

# EPSRC CENTRE FOR PREDICTIVE MODELLING IN HEALTHCARE

Annual Report 2016



*Our mission is to advance fundamental understanding of dynamic mechanisms of non-communicable disease leading to enhanced diagnosis, prognosis and treatment.*

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Living Systems Institute



Independent research fellows Dr Wessel Woldman, Dr Jamie Walker and Dr Jan Sieber

## EPSRC Centre for Predictive Modelling in Healthcare

From the Centre Director, Professor John Terry

"Welcome to our first annual report. 2016 has been a very busy year in which we have established the EPSRC Centre for Predictive Modelling in Healthcare, made possible by a very generous £2m Centre award by the EPSRC. It has also seen us move into a new home within the brand new £52.5m Living Systems Institute at the University of Exeter. The Living Systems Institute is an exciting new interdisciplinary endeavour that brings together mathematicians, physicists, cell biologists, geneticists and clinicians to focus on the fundamental mechanisms through which living systems operate and how they can become disrupted and breakdown leading to disease.

The focus of our Centre within this context is on 'dynamic' health conditions such as autoimmune disease, cardiac arrhythmias, diabetes and epilepsy. Here we aim to revolutionise clinical management through developing mathematical, statistical and computational methods to better understand the emergence of these disorders, leading to the development of mathematically-underpinned decision support systems. In the longer term these will enable clinicians and other healthcare practitioners to make quantitative diagnosis and prognosis through enhanced interrogation of patient data. To make this possible it is critically important for our researchers to engage with a variety of stakeholders, not only with GPs and clinicians, but also with people with lived experience of the disorder itself and throughout the year we have hosted a number of activities to facilitate this.

During 2016 members of the Centre have published approaching 30 pieces of original research, including key findings in Nature Communications, eLife, the Journal of Neuroscience and PLoS Computational Biology. We have hosted a number of workshops and conferences, including the third international BioDynamics conference where mathematics, medicine and biology were brought together in an interdisciplinary melting pot! It has been particularly pleasing to see three of our early and mid-career staff secure prestigious independent research Fellowships. In March, Dr Jamie Walker commenced a five-year MRC Career Development Award. In June, Dr Wessel Woldman commenced a three-year MRC Skills Development Fellowship and in December, Dr Jan Sieber commenced a five-year EPSRC early career Fellowship. These successes are a testimony to the dedication of colleagues in supporting the development of early career researchers, and something that we look to build upon.

Looking forward to 2017 and beyond, we envisage further growth and diversification of our research into new areas of activity, with an increasing emphasis on global healthcare challenges. Thank you in advance for your support and for sharing this journey with us."

*John Terry*



## About the Centre

The Centre for Predictive Modelling in Healthcare was established in 2016 through a £2m award from the EPSRC.

To realise its mission in the long-term, the Centre is focussed on six strategic objectives:

1. To deliver excellence in mathematical and computational research;
2. To drive clinical translation of fundamental research;
3. To establish significant industry engagement enabling exploitation of IP;
4. To engage and involve the public and people with lived experience in co-creating research;
5. To build long-term international partnerships;
6. To develop cross-College educational opportunities at all levels.

## Visit us

We run a lively visitor programme where both short term seminar speakers and longer term visitors can interact with the team.

If you are an academic, a student, a healthcare professional or involved in healthcare technologies and you are interested to visit or work with us, we would love to hear from you. We also have some funding available to support the visits of interested parties who will contribute to the work of the Centre.

For more information please get in touch with the Centre Manager, Sarah Warren: [sarah.warren@exeter.ac.uk](mailto:sarah.warren@exeter.ac.uk)

*Mission statement: To advance fundamental understanding of dynamic mechanisms of non-communicable disease leading to enhanced diagnosis, prognosis and treatment.*

## 2016 at a glance

Here are some of our highlights from 2016



Launch event presenters Professors John Terry, Krasimira Tsaneva-Atanasova and Stafford Lightman

### January 2016

In the month the Centre was established, Dr Wessel Woldman successfully secured a three-year MRC Skills Development Fellowship titled 'Revealing the dynamic mechanisms of seizures: An integrated mathematical and clinical approach' at a value of £260,000. The fellowship will enable him to develop new mathematical models and techniques for interrogating data from people with suspected epilepsy, with the aim of defining new techniques to aid diagnosis and prognosis of epilepsy.

