Computing in Medicine

Edited by J. P. Paul, M. M. Jordan,
M. W. Ferguson-Pell and B. J. Andrews

STRATHCLYDE BIOENGINEERING SEMINARS

COMPUTING IN MEDICINE

Proceedings of a seminar on computing applied to medicine, held at the University of Strathclyde, Glasgow, in August 1981

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COMPUTING IN MEDICINE

PREFACE

The fourth in the series of Strathclyde Bioengineering Seminars was held in August 1981 and considered the wide and highly topical subject of computing applied to medicine. Seminars in the present series were preceded by two broad-spectrum symposia held in 1964 and 1972. The series has covered the areas of Tissue Viability and its Clinical Applications, Extracorporeal Blood Treatment Systems, and Rehabilitation of the Disabled. These seminars were published by the Macmillan Press under the titles of *Bedsore Biomechanics* (July 1976), *Artificial Organs* (July 1977) and *Disability* (December 1979).

The present volume and the associated seminar mark a milestone both for the series and for bioengineering. Professor R. M. Kenedi, who initiated the series, organised the meetings and edited their proceedings, retired from the University of Strathclyde in 1980 and took up the post of Associate Director (Engineering) in Hong Kong Polytechnic. Prior to his departure from Glasgow, Professor Kenedi initiated the preparation for this meeting and it was with great pleasure that we were able to welcome him back to introduce the Adam Thomson Lecture given by Mr Jack Perkins, and to participate in the seminar and its functions.

Dr Monica M. Jordan, one of the editors of this volume, was a member of the Bioengineering Unit until February 1980, when she took up a post in the National Institute of Medical Research, Mill Hill, London. She has been involved at a high level in the planning and organisation of this meeting, both before and after her translation.

The present seminar, the fourth in the series, was held in August 1981 and related to research and development in applications of computers and microprocessors in the field of medical practice. Special sessions included signal and image analysis, medical statistics, teaching, and modelling of physiological systems. It was attended by 190 registrants from the United Kingdom, Australia, Canada, Denmark, Eire, the Faroe Islands, France, Hong Kong, India, Israel, Italy, Japan, Mexico, Netherlands, Norway, Portugal, Turkey, USA and West Germany.

The details for the sections are given in the contents list and the companies and organisations participating in the scientific and industrial exhibition are identified on page viii. The organisers wish to express their particular appreciation for the support of the industrial exhibitors in being present to show their equipment and in contributing to the finances of the occasion.

Being aware of the financial difficulties facing young people starting in their careers who wished to attend seminars of this type, financial support for the registration of six relevant persons was provided by Messrs Ferranti, Hewlett Packard and IBM, and the organisers of the seminar extend to these companies

the thanks of the individuals supported. In the financial crises facing universities at this time, it is easy to forget that the Health Services also are under similar pressures, and the continuing support for the seminar programme by the Greater Glasgow Area Health Board is therefore particularly appreciated. Banking and travel facilities were provided by the Bank of Scotland and Mackays Travel Agency, to both of whom sincere thanks are due. Messrs John Dewar and Sons Limited, whisky Distillers, particularly favoured the occasion with a donation of their products for the benefit of participants at the conference banquet.

A seminar cannot be held on the scale of the present one without adequate publicity and the organisers are indebted to the Biological Engineering Society and the Hospital Physicists' Association for undertaking circulation of information and to the Biomedical Press UV and Taylor and Francis for publicity in their journals.

The organisers acknowledge again their sense of indebtedness to the City of Glasgow District Council for the warmth of the Civic Reception given by them to the seminar participants and guests.

Professor Kenedi, introducing the Adam Thomson Lecture, recalled the contribution to the growth of the Strathclyde Bioengineering Unit made by Emeritus Professor Adam Thomson. From his position as Head of Department of Mechanical Engineering at the Royal College of Science and Technology, which subsequently became the University of Strathclyde, he had been a wise counsellor and guide to many attending the seminar. His very considerable contribution to the University, and Bioengineering, has been gratefully acknowledged by the University's Court who established the Adam Thomson lectures in his honour. The attendance of Professor Thomson and Mrs Thomson was very much appreciated by all present.

