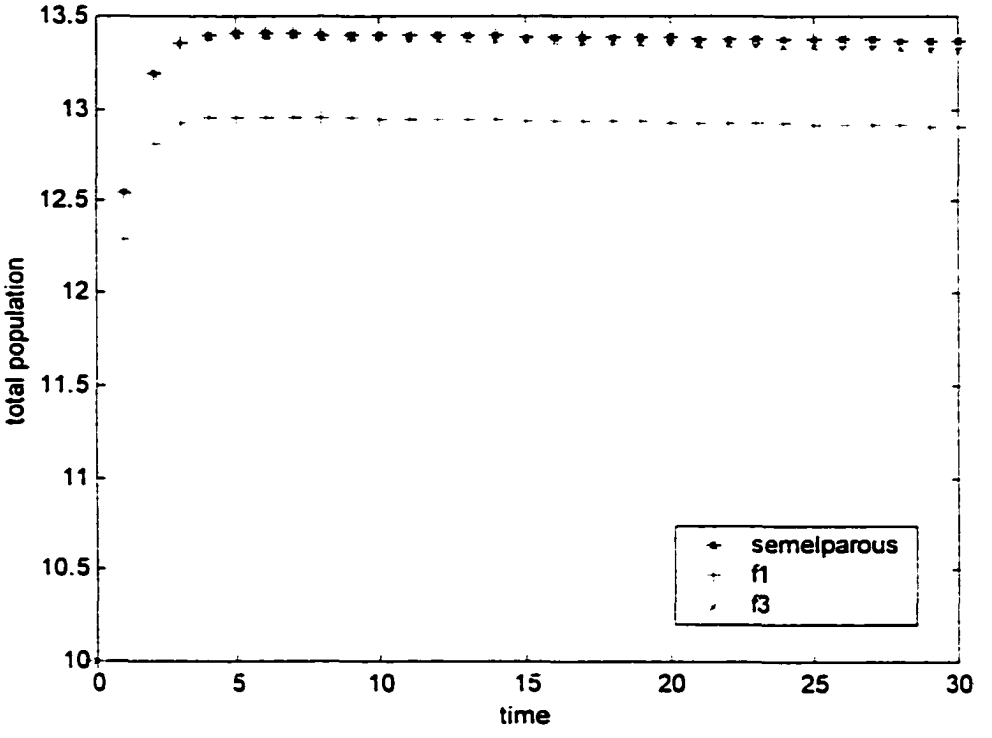

e

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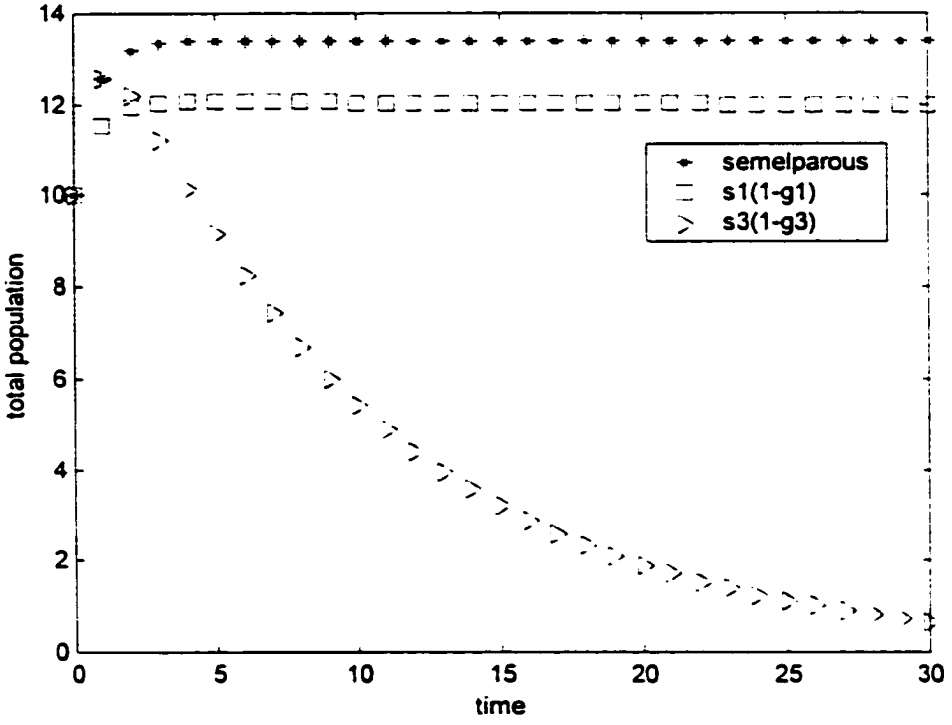

f

Figure 8 (continued).

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Chapter 4

The Shape of Space: Applying Geometric Morphometrics to Geographic Data

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I sometimes ask myself how it came about that I was the one to develop the theory of relativity. The reason, I think, is that a normal adult never stops to think about problems of space and time. These are things which he has thought about as a child. But my intellectual development was retarded, as a result of which I began to wonder about space and time only when I had already grown up.

Albert Einstein

Abstract

Another means is proposed for displaying epistatic change in spatially structured ecologies. The approach uses techniques developed in geometric morphometrics, a relatively new discipline centered on mapping change in bone and other morphologies through evolutionary time or across taxa. Warps analysis is introduced and its terms and protocols explained. An example of warps analysis as applied to geographic data is presented. The example focuses on the AIDS epidemic in two boroughs of New York City. Female adult AIDS incidence and percent newborns exposed to HIV, by zip code for the years 1991-1998, are used to generate annual configurations within an ecological parameter space. A warps analysis of those configurations indicates a clear shift in the relative positions of Manhattan zip codes during the 1990s. The analysis shows the relative positions of two sub-areas comprised of Harlem and Lower Manhattan zip codes were displaced in contrary directions in the parameter space with the introduction of antiretroviral combination therapies (HAART). In contrast, a warps analysis of the Bronx's AIDS parameter space shows few definable zip code groupings or temporal trends before or with HAART. The promises and problems in applying warps analysis to geographic data are discussed.

Key words: Epistatic spatial change, geometric morphometrics, warps analysis, ecolometrics

Introduction

Traditional approaches. Tracking changes in the spatial and temporal distributions of populations or metapopulations is a field-defining problem in geography, ecology, and

epidemiology (Tilman and Kareiva 1997, Hanski and Simberloff 1997). How do patterns of constituent areas interact to form a larger area's ecology? How are system-level patterns formed?

Traditional approaches to representing such changes include graphs sectioned by geographic area. For example, one could show the number of diagnosed AIDS cases by New York City borough over time. A similar approach involves making geographic areas data points in a parameter space with response variables on the axes. Wallace and Wallace (1993) show, for two separate years, a direct relationship between New York county cumulative AIDS cases and the percent of each county's workforce that commutes into Manhattan, one New York City borough. The regressions, 1987 and 1991, show an expected temporal increase in cumulative AIDS cases across the system of counties. More interestingly, the regressions also show a stability in the relationship over time.

A third approach to depicting temporal-spatial data uses a series of maps, each representing the geographical distribution of a response variable at a single time point. Or, one might contrast different variables over the same area on adjacent maps. For example, Wallace and Wallace (1998) produce two maps of the Bronx, another New York City borough. One map shows the average annual drug overdoses between 1978-1982 by health area, a Department of Health administrative district. The other map shows the accumulative AIDS deaths through 1988 by health area. The overlapping incidences in the maps illustrate that intravenous drug use was a primary mode of transmission in the Bronx during the start of the HIV epidemic.

Another way of looking at spatial dynamics over time is to ask: do the relative positions of the locale data points in a parameter space, as in the AIDS-commuting example, change over time? If they do, in what ways?

Figure 1 shows such a configuration of locales (zip codes) for the Bronx 1991. Female adult AIDS incidences and newborns exposed to HIV define the parameter space. Do some zip codes move closer to or further away from each other in next year's parameter space? If so, which ones? How do such changes define the Bronx's HIV-AIDS ecology as a system? What factors correlate or cause the changes in such ecological configurations?

A traditional principal components analysis (PCA) can trace how the variates or the distances among such coordinates covary over time. But interpretation of these data beyond a general size effect or other uniform transformation would be fairly impenetrable as we would be confronted by a large table of multivariate coefficients signaling differences along principal axes that may be unrelated to the coordinates' true geometry (Zelditch et al. 1995, Rohlf 1999). The changes in the borough's 'ecological shape' cannot be easily derived from the PCA.

A better way? Morphometrics, a field of biology concerned with analyzing variation in organismal shape, may provide a better way (Bookstein 1991, 1996a, Rohlf and Marcus 1993, Slice et al. 1998). Its warps analysis involves fitting coordinate *landmarks* of a reference specimen, say, for a hominoid skull, atop sample specimens' homologous landmarks (Figure 2, from Rohlf's tpsSpline program, available with the other TPS programs used in this paper at http://life.bio.sunysb.edu/morph/). The landmark movements needed

to superimpose the reference atop the samples are transformed into an interpolating function and visualized with vectors or deformations in a Euclidean grid, à la D'Arcy Thompson (1917). TpsSpline interpolates from only one specimen to another, but the gist of what geometric morphometricians aim for should be apparent in Figure 2: a graphical, and statistically rigorous, means of displaying changes in configurations.

Bookstein (1989, 1991) showed how these *thin-plate spline* (TPS) functions can help describe the bending and crumpling necessary to overlay specimen landmarks. These deformations can be segregated into *affine* transformations, changes that affect all landmarks uniformly (for example, translation, rotation, size) and *nonaffine* transformations, or localized changes among subsets of landmarks. The localized transformations can be further decomposed into *principal warps*: eigenvectors of declining magnitudes reflecting deformations in the landmarks at increasing geometric scales, from the most localized to the most global.

These transformations, although computed through a hyperspace, can be visualized in the original Euclidean space the landmarks were first plotted. Such changes in shape can also be compared across taxa (or, in this case, boroughs) and regressed against independent variables.

To assess the applicability of geometric morphometrics for geographic data, I apply warps analysis to the HIV-AIDS space introduced in Figure 1 for Manhattan and the Bronx. I thereby address whether geographic sub-units of the Manhattan and Bronx HIV ecosystems evolved together through the parameter space between 1991 and 1998. I also contrast Manhattan and Bronx ecological shapes and explore whether socioeconomic variables are associated with changes in the HIV-AIDS configurations.

Methods

Building a consensus configuration. I closely follow Rohlf's (1993, 1996, 1998, 1999) description of geometric morphometrics and its warps analysis as applied to two-dimensional data.

First order the specimens. Let $\mathbf{X}_i$ be a 2 x p matrix of (x, y) coordinates of the p landmarks of a single specimen (here, a single year's HIV-AIDS configuration of zip codes, as in Figure 1). Let $\mathbf{X}$ be a $2n$ x p matrix of all the coordinates over all the specimens.

A reference configuration is often used to contrast the specimens. Bookstein (1991) defines an a priori configuration, aligning the samples by way of a baseline of two landmarks. Rohlf and Slice (1990), in contrast, make a *consensus* reference configuration by finding the Procrustes average of the specimen landmarks with a generalized orthogonal least-squares superimposition.

The Rohlf and Slice consensus also aligns the specimens in a way that removes the effects of translation, rotation, and size among the configurations in the parameter space. These effects are, in an ecological or epidemiological context, not unimportant. They embody transposition, correlation and variance, respectively. Although staples of epidemiological research, such rigid rotations of the data are considered noise in comparing morphological specimens. Warps analysis, then, aims only to determine differences in *shape* alone, the differences left over in the placement of the landmarks after the differences in the configurations' translation, rotation, and size have been removed (Slice et al. 1998).

Therefore, with the techniques presently available I describe here only the changes in 'ecological shape' of the HIV-AIDS configurations, in comparison to an average shape of the years' HIV and AIDS loads. I aim to get an inkling of how the *relative* positions of the zip codes' HIV-AIDS variables change over time whether or not the epidemic as a whole flowed and ebbed, as it did in New York during the 1990s. This may be an informative way of visualizing the transformations among our 'landmarks,' here the HIV and AIDS loads for New York zip codes over eight years in the 1990s.