### February 2016

The Centre Director, Professor John Terry, visited the Department of Clinical Medicine at the University of Melbourne to collaborate on projects at the interface between mathematics and epilepsy, working alongside engineers, experimental neuroscientists, and neurologists.



Over 60 people attended the launch event

### March 2016

Dr Jennifer Creaser, the Centre's first Research Fellow, joined the team. Jennifer completed her PhD and worked as a PDRA in Auckland, New Zealand before joining the Centre. She is working on network structure and emergent dynamics and in particular applications to transient dynamics, such as the dynamics underlying seizure onset with Professors Peter Ashwin and Krasimira Tsaneva-Atanasova.

### April 2016

The Centre hosted its official launch event, which was opened by Professor John Terry with an introduction to the Centre and an overview of the work it will be doing. Professors Krasimira Tsaneva-Atanasova and Stafford Lightman also presented at the event. After the talks, attendees spent some time celebrating and networking with one another over a drinks reception. The successful event was well attended by a diverse audience of over 60 people with interests in the Centre. This networking session led to a researcher from industry deciding to undertake a PhD within the Centre.

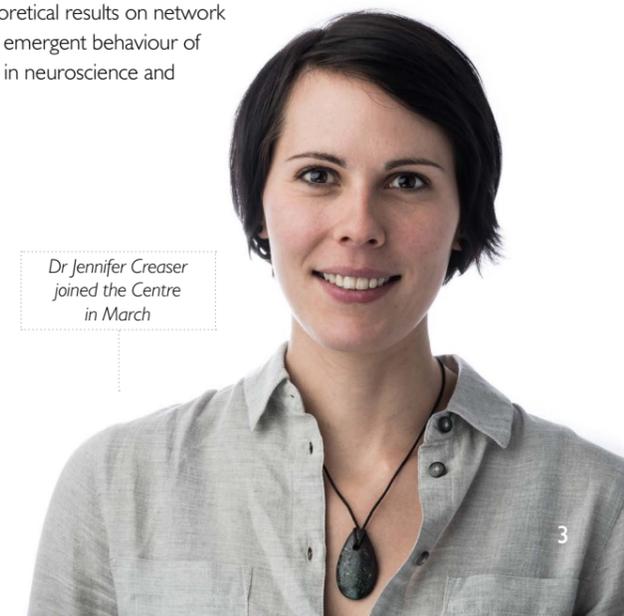


Networking at the Centre's launch event in April

Professor Peter Ashwin and colleagues in the wider team organised a research workshop on synchronization and oscillators with generalized coupling. The workshop discussed the state of the art with regard to the effect of generalised coupling (or phase interaction) functions and the emergent patterns of synchrony in coupled oscillator networks, with a particular emphasis to connections in mathematical neuroscience. The workshop included talks from a number of international speakers, and the topics covered ranged from general theoretical results on network structures and dynamics, through emergent behaviour of coupled oscillators to applications in neuroscience and biological rhythms.



Dr Wessel Woldman secured a prestigious MRC Skills Development Fellowship



Dr Jennifer Creaser joined the Centre in March



Professor Krasimira Tsaneva-Atanasova presenting at Soapbox Science in Exeter

**May 2016**

We welcomed Professors Bernd Krasukopf and Hinke Osinga from the University of Auckland to the Centre, who spent a week working with Professors Krasimira Tsaneva-Atanasova, Peter Ashwin and Dr Jennifer Creaser on emergent phenomena from dynamic networks. While they were visiting they presented research talks on aspects of nonlinear dynamics of fast-slow systems. In addition, Professor Vadim Biktashev gave a presentation about his work on the numerical and asymptotic calculations of the motion of scroll waves in cardiac tissue. The workshop enabled Centre members and associated researchers to explore fast-slow nonlinear dynamical systems, as well seeing their importance in dynamical models of cardiac disease.

