HUMAN MATE CHOICE AND THE EVOLUTION OF MENOPAUSE

INVESTIGATION OF THE ROLE OF MATE CHOICE IN THE EVOLUTION OF MENOPAUSE UNDER SERIAL MONOGAMY

By

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LAYMAN ABSTRACT

Despite decades of research into menopause, there remains no clear understanding of how this deleterious trait came to persist in the human population. It has been proposed that a bias in mate choice such that only younger females are chosen to mate can result in the accumulation of deleterious mutations, ultimately leading to menopause. We analyzed the evolution of menopause under a mating system of serial monogamy by a computational simulation. We came to three main conclusions. Firstly, under modern demographic parameters, menopause cannot evolve under serial monogamy. Secondly, in a population of shortened longevity, similar to chimpanzee, menopause neutrally appears at an age presently experienced by women. Finally, when mate choice is restricted such that only young females are eligible to mate within a system of serial monogamy, menopause can evolve. This means with the current mate choice shift towards older women, menopause can be postponed or even eliminated.

ABSTRACT

Menopause, the cessation of reproductive capabilities before death, is a detrimental trait for female fitness, yet persists in all human populations. Numerous hypotheses have been published to describe how menopause has been maintained but failed to explain the origin and genetic basis of this trait. In 2013, Morton et al. proposed an influence of the mate choice behaviour, specifically a bias in mating ages that could allow for a trait, seemingly detrimental to fitness, to become neutrally fixed in a population. The goal of our research, presented herein, is to understand the role of the mating system, the sexual behaviour of a group, and especially mate choice, on the origin and evolution of menopause under a serial monogamy scenario.

Analysis was conducted using an agent-based computational model that simulated populations. The populations were generated according to specified demographic parameters and reproduced according to a serial monogamy mating system. With the model, parameters were investigated including population lifespan, fecundity, pairing eligibility, age of loss of fecundity, and timing of decay in fecundity. Simulations revealed that, under certain restrictions, menopause can neutrally evolve. When mate choice was restricted to a particular age preference bias, menopause can appear with no diminishment of fitness. This novel mode for the origin of menopause is inferred to result from the accumulation of deleterious mutations in the female genome. By combining this ability of fertility-diminishing mutations to accumulate with research into the genetic basis of menopause, we provide a system for the evolution of menopause in a population of serial monogamy.

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LIST OF ABBREVIATIONS

ANM – Age of Natural Menopause

FRV – Female Reproductive Value

LE – Lifetime Expectancy

PGR – Population Growth Rate

TFR – Total Fertility Rate

TFR_R – Total Fertility Replacement Rate

INTRODUCTION

Menopause

Menopause is defined as the cessation of menstrual cycles and is recognized formally after one full year (Col, Fairfield, Ewan-Whyte, & Miller, 2009). This trait is oftentimes also called 'post-reproductive life', indicating reproductive senescence before biological senescence (Kirkwood & Shanley, 2010). It is speculated that the cessation of menstruation formally occurs when a female no longer has any viable eggs remaining to use to reproduce (Van Valen, 2003). When considering the current human lifespan, specifically in developed countries, menopause occurs just past the mid-point in the human life. Germ cells, the cells of interest in reproduction, begin aging at an accelerated rate in human females at approximately age 35 years; however, in males, germ cell aging begins around age 40 years and is much slower (Kirkwood & Shanley, 2010).

Currently, post-reproductive life in females begins at approximately 50 years and is believed to be characterized by years of diminished fertility beforehand (Kirkwood & Shanley, 2010). While this is assumed to be the general trend in the 20th century, there is some evidence for variation among cultures and over time. Over 2000 years ago, according to Roman data, women entered menopause in their early 40s (Ginsberg, 1991). Over time, this observation changed, and, by the Medieval period women, were reported as experiencing cessation of menses in their early 50s (Ginsberg, 1991). Currently, in developed nations, women continue to experience menses cessation in their 50s with little change in this pattern over the past century (Ginsberg, 1991). These modern data however, seems to be specific to women in modern, industrialized societies as menopausal variation has been noted globally.

A woman is defined as being pre-menopausal from the onset of menarche throughout the years that she experiences no change in menstrual frequency (Dennerstein et al., 2000). Typically, menarche occurs in females at approximately the age of 13 (Morabia & Costanza, 1998; Ismael, 1993; Johnston, 2001; Castelo-Branco et al., 2005; He & Murabito, 2012; Golshiri, Akbari & Abdollahzadeh, 2016). Once menstruation becomes irregular, females are deemed to be in a period of perimenopause. The age at which women enter perimenopause has been seen to differ among different populations. In the United States of America, mid-1990s, the average age entry into perimenopause was reported as 45.7 years (Wise et al., 2002). In England in the same time period, this age ranged from 46-50 years (Hardy & Kuh, 1999). Irregular menstruation has also been seen to last a variable amount of time over populations (however, in general, perimenopause onset and duration is not well researched or documented). Most reports indicate that the average duration of perimenopause transition is approximately four years (Prior, 1998), with noted duration ranges of anywhere from 1 to 10 years (Li et al., 1995; Wise et al., 2002; Kirkwood & Shanley, 2010).

A woman is finally considered to be menopausal once she has been in a state of amenorrhea for a period of 12 months (Dennerstein et al., 2000). In modern, Western societies, natural menopause typically occurs at approximately age 51 (Brambilla and McKinlay, 1989; Morabia & Costanza, 1998; He & Murabito, 2012; Carty et al., 2013). This age of natural menopause (ANM) is seen to vary from one population to another. For example, median ANM was reported to be 48 in Ghana and northern India (Kwawukume, Ghosh & Wilson, 1993; Kriplani & Banerjee, 2005), 42.3 in Bolivian (Castelo-Branco et al., 2005), 45 in a primitive Indian tribe (Biswas and Kapoor, 2004), 47 in Libya (Taher, ben Emhemed & Tawati, 2013),

and 46.4 in Nigeria (Ameh, Madugu, Onwusulu, Eleje, & Oyefabi, 2009). Once a woman has not menstruated for a period of 12 months and in a state of menopause, she is considered to be post-menopausal for the remainder of her life. While it appears that menopause is a variable but common trait to all women globally, what remains unknown is how and why we see menopause in human females.

Menopause Hypotheses

There exist a multitude of hypotheses on the trait of human menopause in females (**Appendix A Table 1**). Hypotheses of human menopause can typically fall under broad categories, including biological and environmental, with some overlap among categories (Barile, 1997). Biological hypotheses commonly attribute the appearance of menopause to changing hormone levels as well as losing function in the ovaries. For example, the Follicular Depletion hypothesis states that females have a fixed store of oocytes and once this store has been depleted, females are no longer reproductively viable (Harris et al., 2009; Kirkwood & Shanley, 2010). Biological hypothesis are typically straightforward with a clear solution – most commonly hormone therapy- however actions do not successfully 'cure' or revert menopause (Barile, 1997).

There also exist sociocultural and environmental hypotheses. These include cultural differences observed globally and have been of greatest focus in research (Barile, 1997). A common hypothesis, the Grandmother hypothesis, falls partially the sociocultural category. Many people have researched the grandmother hypothesis and proposed slight variations on the main idea that females will stop producing their own children and turn their efforts to helping

rear their grandchildren (Kirkwood & Shanley, 2010; Hawkes, 2003; Hawkes et al., 1998; Peccei, 2001). The grandmother hypothesis ultimately states that menopause evolved via kin selection. It implies that either menopause was present and female behaviour changed to compensate for this loss of fertility or assistance in rearing kin was sufficient to allow menopause to appear, either option being equally plausible. Although these hypotheses provide explanations for grandmothering in menopausal women, they fail to address the origin of human menopause, itself.

In 2013, Drs. Morton, Singh & Stone, proposed a mate choice hypothesis on the origin of human female menopause. Their theory acknowledged that an accumulation of late-onset mutations occurred in females over time via the mating system. In this proposed mating system, supported by ample evidence (Tuljapurkar, Puleston, & Gurven, 2007), there exists a bias in the mating system such that only younger females mate. This could arise either by adult males demonstrating a preference for younger females or by competition among females whereby young females out-compete older females in the population for access to mates. This bias led to an accumulation of mutations that are deleterious to female fertility. The mate choice hypothesis proposes that menopause is an old evolutionary trait because mutation accumulation takes a long time and this mating system is an old phenomenon therefore a major issue is that the proposed mutation accumulation requires a great deal of time to occur therefore it is worthwhile to look at the numerous hypotheses working together.

The mate choice hypothesis was modified in 2017 by Takahashi, Singh, & Stone to combine three hypotheses: grandmother, longevity and mate choice, in an attempt to explain

both the origin and maintenance of menopause in humans. This theory proposes a change in mating behaviour such that only young women reproduced, allowing for the accumulation of late-onset fertility diminishing mutations. Along with this came an increase in lifespan that allowed for these mutations to phenotypically take effect in the form of reproductive senescence in adult females. Finally, adult females who were no longer able to reproduce instead assisted in rearing their grandchildren, ultimately leading to menopause in women (Morton, Singh, & Stone, 2013; Takahashi, Singh, & Stone, 2017). In this scenario, longevity and mate choice appear to be sufficient to produce menopause; however, the added influence of grandmothering is assumed to have accelerated the appearance of the trait. The mating system that is the genetic basis of the new hypothesis is believed to have altered fertility for females, constraining the duration of time available for them to reproduce.

PURPOSE OF STUDY

In general, hypotheses of menopause do little to explain the origins of this trait in human females. Specific hypotheses however, such as the Mate Choice hypothesis proposed by Morton et al. (2013) attempt to address this question by explaining that constraining eligibility for pair bond formation and reproduction can result in the accumulation of late-onset, fertility-diminishing mutations that are specific to females. These mutations, which accumulate and are detrimental to female fecundity at advanced ages, however, are effectively neutral because females do not mate at those advanced ages to realize the loss of fertility. The results of the simulation in Morton et al. (2013) provide evidence that these hypothetical mutations can accumulate under very specific conditions and result in menopause within simulated populations. Despite this, there continues to be a lack in the understanding of the dynamic variables that influence the evolution of menopause, specifically the concept of mate choice. For this reason, it is our goal to develop a computational model that emphasizes the role of mating systems, specifically one emulating mating behaviours in real world populations, to elucidate the role of mate selection on the evolution of menopause in human female populations.

CHAPTER 1:

EVOLUTION OF MENOPAUSE UNDER SERIAL MONOGAMY

1.1 BACKGROUND

Mating system refers to the structure of a group with specific regard to sexual behaviour within the group. In the mammalian species, a wide range of mating systems are utilized including clustered mating in leks, uni-male groupings, multi-male groupings, polygyny, harems and territories, and monogamy (Clutton-Brock, 1989). Each of these mating systems has evolved in the species in which it is found and is accompanied by a range of fitness benefits specific to those groups. For example, monogamy can be beneficial to a species in which there is a long period of offspring dependence and a high need for paternal support (Marlowe, 2000). The human species has evolved numerous mating systems and as human populations evolved, those mating systems have undergone significant changes. It is hypothesized that early human ancestors enforced a polygynous mating system in which males had access to more than one female (De La Croix & Mariani, 2015). From this polygynous state, we then transitioned into a monogamous species of one single mate and eventually a species of serial monogamy, permitting divorce and remarriage (De La Croix & Mariani, 2015).

To understand this transition, researchers look at sexual dimorphisms as indicators of mating systems. It is assumed that when sexual dimorphism in body size, as indicated by fossil record, is high, there is evidence of male-male competition in a species, therefore suggesting polygamy or polygyny (Nakahashi & Horiuchi, 2012). Other modern primates demonstrate greater sexual dimorphism than humans, suggesting polygamous mating in these species (Nakahashi & Horiuchi, 2012). Unlike other primates, modern humans typically mate in exclusive, sexual relationships; therefore, investigating fossil evidence of early hominids can give some indication as to historic mating system transitions. Nakahashi & Horiuchi (2012)

provide evidence that *Ardipithecus ramidus*, present 4.4 million years ago, demonstrated low sexual dimorphism in body or canine size, indicating that male-male competition may have already been weak in humans. Fossil evidence from *Australopithecus afarensis* dating back about 3 million years is debated in terms of level of sexual dimorphism. Initially it was believed that *A. afarensis* showed a high level of sexual dimorphism and was a polygynous species however more recent evidence is of sexual dimorphism similar to that of modern humans and would suggest a monogamous species (Nakahashi & Horiuchi, 2012; Dixson, 2009). Overall, results indicate low levels of male-male competition in early hominids and the possibility of a mating system similar to modern humans (Nakahashi & Horiuchi, 2012).

In general, modern humans are considered to engage in long term exclusive relationships of monogamous mating or long term exclusive with instances of harem units, indicating polygyny (Dixson, 2009). Anthropological records indicate that about 85 percent of human societies have permitted polygynous marriages but in more recent times, monogamous marriage has spread globally (Henrich, Boyd & Richerson, 2012). The exact timing of these proposed transitions is still debated. In Medieval times, and through the spread of religious institutions such as Christianity, populations demonstrated strict monogamy and permitted remarriage only after widowhood (De La Croix & Mariani, 2015). Monogamy increased in prevalence in pre-modern England leading up to the industrial revolution and is now considered the apparent norm in Western societies (Buss & Barnes, 1986; Henrich, Boyd & Richerson, 2012). Only recently in human civilization has the introduction of divorce and remarriage allowed for the transition from monogamy to serial monogamy. The term serial monogamy indicates sequential marriage, either for a male of a female. Serial monogamy can also be

considered a form of polygyny where males oftentimes monopolize the mating system and gain access to multiple females, non-simultaneously, through successive mating as well as instances of mating outside of marriage (Buss & Barnes, 1986; De La Croix & Mariani, 2015; Mulder, 2009).

It has been proposed that as societies became increasingly complex, the benefits of monogamy increased, allowing for serially monogamous mating to become increasingly common. Due to economic influences, historical societies contained wealthy males that obtained as many wives as possible ultimately increase their reproductive success (De La Croix & Mariani, 2015). In serial monogamous societies, it is not uncommon to see males marrying more often than females (Mulder, 2009). Males typically marry females younger than themselves and can even divorce their current spouse to remarry a woman who is younger (Mulder, 2009). Serial monogamy in general can lead to greater reproductive success and for males, an extension in the reproductive lifespan (De La Croix & Mariani, 2015). Although debated how long humans have enforced a serial monogamy mating system, it is widely accepted that this mating system is present in numerous societies globally, both industrialized and not.

1.2 METHODS

In order to test the influence of a serial monogamy mating system on the evolution of menopause, we developed a population demographic computational model (**Appendix B).** The computer program code was written in Python and run on Spyder (Python v.2.7) within the Anaconda Navigator interface. Simulations modeled a growing population, analyzed under

different female fecundity decay phenotypes, with a serial monogamy mating system. The different fecundity phenotypes emulate possible menopausal states of females. Each simulation begins with an initial cohort of males and females, all beginning at the same age of 0. As the simulation progresses, time increases in one-year increments. During every year, individuals in the population age, mate, give birth and die, all determined by set parameters. The simulation progresses over a fixed number of years or until the population reaches a pre-determined size and data is collected. Separate models of the different female fecundity phenotypes considered are compared and presence of menopause evolving in the populations is identified.

Survivorship in simulations is determined by mortality risk curves, applied to all males and females in the population. Data for those curves were obtained from a 1999 Great Britain population (Montgomery, 2017). Males and females survive according to separate mortality survivorship curves, with the main difference appearing in old age mortality. This simulation models mortality risk of the population using the Siler 5-component model equation: $ae^{-bx} + c + de^{fx}$, therefore we transposed the original 1999 Great Britain survivorship curves into Siler model mortality risk parameters to produce an identical survivorship curve for our use (**Figure 1, Appendix A Figure 1, Siler model values in Appendix A Table 2**). In the 1999 Great Britain population, there is a very low incidence of infant mortality for males and females, where only 1% of all children born die before the age of 5. Mortality risk remains low until the approximate age of 60 where it begins a rapid decline. Male survivorship declines more rapidly than does female survivorship but overall no individuals in the population survive beyond the

age of 100. When individuals die, they are eliminated from the simulation and the population size is adjusted accordingly.

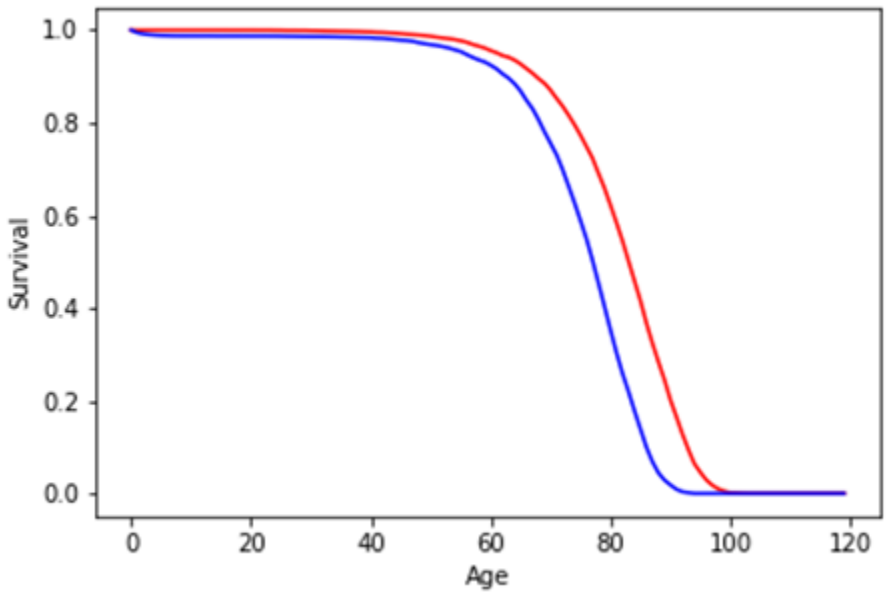


Figure 1: 1999 Great Britain survivorship risk curve, Serial Monogamy simulation. Male curve is shown in blue and female curve is shown in red.

New individuals are introduced into the population as the result of pair formation and successful mating. This mating system of serial monogamy determines the pair bond formations that occur. At the beginning of the simulation we assign minimum and maximum mate eligibility ages. No male or female below a certain age can be chosen as a mate and no male or female above a certain age can be chosen as a mate. For both males and females, the minimum age of eligibility was 13 years. All individuals in the simulation therefore become eligible and begin pairing at age 13 and due to the Siler mortality model, are likely to remain paired through

to old age (**Appendix A Figures 2-4)**. The only way for a pair to be broken is by the death of either the male or the female. The maximum age of eligibility for males and females is a variable parameter, currently set to age 80. If a remaining male or female is below this set 'maximum eligibility age' when the partner dies, he or she will be added the pool of eligible mates and can be chosen again the following year. Alternatively, if he or she is older than the set maximum age when the partner dies, he or she will no longer be eligible to be chosen as a mate. This is a system of serial monogamy as individuals are generally mated for life and only re-mate after the death of their previous mate. It is throughout a monogamous pairing that births can occur.

Each year, a male-female pair can reproduce with some probability and the pair can potentially reproduce every year until death. This potential to reproduce every year until death is hindered by two factors – nursing years and fecundity. When a female has successfully given birth one year, she is considered to be nursing for a period of time directly following the birth year and during this period she is unable to give birth again. This parameter, called nursing years, is set to 4 years in the simulation. Data from multiple populations indicate real-world variation of this parameter. In both the Gainj population of New Guinea and !kung women of Africa, the typical birth interval is about 3.5 - 4 years however in modern, Western societies this interval of time is shorter but also accompanied by fewer offspring (Galdikas & Wood, 1990; Jones, 1986; Meehan & Crittenden, 2016). This nursing period, also interpreted as birth spacing, influences the lifetime reproductive rate of a female. Globally, offspring numbers vary greatly between developing nations and industrialized countries (Lawson & Mace, 2011).

Along with the influence on birth spacing, the probability of reproduction and a successful birth is also dependent on the male and female fecundity.

When male or female fecundity is 0, the associated individual is not able to reproduce; therefore, no successful births will occur in the corresponding mate pair. Males and females in this simulation do not become fecund until the age of 13, corresponding with reports of a global median age of onset of menarche occurring at approximately 13 years (Morabia & Costanza, 1998; Ismael, 1993; Johnston, 2001; Castelo-Branco et al., 2005; He & Murabito, 2012; Golshiri, Akbari & Abdollahzadeh, 2016). At age 13, fecundity immediately reaches its maximum value, 0.9 in males and 0.15 in females. For all males, the maximum fecundity is maintained throughout life, declining at age 95 to reach a minimum value of 0 by age 100 (**Figure 2**). In this simulation, female fecundity is more variable than male fecundity. Females maintain the state of maximum fecundity until a set age. At this age, fecundity declines in a linear fashion until reaching a value of 0. The slope of fecundity decline is dependent on both age at onset of fecundity decline and the set age at which fecundity reaches zero. Figure 2 demonstrates these parameters set at age 30 and 100, respectively. As these fecundity parameters are altered, the resulting decline in fecundity also changed, impacting the probability of births within a pairing. For reproduction to be successful and result in a birth, both the male and female must have a fecundity value greater than 0 and the product of their fecundities must be greater than some random number between 0 and 1 generated in the simulation.

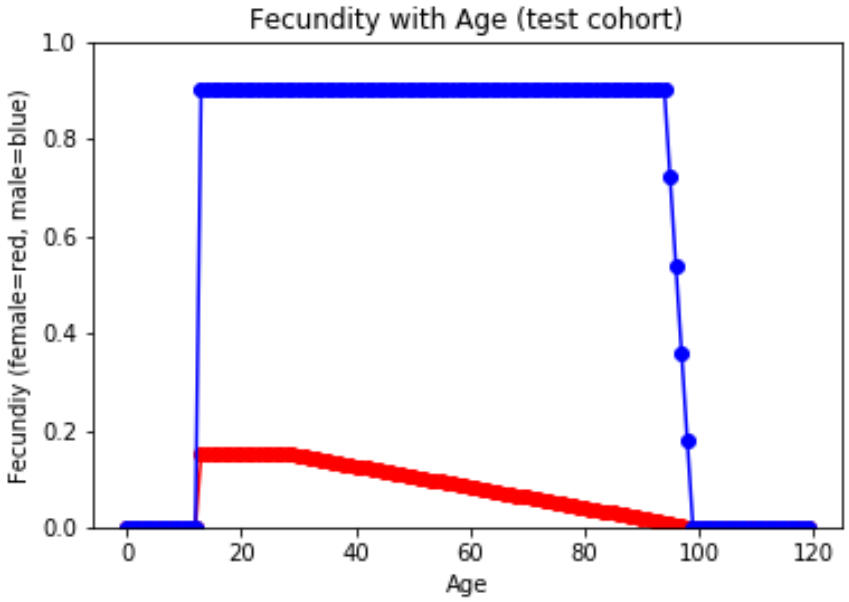


Figure 2: Male and female fecundity parameters, serial monogamy simulation. Onset of fecundity in both males and females occurs at 13. In the female population fecundity remains at a maximum value until the age of 30 and declines in a linear fashion until the 'age of menopause' when fecundity is 0 at age 100. In males, the maximum value is maintained until the age of 95 and declines in a linear fashion, reaching a value of 0 at age 100.

Instead of including a genotype with accumulation of mutations to result in declining female fecundity, this simulation utilizes a fecundity phenotype, from which we can infer a corresponding genotype. For each run of the simulation, all male individuals of the same age have identical fecundity and all females of the same age have identical fecundity. Differences in the female fecundity decline from one run to another and are due to altering the female fecundity parameters. A range of female fecundity decline parameters can be simulated, each within a separate run of the simulation, and runs can be compared to one another. For example, female fecundity parameters can be altered to demonstrate an increasing age of female fecundity reaching zero in 10 year increments from age 30 to age 100 over eight separate runs

of the simulation. The parameter change will alter the slope of declining female fecundity for each run and demonstrate a range of phenotypes that could result from differing magnitudes of mutation accumulation in the genotype. The results of the eight runs can then be compared as a transition from a state of no mutations – female fecundity reaching zero at age 100 – to a state of mutation accumulation - female fecundity reaching zero at age 30 (**Appendix Figure 5**).

There are two major outputs of interest that result from each run of the simulation. Firstly, after each run, the simulation calculates the average growth rate of the population. Population growth rate (PGR) is determined yearly by comparing population size at time t + 1 to t. A negative average growth rate value at the end of a run indicates that the population is decreasing in size at the given parameters whereas a positive growth rate indicates the population is growing. PGRs are dependent on births and deaths and therefore vary depending on the female fecundity phenotypes. We can use the PGR to assess neutrality of declining female fecundity that is interpreted to have resulted from a changing genotype. Changes in PGR from a reference state indicate either a positive or negative effect of the change made within one run of a simulation and ultimately either a loss or gain in fitness. The change from a positive to neutral or nearly neutral state in this simulation identifies the point or approximate age at which menopause can neutrally evolve in our population without resulting in a loss of fitness.

The second output of interest is female reproductive value (FRV). At the end of a run, all of the dead females are counted, along with the number of children they produced over their lifetime. An average is then taken of this total number of children for every dead female to

calculate the total FRV. Runs of the simulation with females of maximal fecundity should produce a larger FRV than runs with females of lesser fecundity. Similar to assessing change from a positive to neutral or nearly neutral growth rate as described above, changes in FRV also indicate time points at which menopause can evolve neutrally without diminishing the fitness of the female, due to the strong correlation between PGR and FRV. If FRV is seen to vary from a neutral state, we can see that the female births are being altered due to changing fecundity. Again, we can assess changes from one run to another for both PGR and FRV to understand deviations from neutrality, interpreted as the evolution of menopause in these populations at a neutral state with no loss of fitness.

Each individual run of the simulation returns an accompanying PGR and FRV. These can be plotted on individual graphs along with female lifetime expectancy (LE) at birth, an output that is population-specific. The female LE at birth is dependent on the accompanying Siler parameters that control population longevity and represents the expectancy for every individual female at time zero. Female LE at birth on average is 78.3 years under the 1999 Great Britain Siler parameters. The presence of menopause after the female LE demonstrates that menopause is a trait that cannot neutrally evolve in the population. Menopause appearance before female LE however can indicate one of two things. Firstly, if there is no change in the female fitness, menopause can neutrally evolve under the specific parameters of that investigation. Secondly, if there is an accompanied decrease in fitness with the appearance of menopause before female LE, the trait will not be able to neutrally evolve in the population at an age younger than female LE.

In this section, we describe the numerous parameters that produce a demographic model of a population. This population survives and dies according to the Siler model, mates based on ages of eligibility and following a serial monogamy mating system, and reproduces based on fecundity parameters. We can therefore alter these parameters to quantify differences in PGR and FRV at a particular female LE at birth and ultimately understand the evolution of menopause in a serially monogamous population.

1.3 Investigation 1: Changing Age of Mate Eligibility

In this simulation, eligibility to be paired and fecundity are the determining factors in successful reproduction and are encoded by two separate parameters. A male or female may be chosen as a mate but not be able to reproduce due to their inherent fecundity. On the other hand, a male or female may still be fecund but due to eligibility parameters may not be chosen as a mate. To reproduce, the male and female in a pair must be mated and be fecund. As this is a serial monogamy model, males and females may remain paired beyond the maximum age of eligibility, as influenced by the mortality risk of the population. The first point of examination here is investigating eligibility ages of females for a range of female fecundity phenotypes to understand how eligibility and age of mate pairings can influence the evolution of menopause in this population.

Mating preferences of older males and younger females is one seen globally, despite cross-cultural variation in the absolute age preferred. Various studies have been conducted into the age of preferred mates in countries such as Germany, Holland, India, New Zealand, China, Brazil, Nigeria, the United States of America and Iran **(**Antfolk et al., 2015; Buss, 1989;

Kenrick et al., 1995; Kokko et al., 2003). While there was a general underrepresentation of rural and low socioeconomic regions, all findings indicate an overall male preference for younger female mates (Buss, 1989). The converging preference of males is for a woman in her 20s (Antfolk et al., 2015). This preference for young female mates is strongest in older males. With this information, we altered the female eligibility parameter to simulate the bias of younger females over older females in the population of serial monogamy.

Biased age preference in mate choice has also persisted over time. A study in India compared mate preferences in 1984 and 2009 (Kamble et al., 2014). It was found that in both samples men preferred a female spouse younger than themselves and females preferred males older than themselves. What did change however, was the age of preferred marriage. From 1984 to 2009, age of preferred marriage increased in both males and females (Kamble et al., 2014). This trend was realized in the United States of America and Brazil as the age of first marriage increased from 1960-1982 and from 1984-2014 respectively (Secord, 1983; Souza, Conroy-Beam & Buss, 2016). Although age of preferred marriage has increased cross-culturally, the trend of male preferences for youthfulness and older males mating with younger females remain constant.

This pattern of older male and younger female mate bias has been described time and time again, but it holds no evolutionary significance unless it is realized. This disparity between mate preference and actual mate choice can result from mate availability, restricted by social and cultural constraints (Buss & Schmitt, 1993). While a certain trait in a mate would be considered ideal, it is not possible for all people in the population to have these traits in their

mate. In modern, Western societies for instance one may only be interacting with a certain subset of people, thus hindering preference from becoming reality (Antfolk et al., 2015). For example, females prefer males of high status but only so many males fit this description therefore not all females would have access to high status males (Zietsch et al., 2011). Preferences for high quality mates may also not be realized due to one's own decreased mate value (Buss & Schmitt, 1993; Symons, 1979). Individuals of high value would have an easier time attracting and obtaining desired partners than those individuals that are not of high mate (Conroy-Beam & Buss, 2016). For this reason, we will investigate not just bias for young female eligibility but instead we will consider a range of female eligibility windows for multiple female fecundity phenotypes.

Female eligibility is determined by both a minimum and a maximum value. For all runs of the simulation, the minimum female eligibility age is set to 13 years old. This age, 13, is also the age of onset of fecundity in females meaning that once they become eligible, all of the females are fecund and able to reproduce. We have investigated the eligibility of females by increasing the maximum age of eligibility in 10-year increments beginning from a maximum age of 20 years old to a final maximum age of 80 years old. For every run of the simulation, males are eligible between the ages of 13 and 80. The female fecundity phenotype was tested for a range of values within each of the female eligibility intervals studied. Onset of decay of fecundity always occurred at age 30 but the age at which fecundity reached a value of zero ranged from 30-100, again in 10-year increments and finally investigated at a value of 150 (**Appendix A Figure 5**). This time at which female fecundity reaches zero is called the 'age of

menopause'. The resulting PGR and FRV from each individual run of the simulation are plotted against the accompanying age of menopause along with female LE at birth.

1.3.1 RESULTS

The plot of PGR and age of menopause can be seen in **Figure 3 (raw data in Appendix A Table 3)**. It is primarily evident that varying the maximum age of female eligibility produces nearly identical PGRs. We also notice that as the age of menopause decreases, so too does the PGR. When the age of menopause is 40 or younger the populations are not sustainable under the specified parameters, as indicated by the negative growth rate. The PGR appears to reach a plateau at a value of 0.02 around the age 80. Between the ages of 60 and 80, the point of inflection of these lines, we can see that PGR is negatively affected by altering the female fecundity phenotype. This decrease in female fitness occurs before the female LE at birth therefore indicating that menopause cannot neutrally evolve in this population before female LE.

