Institution: University of Aberdeen

Unit of Assessment: 10 (Mathematical Sciences)

Title of case study: Foetal-maternal heart rate coordination

1. Summary of the impact

This Impact Case Study illustrates the impact of our research on clinicians and medical researchers. Research conducted by the Institute of Pure and Applied Mathematics (IPAM) at the University of Aberdeen has developed software enabling clinical trials to be carried out in Germany aimed at creating new diagnostic tools for unborn children in order to identify foetal developmental issues. The research, focusing on time series analysis and dynamical systems, derived clinical benefits in that the Groenemeyer Institute, a privately-run research and treatment organisation, used it in the development of pioneering non-invasive methods for the diagnosis of foetal pathological conditions. The research also achieved considerable reach among the non-specialist public through media coverage in the UK and Germany.

2. Underpinning research

It was shown in [1] that respiratory arrhythmia induced by paced breathing results in synchronisation between maternal and foetal heart beats. Absence of synchronisation may indicate problems in the foetal development. This prompted researchers in the Groenemeyer Institute (Germany) to develop non-invasive methods to diagnose abnormal foetus development.

A healthy foetus interacts physiologically with his mother. For example, the heartbeat frequencies of mother and a healthy foetus are expected to synchronise. It is a remarkable fact that even if the frequencies of the heartbeats are different, a minute interaction will lead to synchronisation. The problem is, however, that even in the event of complete lack of interaction, the heartbeats might falsely appear to be synchronised because of their intrinsic regularity. This can be illustrated by two wristwatches which may appear to be perfectly synchronised because they are both designed to exhibit the same frequency, but they are, in effect, two independent systems. Another issue is the fact that synchronisation will not occur instantaneously but with a time delay, as is the problem that synchronisation can be lost for certain periods of time and then re-established.

The challenge becomes to mathematically detect minuscule changes in the synchronisation pattern due to the interaction of the heartbeats. To statistically corroborate the higher level of synchronisation, one needs to establish a “base level” of synchronisation, i.e. how synchronised heartbeats may appear to be, due to their regular nature, in the absence of any interaction at all. This would be easy if one could “switch off” the interaction between mother and foetus - an active experiment - and then quantify and compare the observed level of synchrony. This is, of course, impossible to do.

Looking at the wider context, this is just one example of a problem prevalent in so-called “passive experiments”. In an “active” experiment in which the strength of interaction between two subsystems is measured, the coupling strength between them can be systematically changed, thereby allowing one to measure change in synchronisation, and thus establish a reference (i.e. low versus high degree of synchronisation). In contrast, in a “passive experiment”, it is not possible to change the coupling strength of the subsystems in a controlled manner. This is the case in the mother and foetus example, since the coupling strength between their heart beats cannot be tuned at wish; it is determined by the physiology of the mother and child.

The synchronisation between the magnetocardiographic (MCG) signals of a mother-and-foetus pair can be quantified by a method called synchrogram. This method identifies time-windows during which the mother and foetus heartbeat frequencies exhibit the same pattern, namely are synchronised. A "synchronisation index" can be calculated based on the proportion of time during which signal synchronisation occurs. In theory, the statistical significance of the result can then be assessed, using standard statistical methods, by comparison to synchronisation indices obtained from the heartbeat signals of the foetus under study and signals from a large sample of different pregnant women ("surrogate mothers"). Since interaction between the “surrogate mothers” and the foetus can certainly be ruled out, we may establish in this way a base level of spurious synchronisation, and then test whether the mother and foetus have a higher level of synchronisation or not. Low synchronisation index may suggest abnormal foetal development. This was the approach initially taken by the researchers in the Groenemeyer Institute.

However, due to physiological differences among different women, the statistical significance of the results remained questionable. The problem facing the clinicians was that only “surrogate mother-foetus” pairs with identical physiological parameters to the actual mother are suitable for the calculation of synchronisation indices. The issue is that these parameters inevitably change from one mother to mother, a fact that makes a statistical hypothesis test impossible.

Research carried out by **Romano**, **Thiel** and **Kurths**, at the University of Aberdeen between 2007 and 2009, in collaboration with the Groenemeyer Institute for Microtherapy in Germany, resulted in the development of an approach to mathematically generate MCG time series of surrogate mothers that are physiologically identical. This allows us to statistically test for synchronisation in passive experiments. This method, called the “*twin surrogates method*”, applies to all passive experiments.