The Rohlf and Slice technique for finding a consensus configuration involves first centering a sample configuration of landmarks (S_1) about the origin and superimposing another (S_2) on the first with least-squares Procrustes for each landmark x_i, y_j:

$$S_{\text{superimposed}} = \overline{S_1} + \mathbf{B}S_2 , \qquad (1)$$

where **B** is vector $\begin{bmatrix} \sum (x_1x_2 + y_1y_2) \\ \sum (y_1x_2 - x_1y_2) \end{bmatrix} 1/(\text{size}_2)^2$,

and $(\text{size}_2)^2$ the squared *centroid size* of the second specimen (tpsRelw help file). Centroid size is the square root of the sum of the squared distances of the landmarks from the centroid (Slice et al. 1998).

Next, subsequent configurations are superimposed on the first superimposition. Another sample is added to the first consensus and so on iteratively until a complete consensus configuration is converged upon ($\mathbf{X}_c$), with the differences among the specimens' translations, rotations, and sizes removed and with only differences in shape remaining.

Principal warps. Rohlf (1993), following Bookstein (1989, 1991), next derives the function that moves the consensus landmarks to their homologues on each sample from which isomorphic changes (translation, rotation, size) have been removed. That function first requires the calculation of the 'principal warps' or eigenvectors of the bending energy matrix ($\mathbf{L}_p^{-1}$). To calculate $\mathbf{L}_p^{-1}$, first define a matrix of distances among the consensus landmarks,

$$\mathbf{P} = \begin{bmatrix} 0 & U(r_{12}) & U(r_{13}) & \dots & U(r_{1p}) \\ U(r_{21}) & 0 & U(r_{23}) & \dots & U(r_{2p}) \\ U(r_{31}) & U(r_{32}) & 0 & \dots & U(r_{3p}) \\ . & . & . & . & . \\ . & . & . & . & . \\ . & . & . & . & . \\ U(r_{p1}) & U(r_{p2}) & U(r_{p3}) & \dots & 0 \end{bmatrix},$$

where $U(r_{ij}) = r_{ij}^2 \ln r_{ij}^2$ and r_{ij}^2 is the square of the distance between landmarks i and j in the consensus configuration. Next define

$$\mathbf{Q} = \begin{bmatrix} 1 & x_1 & y_1 \\ 1 & x_2 & y_2 \\ . & . & . \\ . & . & . \\ . & . & . \\ 1 & x_p & y_p \end{bmatrix},$$

with its column vectors of (x, y) coordinates of the consensus configuration. Also define $\mathbf{0}$ as a 3 x 3 matrix of zeros to fill out partitioned matrix

$$\mathbf{L} = \begin{bmatrix} \mathbf{P} & \mathbf{Q} \\ \mathbf{Q}^T & \mathbf{0} \end{bmatrix}.$$

The bending energy matrix ($\mathbf{L}_p^{-1}$) is the upper left $p \times p$ submatrix of the inverse of $\mathbf{L}$.

Rohlf next defines the collection of multidimensional axes, the principal warps, along which the consensus's shape will be warped to overlap each of the specimens, as is done in Figure 2. He takes an eigen decomposition of the bending energy matrix, $\mathbf{L}_p^{-1} = \mathbf{E}\Lambda\mathbf{E}^T$. Λ is a $p \times p$ diagnonal matrix of eigenvalues and $\mathbf{E}$ a $p \times p$ matrix of eigenvectors for the landmarks. The eigenvectors are the principal warps (Bookstein 1989). Principal warps of the largest eigenvalues represent shape deformations at the most localized scales. Three eigenvalues produced here should be zeros, corresponding to the changes at the 'infinite' affine scales brought about by translation, rotation and size. That leaves p - 3 principal warps for localized changes.

It is important to note the principal warps are solely a function of the consensus configuration: to be specific, a function of the pairwise distances among the consensus landmarks alone and not the individual specimens (Bookstein 1991, Zelditch et al. 1992).

Kendall space. Let us define principal warps in a more geometrically intuitive way. The differences in shape among the specimens can be represented in a space named after Kendall. Kendall (1981, 1984, see also Goodall 1991, Small 1996, Rohlf 1999) derived a multi-dimensional space wherein each single point represents a shape of a configuration of landmarks without regard to the size, position or orientation of the configuration (Figure 3a, b, d). Kendall points differ by their configurations' Procrustes distances, the square root of the sum of the squares of their coordinate differences across all landmarks. Because Kendall spaces are curved, the Procrustes distances are measured along the

chord of the sphere in geodesic radians. [For other units and the distinction between partial and full Procrustes fitting see Dryden and Mardia (1998) and Rohlf (1999).]

Kendall space has $pk - k - k(k - 1)/2 - 1$ dimensions, where p is again the number of specimen landmarks and k the number of dimensions the original specimens are situated. Triangles, then, can be pictured on the surface of a sphere ($3 \times 2 - 2 - 2(2 - 1)/2 - 1 = 2$ dimensions). Kendall hyperspaces for shapes with more than three landmarks cannot be graphically represented.

As Kendall space is curved, traditional statistics do not apply. But points on the Kendall hypersphere can be projected orthogonally into a linear vector tangent to the Kendall space (Figure 3c), (Rohlf 1998):

$$\mathbf{X}_{\text{tangent}} = \mathbf{X}(\mathbf{I}_{kp} - \mathbf{X}_c^{\mathsf{T}}\mathbf{X}_c),$$

where $\mathbf{X}$ is a $n \times kp$ matrix of landmarks of the now aligned specimens and $\mathbf{X}_c$ is a matrix of the landmarks of the consensus, both of unit centroid size (partial Procrustes fitting) (Rohlf 1999). The orthogonal projections arise from a space related to Kendall's known as preshape space, but the details are not necessary here [see Rohlf (1996) for the differences among morphometric spaces].

If little variation exists among the specimen shapes, the Euclidean distances of the *tangent space* approximate the Kendall distances, and traditional multivariate statistics can be applied to study shape differences among the specimens. The consensus configuration defines the point of tangency between the Kendall and tangent spaces, and is also why the consensus is known as the tangent consensus (Rohlf et al. 1996). The principal warps are the eigenvectors defining the nonaffine components of the tangent space (Bookstein 1989, Rohlf 1996).

The projection of Kendall points into tangent space is the reason why Rohlf and Slice (1990) recommend using the Procrustes consensus [equation (1)] as the reference configuration: to minimize the distortions in the Procrustes distances among the reference and the sample specimens in the tangent space.

Partial and relative warps. To project the actual deformations needed to overlay the consensus atop each sample configuration, the principal warps are used to generate *partial warp scores* by multiplying the principal warps by the deviations between the samples and the consensus for both x and y coordinates:

$$\mathbf{W} = \frac{1}{n^{1/2}}\mathbf{V}(\mathbf{I}_k \otimes \mathbf{E}),$$

where

$$\mathbf{V} = [\mathbf{V}_x|\mathbf{V}_y],$$

$$\mathbf{V}_x = \mathbf{X}_x - \mathbf{1}_n \otimes [1|0]\mathbf{X}_c,$$

$$\mathbf{V}_y = \mathbf{X}_y - \mathbf{1}_n \otimes [0|1]\mathbf{X}_c.$$

The Kronecker tensor product operator ($\otimes$) multiplies all elements of the second matrix by each term of the first, term by term. The matrix of eigenvectors, **E**, is again the principal warp matrix defined in the decomposition of the bending energy matrix. Matrices $\mathbf{V}_x$ and $\mathbf{V}_y$ define differences between the landmarks of the consensus and those of the ith specimen for x and y coordinates respectively. $\mathbf{I}_k$ is a k x k identity matrix.

The resultant n x $2(p - 3)$ matrix of partial warps are linear combinations of the principal warps of unit length at different geometric scales. The actual elements are

partial warp scores. [For other shape variables see Bookstein (1991) and a summary by Rohlf (1999).]

Geometrically, partial warps are the orthogonal, scale-dependent axes of the tangent space (Rohlf 1998). The partial warp scores instantiate where along the partial warps the reference configuration is locally crumpled and stretched to fit atop the specimen configurations. The scores are weights, telling how much of each principal warp is necessary to account for the actual differences between the specimen and the consensus (Rohlf 1998).

Although the principal warps are orthogonal, the partial warp projections of the specimens are usually correlated (Rohlf 1996). To better emphasize the variation among specimen shapes along a reduced set of statistically orthogonal dimensions, Rohlf (1993, again following Bookstein 1991) subjects the partial warp scores matrix to a singular value decomposition:

$$\mathbf{W} = \mathbf{SDR}^{T} \quad ,$$

where **S** is a matrix of normalized principle component scores known as *relative warp scores*. **D** tells us the singular values (square roots of the eigenvalues from a PCA of a covariance matrix from **W**). **D** describes how much of the variance of shape is in each relative warp. **SD** together project each specimen onto the relative warp (principal component) axes. **R**, a matrix of weighted principal warps, also normalized to one, defines the relative warp axes.

The relative warps are linear combinations of the partial warps, each warp normalized to a length one across all specimens (Rohlf 1993, tpsRelw help file, Les Marcus personal communication). Geometrically, they are the axes of the hyper-ellipsoid the shape points

together occupy in the tangent space (Slice et al. 1998). They differ from the partial warp scores and the tangent space coordinates by rotations alone (Rohlf 1999).

The specimen configurations are projected onto the principal component axes, that is, along the relative warps. Specimens in the relative warp space are best visualized for the two combinations of partial warps that account for the greatest variance in nonaffine shape (see relative warp biplots in the Results section below). The relative warps can also be translated back into the (x, y) coordinate system of the specimens as relative warp loadings (Bookstein 1991). They may also be translated as thin-plate splines (TPS), if scaled properly.

TPS and statistical tests. Thin-plate splines are flat graphical interpolations that minimize the bending energies—the spatial warping—needed to move the consensus landmarks (and the surrounding space) to their specimen homologues (Bookstein 1989, 1991, Rohlf 1993). The spline parameters define all points in the tangent space (Rohlf 1996). For relative warp splines, the unit change in one relative warp score from the reference configuration is

$$\mathbf{N}^{\mathrm{T}} = n^{1/2}(\mathbf{I}_2 \otimes \mathbf{E})\mathbf{RD}\,,$$

giving the nonaffine coefficients for spline or vector displacements. It is these splines and vectors that are computed in Rohlf's program, tpsRelw (Rohlf 1994), and used here for relative warps analysis.

Covariation between two different sets of shapes can be found with Rohlf's tpsPLS program, by correlating partial least-squares combinations of their partial warp scores. The partial warps can be regressed on independent variables of interest (with Rohlf's

tpsRegr program) to address whether any single, or combination of, variables best accounts for the differences in specimen shapes. Rohlf's programs can also generate splines for hypothetical shapes, including shapes expected by regression.

Uniform changes. Global, affine differences among all the landmarks may also exist in the form of *uniform* changes (Bookstein 1991, 1996b). Such changes are best visualized as changes in the parallel lines of a Cartesian grid that defines a configuration's space (imagine the spline in Figure 2 straightened out and defined by a grid of squares or rectangles). *Shear* involves changes in the angle at which the parallel lines, and, it follows, the landmarks in that space, are together arranged (a shear would tilt the grid's strict rectangles into parallelograms). *Dilation* involves changes in the ratio in the x and y components of all the positions of the landmarks. If the x distances shorten, the horizontal spaces between the landmarks shorten, along with the distances between the vertical lines of the grid defining the configurations' space (the grid and shape become thinner).

Bookstein (1996b) derived estimates for the uniform components:

$$u_1 = \frac{(\alpha \sum v_j \delta x_j + \gamma \sum x_j \delta v_j)}{(\alpha\gamma)^{1/2}} \quad .$$

$$u_2 = \frac{(-\gamma \sum x_j \delta x_j + \alpha \sum v_j \delta v_j)}{(\alpha\gamma)^{1/2}} \quad .$$

where u_1 estimates shear along the consensus's principal axis, u_2 estimates dilation along the principal axis, $\alpha = \sum x_j^2$, $\gamma = \sum y_j^2$, δx and δy satisfy constraints brought on by the Procrustes superimposition, and (x_j, y_j) are the coordinates of the jth landmark in the consensus.

What do the uniform estimates define geometrically? Through the point of tangency (that is, the mean shape or consensus), in the space tangent to the Kendall shape space, is a two-dimensional subspace U. In plane U are represented all related shapes that differ only by uniform transformation in the original Cartesian plane (Bookstein 1996b). The uniform components are projected from the Kendall space onto U and are approximated by u_1 and u_2.

As Rohlf's programs do, the uniform components can be concatenated with the partial warp scores matrix for splining and statistical tests.

