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To whom it may concern,

I am writing in strong support of Yohannes Shiferaw's application for a junior faculty position. Yohannes was a postdoc in my group for two full academic years from the start of Fall 2001 through the end of Summer 2003. During this period he has made important theoretical contributions on two experimentally motivated research projects. The results have significantly enhanced our fundamental understanding of the nonlinear dynamics of cardiac arrhythmias.

The study of life-threatening arrhythmias has grown into a vibrant interdisciplinary field of research driven by a strong synergy between basic science research and clinical practice. What triggers ventricular fibrillation, which is the leading cause of death among industrialised nations, is still not clear. Most of the focus to date has been on the study of high-frequency reentrant waves of voltage activity that are strongly believed to cause fibrillation in one form or another. The dynamics of intracellular calcium, however, remains comparatively less understood even though it can potentially play a major role in the initiation or maintenance of fibrillation.

Yohannes's work focused primarily on modeling intracellular calcium dynamics. His first research project was motivated by experimental recordings (Chudin et al., Biophys J, 1999) which showed that the amplitude of the calcium transient can alternate from beat to beat when a single cell is paced with a periodic action potential clamp. This observation is interesting because cardiac alternans have emerged as a marker for sudden cardiac death but it is still unclear if they are of voltage or calcium origin, or both. The goal of this project was to develop a model of calcium cycling to explain these observations. Yohannes got started on this project just after completion of his PhD thesis on theoretical polymer physics at Pittsburgh University with very little background in biology and physiology. He quickly educated himself in this field and digested a vast and diverse experimental literature (reading in detail a hundred articles or more). This allowed him to become the main driving force for the development of a new model of calcium cycling (Shiferaw et al., Biophys J, 2003) that accounts successfully for the observed data and sets forth a new hypothesis for the origin of calcium transient alternans. This model takes into account the spatially localized nature of calcium release events (calcium sparks) and predicts that calcium alternans is caused by a high sensitivity of calcium release on sarcoplasmic recticulum (SR) calcium content. This hypothesis is supported by recent experiments (Díaz et al, Circ Res, 2004) published after the model.

Subsequent to this project, Yohannes has collaborated with one of my graduate students, Daisuke Sato, who spent the past 12 months with Yohannes at UCLA when I was on sabbatical leave in Paris. They coupled this model of calcium cycling to a full set of membrane ionic currents to explore the coupled nonlinear dynamics of voltage and calcium. This work lead to explicit predictions for physiological parameter ranges where alternans are electromechanically concordant or discordant and to the development of low-dimensional iterated maps to identify basic mechanisms that underly these dynamical instabilities (Shiferaw et al., Physical Review E, in press).

Yohannes was the main instigator of the second research project that we collaborated on. He realized that calcium alternans need not always be in-phase in different regions of a cardiac myocyte. He then developed a spatially distributed calcium cycling model that couples diffusively different regions of the cell. Simulations of this model yielded the surprising result that the cell can spontaneously break down into two (or more) out-of-phase regions under certain physiological conditions. Yohannes came up with a simple physical explanation for these subcellular discordant alternans. Furthermore, with minimal input from me, he developed a mathematical model (based on a weakly nonlinear amplitude equation expansion close to the alternans bifurcation) that explains elegantly this phenomenon in terms of a subcellular Turing type instability mediated by calcium and voltage diffusion (Yohannes et al., to be published). This theoretical work provides a new basis to interpret a wide range of experiments, in particular recent observations by several groups of spatially out-of-phase calcium alternans in atrial and ventricular cells. I was very impressed by the way in which Yohannes very successfully combined computer simulations and sophisticated mathematical analysis to make headway in this complex problem.

Since he has been in Jim Weiss's group at UCLA, Yohannes has worked on more molecular level modeling through the development of a Markov model for calcium dependent inactivation of the L-type calcium current. However I cannot comment in detail on his role in this work since I was not involved in it.

At a personal level, Yohannes is a very pleasant person of high integrity who interacts well with others. He did a wonderful job advising my student Daisuke during the past 12 months that I was away. This, together with the fact that Yohannes gives clear and well-organized talks, leads me to believe that he will be a great teacher. He has also excellent english writing skills (as judged by the drafts of his papers and conference abstracts) and some exposure to grant writing that should allow him to secure funding in a reasonably short time.

Yohannes ranks among the top three of about a dozen postdocs that I have supervised. In all our collaborative projects, he has proven to be a deep and

original thinker with excellent computational and analytical skills. Being, in addition, a fast learner and a highly motivated hard working individual, I am confident that he will make important future contributions in almost any interdisciplinary field of research at the border of physics, mathematics, biology, and medicine, which he chooses to work on. I am also confident that he will actively seek and develop fruitful collaborations with experimentalists wherever he is, and perhaps even develop his own experimental program at some point given the right environment.

Yohannes has all the maturity, skills, and drive necessary to succeed in a junior faculty position at a leading research University. I recommend him very strongly. Please do not hesitate to contact me if you wish additional information.

Sincerely,

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