Mr Perkins, Professor Kenedi recalled, has been associated with medical computing for many years and has long been an international leader in his field of study and research. His extensive participation and in particular his presentation of the Adam Thomson lecture contributed greatly to the potential for success of the seminar.

The undersigned wishes to warmly support Professor Kenedi's sentiments and also extends his thanks to Professor Kenedi for introducing the Adam Thomson lecture and more widely for his unflagging support of the Strathclyde Bioengineering Unit, and in particular the seminar series.

This is also the occasion to remember and thank all staff and students of the Bioengineering Unit for their help and forbearance. Similarly, thanks are due to the relevant administrative and supportive staff of the University for their support of the occasion.

Glasgow, 1982 J. P. Paul

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CONTENTS

The 1981 Adam Thomson Lecture

TRANSFORMING DATA AND IDEAS INTO INFORMATION

W. J. PERKINS

'As beauty is to the eye of the beholder,
so is information to the mind of the receiver.'

1. Transforming Data and Ideas into Information

Scientific method

Throughout our development we have sought to obtain a better understanding of ourselves and our environment. Being neither as strong as a lion nor as fast as a gazelle, man has survived by his intellect which has enabled him to make tools to overcome the strongest and to outpace the fastest. These two features, of science and technology, represent our twofold approach in research, using science in the formulation and assessment of ideas, and technology for obtaining data.

An established scientific method, as demonstrated by Darwin, was to observe and deduce. Since then, there has been a transition from qualitative observation to more quantitative analysis. It was William Thomson, Professor of Natural Philosophy at Glasgow University, later Lord Kelvin, who took the view that one could not begin to understand something until one could first measure it and then put numbers to it. This is a perfectly sound philosophy but in basic research where data is both poor and scarce, further information may still be acquired by inference from the available data. Thus at any stage in the study of a biological system, a scientist's understanding of its behaviour arises from a combination of data (real) and ideas (imaginary). It would seem sensible, therefore, to adopt the Darwin approach but to follow Kelvin's advice as far as possible.

Optimisation of effort

The reward for effort usually follows an exponential type curve, rising sharply at the outset – the most rewarding region – to a point where a state of diminishing returns is reached. Here a decision has to be made, whether to continue in this

expert region (in this case, of measurement) or to move into a different but relevant subject of data processing, to try to obtain more information from the same data. For example, design engineers would normally need to operate in this expert region of their subject but those concerned with applications could find it more rewarding to change to a faster train.

The mere collection of data, without facilities for its processing and analysis, may well confuse the situation. Data processing is the sorting and rearrangement of data into a more meaningful form, while analysis deals with an assessment of results. Small changes, which may not be discernible in a direct record of a complex signal waveform, could possibly be detected in a histogram display of the signal components obtained by Fourier analysis. Processing, too, has its expert region but there is still another fast train, that of modelling.

Although this is usually the last train one catches, it ought to be the first, in order to decide which measurements should be made. It is also a well-established method being mentioned in the Old Testament (Ezekiel 5.5), 'Thus says the Lord God: This is Jerusalem, I have set her in the centre of the nations, with countries round about her'. This model, with Jerusalem as the focal point surrounded by Europe, Asia and Africa as three ellipses at 120°, was no doubt realistic at that time.

A model can represent our present understanding of a system; it does not have to be exact as by then there is little need to study it further, only to use it. In science, an idea is usually formalised into a hypothesis to answer specific questions, then tested by experiment. A hypothesis may also be assessed directly by modelling it in a computer and testing it theoretically with respect to the system being considered. If it is shown to be untenable there is little point in establishing experiments to test it biologically. Specific models of this type can be more effective than generalised models of complete biological systems.

