Melanie Stefan
California Institute of Technology
Biology Division
Mail Code 216-76
Pasadena, CA 91125, USA
mstefan@caltech.edu

April 21, 2012

Application: Tenure Track Position in Computational Neuroscience

Dear Prof. Sheinberg,

I would hereby like to apply for a tenure track position in computational neuroscience, as recently advertised.

Both a molecular biologist and a mathematician by training, I obtained a PhD in Computational Neurobiology from the University of Cambridge and from EMBL in 2009 under the supervision of Nicolas Le Novère. My research interests revolve around the regulation of proteins in the brain, especially those involved in learning and memory. I am also interested in the general principles governing complex regulatory systems within the cell.

After finishing my dissertation "On the function of Calcium-regulated allosteric devices in synaptic plasticity", I acquired funding in order to pursue postdoctoral research with two of the leading laboratories in the field, combining computational modelling and experimental approaches. I first joined Shinya Kuroda's lab at the University of Tokyo, and, in 2010, Mary B. Kennedy's group at the California Institute of Technology. Besides pursuing research, publishing and presenting my work over the past few years, I have also had the chance to gain teaching experience, both in the classroom and through student supervision.

Brown University is world famous both for its research and its teaching. The Department of Neuroscience appeals to me both because of its ambitious research programme and its interdisciplinary orientation. It would indeed be a joy and an honour for me to benefit from, and contribute to, this vibrant research community. I am also looking forward to collaborating with other departments within Brown, such as the Center for Computational Biology.

Thank you for considering my application. Please let me know if you have any further questions.

Yours faithfully,

Melanie Stefan

California Institute of Technology
Biology Division
Mail Code 216-76
Pasadena, CA 91125, USA
✉ mstefan@caltech.edu
http://www.caltech.edu/~mstefan

Melanie I. Stefan

Research experience

since Nov 2010 **Postdoctoral fellow**, *Modes of regulation of postsynaptic proteins*.
California Institute of Technology, Pasadena (US), Kennedy lab

Aug 2009–Oct 2010 **Postdoctoral fellow**, *Allosteric regulation and cooperativity in synaptic plasticity*.
EMBL-European Bioinformatics Institute, Cambridge (UK), Le Novère lab

Jan 2010–Jun 2010 **Visiting fellow**, *Understanding CaMKII regulation through modelling and experiment*.
University of Tokyo (JP), Kuroda lab

Oct 2005–Jul 2009 **PhD research**, *On the function of Calcium-regulated allosteric devices in synaptic plasticity*.
EMBL-European Bioinformatics Institute, Cambridge, Le Novère lab

2005 **Research assistant**, *Biomathematical cancer models*.
University of Salzburg (AT), Schöllnberger lab

Jan–Dec 2004 **MSc research**, *Morphological characterisation and genetic mapping of the zebrafish skin mutants pusteln and dandruff*.
Max Planck Institute for Developmental Biology, Tübingen (DE), Nüsslein-Volhard lab

Aug–Sep 2003 **Summer internship**, *Structure and activity of metalloproteases*.
International Institute of Molecular and Cell Biology, Warsaw (PL), Bochtler lab

Sep 2002 **Summer internship**, *Using MatLab for confocal image analysis*.
Weizmann Institute of Science, Rehovot (IL), Reich lab

Academic qualifications

PhD **Computational Neuroscience**, *2009*, EMBL-EBI and Clare College, Cambridge (UK).

MSc **Genetics**, *2005*, University of Salzburg, with distinction.

PG Dip **Mathematics**, *2011*, The Open University (UK).

Research Interests

Computational models of neuronal proteins.
Calcium dynamics and Calmodulin regulation; function and regulation of CaMKII; postsynaptic protein regulation networks

Allosteric regulation and cooperativity.
generalised allosteric models; theoretical relationship between different biochemical frameworks; describing and understanding cooperativity

Software and algorithms for computational biology.
multi-state modelling; agent-based stochastic simulations; sharing of models and techniques

Awards and fellowships

since 2011 **Fast Track fellow**, *Robert Bosch Stiftung*.

2011 **Travel grant**, *EMBL/EMBO Science and Society Summer School*.

since 2010 **Long-term post-doctoral fellowship**, *EMBO*.

2010 **Short-term post-doctoral fellowship**, *Japan Society for the Promotion of Science*.

2009 **Christian Doppler Prize for biology**, *State of Salzburg, Austria*.

2009–2010 **Short-term post-doctoral fellowship**, *EMBL*.

2006 **Student project prize**, *Okinawa Computational Neuroscience Course*.

2005–2009 **Pre-doctoral fellowship**, *EMBL*.

