THE EVOLUTION OF MENOPAUSE ANALYZED COMPUTATIONALLY

INVESTIGATING THE EVOLUTION OF MENOPAUSE THROUGH COMPUTATIONAL SIMULATION

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LAY ABSTRACT

Menopause can be defined generally for a group as a life history characterized by prolonged post-reproductive lifespan. Defined specifically so that at least 25% of adulthood is non-reproductive, menopause has been recorded in only humans and some species of toothed whales. This trait presents an evolutionary puzzle, as it appears to contradict classical evolutionary theory, which suggests that reproduction should continue until the end of life. In this thesis, I use computational modeling to explore why elephants have not evolved menopause despite sharing key features with menopausal species and how aneuploidy might have contributed to the evolution of menopause in humans.

ABSTRACT

Menopause is characterized by prolonged lifespan beyond the point of reproductive cessation. Defined so that at least 25% of adulthood is nonreproductive, humans and some toothed whale species are the only groups that have been found to exhibit menopause. Menopause is a puzzling trait that seems to contradict classical evolutionary theory that equates selection operating on reproduction to selection operating on survival. I created two computational models to gain better understanding of the evolution of menopause. The first model explored why menopause is not observed in elephants despite their being characterized by key features in common with menopausal species, specifically offspring care from older females and longevity. Simulations allowed testing the effects of varying age at reproductive cessation and levels of offspring care, modeled by decreases in interbirth intervals. I found that hypothetical populations with greatest post-reproductive lifespans, characterized by longer interbirth intervals and earlier reproductive cessation, were most likely to be out-competed by contemporary elephants. Conversely, hypothetical populations that were most reproductively competitive, those with shorter interbirth intervals and older ages of reproductive cessation, returned post-reproductive lifespans that failed to meet the 25% post-reproductive lifespan criterion for menopause. I identified a small region in the parameter space where populations that were both menopausal and reproductively competitive evolved, but the majority of that region corresponds to biologically unrealistic scenarios. The scenario that is most feasible involves an interbirth interval of 4 years and an age at reproductive cessation of 40 years. The second model studied how menopause might have evolved in humans through a behavioural strategy of ending reproduction early to avoid risk of aneuploidy later in life and diverting resources toward extant kin. I found that populations that ceased reproduction earlier and exhibited greater post-reproductive lifespan returned lower reproductive success. The model also demonstrated that the aneuploidy avoidance behaviour is most successful when reproduction ends at approximately age 50. These concepts have never been explored computationally before, so these experiments contribute a novel simulation-based perspective to the growing body of knowledge surrounding the origin and evolution of menopause.

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TABLE OF CONTENTS

LIST OF FIGURES

LIST OF TABLES

LIST OF ABBREVIATIONS AND SYMBOLS

AD	Age at death
ALR	Age at last reproduction
ARC	Age at reproductive cessation
ARD	Age at reproductive decline
E	Experimental group
N	Natural group
NRA	No risk of aneuploidy group
PAN	Proportion of adulthood non-reproductive
PR-E	Proportion of replicates where the experimental group out-reproduced the natural group
PR-RA	Proportion of replicates where the risk of aneuploidy group out-reproduced the no risk of aneuploidy group
PrR	Post-reproductive representation
RA	Risk of aneuploidy group

DECLARATION OF ACADEMIC ACHIEVEMENT

I designed the studies included in this thesis and contributed to the development of the computational models, with assistance from Dr. Jonathon Stone and undergraduate lab members. I ran all computer simulations and analyzed, visualized, and interpreted the resulting data. I researched and drafted the manuscript, with contributions and edits from Dr. Jonathon Stone.

CHAPTER 1: INTRODUCTION

In 1816, French physician Charles Pierre Louis de Gardanne proposed the word *ménespausie* as a short form of *cessation des menstrues* (de Gardanne, 1816). The word later was further shortened to *ménopause* (de Gardanne, 1821). As the origin of the name would suggest, clinical menopause is diagnosed after the first year of cessation of menstruation (T. A. Takahashi & Johnson, 2015). Physiologically, this change is associated with depletion of ovarian follicles, a gradual process that takes place throughout the lifespan (T. A. Takahashi & Johnson, 2015). While it can vary regionally, the worldwide median age of menopause onset is 50 years (Morabia & Costanza, 1998).

For the purposes of this research, I consider the evolutionary definition of menopause, which is predicated on prolonged survival past reproductive cessation. Classic life-history theory predicts that reproductive senescence should coincide immediately with somatic senescence (Hamilton, 1966; G. C. Williams, 1957). In a seminal paper on the evolution of senescence, Williams theorized that post-reproductive lifespan should not exist for any species and likened selection operating on infertility to selection operating on death (G. C. Williams, 1957). Humans are an obvious exception to this theory, with women regularly living decades past reproductive termination, even among contemporary hunter-gatherer societies (Hawkes et al., 1997). Menopause poses a conundrum for evolutionary biologists, as it raises questions surrounding how a seemingly maladaptive trait originated and has persisted.

The Rarity of Menopause

One meta-analysis found that post-reproductive lifespans are relatively common among mammals, but these findings are based on the definition of significant post-reproductive lifespan as exceeding one interbirth interval plus two standard deviations (Cohen, 2004). That methodology was shown to be inappropriate and statistically unsound, as it does not consider the age-increasing nature of interbirth intervals and has high rate of type I error (Levitis & Lackey, 2011). Levitis and Lackey (2011) introduced a novel measure for post-reproductive lifespan known as post-reproductive representation (PrR), which helps to eliminate biases associated with other measures. PrR is calculated for an average newborn and is given by the ratio of expected post-reproductive adult years lived (T_M) to total expected adult years lived (T_B). For populations with constant size and growth rate (stationary populations), PrR gives the proportion of adults living in a post-reproductive state. For populations of variable size but constant rate (stable populations), PrR denotes the average proportion of the adult lifespan spent in a post-reproductive state (Levitis & Lackey, 2011). Currently, there is no agreed upon value for the proportion that distinguishes menopausal species from non-menopausal species, but, for this thesis, I will consider the cut-off value of 0.25.

Ellis, Franks, Nattrass, Cant, et al. (2018) calculated female PrR values for 52 species and found that only three showed values significantly greater than zero, indicating that post-reproductive periods for most species comprise a small and insignificant proportion of total adult lifespan (a selection of sampled species is summarized in Table 1.1). Human Hadza hunter-gatherers (*Homo sapiens;* PrR = 0.443), killer whales (*Orcinus orca*; PrR = 0.309) and short-finned pilot whales (*Globicephala macrorhyncus*; PrR = 0.26) each are characterized by over 25% of adult female

lifespan lived by reproductively inactive females. These results indicate that humans, killer whales and short-finned pilot whales are among the only mammal species that experience menopause (Johnstone & Cant, 2010). However, recent evidence tracing age-specific ovarian corpora counts suggests that narwhals (*Monodon monoceros;* PrR = 0.29) and beluga whales (*Delphinapterus leucas;* PrR = 0.27) also might exhibit menopause (Ellis, Franks, Nattrass, Currie, et al., 2018; Table 1.1). Like humans, killer whales and short-finned pilot whales are long-lived species, with killer whales reproducing from ages 12 to 40 years and capable of living up to 90 years (Croft et al., 2015). Short-finned pilot whales typically reproduce from ages 7 to 35, with the oldest killer whales living until age 60 (Croft et al., 2015).

Table 1.1: Species and calculated post-reproductive representations (PrRs). Bold values represent PrR values ≥ 0.25. 1: (Ellis, Franks, Nattrass, Cant, et al., 2018); 2: (Levitis & Lackey, 2011); 3: (Ellis, Franks, Nattrass, Currie, et al., 2018).

Species	**Post-Reproductive Representation (PrR)**
Arctic Fox (*Vulpes lagopus*)	0.002[1]
Leopard (*Panthera pardus*)	0.012[1]
Moose (*Alces alces*)	0.02[1]
Plains zebra (*Equus quagga*)	0.006[1]
Raccoon (*Procyon lotor*)	0.004[1]
Walrus (*Odobenus rosmarus*)	0.018[1]
Brown bear (*Ursus arctos*)	0.002[1]
Wild chimpanzee (*Pan troglodytes*)	0.006[1] - 0.018[2]
Captive chimpanzee (*Pan troglodytes*)	0.23[2]
Human – Hunter-gatherers (*Homo sapiens*)	**0.42 - 0.48**[1,2]
Human – Least developed countries (*Homo sapiens*)	**0.46 - 0.49**[2]
Human – More developed countries (*Homo sapiens*)	**< 0.68**[2]
Short-finned pilot whale (*Globicephala macrorhynchus*)	**0.26**[1]
Killer whale (*Orcinus orca*)	**0.309**[1]
Beluga whale (*Delphinapterus leucas*)	**0.27**[3]
Narwhal (*Monodon monoceros*)	**0.29**[3]

Menopause is not observed in wild chimpanzees (*Pan troglodytes*; PrR = 0006), the closest living relatives to humans (Ellis, Franks, Nattrass, Cant, et al., 2018). However, based on changes in estrous cycling and hormone profiles that mirror those seen in humans, captive chimpanzees might experience menopause (Videan et al., 2006), though they narrowly miss the cut-off criterion, with PrR = 0.23 (Levitis & Lackey, 2011). This indicates that human menopause evolved sometime after the divergence between human and chimpanzee lineages, which is estimated to have taken place approximately 6 million years ago (Glazko & Nei, 2003). Menopause has been observed in all human populations, including contemporary hunter-gatherers (PrR = 0.42-0.48; !Kung, Ache, and Hadza peoples) and United Nations-designated "least developed" (PrR = 0.46-0.49) and "more developed" countries (PrR < 0.68) (Ellis, Franks, Nattrass, Cant, et al., 2018; Levitis & Lackey, 2011). A connection between level of "development" and extent of post-reproductive lifespan exists, but the presence of menopause even among hunter-gatherers, the closest example of humans living in natural environments and practicing natural fertility, suggests that menopause is not just a consequence of advancements in medicine or technology. The omnipresence of menopause across all extant human populations suggests that this trait evolved at a time that predates great human migration events (Mattern, 2019). Some authors have suggested that menopause arose much earlier in hominid life history, during a time marked by rapid encephalization and bipedalism, which imposed constraints on pelvic width (Martin, 1983; Peccei, 2001). These events contributed to the uniquely human phenomenon of secondary altriciality, wherein humans are born dependent for an extended period of time due to underdeveloped infant brain sizes. The fossil record indicates that the pelvic width-limited size of fetal brain development was likely reached about 1.5 million years ago, just before the appearance of *Homo erectus* (Martin, 1983).

Hypotheses on the Evolutionary Origins of Menopause

Lifespan Artifact Hypothesis

The lifespan artifact hypothesis states that ancestral human lifespan was shorter and adaptations toward extended lifespan have allowed for survival past the innate reproductive period (Weiss, 1981). This perspective suggests that menopause is simply an epiphenomenon of the expansion of human life expectancy. Support for the lifespan artifact hypothesis comes from chimpanzees that have been observed to experience extended post-reproductive lifespan in captivity (Videan et al., 2006), presumably due to decreased exposure to mortality hazards. A weakness of this hypothesis is that it does not explain why menopause is observed only in females while male reproductive senescence approximately coincides with biological senescence despite lengthening of lifespan.

Mother Hypothesis

First proposed by Williams (1957), the mother hypothesis posits that menopause arose as mothers strategically ceased reproducing earlier to avoid high maternal mortality risk associated with geriatric pregnancies and instead diverted resources and care toward living offspring. Mothers ensure their own fitness by promoting the survival of dependent offspring and the potential for those offspring to reproduce. This strategy is supported by long dependency periods (altriciality) and evidence that maternal death is linked to severely compromised survival outcomes for young children compared to those with live mothers (Sear et al., 2002).

Grandmother Hypothesis

The grandmother hypothesis is one of the most well-known explanations for menopause and is often considered in conjunction with the mother hypothesis. The grandmother hypothesis is rooted in kin selection theory and posits that menopause evolved through inclusive fitness benefits associated with older, post-reproductive females helping to rear or support the survival of grand-offspring (Hawkes et al., 1998). The known menopausal species provide support for the grandmother hypothesis, as they have been shown to exhibit 'grandmothering.' For example, studies of human populations with natural fertility (populations that do not make conscious efforts to limit reproduction) in rural Gambia and 18-19TH century Finland have shown that grandmothers promote survival and reproductive success among their grand-offspring (Lahdenperä et al., 2004; Sear et al., 2000). Killer whales have been shown to exhibit grandmothering through the sharing of ecological information (Brent et al., 2015). Researchers have observed that post-reproductive females tend to lead group migration toward salmon foraging grounds, especially during times of food scarcity, which is thought to be linked to benefits to survival and reproductive success. The relatedness of a female killer whale to her group interestingly increases with age, and, as such, older females accrue more benefits from preserving kin than do their younger counterparts (Brent et al., 2015).

