Minutes of the Third Ordinary Meeting

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Joint Meeting with the Institute of Physics

'The Eye, Random Numbers, Terrifying Mathematics, Mobile Phones and Handel'

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Prof Colm O'Mahony, Prof Tony Fisher and Dr Harold Stockdale

Professor Fisher was introduced by Dr Harold Stockdale (Institute of Physics, Merseyside Branch).

Prof Fisher originally studied medicine but went on to study Electronics and then Clinical Engineering and Medical Physics. He holds an MD and PhD from the University of Liverpool and is a Fellow of IoP, IET and IPEM. His research interests are centred around biomedical signal processing, specialising in the electrodiagnostics of vision. He is a non-executive director for the Academy for Healthcare Science and a tireless champion of postgraduate training of Clinical Scientists in Medical Physics and Clinical Engineering and Healthcare Informatics. In 2017, he was awarded an MBE for his service to Medicine, Medical Physics and Clinical Engineering.

Prof Fisher's opening statement that "*Doctor: your PC is so much smarter than you! - even Postman Pat's got an iPad*" set the tone for a fascinating and thought-provoking lecture. The lecture discussed the concept of using information technology (especially, mathematics and statistics) in the clinical environment.

The almost countless numbers of articles in professional applied medical and biomedical journals testify to the levels of academic resources potentially available in the practice of clinical medicine, laboratory medicine and in biomedical R&D. Many of these articles develop and explore sophisticated analytical methodologies as diverse as differential diagnosis by expert systems of artificial intelligence, to the parameterisation and rule-based interpretation of technically-challenging electrophysiological signals.

Recent advances in computer science, applicable mathematics, information engineering and neural computing, in principle, herald an enormous change in the way rigorous objective analysis can be brought to bear on problems in medicine. However, the void between accounts of academic study and practical application is large, and, in the majority of instances, unbridgeable: the potential of the emerging mathematics to deliver to medical practice, in clinic, the diagnostics lab or research environment, is seldom realised. The linkage mechanism per se between academic methodology and applicable method is rarely developed. Prof Fisher's work in Liverpool sets out to address this. He described a novel means of bringing smart mathematics and state-of-the-art analytics to the clinical user who needs nothing more than access to the Internet via a simple web-page browser. This mechanism is called MatSOAP, where

sophisticated mathematical resources written in the **Mat**Lab (MathWorks) language are accessed remotely using the **SOAP** (Simple Object Access Protocol) mechanism. The driving rational for this approach to enable access by the clinician (assumed 'non-mathematical expert') to analytical resources for clinical data developed and maintained by computer scientists, informaticians and engineers: the watchword is *accessibility*. Prof Fisher would illustrate the utility of MatSOAP with a number of examples run in real-time over the Internet - the Audience was warned that they would be required to participate … …!

By way of introduction, a "simple" maths question was asked involving log and geometrical function evaluations of a long series of prime numbers and methods of solving it were described. The traditional method (paper & pencil) would have, of course, involved manual calculations taking literally lifetimes of effort. The use of a specific computer program written by an experienced mathematical programmer reduces that time to milliseconds. Access to this solution via MatSOAP was just a click away in an Internet browser, the User being happily oblivious to whether the program was big, small, trivial or complex.

As an introductory example of the use of artificial intelligence, Prof Fisher gave a quick overview of an expert system of artificial intelligence, based on an artificial neural network, used in the risk assessment of developing sight-threatening diabetic retinopathy (STDR). No expert knowledge of computers and mathematics is needed by the User, the PC itself is dumb (it's running a web browser) but with sophisticated mathematical resources available to the clinician. A doctor in general practice can explore with their diabetic patient in real-time the effects of life-style changes which modify disease progression; blood pressure, diet etc. But, more of this later….

Prof Fisher went on to describe in detail three studies using the techniques of data processing with smart mathematics delivered into clinical practice by MatSOAP. (The third study expanded on the STDR project.)

Firstly, *functional* mapping of retinal function with electrophysiology. Prof Fisher introduced these studies by describing how it is possible to unscramble individual waveforms (be they airborne sound waves or electrical signals) from a composite waveform. Sampling of a waveform can be regular at a constant rate and the playback similarly regular and constant which regenerates the original waveforms faithfully. However, if the sampling is irregular at a variable rate and the playback regular, this produces only unintelligible rubbish. Conversely, the original composite waveform can be sampled irregularly and played back also irregularly and this technique allows the original individual waveforms to be recovered. Prof Fisher ably demonstrated these effects with a rendering of Handel's Messiah and a speech from David Cameron extolling his love of the NHS.

The audience was enthused by this graphic demonstration of signal sampling and Prof Fisher stressed his "take home" message from this was that "*information in a sampled data-stream can be exclusively recovered by its own sampling sequence which acts as a key*". However, the audience did gasp somewhat at Prof Fisher's slide showing the Inverse Gabor Transform with its double integrals and their linearity, shifting and modulation properties (hence the "Terrifying mathematics" in the title.) In a somewhat light-hearted observation, Prof Fisher displayed a slide of several mobile phone users having simultaneous conversations over a single medium. He asked the audience, 'Well, how did you think yours worked?!'