2004 **Diploma student fellowship**, *Max-Planck society*.

2003 **Student participant**, *Lindau Meeting of Nobel Laureates*.

2003 **Exchange semester fellowship**, *Erasmus*.

2002 **Scholarship for internship in Israel**, *David-Herzog-Fund*.

2002 **Excellence award for mathematics**, *University of Salzburg*.

Publications

L. Endler, **M. I. Stefan**, S. Edelstein and N. Le Novère. *Using chemical kinetics to model neuronal signalling pathways. In: Computational Systems Neurobiology, N. Le Novère (ed)*. Springer, *in press*, 2012.

L. Li, **M. I. Stefan** and N. Le Novère. Calcium input frequency, duration and amplitude differentially modulate the relative activation of calcineurin and CaMKII, *submitted*, 2012.

M. I. Stefan, D. P. Marshall and N. Le Novère. Structural Analysis and Stochastic Modelling Suggest a Mechanism for Calmodulin Trapping by CaMKII. *PLoS One*, 7(1):e29406, 2012.

G. M. Dall'Olio, J. Marino, M. Schubert, K. L. Keys, **M. I. Stefan**, C. S. Gillespie, P. Poulain, K. Shameer, R. Sugar, B. M. Invergo, L. J. Jensen, J. Bertranpetit and H. Laayouni. Ten simple rules for getting help from online scientific communities. *PloS Comput Biol*, 7(9):e1002202, 2011.

M.I. Stefan, S. Pepke, S. Mihalas, T. Bartol, T. Sejnowski and M. Kennedy. Multi-stage modeling of the kinetics of activation of CaMKII. *Front Neuroinform*, Conference Abstract: 4th INCF Congress of Neuroinformatics, 2011.

S. Edelstein, **M. I. Stefan** and N. Le Novère. Ligand depletion in vivo modulates the dynamic range and cooperativity of signal transduction. *PLoS One*, 5(1):e8449, 2010.

C. Li, M. Donizelli, N. Rodriguez, H. Dharuri, L. Endler, V. Chelliah, L. Li, E. He, A. Henry, **M. I. Stefan**, J. L. Snoep, M. Hucka, N. L. Novère and C. Laibe. Biomodels database: An enhanced, curated and annotated resource for published quantitative kinetic models. *BMC Syst Biol*, 4:92, 2010.

M. I. Stefan, S. J. Edelstein and N. Le Novère. Computing phenomenologic Adair-Klotz constants from microscopic MWC parameters. *BMC Syst Biol*, 3(1):68, 2009.

M. I. Stefan, S. J. Edelstein and N. Le Novère. An allosteric model of calmodulin explains differential activation of PP2B and CaMKII. *Proc Natl Acad Sci USA*, 105(31):10768–10773, 2008.

M. I. Stefan and N. Le Novère. Molecules for memory: modelling CaMKII. *BMC Systems Biology*, 1(Suppl 1):P40, 2007.

A. Anglberger, P. Brössel and **M.I. Stefan**. Rezension: Argumentation in Theorie und Praxis. *Kriterion*, 20:37–41, 2006.

A. Anglberger, P. Brössel, N. Furlan, F. Greinecker, M. Karlegger, N. Pfeiffer, **M.I. Stefan** and A. Ungar. Rezension: Was wir Karl R. Popper und seiner Philosophie verdanken. *Kriterion*, 17:23–27, 2003.

Talks

M.I. Stefan. Computermodellierung neuronaler Proteine. *Austrian Scientists and Scholars in North America, Pasadena (US)*, 2012.

M.I. Stefan. Modelling CaMKII: From StochSim to MCell. *Salk Institute, San Diego (US)*, 2011.

A. Trilling, E. Sünter, **M.I. Stefan** and M. Annoni. New technologies and human identity. *EMBL/EMBO Science and Society Summer School, Heidelberg (DE)*, 2011.

M.I. Stefan. PP2B or PP not to be? *CRG Minisymposium on Systems Biology, Center for Genomic Regulation, Barcelona (ES)*, 2010.

M.I. Stefan. An allosteric model of calmodulin explains differential activation of PP2B and CaMKII. *ZBIT-Colloquium, Center for Bioinformatics, Tübingen (DE)*, 2009.

M.I. Stefan. Modelling allosteric devices in synaptic plasticity. *University of Helsinki (FI)*, 2009.

M.I. Stefan. Modelling CaMKII regulation and autoregulation. *CECAM Workshop: Linking Systems Biology and Biomolecular Simulations, Lausanne (CH)*, 2009.