The data. Zip codes of Manhattan and the Bronx, two boroughs of New York City, constituted the study area (Figure 4). Each borough alone contains population levels comparable to other major cities. The 1990 US Census shows Manhattan with 1,487,536 persons, the Bronx with 1,203,789, both boroughs with populations near those of other US cities like Indianapolis, San Antonio, Portland, and Orlando. Census zip code populations 1990 used in this study range from 3,435 to 107,197 persons, at an average of 43,718. Together the boroughs total 64,039 accumulative AIDS cases or 55% of New York City's geographically identifiable cases as of first quarter 2000 (Office of AIDS Surveillance 2000).

Annual adult AIDS incidences per zip code for Manhattan and the Bronx for 1991-1998 were obtained from the Office of AIDS Surveillance, New York City Department of Health. The Office of AIDS Surveillance collects these data from physicians, infection control practitioners, and other health care professionals in hospitals, clinics, and private practices throughout New York City.

The Office of AIDS Surveillance censors all data cells below five cases for use by outside investigators on the grounds of protecting patient confidentiality. For this study, '3' was entered in all censored cells as a reasonable approximation of the true data. There are no provisions for missing data in warps analysis. All specimens must have the same landmarks (that is, data for all zip codes on the configurations).

The numbers of newborns with HIV antibodies were obtained from New York State's Office of HIV Epidemiology for Manhattan and Bronx zip codes for 1991-1998. The newborn data up through 1996 were collected from the New York State Survey of Childbearing Women (Amy Storfer-Isser, State Department of Health, personal communication). Data for 1997 and 1998 were taken from the state's Comprehensive Newborn Screening Program.

Not all newborns with HIV antibodies are infected. All, however, have been perinatally exposed to the retrovirus. The incidences of newborns exposed act as markers for HIV prevelances among mothers. Many of these mothers may have been infected years previous to giving birth, but because New York State does not keep a registry of new HIV infections, these incidences of newborn exposures provide the best available citywide snapshots of prevailing HIV infection rates, albeit for a restricted population.

Warps analysis of AIDS parameter space. Rohlf's tpsRelw program was used to calculate and plot the relative warps for Manhattan and Bronx zip code HIV-AIDS loads for each year from 1991 to 1998. The coordinates defined in the ecological space are the annual percent newborns exposed to perinatal HIV and adult female AIDS incidence. These give us an indication of the evolution of the heterosexual epidemic or, certainly,

the epidemic for women. Before calculating the relative warps, the percent newborns exposed was multiplied by 10 to frameshift them into a scale commensurate with the AIDS incidences.

TpsPLS was used to determine the covariation between the Manhattan and Bronx shapes, even with a difference in the number of landmarks. TpsRegr was used to determine whether a set of independent variables regress with spline scores for either Manhattan or the Bronx. The independent variables used, and for which there were adequate annual data, were borough-wide homicides and tuberculosis incidences. An additional dummy variable dividing the samples into pre-HAART (-1) and HAART (1) years was introduced to test for changes in ecological shape with the introduction of the antiretroviral combination therapies. Regression, much less multiple regression, for such a small sample size (n = 8) is inappropriate. For multivariate tests more specimens than the number of partial warps plus the number of independent variables are required (tpsRegr help file). I include the results to show the possibilities for satisfactory data sets.

Results

Manhattan relative warps. The first two relative warps in the perinatal exposure-female adult incidence (HIV-AIDS) parameter space together account for 70% of the total variance in ecological shape change among Manhattan's zip codes for 1991-1998. The first relative warp alone explains 53.64%.

Figures 5 and 6 show relative warps plots of the AIDS epidemic for Manhattan and Bronx zip codes from 1991 to 1998. Thin-plate splines and vector displacements are shown for each year. Figure 4 lists the zip codes and their landmark numbers. Keep in mind Rohlf's tpsRelw program rotated the original exposure-incidence axes in arriving at

the consensus configuration. The grids deformed with the splines are visual aids only and unrelated to the parameter space axes in Figure 1.

The vector displacements are another way of showing the transformations embodied by the splines. The landmarks are left positioned in their consensus configuration and the vectors show how the consensus landmarks are displaced by the first two relative warps (to approximate overlapping each specimen's landmarks). The vectors are two-dimensional projections along only the first two relative warps after rotation and transformation have been removed and are not to be taken too literally, particularly because of the distortion in landmarks that can be brought on by the projection into tangent space. But the vectors can give an idea of relative movements of the zip code landmarks from year to year compared to the consensus configuration.

The resultant splines show for any given year the relative positions of the zip codes and how the entire ecological shape is warped in comparison to the consensus configuration. Clearly Manhattan saw in the HAART era (1996-1998) a shift in its shape's shear, from right to left, associated with the first relative warp (see relative warp biplot Figure 7a). The second relative warp may be associated with, among other changes, how Old Chelsea (Landmark 8) and Cathedral (20) are oriented with each other. In 1991, 1992, and 1997 Chelsea is closer than Cathedral to the other zip codes along the horizontal axis.

By 1998, Manhattan shows a trilateral epidemic in the parameter space, according to the relative warps. Most of the zip codes are collapsed by 1998 in a singularity (on the left) or in a group in the middle of the warp, which includes zip codes such as Knickerbocker, Stuyvesant, Manhattanville (in the Lower East Side) and Triborough

(Harlem). A third group exists, though folded over for Manhattan on the right: Old Chelsea, Catherdral and Hellgate. The shape's triptych appears comprised of disparate zip codes. But the thin-plate splines do not show how these groupings were formed.

By looking at how the zip code landmarks are grouped in the consensus configuration and the direction and magnitude of their vector displacements for each year (on the right in Figures 5 and 6), we can see several major trends emerge.

First, Manhattan appears to be divisible into two HIV-AIDS ecologies. For 1991 to 1995, landmarks of Lower Manhattan zip codes (2, 3, 6-12, 15, 18, 19, 20), generally more white and affluent in population make-up, had greater vector displacements to the right along the horizontal axis than their consensus homologues. On the other hand, during this time, landmarks for zip codes primarily situated in Harlem (21, 22, 24-27, 30-32, and 34) have greater vector displacements to the left than their consensus counterparts.

Year-to-year variations do exist. Post Office (1), contiguous with Times Square (31), the latter a functionally Harlem HIV zip code, joins the Harlem ecology for 1993 and 1994. Audubon (27) joins Lower Manhattan for 1993.

Lower Manhattan can be divided into three sub-areas. What changes that do occur for Bowling Green (4), Church St. (5), Grand Central (13), Peck Slip (33)—and in 1993 Midtown (14)—do so along the spline's vertical axis. These zip codes comprise the core of the city's financial districts. Old Chelsea (8) and Cathedral (20) pool together at the extreme top right of the ecology shape. The bulk of Lower Manhattan zip codes line up horizontally along the top of the shape.

With the introduction of HAART in 1996, the dynamics dramatically shift. The horizontal vectors of Lower Manhattan and Harlem zip codes switch in direction, and the splines shear left.

There are exceptions. Radio City (15) joins the Harlem zip codes for 1996-1998, Madison Square (7) does for 1996, and Post Office (1), Knickerbocker (2), and Cooper (3) do for 1997, though Knickerbocker and Cooper have contrary vertical vectors. By 1997 Times Square (31) appears to begin to epidemiologically uncouple from the Harlem zip codes.

Bronx relative warps. For the Bronx, the first two relative warps account for only some 44% of the total variance in the landmarks' relative positions. The first warp accounts for 23.34%, the second 21.23%. Much of the variance is therefore lost in the reduced data dimensionality of the relative warps. That means a more complex interaction in landmark migration exists than can be accounted for by the first two relative warps alone. Bronx zip code landmarks migrate through their HIV-AIDS hyperspace in more complex interplays than Manhattan zip codes do.

The Bronx spline plots bear the complexity out (Figure 6). The number of groups of zip codes moving together is greater than for Manhattan and their stability from year-to-year less. The Bronx zip codes pivot along both relative-warp displacement axes whereas for Manhattan most variation ranged across the horizontal axis. For example, even before HAART's introduction, Morrisania (6) migrates with an array of zip code partners. In 1991, Morrisania moves along the relative warps with Highbridge (2), Tremont (7), Fordham (8), Wakefield (16), Jerome Ave (18) and Soundview (22). In 1992, Morrisania

moves in the opposite direction with Fordham, Wakefield, Jerome Ave and Soundview, but also with Throgs Neck (15), Baychester (19), Woodlawn (20) and Boulevard 2 (24). The year 1993 shows little migration, approximating the consensus configuration. In 1994 and 1995, Morrisania eschews its previous vector partners for Post Office (1), Boulevard 1 (9) and Cornell (23).

For the Bronx, relative warp one involves variation in the ecological space at the left end of the TPS (see biplot, Figure 7b). Landmarks 11, 13-16, 19-21, 23-25 are vertically expansive in 1994 and 1995. In the other years they are collapsed, particularly in 1997 and 1998. The second relative warp appears associated with the other end of the spline. The space marked by Highbridge (2), Morris Heights (3), Mott Haven (4), Morrisania (6), Tremont (7), and Fordham (8) is much wider in 1991 and 1997 than in the other years.

Covariation among shapes and regression with independent variables. The first three combinations (vectors) of partial warp scores calculated by partial least-squares analysis in tpsPLS explain 89% of covariation between Manhattan and Bronx HIV-AIDS shapes (Table 1). TpsPLS correlated only the *i*th shape vectors of Manhattan and the Bronx (i.e., compared the first Manhattan vector only with the first Bronx vector, etc.). All seven vector dimensions compared show correlations between the shape vectors of r^2 = .94 or above, for the eight specimens. In short, Manhattan and the Bronx shared similar tangent spaces.

The boroughs' first shape vectors explain most of the covariation between the Manhattan and Bronx shapes (59%). Their plot (Figure 8, r^2 = .95) shows both boroughs'

shapes separated by pre-HAART (1991-95) and HAART (1996-98) years, bearing out the trends apparent in Manhattan's relative warps (Figure 5).

Although the regression results are inapplicable because the sample sizes are too small (n = 8), they are of methodological interest. Table 2 shows the Manhattan and Bronx partial warps strongly correlated with at least one of the three independent variables introduced: annual borough homicides, incidence of tuberculosis, and HAART availability. The warps are divided into their x and y components.

For the Bronx, most of the strong correlations are on the mesoscale partial warps (9-15), particularly the y components. The y uniform axis is also particularly strong for all three variables. With more landmarks Manhattan had more partial warps than the Bronx. Even so, many more Manhattan partial warps displayed strong correlations with independent variables than for the Bronx, particularly on the x components of partial warps 1-6, 13-24, 31-33, and at the uniform scale.

Some of the stronger multivariate regressions are shown in Table 3a. Three Bronx partial warp components showed results with prob < .05 (3Y, 14Y, uniform Y). Five Manhattan partial warp components were regressed upon with prob < .05 (14X, 23X, 24X, 29Y, uniform X). Table 3b shows the squared Procrustes distances between each specimen and the consensus configuration (ref d^2) and between each specimen and its predicted shape as defined by the regression (resid d^2) (Rohlf's tpsRegr help file). The greater the residual distances the less the regression model explains the actual shapes. Manhattan's configurations were better explained by the multiple regression in relation to the summed Procrustes distance of the predicted configurations.

Discussion

Organisms? A geometric morphometrics approach to geography views the Manhattan and Bronx configurations of the example as integrated 'organisms' comprised of interacting zip codes that undergo epistatic change. To be sure, the resultant 'organisms' are not necessarily functional units, as the biological organisms geometric morphometrics model. The boroughs are administrative divisions separated by the Harlem River, a barrier most pathogens and social pathologies do not respect. On the other hand, how population structures and city services are distributed may be a function of these administrative districts and the politics and histories that accompany them. Wallace and Wallace (2000) show the boroughs do differ in their ecological resiliences, even as they share similar superficial public health and census statistics.

Still, interactions between Manhattan and Bronx sub-areas—embodied by shared social networks and the subway—violate the autonomy the term 'organism' evokes. 'Organism' in this context, then, should be considered heuristic and not literal. We should keep in mind, however, that underlying warps analysis on ecological data is the view that large geographical areas display emergent properties that arise from singular and interacting processes acting at the level of component areas and that tracking these interactions over time is useful.