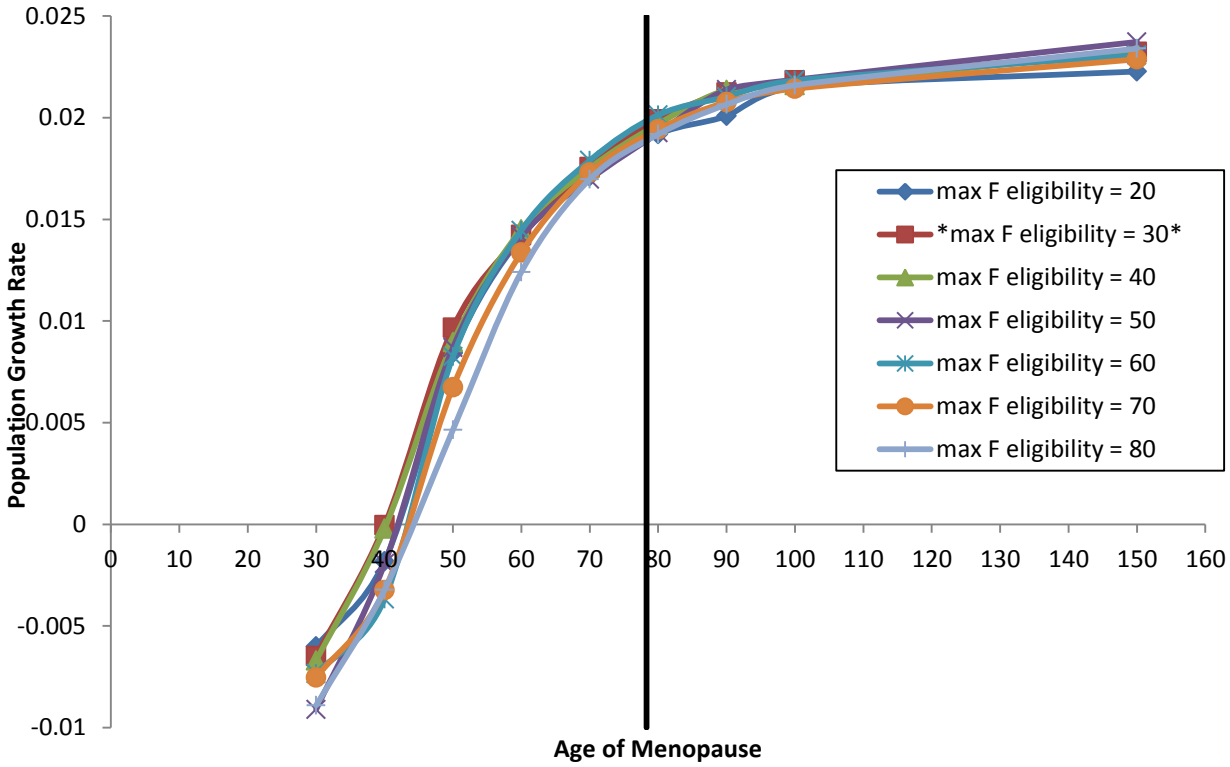


Figure 3: Plot of population growth rate and the age of menopause in the female population. Female LE at birth is 78.3 years, as indicated by the vertical line. Pairing eligibility in females was set to a minimum value of 13 years old and maximum age of eligibility was tested in 10-year increments from age 20 to 80. "Max F eligibility = 30" is used as the reference population throughout Investigation One.

A similar graph can be constructed by plotting FRV and the age of menopause, as seen in **Figure 4 (raw data in Appendix A Table 3).** Again, it is evident that varying the maximum age of female eligibility results in nearly identical FRVs. Additionally, the FRV increases as the age of menopause increases. This is intuitively obvious because females remain fecund to a later age and this, along with remaining paired in the serial monogamy mating system, results in more births in the population. Similar to Figure 3, we see that when the age of menopause is 40 or younger, the population is not sustainable as each female averages fewer than 2 births. There

is no obvious point of inflection between the ages of 60 and 80 as was seen in Figure 3 however, the FRV is seen to be increasing at a slower rate as the age of menopause increases. It is also clear that before the female LE at birth, the population is in a state of diminished fitness therefore menopause will not neutrally evolve.

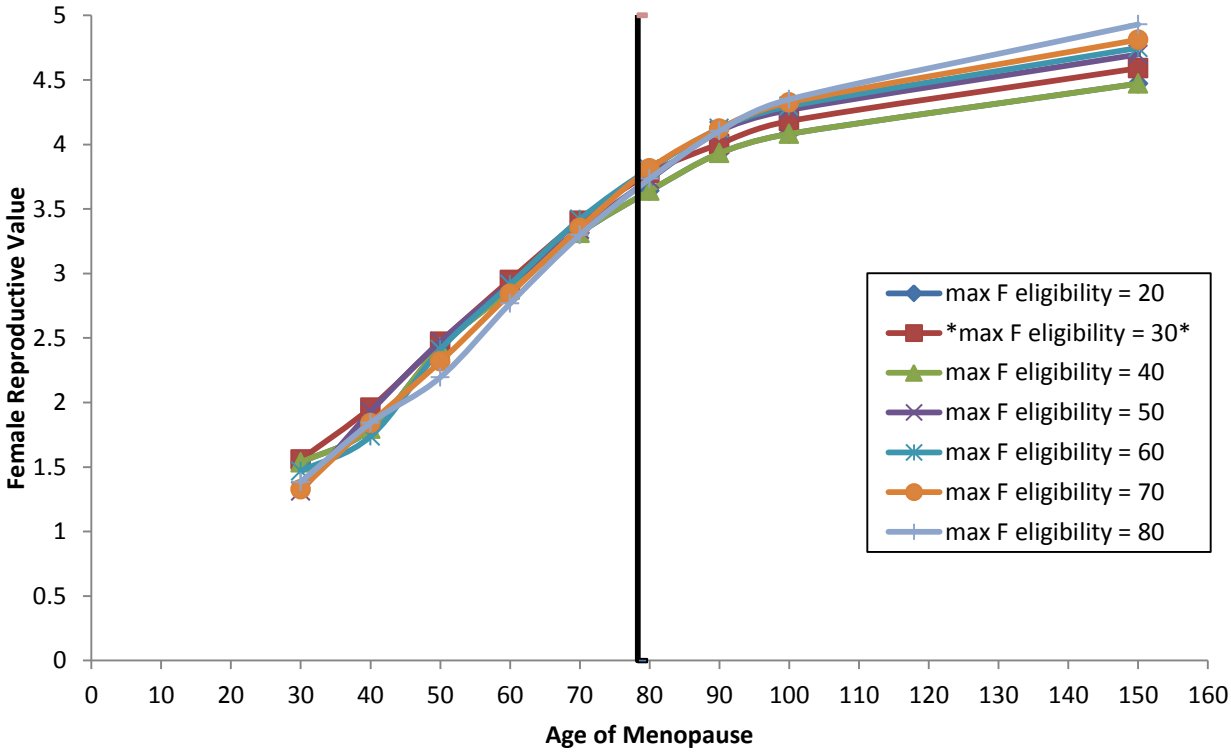


Figure 4: **Plot of female reproductive value and the age of menopause in the female population**. Female LE at birth is 78.3 years, as indicated by the vertical line. Pairing eligibility in females was set to a minimum value of 13 years old and maximum age of eligibility was tested in 10-year increments beginning at age 20 and ending at age 80. "Max F eligibility = 30" represents the reference population.

1.4 Investigation 2: Changing maximum female fecundity

The term fecundity refers to the natural ability or potential of a single person to reproduce whereas fertility rate describes the actual number of offspring produced per couple in a given period of time. In this simulation, females and males possess the attribute of fecundity, a value that directly influences the potential for reproduction. Lower fecundity values result in the production of fewer offspring and as fecundity increases, more children are produced. Successful reproduction results from the product of the male and female fecundities within a pairing, ultimately leading to the eventual growth or elimination of the population. It is the number of births at the end of the simulation that allows us to calculate the FRV and the interaction of births and deaths in the population results in the calculated PGR.

PGR is calculated yearly by comparing population size at time t + 1 to t, with population sizes differing due to births and deaths. Births are often estimated in real world populations by looking at fertility rates. Total fertility rate (TFR) is an average number of births however, to determine if a population is increasing or decreasing in size, we calculate the replacement fertility rate (TFR_R) (Espenshade, Guzman & Westoff, 2003). The TFR_R takes into account the specific mortality risk and produces a fertility at which a population would replace itself from one generation to the next, without migration. TFR_R above this value then would result in a growing population whereas TFR_R below the specified value would result in a decreasing population (Espenshade, Guzman & Westoff, 2003). There is high global variation in TFR_R, largely due to cross cultural differences in mortality (Espenshade, Guzman & Westoff, 2003).

The global range for TFR_R is from 1.4 – 3.5 with a value of 2.1 generally accepted as the value required for the maintenance of a population (Espenshade, Guzman & Westoff, 2003). Typically developed nations have low TFR_R. In the United States of America in 2001 for example, white non-Hispanic populations had an average TFR_R of 1.84, indicating a declining population (Morgan, 2003). Many European nations also have TFR_R values very close to or less than the maintenance value of 2.1 (Morgan, 2003; Espenshade, Guzman & Westoff, 2003). Decreasing fertility rates in developed nations is believed to be due in large part to effective birth control, decreased childhood mortality risk and cultural changes (Bloom, Canning & Lubet, 2015). Developing nations have been found to have the highest TFR and TFR_R, more specifically African countries such as Niger with a TFR_R value of 7.58 (Bloom, Canning & Lubet, 2015).

Overall, nearly all future population growth is expected to occur in Africa, Asia (excluding Japan) and the Latin Americas (Bongaarts, 2009). In other regions, specifically North American and Europe, populations are expected to remain relatively stable or grow very slightly (Bongaarts, 2009). In our simulation, we can see from the resulting PGRs whether a population will increase or go to extinction under specific fecundity parameters. By changing the maximum fecundity of the female population, we control the crude number of births that will be produced in a given run of the simulation and thereby control the growth rate of that population. While altering the maximum fecundity will influence the total number of births, it remains to be seen how changing maximum fecundity along with the female fecundity phenotype will influence the evolution of the menopause trait.

In the current simulation, males and females have different fecundity parameters. The male state of maximum fecundity is 0.9, indicating high likelihood of reproduction but female individuals on the other hand only have a maximum fecundity value of 0.15. We have investigated the resulting PGR and FRV for a range of female maximum fecundity values. Male maximum fecundity remained at 0.9 for the duration of this investigation. Female maximum fecundity was tested at the following values: 0.1, 0.15, 0.2, 0.3, 0.4 and 0.5 (**Appendix A Figure 6**). Each of these maximum female fecundity values was tested over a range of ages of menopause from age 30 to age 100 in 10-year increments and finally investigated at a value of 150. Again, the resulting PGR and FRV from each individual run of the simulation can be plotted on individual graphs along with the accompanying age of menopause to identify variation.

1.4.1 RESULTS

A plot of PGR and age of menopause for the maximum female fecundities tested can be seen in **Figure 5 (raw data in Appendix A Table 3)**. Each line indicates a maximum female fecundity value. We can see that increasing the magnitude of maximum fecundity results in increasing PGR. The shapes of the lines appear to vary from one maximum fecundity value to another. This is specifically seen for the greatest values of fecundity. For the smallest values of fecundity, there are instances of negative population growth. These instances are eliminated by increasing the fecundity while still maintaining the pattern of population growth among groups. The PGR appears to reach a plateau for all maximum fecundities investigated with the age at which the plateau occurs varying depending on the maximum fecundity. Unlike the test of female pairing eligibility, we notice variation in the point of inflection for each parameter

change as well as menopause evolving under some parameters but not under others. For maximum female fecundities at or below 0.3, it is clear that the inflection point appears before the female LE but results in a decrease in fitness. Therefore, we conclude that for maximum fecundities below 0.4 menopause cannot neutrally evolve before female LE. For the greatest maximum female fecundities however, specifically 0.5, we see menopause continuing to appear before LE with no or very small decline in fitness. Menopause in this scenario can neutrally evolve around the ages of 50-70, the age at which we see a point of inflection. It is not known how changing the maximum female fecundity results in the appearance of menopause; therefore, further investigation in the future is necessary.

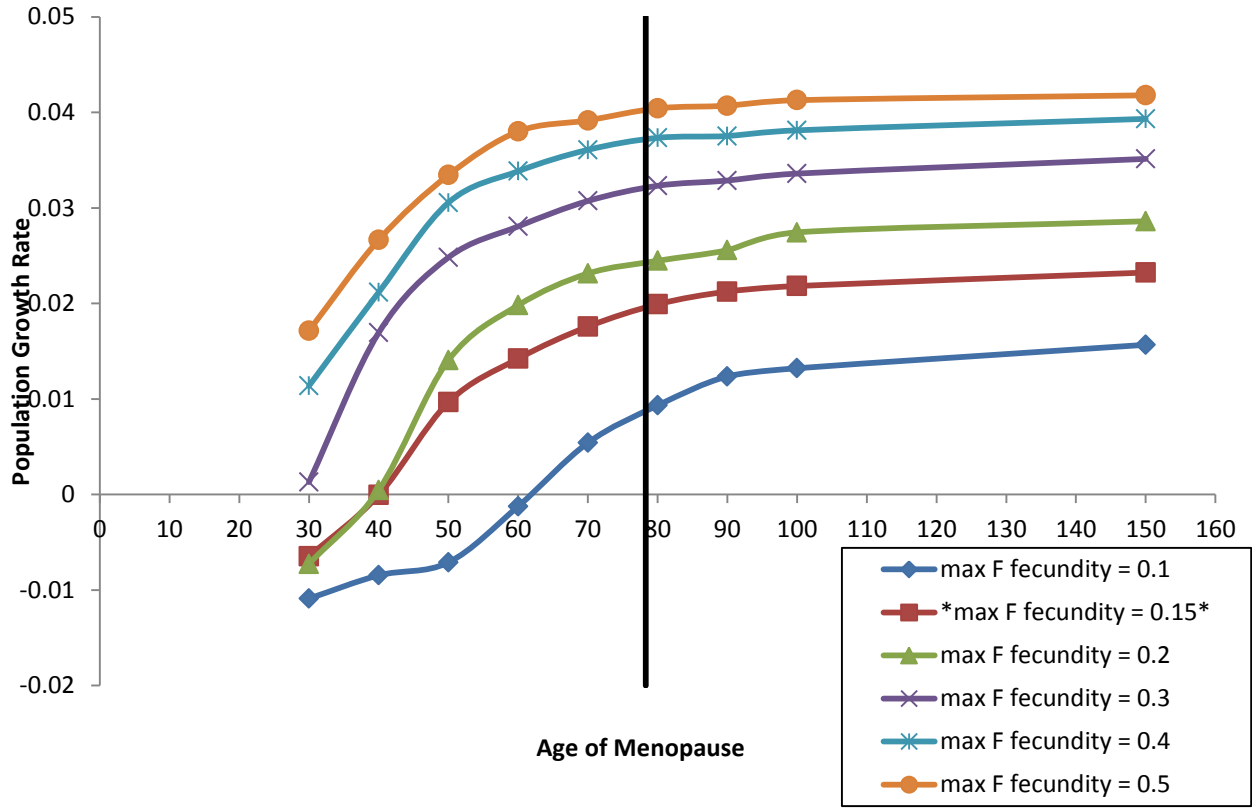


Figure 5: Plot of population growth rate and the age of menopause in the female population for varying maximum female fecundities. Female LE at birth is 78.3 years, as indicated by the vertical line. Maximum female fecundities were tested at the following values: 0.1, 0.15, 0.2, 0.3, 0.4 and 0.5. The maximum male fecundity for all tests was 0.9. "Max F fecundity = 0.15" represents the reference population.

Figure 6 (raw data in Appendix A Table 3) demonstrates FRV as a function of the age of menopause within the female fecundity phenotype. Similar to the trends seen when considering the PGR, increasing the maximum female fecundity results in an overall rise in FRV. Again, the FRV increases as the age of menopause input increases. In some cases, specifically those with low female maximum fecundity values, the FRV is below 2, indicating a declining population. As the age of menopause increases, all maximum female fecundities

produce sustainable and growing populations. In all cases, the FRV does not seem to have reached a plateau as was seen in Figure 5. The FRV results from a maximum fecundity value of 0.5 appear to conflict with the neutral evolution of menopause that was concluded in Figure 5 however, because no FRV line reaches a plateau, it is difficult to draw conclusions from these results.

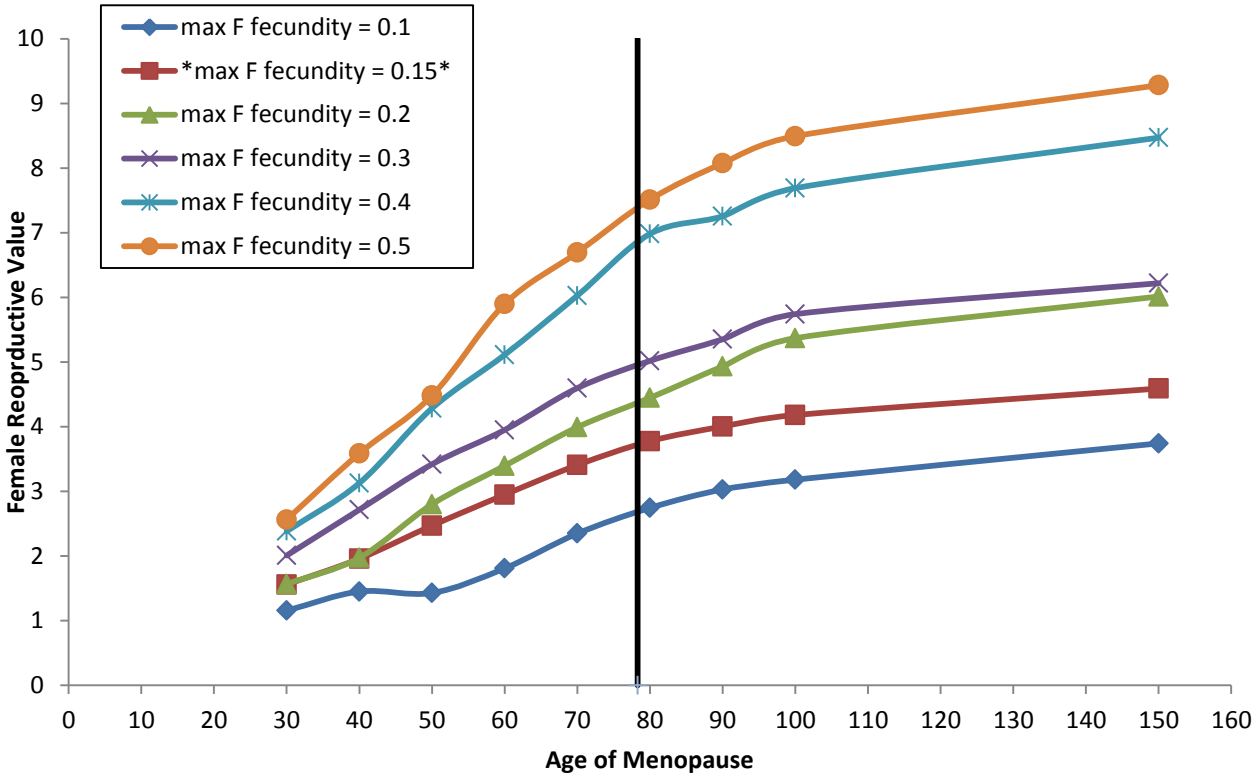


Figure 6: Plot of female reproductive value and the age of menopause in the female population for varying female fecundities: Female LE at birth is 78.3 years, as indicated by the vertical line. Maximum female fecundities were tested at the following values: 0.1, 0.15, 0.2, 0.3, 0.4 and 0.5. The maximum male fecundity for all tests was 0.9. "Max F fecundity = 0.15" represents the reference population.

1.5 Investigation 3: Changing the age of onset of female fecundity decay

As mentioned, fecundity is an attribute given to males and females in these simulations and is one of the determining factors in who will or will not reproduce. Fecundity over life history is regulated by multiple parameters including age of onset, maximum fecundity value, age of fecundity decline and age at which fecundity reaches zero. The age at which males and females experience fecundity onset is 13, in accordance with global literature of menarche onset in females (Morabia & Costanza, 1998; Ismael, 1993; Johnston, 2001; Castelo-Branco et al., 2005; He & Murabito, 2012; Golshiri, Akbari & Abdollahzadeh, 2016). In this simulation, the age at which fecundity begins to decline in the female population is interpreted as the onset of perimenopause, the period of irregular and variable menstruation. Finally, the age at which fecundity reaches zero in the population is deemed to be the age of menopause because this is the age at which the female is no longer capable of reproducing.

The classic female menstrual cycle length ranges from 25-31 days (Chiazze et al., 1968). When a female first undergoes menarche, her cycle is likely to be variable but this unpredictability decreases to a fairly consistent state throughout her fertile years (Chiazze et al., 1968). By her mid- to late-40s however, a female's menstrual cycle typically increases in variability again as she approaches menopause. This second period of high menstrual irregularity is referred to as perimenopause (Brambilla, McKinlay, & Johannes, 1994; Li et al., 1995). Perimenopause is defined as the period of time immediately prior to menopause in which there is a transition from normal cycling to irregularity and periods of amenorrhea, absence of menstruation (Brambilla, McKinlay, & Johannes, 1994). This period of time is not

typically defined until 3 months have passed but once 12 months have elapsed, the female is considered to be menopausal (Brambilla, McKinlay, & Johannes, 1994).

The perimenopause transition in general is poorly researched or documented, largely because of a lack of identification until a female is already undergoing the transition. Records from the United States of America in the 1980s determine the median age of perimenopause to be 45.5 years (Li et al., 1995). In 2002, Wise et al. identified the median age of onset of perimenopause in a sample from Massachusetts, United States of America as 45.7 years old and a sample from the same time period in the United Kingdom placed the median age at inception of perimenopause to be 48 (Hardy & Kuh, 1999). While not all females experience perimenopause in the same way, global estimates indicate that the perimenopause transition has a range in reported durations including 2-8 years, 5 years, 3.5 years and even 1 to 10 years (Li et al., 1995; Wise et al., 2002; Kirkwood & Shanley, 2010). It is this transitional period of time in which a female is still fecund but to a varying and lessening degree before ultimately losing all fecundity and the ability to reproduce.

The computer program models this perimenopause transition period by specifying the age at which fecundity declines along with the age at which fecundity reaches zero. By manipulating these two variables, we can not only control the timing of perimenopause inception but also the duration of the transitional period that ultimately ends with the female population in a menopausal state. Currently, the default age at which fecundity begins to decline in the simulation is set to 30 years old. We proceeded in investigating this age of fecundity decay from the age of 20 to the age of 100 in 10-year increments while maintaining

the age at onset of fecundity as 13 years old (**Appendix A Figure 7**). For each of the specified ages of fecundity decay, we examined a range of ages of menopause. Unlike previous analysis of the simulation, we were unable to investigate the age of menopause range from 30-150 due to the varying timing of inception of fecundity decay. For example, if fecundity was set to begin decaying at age 50, it is impossible to have fecundity reach a value of 0 at age 30. Instead, we tested the female fecundity phenotypes in the range of each specific interval's age of fecundity decay to an age of 100 years old to see the effect that perimenopause inception and duration has on the evolution of menopause.

1.5.1 RESULTS

Figure 7 (raw data in Appendix A Table 3) shows a plot of the relationship between PGR and age of menopause for varying ages of fecundity decay in the female population. In the population of serial monogamy, we can see that altering the age of fecundity decay in females does not produce identical growth rates although general trend seems to be consistent. There appears to be an effect of decreasing the age of fecundity decline in the female population, specifically for the younger ages of menopause. It is evident that younger ages of fecundity decline in females results in a lower PGR. This difference is more obvious at younger ages of menopause and as the age of menopause increases, the difference in growth rate becomes smaller. Overall, despite a magnitude difference in PGR, changing the age of fecundity decline in females produces a similar trend where we see a point of inflection occurring between the age of 60 – 80 and the eventual plateau of PGR. The PGR plateau value varies from 0.02 to 0.025 depending on the age of female fecundity decay however all tests result in decreased female fitness before the LE at birth. Again, it is evident that for all durations and timing of

inceptions of perimenopause, the PGR is being negatively affected by altering the female fecundity phenotype to younger ages of menopause and the presence of decrease in female fitness before the female LE at birth indicates no neutral evolution of menopause.

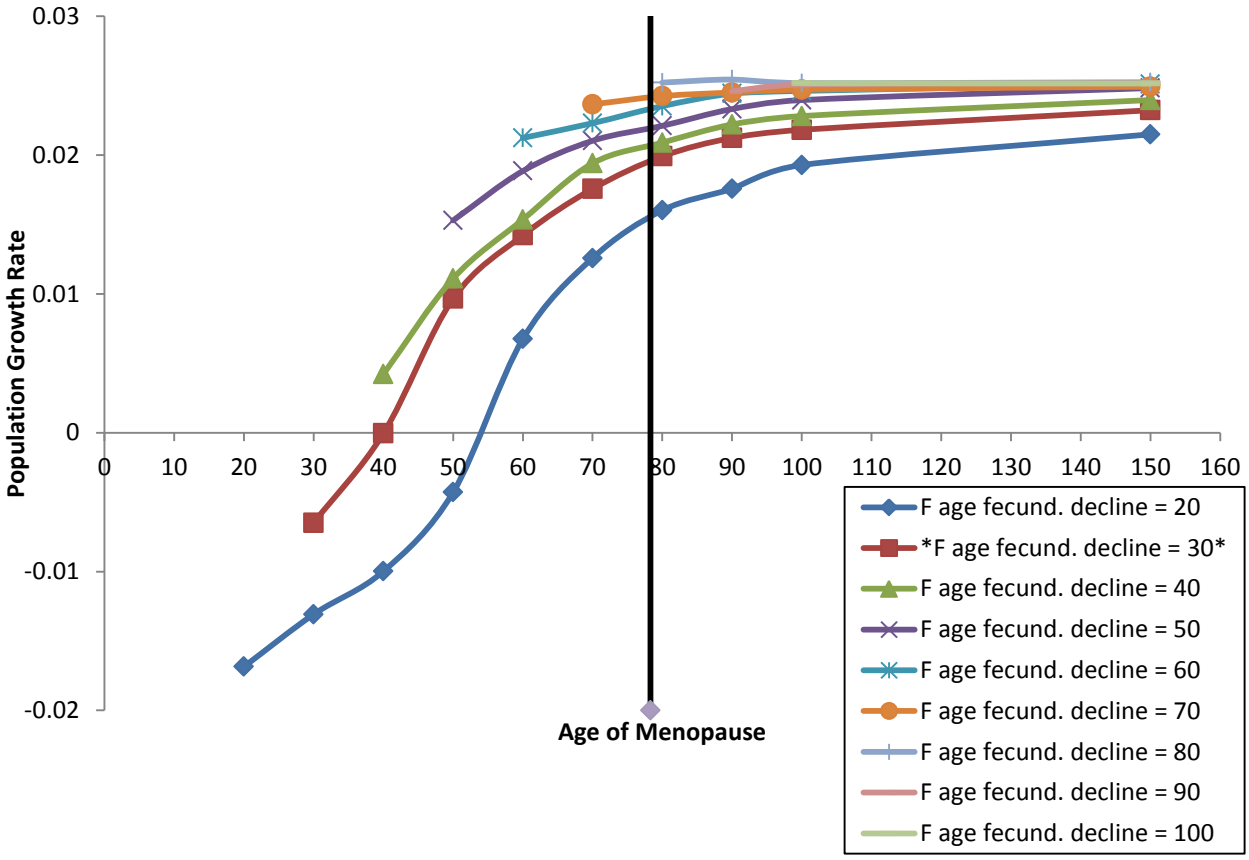


Figure 7: Plot of population growth rate and the age of menopause in the female population for varying age of onset of female fecundity decay. Female LE at birth is 78.3 years, as indicated by the vertical line. Ages of onset of decay in female fecundity tested ranges from 20 to 100 in 10-year increments. Onset of male fecundity decay for all tests occurred at age 95. "F age fecund. decline = 30" represents the reference population.

The plot shown in **Figure 8 (raw data in Appendix A Table 3)** illustrates FRV as a function of the age of menopause for varying ages of onset of female fecundity decay.

Resembling the plot of PGR, FRV appears to be influenced by varying age of onset of female fecundity decay in magnitude but not in trend. For example, when the age of menopause is set to equal 80, the FRV ranges from approximately 3 to 5.5 as the age of onset of decay in female fecundity increases. While the crude FRV increases with older ages of decay, overall all ages of decay result in comparable trend lines. Unlike previous analyses investigating the FRV, altering this perimenopause period appears to result in a plateau of the FRV. This plateau is less defined than in the PGR plot but does appear to occur around the age 100. The plateau occurring beyond the female LE at birth indicates that fitness is in a state of decline when menopause appears in this population therefore it cannot neutrally evolve. Overall, all populations, regardless of the age of inception or duration of the perimenopause transition, appear to respond to an increasing age of menopause, in a similar fashion.

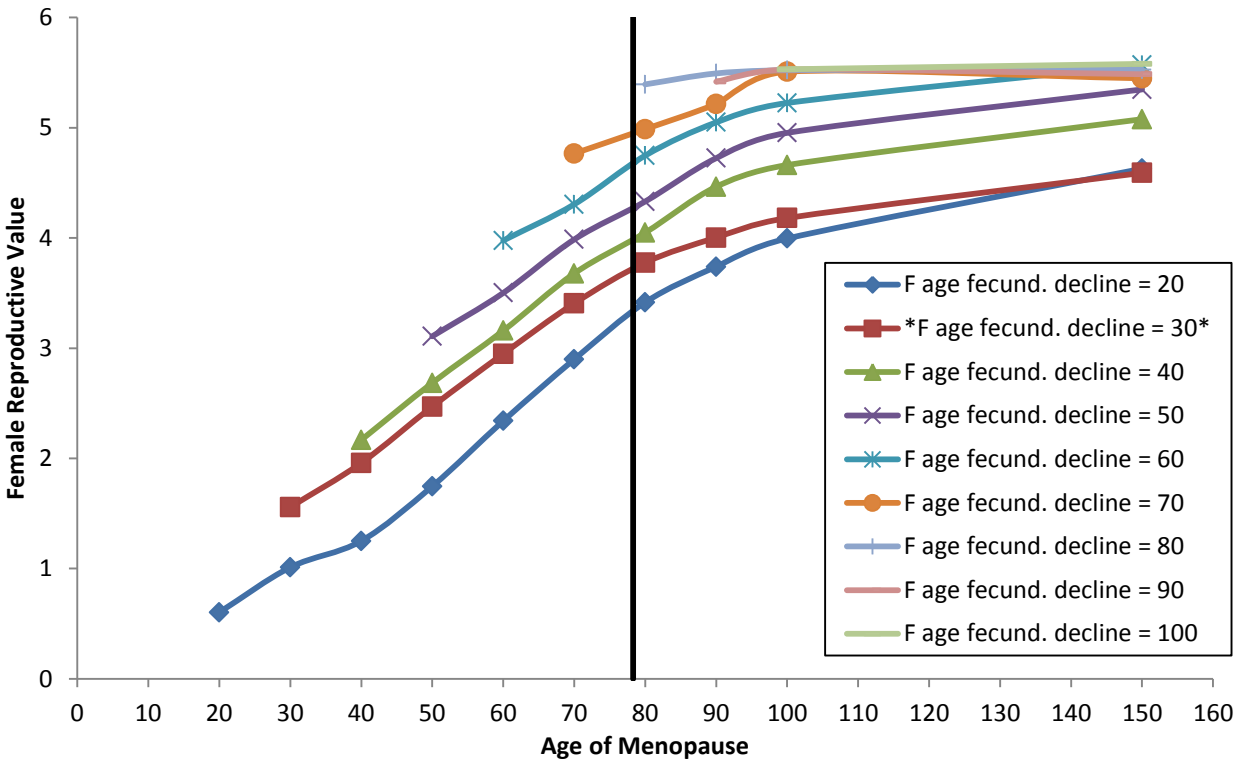


Figure 8: Plot of female reproductive value and the age of menopause in the female population for varying age of onset of female fecundity decay. Female LE at birth is 78.3 years, as indicated by the vertical line. Ages of onset of decay in female fecundity tested ranges from 20 to 100 in 10-year increments. Onset of male fecundity decay for all tests occurred at age 95. "F age fecund. decline = 30" represents the reference population.

