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The heuristic value of redundancy models of aging

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ABSTRACT

Molecular studies of aging aim to unravel the cause(s) of aging bottom-up, but linking these mechanisms to organismal level processes remains a challenge. We propose that complementary top-down data-directed modelling of organismal level empirical findings may contribute to developing these links. To this end, we explore the heuristic value of redundancy models of aging to develop a deeper insight into the mechanisms causing variation in senescence and lifespan. We start by showing (i) how different redundancy model parameters affect projected aging and mortality, and (ii) how variation in redundancy model parameters relates to variation in parameters of the Gompertz equation. Lifestyle changes or medical interventions during life can modify mortality rate, and we investigate (iii) how interventions that change specific redundancy parameters within the model affect subsequent mortality and actuarial senescence. Lastly, as an example of data-directed modelling and the insights that can be gained from this, (iv) we fit a redundancy model to mortality patterns observed by Mair et al. (2003; Science 301: 1731–1733) in *Drosophila* that were subjected to dietary restriction and temperature manipulations. Mair *et al.* found that dietary restriction instantaneously reduced mortality rate without affecting aging, while temperature manipulations had more transient effects on mortality rate and did affect aging. We show that after adjusting model parameters the redundancy model describes both effects well, and a comparison of the parameter values yields a deeper insight in the mechanisms causing these contrasting effects. We see replacement of the redundancy model parameters by more detailed sub-models of these parameters as a next step in linking demographic patterns to underlying molecular mechanisms.

1. Introduction

Unravelling the cause(s) of aging is often approached bottom-up, through the study of molecular mechanisms linked to lifespan. However, a full understanding of the aging process requires that these molecular mechanisms be linked up to the organismal level, which is challenging due to the involvement of multiple complex interacting processes (Chauhan et al., 2015; Kirkwood, 2011; Kriete et al., 2010; Mc Auley et al., 2015). We propose that complementary top-down theoretical work in the form of data-directed modelling may contribute to this daunting task, and in this paper we discuss the potential of a specific form of reliability theory, redundancy models, to achieve this goal.

Many species across the tree of life, including humans, show an initial exponential increase of mortality rate with age and this feature of aging is well described by the Gompertz equation (Gompertz, 1825). As a result, mortality is often modelled using the Gompertz equation, partitioning mortality into an age-independent (baseline) and age-dependent (aging rate) component. We acknowledge the value of this approach, and have applied it ourselves, because it allows more detailed conclusions regarding the effects of, for example, specific experimental interventions that modulate lifespan by investigating which Gompertz parameter is affected by the intervention (e.g. Boonekamp et al., 2014b; Gems et al., 2002; Pietrzak et al., 2015; Pletcher et al., 2000; Simons et al., 2013). On the other hand, the Gompertz equation also has limitations. Firstly, the exponential increase in mortality rate with age is not universal (Abrams and Ludwig, 1995; Jones et al., 2014). For example, in several species, including humans, the increase of mortality rate with age decelerates at older ages, leading eventually to late-life mortality plateaus (Carey et al., 1992; Gavrilov and Gavrilova, 1991) that cannot be described with the Gompertz equation. Secondly, and perhaps more importantly in the present context, for a top-down theoretical investigation of aging mechanisms it is a necessity that mortality patterns emerge from the model, as opposed to being specified by the model. Thus the top-down approach to unravel aging mechanisms requires a mechanistic model.

Building on the work of Gavrilov and Gavrilova (1991, 2001), we explored the heuristic value of redundancy models in the investigation of aging mechanisms. Previous studies have used redundancy models primarily as a means to describe mortality patterns, and hence as an alternative to the Gompertz equation (Gavrilov and Gavrilova, 1991, 2001; Milne, 2008; Vural et al., 2014). We employ the same model structure in a different way, namely as a simple mechanistic model.

It has previously been argued that aging models should fulfil a number of criteria (Strehler and Mildvan, 1960) to clarify the mechanisms

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which determine the lifespan of organisms (Gavrilov and Gavrilova, 1991) and these criteria have been discussed in detail with respect to the redundancy model (Gavrilov and Gavrilova, 1991). We will not reiterate this discussion here, except to note that the redundancy model is flexible, and hence can be made to fit very different mortality patterns with age, including late-life mortality plateaus. Although, redundancy models have been qualitatively investigated (Gavrilov and Gavrilova, 1991, 2001; Li and Anderson, 2009; Milne, 2008; Vural et al., 2014), they have rarely been fitted to empirical data (Vural et al., 2014) and, to our knowledge, redundancy model performance has not been formally compared to other models. Here, we quantitatively explore the explanatory power of redundancy models of aging. We show that redundancy models fit the data well and argue that this is a strength of redundancy models over non-mechanistic models because (i) when contrasting aging patterns can be understood within the framework of a single mechanistic model this indicates that the model may capture the essence of the aging process, and (ii) redundancy parameter inference may teach us something about the underlying mechanisms and can as such be used to develop new hypotheses.

