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AGEING

A stretch in time

Plots of survival against time for nematode worms in different conditions can be superimposed by rescaling the time axis. This observation has far-reaching implications for our understanding of the nature of ageing.

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It is a long-standing mystery why, although the rate of ageing varies greatly among species, the effects of ageing are remarkably consistent. Closely related species such as mice and naked mole rats can have average lifespans that differ by more than tenfold, yet these species (and others as distant as yeast and humans) undergo similar molecular changes throughout ageing. In a paper online in *Nature*, Stroustrup *et al.*[1] rigorously demonstrate that the way in which the risk of death changes over the course of an organism's life is largely independent of the length of that life.

The nematode worm *Caenorhabditis elegans* is often used for studies of ageing, because it has a lifespan of about two weeks and is easy to cultivate in the laboratory. Stroustrup and colleagues used their previously developed[2] 'lifespan machine' to simultaneously measure the survival of tens of thousands of individual worms with 20-minute precision. The authors subjected the worms to a range of lifespan-altering conditions — different temperatures, a damaging compound, a lifespan-prolonging food source and several genetic mutations that extend or shorten lifespan. After analysing the lifespans of more than 100,000 individuals, they demonstrate that the overall shape of the survival curve (a plot of the fraction of the starting worm population alive at any given time) remains unchanged in different conditions. They find that these conditions act only to stretch or squeeze the curve along the time axis (Fig. 1a).

This is altogether unexpected, because it implies that the tested lifespan-altering manipulations change the probability of every possible cause of death in concert and to exactly the same extent. To explain, because each cause of death plays out along a distinct timescale, if a particular condition were to decrease the odds of a fast-acting cause of death but not a slow-acting cause (or vice versa), a particular region of the overall survival curve would be altered, and thus its overall shape changed (Fig. 1b). Even interventions such as temperature shifts might be expected to affect different causes of death differently. After all, death is a biochemical process, and changing temperatures will alter the rates of different death-promoting chemical reactions differently, depending on the activation energies of those reactions. The authors' observation of almost-perfect timescaling across different conditions thus places specific constraints on how these conditions influence survival.

How can this surprising observation be explained? One possibility is that every cause of death in the worms has the same activation energy and responds identically to changes in food source, toxic exposures and diverse genetic mutations. Another is that worms have a single mechanistic cause of death.

A more plausible interpretation is that there is some intermediate state on which all the tested interventions converge, and which determines the risk of death from each possible cause (Fig. 1c). Could this intermediate state involve, for instance, the insulin/insulin-like growth factor signalling (IIS) pathway, which is central to many aspects of ageing across species[3]? No — the authors found that survival curves retain their shape even when the IIS pathway is inactivated, and in response to conditions and mutations known to act independently of the IIS pathway.

The most likely explanation for this intermediate state is that the risk of death is governed not by any single pathway, but by a property that arises from interactions between the various molecular processes that influence ageing. This property, perhaps best called 'resilience', would be an intrinsic biological property of ageing *C. elegans*, just as temperature and pressure are intrinsic thermodynamic properties of gases that emerge from the interactions of the constituent molecules.

The temperature of water in a whistling tea kettle provides an analogy for resilience. There are many ways in which to heat the water — on a stove, in a microwave, or even by adding a strong acid. However, whether a kettle whistles depends not on the source of the heat, but on the water temperature. Similarly, alterations in the molecular processes