1.6 DISCUSSION

The simulation we have performed demonstrates a population in which individuals pair, reproduce and die according to set parameters. When pairs are formed, based on eligibility criteria, the males and females within the pairs remain together for life. Within pairings, births can occur according to the fecundity of the male and female in the pair. Fecundity is governed by four separate parameters, including age of onset, maximum fecundity, age of onset of decay and age at which fecundity reaches zero. By manipulating the female fecundity phenotype,

specifically the age at which fecundity reaches zero, we can further understand the evolution of this trait in a population of serial monogamy. We have analyzed variation within three parameters that determine the female population in relation to the evolution of the age of menopause. These parameters are maximum age of eligibility in pairing, maximum fecundity value and age of onset of decay in the female population, also referred to as onset of the perimenopause transition. For each of these parameters investigated, we obtained average PGRs and FRVs.

Analysis of the FRV at various ages of menopause primarily demonstrate that increasing the age of menopause increases the overall FRV for all parameters investigated. When testing maximum female eligibility age for pair formation, FRV was identical regardless of the maximum eligibility age, due to the serial monogamy nature of the simulation. Although there was an eligibility maximum for pairing, the majority of males and female were mated at approximately the age of 13 when they first became eligible and due to the low mortality risk pairs often remained together well past the eligibility ages that were tested. Altering the maximum female fecundity value resulted in consistent trends of FRV for all fecundities analyzed although magnitude effect varies. For both maximum age of eligibility and maximum female fecundity, the FRVs do not appear to reach a plateau. Analysis of varying the age of onset of perimenopause on the other hand appears to demonstrate an eventual plateau for ages of menopause onset greater than 100. This is believed to be due to the survivorship applied to the population where no individual survived beyond the age of 100 years old. Overall, analysis of the FRV does appear to be influenced by the age at onset of menopause however, in general it was concluded that menopause does not neutrally evolve as there was always a decrease in

female fitness before the LE at birth. Based on the FRV analysis, it is not clear that this trait could have evolved to be present in a neutral or nearly neutral state within modern human lifespans.

We noticed that for all three parameters analyzed, PGR was maximized at high ages of menopause onset. Maximum age of female eligibility had no effect on the PGR. This parameter was investigated in 10-year increments from the age of 30 to the age of 80 and all PGR outputs at specified ages of menopause were equivalent. Age of onset of perimenopause impacted PGR in magnitude alone, with trends appearing consistent for all parameter changes analyzed. Age of onset in decay of female fecundity was studied on 10-year increments from the age of 20 to 100. For both female eligibility and perimenopause onset, the PGR trend was similar and reached an eventual plateau in the PGR beyond the age of 80 and past the female LE, demonstrating that menopause onset in these populations would not occur due to a decrease in fitness before female LE at birth. Results from maximum female fecundity however, demonstrate more variable outcomes. Maximum fecundity was analyzed in a range of values from 0.1 to 0.5. For the greatest fecundities tested, it was shown that perhaps menopause could neutrally evolve in the population as fitness was retained with onset before female LE. For smaller fecundities tested however, results were identical to female eligibility and perimenopause onset.

The plateau state present in all plots of PGR is immediately preceded by an age range of a point of inflection, as seen in Figures 3, 5, and 7, and it is within this point of inflection that that menopause changes to become a state of decreased fitness. We can assume that the plateau

represents a neutral or nearly neutral state with maintenance of fitness. Any deviations from this state, whether positive or negative, would directly result from changes made within runs of the simulation. While three aforementioned parameters were analyzed, within each line graphed, the parameter was held at a constant state. Therefore, any changes from the neutral state in this analysis are due only to the changing age of onset of menopause, in most cases from age of 30 to age 150. In general, the point of inflection and decrease in fitness that is seen before the neutral or nearly neutral state occurs around the age of 60-80, before the age of female LE at birth. This indicates that if menopause evolved in the human population to occur around this age range, menopause would evolve to begin affecting the fitness of the female population and there would be a negative effect on the PGR as the population deviates from a fairly neutral state of fitness. Thus if menopause evolved before or during this point of inflection, the PGR would be negatively impacted, to varying degrees, and ultimately this would indicate the presence of a negative character state in the population.

There are ample data from current human populations that the age of menopause onset is not within this 60-80 age range but instead occurs much earlier. Finding evidence of menopause in early ancestral human populations has proven very challenging. Earliest records of the menopause phenotype place age of onset somewhere in the early 40s (Ginsburg, 1991). These data were inferred from Roman populations 2000 years ago. By the 20th century, reports of cessation in menstruation estimate this onset as somewhere in the late-40s and into the 50s (Brambilla and McKinlay, 1989; Morabia & Costanza, 1998; He & Murabito, 2012; Carty et al., 2013). Although there does exist some cultural variation, in general there have been few to no reports of menopause occurring within the 60 – 80, as indicated by our simulations. It is

possible that the results of our simulation point to a potential future for human populations to experience menopause later in life, between the ages of 60 and 80 at the point of inflection and beyond the current female LE at birth.

Currently, the simulation has shown that for a range of varying parameters, with all individuals surviving according to the survivorship data from 1999 Great Britain, human menopause evolves as a neutral or nearly neutral state if the age of onset is above 80. It is possible that the recent increase in human longevity has not provided sufficient time for the menopause phenotype to respond. Finch (2010) suggested that the human life expectancy doubled during the evolutionary period from great ape ancestors and again doubled within approximately the last 200 years, in correlation with industrialization. There are some modern tribal and hunter-gatherer type cultures that continue to demonstrate shorter lifespans relative to industrialized societies however, this extended longevity is the state for the majority of societies globally (Kaplan et al., 2000).

Because the human lifespan in both men and women has evolved to increase at such a drastic rate, it is conceivable that the menopause state is also dynamic and able to increase in age of onset in response. This [nearly] neutral state of menopause occurring in a woman's 60s to 80s could represent the future direction in the evolution of this trait. By maintaining and even possibly continuing to see an increase human longevity, along with continual reproduction into the perimenopause transition period, human menopause could continue to be pushed later in life. Alternatively, it is possible that our simulation is omitting or falsely simplifying crucial aspects of human demography and mating that would lead to the menopause phenotype

appearing before our point of inflection. For example, our simulation strictly enforces the serial monogamy mating system where reproduction cannot occur outside of a pairing and there is minimal to no change in a mate throughout one's lifetime. In its current state, according to the results of our simulation, menopause appearing in the human population around the age of 50 would indicate the presence and maintenance of a deleterious trait. Population genetics tells us that traits which confer a disadvantage should be eliminated over time; however, the trait of menopause has been seen to persist. It is therefore possible that by including and/or refining other factors such as birth spacing, longevity, grandmothering and the mating system, the point of inflection that we see in our results could vary in timing, indicating alternative evolution of the trait of menopause.

CHAPTER 2:

EVOLUTION OF MENOPAUSE UNDER VARYING LONGEVITY AND BIASED MATING SYSTEM

2.1 Question 1: Influence of Human Longevity

2.1.1 INTRODUCTION

The analysis presented in Chapter One involves a population in which individuals experience the longevity representative of a modern population. The longevity modelled is derived from data acquired from Great Britain in 1999, with females and males experiencing high survivorship until the age of 80 before beginning a drastic decline in old age survivorship. From an evolutionary perspective, this status of extended longevity has not always been the case. Humans globally used to experience much shorter lifespans before the industrial revolution. During urbanization in Europe in the 17th century, life expectancy at birth was only 33-40 years of age (Galor & Moav, 2005) and there were extremely high instances of infant mortality. This '1999 Great Britain' longevity is representative of many modern, Western societies around the globe, especially North America and Europe. In Canada for example, life expectancy in 2007 was approximately 78 and 83 years for males and females respectively, with numerous instances of survivorship beyond these ages (Greensberg & Normandin, 2015). There are, however, current societies that do not experience similar lifespans, as a result of lifestyle, cultural practices or access to modern medicine. In Zambia for example, life expectancy only extends to the age of 39 (Gurven & Kaplan, 2007). Additionally, numerous modern hunter-gatherer type civilizations experience a shorter life expectancy than Western societies, with average life expectancy at birth typically maximizing around 45 years of age (Gurven & Kaplan, 2007).

Overall, human longevity has changed drastically over the course of human evolution. In the 300,000 generations from great ape and chimpanzee shared ancestor, human longevity

has more than doubled. Again, over only the last 200 years, human longevity doubled in response to the industrial revolution, resulting in human populations to experience the longest lifespans of all living primates (Finch, 2010). While evidence on the current state of human longevity indicates great variability, humans, regardless of cultural or social structure, demonstrate long lifespans and the phenotype of menopause along with it. Our previous results indicate that under current human demographics, menopause could have evolved to be a neutral or nearly neutral state in the human population if onset occurred beyond the age of 60-80. Based on physical evidence, we know that this is not the case and menopause onset in human populations occurs around the age of 50. We have postulated that the reason we see menopause occurring before the age of 60 in current populations is that the drastic increase in modern human longevity did not allow for the response of the trait of menopause. This would indicate that the current state of menopause onset is at a time in the female's lifespan more reminiscent of ancestral populations. One way to test this is to alter the survivorship parameters within the simulation to represent an ancestral population and analyze the evolution of menopause in the population of a short lifespan.

2.1.2 METHODS

The simulation used to conduct this analysis is the same on as outlined in Chapter One with few modifications. Firstly, we have modified the Siler parameters to represent the survivorship curve of a modern chimpanzee population (**Appendix A Table 2**). Chimpanzees have often been used as a point of reference to the ancestral state of humans as they are closest living relatives (Kaplan et al., 2000; Lacreuse et al., 2008; Finch, 2010). According to current data of chimpanzee survivorship, typical duration of chimpanzee lifespan extends to 50-55

years old (Kaplan et al., 2000, **Appendix A Figure 8**). Unlike modern, Western human populations, chimpanzees experience a fairly linear decline in survival throughout lifespan (**Appendix A Figure 9**). As a result, the typical LE at birth in chimpanzee populations is 15 years (Hill et al., 2001). The higher rate of infant mortality also results in a smaller proportion of individuals surviving to ages of reproduction than in the original parameters of the simulation. This loss of fecund individuals led us to also alter the fecundity parameters.

In the reference population outlined in Chapter One, female maximum fecundity was 0.15 and male maximum fecundity was 0.9. For the current analysis of decreased longevity, male and female maximum fecundity was set to a value of 1.0, which was required for the population to be sustainable. Additionally, the reference 1999 Great Britain population used in Chapter One experienced onset of fecundity at the age of 13 in males and females. For the current analysis, onset of fecundity and minimum pairing eligibility for males and females was set to 8 years of age, in accordance with information that chimpanzees demonstrate menstrual swelling before the age of 10 (Lacreuse et al., 2008). The age of onset of fecundity decay in the 'chimpanzee' population was set to 45 in males and 30 in females and the age at which menopause decreases to zero, the variation of the female fecundity phenotype, was tested throughout. The age at which fecundity declined to 0 in males was consistently 100. Finally, the number of nursing years was changed from 4 to 5 years. This was chosen as an average from various sources that state birth spacing times in wild chimpanzees as around 66 months/5.5 years (Galdikas & Wood, 1990) and 4.6 – 5.1 years (Sugiyama, 1994). The mating system for this analysis is of serial monogamy, as described in Chapter One.

For each analysis conducted in this investigation of influence of changing longevity on the evolution of menopause, we altered the age of menopause from one run to another. Identical to the output of Chapter One, this simulation analysis produces a PGR and FRV at the end of each run. Again, with a specific parameter investigated, we considered a range of ages of menopause and by analyzing the resulting outputs, we attempted to identify the timing of neutrality or near neutrality of onset of menopause. It is by comparing the modern population simulated in Chapter One to this chimpanzee/ancestral state, both under the influence of a serial monogamy mating system, that we can make inferences about the origin and evolution of menopause to the state in which we see it now.

2.1.3 RESULTS

In Chapter One, based on the point of inflection noted in the graphs of PGR against age of menopause, menopause appears to be neutral or nearly neutral in onset beyond the age of 60 – 80. When analyzing the chimpanzee-longevity reference population under a range of ages of onset of menopause, it is evident that this point of inflection occurs before the 60-80 age range (**Figure 9a, raw data in Appendix A Table 4**). The point of inflection, under the reference parameters specified above, appears to occur between the ages of 40 and 60 in the population of shorter lifespan, well beyond the female LE of 15 years. Additionally, there appears to be a clear inflection point and plateau occurring at the same age in the plot of FRV with age of menopause (**Figure 9b, raw data in the Appendix A Table 4**). In the chimpanzee population and under specific simulation parameters, menopause does not evolve in a neutral state. Despite not occurring within the chimpanzee lifetime, comparing the reference populations indicates that menopause occurs earlier in the life when the lifespan is shorter.

Both figures demonstrate a noticeable difference in the point of inflection between the 1999 Great Britain and chimpanzee-longevity reference populations. It appears that when the lifespan is short in duration, menopause evolves to be neutral or nearly neutral in appearance earlier than in the case of a longer lifespan, however, in this case, menopause appears well beyond the average female LE in the chimpanzee population. There is also a clear magnitude difference for both PGR and FRV between the reference populations. Despite maximizing fecundity to a value of 1.0 in the simulation of shortened longevity, the population is only just above the point of being a sustainable population with FRV being maximized just above a value of 2. This may be due to the decrease in survivorship to ages of reproduction. For all parameters that were further analyzed, PGR and FRV of the population of shortened longevity all indicate a plateau at or just above values required to maintain the population, resulting in a small population maintained throughout each run of the simulation. This small population means that every birth or death occurring within a one-year interval can have quite a dramatic effect on the PGR, ultimately resulting in high variability. The same FRV can result in a wide range of PGRs, completely dependent on the yearly division of births and deaths. This high variance manifests on the plots as inconsistent trends and therefore PGR is not regarded as the most informative output. In future work, multiple iterations can be conducted for a single point to gather information on variation in PGR. Instead, we relied more heavily on analysis of plots of FRV when conducting our analysis on populations of shorter lifespans.

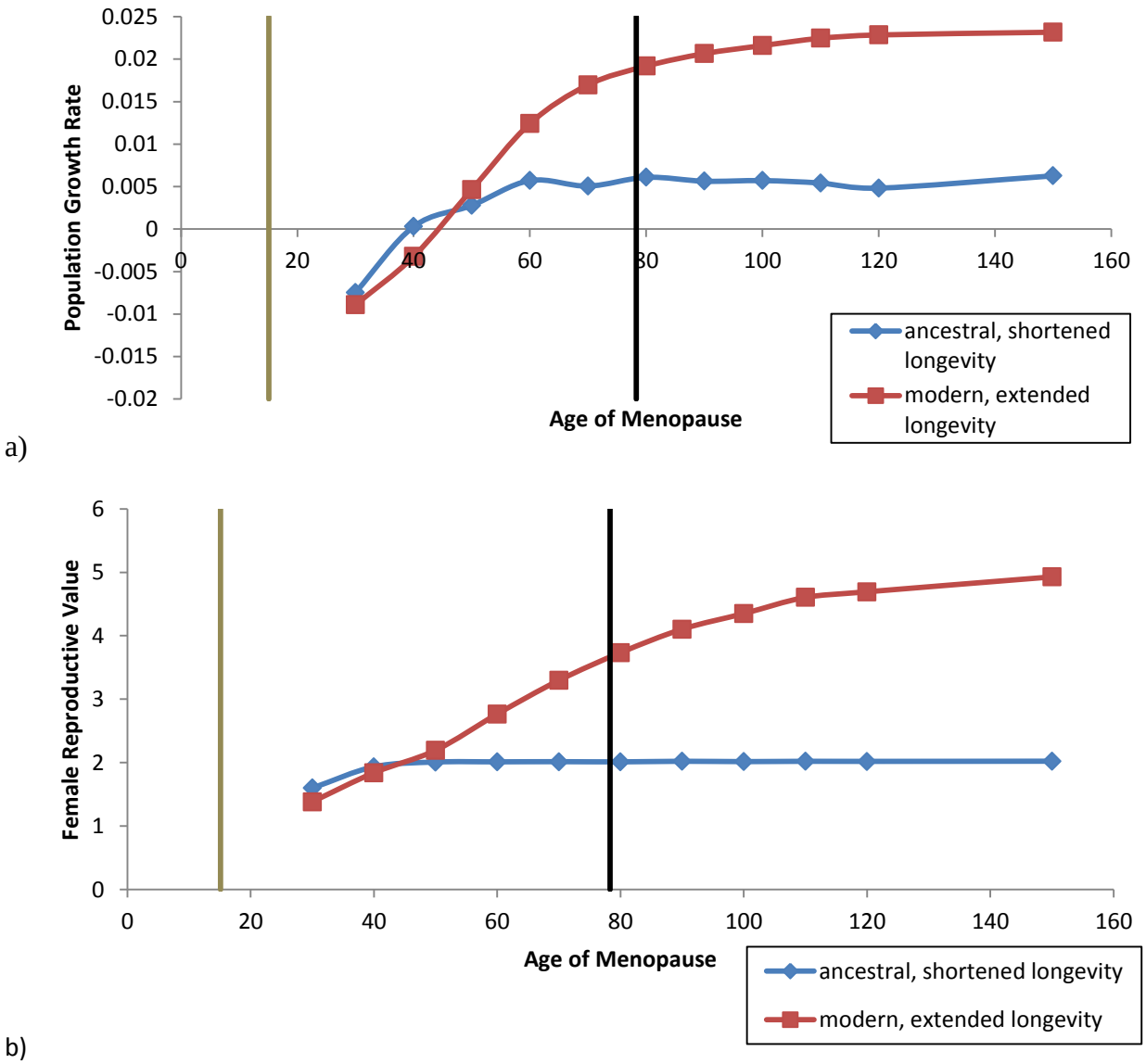


Figure 9: Comparing the neutral evolution of menopause between 1999 Great Britain survivorship reference population and a population of modern chimpanzees with shortened longevity. Female LE at birth is 78.3 years for the 1999 Great Britain population and 15 years for the chimpanzee population, as indicated by the vertical lines. (a) plot of PGR and age of menopause for reference populations of differing longevity. (b) plot of the FRV for reference populations of differing longevity. In both plots, the 1999 Great Britain population demonstrates a point of inflection before the age of 80 whereas this point of inflection occurs around the ages of 40 – 50 in the modern chimpanzee population.

In the chimpanzee reference simulation parameters, both males and females were eligible to be paired between the ages of 8 and 80. The maximum pairing value of 80 extends well beyond the maximum lifespan of any individual in this simulation, as all males and females die around the age of 50. Due to the shape of the chimpanzee mortality curve however, we do see greater instances of infant and child mortality than in the 1999 Great Britain simulation. This indicates that in the chimpanzee simulation, it is more likely throughout an individual's lifetime that pair bonds will be broken by death. Based on this mortality curve and difference in survivorship, we again decided to test varying maximum ages of female pairing eligibility in this mating system of serial monogamy to see if the maximum age of eligibility influenced the evolution of menopause onset.

Maximum female pairing eligibility was tested at ages 30, 50 and 80. For all of these tests, both the male and female minimum eligibility remained constant at 8 years old and maximum male eligibility was 80 years old. For each of the three maximum eligibility ages, the age of onset of menopause was examined in 10-year increments from the age of 30 to 100, and again at age 150. The output PGR and FRV were individually plotted against age of menopause (**Figure 10, raw data in Appendix A Table 4**). It is evident in the plot of PGR that the small population size is having an impact as there is high variability within each line; therefore, we will continue in analyzing the FRV.

Similar to the results of the chimpanzee reference population in Figure 9a, the FRV plot reaches a plateau at just over a value of 2 when the maximum age of female pairing eligibility is altered. In Figure 10b, when maximum age of eligibility is 50 and 80 the resulting lines appear

identical. This is because the majority of deaths occur for both males and females by the age of 50; therefore, these two eligibility maximums generate nearly identical populations in eligibility and pairing terms. This overlap highlights the importance of mortality risk on the simulation outcome, specifically the patterns of pairing in a serially monogamous population. The plot of FRV does differ when the maximum age of female eligibility for pairing is set to 30. There appears to be greater variability for a maximum eligibility of age 30 when testing ages of menopause onset before the age of 60. While this variability is evident, ultimately the trend for all three maximum ages of eligibility investigated is the same. The point of inflection is present in this plot between the ages of 40 and 50 indicating that menopause onset after this age to be a nearly neutral trait in the population. Again, this age of menopause onset occurs beyond the female LE at birth of 15 years. The similar point of inflection can also be seen in the plot of PGR in Figure 10a as well as in Figure 9a and b.

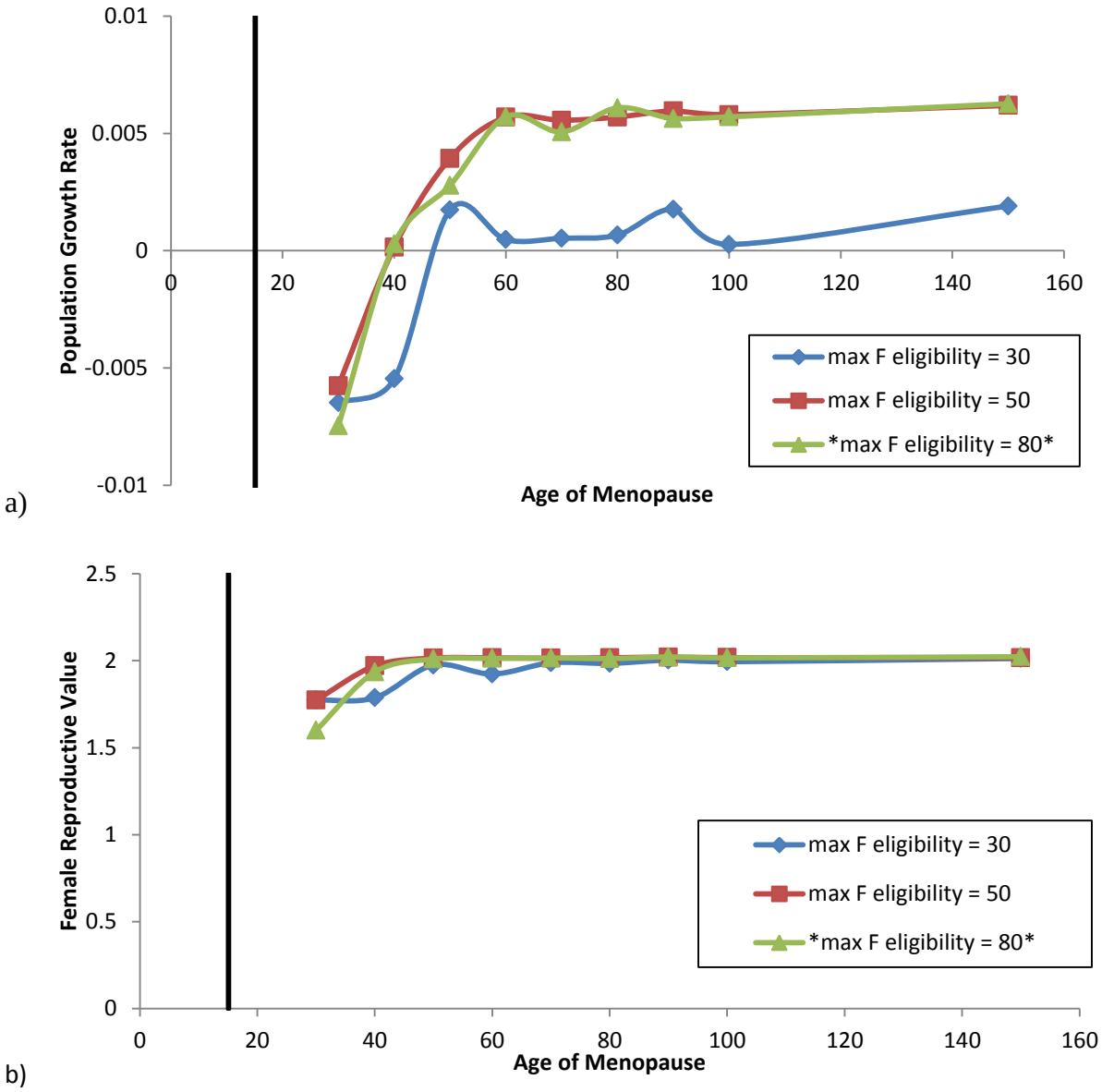
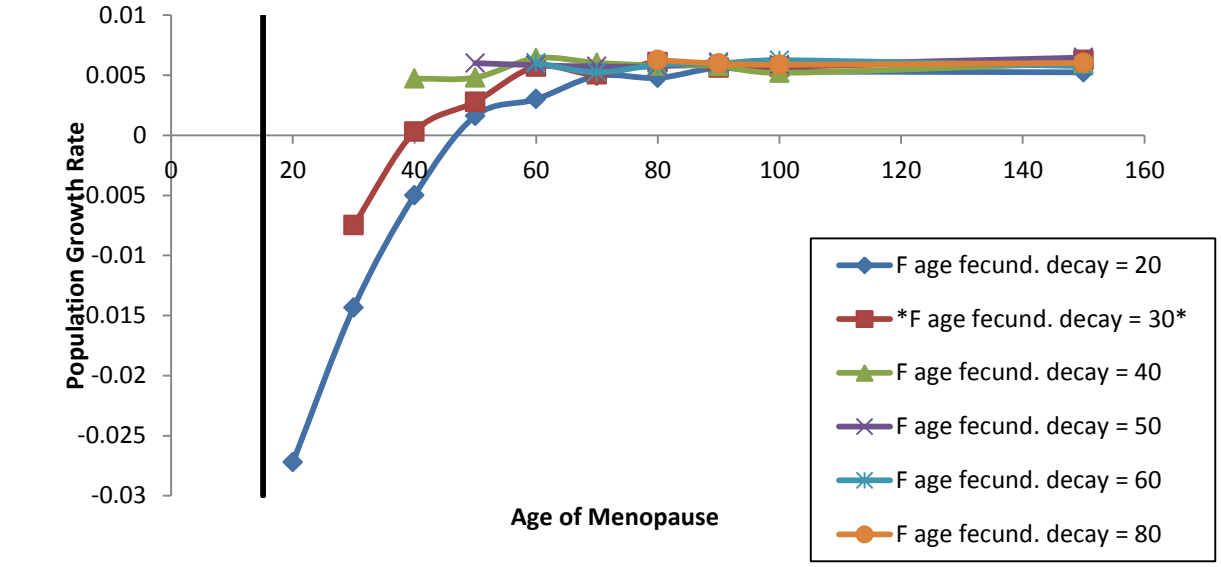


Figure 10: Results of changing the maximum age of female pairing eligibility in a chimpanzee population of shortened lifespan representative of an ancestral human population. Female LE at birth is 15 years, as indicated by the vertical line. a) shows the PGR as a function of age of menopause onset while b) shows the FRV as a function of age of menopause onset. Maximum female pairing eligibility was tested at the ages of 30, 50 and 80. "max F eligibility = 80" represents the chimpanzee reference population.

The next parameter that we investigated in the chimpanzee population of shortened longevity is the age of onset of fecundity decay, referred to as the age of onset of perimenopause. Modern chimpanzees have not been identified to definitively demonstrate menopause as humans do. Most reports indicate continued menstruation of chimpanzees throughout most of their lifespan (Lacreuse et al., 2008). If chimpanzees were to undergo menopause in the same way that humans do, we would expect to see reproductive senescence before death, around the age of 35; however, typical chimpanzee reproductive senescence occurs very close to the age of death (Lacreuse et al., 2008). Working under the assumption however that this modern chimpanzee is representative of ancestral human populations, we altered the age of onset of perimenopause in the simulation population and tested the variation in perimenopause under varying ages of menopause.

Age of perimenopause onset was tested in 10-year increments from the age of 20 to 60 and again tested at age 80. Due to the mortality curve, all individuals in this ancestral population are dead before the age of 60; therefore, we expected no difference among tests of perimenopause onset at ages 50, 60 and 80. As perimenopause is considered to be a female-specific trait, fecundity in the male population remained the same as in the reference population with age of fecundity decline occurring at age 45 and declining to a value of 0 by age 100. For each age of perimenopause tested, we ran the simulation for a range of ages of onset of menopause from age 20-150 when possible. The resulting PGRs and FRVs were then plotted against the ages of menopause (**Figure 11, raw data in Appendix A Table 4**).

The results of both PGR and FRV indicate that regardless of the age of onset of perimenopause, menopause will evolve as a nearly neutral trait in the age range of 40-50 years old, beyond the female LE at birth in the chimpanzee population. Again, the plateau that is present in both Figure 11a and 11b, indicating a steady state in the population and any deviation from this state is in response to a single change, which in this case is the age that we insert as the onset of menopause. It is clear that decrease in fitness from a steady state occurs in both graphs around the age of 40-50. Contrary to previous investigations, altering the age of onset of perimenopause appears to have little magnitude difference in the value of the plateau for both PGR and FRV. In all runs of the simulation, the population experiences a maximum growth rate and FRV just above the threshold for maintenance of the population.