2. The redundancy model

Redundancy models are based on reliability theory (Barlow et al., 1965) and assume that organisms consist of one or more blocks, that are each composed of one or more (redundancy) elements. Elements do not age themselves but fail over time with a constant rate due to damage. Blocks keep on functioning until the last remaining element fails and Gavrilov and Gavrilova (2001) showed that aging (i.e. an increase of mortality rate with age) emerges from the model due to redundancy exhaustion. Thus, redundancy in the present context indicates extra capacity to absorb damage, which can be seen as a form of organismal resilience. The organism dies when the *first* block fails, i.e. when the last remaining element within *any* block fails. Blocks and redundancy elements are abstract concepts, but one can think of blocks as sets of tissues or cells, or possibly an organ, that is vital for survival. Redundancy elements can be thought of as the cells within an organ, or critical functions of cells, where damage to cells do not lead to the organ's failure until a certain threshold is reached (in the context of the model, the moment the last redundancy element fails). Element failure rate is usually assumed to be constant over time and equal across blocks, and we adopt this assumption. It would be a logical extension to let element failure rate depend on other variables such as for example the number of remaining redundancy elements, but such extensions of the redundancy model fall outside the scope of the present paper.

Under these assumptions and following eq. 9 in the paper by Gavrilov and Gavrilova (2001) the mortality rate of the organism can be specified by:

$$\mu(x) = mknqce^{-nq}e^{-kx}\sum_{i=1}^{n}\frac{nq^{i-1}\left(1-e^{-kx}\right)^{i-1}}{(i-1)!\left(1-\left(1-e^{-kx}\right)^{i}\right)} \quad (1)$$

where (m) is the number of blocks containing (n) redundancy elements that become damaged at rate (k) (i.e. in each time step a proportion (k) of the remaining redundancy elements is damaged), and c is a normalizing factor determined by (n) and (q) (see SI–1 for details). Additionally, it is assumed that not all redundancy elements are intact at maturation, i.e. all elements have a probability (q) to be damaged from the time point that mortality is studied. The initial number of redundancy elements within blocks is given by a Poisson distribution $\lambda = nq$. Gavrilov and Gavrilova (2001) gave as biological interpretation of (q) the accumulation of somatic damage before completion of the developmental period. However, the main effect of (q) in the model is to generate variation between individuals in the number of redundancy elements at the start of life (Fig. S1), and biologically that variation can be due to any factor that causes variation in development. For example, manipulated growth trajectories affect lifespan in sticklebacks (Lee et al., 2013), and growing up in an enlarged brood accelerates telomere shortening, which reduces survival in jackdaws (Boonekamp et al., 2014a). Both of these experimental effects can be thought of as reflecting an effect of developmental conditions on the number of redundancy elements an individual has at maturation.

Because it is an important feature of the redundancy model that it can describe mortality plateaus, we illustrate it in Fig. 1 by fitting a simple redundancy model to a particularly well known example of late-life mortality plateaus observed in a group of 1.2 million medflies (Carey et al., 1992). It can be seen that the redundancy model describes the observed mortality pattern well, and certainly better than the Gompertz model that we fitted for comparison (see Fig. 1 legend for details). Note, that simpler forms of redundancy models have also been developed (we fitted the two-parameter model (Gavrilov and Gavrilova, 2001) for comparison to the data of Carey et al. (1992); see Fig. 1). The late-life mortality plateau is a shared feature of reliability-based models (Gavrilov and Gavrilova, 1991, 2001; Li and Anderson, 2009; Milne, 2008; Vural et al., 2014). Nevertheless, that the redundancy model fits the medfly data well does not naturally follow from the fact that it can in principle describe such plateaus, because of constraints in the pliability of the model. We therefore consider the good fit an encouraging result.

In Fig. 2 we illustrate how each of the redundancy model parameters affects mortality rate and its dependence on age. We consider the effect of each parameter on the intercept, slope and plateau of the relation between age and mortality rate. The initial mortality rate (intercept) largely depends on the number of initial intact elements (i.e. qn) and the number of blocks, being lower with an increasing number of elements (n) and a lower number of blocks (m) (Fig. 2). The rate of increase of mortality with age (actuarial senescence) depends mainly on the element failure rate (k) (Fig. 2). The level of the mortality rate

