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J. Grasman, H.M. Salomons, S. Verhulst. Stochastic modelling of length dependent telomere shortening in. *Journal of Theoretical Biology*, 2011, 282 (1), pp.1. 10.1016/j.jtbi.2011.04.026 . hal-00709548

HAL Id: hal-00709548

<https://hal.science/hal-00709548>

Submitted on 19 Jun 2012

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Author's Accepted Manuscript

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PII: S0022-5193(11)00226-8
DOI: doi:10.1016/j.jtbi.2011.04.026
Reference: YJTBI6457

To appear in: *Journal of Theoretical Biology*

Received date: 28 April 2010
Revised date: 27 February 2011
Accepted date: 23 April 2011

Cite this article as: J. Grasman, H.M. Salomons and S. Verhulst, Stochastic modelling of length dependent telomere shortening in *Corvus monedula*, *Journal of Theoretical Biology*, doi:10.1016/j.jtbi.2011.04.026

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Stochastic modelling of length dependent telomere shortening in *Corvus monedula*

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Abstract

It was recently shown that, within individuals, longer telomeres shorten at a higher rate. This explorative study deals with a mathematical model of this process. It is a nonlinear differential equation describing length-dependent decrease that can be linked to a Poisson process. The model also takes in account telomere shortening due to the end replication problem. Parameters are fitted using data from samples of red blood cells of free-living juvenile corvids. The Poisson process can be related to oxidative stress causing DNA strand breaks. The shortest telomeres in a genome are the best predictors of survival, and one can therefore hypothesize on functional grounds that short telomeres should be better protected by some control mechanism in the cellular system. However, the present study shows that such a mechanism is not required to explain length-dependent telomere shortening: agents of telomere shortening such as oxidative stress with a certain strength modeled by a Poisson process with an appropriately chosen parameter suffices to generate the observed pattern.

Key words telomere shortening, end replication, DNA strand break, oxidative stress, stochastic process

1. Introduction

Telomeres are highly structured, non-coding DNA elements at the end of linear eukaryotic chromosomes. In vertebrates they consist of tandem repeated highly conserved DNA sequence (5'-TTAGGG-3')_n. Telomeres play an important role in the protection of chromosome integrity (Blackburn, 1991) and in the longevity of organisms: associations between telomere length and survival were demonstrated in humans (Cawthon et al., 2003; Kimura et al., 2008; Bakaysa et al., 2007; Aviv, 2008), birds (Hausmann et al., 2005; Bize et al., 2009; Salomons et al., 2009) and nematodes (Joeng et al., 2004). Moreover, comparing species, it was found that the telomere shortening rate is correlated with maximum lifespan: short lived species lose their telomeres at a higher rate (Hausmann et al., 2003). It has been anticipated that telomere length, and its shortening rate in particular, may potentially be used as a proxy for the 'life stress' experienced by individual organisms (Epel et al., 2006; Kotrschal et al., 2007) and hence serve as a marker of an individual's 'biological age'. Telomere shortening rate is accelerated by oxidative stress (Von Zglinicki, 2002; Tchirkov and Lansdorp, 2003). Since oxidative stress is often considered a major agent of senescence (Beckman and Ames, 1998), it provides a potential mechanistic link explaining associations between telomeres and life span, in that shorter telomeres may indicate that

the organism experienced higher levels of oxidative stress (Jennings et al., 2000; Monaghan and Haussmann, 2006). The length of the shortest telomere(s) has been suggested to determine when cellular senescence starts (e.g. Hemann et al., 2001; Capper et al., 2007; Di Fagagna, 2003; Shay and Wright 2005). On functional grounds one expects therefore that defensive mechanisms against DNA damage have evolved to act stronger on chromosomes with short telomeres (Karlseder et al., 2002), resulting in a lower shortening rate of shorter telomeres (Hemann et al., 2001; Martens et al., 2000).