The approach is to view the problem in terms of dynamical systems. In short, we mathematically create an ensemble of independent trajectories (or “realisations”) of an unknown, highly complex dynamical system from a single observation of the given system, i.e. a single trajectory of that system. In the language of the mother and foetus problem which motivated this research, these trajectories represent heartbeat measurements from ideal *surrogate mothers*, with exactly the same physiological characteristics of the mother. The remarkable fact is that the entire ensemble is generated from a single measurement of the pregnant woman carrying the foetus.

The twin surrogate method is a special application of a “bootstrap procedure”. In order to generate new trajectories we repeatedly splice randomly selected segments of the original trajectory in the phase space of the mother-and-foetus dynamical system, such that the consecutive segments are dynamically consistent [2,3]; the notion of dynamical consistency is related to Poincaré recurrence. In [2] we showed that recurrences determine the dynamical system. Therefore, the new trajectories we generate belong to the same dynamical system. Importantly they are independent of the original trajectory in the sense that they don't interact with it (in the same way that the “surrogate mothers” do not interact among each other and with the foetus and mother being examined). Hence, this method generates independent perfect surrogate mothers, with exactly the same physiological characteristics. This allows reliable assessment of the statistical significance of the synchronisation indices. More specifically, the twin surrogate data allows us to establish the significance level by which we could reject the null hypothesis that the mother-foetus systems do not interact [3].

3. References to the research

[1] Van Leeuwen, P., Geue, D., **Thiel**, M., Cysarz, D., Lange, S., Romano, M.C., Wessel, N., **Kurths**, J., and Groenemayer, D.H. “*Influence of paced maternal breathing on foetal-maternal heart rate coordination*,” PNAS, 106, 13661-13666 (2009). *In this paper, we showed that paced breathing-induced maternal respiratory arrhythmia increases the degree of synchronisation between the heartbeats of mother and foetus, and we applied the twin surrogate method to show the statistical significance of the results.*

[2] Robinson G. and **Thiel**, M. “*Recurrences determine the dynamics*,” Chaos, 19, 023104 (2009). *In this paper we proved that dynamical systems with the same recurrences are dynamically equivalent. The main theorem states that the recurrence matrix determines the dynamical*

system.

[3] **Thiel**, M. **Romano,** M.C., **Kurths**, J., Rolfs, M. and Kliegl, R., *"Generating Surrogates from Recurrences",* Phil. Trans. Roy. Soc. A, **366 (1864)**, 545-557 (2008). *In this paper we presented the approach to recover the dynamics from recurrences of a system and then generate (multivariate) twin surrogate trajectories. We showed that, in contrast to other approaches such as the linear-like surrogates, this technique produces surrogates that correspond to independent realisations of the underlying system's trajectories. We showed that these surrogates are well suited to test for complex synchronisation*.

[4] **Romano**, M.C., **Thiel**, M., **Kurths,** J., Mergenthaler, K., and Engbert, R. "Hypothesis test for synchronisation: twin surrogates revisited", Chaos, **19**, 015108 (2009). *In this paper we derived new analytical expressions for the number of twins depending on the size of the neighbourhood, as well as on the length of the trajectory. This allowed us to determine optimal parameters for the generation of twin surrogates.*

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4. Details of the impact

The Groenemeyer Institute for Microtherapy in Bochum, Germany is a high profile, privately run medical research and treatment institute. Its main aim is to develop and apply products and processes for minimally invasive therapy, including those in the field of prenatal diagnosis. One of their aims is to find ways to identify and classify foetal pathological conditions very early in the pregnancy, such as growth retardation and foetal stress. The Department of Biomagnetism at the Groenemeyer Institute has taken up research in this direction supported by the evidence [5] of prenatal interaction between mother and foetus on the basis of foetal heart rate. However, as explained above, their research faced the fundamental problem of dealing with passive experiments. This means that it was impossible to obtain, from the data they collected, statistically robust evidence to support their conclusions. A better understanding of this interaction and ways to evaluate its statistical significance were needed for foetal surveillance and the detection of pathological conditions during pregnancy. The breakthrough came from our research at IPAM, which equipped the clinicians at the Groenemeyer Institute with the mathematical and statistical tools to develop the new diagnostic algorithms, as well as computer software which implemented them.

