Genetic and Evolutionary Computation

Wolfgang Banzhaf · Betty H.C. Cheng
Kalyanmoy Deb · Kay E. Holekamp
Richard E. Lenski · Charles Ofria
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Danielle J. Whittaker *Editors*

Evolution in Action: Past, Present and Future

A Festschrift in Honor of Erik D. Goodman

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Dr. Erik D. Goodman, 2016

Preface

The BEACON Congress in August 2018 provided an opportunity to celebrate its founding director Professor Erik Goodman's remarkable achievements on the occasion of his 75th birthday. A number of the presentations at that 2018 BEACON Congress were specifically dedicated to him. This volume *Evolution in Action — Past, Present, and Future* combines some of these with additionally solicited contributions from colleagues and members of BEACON who could not attend the 2018 Congress.

The contributions published here range from refreshingly personal stories of encounters with Dr. Goodman, the history and achievements of the BEACON Center for the Study of Evolution in Action under his leadership, to research topics presented along the lines of the research thrust groups in the BEACON Center. These topics dominate Parts I to V of the book. An important focus of BEACON has always been education about evolution, and this is reflected in the contributions in Part VI. At our request, Dr. Goodman graciously provided us with an account of his own life story, which forms the last part of this volume.

All chapters published in this volume have undergone editorial review. Additionally, some chapters (10, 11, 17, 18, 20, 21, 23) have undergone additional external anonymous peer review at the request of their authors.

We would like to thank all contributors and reviewers for their diligent work in bringing together this exciting volume. We would also like to thank those who have helped the editors, from organizing our group meetings to bringing contributions together in a manageable LaTeX document. In particular, we thank Honglin Bao, Connie James, Stephen Kelly, Iliya Miralavy, Ian Whalen, and Yuan Yuan for their invaluable help.

East Lansing, Michigan
February 12, 2019

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Part I
The BEACON Center for Evolution in Action

Chapter 1
2010: A BEACON Odyssey

Richard E. Lenski

Abstract Life often follows a peculiar and winding path. This paper connects some events in my life with how I got to know Erik Goodman and how the BEACON Center for the Study of Evolution in Action came into being. Some of these events are from memory, while others were recorded in emails. Of course, BEACON has had many participants and so there are many narrative threads, which together are woven into the tapestry of BEACON and our lives.

Key words: Avida, BEACON, chance, contingency, Erik Goodman, experimental evolution, science funding, synergy

1.1 Life's Winding Path

Life often follows a peculiar and winding path. That's true in our individual lives, in the rise and fall of civilizations, and in the history of life on Earth. Understanding what propels an evolving population along a particular path has been a major focus of my group's research. In particular, we study the repeatability of evolution, the roles of chance and necessity, and how outcomes are sometimes contingent on prior events that seemed inconsequential when they occurred [4, 5, 8, 10, 13, 16, 17, 18, 20].

This paper presents a related story, albeit a personal one that connects some events in my academic life with how I got to know Erik Goodman, and how the BEACON Center for the Study of Evolution in Action came into being. Some of these events are from memory, while others were recorded in emails. I'll quote from some of those emails for posterity's sake. I must emphasize that this is *my* story, not *the* story. An important aspect of any complex organization like BEACON is that

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so many people have been instrumental in its genesis and success. Thus, there are many unique and winding narrative threads, and together they are woven into the tapestry of BEACON and our lives.

1.2 A Squash Match

My thread begins on a squash court in 1994. I was playing in a recreational league and had a match with Wolfgang Bauer, a colleague in the Department of Physics and Astronomy here at MSU. I forget who won our match, but no matter—it turned out to be a huge win *off* the court. We chatted about science after playing, and Wolfgang said that he had a visitor coming to his lab who would give a talk on "Self-organized criticality in living systems" or something like that. Self-organized criticality was a fairly new concept then [3], but I had read about it in the popular-science press. An example of a system that exhibits self-organized criticality is a sand pile. Drop one grain after another on a pile and not much happens until, suddenly, one more grain triggers an avalanche that changes the shape of the entire pile. The subtle internal structuring that leads to the sudden transition is what physicists had dubbed self-organization.