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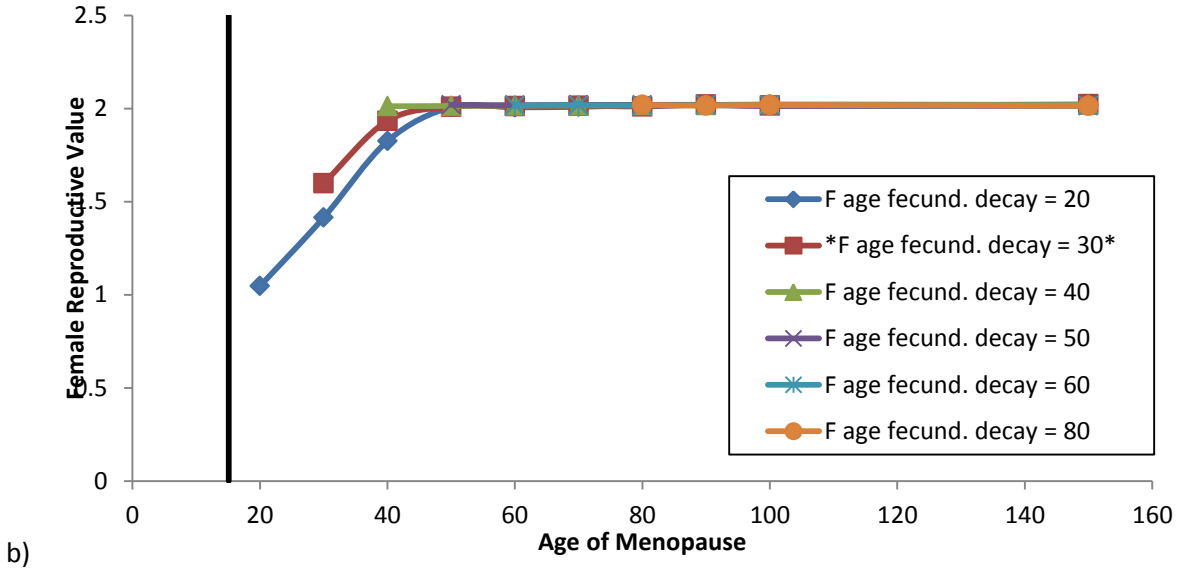


b)

Figure 11: Results of changing the age of onset of fecundity decay in female in a chimpanzee population of shortened lifespan representative of an ancestral human population. Female LE at birth is 15 years, as indicated by the vertical line. a) shows the PGR as a function of age of menopause onset while b) shows the FRV as a function of age of menopause onset. Ages of onset of fecundity decay that were tested were from 20 to 60 in 10-year increments and 80. "F age fecund. decay = 30" represents the chimpanzee reference population.

2.1.4 DISCUSSION

The results of investigating the evolution of menopause in an ancestral population of shortened longevity indicate that menopause could have nearly neutrally evolved in the population around the age of 40-50; however, this age is well beyond the maximum LE at birth for female chimpanzees. Interestingly this 40-50 age range is the range that is currently noted to be present in modern human populations as timing of onset of perimenopause and the transition to menopause (Brambilla and McKinlay, 1989; Morabia & Costanza, 1998; He & Murabito, 2012; Carty et al., 2013). Our results indicate, in the scenarios that were simulated, that it is possible for menopause to have evolved in a neutral state past LE at birth when humans lived shorter lifespans and as longevity drastically increased, especially over the last few centuries, menopause did not respond at the same rate and continues to be present in an ancestral state. This 40-50 age range however is the direct result of the chimpanzee lifespan that was simulated in which individuals survived to a maximum age of approximately 50. It is therefore possible, and remains to be tested, that if populations of different longevity were to be investigated, the age at which menopause neutrally appears would change accordingly.

This interaction of longevity and menopause has been noted in the Lifespan Artifact hypothesis where it is suggested that menopause is built into the genome and humans demonstrate the trait simply because they live longer (Pecci, 2001). The results presented here firstly demonstrate under current human longevity and growth parameters, menopause cannot evolve until beyond the age of 60-80 years. The population modelled after chimpanzees on the other hand show that menopause can evolve much earlier in life, specifically just past the 40-50 age range, however the appearance of menopause at this age resulted from the maximum

lifespan of the population chosen and if other 'ancestral' populations had been used, this age of menopause would differ. It is apparent through these simulations that there is no basis to assume that menopause is built into the human genome as menopause in its current state represents a deleterious rather than neutral trait in terms of overall female fitness. Additionally, this work builds off of the assumption that humans have evolved over time and modern chimpanzees represent an ancestral state therefore there is no reason to believe that the chimpanzee lifespan has always been fixed at 50 years of age; instead it must have evolved over time like in other species with these other ages resulting in differing ages of menopause.

Our results demonstrate that menopause cannot neutrally evolve within the female lifespan under a mating model of serial monogamy. The timing of the neutral evolution of menopause is influenced by the lifespan of the population and occurs beyond the female LE at birth. In a long-living population, menopause cannot evolve until late in life. Therefore, for menopause to have evolved in the human population under the parameters of this model, longevity would have had to be similar to that of an ancestral state. There are other elements of the simulation, such as the mating system, that can be investigated further to see if the influence of longevity is the sole parameters that can alter the age at which menopause neutrally evolves at an age earlier than after 60-80.

2.2 Question 2: Mating System

2.2.1 INTRODUCTION

In the base simulation, described in Chapter One, we modelled populations evolving over time, with pair bonds remaining intact each year and only broken by death of one mate in a pair. Individuals therefore only formed more than one pair if a mate died and the male or female remaining was still of an eligible age. We know however, that oftentimes pair bonds are not formed for life. The idea of breakage in pair bonds is seen historically as well as cross-culturally (despite disproval in some cultures). Separation of pairs and remarriage appears to be common in modern societies. In the United States of America, divorce rates doubled between 1990 and 2008 in people over 35 years of age, with an estimated 44% of marriages ending in divorce (Kennedy & Ruggles, 2014). Pair separation was present in the Roman Empire where a statement of intent for 'divorce' was sufficient to end a bond and permit remarriage (Coontz, 2007). Even within churches, divorce has been acceptable under specific circumstances. While this idea of divorce may be specific to societies that recognize the institution of marriage, historically and in some modern societies the breakage of pair bonds was not uncommon. More recently, there have also been reports of both separation and repairing in many hunter-gatherer type societies that match rates of industrialized societies (Coontz, 2007).

In general, we see that globally, pair bonds are often seen to not last the duration of one's lifespan. This means that not only will pair bonds be broken but new pair bonds are likely to be formed within an individual's lifetime. We therefore have revised our simulation to represent a population in which divorce is strictly enforced for all pair bonds, to see if and how this modified mating system influences the evolution of menopause. The altered simulation

functions in the same way as outlined in Chapter One but with a major change in the termination of pair bonds. The simulation continues to use a 1999 Great Britain mortality risk curve the control deaths in the population. Births continue to occur only within a pair bond and are dependent on the fecundity of the male and female within the pair. Individuals in the population reproduce and die through time as the simulation proceeds and again PGR and FRV plots are returned at the end of each run of the simulation.

In current human populations, when it comes to choosing a mate, some theories propose that there is underlying strategy, whether conscious or unconscious, to optimize fitness benefits (Buss & Schmitt, 1993). Males can choose female mates to optimize reproductive value or fertility. Reproductive value is the potential reproduction including present and future, whereas fertility refers to immediate probability of reproduction (Buss, 1989). In general, females are of peak reproductive value at menarche, in her mid-teens, and decrease in value until the onset of menopause. On the other hand, females are of maximum fertility in early- to mid-twenties and decline after age 35 (Antfolk et al., 2015; Buss, 1989; Buss & Schmitt, 1993; Symons, 1979).

When choosing a long-term mate, males typically express preference for younger mates, ultimately optimizing reproductive FRV as it includes the female's reproductive potential in the future (Buss & Schmitt, 1993). Symons (1979) proposes that the ideal age for males to choose as mates would range from age 17-28 depending on the long term or short term value of the mating: 17-22 years for long term to maximize reproductive output and 23-28 for prime reproductive output and most viable mates. Choosing pre-pubescent or post-menopausal females would minimize reproductive output and is therefore not favoured. For this reason, we

have modified our simulation to demonstrate this preference for younger females by restricting female eligibility for mating. In general, the age of a male does not accurately indicate his fertility (Antfolk et al., 2015); therefore, no such restrictions were imposed on male eligibility for pair formation.

2.2.2 METHODS

The modification made to our simulation is the termination of all existing pair bonds when the female of the pair reaches a predetermined age. In addition to this modification, pair bonds can continue to be broken by death of the male or female within the pair. According to our added modification, when a pair is broken due to the female's age, she will no longer be eligible to re-pair again. That is to say the female age of termination of pair bonds and the maximum age of female eligibility are the same. To further investigate the influence of the mating system on the evolution of menopause, we ran the simulation as outlined in Chapter One with this mate system modification.

All survivorship and fecundity parameters remain the same as described in Chapter One. As for the mating system in this analysis, males and females both become eligible to form pair bonds at age 13. In our reference simulation, this age at which existing pair bond will be broken is when the female is 40. This termination, called "divorce", occurs regardless of the male's age. Males are maximally eligible until the age of 80; therefore when a pair bond is broken due to the female's age, the male can return to the eligibility pool if he is younger than age 80. Female maximum age of pairing eligibility in this simulation is the same age at which pair

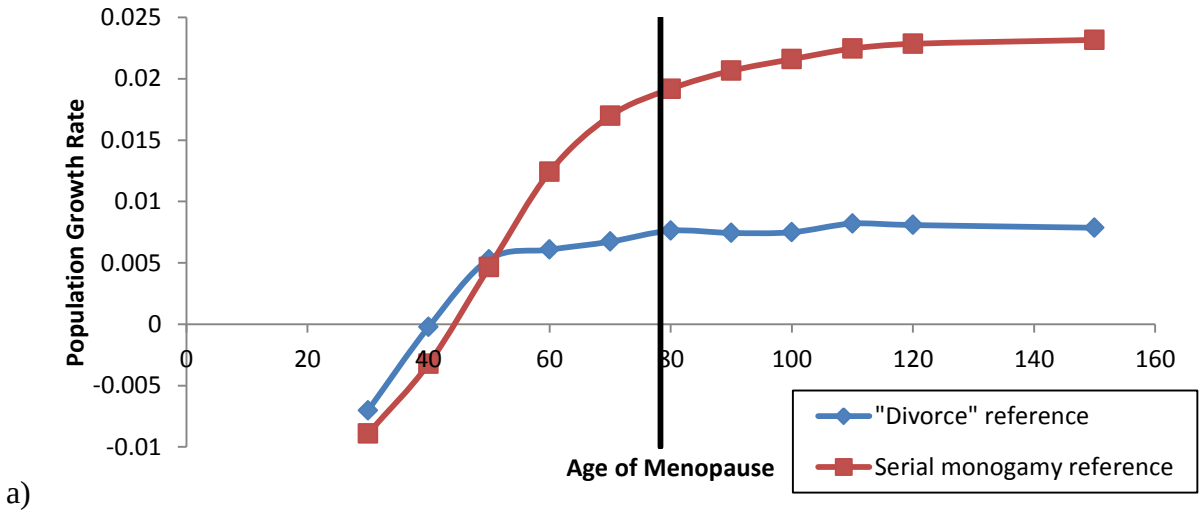
bonds are broken; therefore, she will not return to the eligibility pool. If a pair bond is broken by death, males and females will become eligible for re-pairing based on their age.

2.2.3 RESULTS

We continued the investigation of this modified mating system on the neutral evolution of a menopause phenotype by analyzing the resulting PGR and FRV for various ages of menopause onset. We firstly compared the 1999 Great Britain reference population to this "divorce" reference population that strictly enforces female mate eligibility parameters. The results of both reference populations were plotted together for PGR and FRV (**Figure 12, raw data in Appendix A Table 5**). Both plots indicate that in a "divorce" model mating system with serial pair bond formation and strict enforcement of a maximum age of female eligibility, menopause can neutrally or nearly neutrally evolve beyond the ages of 50-60.

This 50 – 60 age range represents the age just past the point of inflection to a plateau state in both PGR (Figure 12a) and FRV (Figure 12b). For reference, the point of inflection present in the analysis of Chapter One occurs between the ages of 60-80 indicating menopause neutrally evolving in the Chapter One population beyond the age of 80. This age change in presence of a point of inflection indicates that by changing the mating system so that females can only reproduce at younger ages, menopause evolves nearly neutrally and earlier in lifespan, before the female LE at birth. Additionally, there appears to be a distinct magnitude difference between the 1999 Great Britain reference population and this current model for both PGR and FRV. This difference in magnitude occurs because in the current modified model, fewer females are available to reproduce therefore fewer births are occurring. Despite this decrease in

PGR and FRV that occurs in the new strict eligibility simulation, both models demonstrate that menopause can neutrally evolve under the specified parameters and the timing on menopause onset is influenced by the mating system.



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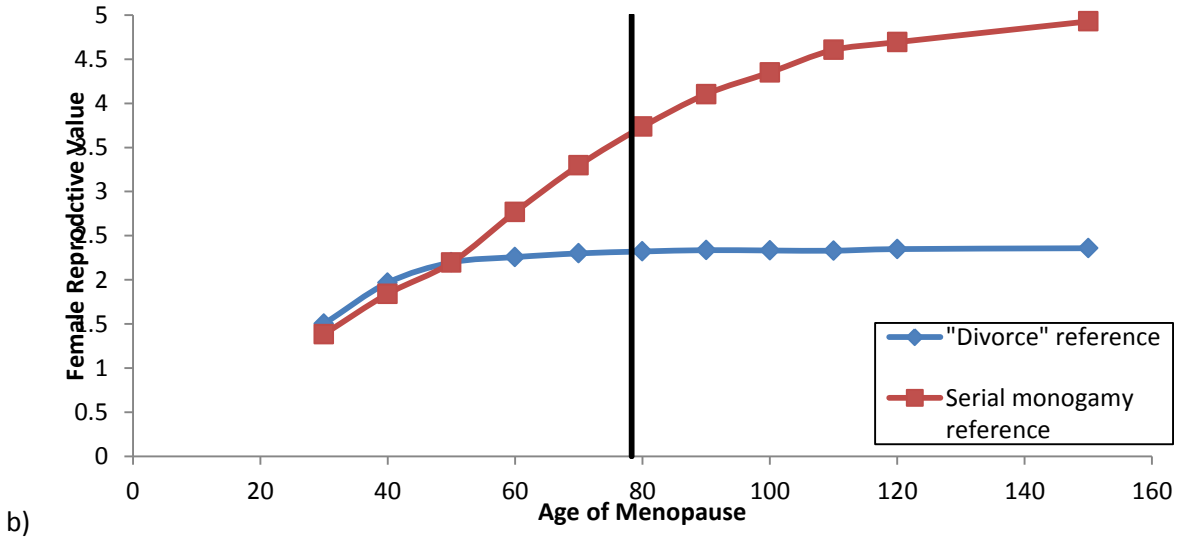

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Figure 12: Comparing the neutral evolution of menopause between a serially monogamous mating system and a 'divorce' model of serial monogamy with strict enforcement of maximum age of female eligibility. Female LE at birth is 78.3 years, as indicated by the vertical line. a) plot of PGR and age of menopause (b) plot of the FRV and menopause. In the serial monogamy population, the point of inflection occurs beyond the ages 60 – 80 and between the ages of 40 – 60 when females experience age-restricted mating within serial monogamy.

In the ‘divorce’ reference simulation, we have specified the maximum age at which females are eligible and the age at which pair bonds are broken to be 40 years old. As noted earlier, when choosing mates, males often identify a mate to optimize fitness benefits, whether this occurs consciously or unconsciously (Buss & Schmitt, 1993). For long-term pair bonds, Buss & Schmitt (1993) state that males should ideally choose females in an age range of 17-28 years. While our ‘divorce’ age in the reference population of the simulation occurs beyond this 28-year maximum of fitness benefits, 40 appears to be more representative of true human populations as divorces in the United States of America commonly occur in individuals over the age of 35 (Kennedy & Ruggles, 2014). To test both biological and realized age maxim, we can alter the age of divorce and female eligibility in our simulation to reflect a range of ages.

For each run of this analysis, female maximum age of eligibility and the female age of pair bond termination were set to be identical. By doing this, we ensure that all eligible females have the opportunity to form a pair but also that no females above the maximum age of eligibility can retain a mate. The maximum age of female eligibility, the age of pair bond termination, was tested at ages 30, 40, 50, and 80. Despite variation in the age of divorce, both male and female age of eligibility remained constant at 13 years old. The maximum age eligibility for males was 80 for all runs within this analysis. For all four of the ‘divorce’ ages tested, we varied the age of onset of menopause from age 30 to age 100 in 10-year increments and finally set the age of menopause to be 150. The resulting PGRs and FRVs for each run

were plotted along with the age of menopause tested to identify trends (**Figure 13, raw data in Appendix A Table 5**).

Unlike when the maximum age of female eligibility was altered in Chapter One, we now notice the parameter changes trends in both PGR and FRV and ultimately identifies variability in the age of neutral evolution of menopause onset. For all four of the 'divorce' ages tested, we see that PGR values have reached a plateau (Figure 13a). There is a noticeable difference in the growth rate at which the plateau occurs, ultimately determined by the females that are reproducing. This plateau is also evident in three of the four maximum eligibility plots of FRV (Figure 13b). When maximum female eligibility is 80 there is no plateau in FVR, however it appears to be increasing at a slower rate. For older ages of female eligibility, we see higher PGRs and FRVs, indicating more fecund females that are able to reproduce therefore more births are occurring in the population.

Arguably the most notable trend however, is that although all simulated populations have reached a plateau, the age at which the point of inflection occurs varies depending on the maximum age of female eligibility. When the maximum female eligibility age is 80, the population behaves identically to populations analyzed in Chapter One. This is because the age range of eligible females in Chapter One of serial monogamy and in this model of serial monogamy plus "divorce" are the same. We notice however, that as the age of maximum female eligibility decreases, so too does the age at which we identify the point of inflection and for maximum female eligibilities of 40 and 50, the age at which menopause neutrally evolves occurs before the female LE at birth. At a maximum female eligibility of 50, the point of

inflection occurs before age 50-70, at maximum female eligibility of 40 this point of inflection occurs around 40-60 and when maximum female eligibility is 30, there does not appear to be a point of inflection present and the population is in a constant state of decline. These identified points of inflection are present in both plots of Figure 13, although appear more obvious when analyzing PGR. The various ages at which we see the point of inflection represent the age at which menopause can [nearly] neutrally evolve in the populations and can occur within the lifespan of females without and resulting decrease in fitness. It is clear that by changing the mating system so that strict female mate eligibility is enforced, menopause can evolve differently to be present at various ages.

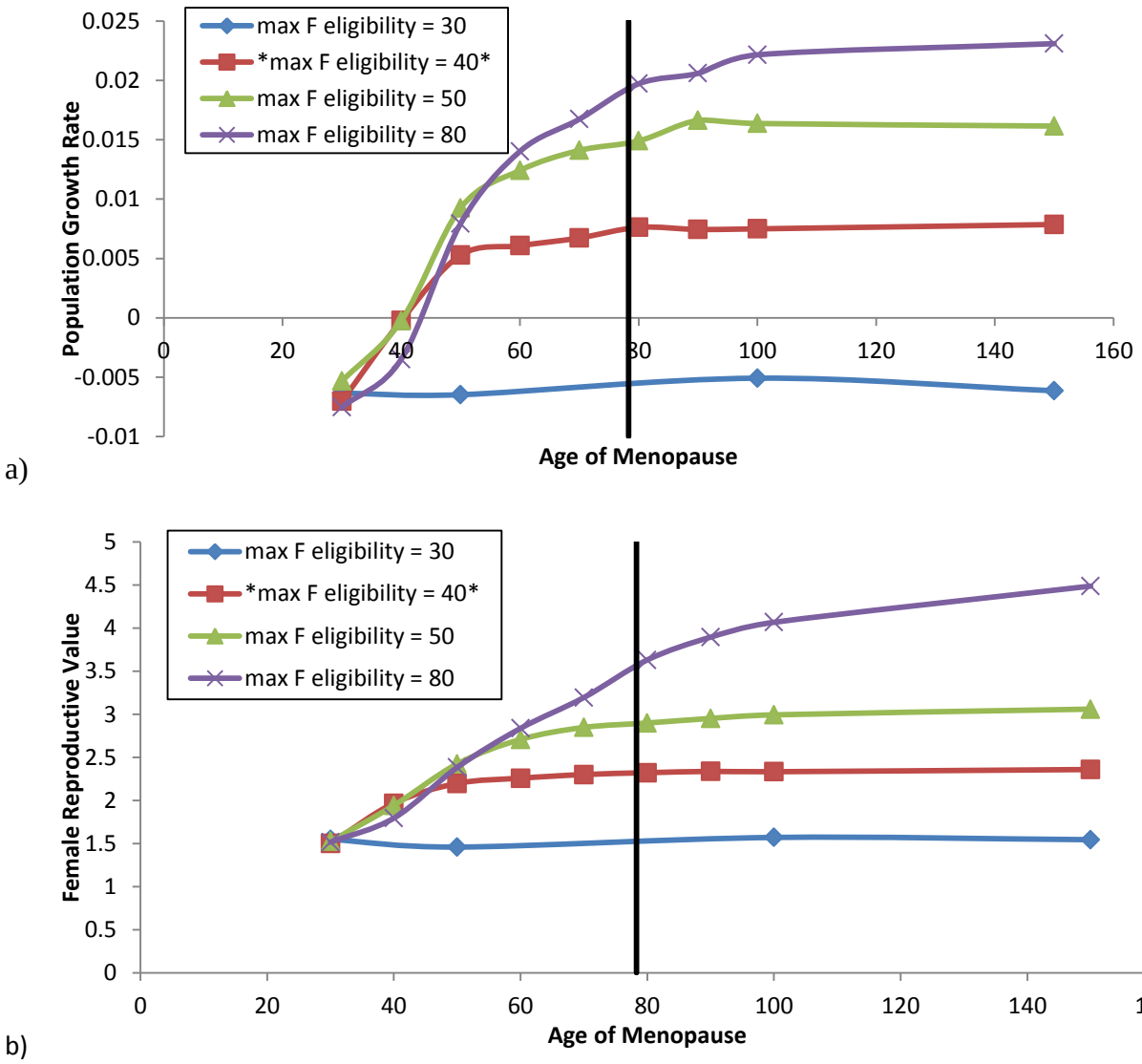
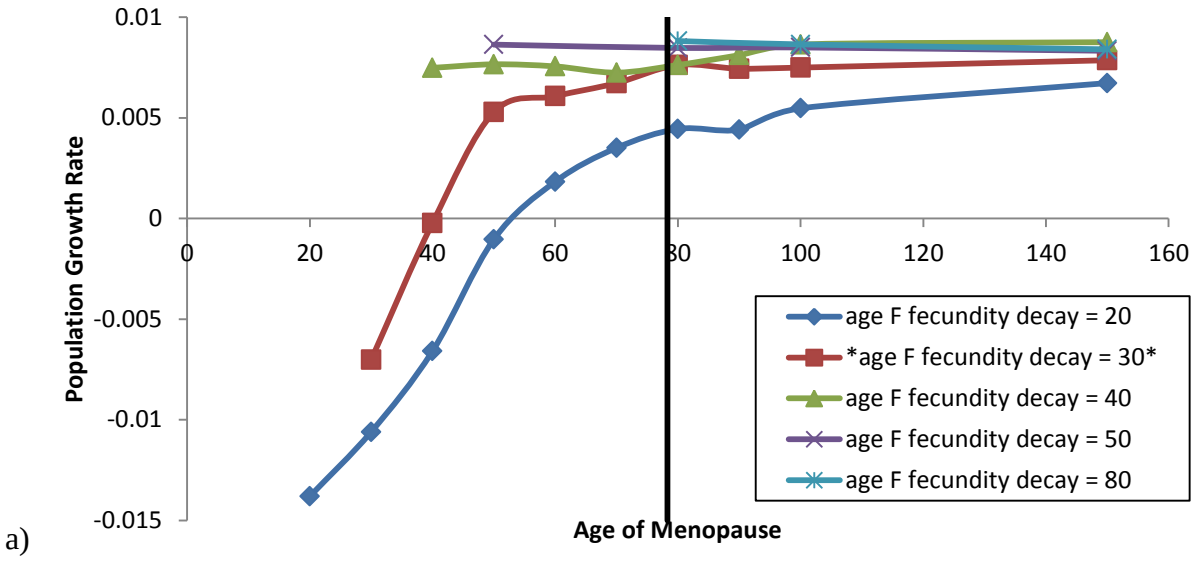


Figure 13: Results of changing the maximum age of female pairing eligibility in a 'divorce' model of serial monogamy with strict enforcement of maximum age of female eligibility. Female LE at birth is 78.3 years, as indicated by the vertical line. a) shows the PGR as a function of age of menopause onset while b) shows the FRV as a function of age of menopause onset. "max F eligibility = 40" represents the reference population.

The final parameter examined in this population of serial monogamy and 'divorce' at a maximum age of female eligibility is the age of onset of perimenopause. The age of perimenopause onset was tested in 10-year increments from the age of 20 to 50 and again tested

at 80. For the duration of this analysis, the age of onset of fecundity remained constant at 13 years old in both males and females. Male fecundity also remained constant in decay with onset of decay occurring at age 95 and decaying to 0 at age 100. Within each of these tests, the age of "divorce"/ maximum age of female eligibility was set to 40 years old, as seen in the reference population. For each of the ages of perimenopause investigated, we again tested a range of ages for onset of menopause and graphed the resulting PGRs and FRVs (**Figure 14, raw data in Appendix A Table 5**).

Figure 14a shows the relationship between PGR and age of menopause for each of the five ages of perimenopause onset that were tested. The plateau that exists in all cases is the result of the interaction between maximum eligibility and fecundity. Because maximum age of eligibility in females was held at 40 for all analyses, PGR was maximized when age of perimenopause was also set to 40 and therefore resulted in a plateau for any age of onset of perimenopause that would occur at a later age. In this population, the maximal PGR was around 0.08. By further analyzing the lines that represent age of perimenopause onset before age 40, it is clear that a point of inflection exists. For ages of perimenopause onset of 30 and 20, this point of inflection occurs around the ages 50-70, resulting in the neutral onset of menopause beyond age 70 but before the female LE at birth of 78.3 years. These trends are further confirmed in Figure 14b which demonstrates the relationship between FRV and age of menopause. In this graph, the point of inflection appears to more clearly exist between the ages of 40 and 60. Overall, the information provided in both graphs of Figure 14 indicate a point of inflection existing in the broad age range of 40-70, consistently younger than the age at which we saw a point of inflection in Chapter One analysis.



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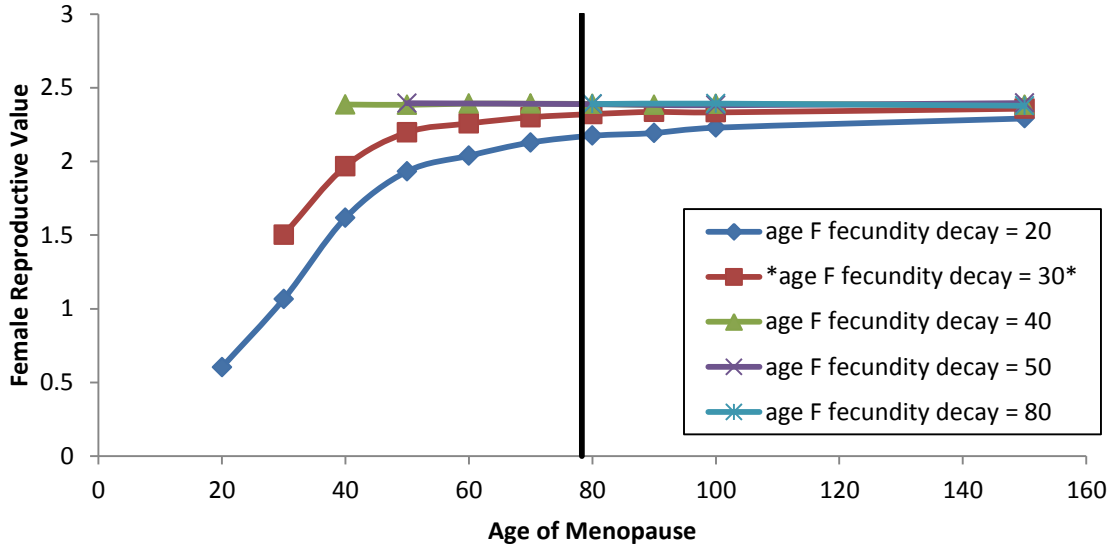


b)

Figure 14: Results of changing age of onset of fecundity decay in a 'divorce' model of serial monogamy with strict enforcement of maximum age of female eligibility. Female LE at birth is 78.3 years, as indicated by the vertical line. a) shows the PGR as a function of age of menopause onset while b) shows the FRV as a function of age of menopause onset. "F age fecund. decay = 30" represents the reference population.

2.2.4 DISCUSSION

The goal of this investigation was to further analyze the role of the mating system on the evolution of menopause in human populations. We compared a population in which individuals mate in a serially monogamous manner but with strict enforcement of the maximum age of female eligibility through "divorce" to a mating system of serial monogamy where pair bonds are only broken by death. It is evident through this analysis that the age at which menopause can neutrally evolve in a population is influenced by the mating system of the population. Overall, it was found that when mating in one sex, here females, is restricted so that paring and reproduction can only occur at younger ages, the age at which menopause neutrally evolves decreases relative to the reference population in Chapter One and can occur before the female LE at birth. When males and females both mate throughout their lifespan into their 80s, menopause onset occurs past the age range of 60-80, however when females can only pair and reproduce until the age of 40, this age of menopause onset changes to beyond 40-60.

It was proposed by Morton et al. in 2013 that a bias in the mating system could have resulted in reproductive senescence in human females. They specifically stated that a mating system where older females are not chosen as mates and only younger females reproduce can lead to accumulation of deleterious mutations and ultimately diminished fertility in women at older ages. The results of this present study thus corroborate the findings by Morton et al. (2013). When females are only able to reproduce until a maximum age of 40, menopause can nearly neutrally appear in the population around the age range of 40-60 under the demographic parameters of the simulated population. This timing of menopause is in contrast to a population where females were permitted to mate until the age of 80. In this scenario, menopause can

neutrally evolve however it would appear later in life, beyond female LE. In summary, we have found that mating behaviour of a population can affect menopause evolution. The timing of the neutral evolution of menopause is influenced by the maximum mate-choice age the younger the maximum eligibility age, the earlier in life menopause will appear.

2.3 Question 3: Biased Mating within Serial Monogamy

2.3.1 INTRODUCTION

In both Chapter One and Follow-up Question 2 we have addressed the influence of the mating system on the evolution of menopause. Chapter One specifically looks at a population that mates in a serial monogamous fashion, with pairings lasting the lifetime either the male or female in the pairing. It was found that in this system of a long living population, menopause neutrally evolves around the age of 80 in females. We realized in Follow-up Question 2 however, that marriages and pairings do not typically last the duration of one's lifetime in modern human populations. Instead, humans mate serially and through divorce and remarriage both males and females are permitted more than one mate in a lifetime. When this system was implemented in our simulation, we discovered that enforcing "divorce" whereby pairings are dissolved when the female reaches a certain age influenced the age of neutral evolution of menopause and younger maximum ages of eligibility in females led to earlier onset of menopause. In this present section, we look to further refine the mating system in this simulation to more closely resemble human populations. What is perhaps more accurate than

serial monogamy and simple divorce is when we consider the bias shown by numerous cultures globally in terms of preferences in ages of mates.