Antagonistic Pleiotropy

Pleiotropy occurs when a single gene controls at least two distinct traits (Stearns, 2010). Pleiotropy is considered to be antagonistic when a single gene has opposing effects on fitness at different life stages (G. C. Williams, 1957). More specifically, genes associated with deleterious effects later in life may be favoured if they are exceeded by beneficial effects earlier in life. Hamilton (1966) provided support for this hypothesis with a mathematical model showing that, as survival tends to decrease with age, genes promoting fecundity later in life would be removed by death, and, thus, earlier reproduction generally would be favoured over later reproduction. The model also provided landmark evidence that selective forces acting on genes affecting survival decrease monotonically from adulthood onwards (Charlesworth, 2000). Together, these findings demonstrate how pleiotropic genes would persist in a population given the strong selective forces acting on fertility early in life and weaker selection for survival later in life. Menopause is proposed to have evolved as a result of antagonistic pleiotropy acting on the process of follicular depletion (Wood et al., 2000). Follicles within the ovaries hold immature oocytes. Oocyte count reaches a peak of approximately 7 million at 5 months gestational age and then quickly falls to 2 million by birth (Baker & Zuckerman, 1963). Surprisingly, ovulation accounts for a relatively small proportion of loss, and programmed degeneration, known as follicular atresia, is the primary cause of depletion (Gosden & Faddy, 1998). Mathematical modeling suggests that clinical menopause coincides with the follicular reserve falling below a threshold value of 1000 follicles (Faddy et al., 1992). Therefore, menopause is thought to result from the antagonistically pleiotropic relationship of positive selection for specific atresia rate and natal follicle supply that allow for the maintenance of regular cycles during young adulthood with the cost of reproductive breakdown later in life (Wood et al., 2000).

Mate-Choice Hypothesis

The mate-choice hypothesis is unique in that it is the only explanation for the evolution of menopause based on sexual selection. It states that mating restricted between adult males and young adult females would eventually weaken selection acting on females later in life, driving

the accumulation and fixation of deleterious mutations affecting fertility in older females (Morton et al., 2013; M. Takahashi et al., 2017). Ultimately this change in mating behaviour would result in early reproductive senescence and thus menopause. The adult male-young female mating dynamic could occur through two possible cases, younger females out-competing older females for mates or males demonstrating a preference for younger females. This hypothesis was published in association with supporting results obtained through computer modeling, described in detail in the following section (Morton et al., 2013).

Computational Modeling of Menopause

The evolutionary origin of menopause has been researched extensively through analytical modelling, which involves the use of mathematical equations and functions to describe a system (Hamilton, 1966; Hill & Hurtado, 1991, 1996; R. D. Lee, 2003; Paquin et al., 2020; Pavard et al., 2008; Rogers, 1993; Shanley et al., 2007; Tuljapurkar et al., 2007). However, computational modelling, involving computer simulation, is a relatively new and powerful approach that enables researchers to explore extremely rapidly many complex scenarios (Edmonds & Hales, 2005). Unlike deterministic analytical models, computer simulations account for stochasticity and allow for the study of a multitude of possible evolutionary outcomes (de Oliveira, 2002). One particularly powerful type of computer simulation is the agent-based model, wherein agents within a computational model act as individuals according to prescribed rules and characteristics (de Oliveira, 2002; Edmonds & Hales, 2005). This contrasts with standard statistical models, which involve groups (Edmonds & Hales, 2005). To my knowledge, only eight studies published to date explore the evolution of menopause through computational simulation.

The earliest computational model developed to study menopause (Moss de Oliveira et al., 1999) adapted an existing model of biological aging (Stauffer, 2009) and a general organismal model in which each individual was coded as a 32-bit string that functions as a "chronological genome", with each bit representing a time interval in the potential lifespan and as well as a gene (Moss de Oliveira et al., 1999). The computational model accounted for deleterious disease-causing genes and mortality risk associated with competition for space and resources. Two main variables were considered: "maternal care risk" and "reproductive risk". The maternal care risk variable represented a juvenile dependent period, wherein a mother's death resulted in all dependent offspring dying. The reproductive risk variable represented maternal mortality associated with childbirth, a risk that increased with number of deleterious mutations. In each simulation, reproductive cessation initially coincided with maximum potential lifespan, at 32 time intervals. This aligned with the assumption that old-age fertility eventually was selected against. Under simulations involving both maternal care risk and reproductive risk, the average age at reproductive cessation declined from 32 to 17.4 time intervals and remained relatively stable during the 100000 time intervals simulated. This mid-life end to reproduction is similar to human menopause and was absent in null simulations with both variables inactive. This provides support for the mother hypothesis, suggesting that post-reproductive lifespan might have evolved as a way for older mothers to ensure survival for their dependent offspring while avoiding high-risk pregnancies (Moss de Oliveira et al., 1999). However, the biological aging model that served as a basis for the computational model has been criticized for its inability to scale its results appropriately from a 32-bit genome to organisms with greater complexity, such as humans with genomes in the order of $2x10^4$ genes (Łaszkiewicz et al., 2005; Malarz, 2011).

Another model rooted in the assumption of early reproductive decline tested the effects of mate preference on life history evolution in a population where ancestral female fecundity remained high through to old age (Morton et al., 2013). Age-specific deleterious mutations affecting fertility and mortality were included in this model. When mating was limited to male preference for younger females, a mid-life decline in fecundity characteristic of menopause was observed, whereas no menopause evolved in freely mating simulations. That paper introduced the mate choice hypothesis for menopause, which involves relaxed selection against late-onset fecundity mutations, ultimately leading to premature reproductive cessation (M. Takahashi et al., 2017). With older females essentially eliminated from the mating pool, initially deleterious mutations that diminished fecundity late in life became effectively neutral and quickly accumulated (Morton et al., 2013). Some researchers (Kim et al., 2014) argued that such a decline in female fertility might be attributable to population size maintenance, which was included in the computational model and promotes overly strong competition between females. They also noted that, while male preference for younger females has been observed in humans, male chimpanzees actually have been shown to prefer older mates (Kim et al., 2014; Muller et al., 2006). The computational model authors (Morton et al., 2013), however, originally had suggested that the reverse relationship might have been true – mate choice evolved due to younger females outcompeting older females for access to males.

Several computational studies focus on the role that grandmothering plays in the evolution of post-reproductive lifespan. One such study (R. Lee, 2008) simulated a single-sex, female population with food sharing within matriarchal kin groups. The model included initial production, consumption, and fertility values based on data from hunter-gatherer populations and age-specific deleterious mutations affecting mortality risk. Simulations showed that intergenerational resource sharing resulted in the evolution of post-reproductive lifespan whereas population-level sharing precluded menopause evolution. These results lend support to the grandmother hypothesis, as post-reproductive females promote their own survival through sharing resources with closely related kin. One weakness of the model is that daughters inherited their mothers' genotypes with a small probability of mutation, which resulted in an 85% chance of producing genetically identical mother-daughter pairs. This high level of relatedness between individuals likely enhanced selection to unrealistically high levels.

Kim et al. (2012) created a computational model that was further developed and used in two follow-up studies (Kim et al., 2014, 2019). Each of the three studies considered Williams' trade-off between longevity and youthful vigour (G. C. Williams, 1957) in that males with longer life expectancies lose their vigour and become less competitive for mates. The characteristic of interest in the computational model was grandmothering, simulated as post-reproductive females with no dependents that took on the care of any weaned dependent in the population. In the first model (Kim et al., 2012), grandmothering was introduced to populations with initial expected adult lifespan similar to that characterizing chimpanzees and fixed age at reproductive cessation. The simulations showed that the average expected adult lifespan transitioned from chimpanzee-like values to modern human-like values within 24000 to 60000 years (Kim et al., 2012).

The second Kim et al. (2014) model sought to improve the realism of the initial model by converting it to an agent-based model that incorporated stochasticity with non-discrete time intervals. With the adjusted model, a similar transition from great-ape-like to modern human-like

average expected adult lifespan was recorded, but this evolution was observed to take 5-10 times longer than the first model. Interestingly, in some simulations, the expected lifespan remained relatively stable even with grandmothering. This suggests that, for populations with grandmothering, a long term great-ape-like equilibrium lifespan ultimately initiates the menopausal transition (Kim et al., 2014). Criticism for the first two models (Kim et al., 2012, 2014) lies in the fact that they fail to track lineages and thus are unable to selectively apply grandmothering to kin rather than the entire dependent population (Kim et al., 2012, 2014). Therefore, the models cannot truly account for the fitness benefits associated with grandmothering. Furthermore, the grandmothers in these models adopt dependents, freeing mothers for their next birth without compromising survival for their other offspring (Kim et al., 2012, 2014). This representation is unrealistic because grandmothers shoulder only partially the childbearing burden, which is shared with mothers (Hawkes et al., 1997).

The aforementioned issues associated with first two Kim et al. (2012, 2014) models were corrected in the third (Kim et al., 2019), with matrilineal lineage tracking and an amendment to grandmothering. In the third model, grandmothering manifests in food sharing and survival benefits rather than full-scale adoption. The fixed age at reproductive cessation from the previous two models also was changed to a heritable trait subject to mutation. When simulations were run for 1000000 years, half the simulations achieved the great-ape-like to human-like expected adult lifespan transition, but the other half remained at the great-ape-like equilibrium. The authors also observed that the evolvable age at reproductive cessation only increased marginally compared to the substantial increase in expected adult lifespan (Kim et al., 2019), suggesting that lifespan increased past a fixed age at reproductive decline. Together, the three Kim et al. (2012, 2014, 2019) models provide support for the grandmother hypothesis, showing that grandmothering can induce a shift from an ancestral life history toward post-reproductive life history akin to that characterizing modern humans.

Another model, by Kachel et al. (2011), analyzed impacts from the grandmother effect on the evolution of longevity and reproductive period. Grandmothering manifested as either survival benefits to grandchildren or decreased weaning age. With both initial age at reproductive cessation and lifespan set to 50, simulations showed that both grandmothering manifestations, considered together and separately, had no effect on longevity. These results suggest that the inclusive fitness benefits associated with grandmothering are not strong enough to overcome the weak selection operating on older post-reproductive females. This model provides evidence against the grandmother hypothesis (Kachel et al., 2011).

The most recently published computational model explores different maternal and grandmaternal investment strategies (Pang, 2020). The model accounts for genetic mutation affecting survival and reproduction rates as well as resource competition. The main variables are grandmother survival benefits conferred to un-weaned grandchildren, maternal survival benefits conferred to un-weaned offspring, and long term maternal reproductive and survival benefits conferred to adult offspring. Post-reproductive lifespan was evaluated using PrR. Simulations were run under different combinations of the variables, and only the grandmaternal care paired with long term maternal reproductive or survival benefits produced PrR greater than the threshold for menopause. These results show that the grandmother hypothesis is insufficient to explain the evolution of menopause, rather the grandmother hypothesis must be combined with the maternal

hypothesis. The author notably chose the menopause cut-off value 0.20 based on the values observed in species with menopause compared to those without, however, this value is arbitrary with no consensus in the literature. As well, to compensate for the stochastic noise and weaker selective forces acting on the small simulated population size, the author assumed that the magnitude of grandmothering effects were equivalent to maternal benefits, despite data from a Gambian population exhibiting relatively natural fertility, indicating that the maternal effect is approximately 6 times greater (Pang, 2020; Shanley et al., 2007). Data from the Gambian population also showed that grandmothers provide the largest protective effect to grandchildren directly post-weaning (Shanley et al., 2007) – an important factor that was unexplored in the computational model. Including grandmother-weaned offspring survival benefits in the model likely would confer shortened maternal interbirth intervals and decreased weaning ages.

In this thesis, I explore two concepts computationally for the first time to gain novel insight into the evolution of menopause. One piece of the evolutionary puzzle that is menopause that has not yet been investigated through computational simulation involves elephants and why this organism has not evolved menopause despite sharing key features with menopausal species that align with the lifespan artifact hypothesis and grandmother hypothesis – longevity (Sukumar et al., 1997) and survival benefits conferred to calves living in matrilineal family units (Lahdenperä et al., 2016). This topic is explored in Chapter 2 where I use computational modeling to study how grandmothering, computer simulated as shortened interbirth intervals, impacts post-reproductive lifespan and reproductive success among Asian elephants.

Recently, a hypothesis was proposed that implicates aneuploidy, abnormalities in chromosome number, in the evolution of menopause. Sirard (2011) posits that aneuploidy is a mechanism to deter reproduction at older ages and instead invest resources towards caring for extant kin. This hypothesis is purely hypothetical and has not yet been tested through modeling or empirical studies. In Chapter 3, I situate that hypothesis in an evolutionary context and simulate an early human population with an aneuploidy-avoidant reproductive strategy that promotes survival in order to test this aneuploidy hypothesis.

CHAPTER 2: GRANDMOTHERING AND THE ABSENCE OF MENOPAUSE IN ELEPHANTS

Abstract
Menopause, defined as extensive post-reproductive lifespan, presents an evolutionary puzzle. Traits that are hypothesised to have contributed to the origin and evolution of menopause in humans and some whale species include long lifespan and assistance in rearing of related young by older females. These traits also are observed in elephants, yet menopause is absent. I sought to explore through computational modelling and computer simulation whether elephants could evolve menopause under a variety of degrees of grandmothering, conferred exclusively as decreased interbirth intervals. Using a parameter space defined by interbirth interval and the age at reproductive decline, I found that populations with the greatest post-reproductive lifespans, those with greater interbirth intervals and earlier reproductive cessation, were also most likely to be out-reproduced by contemporary elephants. Conversely, populations with the greatest likelihood of out-reproducing contemporary elephants, those with decreased interbirth interval and extended age at reproductive decline, had limited post-reproductive lifespan that would not be considered menopausal. I identified a small region in the parameter space where populations were both menopausal and reproductively competitive, but most parameter values therein represented biologically unrealistic scenarios. The scenario that is biologically feasible and meets the criteria for both menopause and reproductive success involves an interbirth interval of 4 years and an age at reproductive cessation of 40. Elephants are constrained by the reproductive physiology and life history that have evolved in their lineage, rendering menopause virtually impossible. These results provide novel computational insight into how menopause potentially could evolve in elephants under specific circumstances of grandmothering, modeled as reduced interbirth intervals

Introduction

Like other menopausal species, elephants are long-lived with a maximum lifespan of about 80 years (Sukumar et al., 1997), and calves have been shown to gain survival benefits from living with grandmothers (Lahdenperä et al., 2016). In particular, for mothers younger than 20 years, cohabitation with grandmothers decreased calf mortality risk by a factor of 8 when compared to grandmothers living in another location (Lahdenperä et al., 2016). Evidence also exists that older females contribute social knowledge gained with age to members of their groups, as groups with older matriarchs are better able to respond to and discriminate between vocalizations compared to groups led by younger matriarchs (McComb et al., 2001). Groups led by older females also produced significantly more offspring per female reproductive year than those led by younger females, indicating a reproductive benefit associated with older females (McComb et al., 2001).