In literature several models of telomere dynamics can be found (Proctor and Kirkwood, 2002a; Sidorov et al., 2004; Rodriguez-Brenes and Peskin, 2010). The present study differs from these studies in that we develop a stochastic model that specifically describes length-dependent telomere shortening. As an alternative for intensified DNA repair (negative feedback control), or some form of increased protection, that may explain why shorter telomeres decrease slower in length (Karlseder et al., 2002), we choose to test whether a simpler mechanism, not based on an active response of the cell, could be sufficient to generate the observed pattern. We assume that over a short telomere interval the risk of breaking of a telomere within a fixed time span is proportional with the length of that interval. Thus, we build on the assumption that telomeres are simply more vulnerable if they are larger targets. In line with Nitecki and Hoffman (1987) and Wilkinson (2006) we choose the Poisson process to describe this effect in a stochastic model. A mathematical model is formulated based on biological and physical arguments. In a next step the parameters of this model are fitted to data of empirical observations (Salomons et al., 2009). We consider data on telomere length of samples of blood cells of nesting jackdaws (*Corvus monedula*) from an observational study (Salomons et al., 2009). The data has random components requiring a robust model with a small number of parameters.

In an earlier study telomere length and its shortening in erythrocytes of jackdaws has been quantified (Salomons et al., 2009). Telomere length varies between erythrocytes and between chromosomes within a genome (Baird et al., 2003; Lansdorp et al., 1996; Martens et al., 1998). A degree of randomness within the population of hematopoietic stem cells that generate the erythrocytes is one of the sources of this variation. Salomons et al. (2009) used pulsed-field gel electrophoresis to measure telomeres. The method produces genome-wide distributions of telomere lengths for each sample. Hence it provides the opportunity to quantify telomere shortening separately for subsets of these size distributions (Haussmann et al., 2008). Indeed these data showed that, within adult and juvenile individuals, shortening of telomeres was size dependent, with longer telomeres losing base pairs at a higher rate.

In Section 2 we describe the way the data has been collected. In nestling jackdaws the shortening of telomeres was quantified by percentiles of the length distribution over the full interval (0, 100) at day 5 and day 30. From a graphical representation of the differences between equal percentiles at the two observation moments we already observe that in the subjects of our study length-dependent telomere shortening occurs in the sense that in the mean shorter telomeres exhibit a smaller shortening rate. In Section 3 we discuss mechanisms that may cause telomere shortening. First, there is the end replication problem being part of the cell division process (Olovnikov, 1996). Secondly, we consider the breaking of a telomere occurring spontaneously, e.g. due to oxidative stress, and model it by a Poisson process. In first instance we only consider a deterministic model based on the mean effect of these two mechanisms. We estimate the parameters in that model and give an estimate of the contribution of the different terms to the process. In Section 4 we use a Brownian motion process related to the Poisson process by choosing drift and diffusion that correspond with those of the Poisson process. Again we estimate parameters, now for

one individual, and compare the results of the different approaches. Finally, we summarize our findings and draw conclusions in Section 5.

2. Data collection

We used data on free-living nestling jackdaws, a hole breeding semi-colonial bird species, in the colony at the Biological Centre in Haren (The Netherlands), a semi-urban environment, and in five smaller colonies located in a more rural area 5-10 kilometres south of Haren, see Salomons et al. (2009) for more details. In brief, at the ages of 5 and 30 days a small blood sample was taken for DNA, and telomere length in erythrocytes was measured using pulsed field electrophoresis. The size distribution of telomeres was determined through densitometry using the open-source software ImageJ version 1.38x (Haussmann et al., 2008). The distribution of terminal restriction fragments is usually characterized using the average telomere length only. However, as explained above, telomere shortening rate may not be the same for chromosomes with short as for the chromosomes with long telomeres. The telomere distributions were characterized not only by the mean, but also by the mode and by 21 equidistant percentiles.

From the two blood samples of 75 jackdaws, taken at 5 and 30 days of age, the distribution of the mean change in length between these two days is given in Figure 1. The global mean of change takes the value -223.7 bp being significantly negative. In Figure 2a we give a graphical representation of the data of one jackdaw: the distribution of the length is depicted by percentiles for both days. In Figure 2b an approximation of the probability density function is derived from these data. Looking in more detail at the change in length for a given percentile of all 75 jackdaws, we observe that percentiles at the lower end (0, 5) behave irregularly compared with the larger percentiles (>10). A similar, but less outspoken, behaviour is found at the upper end. The tails of the distribution are more difficult to measure than the denser parts, and we therefore attribute these fluctuations to measurement error. For this reason we only use the percentiles $p_i = 5i$, $i = 2, \dots, 18$ in our penalty function when making parameter estimates. In a graph for each of the 75 cases (Fig.3) we give the change of length percentiles between day 5 and day 30 as a function of the mean

$$\Delta p_i = \Delta p_i(\underline{p}_i), \quad \Delta p_i = p_i(30) - p_i(5) \quad \text{and} \quad \underline{p}_i = (p_i(5) + p_i(30))/2, \quad i = 2, \dots, 18.$$

The curves show large differences. As possible causes for this strong variation we mention differences in genotype and (non)active cellular processes (telomerase). Moreover, external circumstances like measurement errors are expected to play a role. From the figure we observe indeed that there is a mainstream of curves that have a tendency of a smaller decrease at a smaller length, see Salomons et al. (2009) for a different analysis with the same conclusion.