As noted, it is widely accepted that the mating system used by the vast majority of human societies is serial monogamy. Within serial monogamous populations, and even those populations that continue practicing monogamy or polygyny, it is common to see males marrying wives who are younger than themselves (Mulder, 2009). It has been demonstrated in various studies that overall, human males prefer female mates younger than themselves and conversely females prefer males older than themselves (Antfolk et al., 2015; Buss, 1989; Conroy-Beam & Buss, 2016; Kamble et al., 2014; Kenrick et al., 1995; Kokko et al., 2003; Symons, 1979). Contrary to humans, some primates demonstrate a preference for older females. Muller, Thompson & Wrangham (2006), conducted a study in which they analyzed male chimpanzee behaviour with a female chimpanzee in estrus. They found that male chimpanzees are more attracted to older females, as indicated by number of successful copulation and size of male groupings around females in estrus (Muller, Thompson & Wrangham, 2006). In chimpanzees, display of estrus is a clear indication of fertility; however, this display is not available in humans. Features of youthfulness and physical attractiveness are the best indicators we have of fertility in humans, and thus this preference is a phenomenon that is present in all cultures (Buss & Schmitt, 1993).

Numerous studies into human populations have concluded that mating preferences of older males and younger females is seen globally **(**Antfolk et al., 2015; Buss, 1989; Kenrick et al., 1995; Kokko et al., 2003). Studies concluded that women of all ages prefer partners somewhat older than themselves (Antfolk et al., 2015; Kenrick et al., 1995) with the magnitude

of age difference varying. As previously noted, in general, preferences for females converge on a woman with high fertility and reproductive value (Antfolk et al., 2015), indicating a woman in her late-teens to late-twenties.

Patterns of older male and younger female mate preferences have been described but holds no value unless realized. Despite previously noted disparity between mate preferences and potential realization of these preferences, studies have demonstrated that in many instances, specifically for the preferred ages of mates, preferences hold true. Numerous studies investigated existing mate bonds and found that the females were consistently younger than their male counterparts, confirming that this feature of mate preference has been realized cross-culturally (Kamble et al., 2014; Kokko et al., 2003).

2.3.2 METHODS

In order to replicate this concept of age biased mating in our simulation, we again modified the mating system, specifically male and female eligibility. We continued using a mating system that at its root represents serial monogamy. Males and females continue to only possess one partner at a time. Pairings are dissolved in one of two ways: either one individual within the pair dies or the female reaches an age eligibility maximum. In both of these scenarios the pairing is terminated and any remaining individuals from the pair can re-enter the pool of eligible mates if they are of an eligible age.

Female eligibility is identical to that of the "divorce" model with the minimum age of eligibility is 13 years old, coinciding with the onset of fecundity, and maximum eligibility is 40. In males however, despite onset of fecundity at 13, they do not become eligible until the age of

40 and remain eligible until 80. It is by changing the mating system in this way that we demonstrate a bias mating system, whereby mating only occurs between young females and older males. All other parameters remain unchanged and identical to the reference population outlined in Chapter One. For each parameter altered within this investigation, we continued to vary the 'age of menopause'. By doing this and plotting the resulting PGR and FRVs, we aim to refine our understanding of the evolution of menopause in this specific mating system.

2.3.3 RESULTS

The reference 1999 Great Britain population described an age of menopause consistently nearly neutrally evolving beyond the ages of 60-80. When "divorce" was first introduced to the mating system in Follow-up Question 2, this neutral age of menopause evolution decreased to 40-60 years old. In this current system, when observing both PGR and FRV, we notice the point of inflection occurring at age 40-60 with a trend identical to that of the 'divorce' model (**Figure 15, raw data in Appendix A Table 6**).

In sum, the collection of these three results seems to indicate an influence of mate choice within this mating system on the age of onset of menopause. More specifically these results demonstrate that restricting female mating to younger ages leads to younger age of onset and that restricting male eligibility appears to have no effect. As seen in previous analyses, there continues to be an apparent magnitude difference between the 1999 Great Britain reference population of Chapter One and both the "divorce" model and this model of biased age pairing within serial monogamy. This magnitude difference results from a greater number of eligible females therefore more females reproducing in the 1999 reference model and ultimately

more births occur. Despite this clear difference in magnitude between serial monogamy (Chapter One) and restrictions within serial monogamy (Follow-up Questions 2 and 3), it is evident that mate choice can influence the evolution of menopause in the human female population, specifically in age of neutral onset before the female LE at birth.

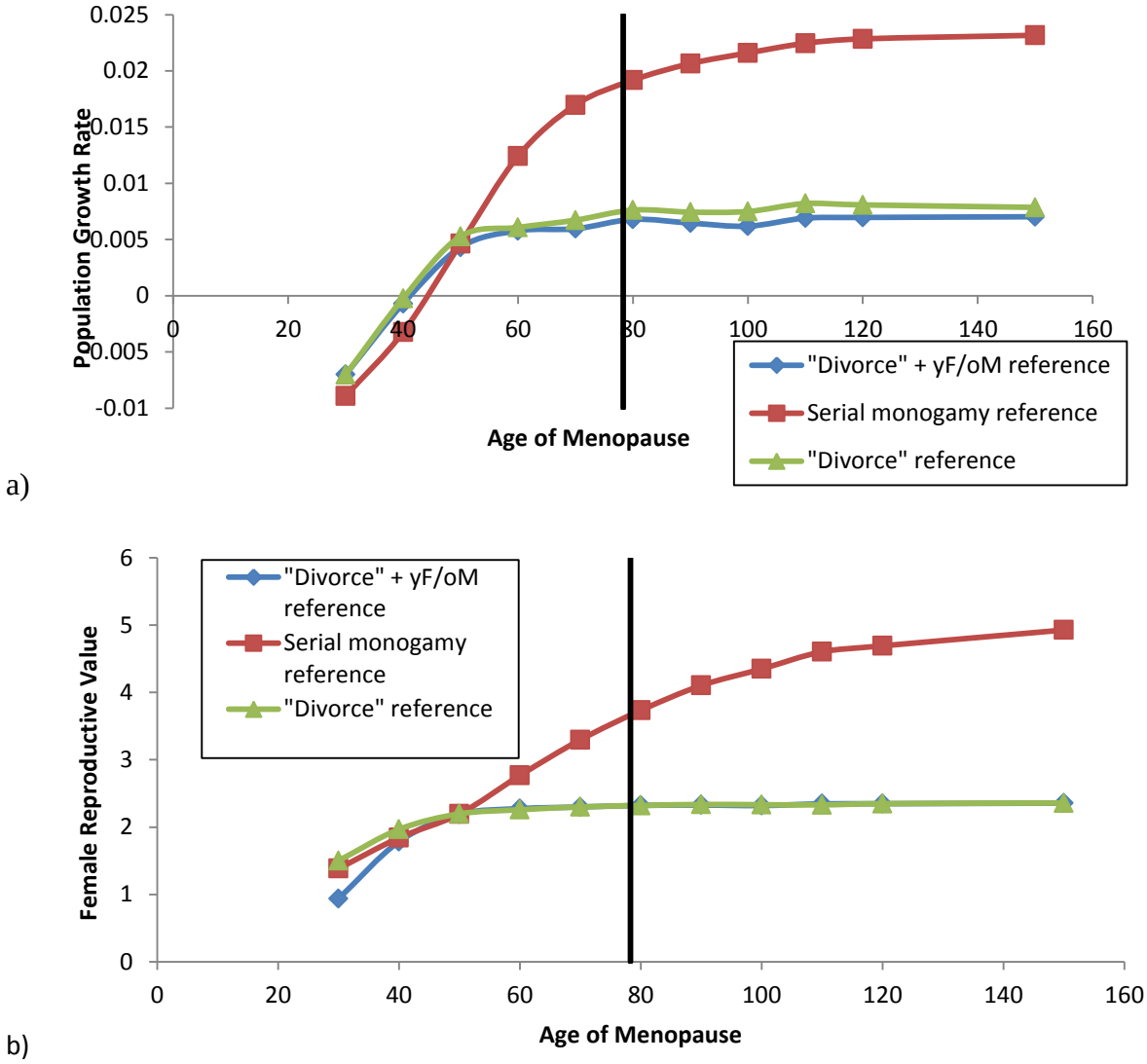


Figure 15: Comparing the neutral evolution of menopause among three separate simulations of various mating systems. The three mating systems illustrated are serial monogamy, 'divorce'-imposed serial monogamy, and biased age preference mating + 'divorce'-imposed serial monogamy. Female LE at birth is 78.3 years, as indicated by the vertical line. a) shows the PGR as a function of age of menopause onset while b) shows the FRV as a function of age of menopause onset.

As was investigated in Follow-up Question 2, restricting pairing eligibility to differing degrees can produce different results. In this specific examination there are two separate eligibility parameters that can be altered within the system of age-influenced biased mate

choice. These are the maximum eligibility of females and the minimum eligibility of males, both of which are currently set to age 40. By varying these parameters, we can control the proportion of each male and female population that can pair as well as the age differential between eligible males and females. Marriage records from the United States of America in 1983 concluded that a significant portion of women marry men who are 5+ years older than themselves (Secord, 1983). This bias in mating was again confirmed by Buss in 1989 as females were found to be years younger than their male partners. Similar findings were discovered in countries such as India, Japan, France, Greece, Canada, Brazil and numerous others (Kamble et al., 2014; Kokko et al., 2003). Although the magnitude of actual age difference was different in each study, the trend remained of a bias in the mating system whereby younger females and older males mate and reproduce.

We have separately investigated varying maximum female eligibility/ age of 'divorce" and minimum male eligibility age. By separating the two controls of eligibility, we can discern which eligibility parameter influences the evolution of menopause and to what extent. Firstly, we will discuss altering the maximum age of female eligibility for pairing. By using the same "divorce" system that was stated in Follow-up Question 2, we can control both pairing and reproduction in females beyond a certain age. Maximum ages of female eligibility were tested at age 30, 40, 50, 60, and 80. Male eligibility was restricted but held constant throughout this investigation with minimum eligibility of age 40 and maximum at age 80. Within each of these tests of maximum female eligibility, the female 'age of menopause' was varied in onset in 10-year increments between the ages of 30 and 100 and finally at age 150. Separate graphs were

constructed utilizing the PGR and FRV outputs plotted against the age of menopause (**Figure 16, raw data in Appendix A Table 6**).

The outcome of varying maximum age of female eligibility in a mating system of serial monogamy with strict enforcement of eligibility confirms previous results of restricted female eligibility. We again see that increasing the maximum age of female eligibility results in a later age of onset of menopause, as indicated by the point of inflections in Figure 16 a and b. The clarity of trends varies between the plots of PGR and FRV. There is greater variability in the PGR output, as was also the case when investigating shortened longevity in Follow-up Question 1; therefore, we will focus on the results of FRV. The points of inflection when looking at Figure 16b indicate ranges in age of menopause onset from around 60 when maximum female eligibility is 40 and 50 to an onset greater than 80 when maximum female eligibility is 80. This range of ages demonstrates that under specific conditions, menopause has the potential to either neutrally evolve before female LE or after female LE. Interestingly, when maximum female eligibility is 30, there appear to be insufficient pairings and resulting births. In this scenario, females are only eligible and reproducing for a 17-year period between the ages of 13 and 30 therefore, no matter the age of menopause, the population is not sustainable.

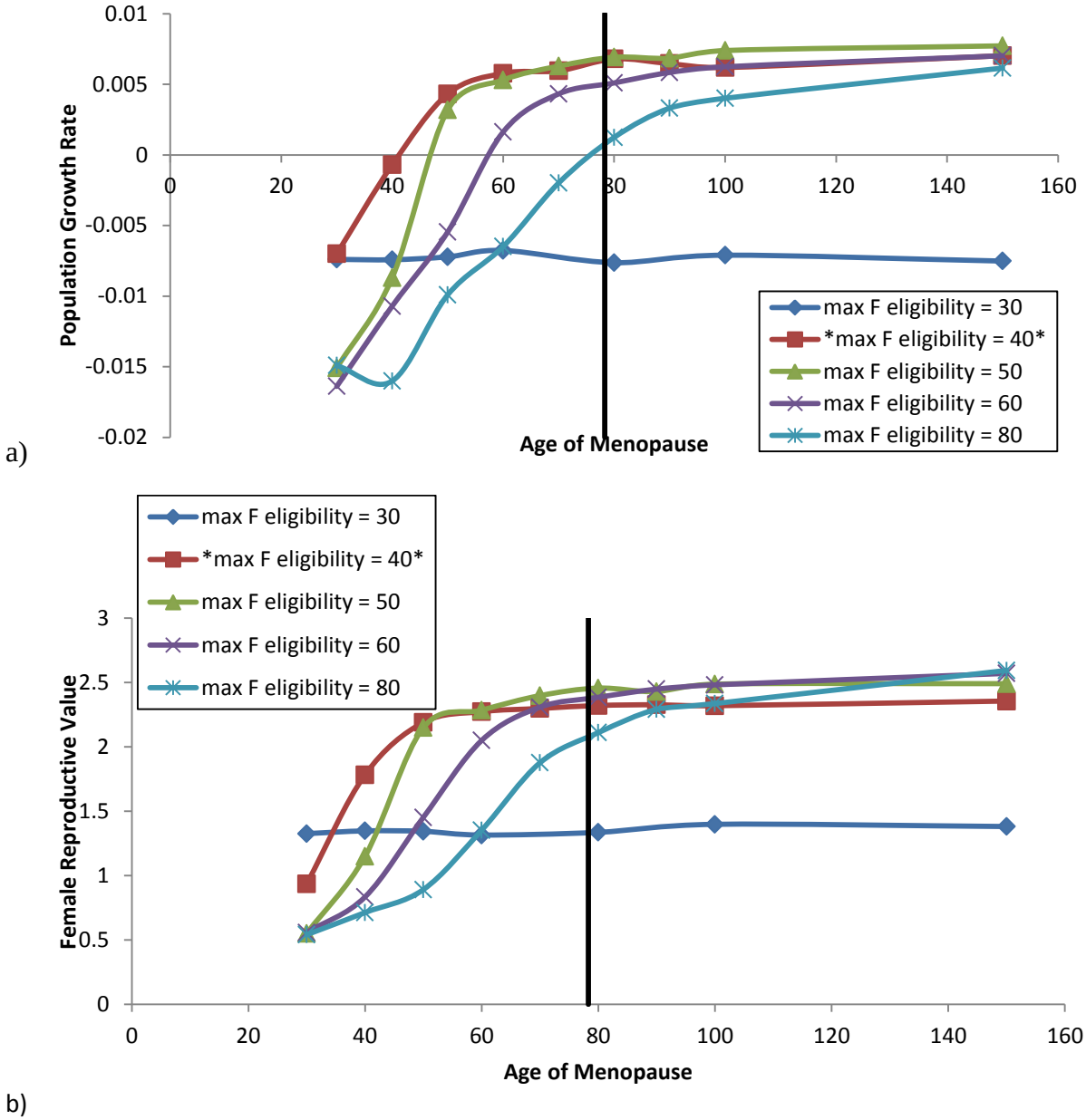


Figure 16: Results of changing the maximum age of female pairing eligibility in a mating system of biased age preference mating + 'divorce'-imposed serial monogamy. Female LE at birth is 78.3 years, as indicated by the vertical line. a) shows the PGR as a function of age of menopause onset while b) shows the FRV as a function of age of menopause onset. "max F eligibility = 40" represents the reference population.

The second way that pairing eligibility was altered was by restricting the minimum male age of eligibility. In all scenarios, female eligibility was maintained at a minimum value of 13 years old and a maximum of 40 years old. Minimum male eligibility was tested at ages 13, 20, 30, 40, and 50. Male maximum age of eligibility remained at 80 years old for the duration of this analysis. By testing a range of ages of onset of menopause in females and plotting the resulting outputs, it is evident that altering male eligibility does not impact menopause as female eligibility is seen to do (**Figure 17, raw data in Appendix A Table 6**). For both outputs of PGR and FRV, we notice an identical trend of a point of inflection present around age 40 – 60. Regardless of the minimum age of male eligibility, the age at which menopause can [nearly] neutrally evolve in this population is maintained as beyond the age range of 40 – 60 years old. Again, this timing of menopause is not seen to decrease the female fitness before the female LE at birth of 78.3 years and consequently appears within the female lifespan. This is believed to be due to fact that altering male eligibility does not further restrict females in any way and we have assumed that menopause is a female specific trait therefore the female experience of pairing and reproduction remain unchanged.

What is interesting in both Figure 17 a and b is the way that the magnitude of both plots is affected by changing the male eligibility. For minimum eligibilities of age 13, 20, 30, and 40, the outputs of both PGR and FRV result in nearly identical lines with a plateaus at approximately 0.006 and 2.3, respectively. When the minimum male eligibility age is set to 50, the trend of the line remains however, the resulting line decreases in magnitude to a PGR plateau of 0.002 and a FRV plateau of roughly 2.05. It is unknown as to why only a minimum value of 50 resulted in this magnitude change while all other minimums tested produced

matching curves in both plots. It is possible that magnitude results due to the male parameter of minimum eligibility at age 50 were the only to generate a gap between male and female eligibility. Because females are eligible for 27 years between the ages of 13 and 40 years old and despite being fecund at 13, males only become eligible at 50, there is a resulting 10-year age gap. Influence of a gap is speculation and in order to further understand this trend we can continue testing the male eligibility parameter at smaller age intervals and identify at what age and under what parameters this magnitude change occurs.

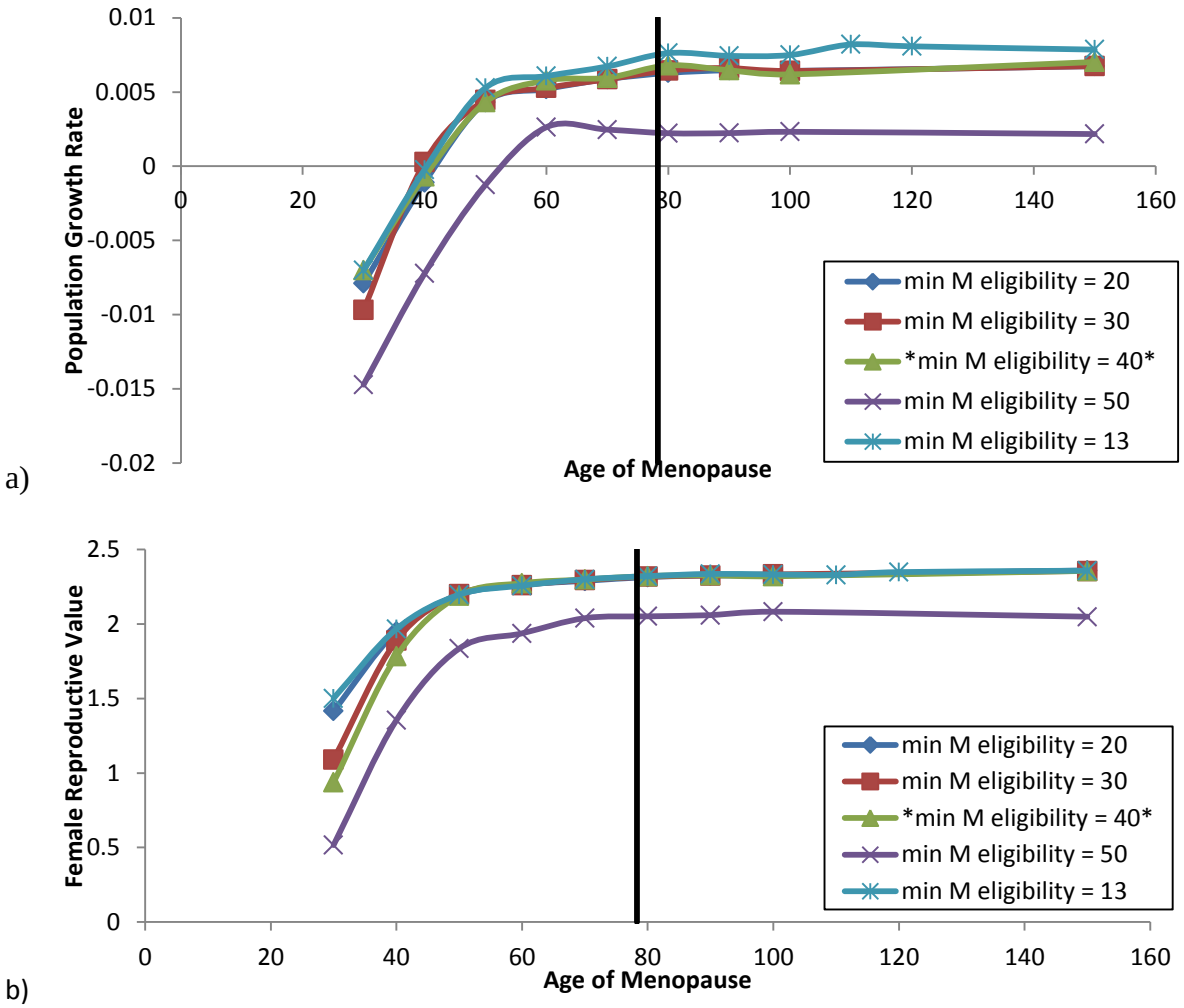


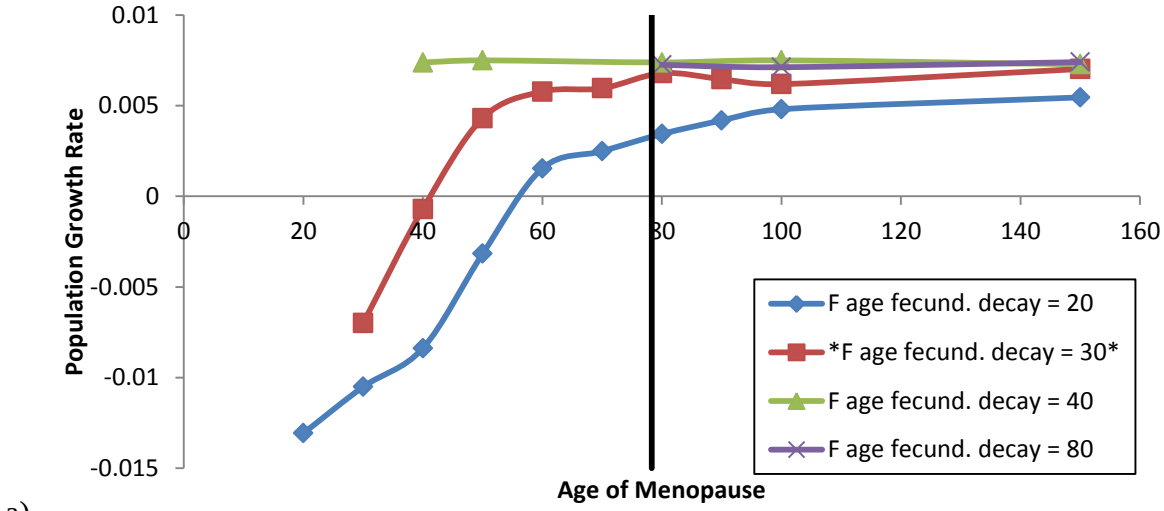
Figure 17: Results of changing the minimum age of male pairing eligibility in a mating system of biased age preference mating + 'divorce'-imposed serial monogamy. Female LE at birth is 78.3 years, as indicated by the vertical line. a) shows the PGR as a function of age of menopause onset while b) shows the FRV as a function of age of menopause onset. "min M eligibility = 40" represents the reference population.

The final analysis that was undertaken for this population of biased age preference in mating was to vary in perimenopause onset in females. Previous analyses have demonstrated that altering the age of perimenopause leads to little variation overall in the neutral age of onset of menopause. When age of perimenopause was changed in a mating system of serial

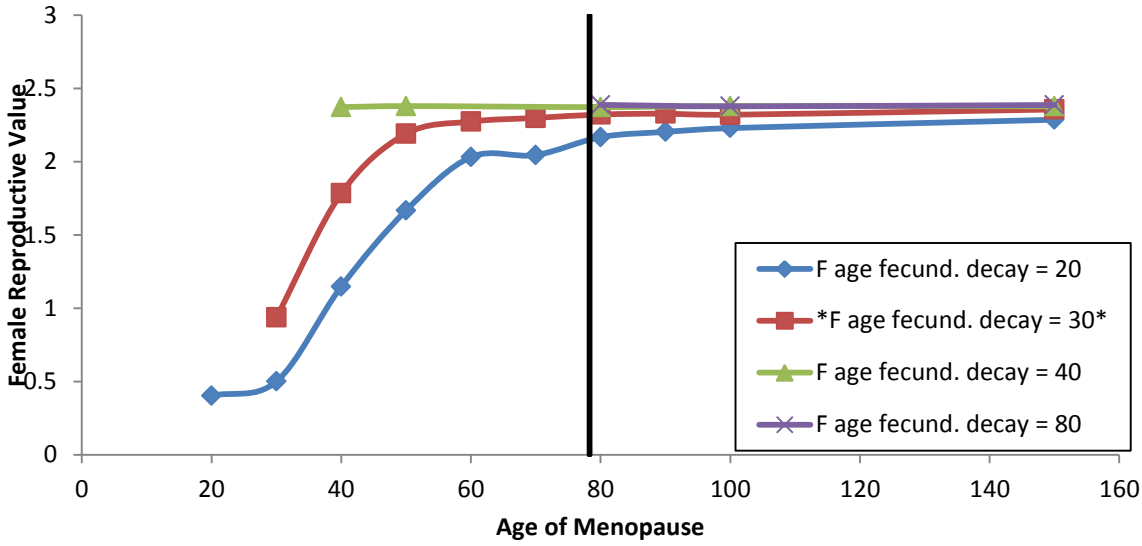
monogamy, the age of menopause continued to occur at the same age, around 60-80. Changing age of perimenopause in a modified version of serial monogamy that included "divorce" when females reached age 40 demonstrated the consistent evolution of menopause around the age 40-60. In this final investigation of perimenopause, we alter the onset of decay of fecundity in the female population when the mating system involves serial monogamy with a maximum age of female eligibility and a minimum age of male eligibility. For the duration of this analysis, females are eligible to mate at younger ages, between 13 and 40. Males however are only eligible later in life between the ages of 40 and 80. Other factors such as survivorship and fecundity are as outlined in Chapter One. The simulation was run for various ages of menopause from age 20 to 100 in 10-year increments and finally at a menopause age of 150.

The resulting PGRs and FRVs were plotted against the age of menopause for further review (**Figure 18, raw data in Appendix A Table 6**). It is evident that, similar to previous tests of perimenopause onset, regardless of the age at which perimenopause begins, the resulting age of neutral menopause remains constant. This is specifically evident in Figure 18b of FRVs. For the various ages of perimenopause onset tested, menopause [nearly] neutrally evolves beyond 40 and 60 but continues to occur before female LE at birth, indicating the presence of menopause within the female lifespan with little to no decrease in fitness. There appears to be little change in the magnitude of lines in both graphs and the variation that is present is believed to be due to the small increases in fecundity that occur at an earlier age when the final 'age of menopause' is altered. The plateau that occurs under this parameter change is at a PGR value of 0.006 and a FRV of 2.35. When comparing these results to the equivalent

plots produced in Chapter One, it is clear that by altering pairing eligibility, fewer offspring are produced overall and the population grows at a slower rate.



a)



b)

Figure 18: Results of changing age of onset of fecundity decay in a mating system of biased age preference mating + 'divorce'-imposed serial monogamy. Female LE at birth is 78.3 years, as indicated by the vertical line. a) shows the PGR as a function of age of menopause onset while b) shows the FRV as a function of age of menopause onset. "F age fecund. decay = 30" represents the reference population.

2.3.4 DISCUSSION

In this concluding analysis of the serial monogamy model, we have further refined the mating system and parameters by which pairs are formed to more accurately describe the evolution of menopause. Adding the "divorce" feature allowed us to express the serial aspect of this mating system with more confidence. It is often through divorce and remarriage that modern societies allow for multiple mating to occur, which can ultimately lead to increase reproductive success and the extension of reproductive lifespan, specifically in males (Mulder, 2009). The newest modification of biased age preferences further refines mate choice within serial monogamy. This idea of preferential mating between young females and older males is one expressed cross-culturally and continues to be realized in modern populations (Kamble et al., 2014; Kokko et al., 2003). This section ultimately presents a population of males and females that mate with a single partner at a time but can serially mate throughout their lifetime. While this concept of every pairing in the simulation strictly experiencing termination seems unreasonable in a real world population, this simplistic view allows us to understand the influence of specific parameters independently on the evolution of menopause.

In sum, the results of this final analysis confirm what was demonstrated in Follow-up Question 2. Restricting eligibility for pair bond formation in a population of serial monogamy alters the age at which menopause can nearly neutrally evolve in the female population. We investigated three separate parameter changes within this modified mating system including maximum age of female eligibility, minimum age of male eligibility and age of onset of perimenopause. Overall we found that altering the female eligibility maximum age led to a

change in the timing of menopause whereas minimum male eligibility age and age of perimenopause seemed to have no effect. Again, when the maximum age of female eligibility decreases, so too does the age at which menopause can neutrally appear in a population, and can even lead to the appearance of menopause within the female lifespan at no fitness cost. This influence of female eligibility over male eligibility is presumably because menopause is set to occur only in the female population; therefore, restricting male mating will have no further influence on the availability of females for reproduction. Biased mate choice therefore does appear to influence the age at which menopause in the female population. This mate choice influence however seems to specifically be in terms of the age at which females are chosen as mates and less so the restriction of male mates to older ages.

CONCLUSION

3.1 Health Implications

What we have aimed to demonstrate in our simulation of menopause is that while appearing to be a detrimental trait in terms of reproductive success and fitness, menopause continues to evolve in the human population and can do so neutrally. Work conducted by Morton et al. (2013) showed that late-onset, fertility-diminishing mutations are able to neutrally evolve in the female population under specific mating conditions and it is through the accumulation of these detrimental mutations that menopause appeared in their simulated populations. In our model, we have not specifically included any genotype or change to a mutated genotype condition. Instead, we utilize variations within a fecundity phenotype, from which we infer a corresponding genotype. By altering what we have referred to as the 'age of menopause', we assume a varying genotype to produce these phenotypic changes. In this way, we can model the complete transition from a genotype with no mutations to a genotype that is fixed for mutant alleles. The range of menopause phenotypes that can be modelled therefore represents mutation accumulation within a genotype to various extents.

Menopause is a condition that is virtually unique to human females. This medical mystery and seemingly maladaptive trait of menopause is unavoidably experienced by all women and is oftentimes the source of distress for middle aged females. Menopause is accompanied by a variety of symptoms including loss of libido, hot flushes, genital itching and dyspareunia (painful sexual intercourse) (Castelo-Branco, et al., 2005). Even though menopause is a global condition experienced by all human females, the evolutionary roots of menopause remain unresolved. One biological proposal is that menopause occurs when the pool of follicles

in the female ovaries has become exhausted (Voorhuis et al., 2011), however further investigation has proven menopause to be far more complex. Study in this field has indicated that properties associated with menopause, such as age of onset, seem to be highly heritable through the use of twin studies (He et al., 2010); numerous genetic studies have been conducted to identify targets of interest.

Genetic studies of menopause have often aimed to investigate both age at menarche and ANM, as the two are seen to be correlated (He et al., 2010). Through the use of genome-wide association studies involving diverse female populations, numerous candidate genes have been identified (**Appendix A Table 7**). These genes play roles in a variety of biological pathways and mechanisms including the steroid-hormone metabolism and biosynthesis pathway, vascular homeostasis pathway, primordial follicle recruitment, regulation of insulin-like growth factors (He et al., 2009; He et al., 2010; Voorhuis et al., 2011). Using these identified candidate genes along with our demonstration of the ability of detrimental mutations to accumulate neutrally in a population, we have provided the framework for continuing this genetic analysis.