Advantages to this warps analysis approach include reducing data dimensionality of shape differences and provisioning pictographs as intuitively graspable as maps. In fact, as changes in relative incidences can be hidden on maps by broad data ranges, thin-plate splines and vector displacements along warp axes can give a clearer view of relative changes in ecological space even as the rigid affine differences (transposition,

correlation, and variance) are removed. This assumes, of course, the first two relative warps can explain much of the variance, as it does for Manhattan in the example.

From a methodological view it is comforting that with warps analysis we detected the sea change in New York's AIDS epidemic (Figures 5 and 8). With the introduction of HAART, Manhattan's HIV-AIDS 'organism', as defined by TPS, shears from right to left. The relative positions of two subareas moved in opposite directions as defined by their relative warp vectors. *Compared to the consensus configuration*, Lower Manhattan zip codes underwent a greater collapse in their epidemics than Harlem zip codes whose *relative* positions reversed. Manhattan's AIDS epidemic in the 1990s was defined by a socioeconomic fault line that ran along the *x*-spine of the borough's ecological shape (Tables 2, 3a). A look at the percents decline for both epidemics (Wallace, in press) shows the decline for AIDS incidences, but not for perinatal exposures, to be generally greater for Lower Manhattan than Harlem zip codes.

In contrast, the Bronx AIDS epidemic is not as easily defined. The Bronx does not cleanly segregate into HIV-AIDS subareas before and with HAART (Figure 6).

The warps are not just confirmatory. The manner in which zip codes Times Square and Post Office moved in the splines with Harlem zip codes offered new insight into the ways the former way be epidemiologically connected to the latter. Another example: that Bronx independent variables tested here correlate well only with the mesoscale partial warps begs further explanation. Is the Bronx's AIDS ecology best defined at a 'superneighborhood' level?

Ecolometrics and morphometrics. This 'ecolometrics' differs from its morphometric parent. Once the variables to be used are determined (see below), the landmarks (the zip codes in the parameter space) are defined by the data themselves, not, as in morphometrics, at the discretion of the investigator. Moreover, we do not define a priori the AIDS ecological units/subareas. They are again defined by the data and the analysis themselves. Still, even zip codes that migrate together in the HIV-AIDS space for several years need not be entrained by the same causes. This is, of course, the classic problem of pattern and process. Harlem uptown and Tribeca downtown may cluster together in any given year, but the prevalent modes of transmission and the population- and patient-level resources to deal with the epidemic may be very different indeed.

Process and pattern may be even more complicated for ecological shapes than morphological ones. Landmarks along the top skull shown in Figure 2 are designated along a known and knowable space. In short, we can see the skull, even if imaging flattens the third dimension. We cannot see ecological shape except by the landmarks themselves: in this case, combinations of administrative and health data sets for each zip code. Moreover, even as two neighbor landmarks on a skull are acted upon by different evolutionary forces, there exists a real physical proximity. On an ecological shape, two proximate landmarks need not have any physical or direct causal connection as our Harlem-Tribeca example insinuates.

Warps analysis for ecological shape has the interesting property of axis choice. While axes for skulls are by definition spatial in nature, we can choose whatever variables we please to define our ecology. I chose perinatal exposures to HIV and female adult AIDS incidences as they seemed to mark the state of the epidemic—transmission rate and

disease incidence—for any given year. I chose female rather than total adult AIDS incidences because percents perinatal exposure are more accurate markers of female than total infections. Geographers and ecologists, for better or worse, have a flexibility in variable choice that morphological warps analysts do not have.

Sensitivity to scalar transformations. An anonymous reviewer expressed concern such free choice with axes introduces arbitrariness. For example, the newborn-exposure variates are multiplied by ten. (This means the proportion of newborns exposed was multiplied by a thousand instead of by a hundred as when generating percentages.) The additional scalar repositions the landmarks along one axis (in a type of shear). Different configurations—even affine changes in the consensus or specimens—generate different principal warps, different shape space distances, and different partitioning into affine and nonaffine components (Rohlf 1996). However, we would otherwise be left with two axes of scales an order of magnitude different. The resultant warps are unreadable. Multiplying by ten only eliminates the difference in axis scale so the splines can be read. The transformation is not arbitrary (as long as it is applied to all landmarks of all specimens).

From a conceptual perspective, ecological scatter plots are only ciphers or graphic translations of real change 'out there' (in the ecology) in ways morphometric configurations are not. Scalar transformations need not, then, be viewed as inherently degenerate and are indeed often used (Sokal and Rohlf 1995). It is just that here the criterion for transformation is not maximal correlation, but axes of the same order of magnitude.

But are the transformations robust? As a test, the original percent data for newborn exposures were substituted instead. The resultant relative warp biplots, the percents covariance between the partial warp scores, the correlations between shape vectors, and the correlations with independent variables did not so differ as to alter the conclusions first arrived at. For example, the correlation of Manhattan's shape vectors is still segregated by HAART availability. The Manhattan model (based on the three independent variables) still explained a greater percent of the specimens' distributions than the Bronx's, with many of the same partial warps of high correlation. The Bronx partial warps that regressed best with the independent variables were still mesoscale. About the relative invariance to data transformation, Rohlf (1996) declares that as long as the specimens are premultiplied by a transformation matrix of full rank, results of statistical tests such as MANOVA and multiple regression should be unchanged.

Rohlf's tps programs do not graphically correct for orders of difference on axis scales as workhorse graphing programs such as SigmaPlot do. We should not be surprised because Rohlf's programs were designed strictly with morphometric applications in mind (with axes of absolute distance). Perhaps the tps series can be reconfigured to permit axis spacing for ecological applications (as is done, for example, for all types of monotonic regression).

What about the lost correlations? A disadvantage to this ecolometric approach is the rotation Rohlf's programs partake in when superimposing specimens (making the configurations' principal axis horizontal). The arbitrary nature of rotations for morphometric specimens is of little consequence because both axes that define the

original space are defined by the same variable—absolute spatial distance. Arbitrary rotation of ecological specimens, particularly in parameter spaces defined by two different variables, hampers easy and precise interpretations of the changes in relative positions of the landmarks in the original parameter space.

Morphometricians often, but not always, view affine transformation as noise. Allometric differences may be of evolutionary interest, but configurations of landmarks that differ in rotation do so, for example, because of crooked digitization of photographed samples. Rotation of a configuration of points in an ecological parameter space, on the other hand, is synonymous with correlation, the heart of much natural and social science.

Three possible fixes come to mind. First, Rohlf's tpsRelw program has an option that eschews the rotation discussed above (when the consensus and the specimen configurations are rotated to make their principal axes horizontal). The rotation is a prerequisite for including Bookstein's simplified uniform estimates (u_1, u_2) in the splines (Rohlf, personal communication, Rohlf 1996). By forgoing the alignment the essential orientation of the configuration in the original parameter space is preserved, perhaps aiding interpretations of the resultant warps (compare Figures 1 and 9). On the other hand, only the localized changes are shown (and for relative warps 1 and 2 only). Perhaps we need an option that forgoes the horizontal alignment and is able to include Bookstein's estimates of uniform transformation. I think that is a practicable option.

Or, perhaps we might eliminate the consensus configuration and build splines among the naked specimens, their differences in translations, rotations and sizes intact. The problem is the consensus configuration cushions the distortions involved in projecting

shapes into the tangent space. The resultant splines would also otherwise be uninterpretably tangled.

Perhaps a different shape space other than Kendall's could be used, one more resilient to distortions brought about by disparate rotations. Rohlf (2000a, 2000b, Monterio et al. 2000) looked at a variety of spaces and concluded Kendall space best for morphometric applications.

But such fixes may only dilute the power of the approach. The third possibility involves geographers coming to terms with the idea of 'ecological shape'; that much can be learned from comparing different configurations with their differences in transposition, correlation, and variance removed. These latter parameters can be explored with more traditional statistical approaches. An ecolometrics may supplement statistical tools already available. A toolbox filled with more than hammers seems desirable.

Satisfying operational standards. These problems and promises aside, we cannot interpret every little warp in thin-plate splines anyway. First, two relative warps alone do not explain the full variance, especially, here, for the Bronx. Second, the temporal scale at which ecologists often examine phenomena evokes the likelihood stochasticity plays a more prominent role for geographies than for comparatively staid bone morphologies. The stochasticities, speeds, and amplitudes of ecological change make ecological shape as defined by our principal warps more varied, perhaps to the point of making the tangent space ill representative of the curved Kendall shape space.

But tpsSmall (Rholf 1997), another of Rohlf's TPS programs, shows the tangent spaces for the Manhattan and Bronx configurations correlate remarkably with their

Kendall homologues (both boroughs with r^2's of .99). So despite what seems greater shape variability for our epidemiological configurations than for typical morphological specimens, the technique used here appears to satisfy geometric morphometrics' operational standards (Rohlf 1996).

As to its real-world applicability, that may be another story. The biological interpretability of warps was recently the focus of much intensive ongoing debate among morphometricians, particularly between Rohlf (1998, Adams and Rosenberg 1998) and Zelditch et al. (1998, Zelditch and Fink 1998). The latter use partial warps to apply scale-dependent changes in bone morphologies to phylogenies across taxa and within ontogenies (for example, Zelditch et al. 1992, 1995, Fink and Zelditch 1995).

Their work on partial warps, though rejected by Rohlf, begs the question whether partial warps can be applied to geographic data as a way of segregating epistatic effects at different scales of interaction. In other words, can partial warps heuristically differentiate local from global effects in the parameter space? And do they do so in relation to independent variables (as hinted at in Tables 2 and 3)? Would such effects matter only if the landmarks closest to each other share geographic mechanisms, linking parameter space pattern with ecological process? Either way, because partial warps are not statistically orthogonal—even as they are geometrically orthogonal—statistics used on partial warp scores must generate results invariant to rigid rotations of the shape space (Rohlf 1998). If not, scale effects may be better addressed by more traditional statistics (see Peterson and Parker 1998).

Even if applying geometric morphometrics ultimately proves ill suited for geographic data, a search for an intuitive and statistically rigorous means of displaying epistatic

spatial changes over time beyond what spatial autocorrelation and maps can show may prove intellectually bountiful.

Acknowledgments

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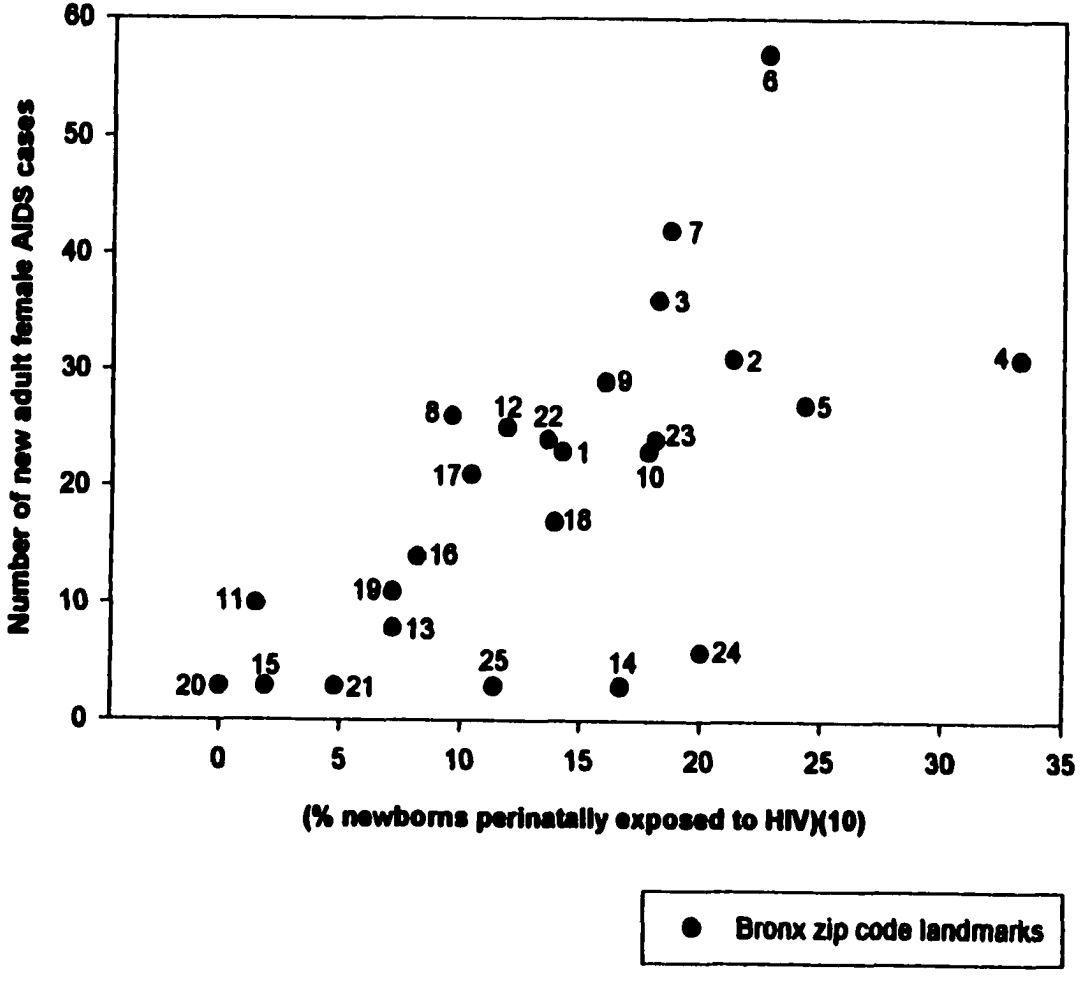


Figure 1. Example of an ecological shape specimen. Percent newborns perinatally exposed to HIV and female adult AIDS incidence for 1991 Bronx zip codes. Points represent landmarks on the Bronx's HIV-AIDS ecology shape for 1991. See Figure 4 for zip code names associated with each numbered landmark. The percent newborns exposed was multiplied by ten to set its coordinates in a scale commensurate with that of the incidences.

