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RESEARCH ARTICLE

The observed pattern and hidden process of female reproductive trajectories across the life span in a non-human primate

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Abstract

1. Age-specific fertility trajectories are fundamental to understanding population structure and the evolutionary ecology of diverse life histories. However, characterizing reproductive ageing has been difficult with cross-sectional data, where senescence especially late in life can be confounded by selective disappearance. Addressing such challenge requires longitudinal data tracking the reproductive life span of known individuals, but such data are rare, especially for very long-lived species such as primates.
2. We analyse the entire life span trajectory of annual fertility, from reproductive maturity to death, for 673 free-ranging female rhesus macaques, *Macaca mulatta*, on Cayo Santiago, Puerto Rico.
3. Using generalized linear mixed-effects models (GLMMs), we first tested if time to death explains the ageing pattern independently of and additionally to chronological age, and if so, whether there is interaction between them. While GLMM captures the patterns in the data well, it is not a generative model. For example, given the GLMM and an individual's reproductive trajectory up to a given age, we cannot directly predict the probability of reproduction or death in the next year. For this reason, we further fitted a hidden Markov chain model (HMM) which allows just such a prediction, and additionally helps infer the process underlying the observed trajectory.
4. We show that, after accounting for individual differences in fertility, reproductive ageing exhibits both age-dependent decline and also an abrupt terminal decline independently of age at death. We infer from the HMM that the underlying process of reproductive trajectory is where individuals cycle between reproductive bouts until they enter an irreversible frail condition that constrains fertility.
5. The findings provide valuable insights into the longitudinal progression of reproductive trajectories in primates, by revealing both age-dependent and age-independent patterns and processes of ageing, and contribute to a growing body of literature on reproductive ageing and senescence across animal taxa.

KEYWORDS
fertility, hidden Markov chain model, primates, reproductive ageing, senescence, terminal decline

1 | INTRODUCTION

How and why fertility differs across the life span has been a long-standing question for demographers and biologists. Reproductive trajectories are a fundamental component of individual fitness, population dynamics, the ecology and evolution of diverse life histories (Healy et al., 2019; Stearns, 1992) and of population projections in conservation planning for vulnerable species (Roach & Carey, 2014). Central to these discussions has been the topic of age-dependent decline in survival and reproduction (i.e. senescence), but reproductive senescence, and its extent and variation across species, remains poorly understood compared to senescence in survival (Lemaître et al., 2020). In contemporary humans, the increasingly delayed first reproduction in the context of low fertility (Mills et al., 2011) not only creates a high need for understanding how fertility differs across life course especially in older ages, but also makes it difficult to fulfil such need given that reproductive potential is not fully revealed. Even in the emerging comparative research on ageing in non-human primates (Emery Thompson et al., 2020), within-individual reproductive trajectory over the life course has not been well-understood, because complete reproductive data from birth to death are extremely difficult to collect from free-ranging populations.

This gap in our knowledge is unfortunate given that senescence, although seemingly likely, is a complex and not necessarily universal phenomenon. Contrary to classic evolutionary theories that generally conclude that senescence is an inevitable outcome of weakening selection at the onset of reproduction (Hamilton, 1966; Kirkwood, 1977; Williams, 1957), recent theoretical (Baudisch, 2008) and empirical evidence (Garcia et al., 2011; Schaible et al., 2015) has shown that ageing may not be synonymous to senescence, and that its pattern differs across the life span (e.g. Barbi et al., 2018). A full understanding of senescence requires studies of a wide range of taxa, and importantly, data based on large number of individuals observed from birth to death. Such data allow for addressing selective disappearance, by statistically dissecting population- and individual-level patterns of ageing. Selective disappearance arises if the number of observable individuals diminish with age, and the attrition is more likely for those with low reproductive potential, resulting in an apparent age-dependent increase in fertility at a population level despite senescence at individual level (Cam et al., 2016; van Noordwijk & de Jong, 1986; Vaupel & Yashin, 1985).

The recent accumulation of high-quality individual-based field data has shown clearer evidence for senescence, highlighting diverse patterns of reproductive ageing across taxa. Most data have come from long-lived vertebrates (Lemaître & Gaillard, 2017; Lemaître et al., 2020), especially large herbivores (Hayward et al., 2013; Weladji et al., 2002) and long-lived seabirds (Froy et al., 2013; Rebke et al., 2010). In primates, who live long lives while reproducing slowly compared to other species of similar body size (Charnov & Berrigan, 1993), reproductive senescence and its comparative patterns have long been of interest especially in regard to the evolution of the post-reproductive life span (Croft et al., 2015; Levitis et al., 2013). Studies suggest that it is the progressive reduction of death rates (i.e. reduction of actuarial senescence), but not the acceleration of reproductive senescence, that may have driven the pronounced post-reproductive life span in women (Alberts et al., 2013; Hawkes & Coxworth, 2013); the pace of reproductive senescence rather appears qualitatively similar across primates (Alberts et al., 2013). An important next step is to take a closer look to clarify the ontogeny of the whole reproductive life course (Atsalis et al., 2008), including its observed patterns as well as its underlying processes. Here, we examine 5,763 annual reproductive states representing the entire reproductive life span from reproductive maturity to death of 673 females from the free-ranging population of rhesus macaques, *Macaca mulatta*, on Cayo Santiago, Puerto Rico. We seek to extend the current literature in two ways.