As part of our commitment to involving and engaging the public in our research, we hosted an evening of talks and activities as part of the Pint of Science festival. Dr Wessel Woldman demonstrated how to record the electrical activity of the brain and explained how it is used to diagnose neurological disorders. Dr Piotr Slowinski discussed his work with Professor Krasimira Tsaneva-Atanasova on movement and schizophrenia. Dr Eder Zavala introduced the human stress response and posed the question: 'Stress, is it all in the head?'

**June 2016**

Professor Peter Ashwin, alongside collaborators in Biosciences, published an article in Nature Communications on cellular organisation in a fungal pathogen.

Professor Krasimira Tsaneva-Atanasova took part in Soapbox Science in Exeter city centre, an event which showcases the research of women who are making significant contributions to the scientific community. Her topic of discussion was: 'What do your moves say about you? Using maths to understand how our movements give a sneak peek to personality traits'.

**July 2016**

Our second Research Fellow, Dr Margaritis Voliotis, joined the Centre. Margaritis joined us from the University of Bristol where he was an MRC Skills Development Research Fellow. He is working on models of cellular dynamics with a focus on endocrine and neuroendocrine systems in health and disease, such as the reproductive system, with Professors Krasimira Tsaneva-Atanasova and John Terry.

Dr Margaritis Voliotis joined the Centre in July

Dr Diane Fraser joined the Centre in July

Professor Peter Ashwin published an article in Nature Communications

Dr Marc Goodfellow was lead author on an article published in Nature Scientific Reports

Dr Jan Sieber secured a prestigious EPSRC early career Fellowship

Dr Leandro Junges joined the Centre in August



Dr Diane Fraser also joined the Centre, as our Scientific Programmer. Diane was initially involved in an MRC Confidence in Concept project to develop a working prototype of a decision support tool for epilepsy diagnosis, underpinned by a mathematical model. She is focussed on building a bridge between fundamental research and applications in the healthcare technologies space, working with Professors John Terry and Peter Challenor.

Dr Marc Goodfellow and Professors Mark Richardson and John Terry published an article in Nature Scientific Reports on the use of a mathematical model to predict surgical strategy for people with intractable epilepsies. The paper received national and international media attention, covered in several outlets including iNews, el Mundo and Medscape Neurology. Marc was also interviewed on the BBC World Service.

Dr Wessel Woldman was awarded his PhD. His external examiner was Professor Wim van Drongeleden, from the University of Chicago.

**August 2016**

Dr Jennifer Creaser was awarded £15,000 as part of institutional sponsorship awarded by the EPSRC to the University of Exeter to support the development of outstanding early career researchers. The aim of Jennifer's project is to develop a theoretical framework for studying transitions between different neurological states and identify how recent advances in the field of critical transitions could contribute to improving prognosis, diagnosis and treatment of neurological disorders. The project also aims to develop a network of collaborative links with academic and clinical researchers studying epilepsy.

Dr Jan Sieber secured a five-year EPSRC early career Fellowship titled 'Exploring instability in complex systems – simulations in no-man's land' at a value of £639,000. This will enable Jan to develop methods for understanding tipping points and identifying them in real-world data. He will also work more closely with Centre investigators on projects of mutual interest. Jan was put through the Fellowship support process developed by Centre members to develop early career researchers into competitive Fellowship candidates.

Dr Leandro Junges joined the Centre as a Research Fellow, from the Federal University of Rio Grande do Sul in Brazil. He is working on the development and improvement of mathematical models to simulate electrophysiological data, especially in the context of epilepsy, with Dr Marc Goodfellow and Professor John Terry.



