

Tessellations

News And Technical Updates From Tessella

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Investigating Hepatotoxicity – working to make drugs safer

Concerns over drug safety issues have resulted in several drugs being withdrawn from the market over the past few years. These failures have not only cost the drug companies billions of dollars but have also cost some patients their lives. New drugs undergo extensive, highly expensive testing for efficacy and safety, so how is it that failures still occur?

Liver damage

Drug-induced hepatic injury (hepatotoxicity) accounts for more than 50% of cases of acute liver failure in the United States and 'is the most frequent reason cited for the withdrawal from the market of an approved drug' according to the New England Journal of Medicine. Unfortunately, by the time such liver damage is discovered it may already have led to very serious health complications, and in some instances, fatalities.

Clinicians measure a range of analytes in the blood to test if a patient's liver is being adversely affected.

However, the interpretation of these measurements is often overly simplistic. For example, in clinical trial data, differences in the mean analyte values of two different patients may be more affected by differences in characteristics such as sex, age, weight, etc than by any effect of the drug. Clinical trial data may also suffer from irregular sampling, missing data and measurement variability between laboratories.

A sea of noise

In many of the phase 3 clinical trials, which are designed to test the effects of the drug on patients in hundreds or even a few thousand subjects, the incidence of hepatotoxicity may be 1 in 5,000, 1 in 10,000 or even lower.

Any 'signal' about the possible problems may, therefore, be lost in a sea of 'noise', and will not be noticed until the drug is approved and goes to market.

At this stage the number of patients treated may be measured in millions worldwide, and the low level hepatotoxicity becomes apparent as patients present serious complications and adverse reactions.

Advanced statistics

It is simply not realistic to run trials of hundreds of thousands of patients per trial in order to detect early indications of problems.

However, by using more sophisticated statistical techniques on clinical trial data, it may be possible to extract information which can help make 'go/no go' decisions earlier in a trial.

For example, it may be possible to identify sub-populations within a trial group who are particularly sensitive to toxic effects.

Principle Component Analysis (PCA) is one method that has proved useful in analyzing clinical trial data. PCA is a technique widely used in the analysis of multivariate, time-series data in applications ranging from astronomy to managing oil refineries. It is noise-tolerant and is suitable for use with the challenging nature of clinical trial data.

Detecting Hepatotoxicity

PCA allows comparisons of datasets based on many variables at the same time.

It could, therefore, be possible to detect hepatotoxicity by correlating numerous measures, rather than by looking at a single blood analyte. The technique can be used to detect outliers in the data (which may show patients having an abnormal reaction to the drug), and to cluster data (eg to identify sub-populations with a high risk of severe side effects).

Tessella has implemented a number of systems for the collection and analysis of clinical trial data, including the use of PCA. One of the challenges has been to develop an effective means of presenting the results of multivariate data analysis to clinicians. Our experience of developing 3D visualization

techniques for scientific data provided some useful advances in this area.

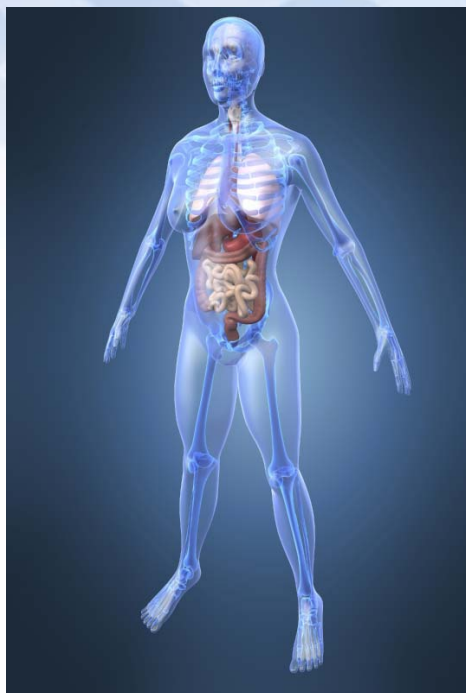
Work continues on refining and extending these techniques, which involves managing data in high dimensional space and presenting it in a fashion which is useful for researchers, clinicians and statisticians, as well as the regulatory bodies. Ultimately, the aim is to develop more effective clinical trials which will reduce costs and maximize patient safety.

Tessella presents

Tom Parke of Tessella is presenting at two clinical trials conferences in London in February 2007.