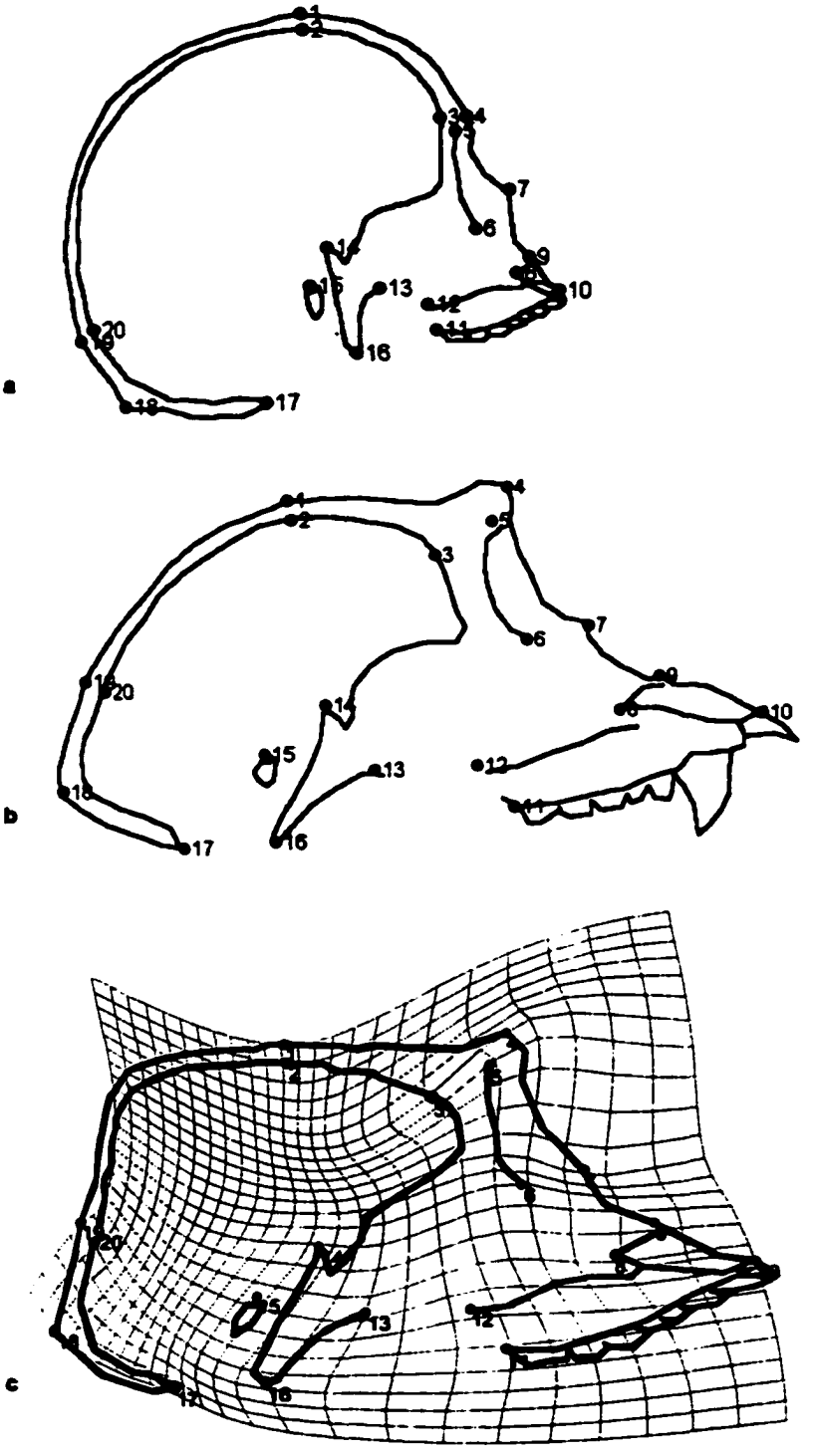
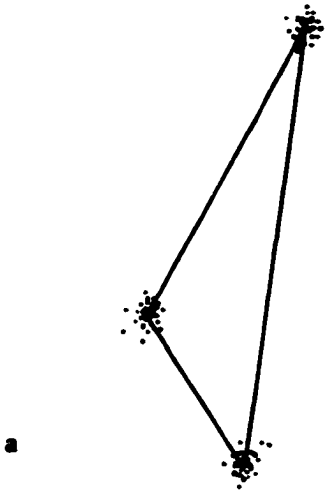


Figure 2. Example of TPS transformation. Twenty landmarks about human skull (a) moved to their homologous landmarks on ape skull (b) via principal warps and thin plate splines (c). These data, from Sneath (1967), are samples used in Rohlf's tpsSpline program. To make an ape skull from a human skull requires collapsing the brain case and extending the brow ridge and upper palate.

Figure 3. Kendall shape space. A la Rohlf (2000), Gaussian error simulated about each of a triangle's three landmarks to generate a distribution of triangles of various shapes (a). These simulated triangles can be plotted as single points on the (kp – k – k(k-1)/2 –1) –1 dimensional surface of a curved, multidimensional Kendall shape space, where k is the number of dimensions of the original (Euclidean) configuration and p the number of landmarks. Kendall space, then, can only be visualized for triangles (two dimensions) (b, with Rohlf's tpsTri program). The distances among the points are measured in geodesic radians. The Procrustes mean shape of the simulated triangles (a) sits in the middle of the clump of shape points. The equilateral triangle sits at this space's North Pole.

Shape points in the Kendall hyperspace can be projected into a Euclidean tangent space and the relative positions of the configurations preserved (c, Rohlf 1998). Only in the tangent space can standard multivariate statistics be applied to the covariation in the distances among the specimens' homologous landmarks. Rohlf shows here two possible tangent lines. Tangent A, through the center point (2), better preserves the relative positions of the configurations. This is why Rohlf and Slice (1990) recommend using the least-squares Procrustes consensus configuration as the reference shape. Even then, the further away from the point of tangency, the more distorted the tangent space becomes.

To better impart what tangent space looks like for triangles, (d), made with tpsTri, shows the tangent space with the specimen in their actual shapes rather than as Kendall shape points. The Gaussian scatter of Kendall shapes from (b) is overlaid atop their true shapes. →



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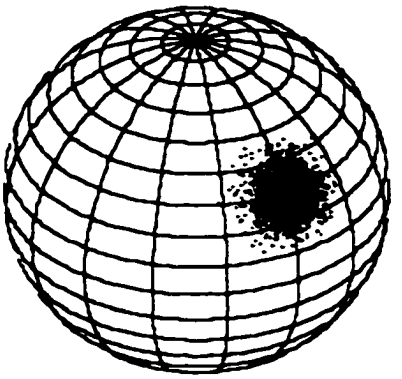

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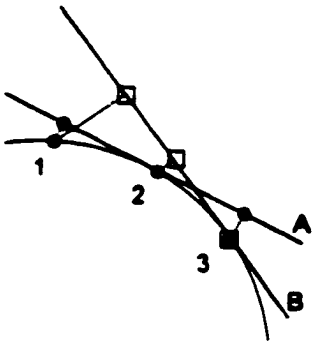

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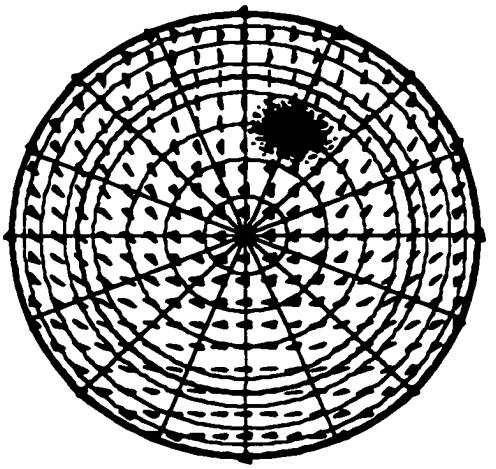

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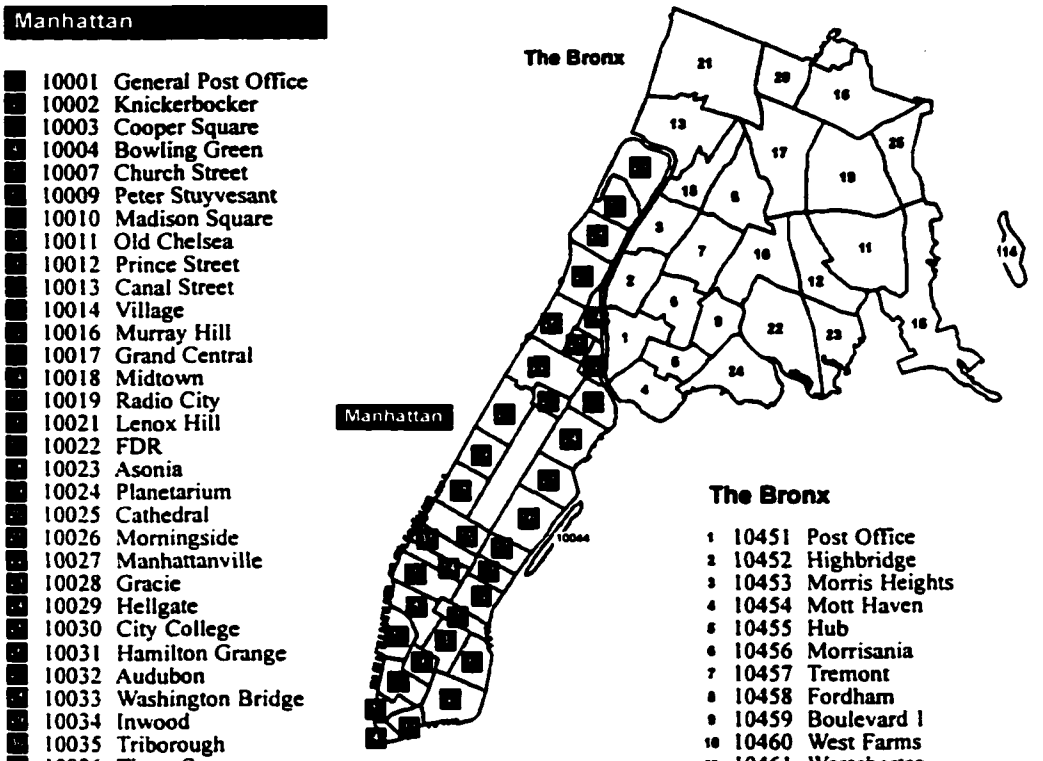

Figure 4. Bronx and Manhattan zip codes. The zip codes are coded by landmark numbers for the warps analyses discussed in the text. Listed are the landmarks for those zip codes used in the warps analysis and their associated names.