When Wolfgang said the talk would be on self-organization and evolution, I might have rolled my eyes. Or at least I thought to myself that this talk might be a physicist trying to explain how evolution works, without understanding natural selection. But I said I'd attend, and I did.

The speaker was Christoph Adami, who was then a postdoc at Caltech. Chris gave a lively and interesting talk about his experiments with Tierra—an artificial living system in which computer programs replicate, mutate, and compete inside a virtual world. And he certainly understood natural selection, so my worry was unfounded. A couple of years earlier I'd read about Tierra in a News and Views piece by the evolutionary biologist John Maynard Smith [15], and I had been intrigued by the idea of such a fast-evolving and novel system.

Back to Chris's talk on self-organized criticality: in one slide that especially caught my attention, he showed a step-like increase in the fitness of an evolving population (figure 1 in [1]). Chris interpreted these dynamics as mutations raining down on the programs, with each mutation having little effect until one of them triggered an adaptive transition—much like grains of sand falling inconsequentially onto a pile until one of them triggers an avalanche. The analogy was intriguing, but I thought it was wrong, or at least incomplete—I thought there was a simpler explanation, which I'll get to in a moment. I was excited by this slide because in our work with bacteria we saw similar dynamics—sudden jumps in the bacteria's fitness punctuating periods of relative stasis (figure 5 in [13]).

My interpretation was that these dynamics were caused by the rise of lineages with new beneficial mutations. Each mutant lineage begins as a single individual, and it spreads more or less exponentially according to its fitness advantage (if it survives loss by random drift). But despite its exponential increase, for a long time

the mutants remain a minority and thus have little effect on the *average* fitness of the population. Only when the mutants become sufficiently common does one see an appreciable rise in mean fitness; and then the mean changes so quickly that the overall trajectory has a step-like appearance. Besides his intelligence and enthusiasm, one thing that I immediately liked about Chris was that, as I explained my interpretation after his talk, he was not defensive and, instead, was receptive to this alternative explanation.

Chris and I corresponded occasionally after his talk, and I gave him feedback about some projects he planned to pursue using Avida, a new program that he was developing to study evolution in digital organisms. Chris also told me that he was working on a book about artificial life, based on a class he was teaching on that subject. He said that he would send me a copy when his book was published.

1.3 The French Connection

My family and I packed our bags and moved to Montpellier, France, after the summer of 1997. My wife Madeleine had spent half a year as a child in Paris when her father took a sabbatical, and she wanted a similar experience for our kids. I knew some evolutionary biologists in Montpellier, but I had no specific plans for new research. Instead, I hoped that some time away from MSU would allow me to catch up on a backlog of writing.

Chris Adami's book, *Introduction to Artificial Life*, was published early in 1998, and as promised he sent me a copy [1]. I remember finding it in our mailbox one afternoon. Along with the book, there was a disc in a sleeve at the back that contained the Avida program. I found an old email from February 24 of that year:

> Bonjour Chris, I just got the book and CD, which look very nice!!

(Only now, while writing this piece, did I realize that the same day I received Chris's book happened to be the tenth anniversary of the start of the LTEE, my long-term evolution experiment with *E. coli.*) Once I started reading the book, I couldn't put it down. Besides being absorbed by the information in the text, I was eager to give Avida a spin. The software ran flawlessly, and soon I was running little experiments and seeing artificial life evolve before my eyes.

In short, I was hooked. I remember telling Madeleine, only half in jest, that maybe I should call my group back at MSU and tell them to close the lab down, that I had switched from evolving microbes to evolving programs. On Madeleine's advice, that didn't happen, and my lab continued its exciting and productive research on the microbial side. However, I think that more than half of my own attention over the next several years was on Avida. I wrote Chris again on March 2, just six days after receiving his book:

> I spent this weekend reading your book from cover to cover and beginning to play around with the avida program. In short, I think the book and program are quite fantastic. You

> should be very proud indeed! ... I have 101 ideas for cool experiments – so many, in fact, that my head is spinning.