Despite these shared traits with menopausal animals, elephants have not been shown to exhibit menopause, with pregnancies and births observed up to age 60 (Smuts, 1975). The female PrR value for African elephants (*Loxodonta africana*) has been calculated to be 0.035, which is not significantly different from zero (Ellis, Franks, Nattrass, Cant, et al., 2018). Female Asian elephants (*Elephas maximus*) tend to have longer post-reproductive lifespans, with one population of semi-captive Asian elephants showing a PrR value of 0.128, however, this value is not considered menopausal (Lahdenperä et al., 2014). This population showed an average female

post-reproductive lifespan of 5.9 years (Lahdenperä et al., 2014). Another study, of semi-captive Asian elephants, found a slightly higher PrR value of 0.162 (Chapman et al., 2019).

This presents a further conundrum as female elephants enter an estrus cycle every 12-18 weeks, made up of follicular, ovulatory, and luteal phases, but the window for conception lasts only 2-10 days (Vidya & Sukumar, 2005). Correspondingly, once a year, males enter a period known as musth, characterized by increased levels of testosterone, aggression, and sexual behaviour (Eisenberg, 1980). Asian elephants begin spermatogenesis as early as age 7 but generally do not develop to adult stature or undergo musth until approximately age 15, at which point the males reach sexual maturity (Eisenberg, 1980; Vidya & Sukumar, 2005). Females reach sexual maturity at 11-14 years (Eisenberg, 1980). Elephants also exhibit extremely long interbirth intervals, lasting on average 4-6 years (de Silva et al., 2013; Lahdenperä et al., 2014), and the longest gestational periods of all mammals, with an average gestational period of 20-23 months (Hildebrandt et al., 2006). Elephants most frequently produce only one offspring at a time, with a low rate of twinning, 1% (Hildebrandt et al., 2006). The infrequency of conception and high degree of maternal investment suggest that elephants likely would thrive under the direct and indirect fitness benefits that have been associated with menopause.

While both males and females mate with multiple partners during a given estrus period, elephants generally are considered to exhibit a polygynous mating system, given the aforementioned observation that females typically only produce one offspring per pregnancy, sired by a single male. Female mate choice has been observed, as females tend to prefer older males experiencing musth (Vidya & Sukumar, 2005)

Interbirth intervals – time periods between successive births – tend to increase with age for most animals, including humans, killer whales, and short-finned pilot whales (Lahdenperä et al., 2014). However, elephant interbirth intervals have been shown to decrease with female age. In a study of semi-captive Asian elephants, the average interbirth interval was found to be 10.1 years for the youngest cohort, consisting of mothers younger than 10 years old, 6 years for the mid-age cohort, aged 20-30 years, and 4.7 years for the oldest cohort, older than 40 years (Lahdenperä et al., 2014). Interestingly, an interplay exists between grandmothering and interbirth intervals, as another study showed that, if a grandmother lived in the same region as her daughter and successive grandcalves, her daughter's interbirth interval decreased by an average of 21% compared to daughters and mothers who lived apart (Lahdenperä et al., 2016).

Elephant fecundity curves tend to increase sharply around age 10, reach a relatively stable maximum value of around 0.1-0.2, and then show gradual senescence at approximately age 40-50 (Lahdenperä et al., 2014; Moss, 2001; Wittemyer et al., 2013). When compared to pre-industrial human populations, elephants do not show the same complete and abrupt loss of fertility characteristic of menopause seen in humans (Lahdenperä et al., 2014).

I created a computational model that simulates two groups of elephants to test the effects of grandmothering, manifested as reduced interbirth interval, on post-reproductive lifespan and other demographic characteristics.

Methods

The model generates a starting population of $N_i = 25$ elephants. Characteristics such as viability (alive or dead), sex, age, reproductive status, and group membership are tracked for each individual. Each individual in the starting population is pseudo-randomly assigned a sex, group identifier, and age between 1 and the maximum potential lifespan of 80 years.

Viability is designated as a value of either 1 or 0, indicating that the individual is alive or dead, respectively. The viability status is determined by generating a pseudo-random real number in the range of 0 to 1 and comparing that value to a mortality risk curve. If the generated number is greater than the mortality risk at the individual's given age, then the individual is assigned a viability value of 1. If the generated number is lower than the individual's age-specific mortality risk, then the individual is assigned a viability value of 0. Individuals with viability = 0 are cleared from the live population after each year of the simulation and transferred to a dead population.

For every year that the simulation runs, potential mothers and fathers are pseudo-randomly selected from the population and paired. Mating potentially occurs only if both individuals have reached the age at sexual maturity. Females who recently have given birth can be paired for mating only if their interbirth interval has elapsed. Potential offspring are subject to risk at conception (t=0), as determined by the mortality risk curve. If the pseudo-randomly generated number between 0 and 1 is greater than the risk at conception, then the pair will produce an offspring that then joins the population. If the value is lower than the risk at conception, then the mate pairing results in no conception. This process of pairing and mating is iterated each year, and the age of each individual increases by one year. Total population size is unlimited, so population growth is not controlled and occurs freely. Previous versions of the model instituted a carrying capacity such that, once a threshold value of population was reached, the oldest individuals in the population were culled, but this often resulted in an unrealistically young population.

Each individual belongs to one of two groups – the natural group (N) or the experimental group (E) – that can differ in interbirth intervals and fecundity schedules. Both groups follow the mortality risk curve obtained from a population of captive Asian elephants, living in Indian timber camps (Sukumar et al., 1997; Figure 2.1). The natural group possesses an interbirth interval of 5 years, similar to the interval observed in Asian elephant populations (Lahdenperä et al., 2014), whereas the experimental group has values for interbirth interval ranging from 2 to 6 years. The interbirth interval for the experimental group (IBI-E) is a parameter that indirectly accounts for the effects of grandmothering under the assumption that interbirth intervals can be reduced if the maternal role of nursing and caring for dependent offspring is taken on by older females in the population.

For both groups, fecundity starts at 0 from birth to the age at sexual maturity, where it rises to a value of 1. Fecundity stays stable until the age at reproductive decline (ARD), at which point it either follows a linear negative slope to the age at reproductive cessation (ARC) in the natural population or immediately drops to 0 in the experimental group. The linear negative slope is a simplification of the reproductive senescence observed in contemporary elephant fecundity curves. The immediate drop in fecundity observed in the experimental group accounts for

behavioural changes in the population to stop reproducing at earlier ages. Fecundity has been shown to decline around the age of 40 to 50 within Asian and African elephant populations (Lahdenperä et al., 2014; Moss, 2001; Wittemyer et al., 2013), but ARD for the natural group is variable in the model to test whether subtle changes in fecundity schedules of contemporary elephants would have an effect on post-reproductive lifespan. Parameter values for ARD range from 30 to 55 years, in intervals of 5 years. ARC is fixed at 60 years. See Figure 2.1 for examples of natural and experimental fecundity curves.

Individuals are allowed to mate freely between the two groups, but group membership is passed on maternally to offspring (e.g., a mother belonging to the experimental group who mates with a father belonging to the natural group will produce an offspring belonging to the experimental group). Unlimited resources exist within the model, so the two groups do not compete for resources. Rather, the two groups are in competition only with respect to reproductive success.

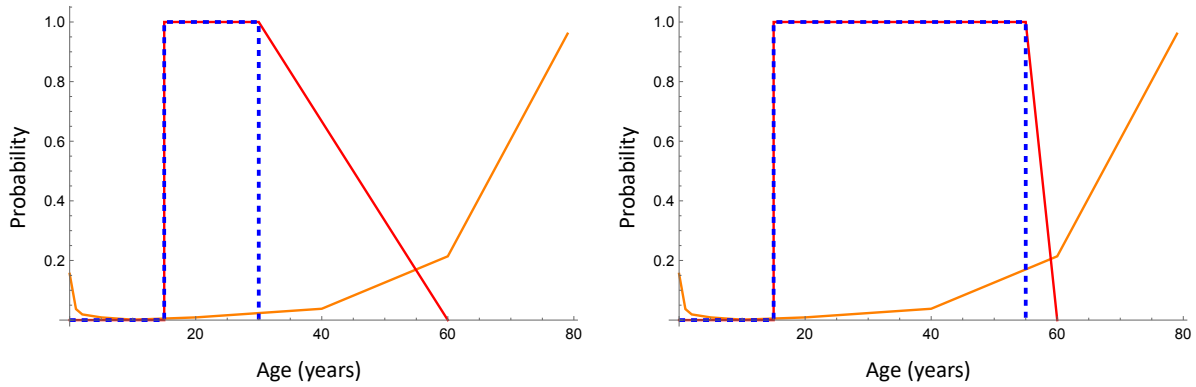

Figure 2.1: Natural fecundity (solid red), experimental fecundity (dashed blue), and mortality risk curves (orange). Left: Age at reproductive decline (ARD) = 35, Right: ARD=55.

Together, the two variables, IBI-E and ARD establish a parameter space that can be explored through computer simulations. Each set of parameter values {IBI-E, ARD} was run as a simulation for 100 time intervals. At the end of each simulation (t=100), the mean age at death (AD), mean age at last reproduction (ALR), and mean number of offspring were calculated for both groups from the pool of all adult females in the dead population over time (viability = 0). Mean AD, mean ALR, and age at sexual maturity allow for the calculation of a simple metric for assessing whether menopause is present in the population, proportion of adulthood non-reproductive (PAN; equation 2.1). The numerator for PAN is the difference between age at death and age at last reproduction, which represents post-reproductive lifespan. The denominator calculates the difference between age at death and age at sexual maturity, or the adult lifespan. Populations with PAN values ≥ 0.25 were considered to be menopausal.

$$PAN = \frac{age\ at\ death\ -\ age\ at\ last\ reproduction}{age\ at\ death\ -\ age\ of\ sexual\ maturity} \qquad (2.1)$$

Computer simulations were run for each pair of IBI-E and ARD parameter values, replicated 100 times, and the following data were collected for both groups: mean AD, mean ALR, mean number of offspring, mean PAN, and proportion of replicates where the experimental group out-reproduced the natural group (PR-E). PR-E was used as a measure of reproductive success,

where experimental populations with PR-E > 0.5 were considered to be reproductively successful or competitive over the natural group.

The program was coded using the Wolfram language on Mathematica v.13.0.1.0. and run on a MacBook Air (running macOS Monterey v.12.2.1).

Table 2.1: Summary of parameter values

Parameter	**Value**
Time (t)	100
Initial population (N_i)	25
Age at sexual maturity	15 years
Age at reproductive decline (ARD)	30, 35, …, 55 years
Age at reproductive cessation (ARC)	60 years
Interbirth interval – natural (IBI-N)	5 years
Interbirth interval – experimental (IBI-E)	2, 3, …, 6 years

Results

The experimental group out-reproduced the natural group in > 50% of replicates for almost all simulations where IBI-E ≤ 4, except for the parameter set of {ARD =30, IBI-E = 4} (Table 2.2). PR-E tended to increase with ARD and decrease against IBI-E. At one extreme, the experimental group out-reproduced the natural group in 99% of replicates for {ARD = 55, IBI-E = 2}, and at the other extreme succeeded in only 9% of replicates for {ARD = 30, IBI-E = 6}.

Table 2.2: Proportion of replicates, out of 100 replicates, where the experimental group out-reproduced the natural group (PR-E). ARD, age at reproductive decline; IBI-E, interbirth interval (experimental).

		ARD (years)					
		30	35	40	45	50	55
IBI-E (years)	2	0.81	0.91	0.97	0.95	1	0.99
	3	0.64	0.79	0.86	0.96	0.89	0.91
	4	0.31	0.63	0.65	0.67	0.67	0.81
	5	0.19	0.31	0.3	0.45	0.48	0.49
	6	0.09	0.15	0.21	0.26	0.22	0.29

Menopausal PAN values ≥ 0.25 within the experimental group (PAN-E) formed a polygonal surface in one corner of the parameter space defined by ARD and IBI-E (highlighted in red, Figure 2.2), where all IBI-E values in combination with ARD = 30, IBI-E > 2 in combination with ARD = 35, and all IBI-E > 3 with ARD = 40 were considered menopausal. The peak PAN-E value of 0.54 ± 0.088 was reached at {ARD = 30, IBI-E = 6} (Table S2.1). In general, PAN-E values increased with IBI-E and decreased as ARD increased. PAN values for the natural group showed menopausal values of 0.25 only for ARD = 30. The PAN-N values tended to decrease as

ARD increased and stayed relatively level across IBI-E values, as expected, because interbirth intervals were fixed at 5 years for the natural group (Table S2.2).