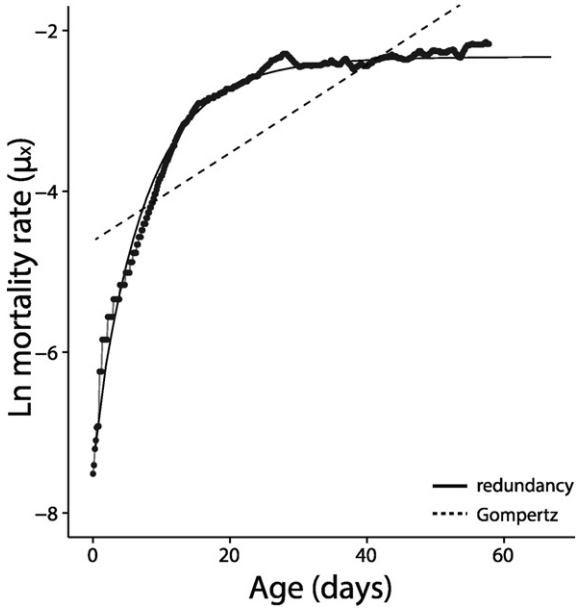

Fig. 1. Gompertz (dashed) and redundancy (solid) models fitted to the actuarial senescence pattern (shown in dots) of 1.2 million medflies (data extracted from Fig. 1C in Carey et al. 1992, using GraphClick). The Gompertz equation ($u(x) = Re^{ax}$) lacks the mortality deceleration property resulting in a low fit, while in comparison the redundancy model (using Eq. (1)) fits the data well. Fitted Gompertz parameters: $R = 0.01$, $a = 0.058$, fit: $R^2 = 0.61$; fitted redundancy parameters: $k = 0.1077$, $m = 1$, $n = 71$, $q = 0.1$, fit: $R^2 = 0.99$. For comparison, we also fitted the simplest 2-parameter redundancy model. This model assumes that organisms consist of 1 block containing (n) redundancy elements that fail at rate (k). The 2-parameter model also outperformed the Gompertz function ($n = 3$, $k = 0.084$, fit: $R^2 = 0.79$). Models were fitted using the nonlinear least squares function in R and R^2 values were calculated 'manually' using the standard formula: $R^2 = 1 -$ residual sum of squares / total sum of squares.

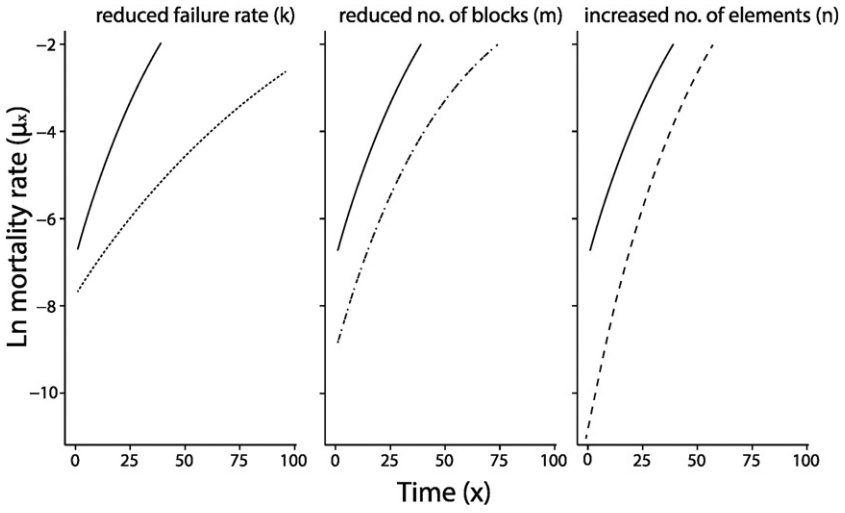

Fig. 2. The effect of the redundancy model parameters (using Eq. (1)) on age-dependent mortality rate: element failure rate (k), number of blocks (m) and elements (n). The high mortality rate lines (solid) are identical in the three panels ($k = 0.0169, m = 500, n = 115$). The low mortality rate lines (dashed) were obtained by changing one parameter at a time (to $k = 0.0073$; $m = 60$; $n = 156$ respectively). Initial damage was invariant at 90% ($q = 0.1$) and age is in arbitrary units. These parameter combinations approximately describe mortality trajectories of fruit flies (see Section 4). Note that there is no clear mortality plateau in these graphs as in Fig. 1, because with the chosen parameters it is not realistic to extend the age-axis sufficiently to reach that stage.

plateau at late ages is equal to the product of failure rate (k) times the number of blocks (m), and is equal to (k) when there is only one block ($m = 1$). This is so because blocks have only one redundancy element left near the end of life, and the probability of death is then given by (k). Mortality rate increases with the number of blocks because the probability of redundancy exhaustion within *any* block increases with the number of blocks. As a result, increasing the number of blocks decreases the proportion of the cohort that reaches the age range of the mortality plateau due to the higher overall mortality. The initial number of redundancy elements (n) has no effect on the mortality plateau. Insight into the effects of the different parameters is best gained by experimenting with them, and to this end we have included an R script in the supporting information (SI–6 "an R script for redundancy demography").

The Gompertz equation is the most widely used distribution for fitting mortality data. We therefore explored how variation in parameters of the Gompertz equation is reflected in the parameters of the redundancy model with the aim to improve the interpretability of redundancy model parameters. The element failure rate parameter (k) best reflected the Gompertz slope and both the redundancy parameter (n) and the number of blocks parameter (m) reflected the Gompertz intercept (see SI–3 for details and supplementary figures and tables).

The redundancy model is phenotypic in nature rather than genetic. This does not imply that genetic variation cannot be accommodated; we see genetic variation as being expressed in different values of the model parameters. Investigating how genotypes associated with aging and/or lifespan affect these parameter values would gain further top-down insight in the mechanisms mediating such genetic effects.

Formal models differ in the level of detail, and model choice is, amongst other considerations, the outcome of the trade-off between generality, precision and realism (Levins, 1966). We here choose to present only simple redundancy models, at the expense of realism, in that model components represent abstract entities rather than traits that can be measured directly. We see this as a stepping-stone towards more realistic models, in which redundancy model parameters are gradually replaced by realistic sub-models of these parameters.

A key difference between redundancy models and real biological systems is that the latter have repair, mitigating damage, while repair is so far absent from the redundancy model. The element failure rate in the models should therefore be thought of as net failure rate, i.e. the damage remaining after repair, rather than gross failure rate (Glaser, 2009). This contrast may be of importance, at least in some cases, and it would be of interest therefore to model damage and repair explicitly and let element failure rate be the process emerging from this balance.

