

Tessellations

News And Technical Updates From Tessella

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Adaptive Clinical Trials – working at the cutting-edge

Running a successful pharmaceutical company is getting harder. The number of new drug submissions to the FDA has halved in the last ten years and there is heightened public sensitivity to the possible risks from the side effects of new drugs. Further, the length of time that a new drug can command a premium price is dwindling, due both to increased development times and to the increasing speed with which competitors manage to get their 'me-too' drugs to market.

With pharmaceutical companies keen to optimize their drug development processes, clinical trials are under particular scrutiny.

Instituted by the US Congress in 1962 (after the Thalidomide debacle in the 1960s), a series of successful clinical trials are required to prove that a drug is safe and efficacious, before submitting it for registration. Trials are designed to establish:

- A safe range of doses to use
- A dose that shows sufficient efficacy
- In a confirmatory trial: that a particular dose will be safe and effective in its use once licensed

Clinical trials are not only hugely expensive to run, but the elapsed time that they take shortens the remaining patent life for the compound, after which generic competitors can be made and the profit margins enjoyed by the original discoverer drop markedly. Every day that passes between the granting of a patent and achieving regulatory approval can represent millions of dollars of lost revenue.

Society too, via the regulatory bodies, has to balance minimizing the number of subjects exposed to clinical trials and speeding up the launch of new therapies, against the desire to ensure the safety and efficacy of new drugs.

Getting the most from a trial

As a result there is a drive to squeeze as much *information* from each trial as possible and to maximize the chance of success by *adapting* a trial as it progresses. Possible trial adaptations include:

- Favouring certain treatments or doses based on the observed levels of response and safety
- Stopping early if a drug is clearly working or not working
- Adjusting the size of a trial in the light of the variability in the responses
- Modifying the type of person recruited to participate in a trial (to exclude or to focus on particular sub-groups)

However, adapting a clinical trial would be tantamount to *cheating* if we didn't account for the adaptation when analyzing the trial data.

This has stimulated developments in both conventional and Bayesian statistics, providing rigorous frameworks for designing adaptive clinical trials (the results of which can then be interpreted with confidence).

Cutting-edge statistics

Tessella has been working with a number of international pharmaceutical companies, and leading biostatisticians, to implement new statistical methods and to incorporate them into clinical trial *simulators*. This allows clinical trial designers to verify the use of these methods on trials, estimate the required trial size, and tune the algorithm.

But the challenges of adaptive clinical trials don't end there:

- The regulators require the implementation of the new statistical method to be validated
- The patients' responses need to be gathered and reported back much more quickly than traditionally required; for some adaptive schemes this needs to be almost instantaneous
- The trial logistics also need to be adaptive, particularly the supply of the trial drug to the investigative centres

The use of such new clinical trial methods will lead to a better understanding of a drug's effect, and therefore fewer failures in phase III trials. They will result in a better use of patients who are enrolled in clinical trials, with fewer subjects being given doses that aren't effective or may be unsafe. The end result should be a reverse in the decline in the number of new drugs being licensed.

Tessella's experience

Tessella has implemented very advanced statistical models; two examples in the public domain are 'bCRM' and 'Toxfinder'.

Tessella has also helped to run adaptive clinical trials, and has built a system that integrates randomization, new statistical methods, and data collection. To communicate with all the participants in the trial, the system provides automated phone response, SMS messaging, automated fax reception, and a web interface, allowing the most suitable and convenient channel to be selected for each communication. The system provides central randomization, rapid collection of response data, and drug supply management, and thus is naturally able to provide the study manager with a real-time view of the state of their trial. This in turn results in a more pro-active style of trial management that yields faster recruitment of subjects, quicker data collection, and better data quality.

To find out more, please complete the enclosed order form or email info@tessella.com



Stop press: Tessella has been selected for inclusion in the UK Government's Catalyst Framework, under the *Specialist Solutions* category (sub-categories 'Applications Development' and 'Electronic Document & Records Management Solutions'). The Catalyst framework is scheduled to commence in April 2006 and will run in parallel with existing frameworks such as S-CAT and G-CAT, which it will eventually supersede. Please see the News page for further details.