First, we characterize the observed pattern of the full life span reproductive trajectory to test the presence, onset and rate of reproductive senescence, as well as to test different time-scales shaping the pattern. Previous studies in primates have suggested the presence of reproductive senescence (Altmann et al., 2010; Atsalis et al., 2008; Emery Thompson et al., 2007; Harley, 1990; Hrdy, 1980; Paul et al., 1993; Pavelka & Fedigan, 1999; Raño et al., 2018), while highlighting qualitative similarity in the pace of senescence in reproduction and survival across species (Alberts et al., 2013; Hawkes & Coxworth, 2013). Yet, these findings are based on either cross-sectional data or analysis that does not account for individual differences in longitudinal fertility data, both of which can potentially bias observed patterns in reproductive ageing via selective disappearance. Moreover, while chronological age has been widely explored, there is growing evidence that individuals age at different rates and exhibit gradual or sudden terminal decline in reproductive performance towards the end of life regardless of the age at which they die (Coulson & Fairweather, 2001; Froy et al., 2019; Martin & Festa-Bianchet, 2011; Nussey et al., 2011; Rattiste, 2004; Tarwater & Arcese, 2017). These findings raise the possibility that proximity to death, independently of chronological age, is an important scale of ageing and demographic driver of behaviours (e.g. in humans; Lechler & Sunde, 2020; Seshamani & Gray, 2004), including allocation of resources for reproduction across species (Curio, 1983; McNamara et al., 2009). We provide one of the first tests in primates

for the hypothesis that fertility declines with age but also towards the end of life, using longitudinal data while accounting for between-individual variation in fertility level.

Second, we fitted a hidden Markov chain model (HMM) to the data to understand the hidden process that generates the observed patterns of reproductive trajectories. The process driving reproductive outcomes is difficult to characterize using a few observable traits. Fertility and fecundity at any given time depend on different physiological and behavioural components (Lemaître & Gaillard, 2017), ranging from oocyte production to parental care (Hayward et al., 2013), each of which may undergo heterogeneous patterns of change (Te Broekmans et al., 2007; Djahanbakhch et al., 2007; Velde & Pearson, 2002); moreover, mechanisms underlying such change are themselves highly multidimensional and emerge from the multiple synergies of different components (Bell, 1972; Bortz, 2010; López-Otín et al., 2013; Walker & Herndon, 2010; Xia et al., 2017). One way to address this complexity is to utilize analytic tools that describe trajectories in their entirety, based on an assumption that observed events such as fertility and death are the reflection of *hidden* states comprised of biologically meaningful constructs, such as health. HMMs provide a parsimonious explanation for time-series data characterized as transitions between a number of distinct hidden states that produce observations. In this study, we applied a HMM to describe the hidden process underlying a female reproductive trajectory as transition between hidden states, whereby each state is characterized by differential probabilistic associations between reproductive output and mortality. Interpreting the distinct associations and their order could help build a heuristic model for detecting the force shaping reproductive trajectories. For example, despite the expected costs of current reproduction to an individual's survival and future reproduction (Williams, 1966), reproductive trajectories often exhibit positive state dependence whereby successful reproduction is often followed by a *higher* probability of surviving and reproducing in the next state (Reznick, 1985; Reznick et al., 2000). In long-lived animals, this observation may be in part due to a conservative strategy that favours survival over reproduction (Hamel et al., 2010). As such, the costs of a current reproductive bout might not manifest immediately but instead develop through a long-term process (Clutton-Brock & Sheldon, 2010).

Taken together, our study aims to provide an integrated view of the progression of fertility changes in a non-human primate, by characterizing the observed pattern and hidden process of female reproductive trajectories. In analysing the observed pattern, we used generalized linear mixed-effects models (GLMMs) to test if time to death explains the ageing pattern independently and additionally of chronological age, and if so, whether there is interaction between them. While GLMM captures the patterns in the data well, it is not a generative model. For example, given the GLMM and an individual's reproductive trajectory up to a given age, we cannot directly predict the probability of reproduction or death in the next year. For this reason, we fitted an HMM, which allows just such a prediction and additionally helps infer an underlying process of observed trajectory.

2 | MATERIALS AND METHODS

2.1 | Study site and population

Cayo Santiago is a 15.2-ha island located 1 km off the South-East coast of Puerto Rico. The monkeys range freely on the island and live in naturally formed social groups with evidence of dissociative mating producing genetic outbreeding (Widdig et al., 2017). Rhesus macaques form multi-male, multi-female groups and individuals of both sexes mating with multiple partners (Southwick et al., 1965). The population exhibits a birth-pulse model of reproduction due to marked seasonality and synchrony in reproduction in an annual cycle, whereby birth seasons and mating seasons alternate at ~6-month intervals (Hernández-Pacheco et al., 2016; Vandenbergh & Vessey, 1968). Average litter size is one, with very rare incidence of twinning (Geissmann, 1990). Demographic information has been recorded continuously since 1956 from birth to death through daily (Monday–Friday) monitoring by the census team at Caribbean Primate Research Center (CPRC). The animals are not handled outside the annual 2-month trapping periods, during which some animals are captured to mark all yearlings with an individual tattoo and ear notch pattern, to obtain their blood samples for the genetic pedigree, and in some years to remove individuals for population control. The Cayo Santiago population lives in the absence of natural predators and is provisioned with commercial monkey chow, between 0.11 and 0.27 kg/day during 1959–1979 (Sade et al., 1985) and currently 0.23 kg/day per animal. As such, the population exhibits high survival and fertility rates, likely extended life span and relatively high demographic stability.

2.2 | Data selection

We carried out data processing, statistical analyses and visualization in R version 3.4.2 (R Development Core Team, 2018).

From the CPRC demographic database, we obtained data on 17,727 observation-years from 2,375 females whoever reached their second birthday, the minimum age at which female rhesus macaques were observed to give birth on Cayo Santiago (2.9 years; 2 out of 2,375) between 1965 and 2017. From here, we selected 758 females, who died on the island (i.e. their entire life span is known) and were observed between the ages of 3 years, when most female rhesus macaques become capable of reproduction (Bercovitch et al., 1998; Pittet et al., 2017), and 25 years, when ovulatory cycles typically cease (Gilardi et al., 1997; Walker, 1995) and by which 99.3% of the Cayo Santiago females are dead. We further excluded observations of reproductive states from the last year of life, because observations of fertility outcomes are incomplete in the year of death depending on whether a female died before or during/after the birth season or not; dying before the birth season would not give a female an opportunity to reproduce, while dying during or after the birth season would give such an opportunity. As a result, the final sample size for the current study was 673 females, whose reproductive records

spanned from age 3 until the year prior to death. Among them, 616 gave birth to at least one offspring, and their age at first reproduction was mostly either 3 (34%) or 4 (55%). The other 57 females, who never reproduced, mostly died between 4 and 5 years old (86%).