So, is there a clinical application of this complicated sampling technique and the extraction of individual waveform signals? Prof Fisher described the example of the electroretinogram (ERG) which is the retinal response to a flash of light on the surface of the eye (i.e. a transient visually evoked potential). A flash of light falling on the retina at the back of the eye generates an electrical signal which travels through the optic nerve, through the mid-brain to the visual cortex where 'vision' is expressed. The electrical current generates a transient voltage field which is detectable at the front of the eye. The ERG contains information about both the photoreceptor function of the retina and the local neural networks. The detecting electrode is traditionally either a set of skin electrodes on the patient's face around the eye and forehead or a precious metal electrode in direct contact with the cornea. In passing, Prof Fisher described the innovative Liverpool ERG electrodes which consisted on a thin silver thread across the eye at the level of the lower eyelid. The Liverpool group manufactures these ERG recording threads with a quarter of a million having been produced to-date.

The ERG signal is a complex noisy signal: the signal-to-noise ratio being something like 1 in a billion ... pretty much the smallest of needles in the largest of haystacks! It is a composite arising from individual parts of the retina, each producing its own waveform. Can we extract the individual signals from individual parts of the retina by sampling the recorded ERG signal using methods described earlier by Prof Fisher? Could we effectively draw an electrical ERG map?

The Liverpool group has devised a technique which separates the individual signals arising from individual parts of the retina from the composite externally detected signal. Prof Fisher showed an example of a patient with normal retinal function showing 19 individual parts of the retina. Each part of the retina had been individually stimulated by its own unique sequence of flashes and subsequently the single composite signal recorded from the single electrode decoded into its 19 component parts ... much like David Cameron's voice had been earlier separated from its mixture with Handel's Messiah. The electrical images of a normal healthy eye and that of a patient's suffering from early-stage neo-vascular acute macular degeneration (AMD) were compared: the difference was remarkable, clearly demonstrating that in AMD it is the central region of the retina that is compromised resulting in central vision loss. This method is used routinely by the Medical Physics and Clinical Engineering Department in Royal Liverpool and Alder Hey Children's hospitals to investigate a wide range of diseases of vision.

Summing up the use of signal sampling in ERG studies, Prof Fisher stated that this multi-focal ERG is state-of-the-art and is used routinely in only three centres in the UK. In the context of R&D, the highest number of parts of the retina that were able to be separated was 1009 but this has reached the limit of signal measurability (a few 10's of nanovolts). But, what will the future hold? Where will multi-focal ERG be in 10 years' time? Who knows, but just look at the quality of magnetic resonance images 25 years' ago and compare them with those commercially available today: the progress has been astonishing.

Secondly, <u>non-invasive foetal ECG</u>. The traditional way of measuring the foetal ECG during the later stages of pregnancy and early labour is via electrodes applied directly to the scalp of the yet-to-be-born baby. The aim here is to measure non-invasively the foetal ECG across the maternal abdominal wall using simple skin electrodes. The signals detected are a mixture of foetal ECG, maternal ECG and noise. The technique uses three active electrodes on the maternal abdomen at specific locations. Each electrode will see all three signal components but at different amplitudes and possibly with different phases: each electrode sees a *mixture* of signals.

Prof Fisher took this opportunity to remind the audience that, as a general principle of physical measurement, and particularly in the biological environment, the recordings that we make are those of *observations* not of the actual *sources* themselves ... we never actually get to see the *sources* and we have to rely on *inference* to 'dig beneath the surface'. The *observations* are the *data*: the *sources* are the *information.*

The technique to disentangle the foetal ECG from these other sources used here is known as Blind Source Separation and is under-pinned by the mathematics of Independent Component Analysis (ICA). It was suggested that the audience might be more familiar with the related technique of Principal Component Analysis (PCA). In the latter, the system is described (characterised) by a set of vectors which are mutually orthogonal: however, in ICA, the separation of the vectors is more strictly specified requiring true independence. The mathematics involved could again be described as "Terrifying" and understandably not within the realm of expertise of the attending obstetrician or midwife whose background is likely to be, at least, *orthogonal (sic*!) to that of the computer scientist. Step forward MatSOAP!

Prof Fisher engaged the audience in a practical demonstration of ICA. Using a local GUI interface to a MatSOAP implementation. The audience was invited to compose sets of 3 waveforms by shouting out arbitrary numbers relating to the amplitudes, frequencies phases and mark-to-space ratios of sinusoids, square waves and white noise; these were to be the unseen *information sources*. These were then mixed linearly to form the *observation data*. With a mouse click, and by the apparent magic of ICA, the *mixtures* were decomposed to their *sources*. The audience generously applauded this apparent mathematical slight-of-hand. By way of illustration with real clinical data, Prof Fisher showed foetal and maternal traces (*observations*) contaminated by typical levels of random pink noise from a patient. The individual ECG's extracted by the ICA Blind Source Separation from three external electrodes on the maternal patient showed a remarkable degree of concordance with the real signal tracings, the maternal ECG and foetal ECG being, apparently, completely recovered. Prof Fisher noted that this method of decomposition of a signal mixture was unsupervised and required no *a priori* knowledge, whereas, conversely in the previous example of the multifocal ERG, the unique sampling sequence key of each component was explicitly required.