When comparing PR-E and PAN-E (Figure 2.3), one can see that the simulations with highest reproductive success (PR-E) also had the lowest PAN-E values. The opposite relationship also can be observed, as the simulations with highest PAN-E tended to have the lowest PR-E values. A select number of simulations met the criteria for both reproductive success (PR-E ≥ 0.5) and menopause (PAN-E ≥ 0.25) and they tended to align with the diagonal of the parameter space. These included ARD =30 in combination with IBI-E values of 2 and 3 years, ARD = 35 for IBI-E values of 3 and 4 years, and ARD = 40 for IBI-E=4.

Mean AD for the experimental group exceeded that of the natural group for almost all ARD values with IBI-E = 6, except for ARD = 45 (Figure 2.4). The experimental group also died at older ages than did the natural group at IBI-E = 4 for ARD values of 30 and 55 years. Experimental AD tended to decrease with IBI-E and reached a maximum value of 40.83 ± 4.98 years at {ARD = 35, IBI-E = 6} (Table S2.3). Mean AD for the natural group remained fairly consistent throughout all simulations, reaching a peak of 39.2 ± 3.37 years at {ARD = 30, IBI-E = 4} (Table S2.4).

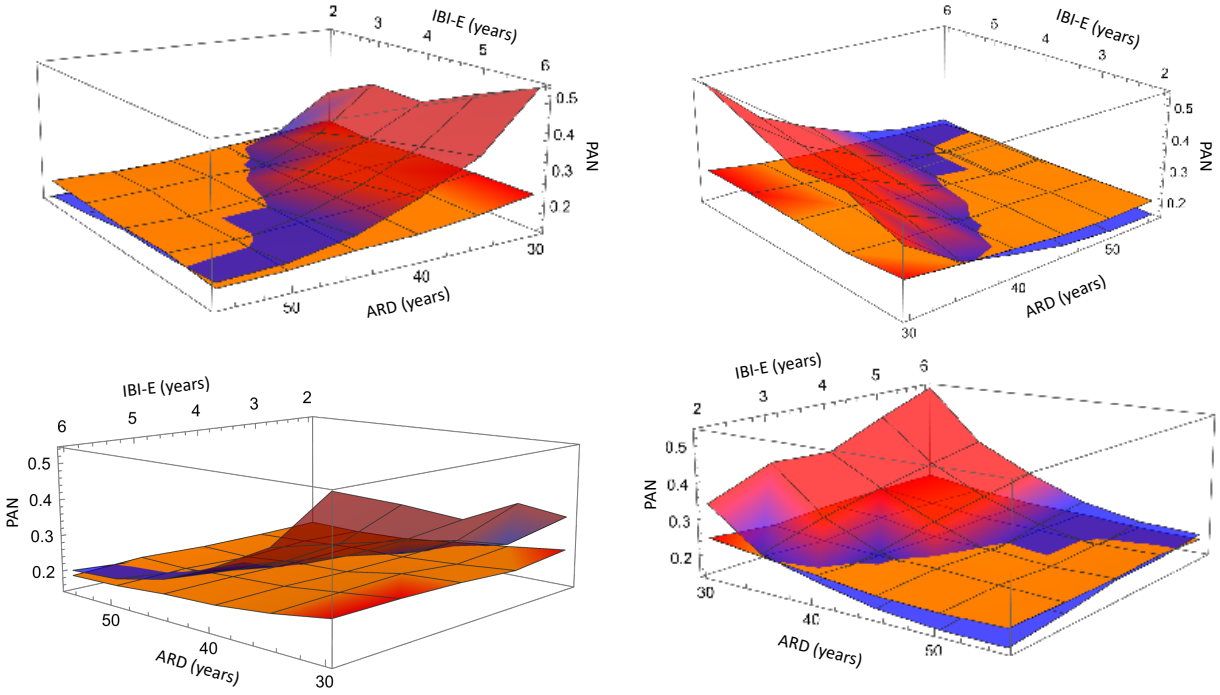

Figure 2.2: 3D plot showing mean proportion of adulthood non-reproductive (PAN) for the experimental group (blue) and the natural group (orange), from different viewpoints. Red regions indicate menopausal PAN values ≥ 0.25 for the experimental group. IBI-E, interbirth interval (experimental); ARD, age at reproductive decline.

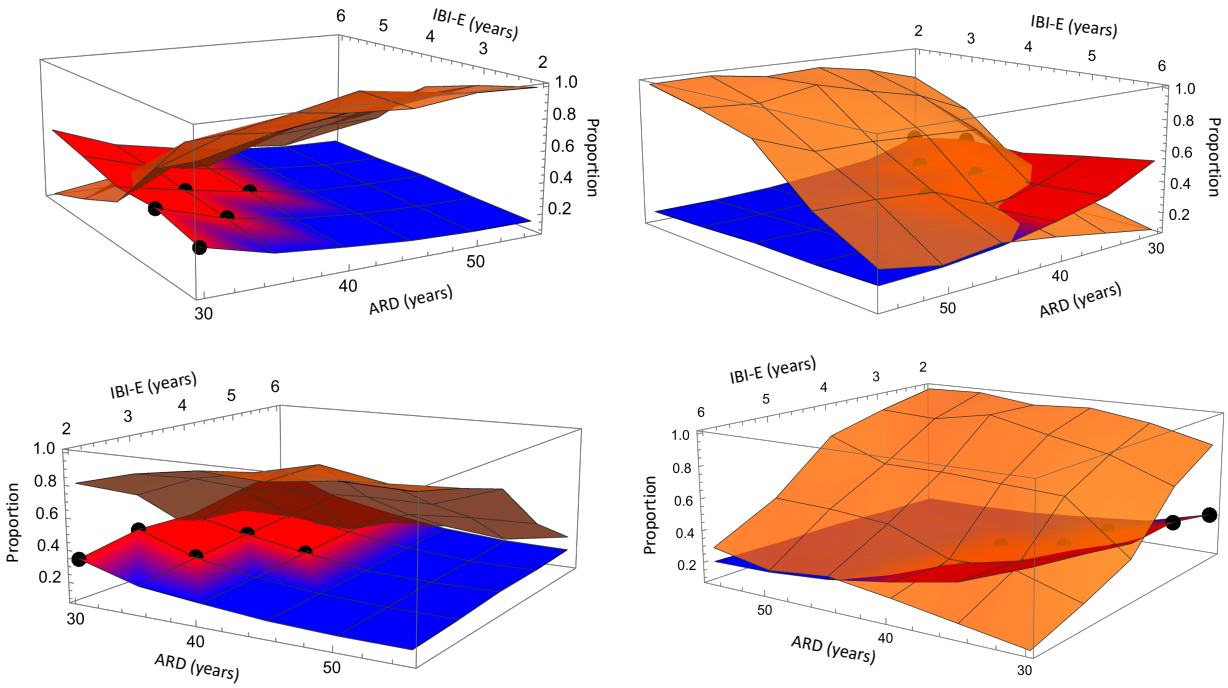

Figure 2.3: 3D plot showing proportion of replicates where the experimental group out-reproduced the natural group (PR-E), in orange, and the proportion of adulthood non-reproductive for the experimental group (PAN-E), in blue, from various viewpoints. Red regions indicate menopausal PAN values ≥ 0.25. Black points indicate simulated populations that were both menopausal (PAN ≥ 0.25) and reproductively successful (PR-E > 0.5). IBI-E, interbirth interval (experimental); ARD, age at reproductive decline.

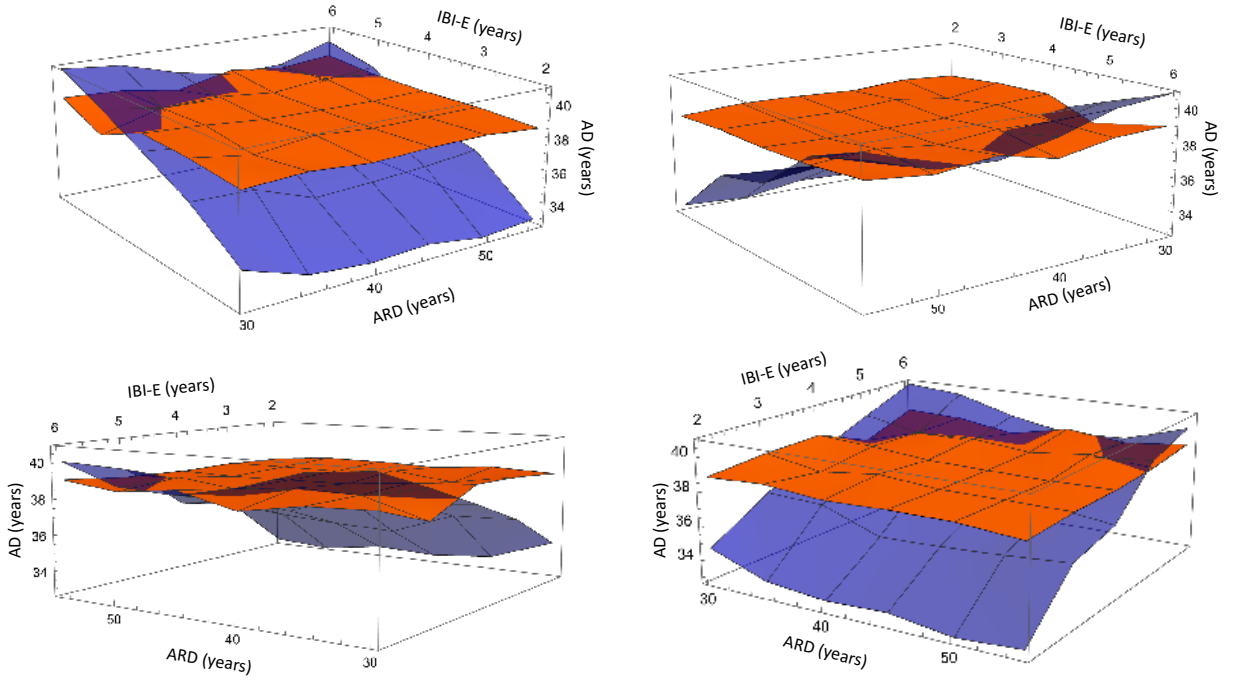

Figure 2.4: 3D plot showing mean age at death (AD) for the experimental group (blue) and the natural group (orange), from different viewpoints. IBI-E, interbirth interval (experimental); ARD, age at reproductive decline.

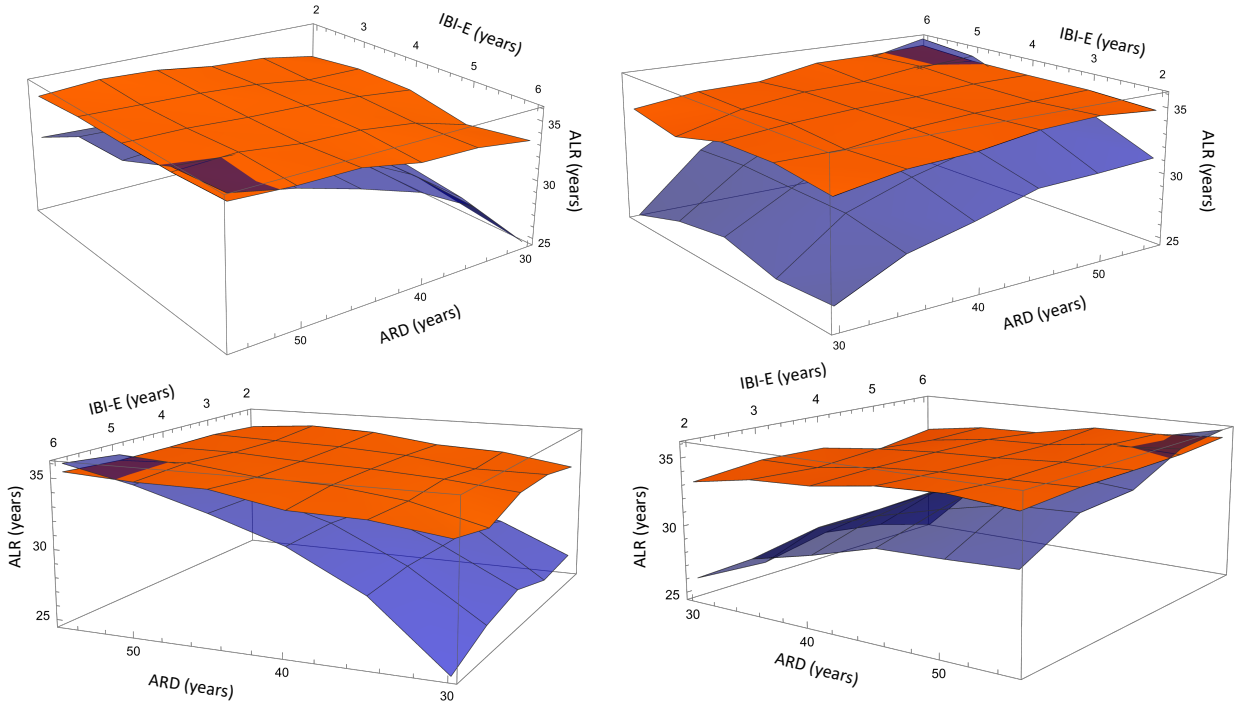

Figure 2.5: 3D plot showing mean age at last reproduction (ALR) for the experimental group (blue) and the natural group (orange), from different viewpoints. IBI-E, interbirth interval (experimental); ARD, age at reproductive decline.