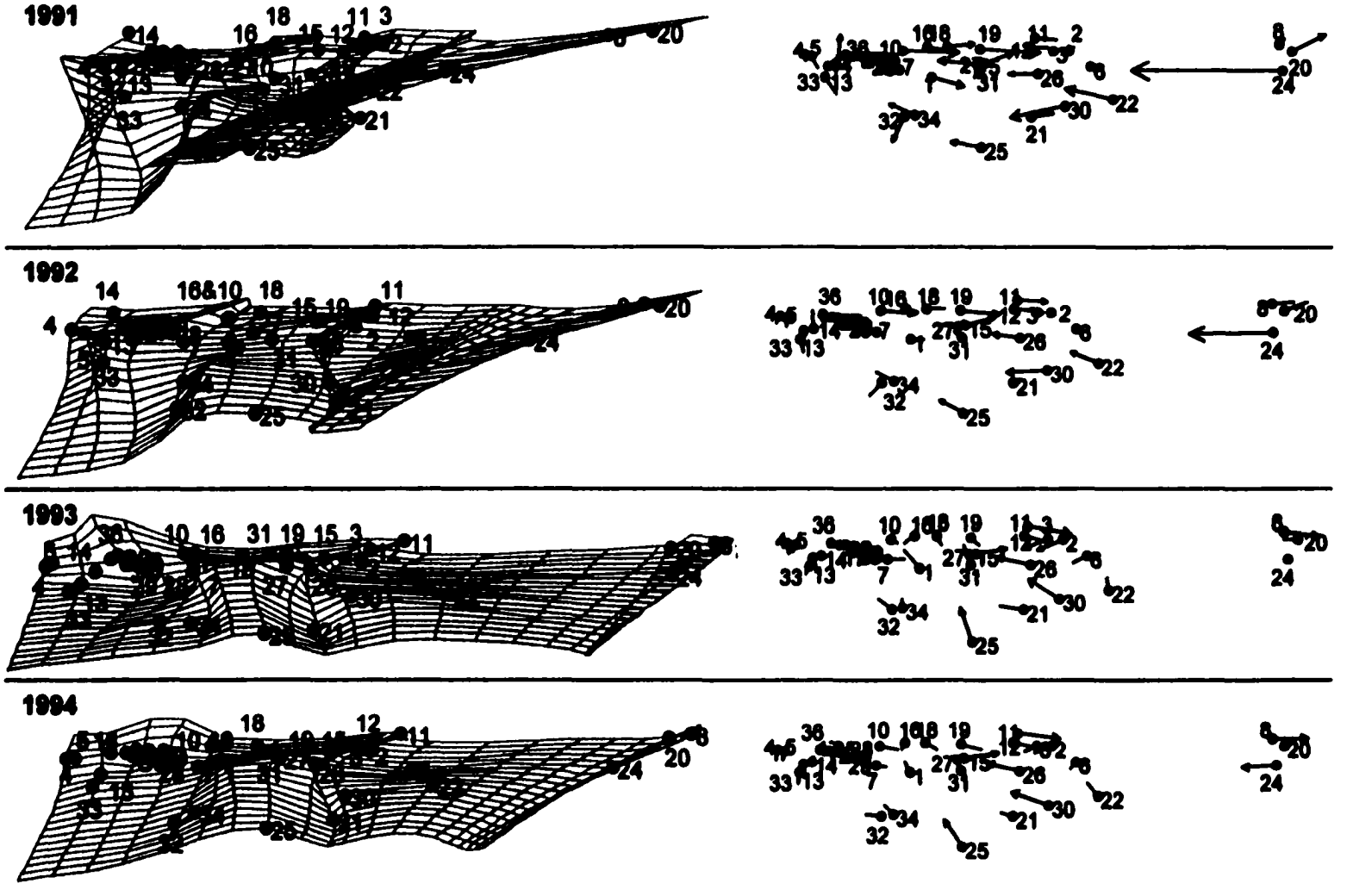

Figure 5. Thin-plate splines (left) and vector displacements (right) for Manhattan zip code relative warps 1991-1998. The vectors displace from the consensus configuration.

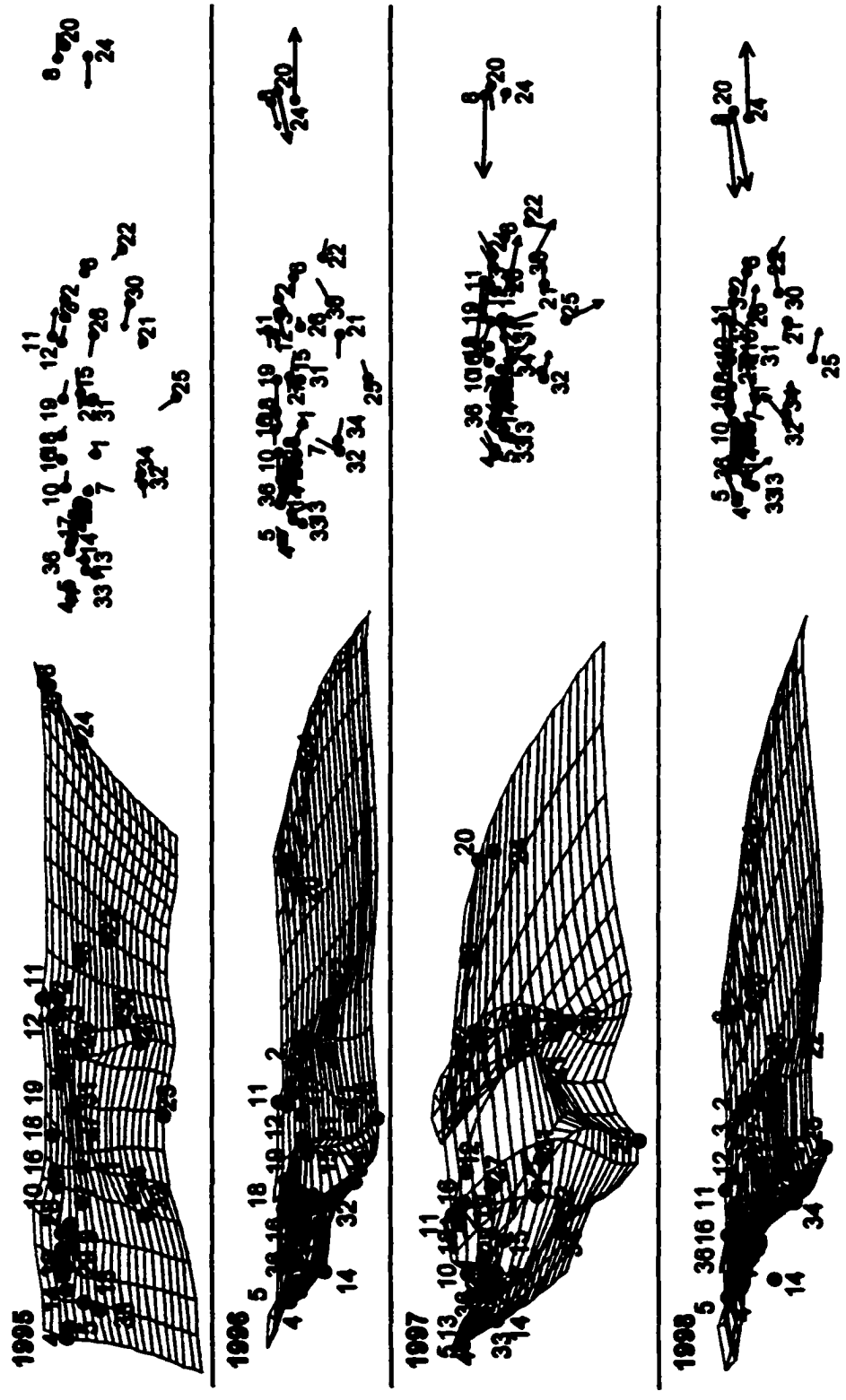

Figure 5 (continued).

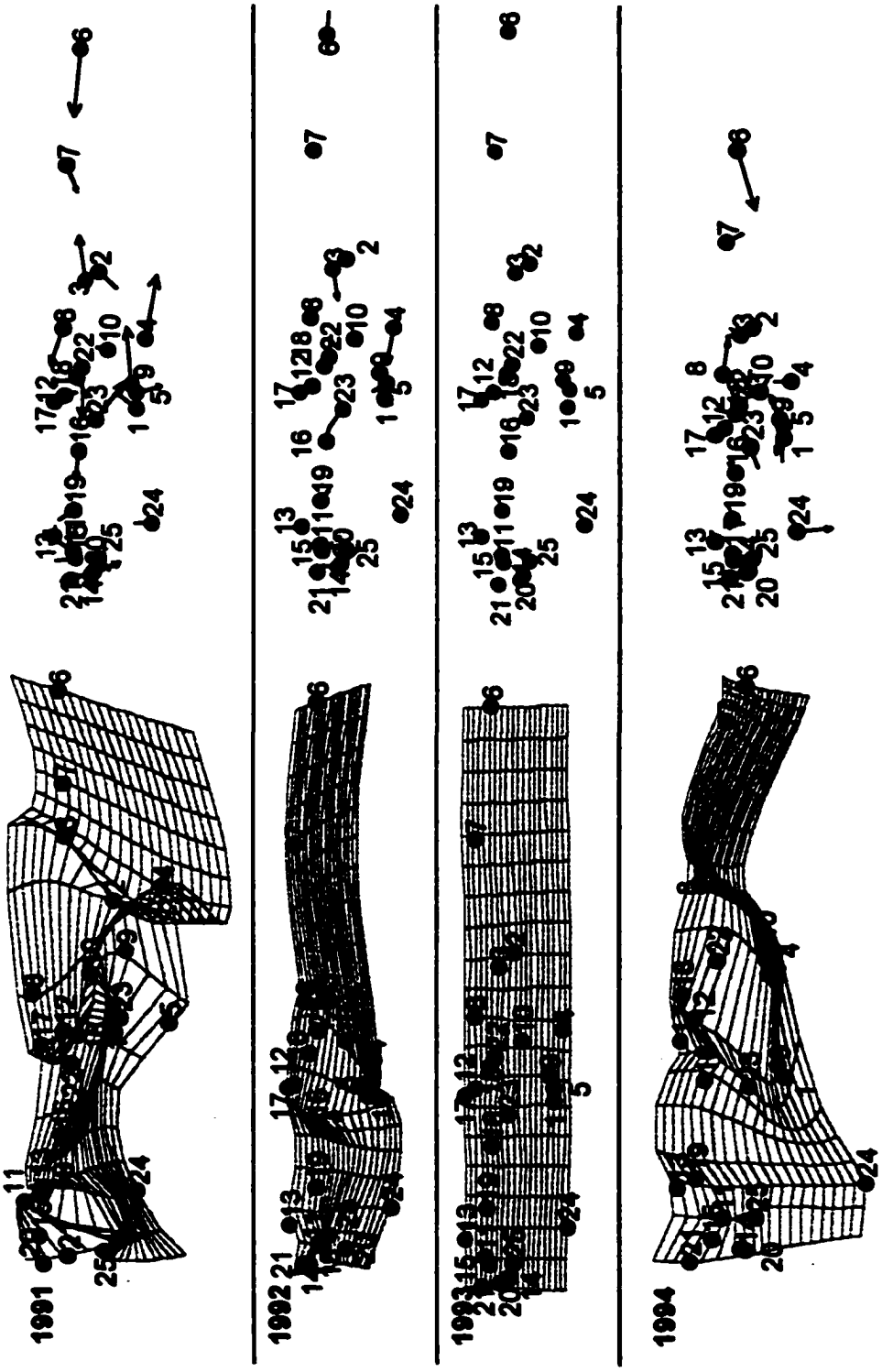

Figure 6. Thin-plate splines and vector displacements from the consensus configuration for Bronx zip code relative warps 1991-1998.