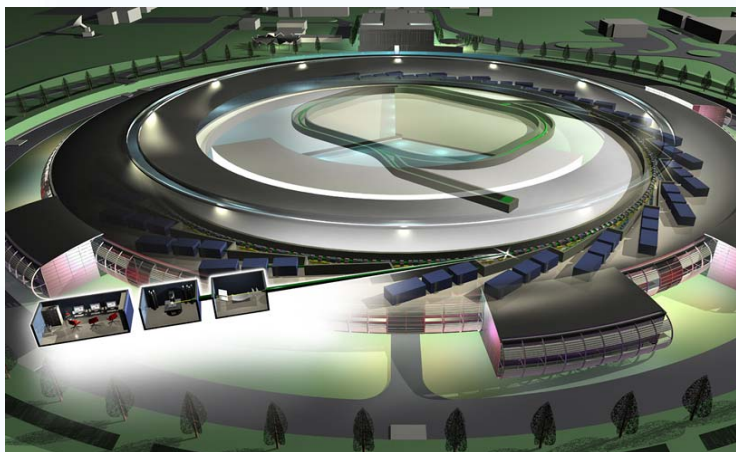

Scientific software solutions

Diamond – the sparkling gem of research science

Synchrotron light is an invaluable tool in key research areas including physics, chemistry, materials science and the biosciences. Many of the everyday commodities that we take for granted, from chocolate to cosmetics and from computers to mobile phones, were developed or improved with the help of synchrotron light. Scientific communities working in life sciences, archaeology, and geological and environmental studies, are increasingly exploiting synchrotron light to achieve their research goals.

A synchrotron light source is a circular-shaped machine that uses arrays of magnets to bend and focus high-energy electrons which generate beams of synchrotron light (X-ray, infra-red and ultra-violet beams of light with exceptional brightness). These highly focused beams of light enable scientists and engineers to probe deep into the basic structure of matter and materials, answering fundamental questions about everything from the building blocks of life to the origin of the planet.

Synchrotrons, as particle accelerators, originated in the 1940s for high-energy physics, and were first exploited as light sources in the 1960s. At present there are some 50 major light source facilities worldwide, with a number of others under construction or planned. The UK's first new synchrotron light source for 25 years is under construction on the Harwell Chilton science campus, in Oxfordshire.



Artist's impression of Diamond (photo © Diamond Light Source Ltd)

Diamond Light Source Ltd will welcome its first scientific users in January 2007, and will be one of the world's brightest synchrotron light sources operating in the scientifically-valuable medium-energy X-ray range. State-of-the-art instrumentation will complement the light source, ensuring that international researchers have access to cutting-edge analytical techniques and services for the next 25 years.

Synchrotron light is advancing research and development in fields as diverse as:

- Biosciences (protein crystallography and cell biology)
- Medical research (microbiology, disease mechanisms, high resolution imaging and cancer radiation therapy)
- Environmental sciences (toxicology, atmospheric research, clean combustion and cleaner industrial production technologies)
- Agriculture (plant genomics, soil studies, animal and plant imaging)
- Minerals exploration (rapid analysis of drill core samples, comprehensive characterization of ores for ease of mineral processing)
- Advanced materials (nanostructured materials, intelligent polymers, ceramics, light metals and alloys, electronic and magnetic materials)

- Engineering (imaging of industrial processes in real time, high resolution imaging of cracks and defects in structures, the operation of catalysts in large chemical engineering processes)
- Forensics (identification of suspects from extremely small and dilute samples)

Extensive consultation between Diamond and the scientific user community resulted in a portfolio of *experimental stations*. The first set to be commissioned will include three concentrating on X-ray crystallography and one on nanoscience.

X-ray crystallography is used to investigate atomic structures. In the life sciences arena, it can provide detailed information about protein folding, which is critical to the understanding of conditions such as Alzheimer's, Parkinson's disease and BSE. In a topical area of medical research, an Australian team used synchrotron light to obtain a high-resolution model of the structure of an important influenza virus enzyme. With this understanding they developed the anti-influenza drug Relenza™, which has recently been proven effective against human strains of 'bird flu'.

The field of *nanotechnology* is developing rapidly with the aim of understanding, in detail, the chemical, electronic and magnetic state of individual nanostructures. Achieving this will enable the construction of nanoscale devices and a bottom-up approach to designing new materials with engineered properties, which will overcome many existing limits on the performance of industrial materials. The ability to manufacture and probe systems at the nanometre scale is important for areas such as quantum computing and data storage, and electronics.

Diamond will steadily increase the number of experimental stations, and eventually as many as 40 will be available for state-of-the-art research.