Interactive computing

In basic biomedical research, problems are rarely clearly defined, but often a handwaving exercise followed by an iterative refinement of the problem after each proposed solution is tested. Thus I became interested in interactive computing to allow researchers to adopt the same attitude in collaboration with the computer and be able to use it as an extension of their own thought processes (Perkins and Hammond, 1975). Suitable input devices and output display facilities are provided, and appropriate programs developed, to enable a user to change the computation, observe immediately the effect of such intervention and so make further changes – an adaptive, on-line, real-time system for obtaining information from data and ideas. This optimises the situation by combining the human qualities of reasoning, pattern recognition, and even intuition, with the high-speed calculation and display facilities of the computer.

One of the best ways to allow handwaving inputs is a tracing tablet which allows drawings to be transferred into a computer. A light pen too is useful for selecting part of an image for further computation by touching the pen on to the

screen. Both devices are usually associated with a menu of options selected by a probe or light pen, respectively, each option calling into operation a predetermined subroutine in the computer program.

The human visual system is the most powerful sensor for taking in large quantities of data and deriving immediate information. Display systems are thus an essential feature of interactive computer systems. Three-dimensional displays can be obtained by adding perspective or by rotating the 3-D structure about the orthogonal X, Y, Z axes either manually or continuously. For static displays, a stereoscopic pair can indicate depth when seen through a suitable viewer (Perkins *et al.*, 1971). Colour systems provide another dimension in discrimination.

Models

Mathematical

Some computer models attempt to represent the behaviour of biological systems with mathematical equations. There are two approaches to the formation of such models. The mathematical approach looks at biological data then fits an equation to its distribution on the transfer function principle. It is usually possible to fit data distributions, however scattered, with some form of equation, irrespective of whether it has any biological relevance, so such papers usually conclude with the phrase 'The model shows a reasonable match with data'. The real value of this approach is in suggesting to biologists how the system might be behaving, as a guide for their studies.

The biological approach is to represent the assumed behaviour of a system by discrete compartments and to derive equations representing the exchange rates between them. A difficulty is that a modeller needs to be familiar with the medium used, in this case to recognise any implicit biological assumptions of the necessary mathematical simplifications.

Deductive models

Having developed an interactive computer system we could consider the possibilities of structural models. These may be deductive in modelling ideas to test their feasibility. When Galileo first observed projections on Saturn, he described them as ears. He might have deduced then, from a consideration of orbital bodies in space, that these could have been part of a continuous ring around the planet. Confirmation or otherwise could come later, when technology was able to provide the necessary resolution. However, he was in enough trouble with his facts without adding any guesswork. The much more precise data obtained by *Voyager*, and enhanced by computer processing, does not negate previous interpretation of the rings but postulates new models to account for the spokes detected within them.

Perhaps the most dramatic example of deductive modelling was the derivation of the double helix structure of DNA (deoxyribonucleic acid) by Crick and Watson from the X-ray data of Wilkins and Franklin (Watson, 1968). Rosalind Franklin was operating in the expert region of seeking even better images but Crick and Watson chose the fast train of modelling. Shape provides an indication

of function so biologists are interested in the shapes of viral and bacterial structures as well as molecular structures such as DNA. Better resolution is always needed but until that is possible we have to deduce from the available data and our ideas. The three-dimensional shape of the adenovirus was known to be an icosahedron and therefore could be modelled as a geometric structure. Attached to its outer surface are protein structures called hexons and to assess their shape an electron microscope with a magnification of around x 500 K was used. The electron micrograph of figure L.1 shows the two-dimensional projections of a