The third international BioDynamics workshop was held at the University of Exeter in September



The Northcott Theatre, Exeter

**September 2016**

Dr Jennifer Creaser organised a one-day workshop on transient dynamics and epilepsy funded by her EPSRC early career researcher award. The workshop was attended by around 40 delegates, including neurologists and experimental physiologists, as well as mathematicians from the Centre. Jennifer presented at the workshop alongside Professor Mark Cook and Philippa Karoly from University of Melbourne, Professor David Liley from Swinburne University of Technology, and Professor Adam Zeman from the University of Exeter. The talks were followed by a discussion on identifying mathematical challenges to studying epilepsy.

Dr Marc Goodfellow, Dr Jamie Walker and Professors Stafford Lightman, Mark Richardson and John Terry co-organised the third international BioDynamics workshop. The event was attended by over 80 delegates, from PhD students all the way up to Professors, and provided a highly interdisciplinary and stimulating environment to learn about recent developments from biologists, mathematicians, clinicians, physicists, and computer scientists with an interest in dynamics and networks in the biological and medical sciences.

As part of our commitment towards the translation of fundamental research into practical clinical tools, a Health Economic Evaluation of an epilepsy diagnostic tool was commissioned and performed by Costello Medical. The report found the potential for significant savings to the NHS. The research underpinning this has been performed by Drs Wessel Woldman and Marc Goodfellow, and Professors Mark Richardson and John Terry.

We secured funding from the EPSRC Impact Acceleration Account to partner with the Northcott Theatre to develop a public engagement activity that builds on the themes of dynamic networks and seizure initiation. We plan to bring a completed performance to production during British Science Week in March 2017 and to local schools and colleges. This type of activity has the potential to make a real difference to the public understanding of our broader work.

Zoe Bright joined the Centre as an EPSRC DTP PhD student. She is working with Dr Jamie Walker, Professor Stafford Lightman, Dr Wessel Woldman and Professor John Terry on the inter-relationship between stress and epilepsy.

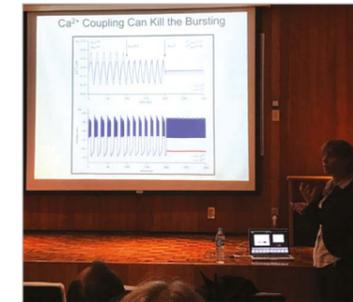
Dr Jennifer Creaser organised a workshop on transient dynamics and epilepsy

Professor Krasimira Tsaneva-Atanasova was interviewed by Euro News for her research project on schizophrenia

Our Engaged Research Fellow, Dr Jo Welsman, organised a public engagement event with Dr Jennifer Creaser in November

Dr Hossein Mohammadi joined the Centre in December

Dr Christopher Marcotte joined the Centre in December



Professor Krasimira Tsaneva-Atanasova presenting to research institutions in Mexico

**October 2016**

The Centre commenced its first seed corn projects. These six-month projects bring together researchers with multidisciplinary but complimentary expertise, to work on a defined research problem related to the work of the Centre. This round of seed corn funding was provided by King's College London, and up to £10k could be requested for each project. The funded projects cover varied topics including cardiac modelling and uncertainty quantification to combat diastolic heart failure, using wearable technology to assess mental health states, and utilising mathematic models to better understand the reproductive system. The next round of seed corn funding will commence in summer 2017.

Professor Krasimira Tsaneva-Atanasova was interviewed by Euro News for her work as part of a European research project which explored the use of complex mathematical models, body scanner technologies and motion tracking systems to provide innovative therapies to people with neurological conditions such as schizophrenia.

Taking advantage of funding provided by the EPSRC to the University of Exeter to scope out global challenges research fund projects, Professor Krasimira Tsaneva-Atanasova and Dr Eder Zavala visited the following research institutions in Mexico to explore collaboration opportunities: Institute of Cellular Physiology – National Autonomous University of Mexico (ICF – UNAM), Department of Physiology, Biophysics and Neuroscience – Centre for Research and Advanced Studies of the National Polytechnic Institute (CINVESTAV-IPN), and Unidad Monterrey – Centre for Research and Advanced Studies of the National Polytechnic Institute (CINVESTAV-IPN).