M.I. Stefan. Stochastic modelling of CaMKII. *California Institute of Technology, Pasadena (US)*, 2009.

M.I. Stefan. An allosteric model of calmodulin. *Cold Spring Harbor Laboratory meeting on Computational Cell Biology, Hinxton (UK)*, 2008.

M.I. Stefan. An allosteric model of calmodulin. *EBI External Seminar, Hinxton (UK)*, 2008.

M.I. Stefan. An allosteric model of calmodulin. *National Institute for Medical Research, London (UK)*, 2008.

M.I. Stefan. Models and brains. *Clare College Research Symposium, Cambridge (UK)*, 2008.

M.I. Stefan. Model curation for the BioModels Database. *Okinawa Computational Neuroscience Course, Okinawa (JP)*, 2006.

Conference posters

M.I. Stefan, S. Pepke, S. Mihalas, T. Bartol, T. Sejnowski and M. Kennedy. Multi-stage modelling of the kinetics of CaMKII activation. *INCF Neuroinformatics, Boston (US)*, 2011.

M.I. Stefan and N. Le Novère. Models of a memory device – understanding CaMKII. *Sanger-Cambridge PhD Symposium, Cambridge (UK)*, 2009.

M.I. Stefan, D. Marshall and N. Le Novère. Stochastic modelling of CaMKII regulation. *The Tenth International Conference on Systems Biology, Stanford (US)*, 2009.

M.I. Stefan, S. Edelstein and N. Le Novère. An allosteric model of calmodulin. *Sanger-Cambridge PhD Symposium, Hinxton (UK)*, 2008.

M.I. Stefan, S. Edelstein and N. Le Novère. An allosteric model of calmodulin explains differential activation of PP2B and CaMKII. *Sixth FENS Forum of European Neuroscience, Geneva (CH)*, 2008.

M.I. Stefan, S. Edelstein and N. L. Novère. An allosteric model of calmodulin explains differential activation of PP2B and CaMKII. *The Ninth International Conference on Systems Biology, Göteborg (SE)*, 2008.

M.I. Stefan and N. Le Novère. A StochSim model for CaMKII regulation. *Synthetic Biology, Systems Biology and Bioinformatics, Manchester (UK)*, 2007.

M.I. Stefan and N. Le Novère. A StochSim model for CaMKII regulation. *The Seventh International Conference on Systems Biology, Yokohama (JP)*, 2006.

M.I. Stefan and N. Le Novère. Molecules for memory. *Okinawa Computational Neuroscience Course, Okinawa (JP)*, 2006.

Teaching and Supervision

2012 **Computational models in biology and biochemistry**, *Reading course*, California Institute of Technology.

since 2011 **Caltech Work Study programme**, *Student supervision*, California Institute of Technology.

2007 **FIND summer programme**, *Research student supervision*, EMBL-EBI.

2005 **1+1=3, ergo: God exists**, *Seminar*, CdE Summer Academy (DE).

2000 **Chemical calculations for biologists**, *Tutorial*, University of Salzburg.

Education

2011 **EMBL/EMBO Science and Society Summer School. The human animal: Scientific, social and moral perspectives**, *Heidelberg (DE)*.

since 2009 **Postgraduate studies in Mathematics**, *The Open University, Milton Keynes (UK)*.

2006 **Okinawa Computational Neuroscience Course**, *Okinawa (JP)*.

2005-2009 **PhD studies in Computational Neuroscience**, *EMBL-EBI and Clare College, Cambridge*.

2003 **Erasmus visiting student in Genetics**, *Charles University, Prague (CZ)*.

2002-2005 **MSc studies in Genetics**, *University of Salzburg*.

2000 **Austrian-Chinese Summer School for Scientists and Economists**, *Shanghai, Beijing (CN)*.

1999-2002 **Undergraduate Studies in Mathematics**, *University of Salzburg*.

1999-2002 **Undergraduate Studies in Biology**, *University of Salzburg*.

Editorial work and reviewing

since 2010 **Reviewer**, *BMC Systems Biology, Theoretical Biology and Medical Modelling*.

2010 **Postdoc Journal keeper**, *Nature Jobs*.

2001–2007 **Editorial board**, *Kriterion: Journal of Philosophy*.

Conference organisation and committee service

2008 **European Science and Society Summer School. Deconstructing and reconstructing life: From classification to design**, *Heidelberg*, Organising committee.

2008 **EMBL-EBI Science and Society Symposium. The personal genome**, *Cambridge*, Organising committee.

2007-2008 **Clare College MCR**, *Cambridge*, Webmaster.

2007 **EMBL-EBI Science and Society Symposium. Biology and language**, *Cambridge*, Organising committee.

