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## Application of in-silico and in-vitro optogenetic tools to cardiac arrhythmia research

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STELLINGEN

behorende bij het proefschrift

APPLICATION OF IN-SILICO AND IN-VITRO OPTOGENETIC TOOLS TO CARDIAC  
ARRHYTHMIA RESEARCH

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1. For any studied geometry of the depolarized region in optogenetically modified monolayers of cardiac cells, primary ectopic excitation originates at areas of maximal curvature of the boundary, where (paradoxically) the stimulating electrotonic currents are minimal. (this thesis)
2. Positive curvature induced unusual behavior, which cannot be observed under normal conditions in a flat geometry. (this thesis)
3. We discover a fundamentally different nonlinear mechanism of resonance in a generic family of spatially-distributed systems, which does not require intrinsic oscillations. Instead, the resonant frequency dependence arises from coupling between an excitable and a monostable region of the medium. (this thesis)
4. Trapped reentry as a latent source of arrhythmogenesis can explain the sudden onset of focal arrhythmias, which are able to transgress into atrial fibrillation. (this thesis)
5. In condensed matter physics, the properties of a bulk solid can differ dramatically from those of its constituent atoms. ... A cardiomyocyte in isolation would behave very differently from one embedded in a two-dimensional culture or one embedded in a real heart—even if the ion channels were identical in all three cases. (McNamara, Harold M., et al. "Geometry-dependent arrhythmias in electrically excitable tissues." *Cell systems* 7.4 (2018): 359-370.)
6. Optogenetics is a research tool; the main goal of those in the field isn't to genetically engineer humans to have opsins. (Williams, Sarah CP, and Karl Deisseroth. "Optogenetics." *Proceedings of the National Academy of Sciences* 110.41 (2013): 16287-16287.)
7. A deeper look into the mechanisms that create, sustain and abolish oscillatory processes requires the language of nonlinear dynamics, well beyond the linearization techniques of equilibrium control theory. Nonlinear dynamics enables us to identify oscillatory ('pacemaking') mechanisms at the cellular, tissue and system levels. (Xiong, Lingyun, and Alan Garfinkel. "Are physiological oscillations physiological?" *The Journal of Physiology* (2023).)

8. While analytical studies have revealed important features of excitable media whose properties are spatially homogeneous, less is understood about abrupt heterogeneities such as sample edges or interfaces. As is often the case with wave mechanics, edges and interfaces can have properties that differ qualitatively from those of the bulk medium. (Scheibner, Colin, et al. "Spiking at the edge: Excitability at interfaces in reaction–diffusion systems." *Proceedings of the National Academy of Sciences* 121.3 (2024): e2307996120.)
9. "... a small critical audience is far more daunting than a large uncritical one". (Plato, Dialogues: Symposium)  
Intensive close discussions with few genuinely smart people usually bear more intellectual fruits than official interactions at prestigious conferences, round tables.
10. "The limits of my language mean the limits of my world." (Ludwig Wittgenstein, *Tractatus logico-philosophicus*, 1922)  
Be it a human language or a language of a particular field of science, a language seriously confines an area of concepts and ideas. In order to traverse intellectual limits one should learn other languages.
11. "Geen man zal ooit een groot man zijn als hij niet ook een vrouw durft te zijn." , (Ilja Leonard Pfeijffer , *Alkibiades*, 2023) [trans. "No man will ever achieve greatness if he does not accept to be also a woman"]  
Pseudo-masculine predatory dominant behaviour often harms science by destroying collaborations and dissuading proper team work.
12. "Mon travail alors ne consiste pas à 'surmonter' la difficulté à la force du poignet, mais à entrer dans mon incompréhension suffisamment pour arriver à comprendre quelque chose, et rendre "facile" ce qui avait semblé 'difficile'" (Alexandre Grotendieck, "Récoltes et semailles", 1983 - 1986) [trans. "My job is not to increase the difficulty by all means. My job is to enter into my nonunderstanding deep enough to understand a subject and to render a 'difficult' subject 'easy'"]  
Often modern research papers are bloated with an air of seriousness and difficulty created by sheer amount of work. The main task of a researcher is to take away this air of seriousness.