3. Mechanisms for telomere shortening

We next explore possible shortening mechanisms and formulated a model as follows. It consists of a sequence of cell generations from which one cell is selected at each generation. The cells have a mother-daughter relation and one of the daughters is selected randomly. Events, such as replication and strand breaks, are only marked in time by the rate they occur per unit of time in this process. In this way we choose a

single path in the branching process of cell proliferation. Repeating this selection of descendents we obtain a set of histories that is representative for the cell population. The fact that the population of cells grows does not play any role in this respect. Compared with other studies in which the event of cell division and cell population dynamics are also included (e.g. Olofsson and Kimmel, 1999) our choice makes the model slightly less realistic. However, the advantage of this approach is that we concentrate more on the mechanism of shortening itself. Instead of making the assumption that length-dependent shortening is the result of some active control mechanism that enhances DNA repair at shorter length (Karlseder et al., 2002), we consider a passive process in which damage occurs at some rate due to external conditions. Proctor and Kirkwood (2002b) gave a detailed description on the possible effect of single strand breaks. In some cases full repair is likely, while in other partial repair or no repair at all may occur leading to shortening of telomeres in daughter cells. Since our modeling is based on realized shortening as accounted for in the data we only consider the end result.

A fixed length at the end of the telomere is lost at the moment of replication (Okazaki fragments), see e.g. Olovnikov (1996) for more about the *end replication problem*. It is modeled by the fixed rate c of shortening. Base pairs form a string: if one base pair is taken out, then the free end part will also be lost. Since we do not have much information how the break of a strand from e.g. oxidative stress takes place, we take the *Poisson process* as starting point of our model formulation, see Nitecki and Hoffman (1987) and Wilkinson (2006) for general information on the prominent place of Poisson processes in biology.

Let us consider a time interval $(t, t + \Delta t)$ and compute the change of the telomere length Δx over that time interval. The constant decrease of length due to the end replication problem is then $c\Delta t$. Given that it was shown that the risk of a double strand break is uniformly distributed (Petersen et al., 1998; Von Zglinicki, 2000; Sitte et al., 2001), we can model the probability that a double strand break occurs by a *Poisson distribution* with parameter $\mu = ax(t)\Delta t$. In fact we have a two dimensional Poisson process: the risk of a break is assumed to be proportional with the length $x(t)$ of the telomere as well as with the length Δt of the time interval. For Δt sufficiently small the event of two or more breaks can be neglected. The probability of a break follows from a stochastic variable $P(t)$ having a standard uniform distribution: $P(t) \sim \text{Uniform}(0, 1)$.

$$\text{If } P(t) \leq \mu \text{ then } x(t + \Delta t) = R(t) x(t)$$

with again $R(t) \sim \text{Uniform}(0, 1)$. In the Appendix we show that for $\Delta t \rightarrow 0$ the expected value of the length satisfies the differential equation

$$x'(t) = -c - \frac{1}{2} ax(t)^2. \quad (1)$$

The above model only accounts for length decrease. It is well known from various studies, see e.g. Jaskelioff et al. (2011), that there are processes in the cellular system that cause an increase of the length of telomeres (telomerase). From the 75 cases of our study 17 showed a slight mean increase of the telomere length over the 25 days. It is also noted that in a small number of cases length decrease speeded up at shorter telomere lengths, see Figure 3. Both phenomena are not taken up in our model. As mentioned above, the data are rather noisy and it is not clear whether either biological forces or measurement errors are responsible for this strong variation. This restriction

only allows us to introduce a model with a small number of parameters if we also want to produce a reliable estimate for the parameters from the available data.

