

Building BORIS - an outreach project on drug design and molecular modelling

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Within university chemistry departments, organic chemists are formulating reaction pathways which will yield a desired chemical product. In most cases, it is most often found that the targeted product exerts some beneficial biological effect towards cellular activity. In my organic chemistry lectureship within the University of Salford, I too am involved in the synthesis of potential biologically active compounds; namely a range of anti-cancer compounds and anti-bacterial agents.

Research chemists are fully aware that our finalised compounds will only show 'activity' if they manage to interact successfully with the targeted organism. Simplistically, any 'drug' must target a host protein that is contributing to a deleterious effect in order for a therapeutic benefit to be felt. Within any research environment, once a disease or virulent is established, the host protein which is to be targeted is quickly identified, and once the structure of a protein has been confirmed, computerised molecular modelling can enable chemists to identify possible 'drug' molecules which could target the protein. With this in mind, in the autumn of 2006, I decided to investigate the possibility of building a life size protein model which could be used to show non-university audiences (namely GCSE and A-level students) what proteins look like in their fundamental 'globular shape', their importance and role within the human body and, crucially, how 'drugs' interact with them when we treat the human body with medicinal products.

A quick look at GCSE Biology syllabuses (AQA, Edexcel, OCR) revealed content on the importance of proteins in the human body (e.g. the need for protein intake in the diet) and the function of enzymes in the body (protease, lipase etc.). Additionally, the AS/A2 Biology and Chemistry syllabuses also highlighted how proteins are formed (transcription and translation), structural identity (primary to quaternary structures), functional group identification within individual amino acids (amino and carboxylic acid portions), how proteins may work, and their tasks in the human body (e.g. antibodies, blood clotting, Na⁺/K⁺ pump in cell membranes etc). It was obvious from this that proteins are given great importance at both key stage 4 and 5. I envisaged that once a reasonable protein model could be constructed, you could highlight how any drug system could 'dock' into the active site of a protein and why some drugs would work on one protein but others would not. By re-emphasizing the importance of proteins in the development of a disease, a session that could showcase the concepts of drug therapy by making it 'hands-on and practical' to the audience could be used to highlight the concept of drug therapy whilst supporting the appropriate syllabus.

The idea in practice

With the idea of explaining drug therapy by molecular modelling in place, work started on building the model protein structure. Early on I decided that a simplified story of a protein responsible for pain would be told. The enzyme cyclooxygenase (COX), found in the human body, is responsible for prostaglandin production and hence pain transmission. The structure of this enzyme is known, but I decided to produce a generic protein structure instead.

With a supply of metal coat hangers and pliers in hand, over a period of two months a twisted metal structure emerged which satisfied me that what was taking shape was a structure resembling the tertiary/quaternary structure of a protein. The metal inner skeleton was then coated in insulating foam and, after the application of a silver tape to give an outer skin, a giant protein structure had emerged! At this point, when questioned by colleagues on what I was up to, I mischievously at first responded that I was building a 'monster', and on the latter stages of constructing the protein, I couldn't get the famous Boris Pickett tune 'Monster Mash' of my head when I was at work. Hence BORIS (the 'Biological ORIGins of Systems', or the 'Monster') was born! (figure 1). Once the giant structure of the model had been built, a selection of Molymod (Spring Enterprise Ltd) was purchased and ibuprofen, aspirin and paracetamol were selected as systems which would be active on 'BORIS', a protein responsible for the signalling of pain in the body.

For simplicity three 'active sites' were constructed on the protein and the drug systems would be 'active' if two criteria were fully met:

1. The drug model must fit into the 'active site'.
2. If the model fits in then certain atom colours must match up: black on the active site to black on the molecule (black being carbon), red to red (oxygen), blue to blue (nitrogen). With this, the idea was to illustrate to students the concepts of Lipinski's rule in a visual way.

Thus, with much patience and care, three carefully colour coded active sites were grafted onto 'Boris', with one site being able to accept ibuprofen, aspirin and paracetamol each. Other molecules built, included cholesterol, oestrogen, progesterone, testosterone, α -glucose, adrenalin, dopamine,

serotonin, glycerol, adenosine triphosphate, nicotine, caffeine, acetylcholine, saccharin, lactic acid, ecstasy, lactic acid, urea, penicillin G, Viagra and mustard gas.

Finding the money and developing the idea

Since 2007, funding has been provided by The Biotechnology and Biological Sciences Research Council (BBSRC), the Research Council UK (RCUK), The Biochemical Society's Outreach Grant Programme and The Royal Society of Chemistry's Outreach Grant Programme. This funding covered the cost of transportation to venues, chemicals for laboratory practical sessions and the purchase of Molymod for the construction of molecules.

Running events

Two types of presentation were developed, one aimed at A-level students and one for GCSE students, and can be modified as appropriate. Sessions are run either at the University of Salford or held at the hosting school/college. On average, fifteen to twenty sessions are held per school year and each session can host up to 25 students. The session starts with introductions and the aims of the session. Questions are then posed to the student-body, testing their knowledge, and a PowerPoint presentation is delivered which illustrates the importance of cell physiology, including: how DNA and proteins are related, how proteins could be responsible for transmission and signalling in the human body and the issues of pharmacokinetics and pharmacodynamics in drug design. Issues of absorption, distribution, metabolism and excretion (ADME) are then brought into the presentation. Once proteins have been introduced, depending on the age and level of the audience, then 'molecular shape', drug shape and chirality of molecules are explained, together with examples of chiral molecules in nature. The presentation then recaps why some chiral molecules may exert biological effect and some may not. For all audiences, the example of the drug Thalidomide is used to explain why we always need to get the correct '3D-shape' of a molecule and what could happen if the wrong 'shape' of a drug is introduced into the body.