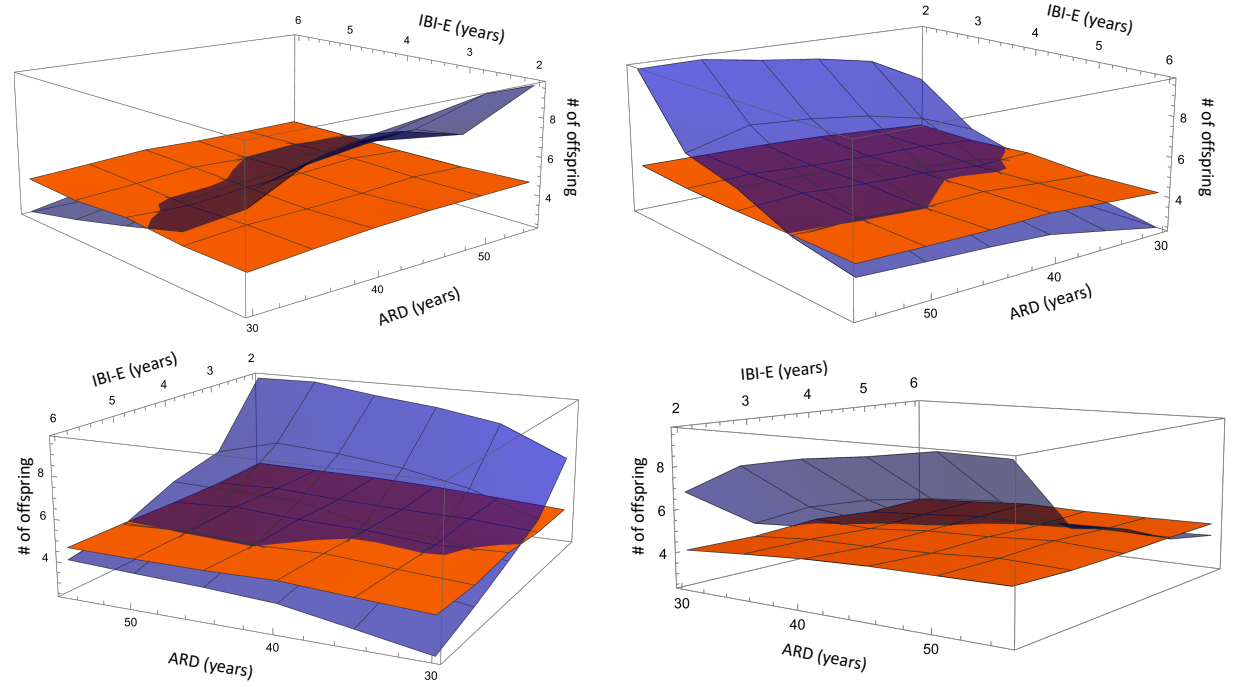

Figure 2.6: 3D plot showing mean number of offspring for the experimental group (blue) and the natural group (orange), from different viewpoints. IBI-E, interbirth interval (experimental); ARD, age at reproductive decline.

The experimental group showed very limited success over the natural group with respect to ALR (Figure 2.5). Only two parameter combinations resulted in the experimental group reproducing at later ages than the natural group – {ARD = 55, IBI-E = 5} and {ARD = 55, IBI-E = 6}. Mean ALR tended to decrease with IBI-E for the experimental group and stayed relatively constant throughout all simulations for the natural group (Tables S2.5, S2.6). The experimental and natural groups reached similar maximum values of 35.97 ± 3.99 and 35.38 ± 3.31 years, respectively, at {ARD = 50, IBI = 6}.

The experimental group produced a peak value of 9.65 ± 0.86 offspring at {ARD = 55, IBI-E = 2}, compared to a maximum of 4.75 ± 0.71 offspring produced in the natural group at {ARD = 50, IBI-E = 4}. The experimental group produced more offspring than did the natural group in the majority of simulations (Figure 2.6). Experimental mean offspring number exceeded natural mean offspring number for all simulations of IBI-E ≤ 4, except for {ARD = 30, IBI-E = 4}. Greater mean offspring values were also seen in the experimental group at IBI = 3 for ARD values of 45 and 50 years (Tables S2.7, S2.8).

Discussion

The goal of this study was to create a computational model to simulate the effects of grandmothering, represented as decreased interbirth intervals, on post-reproductive lifespan and other demographic features in elephants. I found that, within simulations where the experimental group achieved the greatest post-reproductive lifespans, those defined by longer interbirth intervals and earlier end to reproduction, also tended to show the lowest likelihoods of reproductive success over natural group populations. Conversely, in simulations where the experimental group showed the highest rates of reproductive success, typically those with shorter interbirth intervals and delayed reproductive cessation, post-reproductive lifespan values tended to be minimal. Specific combinations of decreased interbirth interval and earlier age at reproductive cessation led to both reproductive success *and* menopause. Some of these combinations are biologically unrealistic as they require substantial to total adoption of care by older females as well as considerable cuts to reproductive lifespan. For example, one of the simulations that met the criteria for both reproductive success and menopause was characterized by cessation of reproduction at age 30 and an interbirth interval of 2 years. Ending reproduction at age 30 effectively cuts the oldest recorded age of elephant pregnancy in half (Smuts, 1975) and an interbirth interval of 2 years represents just the gestational period, suggesting that the role of child-rearing is entirely shifted to a grandmother, including the role of nursing, though allonursing has been observed very rarely (Sukumar, 2003). The simulation scenario characterized by both reproductive success and menopause that is most feasible involves ending reproduction at age 40 with an interbirth interval of 4 years. Other, less plausible scenarios that meet both criteria are defined by an age at reproductive cessation of 35 years combined with an interbirth interval of 3 or 4 years.

Despite the experimental group producing on average more offspring than the natural group for the majority of simulations, many of simulations where menopausal post-reproductive lifespan values were achieved were a part of the minority in which the experimental population produced fewer offspring than did the natural group. Furthermore, very few of the simulations resulted in the experimental group superseding the natural group for age at death and age at last reproduction. Given the disadvantages in lower age at death, age at last reproduction, and

offspring number, it is unsurprising that simulations where the experimental group achieved menopausal post-reproductive lifespan values were often out-reproduced by the natural group.

The act of grandmothering is accounted for indirectly and exclusively in the current model through decreased interbirth intervals, which implies that the burden of child-rearing is partially or wholly (depending on the parameter value) supported by older females. Future modelling should explore the impacts of grandmothering on calf mortality risk, as the presence of grandmothers can promote calf survival, as has been observed in a population of Asian elephants (Lahdenperä et al., 2016). I suspect that the addition of this type of grandmother support would corroborate the current findings. Other models have accounted for grandmothering in a number of ways, including survival benefits conferred to grandchildren (Kachel et al., 2011; Kim et al., 2019; Pang, 2020), decreased weaning age (Kachel et al., 2011), and resource sharing (Kim et al., 2019; R. Lee, 2008). These models provide mixed support for the grandmother hypothesis. It should be noted that these models studied human populations, and caution is warranted before speculating on whether the results could be generalized to elephants. One model of resource sharing supported the grandmother hypothesis, as it showed that menopause evolved under intergenerational resource sharing conditions but not when sharing occurred population-wide (R. Lee, 2008). Kim et al. (2019) showed that menopause could evolve under the conditions of grandmother-associated survival benefits and food sharing. Kachel (2011) modeled the grandmother benefits of increased survival and decreased weaning age but found that neither benefit, together nor separately, could produce the prolonged post-reproductive lifespan characteristic of menopause. Pang (2020) found that grandmother survival benefits were only strong enough to produce menopausal PrR values when combined with maternal survival and reproductive benefits. Using mathematical models where mothers or grandmothers diverted all resources toward promoting the reproductive success of kin, Hill and Hurtado (1991, 1996) only found evidence for a maternal effect.

One limitation of the model is that it utilizes a mortality risk curve obtained from a population of captive working Asian elephants kept in Indian timber camps (Sukumar et al., 1997). That population consisted of both wild-caught and captive-born elephants, tasked with hauling timber to support logging operations and transporting tourists. The camps were located in wildlife sanctuaries, where elephants live in similar matriarchal groups as seen in the wild. Elephants were allowed to exhibit natural foraging behaviours at night and freely socialize and mate with wild elephants that coinhabit the forest. Detailed demographic records of this population, dating back to the late 19TH century have been maintained (Sukumar et al., 1997). To set a distinction from more traditional forms of captivity, such as zoos, elephants living in similar timber camp regimes have been described as “semi-captive” or “semi-wild” elsewhere in the literature (Lahdenperä et al., 2018; Wiese & Willis, 2006). These data might not be generalizable to truly wild populations, but obtaining demographic data on wild populations is challenging, largely due to time and cost constraints (Blake & Hedges, 2004). As a result, existing wild population data are thought to be incomplete and inaccurate (Blake & Hedges, 2004). Approximately a third (~15000) of all Asian elephants are held in captivity, but survivorship tends to differ depending on type of captivity. Asian elephants living in timber camps in Myanmar show significantly better survivorship compared to Asian elephants held in zoos, and survivorship is similar between populations living in timber camps and wild African elephant populations (Clubb et al., 2008).

The results of this study also are limited by the short time span of simulations, a necessary sacrifice to conserve computing time. Each simulation was run for 100 time intervals or "years" which only supports about 4-5 generations as Asian elephants are estimated to have a generation time of 20-25 years (Wiese & Willis, 2006; C. Williams et al., 2020). Running simulations over longer time intervals would help establish whether the observed results are robust over many generations.

To my knowledge, this is the first computational model studying elephant menopause. The results demonstrate how the evolution of menopause theoretically could be possible in elephants under certain circumstances of grandmothering, considered exclusively as shortened interbirth intervals. On the basis of computational modelling and computer simulation, menopause in elephants has not evolved because, in most scenarios where menopause is plausible, the menopausal population would be out-reproduced by natural, non-menopausal populations. The few situations where menopausal populations would out-reproduce non-menopausal populations represent unrealistic biological scenarios, involving total or near-total adoption by older females and major cuts to reproductive lifespan. Elephant reproductive physiology and life history have evolved to make menopause virtually impossible.

S2: Supplementary Material

Table S2.1: Mean proportion of adulthood non-reproductive (PAN) for the experimental group. Bolded values represent PAN ≥ 0.25. ARD, age at reproductive decline; IBI-E, interbirth interval – experimental.

		ARD (years)					
		30	35	40	45	50	55
IBI-E (years)	2	**0.34 ± 0.04**	0.24 ± 0.02	0.2 ± 0.023	0.16 ± 0.021	0.15 ± 0.014	0.15 ± 0.02
	3	**0.41 ± 0.06**	**0.29 ± 0.041**	0.22 ± 0.036	0.18 ± 0.028	0.17 ± 0.03	0.16 ± 0.028
	4	**0.41 ± 0.077**	**0.32 ± 0.048**	**0.25 ± 0.057**	0.19 ± 0.092	0.18 ± 0.051	0.19 ± 0.036
	5	**0.48 ± 0.106**	**0.35 ± 0.097**	**0.28 ± 0.096**	0.22 ± 0.095	0.19 ± 0.039	0.19 ± 0.042
	6	**0.54 ± 0.088**	**0.38 ± 0.077**	**0.3 ± 0.1**	0.24 ± 0.058	0.21 ± 0.064	0.2 ± 0.068

Table S2.2: Mean proportion of adulthood non-reproductive (PAN) for the natural group. Bolded values represent PAN ≥ 0.25. ARD, age at reproductive decline; IBI-E, interbirth interval – experimental.

		ARD (years)					
		30	35	40	45	50	55
IBI-E (years)	2	**0.25 ± 0.07**	0.23 ± 0.06	0.21 ± 0.06	0.2 ± 0.05	0.19 ± 0.04	0.2 ± 0.04
	3	0.23 ± 0.06	0.22 ± 0.05	0.21 ± 0.05	0.21 ± 0.06	0.2 ± 0.04	0.19 ± 0.04
	4	0.24 ± 0.05	0.23 ± 0.11	0.21 ± 0.06	0.2 ± 0.06	0.19 ± 0.04	0.19 ± 0.05
	5	**0.25 ± 0.06**	0.23 ± 0.04	0.21 ± 0.04	0.2 ± 0.06	0.2 ± 0.05	0.2 ± 0.04
	6	**0.25 ± 0.06**	0.22 ± 0.05	0.21 ± 0.04	0.2 ± 0.05	0.19 ± 0.04	0.19 ± 0.04

Table S2.3: Mean age at death ± standard deviation for the experimental group across 100 replicates. ARD, age at reproductive decline; IBI-E, interbirth interval – experimental.

		ARD (years)					
		30	35	40	45	50	55
IBI-E (years)	2	34.65 ± 2.66	33.42 ± 1.69	33.1 ± 2.4	33.26 ± 3.03	32.75 ± 0.65	32.99 ± 1.49
	3	36.7 ± 3.63	36.58 ± 3.14	35.31 ± 2.6	35.43 ± 1.53	35.64 ± 2.55	35.95 ± 4.19
	4	38.15 ± 4.35	37.81 ± 2.51	37.84 ± 3.68	36.82 ± 3.59	37.1 ± 2.69	36.64 ± 1.88
	5	39.54 ± 6.27	38.87 ± 5.01	38.82 ± 5.22	37.97 ± 3.22	38.88 ± 3.5	39.19 ± 3.67
	6	40.83 ± 4.98	40.51 ± 5.21	39.49 ± 4.37	38.82 ± 4.13	38.97 ± 3.17	40.08 ± 4.14

Table S2.4: Mean age at death ± standard deviation for the natural group across 100 replicates. ARD, age at reproductive decline; IBI-E, interbirth interval – experimental.

