

PLOS Science Wednesday: Hi Reddit, my name is Alan Garfinkel and I developed an electrophysiology model of heart failure that shows certain cellular conditions in the heart may be predispose people to cardiac death – Ask Me Anything!

PLOSScienceWednesday <sup>1</sup> and r/Science AMAs<sup>1</sup>

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# PLOS Science Wednesday: Hi Reddit, my name is Alan Garfinkel and I developed an electrophysiology model of heart failure that shows certain cellular conditions in the heart may be predispose people to cardiac death – Ask Me Anything!

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Hi, Dr. Garfinkel! I'm curious about how this might change treatment options. How are at-risk HF patients currently identified and treated? Are these cellular changes common across all modes of HF or just some? Are there existing drug therapies that target SERCA?

[divvyflax](#)

Alan: 1) current situation for HF is based largely on hemodynamic measures like Ejection Fraction and treated with drugs to improve that situation. Our focus was on electrical arrhythmias in this population, which is a known problem but whose mechanism are unclear. 2) your question about types of HF is a good one. There are definitely distinct types of HF: HFpEF, hypertrophic cardiomyopathy, and a few others. We are focussing on HFrEF (r = reduced), and we really have no idea whether this would also hold true of entities like hypertrophic CM. 3) see Cardiac inotropes: current agents and future directions. Hasenfuss G, Teerlink JR. Eur Heart J. 2011 for a good discussion of research-level drugs

Hey Dr. Garfinkel! Are there any plans to transition this work from a rabbit model to a human heart model?

[Fadelin](#)

Alan: yes! we have a protocol in place to obtain some human hearts and image them in DT-MRI. This is clearly the way to go and is absolutely the necessary next step, since we aren't here to treat rabbits! and also, although the rabbit heart is qualitatively similar to the human, we can't just extrapolate trivially to the human. You have to do the model.

Hi Dr. G.

So we know folks with HF with Reduced Ejection Fraction (HFref) sometimes called systolic failure,



have a predisposition to developing sudden and fatal ventricular arrhythmias (Vtach/Vfib), the model of which you published.

When we treat heart failure with standard meds (ACEI/ARB, long acting BB) we expect/hope that the EF will improve. It is assumed that folks who have an improvement in their EF do not need implantable cardiac defibrillator therapy. Do we know what is happening at a cellular level that is making this malignancy rhythms less likely?

[DaZedMan](#)

Alan: What you say is true: current standards for implanting an ICD place importance on the EF. But there is absolutely no mechanistic connection, to my knowledge, between "low EF" and "arrhythmia". "low EF" is a marker for advanced disease, and then you are also at risk for arrhythmias, but I don't know the connection. Of course, as you well know, ACE targeting is supposed to address contractility, and BB is supposed to be anti-arrhythmic. One very interesting recent development is the role of autonomic (parasymp and sympathetic) innervation of the heart as a cause of arrhythmia. See my colleagues work, for example The role of the autonomic nervous system in sudden cardiac death M Vaseghi, K Shivkumar - Progress in cardiovascular diseases, 2008 This actually provides a mechanism whereby BB could act as an anti-arrhythmic

What was the hardest part about making the heart model?

[Solutionflap](#)

Alan: (1) Writing the FiniteElement Code and getting it into computable form. Ponnaluri and Perotti did a fantastic job on this, working under the direction of the late Prof. Klug, who is much missed (2) finding the right combinations of parameters to make the model work. Lots of trial and error (3) finding the data on rabbit cell physiology, since the literature is, like, Old MacDonalds farm, here a pig, there a rabbit, here a rat, etc.

Dr. Garfinkel, I have been hearing lately about the different symptoms men and women exhibit during a heart attack which can lead to women receiving poor or late treatment. Have you noticed any differences between male and female electrophysiology or is the difference only in the presented symptoms?

[JoeyTheGreek](#)

Alan: Definitely sex differences in cardiac EP. women have more  $I_{Ca,L}$  (calcium current) and hence longer QT intervals. Lots of lit on this. see for example Molecular and cellular basis of cardiovascular gender differences ME Mendelsohn, RH Karas - Science, 2005 -

Hi Alan. I've had bigeminy PVCs for most of my life. They go away when exercising but present when I am resting. Does this affect my chances of dying from cardiac problems at all? I'm in my mid 20s.