An experimental session was also incorporated, namely an electrophoresis practical if the session is run over a suitable period of time. A practical of thin layer chromatography and chromatography of amino acids or common organic molecules also took place.¹ In addition to the laboratory session, in the past two years a computing molecular modelling session using AutoDock Vina was also incorporated into the session.

Identification of audiences and future plans

This project has, to date, worked with schools and colleges and members of the public (Rotary Clubs, Manchester and Bradford Science Festivals) throughout the UK. Since 2007,

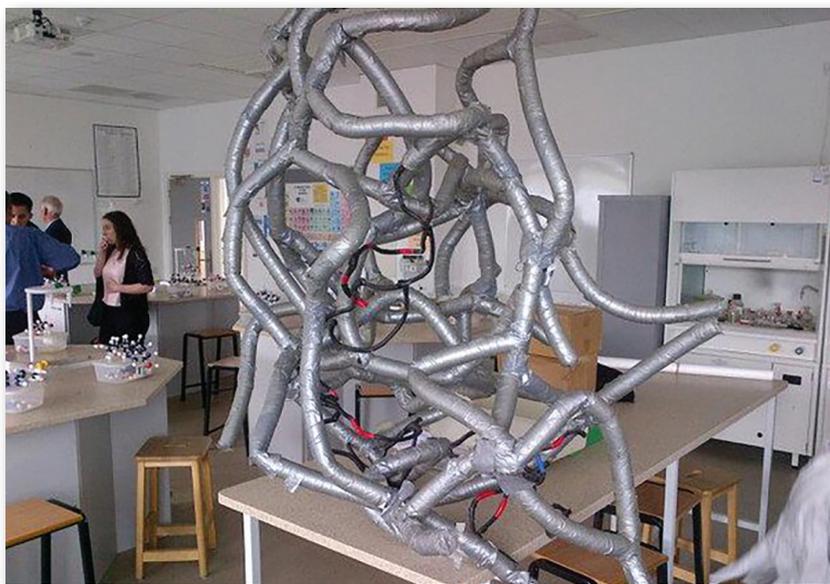


Figure 1. BORIS at Franklin College in Lincolnshire

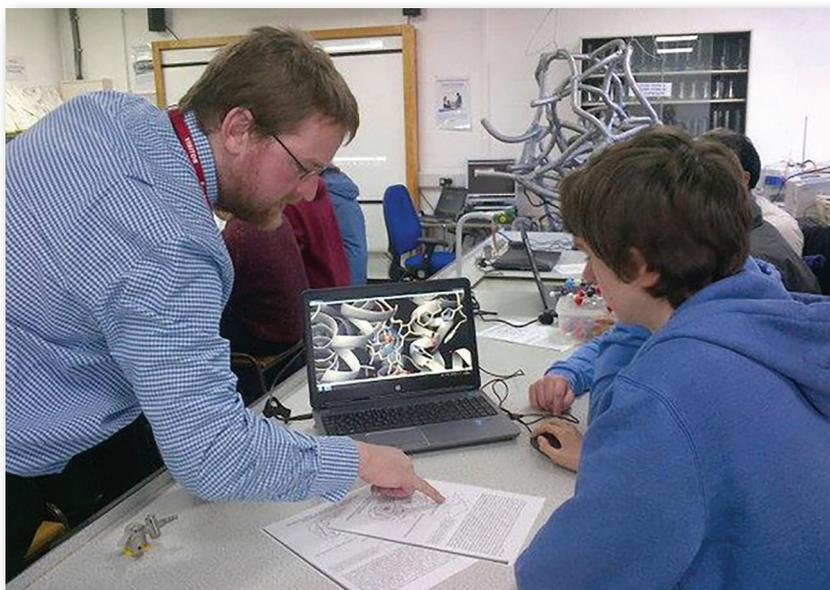


Figure 2. Molecular modelling using AutoDock Vina at Runshaw College in Lancashire.

over 156 secondary schools, colleges and academies have been engaged with records showing 6942 students and 213 teachers took part in events. Schools and colleges are contacted by myself or by the university for 'taster sessions'. I believe future activities will benefit from the inclusion of more Molymod molecule construction, using more computer modelling in sessions as the provision of internet-use in lessons is increasing with greater access to 4G/5G networks, and, for those schools and colleges wishing to receive them, the inclusion of the laboratory sessions. Any interested school/college interested in receiving a visit is encouraged to contact me (S.B.Rossington@salford.ac.uk) for more details. ■

1. For information on the practical sessions offered please refer to: <http://www.srossingtonchem.com/outreach-drug-design-presentation.html>

Figure 3. Image gamma and image histograms.

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The gamma

The brightness of a part of a scene displayed upon a television screen, a cathode-ray-tube-based computer monitor screen, a flat-screen computer monitor and other electronic display devices is increased by increasing the input voltage. Unfortunately, the brightness perceived is not proportional to the input voltage, but is very well approximated by a function of the input voltage raised to a power, where the value of the power varies from screen to screen. In contrast, the level of signal generated by most electronic cameras, including digital cameras, is proportional to the intensity of the signal, or very nearly so (for more details see, for example, <http://www.cgsd.com/papers/gamma.html>).

Consequently, to make the image displayed upon a television screen match the original scene, a correction has to be applied to the input voltage that compensates for the curvilinear relationship between input voltage and perceived brightness. This compensation is known as a gamma adjustment.

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