**November 2016**

Dr Jennifer Creaser and Dr Jo Welsman organised a public engagement activity for people with lived experience of epilepsy, which aligned to Jennifer's workshop on transient dynamics and epilepsy (September). The idea behind this event was to open a conversation between people with a lived experience of epilepsy and our researchers. Fourteen people took part in the workshop; six people had a diagnosis of epilepsy and eight people were family members (supporters and carers) for people with epilepsy. Following the success of this workshop a follow-up has been organised for 2017.

Centre investigators were awarded MRC Proximity to Discovery funding jointly with IBM Research – Haifa (Machine Learning for Healthcare and Life Sciences). This is the Centre's first formalised partnership with industry. The project is focussed on dynamical disease, specifically diabetes and epilepsy, to explore how mechanistic mathematical models can be used along with longitudinal patient data to better inform treatment design and decision-making.

Dr Leandro Junges, Professor John Terry and Dr Wessel Woldman established a partnership with neurologist Dr Andre Palmieri, Professor at the Pontifical Catholic University of Rio Grande do Sul and Director of the neurology department at the São Lucas Hospital in Porto Alegre, Brazil. This project aims to develop mathematical methods to interrogate clinical electrophysiological data, with the objective of improving the outcome of epilepsy surgery. The team will visit Porto Alegre in March 2017.

Dr Margaritis Voliotis and Professor Krasimira Tsaneva-Atanasova took part in an outreach activity at the Exeter Mathematics School, delivering a joint lecture as part of their 'Inspire' lecture series. The lecture exposed the students to some key mathematical concepts that are used in biomedical research.

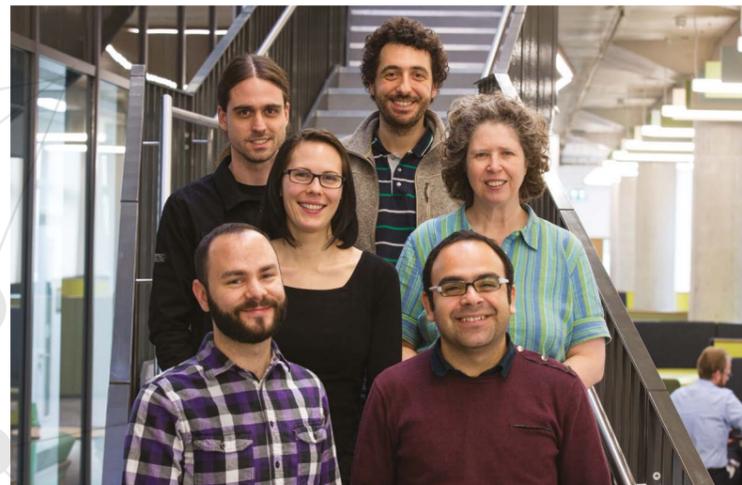
**December 2016**

Dr Christopher Marcotte joined the team from Georgia Institute of Technology in Georgia, USA. He is focussed on fundamental modelling of excitable systems with application primarily to the heart and cardiac arrhythmias. Christopher is working with Professors Vadim Biktashev and Peter Ashwin.

Dr Diane Fraser, Dr Wessel Woldman and Professor John Terry met with several clinical researchers and neurologists, including a group led by Professor Mark Richardson, as part of a MRC Confidence in Concept project. By integrating the feedback from these potential early adopters, a user-friendly working prototype has been developed. Work is continuing to trial this prototype in a clinical setting for further testing and feedback to ensure that it optimally meets clinical demands.

The Centre moved into its new home in the Living Systems Institute. The move brings with it fantastic opportunities not only to work in a truly interdisciplinary environment, with world-class facilities, but to showcase our research and to grow and innovate our activities within this space.