2006–2008 **EMBL science and society committee**, EBI representative.

2006 **EMBL International PhD Student Symposium. Biology of disease**, *Heidelberg*, Organising committee.

Memberships

since 2012 **Society of Biology**.

since 2011 **Austrian Scientists and Scholars in North America**.

Research Statement

Summary

Learning and memory rely on the fine-tuned interplay of proteins within the synapse. My research focuses on constructing detailed quantitative models of these proteins based on structural information, biochemical data and biophysical considerations. Not only can such models help us understand how learning normally functions, but they can also be used for simulating the effects of mutations, illness or drug treatment. I am currently performing my own experiments to complement my models and planning to maintain close collaborations with experimental laboratories in the future.

My work draws on a variety of computational approaches. I am especially interested in stochastic modelling and in algorithms that can simulate protein complexes with a very large number of possible states. I enjoy using cutting edge modelling frameworks, which not only benefits my research, but, through a useful cycle of feedback and improvement, also furthers the development of computational biology software. I am also interested in how phenomena such as cooperativity and allosteric regulation can be described mathematically.

Computational models of neuronal proteins

Learning is mediated by activity-dependent changes in synaptic strength. A key mediator of these changes is the calcium-sensing protein calmodulin: At high calcium levels, it activates the protein kinase CaMKII, leading to a strengthening of the synaptic connection, while at low calcium levels, it activates an alternative pathway, resulting in a reduction of synaptic strength. I have developed an allosteric model for calmodulin activation (M.I. Stefan, S.J. Edelstein, N. Le Novère. *PNAS*, 2008). The model is the first to reconcile previous experimental data and to explain how calmodulin can act as a calcium-dependent switch. For this work, I have been awarded the Christian Doppler Prize in Biology in 2009. The model has been further used to study the dynamic effects of calcium influx into the neuron (L. Li, M.I. Stefan, N. Le Novère, *submitted*). I am currently working on experiments that test one of the most important predictions of the model: That calmodulin can be active even in the total absence of calcium.

CaMKII, a central mediator of synaptic strengthening, is a dodecamer consisting of two stacked hexameric rings. Its activity is controlled by calmodulin binding, but also by interactions between neighbouring subunits within the dodecamer. With the help of research student David Marshall, I have combined structural models and stochastic simulations to study the detailed mechanisms by which calmodulin binds to, and activates, CaMKII (M.I. Stefan, D. Marshall, N. Le Novère, *PLoS ONE*, 2012). The model explains the phenomenon of "calmodulin trapping", an apparent increase in calmodulin affinity if CaMKII is phosphorylated. In 2010, I obtained an EMBO long-term fellowship which allows me to continue my work on CaMKII in the Kennedy lab at Caltech. At the moment, I am combining my findings on CaMKII with biochemical assays to

understand how the dodecameric assembly of subunits affects CaMKII autoregulation (M.I. Stefan et al., *Front Neuroinform*, 2011). I am also interested in how CaMKII activation depends on the cellular environment, a project I started while a JSPS visiting scholar in the Kuroda lab at the University of Tokyo.

In the future, I want to extend the model to include a more detailed representation of CaMKII transport into and out of the postsynaptic density and the direct and indirect effects of CaMKII localisation on synaptic signalling. For instance, interaction of CaMKII with the NMDA receptors increases CaMKII activity directly, but also prevents it from diffusing out of the postsynaptic density, thus affecting its access to calcium, to various phosphatases and to its substrates. Due to the complexity of these effects, it is difficult to predict the behaviour of this signalling system under variable conditions. This is therefore an area particularly well suited for computational modelling.

I am also interested in how calcium signalling and diffusion act together within the dendritic spine and how the spine communicates - chemically - with its parent dendrite. This requires spatial modelling within a realistic representation of a section of a dendrite. I am closely collaborating with the developers of MCell, a spatial stochastic simulation software at the Salk Institute in San Diego, which is at the forefront of geometrically realistic spatial simulations.

Although learning and memory is currently my system of choice, I am interested in applying the insights and computational techniques to other areas of neuroscience. In recent years, there has been a rising interest in the computational modelling of biological systems, while a variety of new experimental techniques has allowed us to gain more insights into brain function than ever before. This is indeed an exciting time to be a systems neuroscientist.

Theoretical frameworks and software

For my model of calmodulin, I extended the classic version of the Monod-Wyman-Changeux (MWC) framework for allosteric proteins in order to cater for proteins with non-identical ligand binding sites. I have also developed equations that relate the MWC framework to the simpler Adair-Klotz model for ligand binding (M.I. Stefan, S.J. Edelstein, N. Le Novère. *BMC Syst Biol*, 2009).