My family has a bit of a history of heart disease.. but they also tend to eat a pretty high fat and sodium diet into old age. Not particularly an obese family, but certainly not healthy eaters either. I assume eating and exercise habits will still be the main factor in my heart health as I get older?

[alexanderthebait](#)

Alan: sorry, site prohibits medical advice. everyone has PVCs, but you might want to see a Cardiac Electrophysiologist ("EP") about the bigeminy

Do you see your model being used for wide scale diagnosis of cardiac arrhythmias?

[Securus777](#)

Alan: Diagnosis of cardiac arrhythmia is already pretty straightforward. 90% of the time a 12-lead EKG (completely non-invasive) will do the trick, while the remaining 10% might need a cath exam. That's easy. what's hard is understanding the mechanics of the arrhythmia, and (related) design therapies. We do hope our model can help design therapies and understand mechanisms

What heart irregularities/problems/etc would an echocardiogram show that an electrocardiogram wouldnt?

[azureice1984](#)

Alan: echo shows motion, which is mechanics. You can see all sorts of problems in contractility, EF, etc. EKG shows electrical activity, which is another dimension: arrhythmias. They are very independent and complementary.

Dr. Garfinkle I have two questions for you. One, do you think this will actually affect how treatments will be done? And two, if it does affect treatments, how significant will something like this be?

[ALJOkiller](#)

Alan: yes, we are looking at those SERCA therapies that we discuss in the PLoS CB in this light. Any advance in therapy would be a big one, since HF is a gigantic health burden in the US

Hi Alan, fantastically interesting work! Could the mathematical models be used to write an algorithm for standard hospital/prehospital cardiac monitors that would assist in early identification and intervention in these predisposed populations?

[tiredgirl](#)

Alan: hey, thanks! Yes, we hope to use our physiologically-correct EKG in a study like you suggest. There have been some prior attempts by other, for example looking at micro-volt T0-wave alternans on EKG, which has had a mixed success.

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Alan: why do you say "besides"? Those three are very powerful!

Why did you choose this particular field to focus your research?

[the\\_white\\_wolf](#)

Alan: cardiac electrophysiology is VERY mathematical. I was a math guy who didn't want to do research math. The problem of VF, the leading cause of sudden cardiac death, can be put totally

mathematically: there is this Partial Differential Equation, which is known, governing cardiac conduction. If that PDE in your heart currently has a rectilinear solution, you are healthy; if it has a periodic solution, you are very sick, and if it has a chaotic solution, you are about to die! I thought "well, this is something that could yield to mathematical analysis and modeling"

Hello, thank you for taking the time to do this. I don't know much about ECG, so I'm wondering how much information we can obtain using ECG alone? I noticed in one of your papers you described some morphological characteristics of the QRS waveform that may be representative of fibrillation risk. Are there ways to analyze ECG data in a real time quantitative manner as a predictive marker for fibrillation risk?

[fireindeedhot](#)

Alan: yes, see answer to "tiredgirl". For example, we think we can detect using characteristics of the QRS complex (eg. QRS alternans), as well as how the T-wave looks in the 12 leads of the full EKG.

Your models tend to be very detailed, consisting of many parameters (for instance the space-dependent diffusivity tensor) and nonlinear interactions. I see computation of the forward problem but not mention of sensitivity analysis and uncertainty quantification for the inverse problem of parameter identification. How confident can you truly be in the utility of your simulations in these complicated models in the face of parametric uncertainty?

[cookiemonster1020](#)

Alan: This is a REALLY good question. VVUQ is becoming a major issue in lots of sciences from cardiology to nuclear engineering, fluid dynamics, etc. Our PLoS one paper concerns the second "V" (validation) but we do not address the hugely important question of UQ. Groups at Mt Sinai (Eric Sobie) Cornell Med (David Christini) and Oxford (Blanca Rodriguez, Gary Mirams, etc.) are beginning to address this, and we will too in the future.

Hi! My Master's research project was using murine models of cardiac hypertrophy to assess the involvement of certain protein kinases in cardiac remodelling.

The thought behind the whole research project was that if we can identify proteins involved in the cascade that lead to remodelling, we could find more effective therapies to intervene in heart failure. How important has your research found this remodelling of cardiac muscle to be?