Parameter estimation

The differential equation (1) with initial value $x(0) = x_5$ has an exact solution

$$x(t; a, c) = \frac{q}{a} \tan \left(\arctan \left(\frac{ax_0}{q} \right) - \frac{1}{2} qt \right), \quad q = \sqrt{2ac} \quad \text{for} \quad ac > 0 \quad (2)$$

For $t = 25$ the variable x denotes the telomere length at day 30. As a matter of fact in the computations needed for doing the parameter estimation a numerical solution of (1) is used because for q close to zero the accuracy of the solution produced by formula manipulation software breaks down; a problem that does not show up in the numerical integration of (1).

In a deterministic model of type (1) different chromosomes remain in time in the same order with respect to their length. The model can be used to predict the length at day 30 of a given percentile using the initial length of the same percentile at day 5. A comparison of the outcome at day 30 with the observation will lead to an estimate of the parameters a and c by minimizing the sum of the squared differences for percentiles 10(5)90 of all 75 cases (Table I). Moreover, we give an estimate $f_{(a)}$ of the size of the quadratic term of the right hand side of (1) by substituting $x = (x_5 + x_{30})/2$ averaged over all runs needed for computing the residual sum of squares for a given choice of the parameters. A similar estimate is made for the other term giving $f_{(c)}$. The estimate for the 1-parameter model ($a = 0$) is given as well. We see that for the 2-parameter model the contribution to the length decrease is about equally distributed over the Poisson process and the replication process (Table 1). It is noted that the difference in the residual sum of squares is small. This is related to a rather high level of collinearity in the 2-parameter model meaning that a fraction of the contribution $f_{(a)}$ could be attributed to $f_{(c)}$ and vice versa.

4. Stochastic modelling of the process

For given values of the parameters a and c a stochastic simulation of the process can be carried out. At discrete times (stepsize Δt) a fixed length $c\Delta t$ is subtracted as well as a randomly chosen part $ax(t)^2 R(t)\Delta t$ with $R(t) \sim \text{Uniform}(0, 1)$. The result depends on the order in which these operations are carried out. For Δt sufficiently small the difference between the two will become negligibly small. However, estimating parameters with this stochastic simulation fails because of lack of convergence of the Monte Carlo process in which simulation runs are repeated until the average of some penalty function stabilizes. The stochastic process can also be described by a Fokker-Planck equation being a linear diffusion equation for the probability density function $p(t, x)$ at time t . In the Appendix we describe a numerical simulation process based on a stochastic differential equation which offers an alternative; it is called a *Brownian motion*. Using (A7)-(A8) and the percentiles at day 5 of one specific nestling with parameter values estimated for this case from (1),

$$(a, c) = (0.73 \times 10^{-6}, 5.7), \quad (3)$$

we generate 1000 starting values and run the simulation over a time interval of 25 days. The so obtained 1000 length values at day 30 are reordered and the percentiles 10(5)90 are read off (Fig. 4a). It is noted that this is only one realization of the process. If it is repeated, slightly different values will be found.

Parameter estimation

We may estimate the parameters using the above Brownian motion process. Again a penalty function is specified for the difference between the observation and the outcome for some choice of the parameters a and c . One has to take the average penalty over a number n of runs. In this so-called Monte Carlo simulation the penalty converges to its limit value at a rate $n^{-1/2}$ for increasing n . In the present problem one has to take $n \geq 25$ to obtain satisfactory results. Then the averaged penalty is at its minimum for

$$(a, c) = (0.41 \times 10^{-6}, 7.5) \quad (4)$$

In Figure 4a we also give the outcome of one run for these parameter values. It is anticipated that the result is better than that for parameter values (3) based on the deterministic model. This is due to the fact that with (4) also the second order statistical moment is taken in account. Figure 4b gives the outcome based on the Poisson process itself. The resulting values are close to those of the Brownian motion. As already remarked we did not succeed in estimating parameters based on a stochastic Poisson type of simulation. The present result makes it likely that the best fitting parameter values for the Poisson process are close to the ones of the Brownian motion model.