Adaptive Designs in Clinical Drug Development (5-6 February) brings together industry leaders to discuss current innovations in adaptive trial design. Tom is presenting on 'Implementation – getting it right before Phase 3', covering dose adaptive Phase 1 and Phase 2 clinical trials. Co-sponsored by Tessella, the Clinical Trials Congress (21-23 February) aims to enable attendees to tackle the changes in the dynamic clinical trials market, and turn them into a competitive advantage. Tom is presenting a talk entitled 'Improving the rate of success at Phase 3 using adaptive clinical trials', discussing how adaptive trial designs can be used to optimize the whole drug development process.

To find out more about Tessella's expertise and experience in clinical trials please email info@tessella.com



Stop press: The National Archives of Malaysia has selected Tessella's Safety Deposit Box (SDB) for their Digital Archive Management System. Working with local partners VersaPAC, Tessella will be rolling out the system during 2007. The National Archives of Malaysia is the third organization to select SDB, since it was originally developed with The National Archives of the United Kingdom, and will be using its new world-leading long-term preservation technology.


Scientific software solutions

Small steps, big changes



Obesity on the increase

Obesity levels in most first world countries are soaring. The issue is increasingly well publicized, and there is public pressure on both governments and the food industry to do something about it. In the US a third of all children are now overweight or obese, and the current generation of children is the first that may display a drop in average life expectancy. It is little different in the UK, where it is estimated that over 30,000 people now die every year from obesity related causes. The trend continues across most of Europe.

Without concerted action, the medical implications of obesity – including heart disease, diabetes and certain cancers – are set to become increasingly common and put a strain on medical resources. However, whilst obesity is a growing concern, the good news is that it is also a highly treatable problem. Obesity is a lifestyle disease, which can be tackled by an improved diet and a reasonable amount of exercise. Even small increases in regular activity levels can lead to major improvements in health. For instance, in the UK the Government's recommended guideline is to achieve thirty minutes of light to moderate exercise, five times a week.

Tackling diet and activity

As a large multi-national company with leading food, home care and personal care brands, Unilever has the ability and the reach to help improve consumers' lives. The company is taking a two-pronged approach to the obesity problem, tackling both nutritional and activity related elements of people's lifestyles.

Unilever Corporate Research provides new science for the company's new business opportunities. With a programme that extends across the academic scientific world, Corporate Research focuses on areas of bioscience, and physical and engineering sciences, and has teams working in the UK, India and China. One of the fundamental aspects of Corporate Research's work is an attempt to develop methods to help change consumer behaviour towards a healthier lifestyle. The Maths and Psychological Sciences group (based within Corporate Research) have been investigating how to interact with consumers through computer-based channels. The natural synergy between these two areas of research has led to a new cutting-edge development named *get.active!*

Developing *get.active!*

With its roots in behaviour change theory, physical activity science and healthy ageing studies, *get.active!* is designed to help ordinary people increase their activity levels, both through exercise sessions and through normal day-to-day activity.

The initial ideas for *get.active!* were pulled together over three years ago, by scientists in Unilever's Port Sunlight (Cheshire) and Colworth (Bedfordshire) research laboratories.

The project draws on a wide range of specialisms, including Psychology, Exercise Physiology, Machine Intelligence, Computational Linguistic, Statistical Analysis, and also draws on Software Engineering expertise provided by Tessella. The process of converting the behaviour change ideas into working software code began in Tessella's Warrington office, with a user interface prototype and some functional capabilities. A full iterative development cycle was then undertaken at Unilever's Colworth laboratory, calling on developers from Tessella's Cambridge and Stevenage offices.

What the user sees

A fundamental component of the *get.active!* system is a website designed to get people to start and to continue with routine exercise. Each user can plan and monitor a personal activity diary, with the system able to send them email or text reminders of planned activity sessions. The system allows users to address the barriers preventing their exercising, to look at the benefits of exercising, and to address motivation and goal setting.

Trialing the system

To test the prototype system, a ten-week trial was run. Volunteers from Unilever Port Sunlight were formed into a test group (with full access to the system, including exercise diary, message boards and SMS reminders) and a control group (with access to only a cut-down version of the system). The results from this first study showed a significant increase in the self-reported activity levels of the main test group when compared to the control group. The results were later published in 'Psychology and Health' (Hurling, Fairley, Dias, 2006). A number of lessons were learned from this initial trial, including the need for a precise measure of physical activity levels. Therefore, in 2005, the Unilever/Tessella team embarked upon a second version of *get.active!* with enhanced web-based content, more facilities, and most importantly a measure of physical activity (from an accelerometer) sent back to the system via users' mobile phones. A second trial, using members of the general public, has recently been successfully completed, with analysis of the results currently underway.