The next day, I wrote the book-reviews editor at the journal *Science*:

> I know that Science does not publish unsolicited book reviews. Therefore, I am writing to ask whether you would consider asking me to write a review of a fascinating book and companion CD. The book is titled "Introduction to Artificial Life" ... After I picked it up, it was hard to put the book down, and I did so only to explore the computer program that comes on the CD. That program quickly and simply demonstrates the real-time evolution of programs that compete for CPU time inside a personal computer.

The editor invited my review, and 11 days later I sent a draft to Chris for his feedback. (My speedy writing about something so interesting and fun as Avida was balm for my soul. In the intervening period, a dear young friend had died, and I flew with one of my children to California for the funeral.) Chris responded that same day:

> I am flattered. In fact, I don't feel the need to change anything in your review (except maybe correct that the official abbreviation of the California Institute is Caltech, not Cal Tech). Also, I was wondering whether there is any way we can give some credit to my graduate student Charles Ofria, who wrote all of avida ...

Those changes were made, and my book review [9] was published on May 8, not long before it was time to return to Michigan. I ended my review with a question about generalization, a nod to a great French biologist, and a look to the future:

> [One] may reasonably ask whether results can be extended to real organisms. In extrapolating from the genetics of bacteria to animals, Jacques Monod is said to have quipped that "What is true for *E. coli* is also true for elephants, only more so." Is what is true for avidians also true for real organisms, or is it less so? It will be interesting to see.

1.4 Strange Creatures and Fun Science

While I was writing the book review, I also ran experiments with Avida. We often think of scientific experiments as carefully planned exercises with explicit hypotheses and precise methods, data collection, and analyses. These are important parts of science, of course, but the process often begins another way—namely, informal experiments that involve *playing* with a system that has caught one's fancy.

In my early experiments, I evolved some strange creatures whose behavior I could not understand. On March 15, I wrote Chris:

> I also saw some strange, persistent genotypes ... They cannot replicate themselves, but are evidently replicated by (or, alternatively, repeatedly spun off from) closely related programs ... Moreover, when I seeded these 'parasites' into an empty lattice – and having set all mutation rates to zero! – some (but not all) of them spun off their self-replicating relatives spontaneously. Weird, huh?

Chris replied that same day:

> I think we've seen that. We have a pretty good idea about what's going on there, and it is definitely 'normal' behavior. I'll let Charles comment on that.

Charles Ofria understood the inner workings of Avida better than anyone. I sent Charles the genomes of what I called a "gallery of weird creatures" to investigate.

Over the following weeks, months, and years, my role grew from discovering weird creatures. Although these curiosities were interesting, and some of them might even have relevance for biology, I thought that they would impede understanding and more rigorous experimentation. Therefore, I suggested to Chris and Charles that the user should be able to turn off these complications "in order to have simpler scenarios to analyze and test."

1.5 Synergistic Science

I also pondered what experiments I most wanted to perform using Avida. Santiago Elena (then a postdoc in my lab) and I had recently published a paper in *Nature* titled "Test of synergistic interactions among deleterious mutations in bacteria" [7]. The point of that paper was to test one of the main hypotheses for the evolution of sexual recombination. According to that hypothesis, sex could be advantageous for eliminating deleterious mutations, provided that genotypes with multiple deleterious mutations tend to be less fit than expected from their individual effects. Santi performed experiments to test the assumption that harmful mutations tend to interact synergistically by generating 225 *E. coli* mutants that had one, two, or three random insertion mutations, and then competing each mutant against the unmutated progenitor to estimate its relative fitness. Although the average fitness declined as the number of mutations increased, there was no tendency for synergistic interactions.

