

# BASIS

## The Biology of Ageing e-Science Integration and Simulation

BASIS is a UK e-Science pilot project jointly funded by the BBSRC, the MRC and the DTI. Our aim is to develop a web-based system for the quantitative study of the biology of ageing. It is a collaborative project between Gerontology and Mathematics and Statistics, coordinated from the multidisciplinary Institute for Ageing and Health at the University of Newcastle upon Tyne.

Ageing is a highly complex process involving many biochemical and cellular mechanisms, which affect multiple tissues within an organism. The underlying cause of ageing is the gradual accumulation of unrepaired molecular damage, leading to an increasing fraction of damaged cells and eventually to functional impairment of tissues and organs. Although there are numerous maintenance and repair systems, they operate at levels lower than that required for indefinite survival due to the competing demands of other physiological functions such as reproduction. The inherent complexity means that although work on the biology of ageing is now advancing quickly, information remains highly fragmented. Our goal is to deliver a web-based system that will serve the biology of ageing research community by helping to integrate data and hypotheses from diverse biological sources.

The project is divided into three stages.

### 1) Virtual ageing cell

The virtual ageing cell will allow key processes to be represented either in relatively simple terms or expanded into more detailed structures as hypotheses and knowledge permit. The majority of modelling work to date has concentrated on the intracellular mechanisms that result in the cell's degeneration and death. This research has emphasized that cellular mechanisms cannot be considered individually, but must rather be taken in the con-

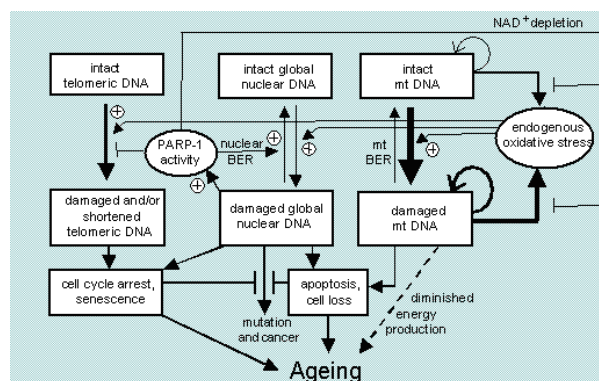


Figure 1

text of interacting forces. For example, Figure 1 shows three subsets of cellular DNA, mitochondrial DNA and nuclear DNA divided into global and telomeric. Each class can be either damaged or undamaged. A major source of DNA damage is oxidative stress, which itself depends on the level of DNA damage already present in the cell.

A further example of the importance of interacting forces is our model of mitochondrial dynamics. Here, very different outcomes are predicted between dividing and non-dividing cells for the accumulation of mtDNA mutations. This has been observed experimentally.

### 2) Virtual ageing tissue

To further our understanding of the processes that lead to altered tissue function in old age, it is essential to consider interconnected cells as opposed to individual cells. This aim will be achieved through our virtual ageing tissue.

The simplest tissue model will comprise a matrix of connective tissue cells (fibroblasts), for which a large body of data exists. An isotropic three-dimensional matrix of cells, each of which will be subject to stochastic ageing processes, will be used to represent the tissue. When surrounded by other cells, fibroblasts divide only rarely, but occasional cell deaths within the matrix may create gaps that will be filled by division of neighbouring cells. Through stochastic modelling, these key cell deaths can be explored, thereby elucidating the fundamental properties of the fibroblast tissue.

The next two models will consider tissues that are more and less proliferative than connective tissue. One will be based on the gut or intestinal epithelium, the most proliferative tissue in the mammalian body. In particular, the functional homeostasis of the tissue will be investigated to determine the role of the small numbers of stem cells present in the tissue.

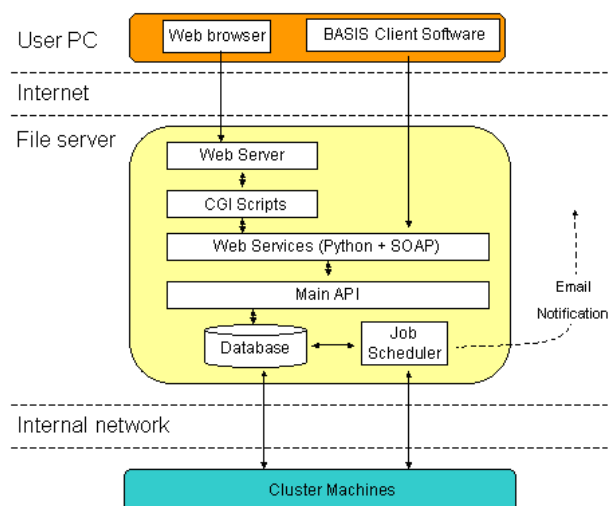
The third model will represent the neuronal networks that comprise part of the non-dividing brain tissue. Through stochastic simulation, the effect of random, single cell death can be assessed, thereby furthering our understanding of the impact of intrinsic cellular ageing on a network system.

### 3) Virtual ageing organism

By extending BASIS to include a virtual ageing organism we will complete the necessary integration that will allow us to begin to assemble the elements of the ageing process as a whole. This is feasible for one of the most extensively studied model organisms, the nematode *Caenorhabditis elegans*. The adult nematode comprises just 959 somatic cells, each of which has been identified within the developmental cell lineage and whose function has been characterised. Although *C. elegans* is characterised by its structural uniformity, the range in lifespan typifies the inherent randomness of the ageing process. BASIS presents an ideal opportunity to investigate the open questions concerning the variability of ageing nematodes, such as whether the random damage accumulated through a nematode's life accounts for the differences in lifespan or whether other processes are involved, for example in neuromuscular junctions.

Returning to the cell, the processes within the cell can be represented by a network of biochemical reactions. These are commonly known as schemas and form the basis of current knowledge. We can represent these networks with the Systems Biology Markup Language (SBML). Any model constructed using this language may then be parsed and simulated on the project's cluster either

stochastically or deterministically. We have installed a 16 x 2.8 GHz CPU Linux Beowulf Cluster managed by a dual 2.4 GHz server for compute power. Once a simulation is complete, the user will be notified by email. The results can then be accessed using web service methods to obtain graphics or summary statistics.



**Figure 2**

Users will also be able to make simple adjustments to existing models stored in our databases through a browser. A more sophisticated client tool will be provided for building models or making structural changes to existing models. We will use the Simple Object Access Protocol (SOAP) for transferring SBML from client to server and vice versa. Our system architecture is shown in figure 2.

We have completed the first year of an initial funding of four years. We have established SBML as a good representation of our models and are involved in the continuing development of this markup language. Several existing SBML models have been placed in our database, with a simple Python interface developed to allow user interaction. To find out more read our article in Nature Reviews of Molecular Cell Biology (2003), 4, 243-249, or see our web-site at [www.basis.ncl.ac.uk](http://www.basis.ncl.ac.uk).

#### The team

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