The research team at IPAM in Aberdeen started working on the general problem of passive experiments in 2007, inspired by the mother-foetus heartbeat synchronisation problem which was presented at a conference by members of the Groenemeyer Institute. Our work on the twin surrogate method was then published [3] in 2008. After that, contact was established between the research group led by Professor van Leeuwen at the Groenemeyer Institute and the IPAM researchers. A collaboration between the two groups followed. As a result we made the twin surrogate method available to clinicians at the Groenemeyer Institute by means of a computer algorithm that was developed at IPAM in 2008. This software made it possible for clinicians at the Groenemeyer Institute to take up their clinical research by analysing and interpreting magnetocardiographic data in a statistically meaningful way [1]. As a result they successfully established the physiological significance of heartbeat synchronization. Beyond a contribution to pure clinical research, our software has also been fundamental to the development of diagnostic methods, since data from pregnant women can now be processed by practitioners in their clinics. Our algorithms have been implemented in a widely used time series analysis software package (*CROSS RECURRENCE PLOT TOOLBOX v5.17,* http://tocsy.pik-potsdam.de/CRPtoolbox/), with more than 2,000 downloads by researchers from a wide distribution of scientific disciplines beyond mathematics, ranging from cognitive neurosciences and cardiology, to medical research and systems biology.

The Head of the Groenemeyer Institute for Microtherapy stated in [c1] that "*the physiological significance (of the research) lies in the demonstration of the physical synchronisation of biological organ systems of separate individuals*. *The fact that it occurs prenatally is a sign that it may have developmental importance.*" In addition, with respect to IPAM's work, he mentioned that "*the methodological significance lies in the fact that procedures have been developed which permit the identification and quantification of such interaction under the conditions of pregnancy*." The Department of Biomagnetism at the Groenemeyer Institute has since taken up this work further through collaboration with other partners, e.g. Humboldt University in Berlin, in order to develop protocols that will enable them to better understand the phenomenon of heartbeat synchronisation between mother and child.

To summarise, our fundamental research in dynamical systems provided the turning point in a new clinical study carried out in Germany. Primarily, our work enabled the researchers in the Groenemeyer Institute to carry out their medical research. Secondly, the software derived from our mathematical results has made it possible to apply the research in actual clinical trials of pregnant women in order to develop diagnostic protocols that identify foetal pathological conditions.

This impact achieved additional reach among the non-specialist public through media coverage in the UK and Germany, raising awareness and understanding of the significance of the findings among non-specialists and the general public. For example, in January 2010, the German popular science magazine *Spektrum der Wissenschaft* (circulation 110,000) published an article on the findings, explaining the circumstances in which maternal and foetal heart rates synchronise [c2]. *BBC News for North-East Scotland, Orkney & Shetland* reported on the diagnostic significance of the findings in July 2010 [c3], as did the written media such as *The Scotsman* [c4]*, Aberdeen Evening Express, Aberdeen Press and Journal, Daily Record,* and the *Irish Examiner* [c5] (combined circulation: over 440,000).

5. Sources to corroborate the impact (indicative maximum of 10 references)

[c1] The Head of Department of Biomagnetism, Groenemeyer Institute for Microtherapy can corroborate the applicability of the twin surrogate method to the development of non-invasive diagnosis of foetal pathological conditions.

[c2] http://www.spektrum.de/alias/physiologie/herzen-von-mutter-und-foetus-im-gleichtakt/1019580 Article from *Spektrum der Wissenschaft*, 22nd January 2010. *This source confirms the impact achieved in non-specialist public in Germany.*

[c3] http://www.bbc.co.uk/news/uk-scotland-north-east-orkney-shetland-10696611 Article from BBC News online for NE Scotland, Orkney and Shetland, 20th July 2011.

[c4] http://www.irishexaminer.com/ireland/foetal-heartbeat-can-adjust-to-mothers-125697.html, Article from the *Irish Examiner*, 21st July 2010.

These last two sources verify the impact on public understanding achieved through media coverage in Scotland and Ireland.