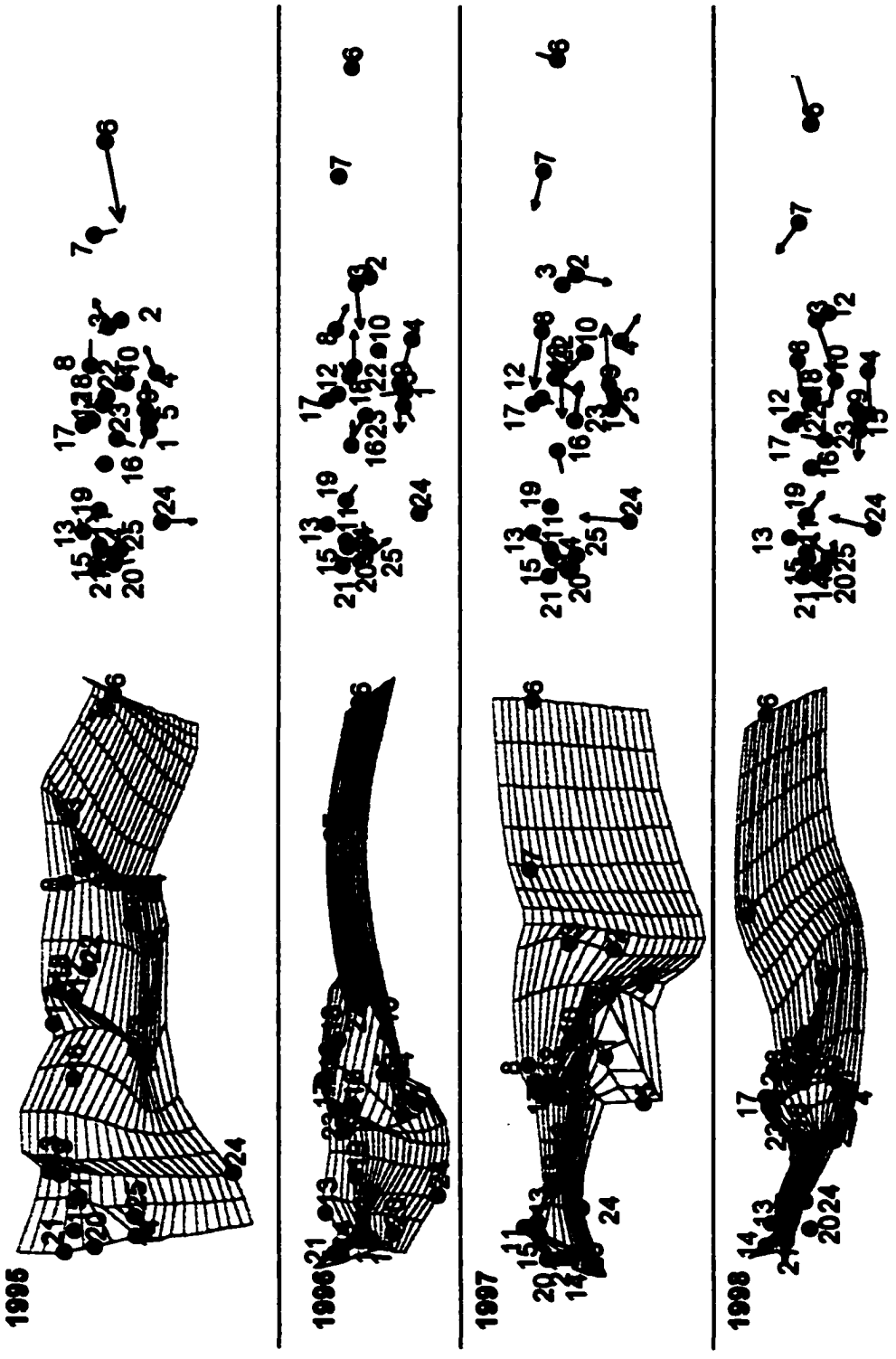

Figure 6 (continued).

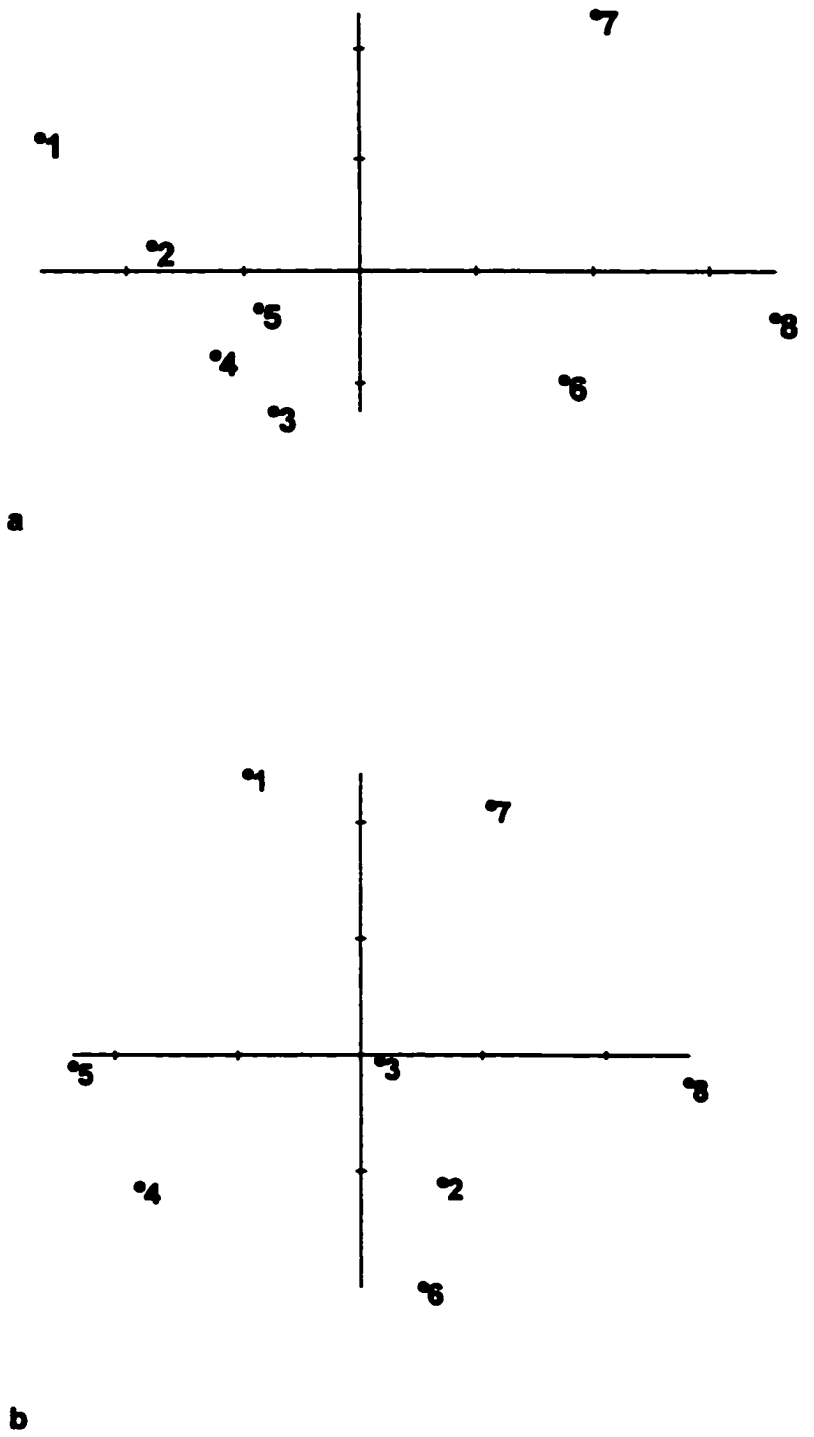

Figure 7. Biplots of relative warps 1 (horizontal axis) and 2 for Manhattan (a) and the Bronx (b) for specimens 1991-1998 (1-8).

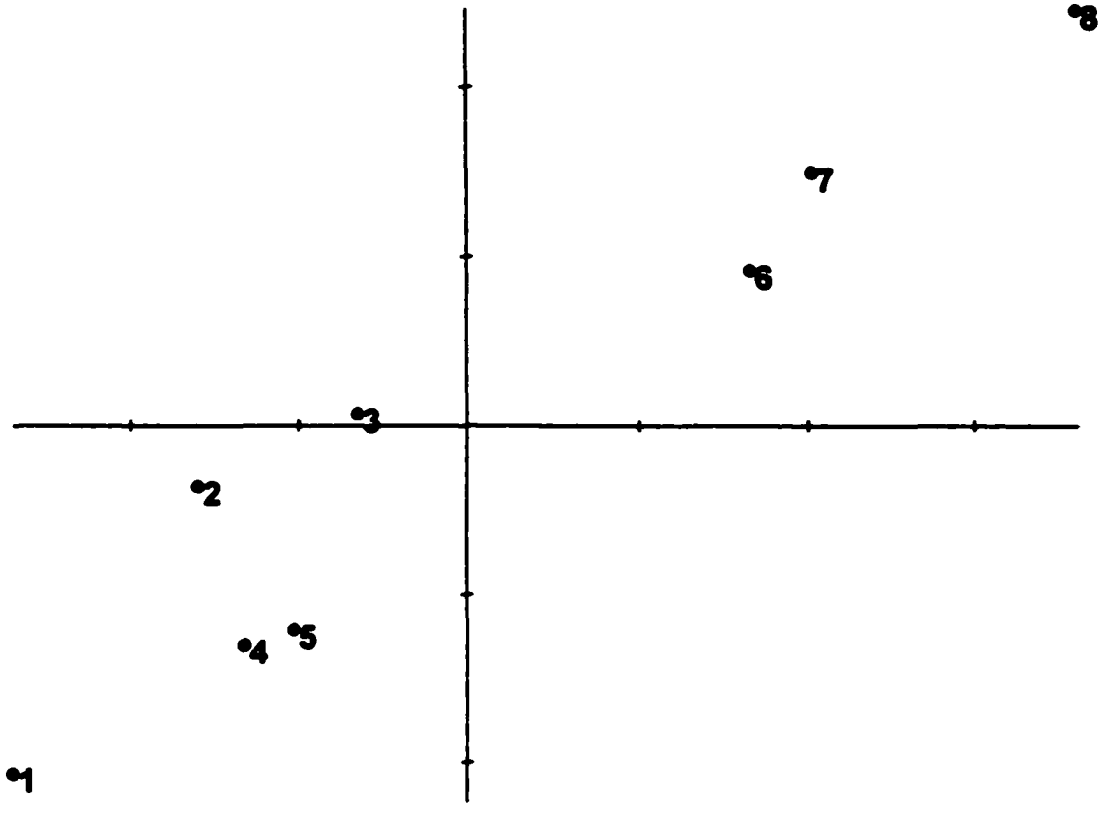

Figure 8. Correlation of first shape vectors for Manhattan and the Bronx, explaining 59% of total covariation between the boroughs' shapes (r^2 = .95). Axes are the partial warp (shape) vectors, in units of .1. Manhattan defines the x-axis, the Bronx the y-axis.

Table 1. Covariances of pairs of vectors of partial warp scores for Manhattan and the Bronx HIV-AIDS shapes. Percents are calculated by dividing each pair's squared covariances by the sum of squared covariances.

Vector Pair	Covariance	Covariances^2	Percent	Cumulative Percent
1	.0322	.001034	59.44	59.44
2	.0172	.000296	17.01	76.45
3	.0148	.000220	12.62	89.07
4	.0092	.000084	4.81	93.88
5	.0069	.000048	2.76	96.65
6	.0059	.000034	1.97	98.62
7	.0049	.000024	1.37	100.00

Sum of squared covariances = .0017402

Table 2. Manhattan and Bronx HIV-AIDS partial warp variables with high correlations (.70+) with at least one of three independent variables tested. The independent variables are borough number of homicides, borough tuberculosis incidences, and a dummy variable for HAART availability (-1 for years HAART not yet available, 1 for years HAART available). The sample sizes are too small (n = 8 specimens) for both boroughs, but the results are shown to illustrate the methodology for samples of sufficient size.

Manhattan

Shape variable	homicide	tuberculosis	HAART
1Y	.65	.51	-.80
2X	-.74	-.73	.70
3X	.73	.83	-.40
5X	-.81	-.89	.70
6X	-.76	-.64	.81
6Y	.67	.72	-.77
13X	-.55	-.74	.44
14Y	.61	.67	-.70
15X	-.63	-.80	.42
18X	-.70	-.62	.60
20X	-.73	-.67	.61
23X	.76	.64	-.98
24X	-.84	-.72	.98
27Y	.63	.57	-.76
29Y	-.52	-.46	.85
31X	.88	.79	-.71
32X	.83	.69	-.84
33X	-.71	.85	.60
UNIFORM X	.92	.90	.90

Bronx

Shape variable	homicide	tuberculosis	HAART
9X	-.75	-.80	.81
10Y	.64	.66	-.78
14Y	.86	.91	-.71
15Y	.54	.59	-.73
UNIFORM Y	.88	.90	-.76

Table 3. (a) Multiple regressions greater than .70 for three independent variables (number of homicides, tuberculosis incidences, and HAART availability) on each Manhattan and Bronx HIV-AIDS shape variable. (b) The squared Procrustes distances between each specimen and the consensus (Ref d^2), the sum of which is a measure of the total variation among the shapes. Also shown are the squared Procrustes distances between each specimen and their predicted shape, based on the regression. These are the residual distances (Resid d^2). The percents unexplained (sum of residual distances/sum of reference distances) can be used to compare different sets of independent variables. The sample sizes are too small ($n = 8$ specimens), but the results are shown to illustrate the methodology for samples of sufficient size. All values are shown in truncated significant digits, the reason why the sums do not add up perfectly.