		ARD (years)					
		30	35	40	45	50	55
IBI-E (years)	2	38.8 ± 3.7	38.97 ± 4.57	38.68 ± 3.12	38.8 ± 2.99	38.81 ± 3.6	38.53 ± 2.65
	3	39.1 ± 3.57	38.53 ± 3.4	38.95 ± 3.81	38.67 ± 3.23	38.68 ± 2.65	38.67 ± 2.51
	4	39.2 ± 3.37	39 ± 5.15	38.68 ± 3.18	38.61 ± 3.3	38.56 ± 3.49	38.63 ± 2.6
	5	37.87 ± 4.37	38.88 ± 3.48	38.97 ± 3	38.63 ± 5.14	39 ± 3.78	38.74 ± 2.89
	6	39.02 ± 3.91	38.9 ± 3.59	38.33 ± 2.62	39.09 ± 4	38.71 ± 3.23	39.08 ± 3.67

Table S2.5: Mean age at last reproduction ± standard deviation for the experimental group across 100 replicates. ARD, age at reproductive decline; IBI-E, interbirth interval – experimental.

		ARD (years)					
		30	35	40	45	50	55
IBI-E (years)	2	26.04 ± 1.1	28.34 ± 1.03	29.47 ± 1.27	30.8 ± 2.08	30.93 ± 0.63	31.17 ± 1.41
	3	25.7 ± 1.4	29.27 ± 1.43	30.89 ± 1.8	32.11 ± 1.38	33.16 ± 2.42	33.38 ± 3.35
	4	26.7 ± 1.6	29.35 ± 1.6	31.56 ± 2.22	33.2 ± 3.19	34.06 ± 2.41	33.66 ± 1.76
	5	26 ± 2.51	29.46 ± 2.73	31.91 ± 3.26	33.42 ± 2.94	35.14 ± 3.2	35.5 ± 3.16
	6	24.68 ± 1.26	29.16 ± 2.05	31.79 ± 3.2	33.46 ± 3.27	34.91 ± 2.97	35.97 ± 3.99

Table S2.6: Mean age at last reproduction ± standard deviation for the natural group across 100 replicates. ARD, age at reproductive decline; IBI-E, interbirth interval – experimental.

		ARD (years)					
		30	35	40	45	50	55
IBI-E (years)	2	33.23 ± 3.2	34.04 ± 3.33	34.28 ± 2.47	34.96 ± 2.7	35.17 ± 3.39	34.78 ± 2.37
	3	33.78 ± 3.25	33.81 ± 2.73	34.46 ± 2.73	34.77 ± 3.02	34.9 ± 2.28	35.05 ± 2.39
	4	33.68 ± 2.49	34.2 ± 4.77	34.53 ± 3.03	34.7 ± 2.97	34.99 ± 3.39	35.04 ± 2.57
	5	32.59 ± 3.74	33.92 ± 2.88	34.53 ± 2.6	34.68 ± 4.32	35.29 ± 3.43	35.08 ± 2.73
	6	33.36 ± 2.67	34.03 ± 2.79	34.14 ± 2.27	35.06 ± 3.64	35.1 ± 3.16	35.38 ± 3.31

Table S2.7: Mean number of offspring ± standard deviation for the experimental group across 100 replicates. ARD, age at reproductive decline; IBI-E, interbirth interval – experimental.

		ARD (years)					
		30	35	40	45	50	55
IBI-E (years)	2	6.84 ± 1.31	8.32 ± 0.68	8.88 ± 0.61	9.24 ± 1.3	9.7 ± 0.3	9.65 ± 0.86
	3	4.74 ± 0.84	5.88 ± 0.89	6.54 ± 0.78	6.92 ± 0.73	7.14 ± 0.72	6.31 ± 1.44
	4	3.9 ± 0.64	4.55 ± 0.65	4.78 ± 1.14	5.45 ± 0.91	5.58 ± 0.88	5.66 ± 0.49
	5	3.12 ± 0.67	3.65 ± 0.92	4.02 ± 0.85	4.49 ± 0.76	4.66 ± 0.78	4.53 ± 0.88
	6	2.48 ± 0.41	3.04 ± 0.6	3.6 ± 0.56	3.78 ± 0.77	3.9 ± 0.77	4.04 ± 0.73

Table S2.8: Mean number of offspring ± standard deviation for the natural group across 100 replicates. ARD, age at reproductive decline; IBI-E, interbirth interval – experimental.

		ARD (years)					
		30	35	40	45	50	55
IBI-E (years)	2	4.11 ± 0.83	4.33 ± 0.78	4.53 ± 0.73	4.64 ± 0.64	4.68 ± 0.75	4.72 ± 0.54
	3	4.09 ± 0.9	4.32 ± 0.82	4.38 ± 0.86	4.48 ± 0.92	4.67 ± 0.54	4.57 ± 0.62
	4	4.32 ± 0.72	4.2 ± 1.05	4.46 ± 0.79	4.55 ± 0.78	4.75 ± 0.71	4.56 ± 0.71
	5	4.11 ± 0.72	4.31 ± 0.79	4.55 ± 0.57	4.46 ± 1.04	4.62 ± 0.82	4.62 ± 0.58
	6	4.23 ± 0.8	4.42 ± 0.62	4.62 ± 0.49	4.55 ± 0.9	4.57 ± 0.81	4.62 ± 0.71

CHAPTER 3: TESTING THE HUMAN ANEUPLOIDY HYPOTHESIS

Abstract
The origins of menopause, evolutionarily defined as substantial post-reproductive lifespan, are not well understood. Recently, the aneuploidy hypothesis was presented as a potential explanation for this rare and seemingly maladaptive trait. Aneuploidy is characterized by abnormal chromosome number, which most often leads to loss of pregnancy or detriments to development. The hypothesis posits that aneuploidy is a mechanism to prevent risky pregnancies at older ages. Instead of expending resources on producing offspring toward the end of lifespan, older women divert resources toward the survival and reproduction of existing children and grandchildren. I situated this hypothesis within an evolutionary framework, created a computational model to computer simulate a population wherein fecundity is impacted by risk of aneuploidy, and used it to test the effects of varying degrees of early reproductive cessation on post-reproductive lifespan and other demographic characteristics. Post-reproductive lifespan was greatest in risk-of-aneuploidy populations when reproduction ended earliest, but such populations likely would become out-reproduced by populations not subjected to risk of aneuploidy. I also observed that reproductive success and offspring number tended to increase with age at reproductive cessation, but peak values were reached when reproduction ceased around age 50, and values plateaued beyond this age. I demonstrate for the first time through computational modelling and computer simulation that the adaptive strategy proposed by the aneuploidy hypothesis is most successful when reproduction ends at approximately the average age of clinical menopause in real populations, 50 years. A gradually developed mating behaviour that fixed reproductive cessation at a particular age can provide evolutionary inertia for the evolution of menopause.

Introduction

Aneuploidy is defined as aberrations in chromosome number often resulting in either the gain of a chromosome (trisomy) or the loss of a chromosome (monosomy). Aneuploidy is the number one cause of birth defects and miscarriage (Nagaoka et al., 2012). Studies of human embryonic stem cell lines indicate that all autosomal monosomies result in lethality very early in development (Biancotti et al., 2012). Monosomy of the X chromosome (XO), known as Turner syndrome, is the only whole organism monosomy that is viable in humans (Biancotti et al., 2012), though survival is rare and results in a female phenotype with detriments in development and fertility (Bondy & Cheng, 2009). Similarly, almost all autosomal trisomies are inviable except for trisomies 13, 18, and 21. Trisomy 13 (Patau's syndrome) and trisomy 18 (Edward's syndrome) are considered viable but result in death within a few months (Torres et al., 2008). Trisomy 21, more commonly known as Down syndrome, is the most common genetic cause of intellectual disability but also impacts the musculoskeletal, neurological, and cardiovascular systems (Antonarakis et al., 2020). All trisomies of sex chromosomes (XXX, XXY, XYY, and XXYY) are viable and associated with varying degrees of learning difficulties, though many cases go undiagnosed (Skuse et al., 2018)

For the most part, aneuploidy exhibits strong maternal bias (i.e., in ova). For example, 93% of cases of trisomy 21 and 96% of cases of trisomy 18 have been linked to maternal inheritance (Hassold et al., 1996). This is true for almost all types of trisomies, with maternal origin rates ranging from 81% to 100% for specific types/groups of trisomies. The exception is Klinefelter's

syndrome (XXY), which has been shown to be maternally-derived in only 56% of cases (Hassold et al., 1996). Aneuploidy is also about 10-times more likely to occur within oocytes (~20%) compared to spermatozoa (1-2%) (Hassold & Hunt, 2001). A recent study involving comprehensive chromosomal screenings of a large sample of trophectoderm biopsies revealed a 'J-shaped' relationship between maternal age and prevalence of aneuploidy (Franasiak et al., 2014). Over 40% of embryos were aneuploid among women aged 22-23 years, prevalence then dropped to 20-27% in women 26-30 years of age. From age 31, the percentage of aneuploid embryos increased steeply, reaching a plateau of about 85% by age 43 (Franasiak et al., 2014).

This maternal bias is thought to be attributable to sex differences in gametogenesis and meiosis. One key difference is that males are capable of continual production of spermatozoa throughout the entire reproductive lifespan, whereas females are born with all of the oocytes they ever will produce (Desai et al., 2022). Meiosis typically consists of two rounds of division. In meiosis I, homologous chromosomes are segregated, which is followed by segregation of sister chromatids in meiosis II, resulting in haploid gametes. Meiosis in males is a process that takes approximately 25.3 days, proceeding sequentially through each meiotic stage until approximately four spermatozoa are produced per cell (Desai et al., 2022) . In comparison, the process of meiosis in females can take decades, requires several extended periods of meiotic arrest, and results in the production of only a single egg. The first few steps of meiosis I are completed *in utero*, but the cycle is arrested with genetic exchange through homologous recombination between non-sister chromatids in stasis, until an oocyte is ovulated, an event that could take place several decades later. The mature oocyte completes meiosis I and arrests again at metaphase II. Meiosis can be completed only after the egg unites with a sperm. The convoluted and protracted process of meiosis in females provides many opportunities for non-disjunction events to occur (Hassold & Hunt, 2001; Wartosch et al., 2021).

The fruit fly *Drosophila* and the yeast species *Saccharomyces cerevisiae* are the model organisms used most frequently to study aneuploidy. Chromosomal non-disjunction rates for these organisms typically fall within the range of 10^{-3} and 10^{-6} (Mason & Resnick, 1986). Incidence of aneuploidy among mice, probably the most well-studied non-human mammal, is approximately 1-2% (Gearhart et al., 1986). Rates of aneuploidy in humans are abnormally high when compared with rates in other organisms. Aneuploidy is estimated to occur in at least 5% of human conceptions, based on incidence figures within spontaneous abortions (fetal deaths occurring at 6-20 weeks gestation), stillbirths (fetal deaths occurring at 20 weeks gestation to term), and livebirths (Hassold & Hunt, 2001). Estimates including data from occult pregnancies, those that go undetected due to spontaneous abortion within the first few weeks, indicate an occurrence rate as high as 25%, though limited data are available for this type of pregnancy (Hassold & Hunt, 2001).

Meiosis is estimated to have evolved early in eukaryote evolution (Ramesh et al., 2005), but, despite millions or perhaps even billions of years of evolution, the process remains error-prone in humans, especially among oocytes. The prevalence of a seemingly maladaptive trait may indicate that evolutionarily adaptive qualities may reside in aneuploidy. Sirard (2011) proposed that aneuploidy evolved as a mechanism to limit pregnancies in older women. When considered in conjunction with adaptive explanations for menopause, including the mother and grandmother hypotheses, the apparent sabotage of compromised pregnancies later in life is offset by the

fitness benefits incurred by supporting the survival and reproduction of living children and grandchildren (Sirard, 2011).

I test this provocative aneuploidy hypothesis, by situating it contextually within an evolutionary scenario *in silico*, with a computational model. The computational model is designed to computer simulate an early human population, after our lineage diverged from the lineage that would become chimpanzees. Females were subject to risk of births affected by aneuploidy and therefore gradually evolved the behaviour of early cessation of reproduction and diversion of resources toward kin. Sufficient time had elapsed for this hypothetical early human population to have evolved the risk-avoidance reproductive behaviour and its associated longer, lower mortality curve. I explore the effects of varying age at reproductive cessation. This population is compared to another, contemporaneous population that is not exposed to risk of aneuploidy and, as such, remains fecund until the end of a short lifespan.

Methods

The initial population in the model consists of 25 individuals, where each is pseudo-randomly assigned a sex, group identifier, and age ($1 \leq \text{age} \leq 80$). Individuals can be members in either of two groups, one in which individuals are subject to risk of aneuploidy (RA) and the other in which individuals experience no risk of aneuploidy (NRA). The NRA group becomes fecund at age 13 and stays fecund until the end of lifespan. The RA group also becomes fecund at age 13, but then adopts a fecundity curve derived from data on prevalence of births affected by Down syndrome as a function of maternal age (Cuckle et al., 1987; Morris et al., 2003; Table S3.1). Prevalence was normalized (i.e., all values were divided by the greatest value), returning probabilities, and their complements were calculated to determine probabilities of births *not* affected by Down syndrome. Down syndrome was chosen as a model for fecundity because it is one of the most well-characterized aneuploidy disorders, has a strong association with maternal-age (Cuckle et al., 1987), and has been found to be highly maternally-derived (Hassold et al., 1996). The parameter under study is age at reproductive cessation (ARC) for the RA group. At ARC, the value of fecundity immediately drops to 0 (Figure 3.1).