We also investigated the cooperativity of conformational change in allosteric proteins. In addition, we were interested in how a system behaves under conditions of ligand depletion, i.e. when the concentrations of ligands and receptors are of a similar order, as is often the case in the cell. We found that ligand depletion reduces cooperativity, but increases the dynamic range of signal response (S.J. Edelstein, M.I. Stefan, N. Le Novère, *PLoS ONE*, 2010).

I am continuing to work on a common framework that links together different descriptions of biochemical phenomena. In general, I am interested in developing the theoretical concepts that underlie protein modulation and emerging behaviours in complex regulatory networks.

I am also interested in how computational biologists and bioinformaticians can share knowledge (G.M. Dall'Olio et al, *PLoS Comp Bio*, 2011) and models (C. Li et al, *BMC Syst Biol*, 2010).

Teaching Statement

Classroom teaching

While at the University of Salzburg (AT), I taught a tutorial entitled "Chemical Calculations for Biologists". It was an intensive class - optional and ungraded - during winter break designed for molecular biology majors who had not taken the Introduction to Chemistry lecture during winter term, but wanted to take more advanced biochemistry classes in the summer. What I learnt from this teaching experience was how to follow a set curriculum while still responding to students' particular needs.

At Caltech, I have been teaching a class called "Computational Models in Biology and Biochemistry" during winter term 2012, introducing students to techniques and algorithms used in computational biology, and illustrating these with classic examples from computational and mathematical biology. I enjoyed the opportunity to pick a topic for a course and work out a curriculum, and to interact with students in a very small group. During my PhD studies at Cambridge, I took a course on small group teaching, which helped prepare me for this particular task.

I have also taught to various audiences outside the university. As a model United Nations enthusiast, I have twice taught a three-week course on the topic at the Deutsche SchülerAkademie, a summer school aimed at highly gifted high-school students. These classes of 15 students and two teachers involved a variety of different teaching methods, including group work, student presentations, discussion and role play. I have also held shorter workshops to prepare students, teachers and conference organisers for model UN meetings. This has taught me to cater for diverse audiences and a wide range of expectations.

Myself a former participant of the Deutsche SchülerAkademie, I am regularly attending and teaching at alumni seminars, meetings of between three days and one week of length. In this context, I have taught a short (3 day) course on the French literary movement Oulipo and a longer (1 week) seminar on analysing the logic structures behind historical proofs of the existence of God. The challenge - and also the beauty - of these classes is that the audience is interdisciplinary and intellectually highly demanding.

I have thoroughly enjoyed all those classroom teaching experiences. I take teaching very seriously, and firmly believe that effort put into carefully preparing classes pays off not only for the students, but also for the teacher. I am excited about having more opportunities to teach in the future. Given my background, I am especially interested in teaching subjects at the interface between biology and mathematics or computer science, but I would be happy to take on other teaching assignments as needed.

Supervision of research students

While a PhD student at the European Bioinformatics Institute, I was one of the supervisors on the FIND project, a summer internship programme where undergraduate students worked with the different groups at EBI to tackle the same problem - signal transmission in the brain - using different bioinformatics research methods. My research student David Marshall helped develop structural models of calmodulin binding to CaMKII, work that has led to a publication (M.I. Stefan, D. Marshall, N. Le Novère, *PLoS One*, 2012). After completion of his undergraduate degree in Molecular and Cellular Biochemistry, David is now pursuing a PhD in Biochemistry at Oxford.

At Caltech, I am currently supervising a research student under the Work Study Programme. This programme allows undergraduate students to work in a research group for a few hours a week throughout the academic year, in exchange for a rebate on their tuition fee. The project involves software development in order to facilitate the sharing of biomathematical models, and it thus situated at the interface between biology and computer science. My research student, a computer science sophomore, is doing very well, and I expect him to get a publication out of this project.

My approach to supervision includes taking time and meeting students on a regular basis, and being there to help with any questions or concerns they have, while at the same time leaving them enough space and freedom to find their own problem-solving strategies and scientific voice.

Mentoring

I firmly believe that teaching extends both beyond the classroom and beyond the laboratory. Some of my former students have later worked on other projects alongside me, and it has always been a privilege to watch former trainees become colleagues. I am always happy and honoured to support my students, be it with career advice, by pointing them to interesting opportunities or by writing reference letters. I have recently signed up to the Caltech mentorship scheme, where postdoctoral fellows serve as mentors for students. I see this as a way of paying forward to the next generation some of the fantastic support and encouragement that I have received from mentors and teachers throughout my own career.