[airmaximus88](#)

the remodeling in hypertrophy has got to contribute somehow to the higher probability of arrhythmias in this pop. We would love to get a really good DT MRI image of this hypertrophy

Hi Dr. Garfinkel. Your study focuses on heart failure. Do you have any insight on the electrophysiological changes that may occur in other presentations of sudden cardiac death (e.g. hypertrophic cardiomyopathy or dilated cardiomyopathy)? Do you think some of the mechanisms may be similar or will they likely be completely different? Also, have you looked into correlating structural changes in the myocardium with electrophysiological changes in the myocardium? I know a group in LA (Dr. Debiao Li's group at Cedars Sinai) has made some spectacular advances in cardiac diffusion imaging which may be able to non-invasively image the cardiac microstructure.

[EeeFortySix](#)

Alan: we would be VERY interested in looking at cardiac microstructure changes in HF. We already have one paper on it. I'm going to get in touch with Dr. Li at your suggestion and compare notes.

Hi Dr. Garfinkel, thanks for doing this AMA!

First of all, I think the work that you've done here is astonishing. My question is: Do you think treating the altered cellular conditions in HFrEF will improve only the patients' mortality, or will it also improve their morbidity and QoL?

[LordDeathigo](#)

Alan: the biggest impact on morbidity and QoL that I see is the possibility of avoiding ICD implantation, which is a) expensive, b) highly invasive and c) requires pre-identification of the at-risk pop. ICD is so bad that several papers have appeared using ICD patients as a model for Post Traumatic Stress syndrome, that's how bad the shock is!

What impacts, if any, do levels of conductive metals in the blood stream (ie. Magnesium, salt, iron, potassium etc) have on the hearts behavior?

[davida357](#)

Alan: huge. imbalances in Mg, K, Fe etc. are major causes of cardiac arrhythmias

Where else do you see similar mathematical models being of used in medicine?

[Securus777](#)

Alan: this is a growing field. Other areas where there is already excellent work include immunology, epidemiology, development and its pathologies, circadian rhythms, molecular biology (feedback control of gene regulation). I tell my students to search "differential equations" + your favorite topic. you will probably get some hits

Hello Dr. Garfinkel!

Thank you for doing this AMA, and I really appreciate the work your lab does. However, my question is more from the perspective of a student seeking guidance.

What did you experience as undergrad/graduate student/post-doc that convinced you to pursue a career in research? Currently, I am having difficulty deciding which route I want to go down: medicine or research. I have been doing research (mainly computational biomechanics) for almost 3 years now, and really enjoy what I do. However, I have been able to work very closely with a primary investigator on not only the technical aspect of research, but the grant-writing process as well. I struggle much more with the grant-writing process, and I think would much rather down the line work as a research physician for an academic institution, where I would have the opportunity to work closely with professors and research scientists, while also being able to see the research I help with 'come to life' through patient contact and treatment.

I am considering applying to a few MD/PhD programs, though they are quite tough to get into. Is this the route I should go? I'm sure you've been through a similar process and would really appreciate you

(or any of your graduate students') thoughts! Thanks in advance, and sorry for the wordy comment!

[EulerHimself](#)

Alan: As a professor of Medicine, I'm a big believer in Academic Medicine. The kings and queens here are the MD/PhDs. However, I have to tell you that the grant-writing-and-rejection process is soul-destroying. With the current NIH policy of funding ~15% of submissions, there is terrible competition. One of my postdocs showed me an article that said that only 1 in 6 PhDs ends up with a faculty position.

Hello Professor Garfinkel!

Do you think it would be valuable to conduct a similar study in a mouse model? I myself conduct cardiology research at UCLA (with a lab you may have worked with) and this has definitely sparked my interest in studying this in a mouse model.

PS: I am currently enrolled in LS30A course with Professor Conley and its really opening my eyes to this other side of Mathematics rather than the 3 series math I've taken earlier in my academic career.

[JusticeKayle](#)

Alan: mouse is a bad model for arrhythmia research (heart is too small). Stick with LS30 and you'll be doing this sort of modeling yourself pretty soon!

Does this same line of research help detect other heart conditions, like SVT?

[kd7uiy](#)

Alan: no. SVT is easily diagnosed on 12-lead EKG