The future

Given that Corporate Research's mission is to provide new science for the company's new business opportunities, the team normally delivers its innovations directly to the parts of the business managing Unilever product categories (from 'hair care' to 'beverages'). However, in the case of *get.active!* the radical science involved demands a new business model; hence, following the team winning investment from Unilever's internal venture capital group, the whole *get.active!* project has moved up a gear. The project is now in transition out of Unilever Corporate Research and into a new business being set up to exploit the technology: truly a landmark event.



Chris Tomkins, Director of Business Development
Unilever Corporate Research



Bruce
Software Engineer
Tessella

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

Tracking systems – that work everywhere

It's the ultimate high-tech accessory – and the culmination of 30 years of development in satellite positioning receivers – but your dog probably won't notice. The falling costs of hardware, and the sheer number of potential customers, make satellite-tracking systems for pet dogs an attractive market. Over a dozen companies now offer products of varying cost and sophistication. Integrated into a normal dog collar, the systems can provide owners with updates via a radio link or even by text message.

Satellite tracking technology has become mainstream, and companies selling both to consumers and to other businesses are developing creative applications to exploit what's on offer. Yet however compelling an idea may be, such systems will only work if the tracking technology is reliable, and this is where difficulties can arise.

The key problem is that satellite navigation systems do not provide reliable information when they are used inside buildings or in dense urban areas: the radio signals are low power and high frequency, and this means they are easily blocked. If you are trying to recover a stray dog roaming the countryside this may not matter, but for many innovative tracking applications this can be such a severe limitation that the whole concept becomes worthless. In particular, many creative ideas for tracking technology are focused on locating people, and people spend most of their time inside buildings.

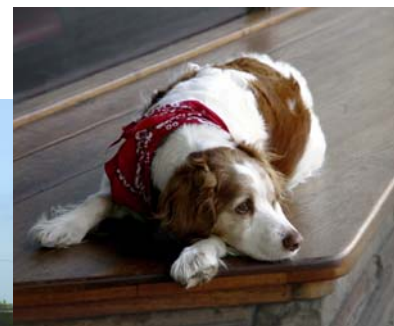
Solving the indoor tracking problem

The obvious solution would be to use a stronger radio signal, and several positioning systems adopt exactly this approach. Innovative methods exist to exploit the ready-made network of transmitters providing mobile phone networks; unlike satellite navigation transmissions, mobile phone signals usually penetrate buildings quite well. Coarse positioning can be obtained purely on the basis of the 'cell' that the user is in, and more refined positioning can be obtained by measuring the signal strength of all detectable transmitters, or by timing the path delay to transmitters. At present, the timing method is most successful, and this is able to deliver positioning with an accuracy of around 100 metres.

Another option, which exploits existing infrastructure, is to use the proximity of Wi-Fi hotspots. In urban areas, where hotspots are very numerous, this can provide accuracy of 50 metres or better.

Radio signals are not the only option for tracking positions in challenging environments. A second technology, which is developing fast, is inertial navigation. Such systems use a combination of motion sensors to keep track of an object's position (given a known starting point) by measuring all the accelerations that the system is subjected to. Traditionally, the technology has been used in defence systems such as aircraft and missiles, but in the last few years sensors have become small and cheap enough to be integrated into consumer devices. At present, low-cost inertial navigation systems are at a less developed stage than radio navigation solutions, but such systems have the potential to deliver much more accurate positioning.

Demonstration systems built using cheap sensors can achieve better than one-metre accuracy inside buildings for long time periods. Understanding and using this technology presents some unique challenges, particularly in maintaining good accuracy, but this is an area where Tessella has extensive experience, through work in both the aerospace sector and the field of low-cost human tracking for biomechanics applications.



Cutting-edge applications

The push for improved performance comes from a number of different application areas. An important driver for improvements in indoor positioning technology has been the need to rapidly locate emergency service workers in distress. For a fire fighter in a smoke-filled building, this means one-metre accuracy in three dimensions. Such challenging requirements can be met either with inertial navigation systems or using a small-area radio positioning network set up when the emergency services arrive at the scene, and working systems are currently undergoing testing and evaluation.

Many mass-market location-based services also exist which require indoor positioning, often delivered via mobile phones. At present, radio-positioning methods dominate in this area but inertial navigation has the potential for more accurate tracking. Indeed, recent work by Tessella has included assessing how inertial navigation might be used for these types of mass-market application.

Another fast developing area is the tracking of offenders, to enforce compliance with exclusion zones and to deter re-offending. Here a combination of tracking systems is used to ensure reliability.