To generate sequences of individual reproductive life spans, we coded a reproductive state of having either 'Reproduced [R]' or 'Not-reproduced [NR]' for a given year (Figure 1). Due to reproductive synchrony and seasonality on an annual cycle, female rhesus macaques on Cayo Santiago can reproduce only once every year in principle. The age in a given year was rounded down to the nearest integer number so that an age is interpreted as whether or not a female past the *i*th birthday. For the HMM analysis, an additional state 'Dead [D]' was added to the end of the sequences so that the transition from each reproductive state to death can be estimated.

2.3 | Statistical analysis

2.3.1 | The observed pattern of reproductive trajectories

We fitted GLMMs with a logit-link function for the response variable of whether (1) or not (0) a female reproduced in a given year. All GLMMs were fitted using the R package 'lme4' version 1.1-21 (Bates et al., 2015) and included: (a) two random effects—female identity and the year of reproduction, to account for the repeated observations from same individuals and the yearly variation in birth rates respectively; and (b) life span as a fixed effect. This model structure formed a 'base model' to which other fixed effects were added (see below). While the random effects of female identity allowed for addressing individual heterogeneity in fertility, the fixed effect of age at death addressed the potential selective disappearance in the data by centring observations within groups that have the same age at death (Bouwhuis et al., 2009; Hayward et al., 2013; Nussey et al., 2006; van de Pol & Verhulst, 2006; Reed et al., 2008). This within-group centring approach can also be undertaken using age at last reproduction. In rhesus macaques, life span closely scales with age at last reproduction and reproductive life span, because more than 90% of females initiate reproduction during a narrow window of age (between late 3 and 4 years; Bercovitch & Berard, 1993; Pittet et al., 2017) and die before post-reproductive life (Johnson & Kapsalis, 1998; Walker, 1995). Using age at death instead of age at last reproduction also enables including individuals who never reproduced into analyses. Furthermore, among the 673 females who comprised our final sample for all analyses, 6.7% were born after 2000 and thus belong to cohorts that are not completely extinct. As a result, our observations of age above 15 years are progressively less represented by younger cohorts, which may induce additional potential of selective disappearance by cohort if there is life span difference between younger and older cohorts. This potential problem is addressed in our study by the inclusion of age at death in our GLMM analyses, assuming that selective disappearance would be an issue to a similar extent across birth cohorts.

In the first set of GLMMs, we determined the functional form of chronological age on fertility, by comparing base models described above with different terms for chronological age (in years, standardized by the average), specified as either linear, quadratic, cubic or threshold fixed effects (see Table S1 for details on the threshold analysis). We compared the Akaike information criterion (AIC) of models and selected the model with the lowest AIC (Burnham & Anderson, 2002).

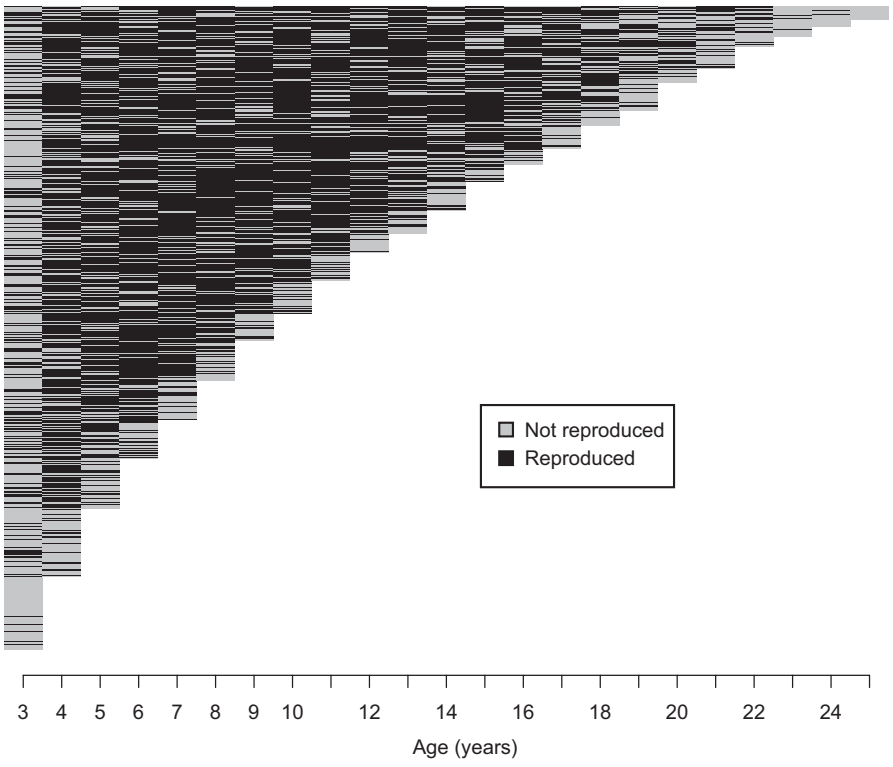

FIGURE 1 Reproductive sequences of female rhesus macaques of Cayo Santiago whose entire reproductive sequence from ages 3 to 25 is available ($n = 758$). The horizontal transition of yearly reproductive states exhibits different temporal patterns within individuals, while the vertical comparison suggests considerable variation in reproductive trajectories between individuals

We ran the second set of GLMMs to compare the effects of chronological age with years to death (YTD). We added the following variables and their combinations to the base model: age, YTD and the interaction between age and YTD. Based on the three stages of ageing identified from the above first analysis (also see Results), age was coded separately into three threshold terms. YTD was treated as a categorical variable (1, 2 and 3 YTD; 4+ YTD as a reference) based on previous findings in other taxa on the abrupt changes in reproductive performance towards the end of life (Froy et al., 2013; Martin & Festa-Bianchet, 2011; Tarwater & Arcese, 2017). Evidence for the interaction between age and YTD would suggest any terminal effect differs by age. In testing the age and YTD interaction, we considered a scenario that the terminal effect manifests differently across the three ageing phases. We created three dummy variables indicating whether a female is in a particular phase in a given year. Once the best-supported GLMM was obtained through model selection, we conducted a supplementary analysis on the subset of individuals whose rank information was available (4,472 birth records from 442 females). In the Cayo Santiago population, higher dominance rank may confer fertility advantages mainly via earlier onset of reproduction and higher offspring survival rate in higher ranking females (Bercovitch & Berard, 1993; Blomquist et al., 2011). We sought to examine if any of the temporal patterns examined might differ by rank categories.