Mating occurs through pseudo-random pairing of males and females. Mating is successful if both individuals have reached sexual maturity (age 13) and for females belonging to the RA group, if a pseudo-randomly generated number is less than or equal to the value of the age-specific fecundity curve. A recent mother cannot successfully mate until her interbirth interval (2 years) has elapsed. This process of pairing and mating is iterated for each time interval (t) in the simulation, which represents a year. Mating can occur freely between and within groups, but group membership is inherited maternally. The female-driven nature of the model was chosen due to the propensity for maternally-derived aneuploidies, which has been attributed to the aforementioned key differences in female meiosis (MacLennan et al., 2015). The total size of the population is not limited and grows freely. Instituting population control via a carrying capacity was shown to be ineffective in earlier versions of the model, as it resulted in a population consisting of mostly young individuals.

Viability for each individual is tracked as either alive or dead. For every year in a simulation, viability is determined by comparing a pseudo-randomly generated real number in the range of 0 to 1 to the mortality risk curve, which differs between groups. An individual is deemed alive if

the generated number exceeds their age-specific mortality risk. Otherwise, the individual is considered to be dead and transferred to a dead population. Mortality risk curves are represented using a mathematical model known as the Siler competing-risk model for animal mortality (Siler, 1979). The Siler model comprises three terms, each accounting for risk at different life stages, that together describe the risk of mortality at any age *t*. The first term models risk at juvenile stage, the second term models risk during adulthood, and the third term models risk during the senescent period:

$$h(t) = a_1 e^{-b_1 t} + a_2 + a_3 e^{b_3 t} \tag{3.1}$$

The NRA group uses average Siler parameters fit to the life tables for twelve ancient (to post-classical) human populations (Gage, 1998; O'Connor, 1995; Table S3.2). The majority of populations date from epipaleolithic times to 1300 AD, with two post-classical populations from 1650-1785. Mean parameter values were used, as the Siler model could not be fit adequately to data in some life tables.

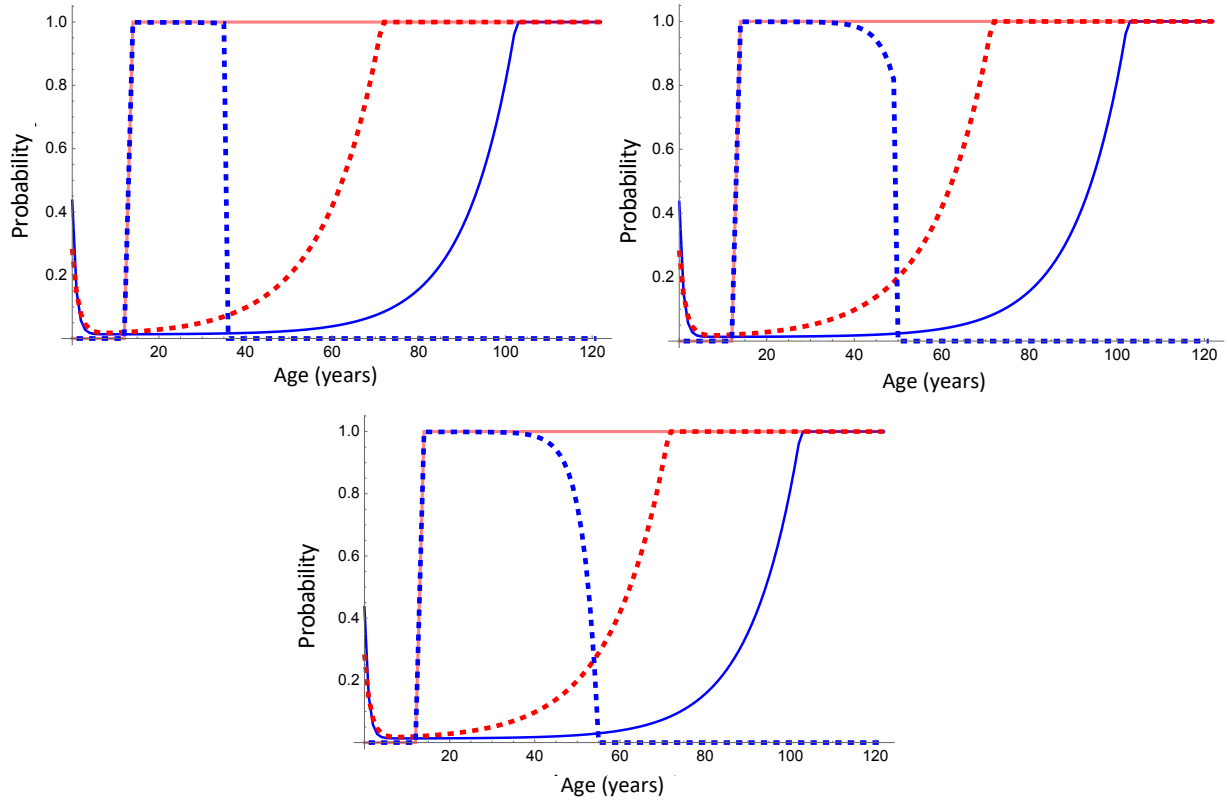

Figure 3.1: Mortality curves for the risk of aneuploidy (RA) group (solid blue) and no risk of aneuploidy (NRA) group (dashed red). Fecundity curves for the RA group (dashed blue) and NRA group (solid red). Left: age at reproductive cessation (ARC) = 35, Right: ARC = 50, Bottom: ARC = 55.

The RA group uses Siler parameter data from extant hunter-gatherer populations (Gurven & Kaplan, 2007). The parameter values were averaged for five hunter-gatherer populations: Hadza, Ache, Hiwi, !Kung, and Agta. These groups have little to no access to modern medicine and do not practice horticulture. The RA group in the evolutionary scenario has evolved longer lifespans

associated with hunter-gatherer populations because the adaptive behaviour of ending reproduction earlier has allowed for reallocation of care and resources to offspring.

Each simulation was run over 100 time intervals. At the end of each simulation, mean age at death (AD), mean age at last reproduction (ALR), and mean number of offspring were calculated for both groups. Means were calculated from a pool consisting of all adult females who had died in the population over the 100 time intervals. Using the outputs of mean AD and mean ALR, as well as age at sexual maturity (13 years), I developed a simple metric to determine whether a population was menopausal, proportion of adulthood non-reproductive (PAN). PAN is the ratio of post-reproductive lifespan to adult lifespan:

$$PAN = \frac{age\ at\ death\ -\ age\ at\ last\ reproduction}{age\ at\ death\ -\ age\ of\ sexual\ maturity} \tag{3.2}$$

Groups were considered menopausal if PAN ≥ 0.25. Each ARC value was used to simulate 100 replicates, and the following data summarizing the 100 replicates were collected for both groups: mean AD, mean ALR, mean number of offspring, mean PAN, and proportion of replicates where the RA group out-reproduced the NRA group (PR-RA). PR-RA was used as a population metric for reproductive success, as the RA group was deemed to be reproductively successful or competitive over the NRA group if PR-RA > 0.5. Means were presented with standard deviations. The model was coded using the Wolfram language in Mathematica v.13.0.1.0., and simulations were performed on a MacBook Air (running macOS Monterey v.12.2.1).

Results

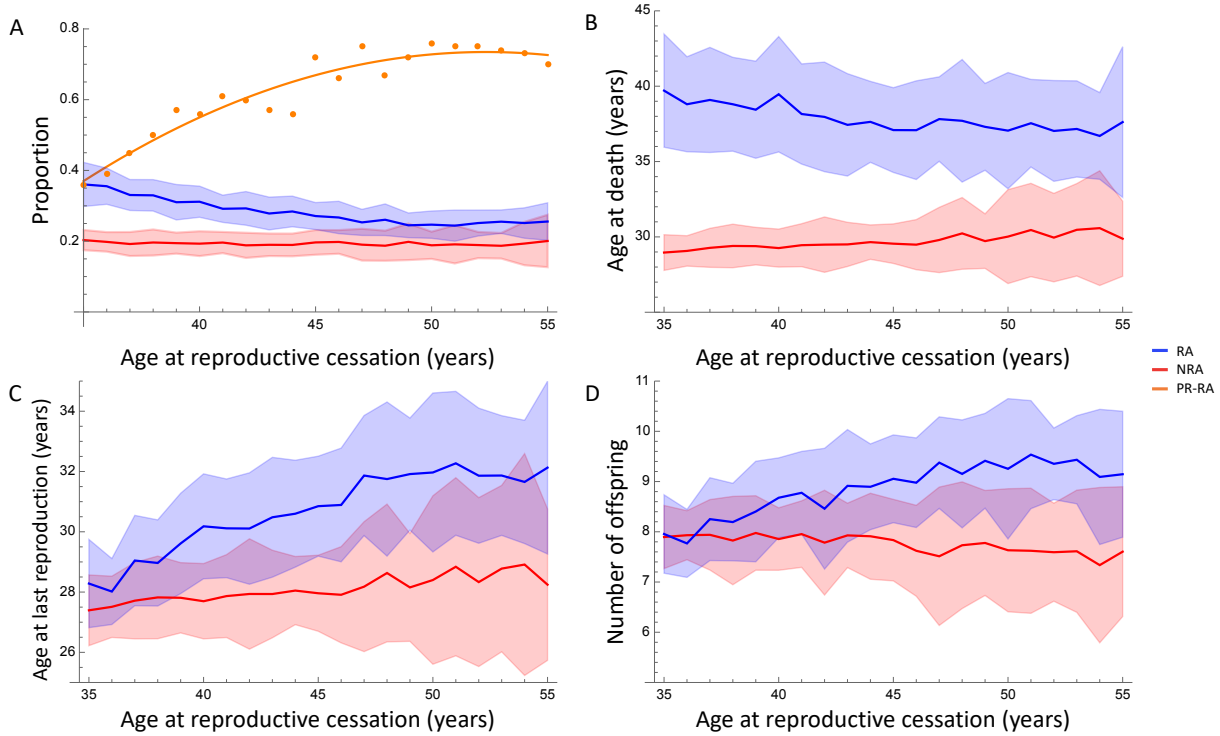

Figure 3.2: A: Mean proportion of adulthood non-reproductive (PAN) and mean proportion of replicates where the risk of aneuploidy (RA) group out-reproduced the no risk of aneuploidy (NRA) group (PR-RA)

with regression line. B: Mean age at death (AD). C: Mean age at last reproduction (ALR). D: Mean number of offspring. Error bands represent standard deviation.

The RA group out-reproduced the NRA group in > 50% of replicates when ARC was between 39 and 55 (Table 2.1). PR-RA steadily increased from 0.36 at ARC = 35, peaked at 76% in simulations where reproduction stopped at age 50, and then decreased from ARC values of 51-55 (Figure 3.2A). The relationship between PR-RA and ARC was best fit to a quadratic equation, $PR\text{-}R = -2.58854 + 0.126971(ARC) - 0.00121281(ARC)^2$ (Figure 3.2A).

PAN-RA tended to decrease as ARC increased (Figure 3.2A). Almost all PAN-RA values were menopausal (PAN ≥ 0.25) except for at ARC values of 49 and 51 years (Table 2.1). The peak PAN-RA value of 0.36 ± 0.06 was reached at the youngest ARC. The mean PAN-NRA across all simulations was 0.20 ± 0.0047 (SE), which is not considered to be menopausal.

Table 3.1: Mean proportion of replicates where the risk of aneuploidy group out-reproduced the no risk of aneuploidy group (PR-RA) and proportion of adulthood non-reproductive (PAN) among the risk of aneuploidy group (RA) and no risk of aneuploidy group (NRA) for all parameter values of age at reproductive cessation (ARC). Means are presented with standard deviation.

ARC	PR-RA	PAN-RA	PAN-NRA
35	0.36	0.36 ± 0.06	0.2 ± 0.03
36	0.39	0.36 ± 0.05	0.2 ± 0.03
37	0.45	0.33 ± 0.04	0.19 ± 0.03
38	0.5	0.33 ± 0.04	0.2 ± 0.04
39	0.57	0.31 ± 0.05	0.19 ± 0.03
40	0.56	0.31 ± 0.04	0.19 ± 0.04
41	0.61	0.29 ± 0.04	0.2 ± 0.03
42	0.6	0.29 ± 0.05	0.19 ± 0.04
43	0.57	0.28 ± 0.05	0.19 ± 0.03
44	0.56	0.28 ± 0.04	0.19 ± 0.03
45	0.72	0.27 ± 0.04	0.2 ± 0.03
46	0.66	0.27 ± 0.05	0.2 ± 0.03
47	0.75	0.25 ± 0.04	0.19 ± 0.04
48	0.67	0.26 ± 0.04	0.19 ± 0.04
49	0.72	0.24 ± 0.03	0.2 ± 0.05
50	0.76	0.25 ± 0.04	0.19 ± 0.04
51	0.75	0.24 ± 0.04	0.19 ± 0.05
52	0.75	0.25 ± 0.04	0.19 ± 0.04
53	0.74	0.26 ± 0.03	0.19 ± 0.04
54	0.73	0.25 ± 0.04	0.19 ± 0.06
55	0.7	0.26 ± 0.05	0.2 ± 0.07

AD for the RA group showed a decreasing trend, reaching a peak of 39.71 ± 3.76 at ARC = 35 (Figure 3.2B). The mean AD across all simulations for the NRA group was 29.69 ± 0.46 (SE) (Table S3.3).