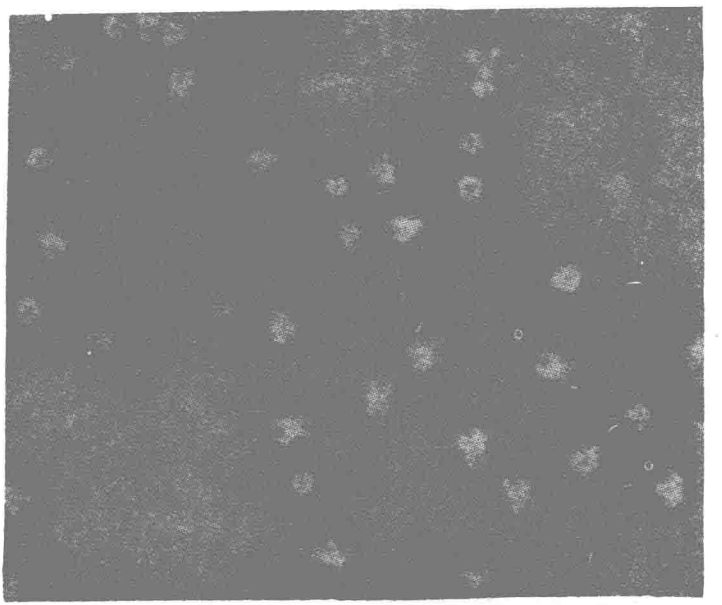

Figure L.1 Electron micrograph of adenovirus hexons. (Dr N Wrigley)

number of diverse orientations of hexons which have been separated from the virus. The problem was to determine their three-dimensional structure. Analytical methods of computer reconstruction were not feasible as the large number of images required from successive tilts of the same specimen would result in radiation damage to the specimen from the electron beam.

The electron microscope provided some information on dimensions, such as a maximum length of about 11 nm and width of around 7.5 nm and 8.5 nm at the two ends. Other sources indicated a three polypeptide structure. Electron micrographs (EMs) of the adenovirus itself suggested that the wider section of the hexon was at the bottom when attached to the virus in its vertical position. Hexons are positioned on to the icosahedral surfaces of the virus in groups of nine

(GONS). EMs of GONS for top and bottom in the stable vertical positions, showed that one end produced an image in the shape of a Y (see a in figure L.2) and the other end produced an image in the shape of an O (see b in figure L.2). The

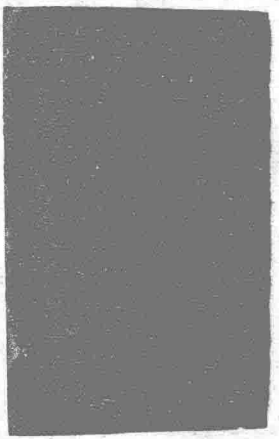

Figure L.2 Electron micrograph of groups of nine hexons (GONS) for upright positions; a: Y shape, b: O shape

O-shaped end was smaller than the Y-shaped end which suggested that the O shape should be at the narrower top. That was the extent of the data, from then on it was a question of deduction and assessing each idea.

I therefore developed a computer model which was built up in sections from spheres, since these, when filled with random dots, could indicate the different densities of the model as it was rotated (Perkins *et al.*, 1976*a*). The model was then successively modified to obtain a reasonable match of its projections with the diverse images seen in the EM (figure L.3(a),(b)). In order to obtain the X shapes observed I found it necessary to associate the O shape of one end with the larger base, which made the O-shaped end of the model larger than the Y shape, contrary to the previous evidence. The images produced by the model were approaching those of the EM but these could never match exactly, as, in order to observe the protein structures in the EM, the specimens had to be stained which could cause some distortion of the resultant images. It was necessary therefore to consider the effect of stain upon the model but the function of the stain was also unknown. Only two of the observed images could be related directly to a defined orientation, the normal and reversed vertical positions of the GONS (O and Y), so these two positions were chosen for simulating the effect of stain. At this stage, I was moving further away from a solution until I decided that the O shape had to be smaller than the Y, but, in order to achieve the X shapes, the O would also have to be associated with the larger base. Two incompatibles, but