2.3.2 | The hidden process underlying reproductive trajectories

Markov chain models describe sequence data using the probabilities of transition between the states ('transition probabilities'). The initial state follows a categorical distribution described with parameters p_s^0, where $s \in \{\mathrm{R}, \mathrm{NR}\}$:

$$p_s^0 := \mathrm{P}(S_{t=0} = s), \tag{1}$$

Then the probability of transitioning from s to s' is the conditional probability that the current state at t is s' given that the previous state at $t-1$ is s, that is

$$p_{s,s'} := \mathrm{P}(S_t = s' | S_{t-1} = s). \tag{2}$$

For example, there are three possible transitions from the state of R, that is, R to R, R to NR and R to D. The transition probabilities from a given state add up to 1:

$$p_{\mathrm{R,R}} + p_{\mathrm{R,NR}} + p_{\mathrm{R,D}} = 1, \tag{3}$$

If each transition depends only on the state at $t-1$, the sequence is called a Markov chain with first-order dependence. The Markovian model thus allows for the incorporation of non-random state dependency in longitudinal data, and HMM expands this approach by assuming that a finite set of *latent* states underlie the series of observations (MacDonald & Zucchini, 1997; Zucchini et al., 2017). A hidden Markov chain assumes a finite number of *unobserved* 'hidden states' that form a Markov chain, which then 'emit' observations. That is, given a hidden state s, each category of an observation y has a certain probability $q_{y,s}$ ('emission probability') to be observed:

$$q_{y,s} := \mathrm{P}(Y = y | S = s), \tag{4}$$

Inference about the sequence of hidden states is made when an HMM is fitted to observations. The fit gives (a) the probability that a hidden process starts in each hidden state ('initial probabilities'; p_s^0), (b) the probabilities of each observed state (R, NR and D) occurring in a particular hidden state ('emission probabilities'; $q_{y,s}$), and (c) the transition probabilities between hidden states ($p_{s,s'}$).

We used the R package 'seqHMM' (Helske & Helske, 2019) version 1.0.14 to fit the HMMs. We first fitted candidate models with the number of hidden states from 2 to 5, because the number of hidden states needs to be determined by model comparison (see below) within a range provided by a researcher based on prior knowledge. We chose to try this range, because previous studies applying HMM to human life course data have found that models with a small number of states were either best supported by model comparison or more interpretable (Han et al., 2020; Helske et al., 2018). Since HMMs with more hidden states are strictly more flexible than those with fewer hidden states, we compared the candidate models with Bayesian information criterion (BIC), which is minimized with the model that most efficiently predicts the data, by penalizes model complexity. A caveat for fitting an HMM is that it is in general not possible to ensure that fitted parameters of an HMM are at the global optimum. Thus we followed procedures recommended by Helske & Helske (2019) to increase the chance by exploring the parameter space. Specifically, for each candidate HMM, we tried 100 initial values for the parameters (initial, emission and transition probabilities) by supplying 'control_em = list(restart = list(times = 100))' option to the fit_model function. The function then fits the parameters using the expectation–maximization algorithm (Helske et al., 2016) until convergence, randomly jitters the fitted parameters with Gaussian noise ($SD = 0.25$), normalizes them so that probabilities sum to one, and then uses the jittered values as the initial values of the parameters for the next fit. It repeats until it has tried 100 fits, and gives the best fit among them. We supply the initial and fitted values of the parameters in Table S2. The values differ qualitatively from each other, showing that the combination of the expectation–maximization algorithm and random jitter successfully explored the parameter space.

3 | RESULTS

3.1 | The observed pattern of reproductive trajectories

The age-dependent trajectory of fertility was best described by a piecewise linear function of age that changes slope at ages 6 and

17 (Figure 2; Table S1), suggesting three stages of reproductive ageing: (a) a maturation period between ages 3 and 5, during which fertility increases (mean posterior log odds of age 3–5: $\beta = 0.69$, 95% confidence interval = [0.63, 0.76]), (b) the reproductive 'prime' period until age 17, during which fertility stays at a high level with minimal decline (Age 6–16: $\beta = -0.07$, [−0.10, −0.05]), followed by (c) the 'post-prime' period after age 17, during which the fertility rapidly declines (Age 17–25: $\beta = -0.48$, [−0.54, −0.41]; Table S3). Thus, while reproductive senescence in fertility begins early during a reproductive career (age 6), a more marked decline appears after 17 years old, which is also reflected in the population-level pattern (Figure 2). According to the model with the best-supported age function (Table 1), individual differences in life span were not related to the variance of annual fertility (Age at death: $\beta = 0$ [−0.01, 0.02]) after accounting for the ageing effect.

Fertility further declined towards the end of life, in particular the year before death (Table 1, YTD1: $\beta = -0.33$ [−0.53, −0.13]), which we term terminal decline. Model comparison results suggested there is no detectable interaction between the terminal decline and age (Table S4), indicating that the terminal decline effect was consistent across age (Figure 3). In a subset of individuals with rank information available, we did not find evidence that rank modulates either the effects of ageing or terminal decline on fertility (Table S5). Our main findings stayed the same also when younger birth cohorts were excluded from the analyses (Table S6), suggesting that, although the average age at death becomes predictably slightly higher when the younger cohorts are excluded (median = 9.7, mean = 11.42) than when included (median = 9.5, mean = 11.10), this difference is not substantive.