Thirdly, <u>risk assessment in diabetic retinopathy (DR) using an artificial intelligence system</u>. To give some background, Prof Fisher cited that 3.2 million people in the UK have Type I or Type II diabetes at a total cost to the UK of £27 billion (2010/11). Sight-threatening DR is usually detected by fundus (retinal) photography in a screening programme and that progression of sight loss can be halted by treatment. In the UK, all individuals with Type I or Type II diabetes are invited for annual screening but uptake is variable: across the general diabetic population, patient compliance is disappointingly poor. This screening interval of 12 months is fixed and unfortunately is seen as too frequent and too

troublesome by many patients who will probably get an 'all clear': i.e. the screening programme is excessively *sensitive*. This fixed-interval programme it not informed by the relative risk that the patient has of their disease progressing and consequently the need for treatment becoming more significant. However, we know quite a lot about the risk profile of Sight Threatening Diabetic Retinopathy (STDR). Earlier in his lecture, Prof Fisher introduced STDR risk stratification using an expert system to describe cross-sectional data. The photography costs £40 and the invitation to screening is irrespective of the risk of developing sight-threatening DR. This approach is highly sub-optimal and the objective of a new approach pioneered in Liverpool is to optimise the screening interval for any individual by assessing the risk of development of sight loss and discussing this with the patient concerned. What does this mean? A patient with very low risk would be required for screening, say, every 36 months whereas as a high-risk patient might benefit from examination every 6 months. In order that such a programme can be delivered, a longitudinal risk analysis system is required tailored to the individual patient. The headline objectives are optimised sensitivity of DR detection and best targeting of resources and patient compliance, the new approach, *Individualised Screening for Diabetic Retinopathy* (ISDR) is being funded by the NIHR (Harding, Broadbent, Fisher et al).

The initial stage was to establish a large database from local GP practices (about 50) and collate information of patient medical history and medical data, principally the *risk factors* (model covariates) established in the early cross-sectional study and from the screening service, retinopathy gradings derived from fundus photography. For the initial analytical modelling the data-set amounted to about 11,000 patients and 40,000 retinopathy grading fundus photographs and some 750,000 other items of medical data … about 3.5 million items of data in total. Not truly *Big Data* in the modern vernacular but nevertheless *substantial*. The initial cross-sectional expert system had been implemented with an artificial neural network and then later by a linear discriminatory network. The longitudinal *STDR Risk Engine* required a more sophisticated approach using a Markov state model. In Markov, the model assumes that the information flows along a network of transition states, the rate and direction between any 2 states being described by a *reaction coefficient*. It is solving for these coefficients which produces the risk model, the ultimate state being the risk of succumbing to sight threating retinopathy. The significance threshold of this risk, as far as the mathematical model is concerned, is arbitrary. However, in the clinical implementation, this was set at 5% in consultation with the Diabetes Patient Group i.e. patients would be called for screening when their risk was estimated to be ≥5% ... hence, the screening interval is set on an individualised basis.

The present work will compare the outcomes over 5 years of the patient group selected for individualised screening at intervals based on risk with patients screened conventionally at fixed 12-month intervals. Invitations to patients in the individualised group to attend screening clinics are generated automatically based on the Markov *STDR Risk Engine* implemented over MatSOAP. This programme will report its results in 18 months' time.

Prof Fisher demonstrated the *STDR Risk Engine* showing how risk estimates could be made by full (5) and sparse {1,2,3,4} sets of *risk factors* (covariates) and how the screening intervals resulting in the 5% acceptable threshold risk could be estimated.

In summing up his lecture, Prof Fisher said that "Being *smart per se* is one thing but it is making *smart* accessible to colleagues in clinical and laboratory medicine that gives value and purpose".

Prof Fisher acknowledged his colleagues: Dr Antonio Eleuteri, Prof Azzam Taktak & Steve Lake (MP & CE, RLUH) and Prof Simon Harding & Dr Deborah Broadbent (CERC & SPEU, RLUH).

At the end of Prof Fisher's lecture, Dr Stockdale invited questions and Prof Fisher responded to several questions for the audience. The question session lasted about 15 minutes showed the level of interest and enquiry generated by the lecture.

Following questions, Prof Colm O'Mahony (LMI President) thanked Prof Fisher for his excellent talk and was pleased to present him with the LMI commemorative medal to recognise his presentation. The audience showed its appreciation in the usual manner.

Dr Harold Stockdale