3. Interventions

In this section we utilize the redundancy model to make predictions regarding the effects of lifestyle changes and medical intervention on actuarial senescence and remaining lifespan. These predictions may help unravelling mechanisms underlying empirical results of aging interventions.

Instantaneous mortality rate can change during life due to changes in environmental circumstances, lifestyle, disease or medical interventions. Given the redundancy model framework, such interventions can affect mortality either through an effect on element failure rate (k), or an effect on somatic redundancy (n). Furthermore, the effect of an intervention may depend on the age at which it occurs. We investigated effects of interventions on age-dependent mortality rate and remaining lifespan with an individual based simulation (see SI–4 for details on simulation procedures). For simplicity, our approach is limited to the investigation of effects of changes in element failure rate and the number of redundancy elements, but more complex changes can also be envisioned.

Reducing the element failure rate (by 50%, from 0.02 to 0.01) had two distinct effects: (i) a reduction in the age specific mortality rate immediately after the intervention and (ii) a reduction in the rate of actuarial senescence (mortality increase with age) from the moment of intervention onwards (Fig. 3). Identical interventions were modelled to onset at ages 20, 40 and 50 (early, mid and late life in our simulation) to investigate their consequence for remaining life expectancy. Not surprisingly, the effect on life expectancy of an intervention causing a reduction of element failure rate was larger on an absolute scale when started earlier in life (Table 1).

Restoring a single redundancy element also had two distinct effects: (i) a large instantaneous reduction in the mortality rate at the moment of the intervention, followed by (ii) an increase in the rate of actuarial senescence relative to the control group (shown in black) (Fig. 3). The mortality reduction is caused by the restoration of one damaged element, which instantly increases the system's capacity to absorb damage. However, this beneficial effect is compensated by a subsequent increase in actuarial senescence, a process known as mortality rate convergence. Mortality rate convergence arises because systems with more redundancy elements receive more damage per unit of time relative to

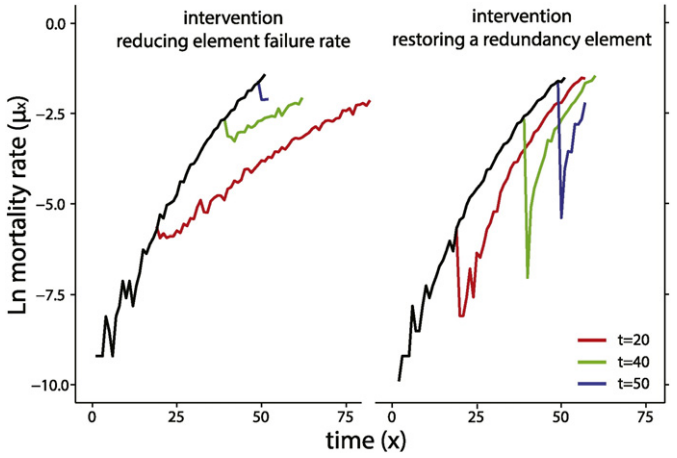

Fig. 3. The effect of an intervention that either reduces element failure rate (left panel) or restores redundancy (right panel) on age-dependent mortality. Data were obtained through individual based simulations (see SI–4 for details). Intervention reduced element failure rate from 0.02 to 0.01 (left panel) or restored 1 redundancy element per block (right panel) at ages 20 (red), 40 (green), or 50 (blue). The initial (control) mortality groups (black lines) were generated for 10.000 individuals with $q = 0.1$, $m = 500$, $n = 152$ and $k = 0.02$. Age at death was used for the calculation of life tables and life expectancy (Table 1).

systems with few elements, causing convergence of redundancy state and mortality trajectories over time (Boonekamp et al., 2013; Gavrilov and Gavrilova, 2001). The effect on life expectancy of the restoration of one redundancy element was largest at an intermediate age (Table 1).

The implication of these findings is that different types of interventions have different effects on life expectancy, depending on the age at which the intervention took place. This may help to understand why some interventions appear to have larger effects early in life. For example, quitting smoking had larger beneficial effects when started earlier in life (Taylor et al., 2002), which qualitatively matches the effect of element failure rate on mortality. Restoring a redundancy element could reflect medical intervention, e.g. cardio surgery, which has relative large effects during middle or late life. Note that we cannot quantitatively compare the effects of interventions of element failure rate versus redundancy due to the lack of knowledge on the biology of these parameters, but the difference in dependency on age can be inferred from our simulations because the pattern differs qualitatively (Table 1).

4. An example of fitting the redundancy model to real data

Dietary restriction (DR) and modulation of environmental temperature are classic tools to modulate lifespan. DR restriction extends lifespan in many species (Fontana et al., 2010; Nakagawa et al., 2012), and the same is true of low environmental temperature in ectotherms (Pearl, 1928). Such effects can arise either through an effect on instantaneous mortality rate, an effect on aging (actuarial senescence), or a combination of the two. Mair et al. (2003) carried out a clever experiment to distinguish between these hypotheses using *Drosophila*. They applied both treatments, and for each treatment switched flies between the low/high lifespan regimes at different ages. They concluded that DR affected instantaneous mortality rate without affecting aging, while the temperature manipulation affected only aging. However, the mechanism(s) that causes the effect of DR on mortality risk are not fully understood and Mair et al. (2003) did not discuss how these effects might arise. We here explore whether the observed effects can be described with the redundancy model, as a step towards a better understanding of the mechanisms causing the observed complex patterns. Given that the results of the two experimental interventions are very different it is a challenge to generate both effects with one model. Hence, confirmation of whether the redundancy model can explain both effects would support the hypothesis that redundancy models of aging capture the essence of the mechanisms causing the observed variation in actuarial senescence and lifespan.