3.2 Future Directions

Our study specifically investigates the evolution of menopause under a mating system of serial monogamy. Serial monogamy was chosen, as it is accepted to be the mating system most prevalent globally in the modern world (Dixson, 2009). By further refining serial monogamy to first enforce strict pairing eligibility in females and then to also restrict pairing eligibility in males, we have demonstrated a range of ways in which serial monogamy can manifest in human populations. The results presented herein demonstrate that the structure of the mating

system, specifically serial monogamy in this case, is sufficient in allowing for menopause to neutrally evolve, perhaps in two separate ways.

Firstly, the investigation of longevity and menopause illustrated that in a population with survivorship similar to that of ancestral humans, menopause can evolve to be present before the age of 60. In a population of current, modern longevity however, menopause does not appear until closer to an age of 80. In general, the age at which menopause neutrally evolves seems to be dependent on the lifespan of the population simulated indicating that as longevity increases, so too does the age at which menopause becomes neutral. These results support the possibility that menopause was present in ancestral humans and when longevity dramatically increased, the menopause phenotype did not respond at the same rate. Therefore, we continue experience menopause in an ancestral state with the possibility that menopause will be experienced by human females in the future at a later age.

Future work on this topic of a transition in human longevity can be done using simulation studies. In our simulation, the transition from a modern chimpanzee population longevity, representative of ancestral human populations, to lengthened longevity as seen today was one in which multiple parameter changes occurred. Not only were the Siler parameters altered, so too was maximum fecundity, birth spacing and age of pairing eligibility. To further understand the evolution of menopause in these two populations of distinct longevity, testing the parameters at different values and even parameters in combination may provide more insight. For example, increasing maximum fecundity beyond a certain value demonstrated novel presence of menopause in a population of modern longevity (Figure 5); however, this

parameter was not further analyzed or tested for shorted longevity. Birth spacing and fecundity together can also be adjusted to better represent the transition from shortened longevity to increased lifespan, whether that is an increase in both, decrease in both, or increase in one with a decrease in the other. By continuing to investigate the transition in human longevity in an assumed constant state of serial monogamy, we may be able to identify novel parameter combinations under which menopause can evolve.

The second way our serial monogamy model demonstrated the neutral appearance of menopause is through a bias in mate choice. This bias occurs such that young females are preferentially chosen as mates. When this restriction occurs, specifically in female part of this bias, it is evident that the age of menopause also varies to differing degrees. Limiting mate choice demonstrated that when female mating is restricted to younger ages, the age at which menopause neutrally evolves decreases. Additionally, it was later demonstrated that a preference for older males as mates does not further enhance this correlation. In sum, regardless of male pairing age, menopause neutrally evolves according to female restrictions.

The mating system of serial monogamy investigated in this analysis was chosen due to its global ubiquity and belief that it has been present for a substantial amount of time in human history. Within this analysis alone however, we have proven that there is more to serial monogamy than just mating through life, as pairs can be broken and re-pairings can occur. As a result, due to the serial nature of this mating system, serial monogamy has also been referred to as polygyny in human populations (Mulder, 2009). Polygyny refers to males possessing more than one mate at a time. This can also occur through the accumulation of multiple wives at a

single time and/or extra pair copulations. Anthropological records indicate that about 85 percent of human societies have permitted polygynous marriages, even reaching extreme levels, with emperors having over one hundred wives (Buss & Schmitt, 1993; Henrich, Boyd & Richerson, 2012). Typically, the presence of multiple wives to a single male, also called harems, occurs in complex societies with a clear social hierarchy (Henrich, Boyd & Richerson, 2012). This inclusion of multiple mates at a single time can be further investigated in simulations similar to the one described herein to see if the presence of harems influences mate choice and ultimately the evolution of menopause.

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APPENDIX A – Supplementary Figures and Data

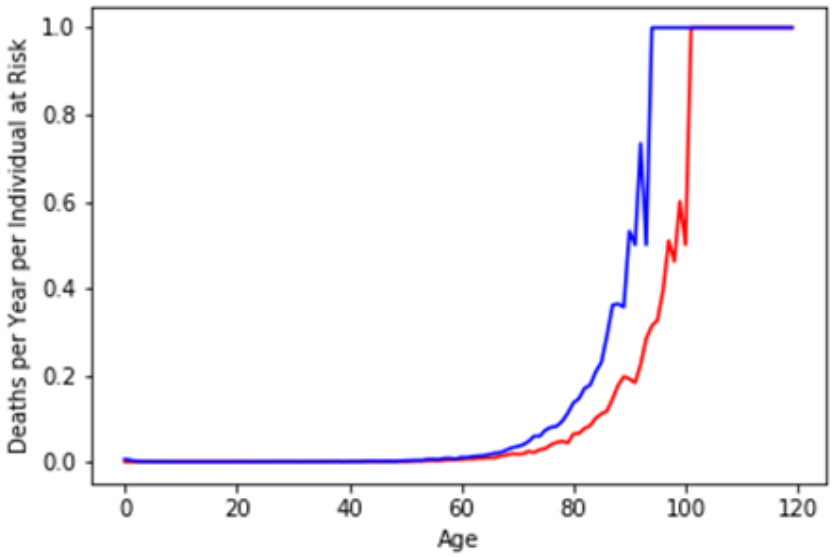
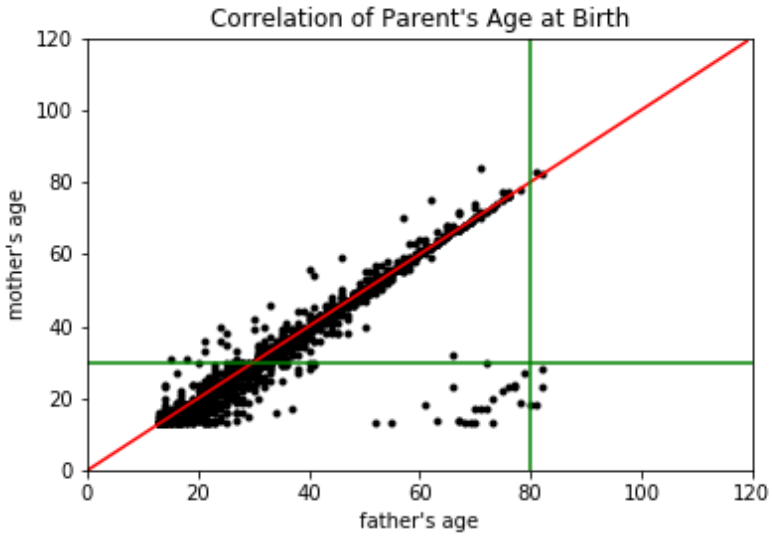
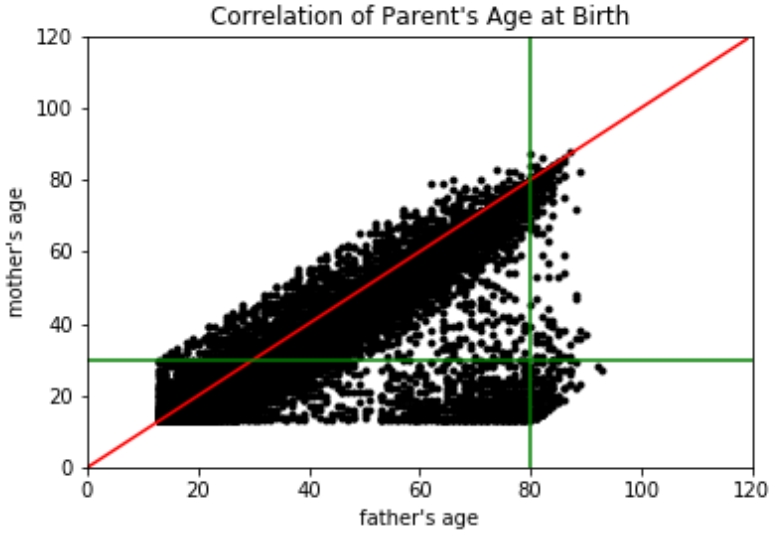


Figure 1: Siler mortality risk curve for 1999 Great Britain population

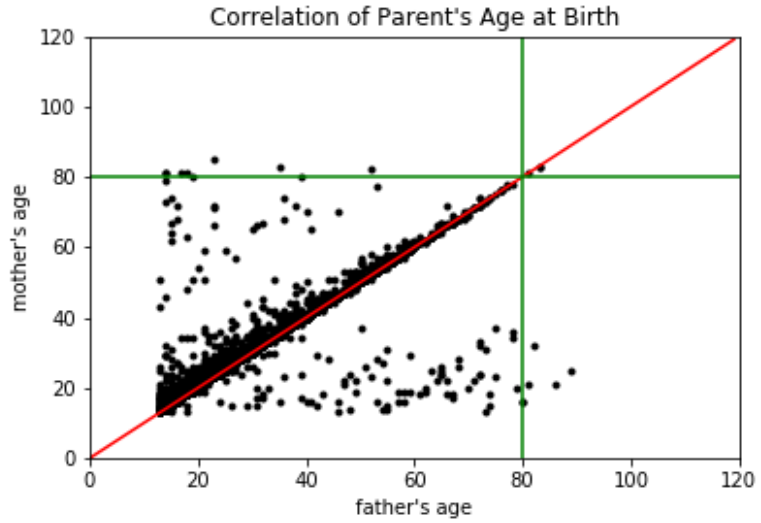


a)

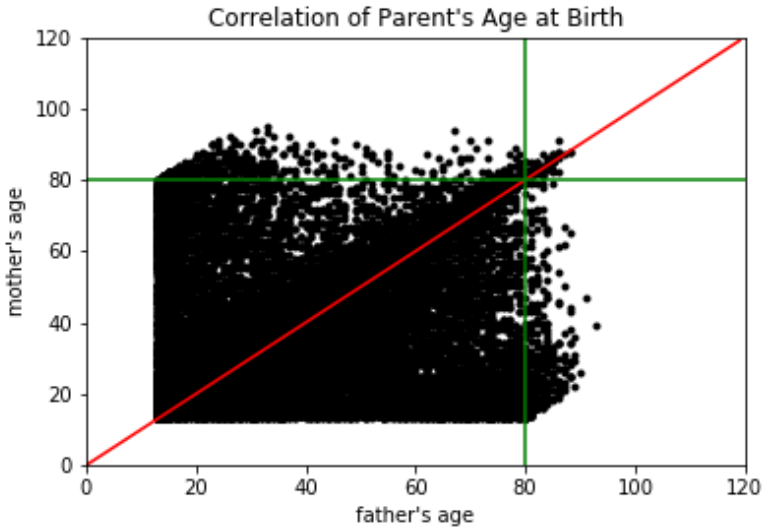


b)

Figure 2: Correlation of mother's age and father's age at birth after 100 (a) and 250 (b) years/time steps. The males have a maximum age eligibility of 80 and the females have a maximum age eligibility of 30. Both males and females continue to reproduce beyond their respective maximum ages of eligibility, as indicated by points beyond the green lines. This indicates that pair bonds have not been broken due to death. In a) there appears to be a strong correlation between age of mother and father indicating that many bonds that were established at time = 0 were not broken and new matings that resulted in births occurred between males and females of similar ages. b) continues to demonstrate similar results with more variability, possibly due to future births introduced into the population



a)



b)

Figure 3: Correlation of mother's age and father's age at birth after 100 (a) and 250 (b) years/time steps. The males have a maximum age eligibility of 80 and the females have a maximum age eligibility of 80. Both males and females continue to reproduce beyond their respective maximum ages of eligibility, as indicated by points beyond the green lines. This indicates that pair bonds have not been broken due to death. Graph a) continues to demonstrate a strong correlation between age of mother and age of father, again indicating pair bonds formed at time = 0 were not broken. Graph b) appears to show more randomness in ages of mothers and fathers, indicating pairs of uncorrelated ages are formed.

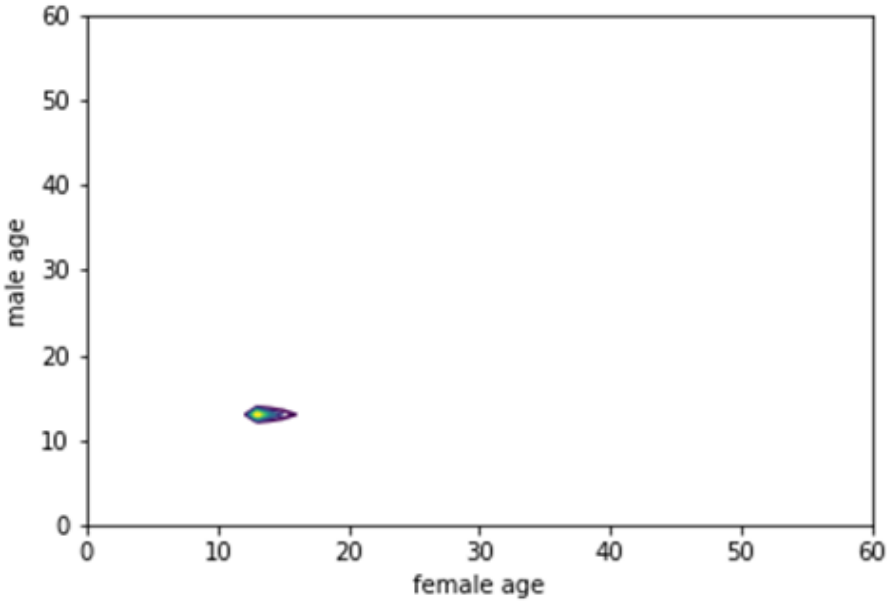


Figure 4: Contour plot describing incidence rates of female age and male age in mate pairings. It is evidence that most mate pairs are formed early in life, around the minimum age of eligibility. This is further confirmation that mate pairs generally remain mated for life.

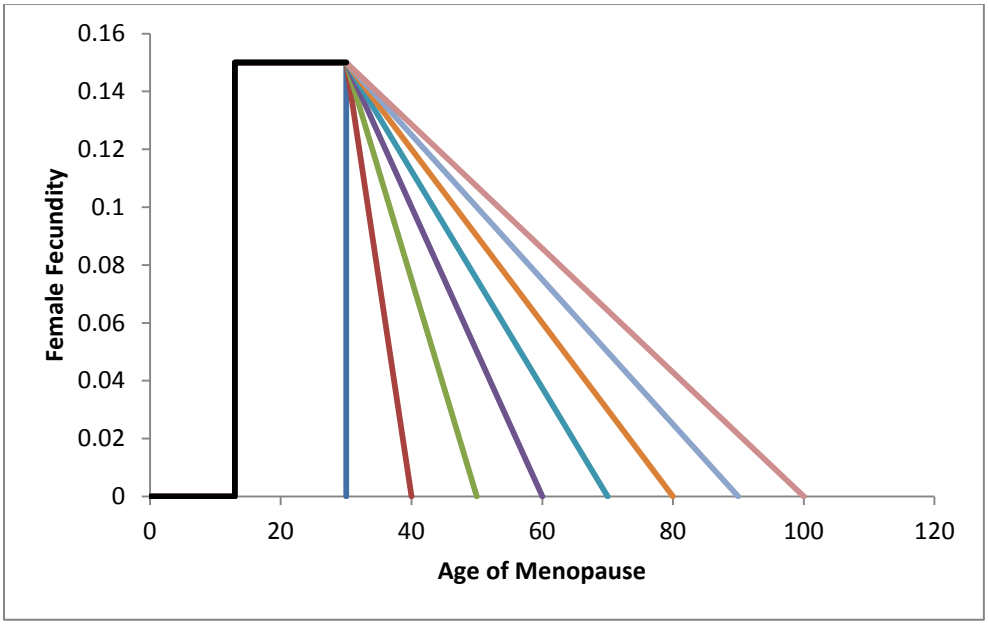


Figure 5: Decline in female fecundity to various 'ages of menopause'.

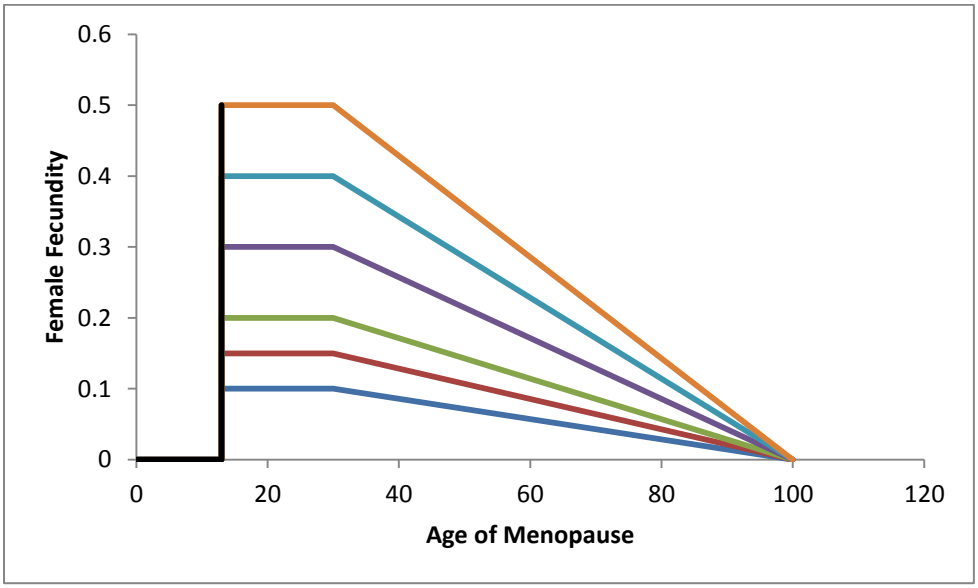


Figure 6: Various maximum female fecundities set to begin decay from a maximum state by age 30 and decline to an 'age of menopause' of 100 years old.

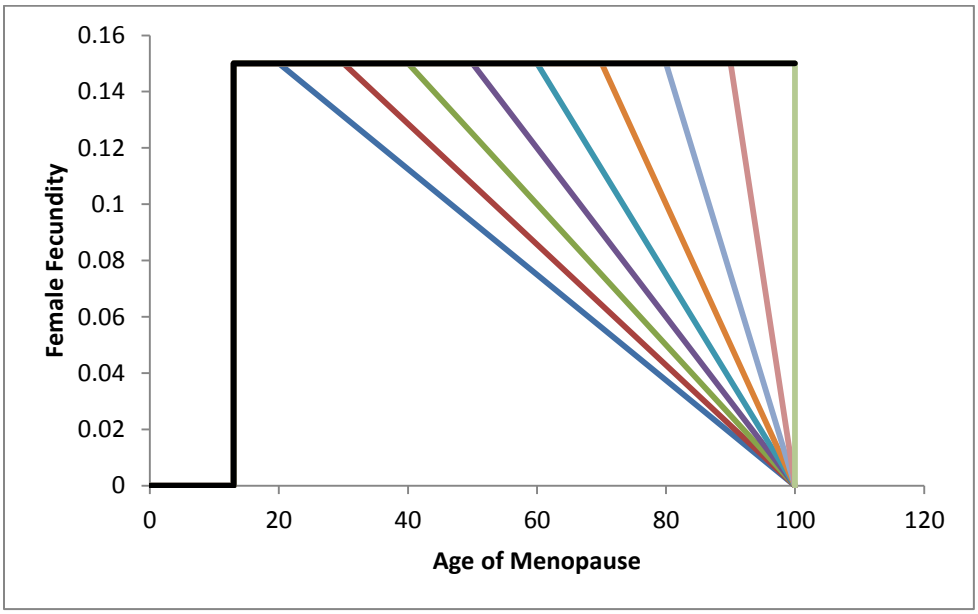


Figure 7: Various ages of onset of decay in fecundity, also called 'ages of perimenopause'. Ages of perimenopause range from 20 to 100 with decline to an 'age of menopause' of 100 years old.

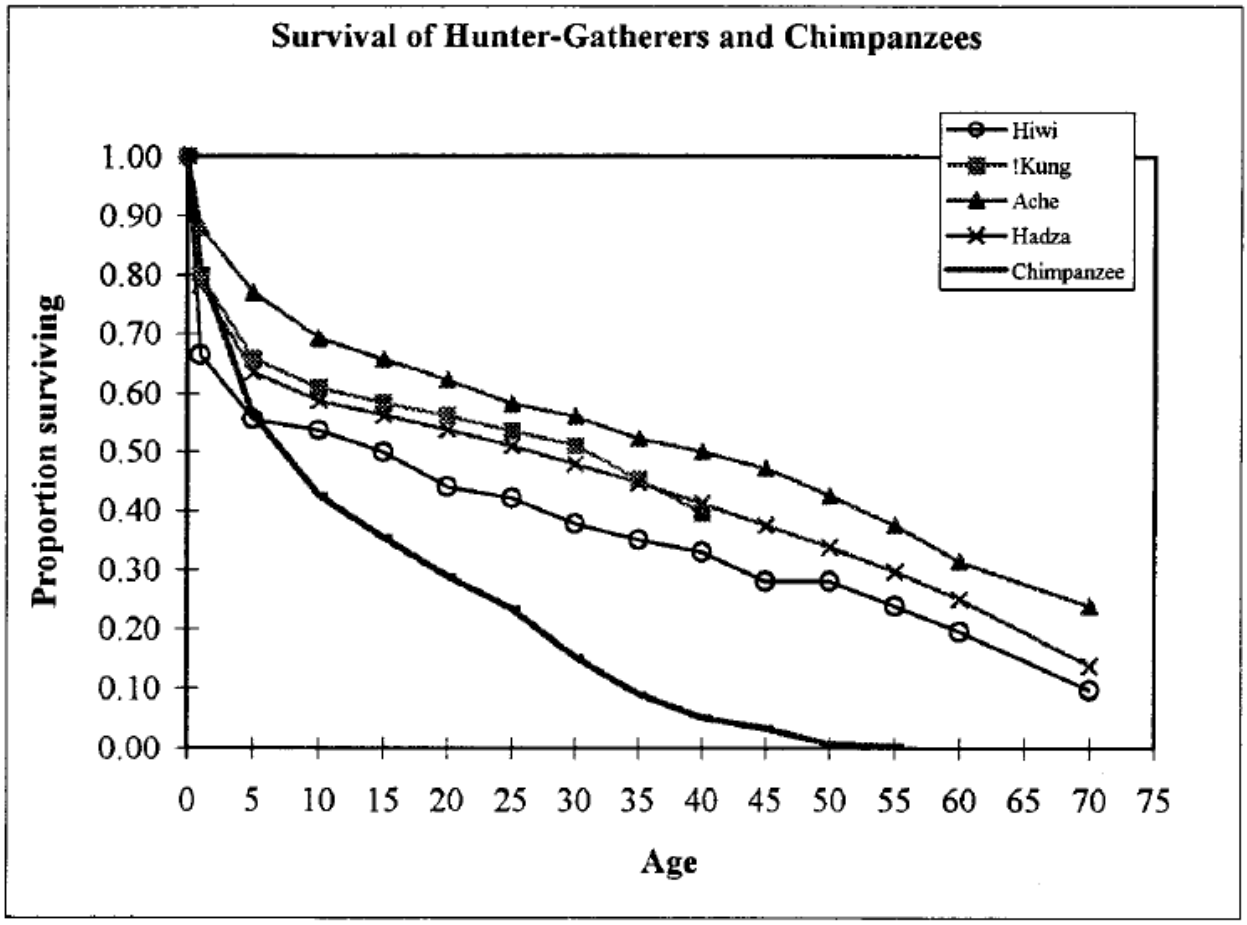


Figure 8: Mortality risk curves for modern forager and chimpanzee populations. Information on chimpanzee mortality was compiled from mortality data on Bossou, Gambe, Kibale, Mahale and Tai chimpanzee populations. Retrieved from Kaplan et al., 2000

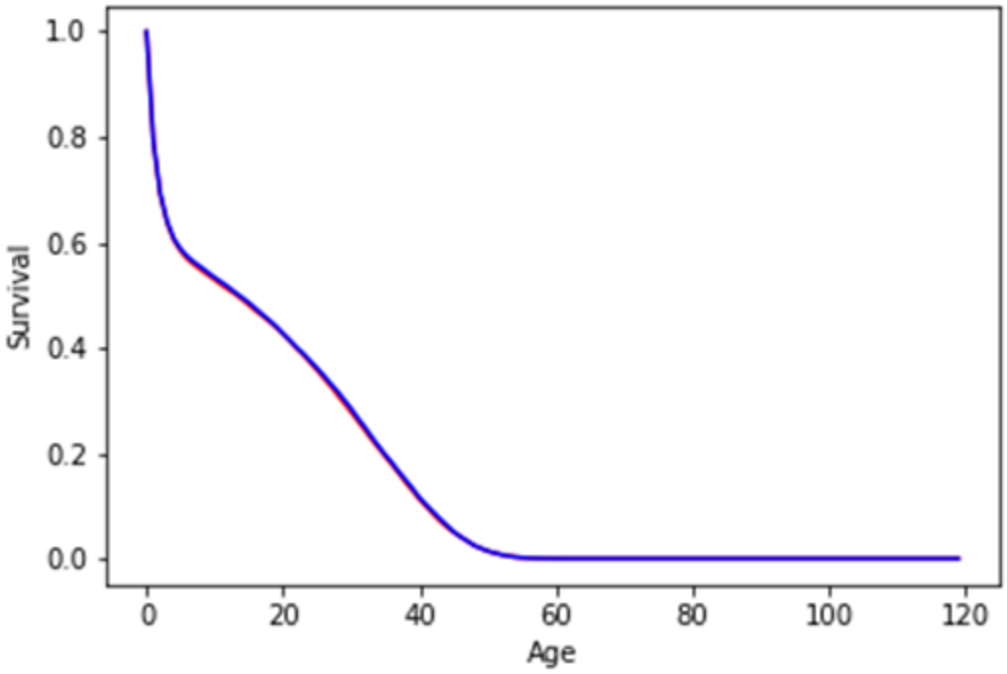


Figure 9: Modern chimpanzee mortality risk curve for both males and females produced from the Siler 5-component model equation.

Appendix Table 1: Hypotheses of menopause and sources, modified from Morton et al., 2013

Hypothesis Name	Description	Source
Follicular Depletion Hypothesis	women have a fixed number of eggs, and menopause ensues when that supply becomes depleted	Van Valen, L. (2003). Ovarian excess and the evolution of menopause. *Evol. Theory*, *12*, 131-153.
Lifespan-Artifact Hypothesis	in the past, human longevity was too short for females to experience menopause; menopause is the by-product of an increase in longevity or life expectancy; menopause may be considered as an epiphenomenon or neutral trait that may have become useful after its origin	Caspari, R., & Lee, S. H. (2004). Older age becomes common late in human evolution. *Proceedings of the National Academy of Sciences of the United States of America*, *101*(30), 10895-10900. Cooper, G. S., & Sandler, D. P. (1998). Age at natural menopause and mortality. *Annals of epidemiology*, *8*(4), 229-235. Amoss, P. T., & Harrell, S. (1981). *Other ways of growing old: Anthropological perspectives*. Stanford University Press. Peccei, J. S. (2001). Menopause: adaptation or epiphenomenon?. *Evolutionary Anthropology: Issues, News, and Reviews*, *10*(2), 43-57.
Senescence Hypothesis	menopause is a natural effect of aging; unlike other physiological functions, which senesce gradually and can function at less than 100% capacity, female reproduction might have evolved as a threshold trait with minimal tolerance to perturbation	Ward, E. J., Parsons, K., Holmes, E. E., Balcomb, K. C., & Ford, J. K. (2009). The role of menopause and reproductive senescence in a long-lived social mammal. *Frontiers in Zoology*, *6*(1), 4. Cohen, A. A. (2004). Female post-reproductive lifespan: a general mammalian trait. *Biological Reviews*, *79*(4), 733-750.
Reproduction-Cost Hypothesis	investment in reproduction is greater for women than men, leading to physiological deteriorations that amplify susceptibility to becoming infertile	Penn, D. J., & Smith, K. R. (2007). Differential fitness costs of reproduction between the sexes. *Proceedings of the National Academy of Sciences*, *104*(2), 553-558.
Mother Hypothesis	(an adaptive version of the reproduction-cost-hypothesis) by entering into menopause, aging mothers increase the survival probability of their children; menopause also would preclude fertilization of nonviable ova	Williams, G. C. (1957). Pleiotropy, natural selection, and the evolution of senescence. *evolution*, *11*(4), 398-411. Pavard, S., Metcalf, E., Jessica, C., & Heyer, E. (2008). Senescence of reproduction may explain adaptive menopause in humans: a test of the "mother" hypothesis. *American journal of physical anthropology*, *136*(2), 194-203.
Grandmother Hypothesis	menopause allows older women to contribute to the survival of their grandchildren and thus increase their inclusive fitness	Hawkes, K. (2003). Grandmothers and the evolution of human longevity. *American Journal of Human Biology*, *15*(3), 380-400. Hawkes, K., O'Connell, J. F., Jones, N. B., Alvarez, H., & Charnov, E. L. (1998). Grandmothering, menopause, and the evolution of human life histories. *Proceedings of the National Academy of Sciences*, *95*(3), 1336-1339. Jamison, C. S., Cornell, L. L., Jamison, P. L., & Nakazato, H. (2002). Are all

		grandmothers equal? A review and a preliminary test of the "grandmother hypothesis" in Tokugawa Japan. *American Journal of Physical Anthropology*, *119*(1), 67-76.
Patriarch Hypothesis	the origin of menopause allowed men to mate with younger women, resulting in increased longevity (for men and women) and increased status in society (for men)	Lahdenperä, M., Gillespie, D. O., Lummaa, V., & Russell, A. F. (2012). Severe intergenerational reproductive conflict and the evolution of menopause. *Ecology letters*, *15*(11), 1283-1290.
Absent Father	reduced paternal investment and increasing maternal age were factors in the evolution of menopause; this hypothesis is a complement (rather than alternative) to the grandmother hypothesis.	Rogers, A. R. (1993). Why menopause?. *Evolutionary Ecology*, *7*(4), 406-420.
Reproductive Conflict	menopause is the evolutionary outcome of resource-based competition between generations (i.e., between grandmothers and their daughter-in-laws, who are unrelated and therefore 'immigrants' to families); on the basis of genetic relatedness between grandmothers and her daughters vs. grandchildren and between grandmothers and daughters-in-law vs. grandchildren, fitness can be optimized if daughters-in-law reproduce and grandmothers help	Hill, K., & Hurtado, A. M. (1991). The evolution of premature reproductive senescence and menopause in human females. *Human Nature*, *2*(4), 313-350. Kirkwood, T. B. (1997). The origins of human ageing. *Philosophical Transactions of the Royal Society B: Biological Sciences*, *352*(1363), 1765-1772.
Evolutionary Trade-off	menopause is a trade-off between female future production and enhanced survival of offspring	Kirkwood, T. B. (2002). Evolution of ageing. *Mechanisms of ageing and development*, *123*(7), 737-745.
Mate Choice	a change in mating behaviour such that only young females and adult males mate; allowed for the accumulation of late-onset, fertility-diminishing mutations that ultimately led to the reproductive senescence (i.e. diminished fertility in women at older ages)	Morton, R. A., Stone, J. R., & Singh, R. S. (2013). Mate choice and the origin of menopause. *PLoS computational biology*, *9*(6), e1003092.
Inclusive Mate Choice Hypothesis/Non-Mutually Exclusive Hypothesis	explains at multiple levels the ultimately genetic origin and evolution of menopause; mating behaviour change allowing for accumulation of deleterious mutation, lifespan increase allowing this reproductive senescence to be expressed, and [contributory explanation] older non-reproductive women assisting in rearing grandchildren	Takahashi, M., Singh, R. S., & Stone, J. (2017). A theory for the origin of human menopause. *Frontiers in genetics*, *7*, 222.