5. Conclusions

Telomere length and telomere shortening can be seen as biomarkers of ageing in that they have repeatedly been shown to predict survival probabilities in humans and birds (e.g. Cawthon et al., 2003; Hausmann et al., 2008; Bize et al., 2009; Salomons et al., 2009). With the availability of detailed longitudinal data it has become possible to fit new dynamical models to these data to develop insights in the mechanisms underlying the shortening process. We explored possible physical processes for the terms of this expansion that significantly may contribute to the decrease of telomere length in time. We focused our attention upon two such mechanisms: a decrease at a fixed rate from the replication process and random strand breaks. The replication of the DNA sequence during cell division is incomplete due to the end-replication problem. As long as this part consists of telomere base pairs only no essential information is lost. However, eventually the telomere chain will become sufficiently short to induce cell death. Processes acting in a cell, such as DNA repair and telomerase, may prevent or reverse telomere shortening. These processes may still fall short in counterbalancing telomere shortening or have harmful side-effects such as an increase in the risk of developing cancer. In this study we did not consider these processes and attributed the net shortening fully to the two physical processes of length decrease we incorporated.

Our main result is that the Poisson model for strand breaks shows that length-dependent decrease of telomere length can be explained without requiring a feedback mechanism that protects short telomeres. In our analysis we compared the result for the 2-parameter model with the minimal model allowing only a length decrease at a constant rate ($a = 0$). Although the approximation error went down only slightly the contribution to the length decrease changed strongly in such a way that the two mechanisms contribute about equally to the length shortening (Table I). In literature

several studies on the stochasticity of telomere shortening appeared. In some cases the mathematical analysis dealt only with the behavior in the mean or telomere length distributions at different times were presented without a formulation of the dynamical process. In some other cases data of experiments were fitted to a dynamical model. Von Zglinicki (2002) has demonstrated that oxidative stress increases the speed of telomere shortening. Given a certain stress level we have shown that this process causes a length dependent decrease. Op den Buijs et al. (2004) describe a type of feedback mechanism for this length dependency based on the observation that the distribution of lengths is close to a Weibull distribution.

It is noted that a stochastic model based on the Poisson process itself, instead of the Brownian motion we introduced in Section 5, did not lead to successful parameter estimation. The large influence of the higher statistical moments in such model requires data with a lower external noise level. Finally, it is remarked that it might very well be possible to analyze a differential equation model that describes length-dependent telomere shortening as a process in which the cell actively decreases the shortening rate by some negative feedback. More parameters are then needed and so in comparison it should result in a much better fit in order to serve as a useful alternative. A same argument applies to a model in which, next to telomerase, also a break in a specified end part of the 3' strand is allowed (Rodriguez-Brenes and Peskin, 2010). As in our model the risk of such a break is supposed to be uniformly distributed.

Appendix

The stochastic model of telomere length decrease contains two stochastic variables: the event of a possible break within a time interval $(t, t + \Delta t)$ and the position of such a break within the telomere chain. Furthermore there is the constant length decrease from replication. The expected value of the change Δx of the length over the time interval is computed as follows with K the stochastic variable denoting the event of a break ($K = 1$) and the realisation $X(t) = x$:

$$\begin{aligned}\Delta x &= E_K E_X(\Delta X | K) = -c\Delta t + \sum_{k=0}^1 E_X(\Delta X | K = k) P(K = k) \\ &= -c\Delta t + E_X(\Delta X | K = 0)(1 - ax\Delta t) + E_X(\Delta X | K = 1)ax\Delta t.\end{aligned}\quad (A1)$$

Since the break position is uniformly distributed over the interval $(0, x)$, its expected value equals $x/2$ and its variance is $x^2/12$. This leads to the following expression for the expected change

$$\Delta x = -(c + \frac{1}{2}ax^2)\Delta t. \quad (A2)$$

Letting $\Delta t \rightarrow 0$ we arrive at the deterministic differential equation for the mean change in the telomere length

$$x'(t) = -c - \frac{1}{2}ax(t)^2. \quad (A3)$$

For the variance of ΔX we obtain in a similar manner

$$\begin{aligned}
 \text{Var}(\Delta X) &= \text{Var}_K \{E_X(\Delta X | K)\} + E_K \{\text{Var}_X(\Delta X | K)\} \\
 &= E_K \{E_X(\Delta X | K)^2\} - (E_K \{E_X(\Delta X | K)\})^2 \\
 &\quad + E_K \{E_X((\Delta X)^2 | K) - E_X(\Delta X | K)^2\} \\
 &= -(E_K \{E_X(\Delta X | K)\})^2 + E_K \{E_X((\Delta X)^2 | K)\} \\
 &= -E\{\Delta X\}^2 + E_K \{\text{Var}_X(\Delta X | K) + E_X(\Delta X | K)^2\} \\
 &= -\{-c\Delta t - \frac{1}{2}ax^2\Delta t\}^2 + (0+0)(1-ax\Delta t) + (\frac{1}{12}x^2 + \frac{1}{4}x^2)ax\Delta t
 \end{aligned}$$

or

$$\text{Var}(\Delta X) = \frac{1}{3}ax(t)^3\Delta t + O\{(\Delta t)^2\}. \quad (\text{A4})$$