Our approach was as follows. For each treatment (temperature/dietary restriction) we first fitted the redundancy model (eq. 1; see SI–5 for details on fitting procedure) to the continuous treatment groups (i.e. the flies that were not switched between treatments). Our aim here was to let the high and low lifespan models differ in only one biologically plausible parameter chosen a priori. A good fit however does not necessarily imply that the redundancy parameter difference between the control groups resembles the essence of the mechanisms causing these effects, because such differences can possibly also be achieved with other model adjustments. The data of Mair et al. (2003; from hereon we refer just to 'the experiment') included switches between the high and low mortality regimes. This provides us with the opportunity to investigate whether the parameter differences between treatments also explained the observed pattern following switches between treatments. To this end, we simulated the experimental switches between the high/low lifespan treatment parameters at the various time points as in the experiment, and compared the predictions derived in this way to the results observed in the experiment.

Manipulation ambient temperature

Because the redundancy element failure rate parameter (k) has the largest effect on the rate of actuarial senescence (Fig. 2) we hypothesized that this parameter was modified by ambient temperature in the experiment. We therefore constrained the model by allowing only the element failure rate parameter (k) to vary between the two continuous treatments (i.e. (q), (m), and (n) were optimized but kept identical) when fitting the redundancy model to the 27 °C and 18 °C temperature groups (data from Fig. 3A in Mair et al. (2003)). The best fit combined over the two continuous treatments was $R^2 = 0.92$ and 0.89 to the 27 °C and 18 °C groups respectively. Results of individual based simulations illustrate the good fit of the model to the control group mortality patterns (Fig. 4A—black and red lines). Note that these fits were not optimal due to the restriction of keeping the parameters other than (k) equal, but our purpose was to test whether temperature increased mortality via an effect on (k), requiring that the other parameters are kept constant. Individual based simulations of the experimental switches between temperature regimes reproduced the data well (green, blue, and purple lines), regardless of the direction of the switch (Fig. 4A; $R^2 = 0.70$, pooled over the four switch experiments, two in each direction). It is worth emphasizing that the predicted effects of the switches were simulated using the parameters fitted only on the continuous treatments. That these predictions fit the data of the switches well suggests that the effect of ambient temperature on actuarial senescence in *Drosophila* can be well described by the redundancy model via changes in the element failure rate parameter (k).

Table 1
The effect of interventions that reduce element failure rate (k) or restore redundancy elements (n) on life expectancy at age x (e_x). Element failure rate (k) was reduced from 0.02 to 0.01 and redundancy was restored with a single element. The life expectancy difference denotes the difference between no intervention versus intervention. Life expectancy was calculated on the basis of life tables generated with the individual based simulations. See legend of Fig. 3 for parameter settings and other details.

Intervention		Life expectancy (e_x)		
Type	*Moment* (x)	*No intervention*	*With intervention*	*Difference*
Rate (k)	20	18.81	38.98	20.17
	40	4.48	10.74	6.26
	50	0	1.55	1.55
Redundancy (n)	20	19.07	25.91	6.84
	40	4.53	13.01	8.48
	50	0	4.33	4.33