(a)

Manhattan				**Bronx**			
Shape Variable	R^2	Fs	Prob	Shape Variable	R^2	Fs	Prob
3X	.80	5.42	.067	1X	.76	4.41	.092
5X	.81	5.86	.060	1Y	.74	3.84	.113
6X	.70	3.09	.151	2Y	.71	3.41	.133
6Y	.70	3.11	.150	3Y	.95	31.75	.003
14X	.94	22.19	.005	7Y	.82	6.15	.055
15X	.73	3.66	.120	9X	.77	4.61	.086
23X	.97	44.37	.001	14Y	.92	16.10	.010
24X	.97	54.35	.001	21Y	.81	5.71	.062
26Y	.75	4.00	.106	22X	.77	4.65	.085
29Y	.83	6.66	.049	UNIFORM Y	.84	7.36	.041
30X	.71	3.40	.133				
30Y	.77	4.68	.085				
31X	.78	4.81	.081				
32X	.79	5.07	.075				
33X	.73	3.60	.123				
UNIFORM X	.95	25.35	.004				

Table 3 (continued).

(b)

Manhattan			Bronx		
Specimen	Ref d^2	Resid d^2	Specimen	Ref d^2	Resid d^2
1991	.099	.017	1991	.117	.049
1992	.056	.014	1992	.077	.017
1993	.038	.007	1993	.063	.060
1994	.042	.017	1994	.093	.054
1995	.042	.010	1995	.101	.030
1996	.063	.037	1996	.078	.068
1997	.099	.052	1997	.107	.081
1998	.140	.040	1998	.097	.052
Sum	.581	.198	Sum	.738	.415
Sum of d^2 of predicted fit = .39			Sum of d^2 of predicted fit = .33		
Percent unexplained = 34.12			Percent unexplained = 56.27		

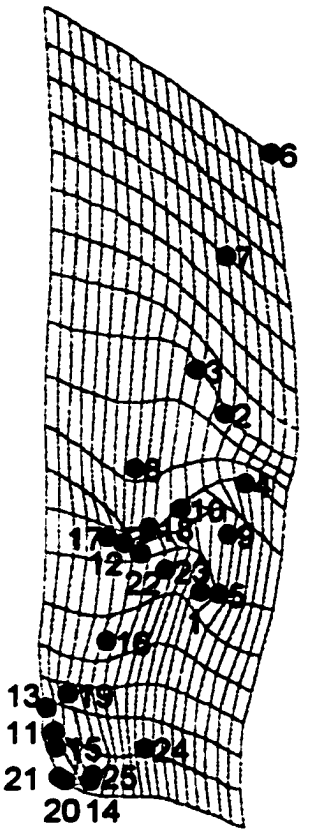

Figure 9. Relative warp for the Bronx 1991 ecological specimen shown in Figure 1. As with the relative warps shown in Figure 6, the affine differences defined by translation, rotation and size have been removed. The consensus and specimen, however, are not horizontally aligned on their principal axes, as is required for including Bookstein uniform estimates (u_1, u_2). In short, this warp contains no affine transformations whatsoever. On the other hand, it approximates the specimen's original orientation in the parameter space, perhaps facilitating interpretation.

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Chapter 5

Conclusion: Avoiding the Pesticide Effect and Other Projects for a Public Health Ecology

Ecology is the science of wholeness, complexity, interaction, context, dynamics and historicity. It constantly reminds us that things happen in some circumstance and not others, that pathways of causation run in both directions, and that things are the way they are because they got that way: history matters...

The ecological approach to health...is daunting in scope. It requires the consideration of such diverse topics as the coevolution of microbes with medical practice, the design of work, the interactions among pollutants and stressors, socioeconomic inequality, research strategy, individual and population vulnerability, the geography of disease, diet change, social influences on health-relevant behavior and urban planning. It leads to measures beyond the usual domain of public health that involve such matters as the technologies of agricultural and industrial production, combating racism, reducing inequality of income, monitoring of wildlife, democratizing science and organizing daycare for children and the aged. Some goals can be shared, others will be foci of conflict. Some are immediately feasible while others presuppose a long range change in values and priorities.

The need for a long term approach should not negate the urgencies of immediate measures. The inevitable conflicts around the allocation of resources or between health needs on the job and the prerogatives of management do not negate the cooperative efforts to improve epidemiological surveillance. The search for alternatives to a narrow reliance on vaccines should not prevent immunization coverage. The critique of inadequacies in medical practice coexists with the need to get everybody access to health care. With some division of labor among agencies and constituencies, we have to incorporate a health agenda into the major decisions around national goals. Otherwise our welfare will remain a side effect of decision taken for other reasons.

Richard Levins (1998)

There's keys in their eyes but they lock from the inside.

Blake Schwazenbach

Integrated Pathogen Management. A public health consensus has arisen around diagnosing HIV infections earlier, as a way of curtailing the AIDS epidemic (Cates et al. 1997). It is argued that giving patients HAART earlier in their infections reduces viral load below a threshold necessary for transmission, contracting the time people with HIV are infectious (Quinn et al. 2000). The rate of new infections should subsequently decline to a point the epidemic can no longer sustain itself.

At the level of the individual patient, earlier diagnosis is clearly desirable. Patients can receive suitable medical attention, including HAART, while their immune systems are still relatively intact. But earlier intervention as public health policy, even greatly reducing time to diagnosis to on average only two years after initial infection, does not address the first viremia some investigators have identified as epidemiologically key. Earlier HAART prescription permits greater opportunity for multiple drug-resistant quasispecies to evolve and for side effects to accumulate. Resistant quasispecies evolve even in patients with complete adherence. Earlier prescription, as the second paper of this dissertation suggests, may select for other responses from HIV, including changes in reproductive strategy.

Much political effort is currently directed at making HAART more widely available. Farmer et al. (2001) call for worldwide DOT-HAART, showing such a program successful even in a poor rural area of Haiti. Brazil and India have broken patents to produce cheaper versions of the component HAART drugs. The United Nations has launched the Global Fund for AIDS, Tuberculosis and Malaria to raise billions in funding for the purchase of drugs currently unavailable in non-industrial countries (see Epstein and Chen 2002 for a critique). At the level of the individual, we are obligated to provide

everyone on this planet access to the latest medical innovations, including HAART, if needed. It is imperative, however, that we recognize there may be population-level overhead in such efforts, including drug resistance and shifting viral life histories.

The affixation with a medical magic bullet for HIV appears to replicate a failure community ecologists understand all too well. The post-WWII Green Revolution was engineered primarily with pesticides. In consequence, cotton can no longer be grown in south Texas, Mexico and Central America where pests have evolved out from underneath any and all pesticides. Debach (1974) showed monthly DDT applications led to an increase in California red scale infestation on lemon trees because the chemical killed the scales' natural predators and parasites. Agriculturalists are now trying a different approach. Along with pesticide suppression, natural, biological and cultural controls are instituted under a policy of integrated pest management (IPM).

HIV ecologies, as the first and third papers of this dissertation show, are complex synergies of causal factors and effects (see also Wasserheit 1994, D Wallace and R Wallace 1998, Porter and Ogden 1998). Such synergies include—up the levels of organization—viral subtypes, host genetics, immune kinetics, coinfections, baseline health and diet, modes of transmission, individual and group behaviors, cultural practices, sex and drug economies, social inequities, public health infrastructure, and domestic and international travel (Quinn et al. 1987, Marlink et al. 1994, Hogg et al. 1994, Fauci 1996, Liuzzi et al. 1996, Liu et al. 1997, Cohen et al. 1997, Eldred et al. 1998). Attempts to defeat HIV will require acknowledging, reacting to, and anticipating such interactions.

While thousands of scientists struggle to devise cures to HIV, HIV boasts a laboratory of 50 million infections evolving solutions to myriad problems under diverse, locale-

specific conditions. Several million infections are working on a relatively new problem: concocting cures to HAART. Focussing on the virion level alone is unlikely to suffice: HIV plays chess, while strict reductionists play checkers. A more holistic approach to intervening in the epidemic, at all levels of HIV's biological and cultural phenospace, appears both reasonable and requisite.

Some next steps. According to the Center for Disease Control and Prevention (2001), since the end of 2001, the epidemic in New York City has rebounded. Sixty-five percent more New York AIDS cases were diagnosed in 2001 than in 2000. I would like to conduct a follow-up study to determine in what New York neighborhoods the AIDS rebound is located.

As discussed in the first paper, we cannot tell whether the decline in AIDS in 1990s New York was brought about by a changes in HIV incidence, the advent of HAART (which suspends the HIV infection in its asymptomatic stages), or by some combination of the two. A geography of HAART prescription would do much to better tease apart the possible causes for New York's AIDS dynamics. Prescription data are collected both by state AIDS Drug Assistance Programs and the federal Healthcare Finance Administration. The data, sectioned by small area, can tell us what proportion of patients were prescribed 0-3+ antiretrovirals. Although New York State's data do not address adherence, they would be a good first step in directly testing for the relationship between antiretrovirals and the geography of disease prevalence. It would be an excellent test whether access to HAART is neighborhood-specific, a possibility of social import for New York, one of the most residentially segregated cities in the western world.

The temporal and spatial distributions of HIV/AIDS may not be the only population-level attributes that HAART effects. The stage-classified Lefkovitch population matrix model of HIV's life history developed in the second paper conceptualized a semelparous HIV that can invade a population of HAART-treated HIV infections. I would like to develop this model, adding the variables discussed at the end of the paper. I am particularly interested in adding spatial dynamics, an especially important addition given the possibility HAART may be heterogeneously distributed.

I had originally intended for this thesis an epidemiological test on models of the evolution of virulence. A growing literature models the trade-offs between pathogen virulence, transmission efficiency and immunal clearance. A primary result hypothesizes greater virulence with greater transmission rates if enough susceptibles are available.

The test would have involved using zip code level epidemiological data for HIV. New York City zip codes with greater rates of transmission should host HIV strains of greater virulence. I would have used clinical data measuring the progression of HIV infections for patients residing in high- and low-transmission neighborhoods in conjunction with zip code level measures of virulence such as AIDS incidence and AIDS mortality to test the virulence-transmission hypothesis.

There are, however, problems with the proposed study:

1. Clinical data sorted by zip code are hard to obtain.

2. The only small-area measure of transmission rates available for 1990s New York is incidence of perinatal exposure to HIV which is unlikely to reflect adult rates. At best they reflect maternal infections alone and not for any specific year at that.

3. Any part of the variance in virulence, however operationalized, not attributable to a variety of possible confounding factors in a multiple regression can not be simply attributable to the difference in transmission rates. The leftover variance could be a combination of still more, unmeasured confounders and error variance.

I still like the approach very much and have seen nothing like it in the literature. It just needs the appropriate data and some fine-tuning. Perhaps a different pathogen would be better, one less inundated by privacy issues and one with a more truncated incubation time, to better control for host dispersal.

There are additional little projects that I have had in mind for some time, but never the chance to do. For example, I would like to study the geography of New York's AIDS-related opportunistic infections. The finest scale I have seen this issue addressed is Northern Europe vs. Southern Europe, too coarse of a scale to be of practical use. Are opportunistic infections neighborhood-specific? If they are, it would open up a whole line of questioning. Are opportunistic infections transmittable? Do population-specific ecologies select for within-host immune environments, permitting some infections to arise over others?

The latter question is related to another interest. I am intrigued by the ways culture and population-level dynamics shape phenotypes we often imagine as strictly biological. Culture has been shown to have fundamental roles in molding mental cognition, the immune system, even our sense of smell. Rodrick Wallace and I (2002) introduce a cultural immunology. As a cognitive system, the immune system may also interact with culture to form a composite object. We critique work that has attributed differences in

immune function solely to putative genetic differences and suggest possible tests for characterizing such an immune-culture composite.

There appears much opportunity to learn how our intensely socialized worlds interact with human biologies, including our health. *If* we choose to take such chances.

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