The Diamond Controls Team is currently developing and integrating control system software that will be used to drive the experimental stations. It is essential that such critical control and safety systems are designed effectively to help academic researchers and commercial R&D scientists – from the life sciences and materials science worlds – maximize the usefulness of their Diamond synchrotron experiments. Tessella is proud to be supporting the Controls Team in their development of the crystallography and nanoscience beamlines.

Diamond Light Source Ltd is funded by the UK Government (via the CCLRC) and the Wellcome Trust. For further information please visit www.diamond.ac.uk

Building on Tessella's 25-year track record of supporting the UKAEA JET nuclear fusion facility, and with extensive academic and client-based scientific research experience within the branch, staff at the Abingdon headquarters are looking forward to having the UK's new eminent scientific facility just down the road.

To discuss how Tessella might support your scientific research please email info@tessella.com



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For further information and free Technical Supplements please complete the enclosed form or email info@tessella.com

Digital Preservation – ‘Mind the Gap’

Despite a number of recent high profile cases helping to raise awareness of the risks of digital data loss, a key research study has identified that major gaps still exist in the long-term management of digital assets.

With the release of the report ‘Mind the Gap: assessing digital preservation needs in the UK’, the Digital Preservation Coalition (DPC) aims to help government, public institutions and private companies turn high awareness of the problem into concerted action towards a solution.

The study – undertaken by Tessella for the DPC – looked at digital preservation practice in government bodies, archives, museums, libraries, education, scientific research organizations, pharmaceutical, environmental, nuclear, engineering, publishing and financial institutions. Whilst the report focuses on the state of play within the UK, it is clear that digital preservation is an *international* issue, best solved by governments, public and private sector organizations, and regulatory and funding bodies, pooling their experiences, resources and ideas.

Key findings

The survey found that:

- There was a high level of awareness of the risks and potential economic penalties associated with digital preservation
- Loss of digital data is commonplace – it is seen as an inevitable hazard by some – with more than 70% of respondents saying that data has been lost in their organization
- Awareness of the potential economic and cultural risks is high, with 87% recognizing that corporate memory or key cultural material could be lost, and 60% admitting that their organization could lose out financially
- In 52% of surveyed organizations there was management commitment to digital preservation, but despite this only 18% had a strategy in place to deal with the risk of loss or degradation to their digital resources

Key recommendations

The report identifies 18 core digital preservation needs, with associated recommendations being addressed to organizations, governments, and funding bodies.

The report recommends that organizations should:

- Create a long-term proactive information/knowledge management plan; commencing with an information audit; then once the problem has been sized, the task of creating a solution should be properly resourced (with clear responsibilities assigned)
- Perform regular information audits to measure and re-measure digital preservation needs, and ensure that these are being met
- Consider the long-term value of digital material when putting together plans and budgets
- Encourage an international ‘market’ for digital preservation tools
- Consider the long-term preservation characteristics of the file formats used; working with other organizations and with software vendors to encourage the development of open standards

The report also recommends that:

- Funding bodies should support research into the long-term value of digital information and models of how that value may change with time
- Government and funding bodies should promote the creation of more digital archives across relevant sectors and organizations



- In formulating policies, governments should take into account their impact on the digital information lifecycle
- Governments should work with the digital preservation community and the legal profession to establish clearer guidelines for ensuring that digital information is legally admissible
- Regulatory bodies need to work within their sectors, and the digital preservation community, to map out a framework to allow organizations to store information in an exploitable form while retaining the ability to satisfy regulatory concerns

Working towards a solution

Digital preservation is very much a new discipline which is still being developed, and for which there are few people with the necessary skills. It is a complex activity to undertake and is often perceived as risky. However, there is help at hand.

The DPC is a cross-sectoral membership organization formed to foster joint action to address the urgent challenges of securing the preservation of digital resources in the UK and to work with others internationally to secure our global digital memory and knowledge base. To find out about joining the DPC please email info@dpconline.org

In recent years a number of mainly academic and government organizations have been at the cutting-edge of facing up to the digital preservation challenge, and Tessella has played a key role in a number of the most practical of these initiatives.

The ‘Mind the Gap’ report is a wake-up call to each one of us to ensure proper and continuing attention to our digital records.