The RA group showed an increasing trend for ALR, reaching a maximum value of 32.27 ± 2.39 at ARC = 51 (Figure 3.2C). In contrast, the NRA group showed an overall mean of 28.10 ± 0.42 (SE) (Table S3.3).

Mean offspring number tended to increase with ARC for the RA group, with a maximum value of 9.54 ± 1.08 at ARC = 51 (Figure 3.2D). The NRA group showed a mean offspring value of 7.76 ± 0.17 (SE) across all simulations (Table S3.3).

Discussion

I sought to test the aneuploidy hypothesis by creating a computational model that computer simulates populations that have evolved the behaviour of terminating reproduction prematurely to avoid risk of aneuploidy and refocus resources toward promoting survival of young. Simulations revealed that, when reproduction stopped at the earliest age of 35, post-reproductive lifespan reached its peak, but this scenario is evolutionarily unfavourable, as the menopausal group would likely be out-reproduced by the group that is not subject to risk of aneuploidy. Menopausal populations became competitive when reproduction ceased at age 39 and likelihood of reproductive success along with offspring number increased. Optimal values for reproductive success, age at last reproduction, and offspring number were reached when reproduction stopped around the age of 50, beyond which little change occurred. These results suggest that the strategy of ceasing reproduction earlier to avoid risk of aneuploidy is most effective around the natural observed age of clinical menopause and advantages appear to plateau at older ages.

This model assumes an ancestrally long reproductive period with a learned reproductive behaviour to stop reproducing at an earlier age. Others argue that human longevity extended past the ancestral fertile period over time (Weiss, 1981). This idea of lifespan extension is supported by evidence that chimpanzees experience similar rates and timings of fertility decline and follicular depletion (Jones et al., 2007; Thompson et al., 2007). The findings of these comparative studies suggest that the age and timing of reproductive senescence is conserved.

The model currently converts risk of trisomy 21 data to a fecundity curve based on the assumption that affected pregnancies would be inviable or that offspring would not reach reproductive age. This might be a safe assumption for the simulated early human population, given that the life expectancy for people born with Down syndrome reached reproductive age only as recently as the 1940s (Penrose, 1949). Future modeling should explore the possibility that some aneuploid pregnancies are viable and that affected offspring reproduce. Future modeling also might account for improvements in aneuploidy outcomes over time, as has occurred historically – for instance, the life expectancy of children affected by Down syndrome currently has nearly reached age 60 (Glasson et al., 2002).The model also makes the simplification that aneuploidy is passed on only maternally. However, Down syndrome is maternally-derived in 93% of cases, leaving 7% to paternal contributions, and maternal-derivation rates are as low as 56% for Klinefelter's syndrome (XXY) (Hassold et al., 1996).

The mortality risk curve for the ancient (to post-classical) human populations used for the NRA group was obtained from paleodemographic studies that involved determining population statistics from skeletal remains. A number of issues are associated with paleodemographic data, including low levels of accuracy and reliability of age at death estimation techniques, representativeness of the cemetery sample to the intended population, and the construction of life tables based on potentially false assumptions of closed, stationary populations (O'Connor, 1995). However, paleodemographic data still are valuable for understanding ancient and prehistoric populations for which there are paucities of source material.

One weakness of the model design is that survival benefits associated with early reproductive cessation strategy are not scaled according to level of early reproductive cessation. That is, all members of the RA group experience the same extended mortality risk curve regardless of whether ARC is set to 35 or 55 years. Ideally, future modeling should award greater benefits for groups where reproduction ceases at earlier ages. This is intuitive, as stopping reproduction at an earlier age would translate to more time and resources invested in children and grandchildren.

To my knowledge, this is the first study to test the aneuploidy hypothesis via computational modelling and computer simulation. These results provide valuable insight into the optimal timing of strategic reproductive cessation that allows for maximal fitness gains while avoiding later pregnancies associated with risk of aneuploidy. A mating behaviour that emerged gradually and ultimately fixed reproductive cessation at a particular age could have provided evolutionary inertia for the evolution of menopause.

S3: Supplementary Material

Table S3.1: Estimated risk of birth affected by Down syndrome according to maternal age, adapted from Morris et al. (2003), original data sourced from Cuckle et al. (1987).

Maternal age at birth	Risk, per 1000 births
15	0.63
16	0.64
17	0.64
18	0.64
19	0.65
20	0.65
21	0.66
22	0.67
23	0.69
24	0.71
25	0.74
26	0.78
27	0.83
28	0.89
29	0.98
30	1.1
31	1.25
32	1.46
33	1.74
34	2.11
35	2.6
36	3.25
37	4.12
38	5.27
39	6.81
40	8.86
41	11.59
42	15.22
43	20.05
44	26.48
45	35.03
46	46.43
47	61.59
48	81.77
49	108.64
50	144.4
51	192.01
52	255.37
53	339.71
54	451.98
55	601.42

Table S3.2: Characteristics of populations used for the no risk of aneuploidy (NRA) group mortality curve. Adapted from O'Connor (1995). ya: years ago.

Sample	**Time Period**	**Location**
OLD WORLD		
Taforalt	Epipaleolithic	Morocco
Kulubnarti I (Island)	550-750 AD	Nubia
Kulubnarti II (Mainland)	550-1300 AD	Nubia
NEW WORLD		
Pre-contact		
Carrier Mills	3955-2910 BC	Illinois
Carlston Annis	5000-3500 ya	Kentucky
Indian Knoll	5302 ya	Kentucky
Dickson Mounds (Late Woodlands)	950-1200 AD	Illinois
Dickson Mounds (Middle Mississipian)	1200-1300 AD	Illinois
Libben	250-750 AD	Ohio
Mesa Verde (Late)	975-1300 AD	Colorado
Post-contact		
Mobridge II	1650-1700	South Dakota
Larson	1750-1785	South Dakota

Table S3.3: Summary of mean age at death (AD), mean age at last reproduction (ALR), and mean number of offspring with standard deviation among the risk of aneuploidy group (RA) and no risk of aneuploidy group (NRA) for all parameter values of age at reproductive cessation (ARC).

ARC	AD-RA	AD-NRA	ALR-RA	ALR-NRA	OS-RA	OS-NRA
35	39.71 ± 3.76	28.96 ± 1.18	28.28 ± 1.46	27.39 ± 1.17	7.96 ± 0.78	7.9 ± 0.63
36	38.8 ± 3.15	29.07 ± 1.01	28.02 ± 1.09	27.51 ± 1.02	7.77 ± 0.68	7.93 ± 0.49
37	39.09 ± 3.49	29.27 ± 1.29	29.05 ± 1.5	27.71 ± 1.27	8.25 ± 0.82	7.94 ± 0.7
38	38.8 ± 3.11	29.4 ± 1.44	28.97 ± 1.43	27.82 ± 1.37	8.19 ± 0.77	7.83 ± 0.88
39	38.44 ± 3.22	29.39 ± 1.25	29.61 ± 1.66	27.81 ± 1.17	8.4 ± 1	7.98 ± 0.74
40	39.47 ± 3.83	29.26 ± 1.26	30.18 ± 1.74	27.7 ± 1.25	8.68 ± 0.79	7.86 ± 0.62
41	38.15 ± 3.32	29.45 ± 1.43	30.11 ± 1.64	27.87 ± 1.37	8.78 ± 0.82	7.95 ± 0.66
42	37.96 ± 3.64	29.49 ± 1.84	30.11 ± 1.85	27.94 ± 1.83	8.46 ± 1.2	7.78 ± 1.04
43	37.43 ± 3.4	29.5 ± 1.47	30.48 ± 1.99	27.94 ± 1.45	8.91 ± 1.12	7.93 ± 0.64
44	37.63 ± 2.69	29.65 ± 1.14	30.6 ± 1.77	28.05 ± 1.13	8.9 ± 0.85	7.91 ± 0.86
45	37.09 ± 2.81	29.55 ± 1.31	30.85 ± 1.66	27.96 ± 1.26	9.05 ± 0.87	7.83 ± 0.81
46	37.08 ± 3.27	29.48 ± 1.66	30.89 ± 1.89	27.91 ± 1.6	8.98 ± 0.89	7.62 ± 0.91
47	37.82 ± 2.8	29.8 ± 2.16	31.87 ± 1.99	28.18 ± 2.15	9.38 ± 0.91	7.51 ± 1.38
48	37.7 ± 4.07	30.23 ± 2.38	31.75 ± 2.56	28.63 ± 2.29	9.15 ± 1.07	7.73 ± 1.26
49	37.3 ± 2.88	29.72 ± 1.81	31.91 ± 1.86	28.15 ± 1.79	9.41 ± 0.94	7.78 ± 1.04
50	37.05 ± 3.86	30.02 ± 3.12	31.97 ± 2.64	28.4 ± 2.79	9.25 ± 1.4	7.63 ± 1.23
51	37.54 ± 2.91	30.46 ± 3.1	32.27 ± 2.39	28.84 ± 2.95	9.54 ± 1.08	7.62 ± 1.24
52	37.03 ± 3.34	29.95 ± 2.93	31.86 ± 2.24	28.33 ± 2.8	9.35 ± 0.71	7.59 ± 0.98
53	37.16 ± 3.19	30.47 ± 3.07	31.87 ± 1.99	28.78 ± 2.76	9.43 ± 0.88	7.61 ± 1.22
54	36.7 ± 2.88	30.58 ± 3.81	31.65 ± 2.05	28.91 ± 3.68	9.09 ± 1.35	7.34 ± 1.55
55	37.62 ± 5	29.88 ± 2.49	32.13 ± 2.86	28.25 ± 2.51	9.15 ± 1.25	7.6 ± 1.29

CHAPTER 4: CONCLUSION

Evolutionary biologists have puzzled over menopause for decades because of its rarity among species and the contradiction it seems to present against foundational evolutionary theories. The goal of this thesis was to develop computational models to better understand two concepts: (1) why menopause has not evolved in elephants despite their sharing features that are thought to be involved in the evolution of menopausal species, namely care for offspring by older females and long lifespan; and (2) how menopause might have evolved in humans through a reproductive behavioural adaptation, involving avoiding risk of aneuploidy at older ages.

The first model involved testing the effects of ending reproduction earlier and grandmother benefits conferred as reduced interbirth intervals. I found that populations wherein post-reproductive lifespan was greatest, which tended to occur with longer interbirth intervals and earlier ages of reproductive cessation, also were more likely to be out-reproduced by the contemporary elephants. In contrast, simulations that were most reproductively successful, those typically characterized by shorter interbirth intervals and later end to reproduction, were not menopausal. These findings show that, given the reproductive physiology and life history that have evolved, involving long gestation and nursing periods, grandmothering, considered as benefits that shorten the juvenile dependent period and thus the interbirth interval, is not adequate to produce menopause in elephants.

The second model was designed to test the aneuploidy hypothesis, which states that chromosome-level mutations discourage pregnancies among older women and instead promotes investment of care and resources in extant children and grandchildren. Computer simulations, set within an evolutionary context, revealed that, while stopping reproduction earlier resulted in greater post-reproductive lifespans, populations that stopped earliest were most likely to be out-reproduced by the comparison population of ancient humans. Populations that were most successful stopped reproduction at approximately age 50, which coincides with the observed age of clinical menopause. Reproductive success tended to plateau at reproductive cessation ages beyond age 50 and decreased at earlier ages. Reproductive behaviour, emerging gradually and ultimately fixing reproductive cessation at 50 years, provided evolutionary inertia for the evolution of menopause.

To quantify post-reproductive lifespan within the models, I developed a metric called proportion of adulthood non-reproductive (PAN), which divides the post-reproductive lifespan by the adult lifespan. This is a simple and computationally inexpensive measure and since populations within simulations grew at constant rates and to variable sizes the use of PAN, a measure of average proportions, was justified. Other researchers have suggested using post-reproductive representation (PrR) as a metric for measuring post-reproductive lifespan. PrR is less intuitive and involves more complicated calculations but has been found to be statistically sound with low type I error rates (Levitis & Lackey, 2011). Post-reproductive lifespan has been defined and measured inconsistently in the literature of computational studies of menopause, which can make it difficult to compare findings, and, since PrR is a relatively new metric, it has only been adopted in one such study (Pang, 2020). Ideally, modeling in this research area should shift towards a more unified method of measuring menopause.

Evolutionary menopause research has been approached from two frameworks, both starting with the assumption that reproductive and somatic senescence coincided ancestrally. The first framework argues that female fertility experienced a premature decline whereas the second framework suggests that female lifespan extended past reproductive cessation. The models developed for this thesis rely on fixed mortality risk curves and variable ages of reproductive cessation, aligning with the first framework. Future studies should attempt to put this dichotomy to rest by creating more dynamic models that account for both lifespan and fertility as evolvable traits that are subject to change through mutation.

One important limitation of the models is that neither tracks lineages, and therefore grandmother or mother benefits are conferred to all individuals in the experimental group regardless of whether an individual has a live mother or grandmother. This may have impacts on my findings because another model that tested population-wide sharing of resources compared to sharing restricted to kin found that menopause was observed only in simulations of intergenerational sharing (R. Lee, 2008). Kim et al. (2012, 2014, 2019) developed a series of models where lineage was not tracked in the first two models but adapted the third model to track lineages and apply true grandmother benefits, but all three models showed evidence in support of the grandmother hypothesis.

Collectively, these findings provide novel computer simulation-based insight into how menopause potentially could have evolved in humans and why it has not appeared in the elephant lineage.

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