3.2 | The hidden process underlying reproductive trajectories

To determine the number of hidden states, we compared HMMs with different number of hidden states with BIC, which gave overwhelming support for the model with four hidden states (BIC=8,634.11, 8,088.93, 8,125.99 and 8,131.34 for HMMs with two, three, four and five hidden states respectively; $\Delta BIC > 37$ ['very strong' support; Kass & Raftery, 1995] in favour of four hidden states compared to each of the alternatives considered). To identify qualitative features that supported the four-hidden state model, we compared it with the next best model, the three-hidden state model, by simulating the data with both models and replicating Figure 3. For the simulation, we first sampled the initial states of simulated individuals (whose number is matched with data) from a categorical distribution parameterized as in Equation 1. Then we sampled the observation of each individual using Equation 4, and sampled the next state using Equation 2, until the observed state is death for the individual. When data simulated from the four-state HMM and three-state HMM are compared, the four-state HMM captured the dependence of fertility on both age and YTD (Figure S1 top, difference between black [$YTD \leq 3$] and grey [$YTD > 3$] lines), while the three-state HMM failed to capture the dependence on YTD (Figure S1 bottom). This suggests that the four-state HMM is better in line with the evidence suggested from the GLMM, which shows that fertility depends on both age and YTD (Figure 3).

The estimated parameters of the four-state HMM are shown in Table S7. According to the four-state HMM, an individual's reproductive trajectory begins either in the hidden state 1 (with the probability of 0.69) or the hidden state 2 (with the probability of 0.31) which only emit the observed states of either 'Not-reproduced [NR]' or 'Reproduced [R]' respectively. This initial characteristic of the process reflects that some individuals gave birth to their first offspring after age 3, while others did so at age 3, the age at which the reproductive sequences used for the HMM analysis started from. Based on this information, the hidden states 1 and 2 were interpreted as 'Not-reproducing' and 'Reproducing' states respectively. The trajectory ended in the hidden state 4 to which other hidden states enter but from which no transition to other hidden states is made (Figure 4a). This absorbing state is also characterized by its emission of the observed state of 'Dead [D]' only. We thus interpreted this

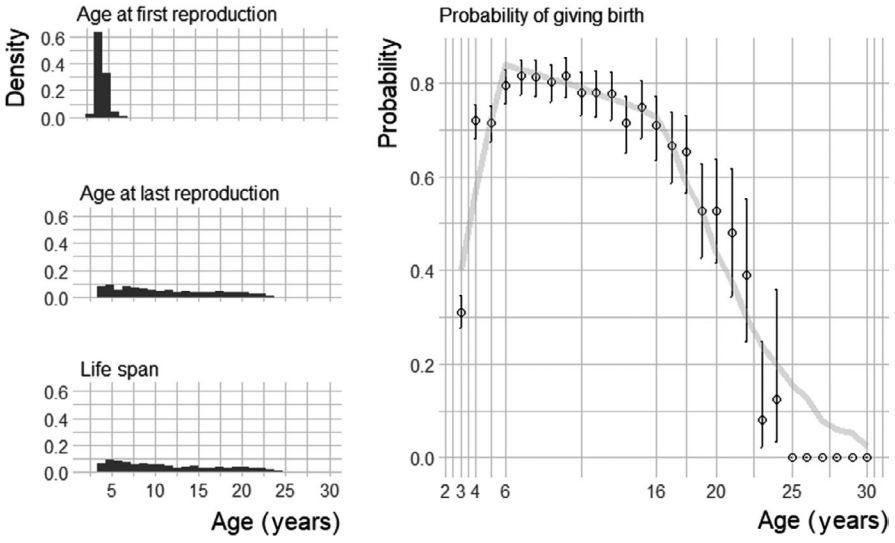

FIGURE 2 Age-related reproductive parameters in the female rhesus macaques of Cayo Santiago ($n = 673$). The right panel shows birth rate depicted by black open points (probability of giving birth) and lines (95% confidence interval): the former is calculated as the proportion of offspring born by females who reach the *i*th birthday (Caswell, 2000), and the latter is calculated by Bayesian inference which uses a beta prior on the probability of success for a binomial distribution. The bold grey line is the fit from the model presented in Table 1

TABLE 1 GLMM outputs on the annual fertility in the female rhesus macaques on Cayo Santiago ($n = 673$). The model is supported by model comparison results (Table S4). The Gelman sim technique was used to estimate 95% confidence intervals (Gelman & Su, 2018), and estimates with the CI not including zero are bolded

	Posterior mean of log odds	Lower 95% CI	Upper 95% CI
Fixed effects			
(Intercept)	1.76	1.48	2.04
Age: 3–5	**0.71**	**0.64**	**0.77**
Age: 6–16	**−0.07**	**−0.09**	**−0.04**
Age: 17–25	**−0.45**	**−0.52**	**−0.38**
Age at death	0	−0.02	0.0
YTD1	**−0.33**	**−0.53**	**−0.13**
Random effects	***SD***		
Individual ($n = 673$)	0.42	0.35	0.47
Calendar year ($n = 57$)	0.14	0.13	0.16

hidden state as the state of being dead (as distinct from the event of 'death').