Dr Hossein Mohammadi was the final of our five Research Fellows to join the Centre. He received his PhD in Applied Mathematics from Ecole des Mines de Saint Etienne, France and he is working on data-model fusion and uncertainty quantification with Professor Peter Challenor and Dr Marc Goodfellow. This project is designed to find efficient methods to enable patient specific models for use in diagnosis of disease.



The Centre's Research Fellows Dr Jennifer Creaser, Dr Margaritis Voliotis, Dr Leandro Junges, Dr Christopher Marcotte and Dr Hossein Mohammadi, and Scientific Programmer Dr Diane Fraser



The Living Systems Institute

## Facts and figures

An overview of some of our key activities in 2016

### Funding

Details	Centre contributor
"Mathematical approaches to transient dynamics of neurological disorders" EPSRC ECR scheme 01.09.2016 – 31.03.2017 <b>£15,000</b> (PI)	Jennifer Creaser
"A mechanistic investigation into the emergent functional dynamics of the HPA axis" MRC Career Development Award 01.03.2016 – 28.02.2021 <b>£830,679</b> (PI)	Jamie Walker
"Exploring instability in complex systems - simulations in no-man's land" EPSRC Fellowship 01.01.2017 – 31.12.2021 <b>£639,000</b> (PI)	Jan Sieber
"The sound of seizures / Making your team sing" EPSRC Impact Acceleration Account 01.01.2017 – 31.03.2017 <b>£34,500</b> (PI)	John Terry
"A prototype diagnostic tool for epilepsy" MRC Confidence in Concept 01.06.2016 – 31.01.2017 <b>£49,816</b> (PI)	John Terry
"A Multiphoton Imaging Facility" Wellcome Trust 01.09.2016 – 31.08.2021 <b>£584,000</b> (CI – PI: Andrew Randall)	John Terry
"Translational Research Exchange @ Exeter" Wellcome Trust Institutional Strategic Support Fund 01.10.2016 – 30.09.2021 <b>£1,500,000</b> (PI)	John Terry
"Inter-disciplinary collaborations in the domain of healthcare technologies" EPSRC Global Challenges Research Fund 01.10.2016 – 31.03.2017 <b>£14,993</b> (PI – John Terry)	John Terry, Krasimira Tsaneva-Atanasova and Marc Goodfellow
"Dynamical Disease: Integrating mathematical models and machine learning for personalised healthcare" MRC Proximity to Discovery funding 29.11.2016 – 31.08.2017 <b>£27,588</b> (PI – John Terry)	John Terry, Krasimira Tsaneva-Atanasova, Peter Challenor and Jonathan Fieldsend
"Inter-disciplinary collaborations in the domain of Type I and II diabetes in India" EPSRC Global Challenges Research Fund 01.10.2016 – 31.03.2017 <b>£15,000</b> (PI)	Krasimira Tsaneva-Atanasova
"Revealing the dynamic mechanisms of seizures: An integrated mathematical and clinical approach" MRC Skills Development Fellowship 01.06.2016 – 31.05.2019 <b>£260,000</b> (PI)	Wessel Woldman
Total PI funding secured during 2016: <b>£3,386,576</b>	

## Publications

**Ashwin P**, Coombes S, Nicks R. Mathematical frameworks for oscillatory network dynamics in neuroscience. *Journal of Mathematical Neuroscience* **6**: 1-92 (2016).

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Avitabile D, **Slowinski P**, Bardy B, **Tsaneva-Atanasova K**. Beyond in-phase and anti-phase coordination in a model of joint action. *Biological Cybernetics* **110**: 201-216 (2016).

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**Goodfellow M**, Oza HB, Pandey R, Roper D, Al-Nuaimi Y, Spurgeon SK. Modelling and finite time stability analysis of psoriasis pathogenesis. *International Journal of Control* DOI: 10.1080/00207179.2016.1217566 (2016).