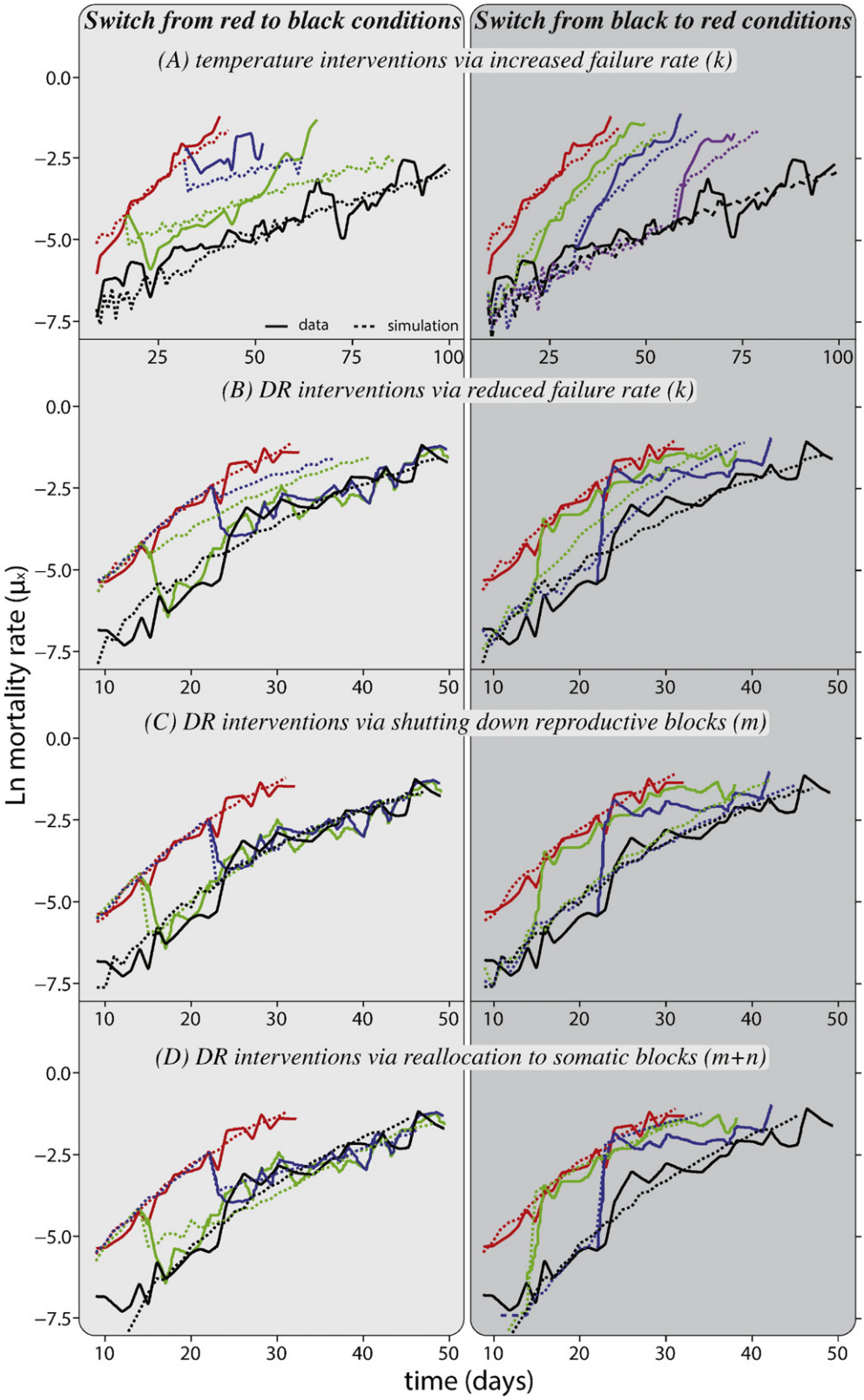

Fig. 4. The redundancy model fitted to aging experiments on fruit flies. Individual based simulation based on the redundancy model (dashed lines) optimized to reproduce the observed actuarial senescence patterns of *Drosophila* (solid lines) that were either subjected to ambient temperature manipulations (4A) or dietary restriction (DR; 4A–D) (data extracted from Figs. 1 and 3 in Mair et al. (2003)). Solid black and red lines represent the groups in which temperature (panel A; red = 27°C, black = 18°C) and diet conditions were kept constant (panels B to D; red = fully fed, black = DR). These red and black lines are termed the continuous treatments, and they are identical in the left and right figures within each panel. Solid green, blue, and purple lines reflect switches of experimental conditions at different time points from one continuous treatment group to the other: from red to black (left panel); from black to red (right panel). Dashed red and black lines reflect individual based simulations using redundancy parameter settings fit to the continuous treatment data. Dashed green, blue, and purple lines reflect switches in redundancy parameters from one continuous groups parameters to the others. Parameter values: panel A: m=500, n = 110, q = 0.1, k = 0.0163 (27°C) or 0.0064 (18°C); panel B: m = 500, n = 140, q = 0.0298, k = 0.0298 (fully fed) or 0.0193 (DR); panels C–D: m = 500, n = 140, q = 0.0298, k = 0.0298 and where DR was modelled to reduce (k) to 0.0001 in 380 out of 500 blocks (panel C). In panel D, 2 redundancy elements were reallocated from reproductive to somatic blocks in addition to the parameter interventions in panel C. See SI–5 for details on the fitting procedures, and SI–4 for individual based simulation procedures.

Dietary restriction

The DR effect is complex and could affect mortality via several physiological pathways. We therefore devised multiple models of the DR effect with increasing complexity to compare which redundancy-based mechanism best fit the observed pattern. As with the temperature manipulations, for each of these models we first fit the redundancy model (eq. 1) to the fully fed and DR groups (Fig. 1A in Mair et al. 2003) and subsequently tested whether the required adjustment to accommodate the DR effect in the continuous treatment groups yielded predictions for the switching experiments that fitted the observed results.

A simple mechanism by which DR could reduce mortality risk is through a reduction in the net element failure rate (i.e. reducing parameter (k)). The logic behind this model adjustment is that DR causes reallocation of resources from reproduction towards somatic maintenance, which is in line with a reduced net element failure rate. However, as shown in the analysis of the temperature manipulations (Fig. 4A), element failure rate modulates the slope of actuarial senescence, which is not in qualitative agreement with the data. The fit to the control groups (Fig. 4A—black and red lines) is nevertheless reasonably high ($R^2 = 0.9$), but breaks down when we simulate the switch experiments ($R^2 = -0.43$; Fig. 4B—green, blue and purple lines). Thus the DR effect cannot be explained by a change in element failure rate alone.

It has been hypothesized that the life-extending effect of DR is due to animals re-allocating resources from reproduction towards somatic maintenance when resource intake is insufficient for reproduction (Partridge et al., 2005; Shanley and Kirkwood, 2000). Fruit flies require yeast for reproduction and the absence of yeast during DR by itself causes females to remain reproductive-inactive (Carey et al., 1998; Good and Tatar, 2001). It seems reasonable therefore to assume that DR reduced mortality in Mair's experiment at least in part through a diminishing effect of DR on reproduction (Carey et al., 1998; Good and Tatar, 2001). We therefore looked at ways to accommodate this effect in the redundancy model.