For a further description of the stochastic process of telomere shortening including a constant decrease from the end replication one may switch to a linear diffusion equation, the so-called Fokker-Planck equation (Gardiner, 1990). Let $p(t, x)$ be the probability density function for the length X at time t . This function then satisfies the partial differential equation

$$\frac{\partial p}{\partial t} = \frac{\partial}{\partial x} \{(c + \frac{1}{2}ax^2)p\} + \frac{1}{2} \frac{\partial^2}{\partial x^2} \{(\frac{1}{3}ax^3)p\}. \quad (\text{A5})$$

Together with a starting distribution at the initial time this equation yields the distribution at any time t . The stochastic process itself can be simulated by using the so-called Langevin equation to which the Ito calculus applies

$$dX = -(c + \frac{1}{2}aX^2)dt + \left(\frac{1}{3}aX^3\right)^{1/2} dW(t), \quad (\text{A6})$$

see Gardiner (1990). In this stochastic differential equation $dW(t)$ denotes a Wiener increment (Gardiner, 1990). Using a forward Euler scheme with step size Δt (Grasman and Van Herwaarden, 1999) a realization of the process can be derived from

$$X(t + \Delta t) = X(t) - (c + \frac{1}{2}aX(t)^2)\Delta t + \left(\frac{1}{3}aX(t)^3\right)^{1/2} Z(t)\sqrt{\Delta t}, \quad X(0) = X_0 \quad (\text{A7})$$

with stochastic variable $Z(t)$ having a standard normal distribution $N(0, 1)$ and X_0 having some prescribed distribution. If we have an approximation of the corresponding cumulative distribution function $F(x_0)$ e.g. by means of a set of percentiles, we can easily generate starting values using the standard uniform distribution. Let R be $\text{Uniform}(0,1)$, then

$$X_0 = F^{-1}(R) \quad (\text{A8})$$

has the required distribution. In simulation one may as well take a large number of values for R being equally distributed over the interval $(0, 1)$.

Acknowledgements

We thank Gerrit Gort (Biometris) for his statistical advices and Arjen Wassink for his help with programming ImageJ. H.M.S. and S.V. were supported by a NWO Vici-grant to S.V.

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Figure captions

Figure 1: Histogram of mean change of telomere length between day 5 and day 30 in blood cell samples of 75 jackdaws.

Figure 2: Data of one individual: (a) length percentiles at day 5 and day 30 approximating the cumulative distribution functions. (b) approximation of the probability density function using (a).

Figure 3: From all 75 jackdaws the change of length of the population of telomeres from day 5 to day 30 is represented in a graph. From each of the length percentiles $p = 10(5)90$ at both days the change of length $\Delta p = p(30) - p(5)$ is given as a function of the mean of the lengths at both days, $\bar{p} = (p(5) + p(30))/2$, and represented as a graph connecting the percentiles 10(5)90. It is noted that at day 30 an interval between to consecutive percentiles may be composed out of cells different from the ones in the same interval at day 5.

Figure 4. A comparison of model results with the observation of the telomere length percentiles at day 30 for one specific nestling. (a) The deterministic model is given by (1) with parameter values (3): the computed lengths at day 30 are connected by a curve. For the same parameter values the Brownian motion (A7)-(A8) gives the result indicated by (+). For the parameter values (4) obtained from a parameter estimation, based on the Brownian motion model, one run of that model gives percentiles indicated by (\times). (b) The simulation result obtained by a Poisson process with values (4) is indicated by (O).

Figure 1: Histogram of mean change of telomere length between day 5 and day 30 in blood cell samples of 75 jackdaws.