Appendix Table 2: Siler parameters for populations analyzed

Siler Parameter	**1999 Great Britain**		**Modern Chimpanzee**	
	MALE	FEMALE	MALE	FEMALE
a	0.006	0.005	0.2	0.2
b	-0.6	-0.5	-0.55	-0.55
c	2.1×10^{-15}	2.0×10^{-15}	0.005	0.005
d	4.1×10^{-6}	4.0×10^{-6}	0.005	0.005
f	0.13	0.12	0.08	0.08

Appendix Table 3: Serial monogamy investigation data

1999 Great Britain, serial monogamy																				
	max F eligibility = 20		max F eligibility = 30		max F eligibility = 40		max F eligibility = 50		max F eligibility = 60		max F eligibility = 70		max F eligibility = 80							
age of menopaus	PGR	FRV	PGR	FRV	PGR	FRV	PGR	FRV	PGR	FRV	PGR	FRV	PGR	FRV						
30	-0.00601714	1.535545024	-0.00648546	1.558404558	-0.00669968	1.489971347	-0.00910799	1.311418685	-0.00735112	1.467391304	-0.00753297	1.326007326	-0.00890713	1.384083045						
40	-0.00182568	1.794214876	-4.60E-05	1.959040959	-0.00022314	1.935638809	-0.00193971	1.928515318	-0.0036779	1.737605804	-0.00324701	1.839134525	-0.00322781	1.841415465						
50	0.008420604	2.426454139	0.009663335	2.470425565	0.008960668	2.472660457	0.008684956	2.47200913	0.008253378	2.410507754	0.006740068	2.317431536	0.00464799	2.195367789						
60	0.01414257	2.875	0.014223702	2.948919833	0.014493821	2.944455734	0.014159993	2.924321238	0.014458354	2.914081146	0.013363184	2.842435485	0.012410602	2.76714021						
70	0.017106272	3.313099893	0.017574182	3.406559286	0.017518043	3.406187823	0.016965707	3.341000575	0.01789761	3.419915091	0.017297055	3.35193133	0.016973059	3.29716867						
80	0.019192596	3.640051438	0.019916151	3.776908023	0.019690176	3.747311828	0.019244556	3.729537795	0.020130479	3.810087557	0.019428681	3.813841642	0.01918394	3.734169008						
90	0.020079161	3.932047516	0.021242378	4.003367476	0.021366074	4.085205043	0.021372704	4.103850478	0.021025889	4.123813632	0.020768352	4.121898009	0.020648627	4.103779885						
100	0.02150435	4.081855008	0.02182608	4.180896155	0.0216029	4.198744159	0.021869917	4.266916121	0.02183533	4.296218487	0.021427849	4.326231691	0.021595213	4.349504662						
150	0.02227134	4.471183673	0.02323663	4.59063173	0.023270392	4.687589928	0.02372795	4.697419001	0.023081629	4.748169839	0.022873892	4.811300254	0.023400199	4.9302533						
	max F fecundity = 0.1		max F fecundity = 0.15		max F fecundity = 0.2		max F fecundity = 0.3		max F fecundity = 0.4		max F fecundity = 0.5									
age of menopaus	PGR	FRV	PGR	FRV	PGR	FRV	PGR	FRV	PGR	FRV	PGR	FRV								
30	-0.01089301	1.155913978	-0.00648546	1.558404558	-0.00725883	1.565320665	0.001306981	2.008075221	0.011378112	2.383492932	0.017150201	2.563560874								
40	-0.00845881	1.450479233	-4.60E-05	1.959040959	0.000470004	1.973428649	0.016944729	2.716043603	0.021166979	3.128075628	0.026646331	3.586715867								
50	-0.00710763	1.428571429	0.009663335	2.470425565	0.014054717	2.800315262	0.024815039	3.419436052	0.030552249	4.28447205	0.033441465	4.481365241								
60	-1.24E-03	1.80910683	0.014223702	2.948919833	0.019808447	3.395548317	0.028061937	3.949871164	0.033840331	5.112270451	0.037999277	5.897959184								
70	0.005414455	2.347622727	0.017574182	3.406559286	0.023131405	3.99153605	0.030726352	4.597704715	0.036079498	6.028587764	0.039164817	6.695557174								
80	0.009323963	2.744104093	0.019916151	3.776908023	0.024462336	4.447476929	0.032317034	5.019217331	0.037334189	6.983198925	0.040422271	7.514529915								
90	0.012364758	3.029516325	0.021242378	4.003367476	0.025570095	4.932579286	0.032862055	5.352471483	0.03752324	7.255813953	0.040695921	8.074139453								
100	0.013215293	3.181675336	0.02182608	4.180896155	0.027441463	5.370206105	0.033592013	5.741465445	0.038123927	7.690642458	0.041276231	8.494581281								
150	0.015670518	3.741958946	0.02323663	4.59063173	0.028602788	6.014139591	0.035130837	6.219647822	0.039320666	8.471208435	0.041786099	9.282375852								
	F age fecund. decline = 20		F age fecund. decline = 30		F age fecund. decline = 40		F age fecund. decline = 50		F age fecund. decline = 60		F age fecund. decline = 70		F age fecund. decline = 80		F age fecund. decline = 90		F age fecund. decline = 100			
age of menopaus	PGR	FRV	PGR	FRV	PGR	FRV	PGR	FRV	PGR	FRV	PGR	FRV	PGR	FRV	PGR	FRV	PGR	FRV		
20	-0.01685315	0.603603604																		
30	-0.01307805	1.01183432	-0.00648546	1.558404558																
40	-0.00997983	1.250965251	-4.60E-05	1.959040959	0.004223177	2.167416272														
50	-0.00429183	1.746987952	0.009663335	2.470425565	0.011112288	2.685172561	0.0152997	3.107844608												
60	0.006755888	2.340270755	0.014223702	2.948919833	0.0153619	3.15882307	0.018855925	3.501356102	0.021239926	3.976914865										
70	0.012582141	2.89883409	0.017574182	3.406559286	0.019411438	3.677886234	0.021036728	3.986440678	0.022302994	4.305301357	0.023659879	4.766170058								
80	0.016023943	3.416055386	0.019916151	3.776908023	0.02090251	4.048378305	0.022112139	4.331277941	0.023532199	4.747844828	0.024253505	4.987670465	0.025226752	5.393822394						
90	0.017578646	3.739279767	0.021242378	4.003367476	0.022211966	4.464973178	0.023320799	4.724425131	0.024436402	5.048854041	0.024513482	5.216026435	0.025448782	5.493263798	0.024597035	5.418072038				
100	0.019288781	3.995294671	0.02182608	4.180896155	0.022816396	4.661633954	0.023969252	4.953747404	0.024628689	5.224969098	0.024722255	5.508459679	0.025192164	5.522081329	0.025088005	5.528599606	0.025178731	5.530723814		
150	0.021499226	4.628122545	0.02323663	4.59063173	0.023968623	5.077779912	0.024831881	5.347816688	0.025119741	5.570774164	0.024932095	5.448647506	0.025255666	5.525979745	0.02518396	5.485817872	0.025162333	5.579693832		

Appendix Table 4: modern chimpanzee longevity, serial monogamy investigation data

Modern chimpanzee, shortened longevity														
	max F eligibility = 30		max F eligibility = 40		max F eligibility = 50									
age of menopaus	PGR	FRV	PGR	FRV	PGR	FRV								
30	-0.00648546	1.773662551	-0.00575714	1.7731569	-0.00746464	1.599690881								
40	-0.00546479	1.786937902	0.0001441	1.970054606	0.00029267	1.934802856								
50	0.001743094	1.974859487	0.003934762	2.014972864	0.002787169	2.009460485								
60	0.000473124	1.923227384	0.005689768	2.016066626	0.005709826	2.012733358								
70	0.000530628	1.987693885	0.005558988	2.014103011	0.005060853	2.015360213								
80	0.000667829	1.984295667	0.005698183	2.016749395	0.006089769	2.012166443								
90	0.0017613	2.003139952	0.005960642	2.020609783	0.005634897	2.021766015								
100	0.000266203	1.994089347	0.005798959	2.017469612	0.005705564	2.016118487								
150	0.001904344	2.012832676	0.006193973	2.017231944	0.006264757	2.022737546								
	F age fecund. decay = 20		F age fecund. decay = 30		F age fecund. decay = 40		F age fecund. decay = 50		F age fecund. decay = 60		F age fecund. decay = 80			
age of menopause														
20	-0.02721612	1.046728972												
30	-0.01434284	1.415584416	-0.00746464	1.599690881										
40	-0.00500381	1.825581395	0.00029267	1.934802856	0.00471151	2.012892465								
50	0.00160543	2.007740399	0.002787169	2.009460485	0.004803898	2.014607741	0.006004168	2.020380667						
60	0.00300494	2.007062354	0.005709826	2.012733358	0.006415109	2.017244604	0.005831229	2.018386222	0.00601785	2.01679951				
70	0.004930979	2.009859286	0.005060853	2.015360213	0.006027795	2.017119542	0.005720492	2.020289271	0.005240741	2.019000877				
80	0.004776178	2.01801535	0.006089769	2.012166443	0.005799	2.01908289	0.005742714	2.020438635	0.005870384	2.016322709	0.006260317	2.020627806		
90	0.005613985	2.018421542	0.005634897	2.021766015	0.005767656	2.018655273	0.006082079	2.020632665	0.005957816	2.020334991	0.005961701	2.016363563		
100	0.005333588	2.018197113	0.005705564	2.016118487	0.005194594	2.022863948	0.005865273	2.014630645	0.006247165	2.019158867	0.005869271	2.020156511		
150	0.005236602	2.01974971	0.006264757	2.022737546	0.006001259	2.020189415	0.006467176	2.015650313	0.005756994	2.016788859	0.006021223	2.015439913		

Appendix Table 5: serial monogamy + "divorce" investigation data

Serial monogamy + "divorce"											
	max F eligibility = 30		max F eligibility = 40		max F eligibility = 50		max F eligibility = 80				
age of menopaus	PGR	FRV	PGR	FRV	PGR	FRV	PGR	FRV			
30	-0.00633867	1.547692308	-0.0070188	1.501492537	-0.00532494	1.523584906	-0.0075368	1.51497006			
40			-0.00022941	1.966639871	-0.00024846	1.940812379	-0.00348553	1.794432548			
50	-0.00647572	1.458333333	0.005282391	2.197131186	0.009261029	2.423433274	0.007940545	2.382252023			
60			0.006076317	2.257518731	0.012420268	2.707183133	0.014025539	2.836230066			
70			0.00672587	2.299850219	0.014104441	2.846515605	0.016734413	3.193756818			
80			0.007623407	2.321309388	0.014904309	2.897816536	0.019716666	3.629820937			
90			0.007438	2.336430039	0.016633619	2.950908198	0.020591874	3.893764144			
100	-0.0050833	1.569868996	0.007496061	2.332676504	0.016369767	2.992761819	0.022154731	4.06637618			
150	-0.00614242	1.543778802	0.007860847	2.358183763	0.016152374	3.058735059	0.023095407	4.486568677			
	F age fecund. decay = 20		F age fecund. decay = 30		F age fecund. decay = 40		F age fecund. decay = 50		F age fecund. decay = 80		
age of menopaus	PGR	FRV	PGR	FRV	PGR	FRV	PGR	FRV	PGR	FRV	
20	-0.01380295	0.603448276									
30	-0.01060081	1.066037736	-0.0070188	1.501492537							
40	-0.0065902	1.616591928	-0.00022941	1.966639871	0.007483387	2.386396602					
50	-0.00103564	1.932343234	0.005282391	2.197131186	0.007659924	2.384362576	0.00863679	2.395325828			
60	0.00182777	2.038694075	0.006076317	2.257518731	0.007555033	2.392281075					
70	0.003506308	2.128355582	0.00672587	2.299850219	0.007246517	2.392057166					
80	0.004449685	2.174206194	0.007623407	2.321309388	0.007625431	2.389829607	0.008471301	2.388959627	0.008815978	2.389562126	
90	0.004411707	2.192589892	0.007438	2.336430039	0.00811302	2.384324835					
100	0.005472796	2.229060374	0.007496061	2.332676504	0.008644347	2.389515266	0.008496544	2.381370638	0.008649197	2.39277839	
150	0.006725531	2.291501938	0.007860847	2.358183763	0.00875752	2.383919545	0.008329799	2.396137731	0.00840343	2.377829259	

Appendix Table 6: serial monogamy + "divorce" + bias age preference mating investigation data

Serial monogamy + "divorce" + bias age preference mating											
	max F eligibility = 30		**max F eligibility = 40**		**max F eligibility = 50**		**max F eligibility = 60**		**max F eligibility = 80**	
age of menopaus	PGR	FRV	PGR	FRV	PGR	FRV	PGR	FRV	PGR	FRV
30	-0.00739708	1.326460481	-0.00700149	0.936781609	-0.0150851	0.551181102	-0.01639181	0.558558559	-0.01491415	0.540816327
40	-0.00742219	1.347639485	-0.0007002	1.783783784	-0.00869631	1.149758454	-0.01070774	0.834482759	-0.01600753	0.713114754
50	-0.00721721	1.344262295	0.00431496	2.190321148	0.003190477	2.149600362	-0.00545322	1.45276873	-0.00990761	0.891566265
60	-0.00676407	1.315457413	0.005781003	2.273845553	0.005306221	2.285566382	0.001627005	2.050488599	-0.00648744	1.353612167
70			0.005958193	2.298474464	0.006287308	2.39854425	0.004320692	2.308772756	-0.00198575	1.876884422
80	-0.00763164	1.336244541	0.006794849	2.321824178	0.006917847	2.456952839	0.005097428	2.385536511	0.001243756	2.11094933
90			0.006467824	2.32733268	0.006846571	2.42921518	0.005840939	2.449102976	0.003312928	2.291700904
100	-0.00709988	1.398601399	0.006188386	2.32009931	0.007392814	2.487817072	0.006245232	2.482144368	0.004011827	2.336776272
150	-0.00751786	1.381538462	0.007026765	2.356262734	0.007724303	2.491426839	0.007022081	2.57096331	0.006150036	2.594169385
	min M eligibility = 20		**min M eligibility = 30**		**min M eligibility = 40**		**min M eligibility = 50**			
age of menopaus	PGR	FRV	PGR	FRV	PGR	FRV	PGR	FRV		
30	-0.00789361	1.41576087	-0.00969362	1.091370558	-0.00700149	0.936781609	-0.01472309	0.516129032		
40	-0.00109775	1.949921136	0.000271949	1.888888889	-0.0007002	1.783783784	-0.00723484	1.354243542		
50	0.004318233	2.194904808	0.004451258	2.200570183	0.00431496	2.190321148	-0.00125356	1.83518931		
60	0.005199994	2.262663249	0.005275313	2.260674571	0.005781003	2.273845553	0.002631774	1.937325905		
70	0.00587142	2.289537467	0.005860998	2.295560186	0.005958193	2.298474464	0.002465909	2.039231712		
80	0.006287377	2.314958598	0.006453731	2.317798338	0.006794849	2.321824178	0.002223639	2.051464316		
90	0.006465097	2.325896949	0.006617765	2.325194805	0.006467824	2.32733268	0.002230051	2.059341501		
100	0.006424289	2.325262236	0.006420153	2.333003619	0.006188386	2.32009931	0.002321641	2.082522303		
150	0.006744818	2.359590176	0.006744781	2.356145352	0.007026765	2.356262734	0.002168761	2.049194602		
	F age fecund. decay = 20		**F age fecund. decay = 30**		**F age fecund. decay = 40**		**F age fecund. decay = 80**			
age of menopaus	PGR	FRV	PGR	FRV	PGR	FRV	PGR	FRV		
20	-0.01307551	0.403225806								
30	-0.01051534	0.5	-0.00700149	0.936781609						
40	-0.00838336	1.147826087	-0.0007002	1.783783784	0.007387689	2.372317149				
50	-0.00316895	1.667269439	0.00431496	2.190321148	0.007502955	2.379420793				
60	0.001540833	2.031357049	0.005781003	2.273845553						
70	0.002490118	2.045112782	0.005958193	2.298474464						
80	0.003440343	2.167531209	0.006794849	2.321824178	0.007387689	2.372317149	0.007256119	2.387724072		
90	0.004182693	2.203164557	0.006467824	2.32733268						
100	0.004806586	2.229021246	0.006188386	2.32009931	0.007502955	2.379420793	0.007124797	2.377654312		
150	0.005459258	2.286178743	0.007026765	2.356262734	0.007284976	2.378062678	0.007407213	2.386800711		

Appendix Table 7: Genes implicated in menopause

Gene(s)	Identification	Source
FOXO3a[1]	- GWAS of European women[1] - GWAS of combined women[2]	He & Murabito, 2012 Voorhuis et al., 2010 Lunetta et al., 2007 He et al., 2009 Stolk et al., 2009 Stolk et al., 2012
CYPI9A1[1]		
MCM8[1,2]		
BRSK1[1,2]		
UIMC1[1]		
SYCP2L[1]		
ARHGEF7[1]		
TMEM150B[1]		
HEL308[1]		
PRIM1[1]		
RHBDL2[1]		
BAT2[1]		
TLK1[1]		
ASH2L[1]		
POLG[1]		
FNDC4[1]		
GSPT1[1]		
TNFRSF17[1]		
C11orf46[1]		
PPED2[1]		
TDRD3[1]		
EXO1[1]		
NLRP11[1]		