Once the process initiates, individuals make different transitions depending on the hidden state they started in. While the majority of transitions (0.74) from the hidden state 1 ('Non-reproducing') is to the hidden state 2 ('Reproducing'), most of the transitions from the 'Reproducing' state are back to itself (0.66). This strong tendency for the hidden state 'Reproducing' to repeat may characterize the reproductive prime period. In support of this, the predicted probability of the hidden state 2 peaks at age 6 and remains higher than any other hidden states until around 17 years old (Figure 4b). Apart from self-transitioning, the 'Reproducing' state transitions to the 'Non-reproducing' (0.24) or the 'Dead' state (0.1). The 'Non-reproducing' state predominantly transitions back to the 'Reproducing' with high probability (0.9) and repeats itself only with relatively low probability (0.1). We thus interpreted the loop formed between the 'Reproducing' and the 'Non-reproducing' states as the 'Reproductive prime loop' where individuals mostly repeat reproduction but also occasionally pause (skip a year) before resuming reproduction. The loop weakens as the frequency of pause (i.e. entering the hidden state of 'Non-reproducing') increases after around 17 years, possibly marking the onset of senescence (Figure 4b). The 'Reproductive prime loop' ends when the hidden state 1 or 2 transitions into the hidden state 4 ('Dead'), or when the hidden state 2 transitions to the hidden state 3. Once in the hidden state 3, not only the emission of the observed state 'Not-reproduced' increases markedly compared to that during the 'Reproductive prime loop', but also it is no longer possible to return either to the previous 'Reproducing' or 'Non-reproducing' states. Once entered, the hidden state 3 mostly stays in itself (0.81) or makes transition to the 'Dead' state (0.19). Given this dynamic, having reproduced in this hidden state entails a higher chance of not-reproducing or even dying, compared to the reproduction observed during the hidden state 1. We therefore interpreted the hidden state 3 as representing an 'Inescapable terminal decline', a hidden frail condition (hence decline), from which females can never recover to prior healthier states (hence inescapable), and from which they can only transition to death (hence terminal). The prevalence of the hidden state 'Inescapable terminal decline' remains low (but is not zero) until it rapidly increases after mid-teens (Figure 4b).

4 | DISCUSSION

In this study, we examined the observed pattern of annual fertility across the life span within individuals and applied an HMM to our data, an approach that has been rarely used to characterize the underlying processes of the life course trajectory. Our results showed both age-dependent and -independent declines in fertility that are independent from each other. The mode of reproductive senescence comprised of an initial improvement, a plateau with minimal decline, and then a rapid decline in fertility starting from mid-teens, after accounting potential influence of selective disappearance in the data. The best-supported four-state HMM represents the transitions across reproductive trajectory as a process that begins with a strong tendency to repeat reproduction until entering an irreversible state in which the tendency to not reproduce is lowest and the transition to death is highest.

Our results on the observed pattern of within-individual fertility provide clear evidence for reproductive senescence in female primates, which was previously indicated by cross-sectional analyses of smaller samples. While there was strong support for fertility declines with age, we also find several nuances to this general pattern. First, although the strength of selection is generally assumed to start declining upon the onset of reproduction, hence the beginning of senescence (Williams, 1957), we find that the beginning of reproductive senescence is a few years after the average age at first reproduction and is preceded by a short period of fertility improvement. This is also the period when the majority of female rhesus macaques who never reproduced or reproduced only once died, reflected in the steep increase in age-specific mortality after age 2 (Figure S2),