**Goodfellow M**, Rummel C, Abela E, **Richardson MP**, Schindler K, **Terry JR**. Estimation of brain network ictogenicity predicts outcome from epilepsy surgery. *Scientific Reports* **6**: 29215 (2016).

Griffith T, **Tsaneva-Atanasova K**, Mellor J. Control of Ca<sup>2+</sup> influx and calmodulin activation by SK-channels in dendritic spines. *PLoS Computational Biology* **12**: e1004949 (2016).

Jedynak M, Pons AJ, Garcia-Ojalvo J, **Goodfellow M**. Temporally correlated fluctuations drive epileptiform dynamics. *NeuroImage* **14**: 188-196 (2016).

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Mina P, **Tsaneva-Atanasova K**, Bernardo MD. Entrainment and Control of Bacterial Populations: An in Silico Study over a Spatially Extended Agent Based Model. *ACS Synthetic Biology* **5**: 639-653 (2016).

Mirams GR, Pathmanathan P, Gray RA, **Challenor P**, Clayton RH. Uncertainty and variability in computational and mathematical models of cardiac physiology. *The Journal of Physiology* **594**: 6833-6847 (2016).

Movassagh M, Alomran N, Mudvari P, Dede M, Dede C, Kowsari K, Restrepo P, Cauley E, Bahl S, Li M, Waterhouse W, **Tsaneva-Atanasova K**, Edwards N, Horvath A. RNA2DAlign: nucleotide resolution allele asymmetries through quantitative assessment of RNA and DNA paired sequencing data. *Nucleic Acids Research* **44**: e161 (2016).

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**Schmidt H**, **Goodfellow M**, **Woldman W**, Chowdhury FA, Koutroumanidis M, Jewell S, **Richardson MP**, **Terry JR**. A computational biomarker of idiopathic generalized epilepsy from resting state EEG. *Epilepsia* **57**: e200-e204 (2016).

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## Visitors

Name	Institution	Date
Stephen Coombes	University of Nottingham, UK	January 2016
Hans Dierckx	Ghent University, Belgium	March 2016
Alona Ben-Tal	Massey University, Auckland, NZ	April 2016
Roman Borisyuk	University of Plymouth, UK	April 2016
Oleksandr Burylko	Institute of Mathematics of NAS of Ukraine, Ukraine	April 2016
Andreas Daffertshofer	VU University Amsterdam, Netherlands	April 2016
Gemma Huguet	UPC Barcelona, Spain	April 2016
Erik Martens	University of Copenhagen, Denmark	April 2016
Georgi Medvedev	Drexel University, Philadelphia, USA	April 2016
Mason Porter	University of Oxford, UK	April 2016
Tomislav Stankovski	Lancaster University, UK	April 2016
Bernd Krauskopf	University of Auckland, NZ	May 2016
Hinke Osinga	University of Auckland, NZ	May 2016
Christopher Marcotte	Georgia Institute of Technology, USA	June 2016
Wim van Drongelen	University of Chicago, USA	July 2016
Dean Freestone	University of Melbourne, Australia	August 2016
Philippa Karoly	University of Melbourne, Australia	August 2016
Ya'ara Goldschmidt	IBM Research - Haifa, Israel	September 2016
Mark Cook	University of Melbourne, Australia	September 2016
Duncan Turner	University of East London, UK	November 2016
Alexander Skupin	University of Luxembourg, Luxembourg	November 2016
Ajaya Jha	Medanta Hospital, Gurgaon, India	December 2016

EPSRC Centre for Predictive Modelling in Healthcare  
Living Systems Institute  
University of Exeter  
Stocker Road  
Exeter  
EX4 4QD

Tel: +44 (0)1392 726447  
Email: [sarah.warren@exeter.ac.uk](mailto:sarah.warren@exeter.ac.uk) (Sarah Warren, Centre Manager)  
Web: [www.exeter.ac.uk/pmh](http://www.exeter.ac.uk/pmh)

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