To receive a free copy of ‘Mind the Gap’ please email info@tessella.com



Martin
Tessella
Project Manager



Maggie Jones
DPC
Executive Secretary

Market Focus – Defence

There is a constant drive in the defence industry for better, faster and cheaper systems. These pressures mean that smart systems must be developed in smarter ways. This is where Tessella subsidiary, Analyticon, can help. Our consultants have the skills to develop the technical innovations demanded by today's defence industry within the constraints of the real world.



We draw on a range of skills including:

- Design and analysis of complex systems
- Systems engineering
- Control theory
- Mathematical modelling and simulation
- Software development
- Mathematical and statistical analysis
- Estimation theory
- Algorithm design and assessment

Our analytical expertise, and knowledge of working with defence projects, has enabled us to provide robust solutions in a range of defence application areas including:

- Radar tracking algorithms
- Tracking system design and analysis
- Missile guidance, navigation and control
- Data fusion
- System analysis, simulation and performance assessment
- Estimator and filter design
- Ordnance safety

Analyticon's range of analysis, simulation and modelling skills is ideally suited to today's competitive defence market.

The Stockholm Challenge Awards

iShakti – developed by Unilever Corporate Research, Hindustan Lever (India), and Tessella – has been shortlisted in the Economic Development category of the prestigious *Stockholm Challenge Awards*. iShakti provides a direct-to-consumer channel specifically tailored for rural India.

The awards bring together research communities, development organizations and major corporate programmes, rewarding the initiatives that best accelerate the use of IT for the social and economic benefit of citizens and communities, whilst pro-actively helping local entrepreneurs to close the digital divide. The winners will be announced in Stockholm on May 11th.

Advances in Astrophysics

Since the Earth's atmosphere blocks and blurs the light coming from space, placing telescopes outside the atmosphere provides opportunities to make advances in astrophysics. For this reason, the European Space Agency commissioned the construction of two scientific satellites (scheduled to launch in spring 2008):

- Herschel – will provide insights into the origin of galaxies and formation of stars
- Planck – will survey the cosmic microwave background radiation, to enhance our understanding of the evolution of the universe

Analyticon has worked on the Herschel/Planck project since its early stages, and is part of the consortium (along with Dutch Space and SENER) designing the attitude control and measurement subsystem (ACMS). Specifically, we are responsible for:

- Designing the controller which will be used during Herschel's scientific observations
- Creating 'pointing error budgets', a statistical analysis of the pointing performance of both satellites
- Modelling of the control system hardware, such as gyroscopes and thrusters

NB: The ACMS is part of the service module for which Alcatel Alenia Space Italy is responsible. The prime contractor is Alcatel Alenia Space France.

Catalist – in more detail

The UK government's Catalist Framework has been established to provide the public sector with the best possible range of goods and services, aligned to their particular requirements, and to offer complete value for money. To be selected for the *Specialist Solutions* category Tessella was rigorously checked for suitability, via a process that was fully compliant with EU legislation.

The Specialist Solutions category offers customers an end-to-end solution, and can include solutions identification, design, development, implementation, integration, data take-on, data migration, systems security, user training, maintenance and support, managed services and review services. The category also includes bespoke (custom-built) applications design and development, and the ongoing maintenance and support of applications during their life cycles. This may include prototyping, the tailoring of existing products, data migration and user training.

Tessella is delighted that public sector organizations will now have easy access to our services through Catalist.

Tessella – Providing innovative solutions to scientific, technical and engineering problems

Tessella uses its unique blend of scientific, engineering and IT skills to solve the most complex of technical and business problems in a highly cost-effective way.

We have a proven 25-year history of excellence, adding value to demanding public sector and commercial R&D based customers. Tessella now comprises Tessella Support Services plc, Tessella Inc and Analyticon Ltd.

Tessella's services cover software design and development, IT consultancy, infrastructure support and project management. Our enviable reputation for providing high-quality, low-risk, value for money services is backed up by many successful, high-profile projects, plus a high level of repeat business.

Formed in 1994, Analyticon specializes in the design of solutions requiring mathematical modelling, analysis and creative thinking. For each problem we develop a fundamental understanding within the 'big picture' context – so our solutions fit. We focus on the details however intricate – so our solutions work.

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Tessellations is published by Tessella Support Services plc. Our aim is to provide you with interesting information on topical technology issues and to outline key projects which we hope you will find of use. We depend on the feedback from our readers to help us develop *Tessellations* and to maximize its usefulness. Your input is always appreciated; please send to The Editor (Alison Smith) at info@tessella.com