

Machines for Unravelling DNA, Molecule by Molecule by **Dr Daniel Burnham** on 17-2-2017

Dr Burnham began by describing the Francis Crick Institute, which is in Camden close to Kings Cross station. Sir Paul Nurse saw the need for a multidisciplinary institute for biomedical discovery, organised its building and its occupancy by a number of separate biomedical centres working in this field. The building is basically open plan with a vast atrium with four underground floors and five above ground; laboratories surround the atrium on each floor. Dr Burnham commented that, contrary to his initial reaction, the ambience is quiet. Each of the constituent bodies has its strengths, so advice is always at hand. The ethos is to find new methods for treating human disease, and to speed up their introduction to general medical practice. Outreach with the general public, particularly in Camden, is a condition of working there.

Cell Division - Bodies are made of cells, each with a nucleus containing a tiny (but of 6bn base pairs, 2m long) DNA molecule. Dr Burnham is studying what happens to DNA during cell division. To do this the two DNA strands are separated, and each acquires a second matching strand. The cell then divides its constituents to either side and the centre pinches off to give two cells. This takes about a day, the copying having been done at a rate of 70,000 base pairs a second. All this is done with great precision – mutations do occur, but very seldom.

The first stage of cell division is to ‘un-zip’ the DNA. This is done by a protein hexamer (a grouping of 6) which travels along the DNA. Behind it a ‘bubble’ develops before the two new DNAs are formed and separate out.

Seeing this is not easy. One needs to be able to see dimensions half the wavelength of observable light, impossible according to the Raleigh criterion. However, it can be achieved by the use of flashing dies – if two adjacent elements, containing the die, flash randomly one may be on when the other is off and vice versa. By recording the flashes over a long enough period a picture can be built up. (The dies are made to flash by a high energy laser pulse.) Another technique for seeing what is happening is to use a magnetic tweezer. A magnetic bead is attached to a molecule and attracted by magnet - movement in the molecule is enhanced by the magnetic force and can be detected at the magnet. Dr Burnham showed us pairs of 4mm magnetic cubes, which adhered to one another very strongly.

Much was already known from crystallography by x-ray imaging – but only of DNA frozen in a crystalline form. This suggested that un-zipping the DNA was done by a mechanism that ‘walks’ steadily along the DNA. Dr Burnham has obtained results that show it is not steady but stops and starts. DNA division takes place in a cellular soup, and the delivery of the required building proteins may not be timely.

In order to design his experiments and make sense of the results Dr Burnham made good use of the multidisciplinary nature of the Institute. He had to consult people who had written similar software (derived from ‘first passage time’ financial programmes to find when a threshold is reached), and then write his own – he flashed up a daunting page of lines of code. Even then he found that he had to add retrograde movement (when the DNA temporarily re-zips) to the stochastic ‘walk’ he had already discovered, before the theory matched the results. There are seven variable parameters in the theory, which still has unresolved difficulties...

One question after the talk was to ask how cell division was done in very early forms of life – to which the reply was, as far back as we can see, the same as now, even to having a hexamer to do the unzipping. However there is a belief that initial life was based on RNA rather than DNA.

Dr Burnham closed by telling us about his Week in Westminster. Nowadays Parliament invites professionals to shadow members of select committees for a week, to see how parliament works and to impart some of their knowledge. He was paired with Nicola Blackwood, who greatly impressed him with her grasp of science and her ability to quickly understand a business presentation - and to ask probing questions. He was completely disabused of the notion that Parliament is unscientific, and came away with a greater respect for it.