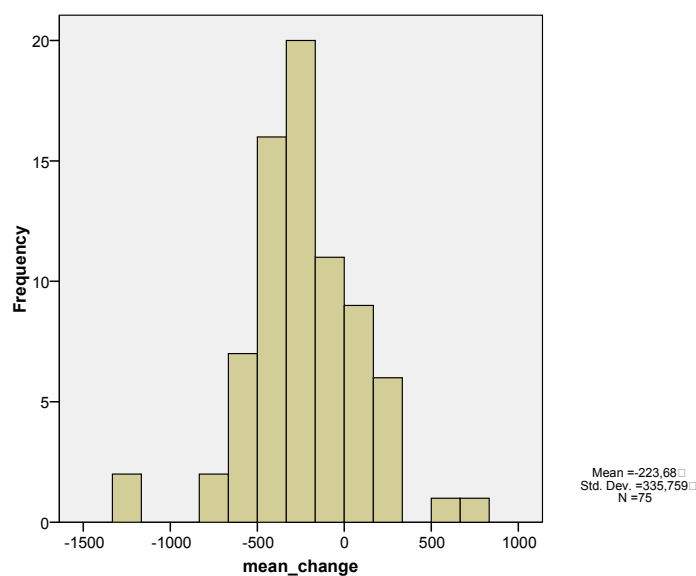
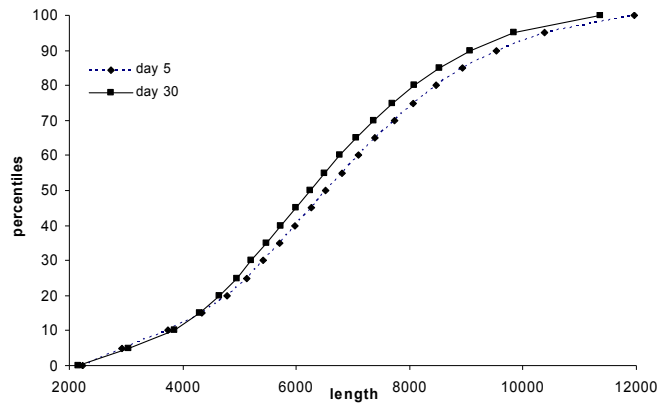
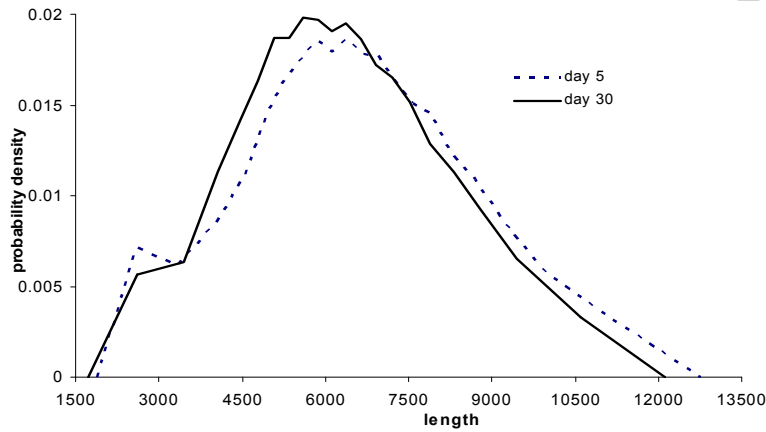


Figure 2: Data of one individual: (a) length percentiles at day 5 and day 30 approximating the cumulative distribution functions. (b) approximation of the probability density function using (a).

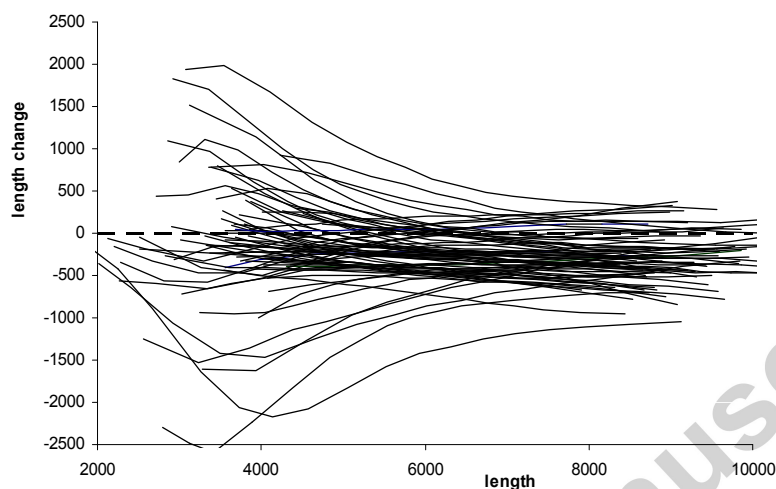
(a)