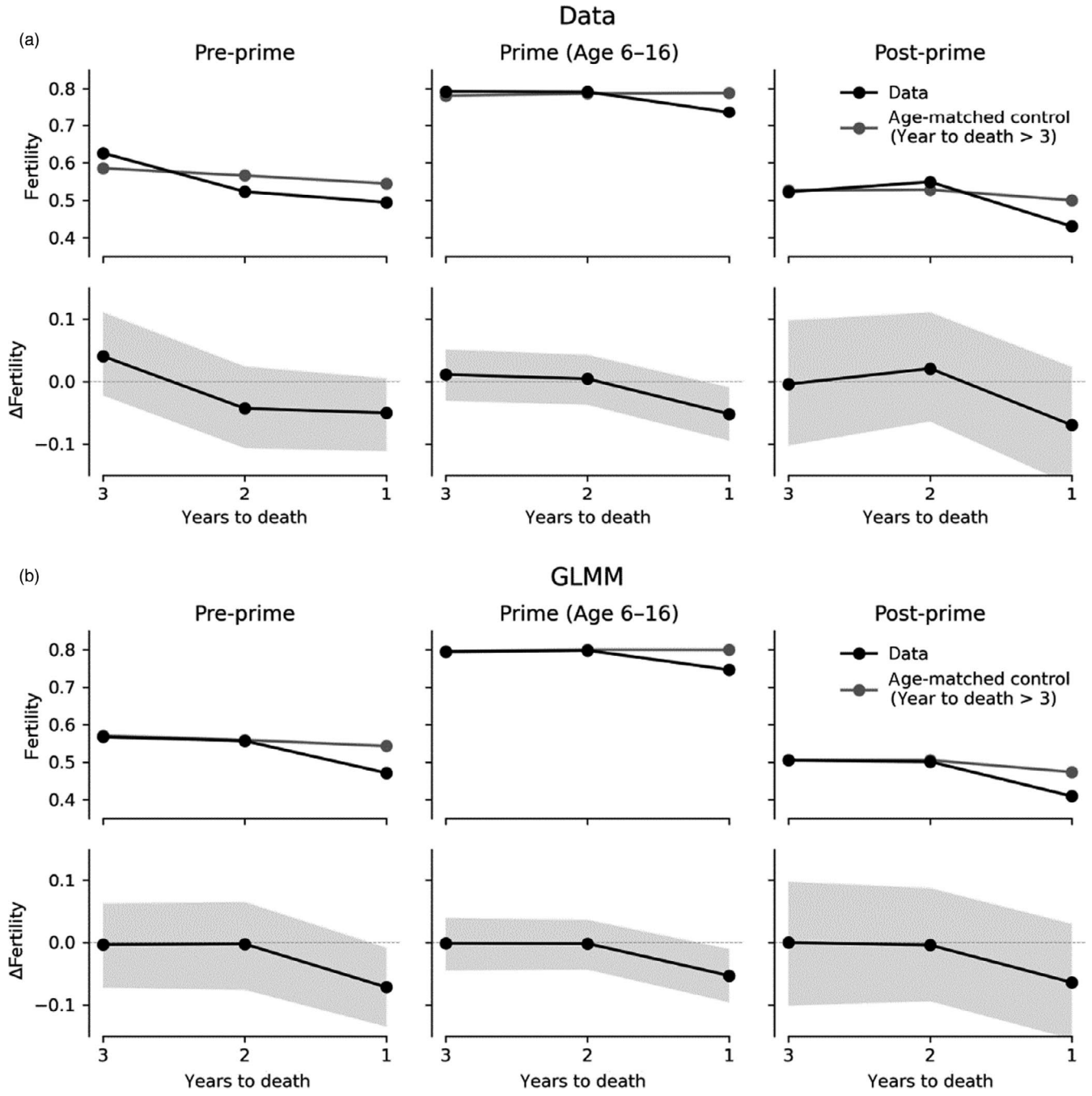

FIGURE 3 Fertility as a function of years to death (YTD). To compare data (a) with the prediction of the GLMM (b), we simulated the dataset using the fitted parameters of the model (Table 1) 1,000 times, and plotted the average prediction and the middle 90% interval (shade). The prediction replicated fertility's dependence both on age and on YTD. For each A and B: top panel shows proportion of females reproducing 3, 2 or 1 years before death in the data (black) and in an age-matched control (YTD ≥ 4; grey). The age-matched control is computed separately for each YTD. It is the fertility of the females with YTD ≥ 4 averaged across ages, with each age weighted by the proportion of that age among the females with the corresponding YTD, and bottom panel shows difference of the data from the control (black line) and middle 90% quantile of the 1,000 samples from the null distribution (grey shade). The null distribution was constructed by shuffling the YTD label in the original data within each age

suggesting a selection potentially based on individual reproductive potential driving the early improvement in fertility. In the threshold models we ran to determine age segments, we obtained the same threshold ages for age segments whether we do or do not include the first reproduction into the analyses. That is, the 'pre-prime period' ends at 6 years. This suggests that the improvement in fertility during the early years is not entirely explained by primiparity. Second, we also find that senescence is not linear but comprises of earlier plateau and later acceleration phases, in line with previous findings from long-lived mammals (Gaillard et al., 2000). The beginning of

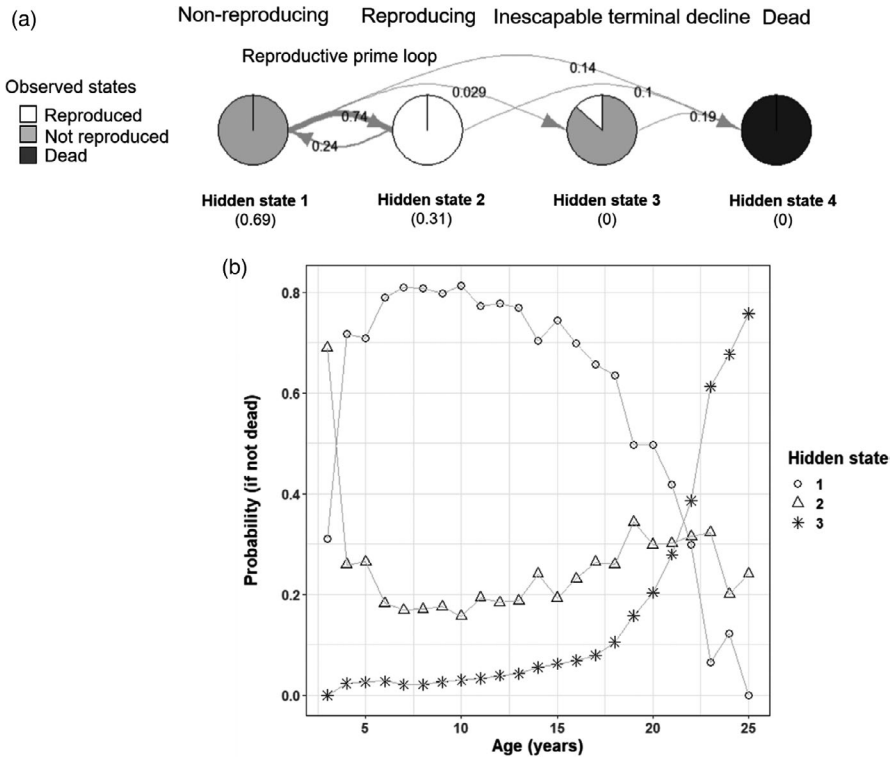

FIGURE 4 The four-state hidden Markov chain model output summarized as a set of pie charts comprised of nodes and edges (a), and the proportion of surviving individuals occupying the hidden states 1 to 3 (b). (a) Each 'pie' is a hidden state, and each slice in a pie chart represents the probability that an observed state occurs given the hidden state ('emission probability'). Each arrow and the associated number show the probability of transition between the hidden states ('transition probability'). The probability that a sequence initiates in each state ('initial probability') is shown in parentheses below each pie chart. (b) Age-specific occupancy predicted for the hidden states 1 to 3, conditional on not yet having been absorbed by the hidden state 4 ('Dead'). Each point corresponds to the average proportion of individuals predicted to be at the respective hidden state in a given age

the earlier plateau phase is when the age-specific mortality remains low and begins to increase thereafter (especially after 10 years old; Figure S2). Thus, the high-level of fertility, with only minimal degree of senescence, that is characteristic of this phase reflects the performance of individuals who survived the earlier selection (during the first few years of reproductive career) in line with a recent evolutionary model of ageing that predicts plateau in mortality and fertility to arise when vitality cannot increase indefinitely (Baudisch, 2008). After the earlier phase of minimal senescence, a much stronger age-dependent decline begins after around 17 years, a few years after the senescence in terms of survival decline begins (Figure S2). Taken together, there is some degree of asynchrony in the onset and rate of senescence between reproduction and survival, similar to the previous findings that patterns of senescence differ between traits and even within reproductive traits (Gaillard & Lemaître, 2017; Hayward et al., 2013, 2015). The clear pattern of senescence in fertility suggested from the present study encourages future studies to test senescence in other reproductive traits (e.g. offspring weight, maternal body condition, maternal care behaviours) that are available on Cayo Santiago, to better assess various hypotheses regarding optimal allocation of resources to reproduction over time (e.g. terminal allocation Weladji et al., 2010 or investment Clutton-Brock, 1984).