We hypothesized that organisms consist of two different types of blocks (reproductive and somatic blocks) and that DR reduces the element failure rate only in reproductive blocks. This adjustment is in line with the idea that the functions affected by reproduction will sustain little damage in DR conditions because there is little investment in reproduction. To investigate this hypothesis we first fitted the model to the fully fed group ($R^2 = 0.97$; Fig. 4C—red line; see SI–5 for details). Subsequently, we fitted the model to the DR group (Fig. 4C—black line), by optimizing the number of reproductive blocks in which the element failure rate was reduced (from $k = 0.0298$ to almost zero: $k = 0.0001$), while constraining the other parameters to the level fitted to the control group. The good fit ($R^2 = 0.95$) to the continuous DR group is encouraging but the individual based simulations of the treatment switches fitted well in only one of the two directions (Fig. 4C—green and blue lines). The simulation fitted the switch from fully fed to DR conditions very well but failed to reproduce the reversed switch resulting in a relatively poor fit over the four switch experiments combined ($R^2 = 0.46$; Fig. 4C). This is because when DR diminishes damage accumulation in reproductive blocks, subsequent damage accumulation in these blocks after switching does not increase mortality rate instantaneously as in the experiment due to the lag in damage accumulation relative to reproductive blocks in the fully fed group. We conclude therefore that, given the context of our model, the mechanism by which DR reduces mortality is more complex than the reduction of damage accumulation in reproductive blocks.

When implementing the re-allocation hypothesis we reduced element failure rate in reproductive blocks and as a next step, we simultaneously reallocated redundancy elements from reproductive blocks towards somatic blocks (Fig. 4D). Redundancy is the resilience to withstand aging damage and therefore redundancy reallocation is another way (next to changes in element failure rate) to model reallocation from reproduction towards somatic maintenance. The model adjustments fitted the data of the continuous treatment groups well (Fig. 4D; red line—fully fed: $R^2 = 0.97$; black line—DR: $R^2 = 0.95$). More importantly, individual based simulations based on these adjustments fitted well to the switches in both directions (Fig. 4D—green and blue lines; $R^2 = 0.81$, pooled over 4 switches in two directions). We emphasize again that the model parameters were optimized to fit the data of the continuous treatment groups only, and we are fitting the data of the experimental switches to predictions based on the fit to the continuous treatment groups. Reallocation of redundancy elements when switching from DR to fully fed instantly increases the mortality rate due to the reduction of redundancy in the somatic blocks. We conclude that re-allocation of redundancy elements from reproductive to somatic blocks within the context of the redundancy model can explain the DR effect on the mortality pattern observed by Mair et al. (2003).

The redundancy model as we applied it is devoid of any mechanistic detail. It is encouraging therefore that these simple models were able to reproduce the contrasting effects of DR and environmental temperature on the pattern of actuarial senescence. This indicates that the interdependencies of blocks, elements, and damage may, in an abstract way, capture the essence of the aging process in *Drosophila*.

5. Redundancy in the wild

The antagonistic pleiotropy theory of senescence proposes that senescence could evolve when alleles conferring a fitness benefit early in life also confer a detrimental effect on fecundity and/or survival late in life (Williams, 1957). Such alleles may for example increase investment in reproduction early in life, at the expense of the reproductive output late in life (an effect known as the costs of reproduction). When investment in reproduction is made at the expense of the system's redundancy, e.g. through an increase in element failure rate, this is a mechanism by which a negative association could arise between early reproduction and late life survival. We view redundancy to be conceptually similar to the disposable soma in the disposable soma theory of aging (Kirkwood, 1977) which is a special case of the antagonistic pleiotropy theory of aging (Kirkwood and Holliday, 1979). Thus the redundancy model is compatible with one of the main evolutionary theories of aging.

Senescence patterns show large variation both between and within species (Bouwhuis et al., 2010, 2012; Nussey et al., 2013). Much of this variation has been attributed to ecological factors (e.g. extrinsic mortality rate) in combination with life-history trait optimization, but it is largely unclear how these factors mechanistically link up to the aging process. It would therefore be of interest to investigate to what extent variation in lifespan and mortality patterns between natural populations can be attributed to redundancy vs. element failure rate variation (or a combination of the two).

When applying the redundancy model to natural populations, it is important to realize that the model is only concerned with intrinsic sources of mortality, while in natural populations the mortality pattern is also shaped by interactions between internal state (redundancy) and the environment, and extrinsic mortality independent of state. For example, the ability to withstand environmental adversity may be higher when remaining redundancy is high, but presently such interactions between environmental conditions and internal state are not included in the model. So without further extension, the model is best suited to analyse mortality patterns of populations of humans and laboratory animals where extrinsic factors such as famine and predators are less important. The model can be fitted to aging in natural populations as it is, but the parameter estimates would be a mixture of external and intrinsic mortality effects. It would be more informative therefore to build a shell around the redundancy model that introduces extrinsic effects and perhaps also interactions between extrinsic factors and redundancy state or element failure rate. This may initially be as simple as the

multiplication of age dependent mortality with an extrinsic (age independent) mortality factor.