(b)

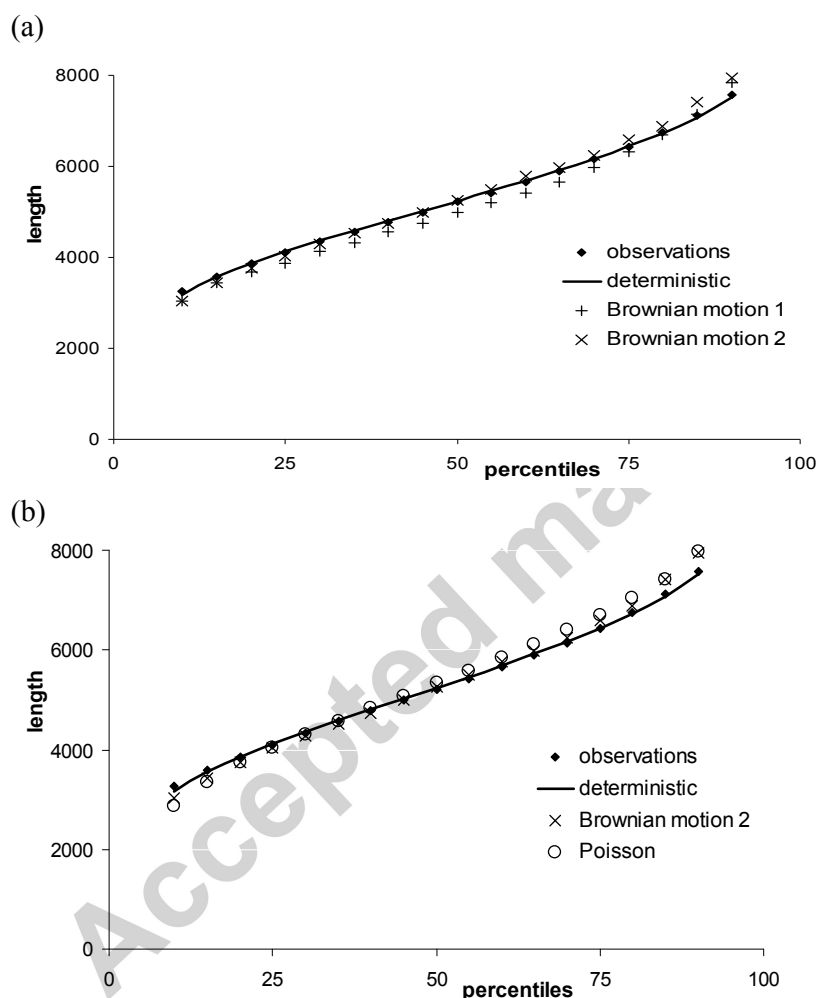


1 Figure 3: From all 75 jackdaws the change of length of the population of telomeres from
 2 day 5 to day 30 is represented in a graph. From each of the length percentiles $p =$
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Figure 4. A comparison of model results with the observation of the telomere length percentiles at day 30 for one specific nestling. (a) The deterministic model is given by (1) with parameter values (3): the computed lengths at day 30 are connected by a curve. For the same parameter values the Brownian motion (A7)-(A8) gives the result indicated by (+). For the parameter values (4) obtained from a parameter estimation, based on the Brownian motion model, one run of that model gives percentiles indicated by (\times). (b) The simulation result obtained by a Poisson process with values (4) is indicated by (O).



1 Table I. Estimates of the parameters a and c of the 2-parameter model and the
 2 contribution of the corresponding two terms to the length decrease. In the text it is
 3 explained how these contributions are computed. The estimate for the 1-parameter
 4 model is given as well.

5

# parameters	a	c	*SSR ($\cdot 10^8$)	$f(a)$	$f(c)$
1	0	9.3	2.14	0	9.3
2	0.22×10^{-6}	4.5	2.08	4.4	4.5

6 * Sum of Squared Residuals

7

- 1 >Data from juvenile Corvids shows length dependent telomere shortening.
- 2 >Telomere shortening from oxidative stress is modelled by a Poisson process.
- 3 >The 2-parameter telomere model covers shortening from replication and stress.
- 4

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