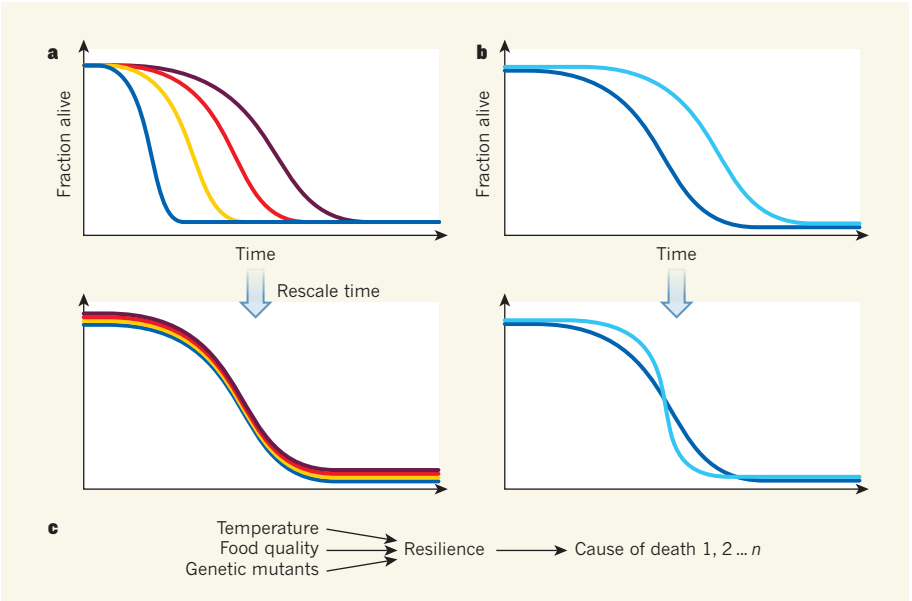

Figure 1 | Resilience as a measure of ageing. **a**, Stroustrup *et al.*[1] measured the fraction of a population of nematode worms that remained alive over time in various conditions, constructing 'survival curves' (coloured lines) for each condition. The survival curves for many different conditions can be superimposed simply by rescaling the time axis. This observation implies that each condition alters the probability of every cause of death to the same extent. **b**, If this were not the case, the curves would not be superimposable. For example, if a fast-acting cause of death is made less likely, but not a slow-acting one, then the curve's shape will change in one particular region (as in the light blue compared to the dark blue curve). **c**, To obtain the scaling observed by Stroustrup and colleagues, there must be an organismal state, here dubbed 'resilience', that is influenced by many determinants of lifespan, and that is the sole determinant of the risk of death from any particular cause (different causes are represented by numbers).

that contribute to resilience could change the rate of ageing (the heating rate of the water) without changing its underlying nature (the relationship between temperature and whistling).

The authors use detailed simulations to demonstrate how such a property could emerge. If resilience is a measure of the fraction of biological processes in a densely interconnected network that have failed, then manipulations that alter a subset of these processes will extend or shorten lifespan without changing the shape of the survival curve. Alternatively, a single physical property, which is acted on by many molecular processes and affects the risk of death from diverse causes, could underlie an organism's resilience. Potential candidates for such physical properties include intracellular redox levels[4,5] or global protein solubility levels and turnover rates[6,7]. Whatever the case, the current work provides a strong constraint on any proposed molecular mechanism of resilience — measurements of the levels or activity of that mechanism must correlate exactly with lifespan across temperatures and among different genetic mutants.

This study suggests that concepts such as resilience and frailty, long used in the ageing literature, might have a concrete biological meaning. In particular, the Rockwood frailty index, which calculates the fraction of measured clinical markers considered to be in a deficient state[8], is a close theoretical match for the authors' interpretation of resilience. Most importantly, these results demonstrate that, although students of ageing biology have learnt much about how to manipulate the rate of ageing, the nature of organismal frailty is almost completely unknown. The few interventions the authors identify that do change the shape of the survival curve in *C. elegans* (such as a mutation that alters feeding ability, and another that alters function in mitochondria, the cell's energy centres) may point the way towards understanding this previously unappreciated biology.

Finally, although Stroustrup *et al.* consider only lifespan, increasing chronological lifespan does not necessarily increase the fraction of lifespan spent in good health[9]. Further work of a similar experimental and analytical rigour will be necessary to clarify the relationship between quality and quantity of life. ■

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