

Modelling the origins of ageing

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The ultimate goal of ageing research is to learn how to avoid the adverse consequences of human ageing. One common approach is to directly study human ageing and age-related diseases. Alternatively, one may choose to study ageing in simple model organisms, particularly low eukaryotes, and then extend the results to high eukaryotes such as humans. Both approaches are appropriate for investigating *how* ageing occurs. To have a more profound understanding of ageing, however, it is of utmost importance to understand *why* it occurs. To achieve this, one has to take an evolutionary approach.

Ageing is a more universal phenomenon than once thought. Even unicellular organisms such as bacteria and yeast do senesce (Aguilaniu et al. 2003; Ackermann et al. 2003). It is therefore rather tempting to speculate that multicellular ageing may have evolved from unicellular ageing. I am interested in studying the evolutionary forces that drive unicellular ageing, hoping that the same forces operate in the ageing process of more complicated forms of life. Unicellular ageing has been attributed to asymmetric segregation of damaged macromolecules at mitosis. If one of the daughter cells that arise from cell division contains, as a result of asymmetric inheritance of maternal damage, more damage (i.e. is functionally older) than the other, the population will evolve into a heterogeneous mixture of old and rejuvenated cells. With sufficient asymmetry and sufficiently low rates of damage accumulation, the population may continue to grow and survive, owing to the rejuvenated cell arising from each division. Otherwise, the population reaches clonal senescence.

Mathematical modelling is a promising alternative to experimental evolution studies because the latter are time-consuming and the experimenter needs to have the environment tightly under control and have all relevant information about the intra-organismal events as well as the ecological conditions that may influence the evolution of the phenomenon of interest. These problems are particularly relevant in studying the evolution of asymmetric damage segregation because experimental data are currently scarce. I use theoretical modelling to investigate the evolution of asymmetric segregation of non-genetic macromolecular damage, e.g. oxidised proteins.

One should account for both extrinsic (environmental changes) and intrinsic noise that accompany the evolution of asymmetry. Intrinsic stochasticity in segregation of damage arises from the reduction of damage entities in the cell following the aggregation of damaged proteins. Damaged particles that form an aggregate are not free to choose the daughter cell to segregate to. Rather, all particles in an aggregate have the same fate, i.e. the aggregate's fate. This phenomenon introduces substantial noise to the system that can be accounted for only by a stochastic model. The literature is lacking such models at present. Deterministic models have suggested that asymmetric damage segregation allows the lineage to withstand higher levels of

damage before entering clonal senescence (Erjavec et al, 2008). However, due to the omission of stochastic effects, such models have not been able to explain all experimental observations.

Using stochastic models, I have determined the evolutionary forces that drive the evolution of asymmetry (Figure 1). Specifically, high rates of damage, the severity of damage, and slow proliferation rates promote higher levels of asymmetry. The results help us determine the contributions of individual asymmetry determinants, both environmental and organismal. In particular, environmental stress favours cells with more asymmetric segregation strategies. One interesting prediction is that the yeast *Saccharomyces cerevisiae* (*S. cerevisiae*), which produces at division an old mother cell and a rejuvenated daughter cell (Haber 2003), has probably evolved in harsher environments than *Schizosaccharomyces pombe* (*S. pombe*), which has almost symmetric distribution of damage between the daughter cells (Minois et al. 2006).

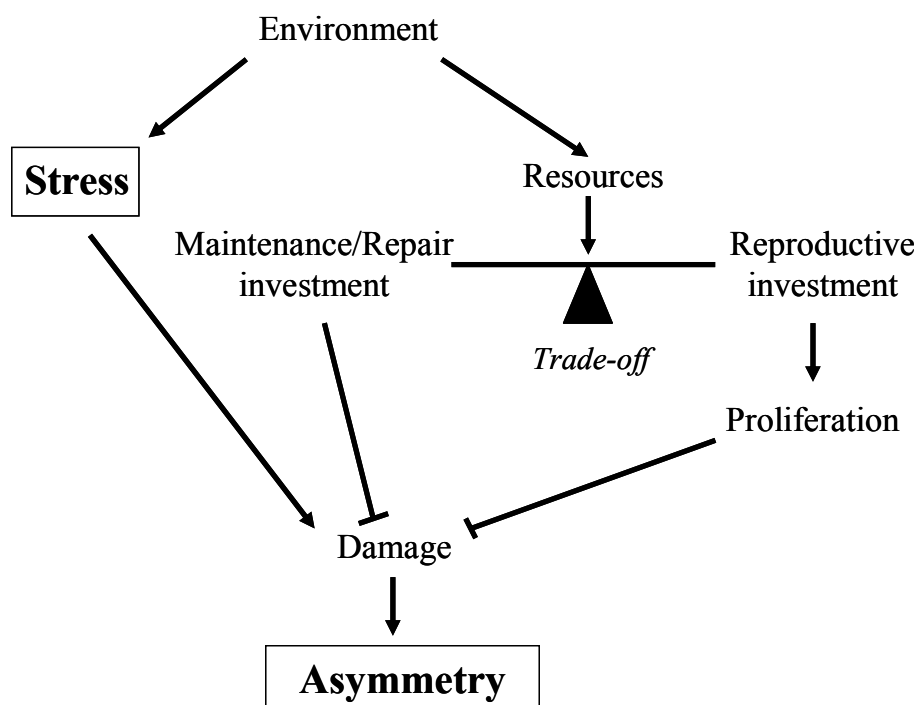


Figure 1. Due to limited resource availability, there is a trade-off between investments in reproduction and maintenance/repair, and the model predicts that investment in either function acts to reduce the selection pressure for asymmetry. Since damage accumulation is the product of the incoming stress and the strength of cellular defence/repair systems, the impact of alterations in the environmental stress on selection pressure will be major and dominant.

Evolution of multicellularity is known as one of the major evolutionary transitions. A unicellular organism is directly exposed to the environment, and unless the environment changes on rapid time scales, it does not evolve complex signalling pathways to respond to environmental changes. In a multicellular organism, however, a cell experiences the *microenvironment* which before the evolution of advanced homeostatic systems may have well been exposed to transient perturbations (even with constant external environment surrounding the whole organism). Therefore, multicellular organisms need intracellular signalling pathways capable of responding

to both environmental and micro-environmental cues. The other complication at the transition to multicellularity is that such cellular responses need to be tuned for the well-being of the organism, rather than the particular cell. I am trying to see how asymmetric damage segregation is modified as multicellularity evolves. Insights into the events that have occurred at this transition may then help proceed to humans.

References

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