

## Melanie Stefan

Following my retirement at age 65 as Professor of Biochemistry at the University of Geneva in 2006, I joined the group of Nicolas Le Novère at the European Bioinformatics Institute and began interacting regularly with Melanie Stefan. She had just started her Ph.D. in the group working on models for calcium/calmodulin kinase II (CaMKII). In early discussions, it became apparent that the existing models for calmodulin were not adequate, in spite of the many years that calmodulin has been intensively investigated. It was decided to construct a two-state allosteric model, based on the interconversions between the high-affinity R state and the low affinity T state. In this scheme, each of the four binding constants for calcium would reflect the influence of the four distinct binding sites, as well as the different affinities of the T and R states. The master equation for this process is relatively complex, and from my long experience working with the allosteric model, I offered to derive it, thinking that it would be overly demanding for a beginning Ph.D. student, but Melanie Stefan soon demonstrated a full understanding of the principles involved and a high degree of proficiency in deriving such complex equations.

Following this first interaction, I was continually impressed by Melanie's scientific maturity and outstanding ability to handle all aspects of her challenging project. Her first-author publications are excellent (as will be, I am confident, others in preparation on the modeling approaches she developed for CaMKII). Her thesis, entitled "ON THE FUNCTION OF CALCIUM-REGULATED ALLOSTERIC DEVICES IN SYNAPTIC PLASTICITY," is a superbly crafted document and the investigations to be published on CaMKII are elegantly presented. In order to produce these results, she also made important modifications to the computational platform used for the simulations. The findings shed new light on the mechanism of calmodulin trapping by CaMKII and plausible interactions between subunits in the opposing hexameric rings of the dodecameric structure.

Overall, I would place Melanie Stefan in the small group of the very best Ph.D. students that I have interacted with in my 40+ years of academic research. She is very intelligent and motivated, thinks deeply about her problems, and has the valuable combination of first-rate skills in both computer modelling and the mathematical intricacies of biological systems. We met once in California earlier this year and from our discussions it is clear that she is continuing to make excellent progress in her post-doctoral research at Cal Tech. I am sure she would be an excellent and enthusiastic teacher and I know she is participating in teaching during her postdoctoral work. I have every confidence that Melanie Stefan will make a major contribution to your program and I support her for a position at Brown with my highest enthusiasm.

Stuart Edelstein

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