Mortality rate does not always increase with age. In many species mortality rate declines with age early in life, before maturation, but in addition there are species where mortality rate continues to decline over a large part of their lives, for example because they become less vulnerable due to an increase in size. This phenomenon can be thought of as negative senescence (Vaupel et al., 2004). Within the context of the redundancy model this effect can be achieved through an increase of the number of redundancy elements with age (Milne, 2008), which is conceivable in species showing continuous growth. It may also accommodate the typical u-shaped mortality that is observed in humans, amongst other species, where the initial decline in mortality rate is caused by growing redundancy due to development (Milne, 2008).

To illustrate how the redundancy model might elucidate unexplained aging characteristics we here briefly discuss some examples, mainly from our own work, where other concepts known to us did not yield a satisfactory explanation.

The association between telomere length and mortality diminishes with age in humans, which finding does not fit the concept that telomere length is a measure of biological age in its most simple form (Boonekamp et al., 2013). Instead, we showed that telomere length can be interpreted as measure of somatic redundancy: the diminishing association between telomere length and mortality with age fitted the redundancy model, because variation in redundancy between individuals diminishes with age, causing the remaining redundancy to be a poor predictor of mortality (Boonekamp et al., 2013). Furthermore, we could make the prediction that the association between telomere shortening rate and mortality should increase with age (i.e. because when telomere shortening rate reflects element failure rate it strongly determines the late-life mortality plateau), and evidence confirming this prediction is emerging (Epel et al., 2009), but more studies are needed to verify this point.

In wild jackdaws (a small corvid), we found that effects of reproductive effort on survival became apparent only after birds had been subjected to multiple years of manipulation (Boonekamp et al., 2014b); a single year of reproductive effort manipulation did not noticeably affect mortality. The latter finding may be the general pattern (with exceptions) because a recent meta-analysis showed that on average there is no discernible survival cost of increased reproductive effort when birds are manipulated in a single year (Santos and Nakagawa, 2012). Thus, it appears that birds have a buffer to resist high effort for one season. We think of the buffer in this explanation as redundancy, and an increase of reproductive effort as in increase in element failure rate, where an increase in element failure rate for a single season does not yet exhaust redundancy to the extent that it yields a significant effect on survival. A prediction based on this interpretation is that experiments that manipulate reproductive effort for a single season without a discernible effect on survival until the next year (Santos and Nakagawa, 2012) may find an effect at the end of life of life, i.e. on lifespan. This could arise when the effort manipulation did induce a difference between experimental categories in remaining redundancy level, but this difference is only translated in a survival effect at the end of life, when redundancy levels are low. To our best knowledge this hypothesis has not yet been tested.

Lastly, it was recently shown that malaria infection had a delayed effect on lifespan in great reed warblers, but no discernible immediate effect on mortality (Asghar et al., 2015). As in the Jackdaw example discussed above, a redundancy buffer to withstand such a physiological challenge might explain this pattern. This interpretation is supported by the finding that malaria accelerated telomere shortening (Asghar et al., 2015), because we previously showed that human telomere length variation can be interpreted as a measure of somatic redundancy (Boonekamp et al. 2013). These three examples suggest an explanatory power provided by the redundancy model not (yet) offered by other models.

6. Concluding remarks

Our main aim with this paper is to advocate more interaction between theoretical and empirical work in aging research through data-directed modelling. In this context we see modelling as complementary method for hypothesis testing regarding mechanisms causing the observed patterns (Servedio et al., 2014), and as a way to integrate theoretical and empirical perspectives. In this integration process there is a part to play for models that differ strongly in level and realism, ranging from top-down models as presented in this paper, to very detailed biochemical models (e.g. Mc Auley et al. 2015). When it comes to the top-down approach, we like to emphasize that we have at present little reason to advocate the redundancy model over other models (e.g. (Li and Anderson, 2009; Milne, 2008; Pletcher and Neuhauser, 2000; Vural et al., 2014)), if only because a formal comparison with the performance of other models is lacking. Nevertheless, there are factors speaking in favour of the redundancy model. Firstly, there is the practical point that at least so far it seems to do the job we adopted it for. Another important criterion the redundancy model fulfils is that, at least to us, the redundancy concept is intuitively plausible, in that the model components can reasonably be mapped onto real biology. Lastly, with three parameters (we keep initial damage mostly constant), the model is tractable to an extent that is difficult to attain with more complicated models.

We see three main routes to take this work forward. Firstly, it would be of interest to fit the redundancy model to other data sets. This may yield more insights in those data sets and the experiments that generated them, and may be of interest for comparative analyses, for example to explain the difference in fitness costs of senescence between birds and mammals (Bouwhuis et al., 2012), and to explain the large range of mortality patterns seen more generally in nature (Nussey et al., 2013). Fitting the model to existing and new data sets may also help to identify the model's limitations. This in turn would be useful input to develop better fitting models; finding out what changes are necessary to yield a better fit is in itself of interest. Moreover, this exercise would teach us something about how many models we would need to describe mortality patterns in a larger number of species—that one size fits all is unlikely. Secondly, the redundancy model is only one of an infinite number of possible mechanistic models, and a competition between such models is clearly desirable to see which model serves our purpose best, and model performance should be formally compared. Lastly, a logical next step would be to replace parameters in the model with sub-models of those parameters. For example, coming back to the data of Mair et al. (2003) discussed in Section 4, redundancy element failure rate could be made a function of physiological variables or molecular processes that change in response to ambient temperature.

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Appendix A. Supplementary data

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