APPENDIX B – Simulation

```
#!/usr/bin/python
# -*- coding: utf-8 -*-
import math
import random
import sys
from  scipy.stats import norm
import matplotlib.pyplot as plt
import numpy as np
import time

# These are values of the Siler model- chosen to resemble a current human population
fa1 = 0.005
fa2 = 2.0e-15
fa3 = 4.0e-6

fb1 = -0.5
fb3 = 0.12

ma1 = 0.006
ma2 = 2.1e-15
ma3 = 4.1e-6

mb1 = -0.6
mb3 = 0.13

# female fecundity parameters
class femaleReproduction:
   def __init__(self,atype):
      self.type = atype
      self.max_fecundity = 0.0
      self.age_fecundity_begins = 0
      self.age_fecundity_decline = 0
      self.menopause_age = 0
   def __str__(self):
      cr = "\n"
      s = "type is " + repr(self.type) + cr
      s = s + "age that fecundity begins is " + repr(self.age_fecundity_begins) + cr
      s = s + "maximum fecundity is " + format(self.max_fecundity,"0.3f")    + cr
      s = s + "age that fecundity begins to decline is " + repr(self.age_fecundity_decline) + cr
      s = s + "age that fecundity reaches zero (menopause age) is " + repr(self.menopause_age) + cr
      return s
fr0 = femaleReproduction("default female reproductive system")
fr0.max_fecundity = 0.15
fr0.age_fecundity_begins = 13
fr0.age_fecundity_decline = 30
fr0.menopause_age = 100
```

```
# fmax_female = 0.15 <- this is now an attribute of the female
# minAge_female = 13  <- this is now an attribute of the female
# declineAge_female = 40 # <- this is now an attribute of the female
# menoAge_female = 40  <- this is now an attribute of the female
print "-female reproductive system: " , fr0

# male fecundity parameters
class maleReproductiion:
   def __init__(self,atype):
      self.type = atype
      self.max_fecundity = 0.0
      self.age_fecundity_begins = 0
      self.age_fecundity_decline = 0
      self.menopause_age = 0
   def __str__(self):
      cr = "\n"
      s = "type is " + repr(self.type) + cr
      s = s + "age that fecundity begins is " + repr(self.age_fecundity_begins) + cr
      s = s + "maximum fecundity is " + format(self.max_fecundity,"0.3f")    + cr
      s = s + "age that fecundity begins to decline is " + repr(self.age_fecundity_decline) + cr
      s = s + "age that fecundity reaches zero (menopause age) is " + repr(self.menopause_age) + cr
      return s
mr0 = maleReproductiion("default male reproductive system")
mr0.max_fecundity = 0.90
mr0.age_fecundity_begins = 13
mr0.age_fecundity_decline = 95
mr0.menopause_age = 100
# fmax_male = 0.9  <- this is now an attribute of the male
# minAge_male = 13 # <- this is now an attribute of the  male
# declineAge_male = 80 # <- this is now an attribute of the male
# menoAge_male = 80 # <- this is now an attribute of the male
print "+male reproductive system: " , mr0

# eligibility for mate pair formation
class serialMonogamy:
   def __init__(self,atype):
      self.type = atype
      self.emin_female = 0.0
      self.emax_female = 0
      self.emin_male = 0
      self.emax_male = 0
      self.max_years_nursing = 0
   def __str__(self):
      cr = "\n"
      s = "type is " + repr(self.type) + cr
      s = s + "minimum FEMALE age for pair formation is " + repr(self.emin_female) + cr
      s = s + "maximum FEMALE age for pair formation is " + repr(self.emax_female)    + cr
      s = s + "maximum years a MOTHER will nurse (cannot be fertilized) is " + repr(self.max_years_nursing)    + cr
+ cr
      s = s + "minimum MALE age for pair formation is " + repr(self.emin_male) + cr
```

```
    s = s + "maximum MALE age for pair formation is " + repr(self.emax_male) + cr
    return s

  def eligibleFemaleList(self,fpop):
    eligible_female_list = []
    for fkey in fpop:
      if fpop[fkey].id != fkey:
        print "eligibleFemaleList: key <-> id mismatch; key = " , fkey
        print fpop[fkey]
        sys.exit(1)
      if fpop[fkey].mate == 0 and fpop[fkey].nursing == -1:
          if fpop[fkey].age >= self.emin_female and fpop[fkey].age <= self.emax_female:
            eligible_female_list.append(fkey)
    return eligible_female_list

  def eligibleMaleList(self,mpop):
    eligible_male_list  = []
    for mkey in mpop:
      if mpop[mkey].id != mkey:
        print "eligibleMaleList: key <-> id mismatch; key = " , mkey
        print mpop[mkey]
        sys.exit(1)
      if mpop[mkey].mate == 0:
          if mpop[mkey].age >= self.emin_male and mpop[mkey].age <= self.emax_male:
            eligible_male_list.append(mkey)
    return eligible_male_list

  def randomMatePairs(self,mpop,fpop,eligible_male_list,eligible_female_list):
    nmated = 0
    nef = len(eligible_female_list)
    females_needing_mates = []
    for key in eligible_female_list:
      females_needing_mates.append(key)
    # print "females_needing_mates " , len(females_needing_mates)
    # print females_needing_mates
    for i in range(1):
      random.shuffle(females_needing_mates)
    # print "shuffled females_needing_mates " , len(females_needing_mates)
    # print females_needing_mates

    nem = len(eligible_male_list)
    males_needing_mates = []
    for key in eligible_male_list:
      males_needing_mates.append(key)
    # print "males_needing_mates " , len(males_needing_mates)
    # print males_needing_mates
    for i in range(10):
      random.shuffle(males_needing_mates)
    # print "males_needing_mates " , len(males_needing_mates)
    # print males_needing_mates
```

```
      mated_pairs = [] # a list of mate pairs [ [] , [] , etc ]
      f_mated_index = 0 # index of next mated female
      for male_key in males_needing_mates:
         female_key = females_needing_mates[f_mated_index]
         mated_pairs.append( (male_key,female_key) )
         nmated = nmated + 1
         f_mated_index = f_mated_index + 1
         if f_mated_index >= nef :
            break
      # print "update randomMatePairs:"
   # now update mate on population cards
      for apair in mated_pairs:
         mkey = apair[0]
         fkey = apair[1]
         # print apair, mkey, fkey
         if malePop[mkey].mate != 0:
            print "something wrong with mate value"
            print malePop[mkey]
            sys.exit(1)
         malePop[mkey].mate = fkey

         if femalePop[fkey].mate != 0:
            print "something wrong with mate value"
            print femalePop[fkey]
            sys.exit(1)
         femalePop[fkey].mate = mkey

      return mated_pairs


sm0 = serialMonogamy("default serial monogamy mating system")
sm0.emin_female = 13
sm0.emax_female = 39
sm0.emin_male = 40
sm0.emax_male = 80
sm0.max_years_nursing = 4
# emin_female = 13
# emax_female = 30
# emin_male = 13
# emax_male = 80
# maximum years nursing (cannot be fertilized)
print "*mating system: " , sm0

# There is no longer a genotype; the old-age decline in fecundity is determined by an attribute called
"menopaue_age"
# delta = (fmax_female)/(menopause_age - fmaxAge_female)
# using a linear model for decline
# the age at which fecundity reaches zero is the menopause age
```

```
# in order to classify attributes into yearly age groups a finite number is defined
# note that the maximum age of an individual is not limited (except by death)
age_groups = 120
# age_axis is used to plot age-specific data against age
# age=0 means age in interval 0 to 1 year
age_axis = []
for age in range(age_groups):
   age_axis.append(age)
########################## Now we make a test female and test male so that the fecundity van be displayed
# define the femaleIndividual class
################ The class femaleIndiivdual represents the life history traits for a single female
class femaleIndividual:
   def __init__(self,year,byear,iid,fr0):
      self.id = iid # each female has an id
      self.birth_year = byear # each female has a year of birth
      self.death_year = -1
      self.age = year - byear # the female may be initiated at any age by year of initiation
      self.menopause_age = fr0.menopause_age
      self.maximum_fecundity = fr0.max_fecundity
      self.age_fecundity_begins = fr0.age_fecundity_begins
      self.age_fecundity_decline = fr0.age_fecundity_decline
      self.mate = 0 # not mated yet
      self.nursing = -1
      self.mortality_risk = self.mortality_risk_Siler() # females mortality risk is caclulated according to the Siler
function
      self.fecundity = self.fecundity_risk() # fecundity is a probability
      self.parturitionAges = []


   def __str__(self):
      if self.mate > 0:
         sm = "Mated to individual (by male key) " + repr(self.mate)
      else:
         sm = "Has no mate "
      cr = "\n"
      s = "Female#" + repr(self.id) + cr
      s = s + sm + cr
      s = s + "Age is " + repr(self.age) + cr
      s = s + "Birth Year is " + repr(self.birth_year) + cr
      s = s + "Death Year is " + repr(self.death_year) + cr
      s = s + "Age fecundity begins " + repr(self.age_fecundity_begins) + cr
      s = s + "Maximum fecundity is " + repr(self.maximum_fecundity) + cr
      s = s + "Age fecundity decline begins " + repr(self.age_fecundity_decline) + cr
      s = s + "Age menopause (fecundity zero) " + repr(self.menopause_age) + cr
      if self.nursing >= 0:
         s = s + "Has been nursing " + repr(self.nursing) + " years" + cr
      else:
         s = s + "Not nursing" + cr
      s = s + "Parturition Ages " + repr(self.parturitionAges) + cr
      s = s + "Mortality Risk (per year) is " + format(self.mortality_risk,'0.3f') + cr
```

```
        s = s + "Fecundity Risk (per year) is " + format(self.fecundity,'0.3f') + cr

        return s

    def mortality_risk_Siler(self):
# this function calculates the mortality risk (age-specific death rate per year) for the Siler model
# I made a cut-off so that risk cannot be greater than 1.0
        risk = fa1*math.exp(fb1*self.age) + fa2 + fa3*math.exp(fb3*self.age)
        if risk > 1.0:
            self.mortality_risk  = 1.0
        else:
            self.mortality_risk  = risk
        return self.mortality_risk


    def fecundity_risk(self):
        if self.age < self.age_fecundity_begins:
            self.fecundity = 0.0
            return self.fecundity
        elif self.age >= self.menopause_age:
            self.fecundity = 0.0
            return self.fecundity
        elif self.age >= self.age_fecundity_begins and self.age < self.age_fecundity_decline:
            self.fecundity = self.maximum_fecundity
            return self.fecundity
        else:
            decline = self.maximum_fecundity / (self.menopause_age - self.age_fecundity_decline)
            self.fecundity = self.fecundity - decline
            if self.fecundity < 0.0:
                self.fecundity = 0.0
        return self.fecundity

    def detemineIfDies(self):
        mx = self.mortality_risk
        r = random.random()
        if mx < 0.0:
            mx = 0.0
        if mx > 1.0:
            mx = 1.0
    # print "detemineIfDies " , r , mx
        if r < mx:
            return True # dies
        else:
            return False # survives

    def determineIfBirth(self, mpop):
        # print "determineIfBirth: female#" , self.id , " mate id " , self.mate
        if self.mate == 0: # here must have only one mate
            return False
        #print self.nursing
```

```
      if self.nursing >= 0:
         return False # a positive number (or zero) means nursing
      mate_key = self.mate
      if mpop.has_key(mate_key) == False:
         print "female #" , self.id
         print self
         print "\nmale mate not found"
         print "stop"
         sys.exit(1)
      # print "determineIfBirth: test female " , self.id , " mate " , mate_key

      if mpop[mate_key].mate != self.id:
         print "determineIfBirth: mother is " , self.id
         print "mate is " , mpop[mate_key].mate
         print "something wrong, male should be paired"
         print "mother"
         print self
         print "\nmale"
         print mpop[mate_key]
         print "stop"
         sys.exit(1)
      r = random.random()
      ff = self.fecundity
      fm = mpop[mate_key].fecundity
      if r < fm*ff:
         return True
      else:
         return False
### the test fenale
testFemale = femaleIndividual(0, 0, 1, fr0)
print "test female: ", testFemale

######## similar for a male individual's life history
class maleIndividual:
   def __init__(self,year,byear,iid,mr0):
         self.id = iid # each female has an id
         self.birth_year = byear # each female has a year of birth
         self.death_year = -1
         self.age = year - byear # the female may be initiated at ant age by year of initiation
         self.menopause_age = mr0.menopause_age
         self.maximum_fecundity = mr0.max_fecundity
         self.age_fecundity_begins = mr0.age_fecundity_begins
         self.age_fecundity_decline = mr0.age_fecundity_decline
         self.mate = 0 # not mated yet
         self.mortality_risk = self.mortality_risk_Siler() # females mortality risk is caclulated according to the Siler
function
         self.fecundity = self.fecundity_risk() # fecundity is a probability

   def __str__(self):
      if self.mate > 0:
```

```
            sm = "Mated to individual (by female key) " + repr(self.mate)
        else:
            sm = "Has no mate "
        cr = "\n"
        s = "Male#" + repr(self.id) + cr
        s = s + sm + cr
        s = s + "Age is " + repr(self.age) + cr
        s = s + "Birth Year is " + repr(self.birth_year) + cr
        s = s + "Death Year is " + repr(self.death_year) + cr
        s = s + "Age fecundity begins " + repr(self.age_fecundity_begins) + cr
        s = s + "Maximum fecundity is " + repr(self.maximum_fecundity) + cr
        s = s + "Age fecundity decline begins " + repr(self.age_fecundity_decline) + cr
        s = s + "Age menopause (fecundity zero) " + repr(self.menopause_age) + cr
        s = s + "Mortality Risk (per year) is " + format(self.mortality_risk,'0.3f') + cr
        s = s + "Fecundity Risk (per year) is " + format(self.fecundity,'0.3f') + cr

        return s

    def mortality_risk_Siler(self):
# this function calculates the mortality risk (age-specific death rate per year) for the Siler model
# I made a cut-off so that risk cannot be greater than 1.0
        risk = ma1*math.exp(mb1*self.age) + ma2 + ma3*math.exp(mb3*self.age)
        if risk > 1.0:
            self.mortality_risk  = 1.0
        else:
            self.mortality_risk  = risk
        return self.mortality_risk

    def fecundity_risk(self):
        if self.age < self.age_fecundity_begins:
            self.fecundity = 0.0
            return self.fecundity
        elif self.age >= self.menopause_age:
            self.fecundity = 0.0
            return self.fecundity
        elif self.age >= self.age_fecundity_begins and self.age < self.age_fecundity_decline:
            self.fecundity = self.maximum_fecundity
            return self.fecundity
        else:
            decline = self.maximum_fecundity / (self.menopause_age - self.age_fecundity_decline)
            self.fecundity = self.fecundity - decline
            if self.fecundity < 0.0:
                self.fecundity = 0.0
            return self.fecundity

    def detemineIfDies(self):
        mx = self.mortality_risk
        r = random.random()
        if mx < 0.0:
            mx = 0.0
```

```
        if mx > 1.0:
            mx = 1.0
        # print "deteminelfDies " , r , mx
        if r < mx:
            return True # dies
        else:
            return False # survives
### the test nale
testMale = maleIndividual(0, 0, 1, mr0)
print "test male: ", testMale

########## This plots the fecundity of the test male and female as a birth cohort of one
print "\nTTTTTTTTTTTTTTTTTTTTTTTT"
print "determine cohort fecundity of test female / male assuming no deaths"
test_female_fecundity = []
for age in range(age_groups):
    test_female_fecundity.append(testFemale.fecundity)
    testFemale.age = testFemale.age + 1
    testFemale.fecundity_risk()

test_male_fecundity = []
for age in range(age_groups):
    test_male_fecundity.append(testMale.fecundity)
    testMale.age = testMale.age + 1
    testMale.fecundity_risk()
# test male & test female will not be used again
print "plot test cohort  fecundity"
plt.plot(age_axis,test_female_fecundity,color="red",marker='o')
plt.plot(age_axis,test_male_fecundity,color="blue",marker='o')
plt.ylim(0.0,1.0)
plt.title("Fecundity with Age (test cohort)")
plt.xlabel("Age")
plt.ylabel("Fecundiy (female=red, male=blue)")
plt.savefig("fecundity_test_cohort.png")
print "\n!! close window to continue"
plt.show()

########################## NOE DEFINE STUFF FOR DEMOGRAPHIC CALCULATIONS ###################
########################## functions ################################

def write_string(file,str):
    fo = open(file,"w")
    fo.write(str)
    fo.write("\n")
    fo.close()

def add_string(file,str):
    fo = open(file,"a")
    fo.write(str)
    fo.write("\n")
```

```
    fo.close()

# these functions are used for age groups, whiuch are collections of age-dependent values
def initializeAgeGroups(alist):
    global age_groups
    for age in range(age_groups+1):
        alist.append(0)
    return

def incrementAgeGroups(alist,list_add):
    global age_groups
    for age in range(age_groups+1):
        alist[age] = alist[age] + list_add[age]
    return

def averageGroupAge(group,pop):
    ta = 0.0
    na = 0
    for key in group:
        na = na + 1
        ta = ta + float(pop[key].age)
    if na == 0:
        return 0.0
    return  ta / float(na)

# function used for demographic paramters
def populationGrowthRate(p1,p0):
    return math.log(float(p1)/float(p0))

def aveFecundity(pop):
    a = 0.0
    n = 0
    for key in pop:
        n = n + 1
        a = a + pop[key].fecundity
    if n <= 0:
        print "aveFecundity: no count " , len(pop)
        return 0.0
    return a / float(n)

def aveMortalityRisk(pop):
    a = 0.0
    n = 0
    for key in pop:
        n = n + 1
        a = a + pop[key].mortality_risk
    if n <= 0:
        print "aveMortalityRisk: no count " , len(pop)
        return 0.0
    return a / float(n)
```

```
def test_reciprocal_female_mate_pair(malePop,femalePop,female_key):
   female_mate_key = femalePop[female_key].mate
   father_mate_key = malePop[female_mate_key].mate
   if father_mate_key != female_key:
      print "\n" , femalePop[female_key]
      print "\n" , malePop[female_mate_key]
      print "test_reciprocal_female_mate_pair: pair error " , father_mate_key , female_key
      return False
   return True


def birthsMatedFemales(malePop,femalePop,female_age_count,female_births_by_age):
   mated_list = []
   for female_key in femalePop:
      if femalePop[female_key].mate > 0 and femalePop[female_key].nursing == -1:
         if test_reciprocal_female_mate_pair(malePop,femalePop,female_key) == False:
            print "birthsMatedFemales mismatch key <-> id error"
            sys.exit(1)
         female_mate_key = femalePop[female_key].mate
         mated_list.append( (female_mate_key,female_key) )
   # print "birthsMatedFemales: potential parents"
   # print mated_list
   if len(mated_list) <= 0:
      return mated_list
   parent_list = []
   # print "birthsMatedFemales: form parent list"
   for apair in mated_list:
      # print apair
      male_key = apair[0]
      female_key = apair[1]
      if test_reciprocal_female_mate_pair(malePop,femalePop,female_key) == False:
         print "reciprocal test failed"
         print malePop[male_key]
         print femalePop[female_key]
         sys.exit(1)
      # print "female -? mother " , female_key , " female has mate " , male_key
      if femalePop[female_key].determineIfBirth(malePop) == True:
         father_key = femalePop[female_key].mate
         # print "female -> mother " , female_key , " female had mate " , male_key , " father " , father_key
         if malePop.has_key(father_key) == False:
            print "father #" , father_key , " not found in male population-> error"
            sys.exit(1)
         motherage = femalePop[female_key].age
         if motherage < age_groups:
            female_age_count[motherage] =  female_age_count[motherage] + 1
            female_births_by_age[motherage] =  female_births_by_age[motherage] + 1

         father_mate_key = malePop[father_key].mate
         if father_mate_key != female_key:
```

```
            print "\n"
            print "birthsMatedFemales: pair not mate paired -> error"
            print femalePop[female_key]
            print "\n"
            print malePop[father_key]
            print "\nstop!"
            sys.exit(1)
         birth_pair = (father_key,female_key) # father key , mother key
         parent_list.append(birth_pair)
         femalePop[female_key].parturitionAges.append(femalePop[female_key].age)
         femalePop[female_key].nursing = 0 # begin nursing

   return parent_list

def addBirths(malePop,femalePop,parent_list,mr,fr):
   global male_index, female_index
# parent_list = [ (male parent , female parent ) ....]
   nMaleBirths = 0
   nFemaleBirths = 0
   for pair in parent_list:
# print " pair [father,mother]" , pair
      mother_key = pair[1]
      # print "mother is " , mother
      if femalePop.has_key(mother_key) == False:
         print "error in mother key " , mother_key
         sys.exit(1)
      father_key = pair[0]
      # print "father is " , father
      if malePop.has_key(father_key) == False:
         print "error in father key " , father_key
         sys.exit(1)
      sex = "male"
      if random.random() < 0.5:
         sex = "female"
         female_index = female_index + 1
         # print "addBirths pair " , pair , " -> female birth with index = " , female_index
         femalePop[female_index] = femaleIndividual(year,year,female_index,fr)
         nFemaleBirths = nFemaleBirths + 1
      else:
         male_index = male_index + 1
         # print "addBirths pair " , pair , " -> male birth with index = " , male_index
         malePop[male_index] = maleIndividual(year,year,male_index,mr)
         nMaleBirths = nMaleBirths + 1

   return  ( nMaleBirths , nFemaleBirths )

def   deathsFemales(year,femalePop,deadFemales,malePop,female_age_count,female_deaths_by_age):
   female_deaths = []
   for key in femalePop:
      age = femalePop[key].age
```

```
      if age < age_groups:
         female_age_count[age] =  female_age_count[age] + 1
      if femalePop[key].detemineIfDies() == True:
         femalePop[key].death_year = year
   # if female has mate he is now unmated
         mmate = femalePop[key].mate
         if mmate > 0:
            malePop[mmate].mate = 0
         female_deaths.append(key)
         if age < age_groups:
            female_deaths_by_age[age] =  female_deaths_by_age[age] + 1
   for key in female_deaths:
      if deadFemales.has_key(key) == True:
         print "female already dead error"
         print deadFemales[key]
         print femalePop[key]
         sys.exit(1)
      deadFemales[key] = femalePop[key]
      del femalePop[key]
   return female_deaths

def    deathsMales(year,malePop,deadMales,femalePop,male_age_count,male_deaths_by_age):
   male_deaths = []
   for key in malePop:
      age = malePop[key].age
      if age < age_groups:
         male_age_count[age] =  male_age_count[age] + 1
      if malePop[key].detemineIfDies() == True:
         malePop[key].death_year = year
   # if male has mate he is now unmated
         fmate = malePop[key].mate
         if fmate > 0:
            femalePop[fmate].mate = 0
         male_deaths.append(key)
         if age < age_groups:
            male_deaths_by_age[age] =  male_deaths_by_age[age] + 1
   for key in male_deaths:
      if deadMales.has_key(key) == True:
         print "male already dead error"
         print deadMales[key]
         print malePop[key]
         sys.exit(1)
      deadMales[key] = malePop[key]
      del malePop[key]
   return male_deaths


########################################## DEFINE INITIAL COHORT
print "\nCCCCCCCCCCCCCCCCCCCCC"
#sys.exit(1)
```

```
#########################
year = 0
initial_cohort = 100
femalePop = {} # females will be in a dictionary femalePop
deadFemales = {} # dictionary for dead females
for index in range(1,initial_cohort+1):
# def __init__(self,year,byear,iid,fmax_female,minAge_female,declineAge_female,menoAge_female):
   byear = random.randint(-29,0)
   femalePop[index] = femaleIndividual(year,byear,index,fr0)
print "\nnumber of females at year " , year , " is " , len(femalePop)
female_index = index
print "population index for females = " , female_index
print "\ncard for female #" ,female_index
print femalePop[female_index]

malePop = {}
deadMales = {}
for index in range(1,initial_cohort+1):
# def __init__(self,year,byear,iid,fmax_male,minAge_male,declineAge_male,menoAge_male):
   byear = random.randint(-80,0)
   malePop[index] = maleIndividual(year,byear,index,mr0)
print "\nnumber of males at year " , year , " is " , len(malePop)
male_index = index
print "population index for males = " , male_index
print "\ncard for male #" , male_index
print malePop[male_index]

############ Section II Get ready for yearly cycle
# lists for average fecundity, yearly
average_female_fecundity = []
average_male_fecundity = []
#average mortality risk is average of individual.mortality_risk
# for each year
average_male_mortality_risk = []
average_female_mortality_risk = []
# population size, stored as log10(size)
total_female_population = []
total_male_population = []
# total births is a list the total births in a time interval
# female and male births are not distinguished
total_births = []
birth_rate = [] # is births per female in year
# total deaths is a list of the deaths in a year interval
# female and male deaths are also distinguished
total_deaths = []
total_female_deaths = []
total_male_deaths = []
#  deaths per individual in  year
# female and male age-specific death rates are also distinguished
death_rate = []
```

```
female_death_rate = []
male_death_rate = []

# running avearages, age_count is the number of years counted
# age_period is when a new period of averages is initiated
age_period = 45
age_count = 0
male_age_period_deaths = [] # Cumultive count of male deaths by age
male_age_period_counts = [] # cumulative count of makes by age
initializeAgeGroups(male_age_period_deaths)
initializeAgeGroups(male_age_period_counts)
female_age_period_deaths = [] # Cumultive count of deaths by age
female_age_period_counts = [] # cumulative count of females by age
initializeAgeGroups(female_age_period_deaths)
initializeAgeGroups(female_age_period_counts)
mother_age_period_births = [] # cumultive count of mothers giving birth by age
mother_age_period_counts = [] # cumulative count of mothers by age
initializeAgeGroups(mother_age_period_births)
initializeAgeGroups(mother_age_period_counts)
# correlation of mothers age at birth with father's age
mother_age = []
father_age = []

time_count = []
growth_rate = []
age_mate_pairs = []

################ Section IV  time cycle
# time begins at year=0 and steps forward for time_max years by one year increments=
year_max = 1000
size_max = 30000 # for either male or female, total will be ~2x
# text data
localtime = time.asctime( time.localtime(time.time()) )
print "\nLocal time is " , localtime
## data for writing to text file
data_str = "popSimV5 begins; time is " + repr(localtime) + "\n\n"
data_str = data_str + "age_groups = " + repr(age_groups) + "\n\n"
data_str = data_str + "female maximum fecundity is " + format(fr0.max_fecundity,'0.3f') + "\n"
data_str = data_str + "female age fecundity begins is " + repr(fr0.age_fecundity_begins) + "\n"
data_str = data_str + "female age fecundity decline begins is " + repr(fr0.age_fecundity_decline) + "\n"
data_str = data_str + "female menopause age (zero fecundity) is " + repr(fr0.menopause_age) + "\n\n"
data_str = data_str + "male maximum fecundity is " + format(mr0.max_fecundity,'0.3f') + "\n"
data_str = data_str + "male age fecundity begins is " + repr(mr0.age_fecundity_begins) + "\n"
data_str = data_str + "male age fecundity decline begins is " + repr(mr0.age_fecundity_decline) + "\n"
data_str = data_str + "male menopause age (zero fecundity) is " + repr(mr0.menopause_age) + "\n"
data_str = data_str + "mother maximum years nursing is " + repr(sm0.max_years_nursing) + "\n\n"
data_str = data_str + "mate choice parameters" + "\n"
data_str = data_str + "minimum FEMALE age for pair formation is " + repr(sm0.emin_female) + "\n"
data_str = data_str + "maximum FEMALE age for pair formation is " + repr(sm0.emax_female) + "\n\n"
data_str = data_str + "minimum MALE age for pair formation is " + repr(sm0.emin_male) + "\n"
```

```
data_str = data_str + "maximum MALE age for pair formation is " + repr(sm0.emax_male) + "\n\n"
data_str = data_str + "Initial cohort = " + repr(initial_cohort) + "\n\n"

print "\nYYYYYYYYYYYYYYYYYYYYYYYYYYYYYY"
print "project forward in one year increments until > " , year_max , " years"
print "note in line data below; -F means for females, -M means for males"
print "Begin\n"
# print a header for the data that will be plotted at each t
# data for female population, number (NF), female births (BF), female deaths (DF), abe. female fecundity (FEC-F),
average female mortality risk (MR-F), average allele 1 frequency in females (p1-F) , population growth rate over
year (GR)
print "year" , "\t" , "NF " , "\t" , "B" , "\t" , "D-F", "\t" , "D-M" , "\t" ,  "FEC-F" , "\t" , "MR-F", "\t" , "GR"
while year <= year_max:
   # print "\n begin year " , year , " to " , year+1
   if len(femalePop) < 20 or len(malePop) < 20:
      print "population vanishing, terminate"
      break
   if len(femalePop) > size_max or len(malePop) > size_max:
      print "population too large, terminate"
      break

   # print "check key list for females"
   # key_list = []
   # for key in femalePop:
      # key_list.append(key)
   # print key_list

   nfemales = len(femalePop)
   total_female_population.append(math.log10(nfemales))
   nmales = len(malePop)
   total_male_population.append(math.log10(nmales))
   ipop = nmales + nfemales # population size at beginning of year
   time_count.append(year)
   avFec_f = aveFecundity(femalePop)
   average_female_fecundity.append(avFec_f)

   avFec_m = aveFecundity(malePop)
   average_male_fecundity.append(avFec_m)

   avMor_f = aveMortalityRisk(femalePop)
   average_female_mortality_risk.append(avMor_f)

   avMor_m = aveMortalityRisk(malePop)
   average_male_mortality_risk.append(avMor_m)

########## things happen now ###############
############# 1 - make lists of eligibles
   eligible_male_list = sm0.eligibleMaleList(malePop)
   eligible_female_list = sm0.eligibleFemaleList(femalePop)
   # print "eligible   males = " , len(eligible_male_list)
```

```
   # print "eligible females = " , len(eligible_female_list)

############## 2 - mate eligibles
   if len(eligible_male_list) > 0 and len(eligible_female_list) > 0:
      am = averageGroupAge(eligible_male_list,malePop)
      af = averageGroupAge(eligible_female_list,femalePop)
      print "eligible   males = " , len(eligible_male_list) , " average age = " , am
      print "eligible females = " , len(eligible_female_list) , " average age = " , af
      mated_pairs = sm0.randomMatePairs(malePop,femalePop,eligible_male_list,eligible_female_list)
      if len(mated_pairs) > 0:
         for pair in mated_pairs:
            male_key = pair[0]
            female_key = pair[1]
            age_mate_pairs.append( (malePop[male_key].age , femalePop[female_key].age) )
      print "pairs formed = " , len(mated_pairs)
      # print mated_pairs

############# 3 - determine births to mated pairs
   female_age_count = []
   female_births_by_age = []
   initializeAgeGroups(female_age_count)
   initializeAgeGroups(female_births_by_age)
   parent_list = birthsMatedFemales(malePop,femalePop,female_age_count,female_births_by_age)
   nbirths = len(parent_list)
   total_births.append(nbirths)
   birth_rate.append(nbirths/float(nfemales))
   if nbirths > 0:
################# here we add new births to the population
      for pair in parent_list:
         father_key = pair[0]
         mother_key = pair[1]
         father_age.append(malePop[father_key].age)
         mother_age.append(femalePop[mother_key].age)
      # print "male index = " , male_index , " female index = " , female_index
      (nmale_births , nfemale_births) = addBirths(malePop,femalePop,parent_list,mr0,fr0)
      # print "+male index = " , male_index , " female index = " , female_index
      print "nmale_births = " , nmale_births , " nfemale_births = " , nfemale_births , " nbirths = " , nbirths
      print "ipop = " , ipop , " ipop+nbirths = " , ipop+nmale_births+nfemale_births , " current size = " ,
len(femalePop) + len(malePop)
      if nmale_births + nfemale_births != nbirths:
         print "birth count error, nmale_births = " , nmale_births , " nfemale_births = " , nfemale_births
         sys.exit(1)

# here births by parents age
################# calculate deaths from mortality risk
   female_deaths_by_age = []
   female_age_count = []
   initializeAgeGroups(female_deaths_by_age)
   initializeAgeGroups(female_age_count)
```

```
    female_death_list =
deathsFemales(year,femalePop,deadFemales,malePop,female_age_count,female_deaths_by_age)
    nfemale_deaths = len(female_death_list)
    total_female_deaths.append(nfemale_deaths)
    female_death_rate.append(nfemale_deaths / float(nfemales) )

    male_deaths_by_age = []
    male_age_count = []
    initializeAgeGroups(male_deaths_by_age)
    initializeAgeGroups(male_age_count)
    male_death_list = deathsMales(year,malePop,deadMales,femalePop,male_age_count,male_deaths_by_age)
    nmale_deaths = len(male_death_list)
    total_male_deaths.append(nmale_deaths)
    male_death_rate.append(nmale_deaths/ float(nmales) )

    ndeaths = nmale_deaths + nfemale_deaths
    total_deaths.append(ndeaths)
    death_rate.append(ndeaths/float(ipop))
    n1_males = len(malePop)
    n1_females = len(femalePop)
    npop = n1_females + n1_males
    gr = populationGrowthRate(npop,ipop)
    growth_rate.append(gr)
    print "ipop = " , ipop , " nbirths = " , nbirths , " ndeaths = " , ndeaths , " total = " , ipop+nbirths-ndeaths
    print "npop = " , npop

    if ipop+nbirths-ndeaths != npop:
        print "population balance error"
        sys.exit(1)

    print year , "\t" , nfemales , "\t" , nbirths , "\t" , nfemale_deaths , "\t" , nmale_deaths , "\t" ,
format(avFec_f,'.3f'), "\t", format(avMor_f,'.3f') , "\t" , format(gr,'.3f')
########## The purpose of this section is to accumulate demographic data over a period for calculating syntheic
data at end
    if age_count < age_period:
        incrementAgeGroups(female_age_period_deaths,female_deaths_by_age)
        incrementAgeGroups(female_age_period_counts,female_age_count)

        incrementAgeGroups(male_age_period_deaths,male_deaths_by_age)
        incrementAgeGroups(male_age_period_counts,male_age_count)

        incrementAgeGroups(mother_age_period_counts,female_age_count)
        incrementAgeGroups(mother_age_period_births,female_births_by_age)
        age_count = age_count + 1
    else:
        age_count = 0
        male_age_period_deaths = [] # Cumultive count of male deaths by age
        male_age_period_counts = []
        initializeAgeGroups(male_age_period_deaths)
        initializeAgeGroups(male_age_period_counts)
```

```
      female_age_period_deaths = [] # Cumultive count of female deaths by age
      female_age_period_counts = []
      initializeAgeGroups(female_age_period_deaths)
      initializeAgeGroups(female_age_period_counts)

      mother_age_period_births = [] # Cumultive count of mother's births by age
      mother_age_period_counts = []
      initializeAgeGroups(mother_age_period_births)
      initializeAgeGroups(mother_age_period_counts)
##################################### here we update things for next year
      # update age by one year
      # update mortality risk for new age
      # update fecundity risk

   for key in femalePop:
      femalePop[key].age = femalePop[key].age + 1
      if femalePop[key].age >= 40:
        femalePop[key].mate = 0
      if femalePop[key].nursing >= sm0.max_years_nursing:
         femalePop[key].nursing = -1 #reset to not nursing
      if femalePop[key].nursing >= 0: # increment years nursing, if becomes max_years_nursing, will go back to -1
next year and then back to fecund the year after
         femalePop[key].nursing = femalePop[key].nursing + 1
      femalePop[key].mortality_risk_Siler()
      femalePop[key].fecundity_risk()


   for key in malePop:
      malePop[key].age = malePop[key].age + 1
      malePop[key].mortality_risk_Siler()
      malePop[key].fecundity_risk()

      fmate = malePop[key].mate
      if fmate != 0:
        if femalePop[fmate].age >= 40:
          malePop[key].mate = 0


   ################ increment year
   year = year + 1
   print "----"
   if year >= year_max:
      print "year limit (", year_max , ") exceeded, terminate"
      break

############################## year loop finished
print "\nFFFFFFFFFFFFFFFFFFFFFFFFF"
localtime = time.asctime( time.localtime(time.time()) )
print "Local time is " , localtime
```

```
data_str = data_str + "popSimV5a finished; time is " + repr(localtime) + "\n"
data_str = data_str + "Year Terminated = " + repr(year) + "\n"
data_str = data_str + "final population size is " + repr(len(malePop)+len(femalePop)) + "\n"
data_str = data_str + "final year growth rate is " + str(format(gr,'0.4f')) + "\n"

########## alive female card
print "alive female card -> "
n = 0
for key in femalePop:
   if femalePop[key].age <= 40:
      print "\ncard for  female #" ,key
      print femalePop[key]
      n = n + 1
   if n >= 1:
      break

index = 1
print "\n**************************"
print "dead available for analysis"
print "Dead females = " , len(deadFemales)
n = 0
for key in deadFemales:
   print "\ncard for dead female #" ,key
   print deadFemales[key]
   n = n + 1
   if n >= 1:
      break
print "\n"
print "Dead males = " , len(deadMales)
n = 0
for key in deadMales:
   print "\ncard for dead male #" ,key
   print deadMales[key]
   n = n + 1
   if n >= 1:
      break
########## determine female life expectancy from birth usingf deadFemales cards
years_lived = 0
for key in deadFemales:
   l = deadFemales[key].age
   years_lived = years_lived + l
flp = years_lived / float(len(deadFemales))
print "female life expectancy from birth = " , flp
data_str = data_str + "female life expectancy from birth is " + format(flp,'0.4f') + "\n"
############### determine ttal children per female in lifetime (call "reproductive value"), use deadFemales
cards
total_females = len(deadFemales)
total_children = 0
for key in deadFemales:
   c = len(deadFemales[key].parturitionAges)
```

```
   total_children = total_children + c
print "total children (lifetime) = " , total_children
print "total females = " , total_females
rv = total_children / float(total_females)
print "reproductive value (average children per female, over lifetime) = " , rv
data_str = data_str + "reprodutive value (average children per female, over lifetime) is " + format(rv,'0.4f') + "\n"
print "\n*****************"
print "plot LOG population size"
plt.plot(time_count,total_female_population,color="red")
plt.plot(time_count,total_male_population,color="blue")
plt.title("Log base 10 [Population Size] (male=blue, female=red)")
plt.xlabel("Time")
plt.ylabel("LN[Population Size]")
plt.savefig("ln_pop_size.png")
plt.show()
print "\n*****************"

tot = np.sum(growth_rate[-250:])
avgGR = tot/len(growth_rate[-250:])
print "average growth rate is" , avgGR

print "plot growth rate"
plt.plot(time_count,growth_rate,color="black")
plt.title("Growth Rate {LN(N(t+1)/N(t)}")
plt.xlabel("Time")
plt.ylabel("Growth Rate")
plt.savefig("growth_rate.png")
plt.show()
print "\n*****************"
print "plot synthetic age-specific mortality rate, age_count = " , age_count
data_str = data_str + "age count = " + repr(age_count) + "\n"
mrf = []
mrm = []
for age in range(len(age_axis)):
   #print "age-", age_axis[age] , " count/y-" , female_age_period_counts[age]/float(age_count) , "death/y-" ,
female_age_period_deaths[age]/float(age_count)
   if female_age_period_counts[age] > 0:
      mrf.append(female_age_period_deaths[age]/float(female_age_period_counts[age]))
   else:
      mrf.append(1.0)
   if male_age_period_counts[age] > 0:
      mrm.append(male_age_period_deaths[age]/float(male_age_period_counts[age]))
   else:
      mrm.append(1.0)
plt.plot(age_axis,mrf,color="red")
plt.plot(age_axis,mrm,color="blue")
plt.title("Synthetic Mortality Risk (male=blue, female=red)")
plt.xlabel("Age")
plt.ylabel("Deaths per Year per Individual at Risk")
plt.savefig("age_specific_death_rates.png")
```

```
plt.show()
print "\n*****************"
print "plot synthetic survival curve, cohort 1.0"
sm = [ ]
sma = 1.0
sf = [ ]
sfa = 1.0
for age in range(len(age_axis)):
   sm.append(sma)
   sf.append(sfa)
   sma = sma - sma*mrm[age]
   sfa = sfa - sfa*mrf[age]
plt.plot(age_axis,sf,color="red")
plt.plot(age_axis,sm,color="blue")
plt.title("Synthetic Survival Curve (cohort = 1.0; male=blue, female=red)")
plt.xlabel("Age")
plt.ylabel("Survival")
plt.savefig("synthetic_survival.png")
plt.show()
print "\n*****************"
print "plot synthetic female birth rate by age"
br = []
for age in range(len(age_axis)):
   if mother_age_period_counts[age] > 0:
      br.append(mother_age_period_births[age] / float(mother_age_period_counts[age]) )
   else:
      br.append(0.0)
plt.plot(age_axis,br,color="red")
plt.title("Synthetic age-specific births per female at Risk")
plt.xlabel("Age")
plt.ylabel("Births per year per female at risk")
plt.savefig("synthetic_age_specific_birth_rate.png")
plt.show()
print "\n*****************"
print "plot correlation of mother & father age at birth"
# draw vertical line from (70,100) to (70, 250)
#plt.plot([70, 70], [100, 250], 'k-', lw=2)
line = []
female_max = []
for y in range(age_groups):
   line.append(y)
   female_max.append(sm0.emax_female)

plt.scatter(father_age,mother_age, c='black', marker='.')
print "There are " , len(mother_age) , " mother's age data points"
print "There are " , len(father_age) , " father's age data points"
plt.plot(line, c="red", )
plt.plot([sm0.emax_male,sm0.emax_male],[0,age_groups], 'k-', c="green", )
plt.plot([0,age_groups],[sm0.emax_female,sm0.emax_female], 'k-', c="green", )
plt.title("Correlation of Parent's Age at Birth")
```

```
plt.ylabel("mother's age")
plt.xlabel("father's age")
plt.xlim(0,age_groups)
plt.ylim(0,age_groups)
plt.savefig("correlation_parents_age.png")
plt.show()
print "\n*****************"
print "plotcontour of count of mate pairs according to age of male & age of female"
print "number of mate pair ages " , len(age_mate_pairs)
# x = np.zeros(shape=(lmax+1,lmax+1),dtype=int)
x = np.zeros(shape=(61,61),dtype=int)
for pair in age_mate_pairs:
   fage = pair[1]
   mage = pair[0]
   if mage <= 60 and fage <= 60:
      x[mage][fage] = x[mage][fage] + 1
   # x[pair[0]][pair[1]] = x[pair[0]][pair[1]] + 1
plt.contour(x)
plt.title("contour of number_mated[female age][male age]")
plt.xlabel("female age")
plt.ylabel("male age")
plt.savefig("contour_map_age_at_mating.png")
plt.show()
print "\n"
print "plot mate pair ages by category of female age"
age_categories = [15,20,25,30,35] # must have 5 catagories
ccolor = [ "red" , "darkgreen" , "fuchsia" , "blue" , "black" , "yellow"]
female_age_catagories = []
for a in age_categories:
   female_age_catagories.append( [])
for pair in age_mate_pairs:
   fage = pair[1]
   if fage < age_categories[0]:
      female_age_catagories[0].append(pair)

   if fage >= age_categories[0] and fage < age_categories[1]:
      female_age_catagories[1].append(pair)

   if fage >= age_categories[1] and fage < age_categories[2]:
      female_age_catagories[2].append(pair)

   if fage >= age_categories[2] and fage < age_categories[3]:
      female_age_catagories[3].append(pair)

   if fage >= age_categories[3]:
      female_age_catagories[4].append(pair)
# print female_age_catagories

age_plot_categories = []
for a in age_categories:
```

```
   age_plot_categories.append([])
# print age_plot_categories
for c in age_plot_categories:
   for age in range(age_groups):
      c.append(0)

print "age_groups = " , age_groups
findex = 0
for a in female_age_catagories:
   #print "\n findex " , findex , "\n" ,  a
   for pair in a:
      mage = pair[0]
      if mage < age_groups-1:
         age_plot_categories[findex][mage] = age_plot_categories[findex][mage] + 1
      else:
         print "pair out of range " , pair
   findex = findex + 1
# print "age plot catagories"
# for c in age_plot_categories:
   # print c
print "\n"
for i in range(len(age_plot_categories)):
   plt.plot(age_axis,age_plot_categories[i],color = ccolor[i] )
   print " plot female age category " , i , "age < " , age_categories[i] , " color = "  , ccolor[i]
plt.title("mate pair count by female age category")
plt.xlabel("Male Age")
plt.ylabel("Count")
plt.savefig("mate_pair_count_by_female_age_category.png")
plt.show()
print "\n*****************"



write_string("data.txt",data_str)
print "FINISHED!"
```