Meeting the challenge

Common, outdoor-based applications like fleet management or pet tracking are well catered for by existing turnkey solutions, but there are many situations where an innovative approach is needed and something custom-built is required. The problem may demand indoor tracking, or data processing to couple the tracking information with another system.

In these projects, success depends on the right combination of technology and experience, and Tessella's expertise in both positioning technology and complex distributed IT systems provides a unique capability to reach a solution. To find out more please email info@tessella.com



Ian
Consultant
Tessella

Market Focus – Gas Industry

All over the world, natural gas is increasing in importance within the energy market. Many in the industry would position it as the core energy resource for the next 20-30 years, as governments and markets seek new ways to balance the public interest (in energy availability, security and environmental protection) with the needs of business.

Three European gas companies: N.V. Nederlandse Gasunie (the Netherlands), Gaz de France (France), and SNAM Rete Gas S.p.A. (Italy), have been working together with the aims of developing a common approach for assessing the safety of natural gas compressor stations and of implementing a prototype software system (which they engaged Tessella to develop).

June 2006 saw many major players from the gas industry gathering at the 23rd World Gas Conference in Amsterdam. At the conference, representatives of the three companies presented a paper entitled 'A common approach for assessing the safety of natural gas compressor stations', making mention of Tessella's contribution.

The group is now planning to work on future enhancements of the methodology and of the related software.

Digital Archiving at NARA

In September 2005, following a year-long preliminary design phase, the US National Archives and Records Administration (NARA) selected the Lockheed Martin led team, which includes Tessella Inc, to develop its Electronic Records Archives system (ERA).

ERA will be a comprehensive, systematic, and dynamic means for preserving virtually any kind of electronic record, free from dependence on any specific hardware or software. It will store, maintain and make available all federal electronic records with the aim of preserving the recorded history and heritage of the United States.

The first increment of ERA is scheduled for deployment in September 2007.

It will lay down the infrastructure for future increments that will provide the capability for a number of US government agencies to create retention schedules, request transfers, and submit electronic transfers to NARA.

ERA's technology promises to be useful to many kinds of archives, libraries, agencies, and businesses, regardless of size.

FATS membership scheme

Analyticon is pleased to announce its membership of the MoD Framework Agreement for Technical Support (FATS), covering Technical Studies, Project Support and Engineering Support.



The FATS scheme helps customers within the MoD to obtain value for money by providing a route that enables them to buy the technical services they need quickly, efficiently and at pre-agreed prices.

Via the FATS scheme, the MoD gains easy access to companies who can provide technical support, but with contracting made faster and more efficient through pre-agreed terms and conditions and standard tasking forms. MoD purchasers can identify individual FATS members' expertise by consulting a Market Knowledge Matrix.

For more information please email info@analyticon.co.uk

Nuclear Information Management

In November 2006, Tessella hosted a workshop to discuss the issues surrounding information management in the nuclear sector, featuring presentations by the NDA, Nirex, BNG, Tessella, and key industry bodies.

The nuclear sector is unique in that no other industry has the same complex combination of knowledge management, records management and information preservation issues. No other sector needs to keep records for countless millennia or maintain the knowledge of how to use those records over such long timeframes.

With the recent changes in the nuclear landscape within the UK, it is clear that there needs to be a wider understanding of the issues of information management over an effectively unending time frame.

Not only does the right archive data need to be chosen, an appreciation of how that data moves between various stakeholders, over many generations, needs to be taken into consideration. At no point will the data be stored away and forgotten, as is the public perception of an archive.

To find out more please visit: www.tessella.com/digitalpreservation

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 26-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.

The group's services include software design & development, mathematical modelling & simulation, algorithm development, infrastructure support, project management and consultancy.

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 is now the space and defence division of Tessella, and provides the full range of services to its clients.

www.tessella.com
www.analyticon.co.uk

info@tessella.com
info@analyticon.co.uk

Abingdon, UK (Head Office)

Tel: +44 (0)1235 555511

Burton upon Trent, UK

Tel: +44 (0)1283 553300

Cambridge, UK

Tel: +44 (0)1223 897770

Stevenage, UK

Tel: +44 (0)1438 731317 (Tessella)
Tel: +44 (0)1438 749886 (Analyticon)

Warrington, UK

Tel: +44 (0)1925 286800

Winchester, UK

Tel: +44 (0)1962 850055

Den Haag, the Netherlands

Tel: +31 70 354 2296

Boston, USA

Tel: +1 617 454 1220

Washington DC, USA

Tel: +1 240 235 6052

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