We also found the presence of an age-independent terminal decline according to time to death, a scale of tempo in ageing that has gained increasing attention to date (Gaillard & Lemaître, 2020). In the female rhesus macaques of Cayo Santiago, fertility drops during the year before death independently of age at death and similarly across the age range, suggesting a robust presence of such terminal decline in fertility. The finding highlights the need for considering different time-scales when testing various predictions regarding how the allocation of resources to reproduction changes towards the end of life (Duffield et al., 2017; McNamara et al., 2009). For example, facing increased costs of reproduction, female rhesus macaques may allocate more resources to current reproduction with age, such as increased contact time with newborn offspring among older mothers (Hoffman et al., 2010). Whether such behavioural strategy develops within individuals as they reach old age and/or time to death, and how the temporal pattern helps mitigate offspring mortality that rapidly increases after around mid-teens (Blomquist, 2013) will need to be tested, to link reproductive senescence to various hypotheses regarding how it might shape strategies of resource allocation to reproduction (Weladji et al., 2010). Moreover, distinguishing different time-scales of change late in life helps better understand why large individual variation in the rate of ageing exists. For example, individual variation in underlying physiological condition may determine the allocation of resources to reproduction in addition to the chronological age per se (McNamara et al., 2009; Ricklefs, 2008). Studies on the physiology of ageing have shown that female rhesus macaques experience a number of physical and physiological declines with age. For example, cross-sectional data have shown that body mass index and body fat (as measured by abdominal fat thickness) begin to decline between ages 15 and 19 (Schwartz & Kemnitz, 1992), and that anti-Müllerian hormone, a predictor of ovarian reserve in humans and non-human primates, begins to negatively correlate with age from 12 years onward (Long et al., 2018). It remains to be seen whether these measures exhibit terminal decline towards the end of life independently of age, and if so, how such change is related to the terminal decline in fertility observed in the present study.

While serving as useful proxies of ageing, physical and physiological measures often represent just one component of the overall reproductive phenotype and also may themselves interact and undergo their own trajectory of change. The HMM inferred a latent process driving the complex transitions between observed states as a whole. The presence of hidden state 3, which we interpreted as 'Inescapable terminal decline', provides a unifying explanation for the coexistence of the age-dependent and -independent decline in fertility as identified from the observed pattern. An individual who entered this hidden state at any age would show both low fertility and high mortality, explaining the age-independent fertility decline, but at the same time, the proportion of individuals who are in this hidden state increases with age (because the state is inescapable), also explaining the age-dependent fertility decline.

We interpret and conceptualize such a terminal condition as frailty, a syndrome of decreased resiliency and reserves, resulting from crossing a threshold of aggregate dysfunction with ageing which prevents physiological recovery (Fried et al., 2001, 2009). Increasing evidence from gerontology suggests that frailty involves nonlinear change in multiple systems and is independent of chronological age (Fried et al., 2009), while frailty can become a significant feature of health in older individuals (Clegg et al., 2013). In the light of our findings on the observed pattern of reproductive trajectory, we may also interpret that frailty depends on both chronological age and time to death. In terms of former, the presence of senescence at slower rates at younger ages may indicate that the critical threshold for frailty has not been reached even though senescence has already begun. However, even if an individual dies before senescence begins, a terminal decline is present (Figure 3), and a non-zero proportion of individuals is predicted to be in the 'Inescapable terminal decline' before mid-teens (Figure 4b), suggesting that the threshold for frailty is not entirely age dependent. In this regard, our findings spur questions about factors that predict the entering of the terminal state. The possibility of incorporating covariates into the model is another attractive aspect of HMM, but, to our knowledge, computational options are as yet challenging for doing so for state sequences comprised of more than three observed states. Building on the HMM identified from the present study, future applications of HMM could further investigate whether and how transition rates between hidden states change over time, for example by modelling the state dwell-time distributions (e.g. time spent in a reproductive state, such as inter-birth interval length; Langrock & Zucchini, 2011) or by directly incorporating different time-scales as covariates to the model (Zucchini et al., 2017).

Taken together, our findings not only contribute to the growing body of evidence on reproductive senescence across life span across multiple taxa, but also highlight that time to death independently influences the observed pattern of female reproductive trajectories. Taking advantage of an already existing literature on the physiological senescence in rhesus macaques, future studies can demonstrate underlying mechanisms of the terminal decline in fertility. Differences in the rates of senescence across different reproductive components have been demonstrated in other large-bodied mammals (Gaillard & Lemaître, 2017; Paterson et al., 2016; Weladji et al., 2010). Future studies could also measure physiological and social traits (Kaplan, 2008) that might contribute to the greater ability to return to the fully reproducing state during the early period of a female's reproductive career (in rhesus macaques, prior to 16 years old). Other next steps would be to examine temporal patterns in male reproductive output (Lemaître & Gaillard, 2017; Muller et al., 2020), as well as how the temporal change in female fertility interacts with maternal effect senescence (e.g. offspring quality; Ivimey-Cook & Moorad, 2020; Moorad & Nussey, 2016). Methodologically, we demonstrated that repeated measures in longitudinal data provide a compelling context in which to account for the individual heterogeneity and age-related difference in reproductive outputs using mixed-effects models (de Pol & Verhulst, 2006; van Nussey et al., 2008). We also presented HMM as a useful tool for modelling latent processes in life-history trajectories that are difficult to observe over time. We hope that the present study stimulates applications of HMM and related models (Bartolucci et al., 2009; Piccarreta & Studer, 2019) for future research on the trajectory of life-history traits and their underlying mechanisms.

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CONFLICT OF INTEREST

The authors have no conflict of interest to disclose.

AUTHORS' CONTRIBUTIONS

D.S.L. designed and performed research, analysed data and wrote the paper; Y.H.R.K. analysed the data and wrote the paper; A.V.R.-L. provided the data and translated the abstract into Spanish; J.H. designed and performed the research, and wrote the paper.

DATA AVAILABILITY STATEMENT

All data used in this study are publicly available at https://figshare.com/s/e3967fac50ad90c6c2d9 (Lee et al., 2021).

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