What might a similar experiment with Avida reveal? Would it support our findings with bacteria, or would it instead provide evidence in favor of the hypothesis of synergistic interactions? The experiments and analyses seemed straightforward. And with Avida, one could have much greater statistical power, with more mutants in each class and more mutations in the most highly mutated classes. On April 13, I wrote Charles and asked for tools that would help us perform these experiments in Avida:

> I would like to be able to take a given creature and generate any number of mutants derived from it. Each mutant genotype should have exactly N (e.g., 1, 2, or 10) random mutations ... I would like to be able to take a specific pair of mutants derived from the same progenitor (as above) and introduce all of their mutations together into the same creature ... I would like a new routine that allows me to take a given genotype, inoculate it into an empty grid, and obtain [its] fitness [when] mutation [is] "turned off" ...

Charles responded the same day. He had already implemented a "landscaping" tool (as in fitness landscapes), one

> where you can either ask it to try ALL possible mutations up to n steps away, or to sample them ...

He thought everything else I wanted could be done as well. He also had a request:

> I'm not sure when you'll be back in the US, but if you have time I wouldn't mind taking a few days at some point this summer to come to Michigan and work more directly with you.

We continued to correspond as Charles developed the necessary tools, and together we worked on details of the experimental plan. On May 12, I emailed Charles an ambitious plan that involved examining over half a million mutant Avidians. Charles replied the next day, making it all sound so easy:

> No problem ... Sounds good ... Currently it takes about 1 second to run about 500 genotypes through a test CPU.

On July 3 he sent an update, saying things were proceeding well and he was expanding the scope of a key analysis by 10-fold. On July 13, I received by fax (remember those things?) a set of figures with preliminary data. As I'm prone to do, I replied with questions and asking for additional analyses. And as Charles is prone to do, he proposed to increase the scale of the experiment even further.

We also arranged for Charles, Chris, and Travis Collier (a Caltech undergrad working with them) to visit MSU in early August to work on this, our first, paper. I don't have emails from those days because they were here visiting, but as I recall we spent about 16 hours a day for several days holed up in a small office with a whiteboard and a computer—Charles and Travis tweaking the Avida software and running experiments, and Chris and me hashing out how to parameterize the effects we were trying to measure. Soon Chris was sending me various models fit to the data. I replied by suggesting an alternative model, and Chris wrote back triumphantly—and with his customary enthusiasm—on August 26:

> The new function fits the data perfectly! I remember now that I had suggested this form earlier (in the car when we were driving to the restaurant) but for some reason decided that it would not change anything from the quadratic fit. Obviously that is wrong ... There is very little (actually, none at all) doubt that this is the way to fit.

Things slowed down a bit after that, as I settled back into microbial research, faced deadlines that had accumulated while I was on sabbatical, and both Chris and I began a semester of teaching. But on March 10, 1999, I wrote Chris and Charles, after I had begun to convert our results into a paper:

> I've gotten so excited thinking about Avida that I'm back to working on the "epistasis" paper even though it is only about 10th on my must-do list ... Maybe I really should close my bacterial lab!

I had some questions about details of methods and requests for more polished figures, and I proposed we submit the paper to *Nature* "because it echoes issues from our E. coli paper there." On March 20, I sent them a draft of the paper. After a few rounds of editing, we submitted it in early April.

The reviews arrived on May 21, and I wrote with considerable excitement to Chris and Charles:

> The cover letter and two reviews are on their way. As you read over them, you'll see how favorable the reviewers were! There really isn't that much to do ... My hope is that we can get a quick acceptance and be able to list this manuscript as "in press" on our proposal.

> That would lend some extra credibility to the Avida work for microbiologists who might not fully understand or sympathize with digital microbes! So far, I've been working on reorganizing the abstract and next two paragraphs to fulfill [the editor's] instructions. I've also changed the title and elsewhere to avoid the jargon-ish "epistasis" as much as possible, instead talking about the form of interaction more generally.

The paper was revised and accepted for publication on May 27, and our first collaborative project—"Genome complexity, robustness and genetic interactions in digital organisms"—appeared in *Nature* that August [11]. We had evolved 174 Avidian progenitors; then, starting from each of those progenitors, we obtained the relative fitness of every possible mutant with exactly one point mutation and a million or more mutants with two through ten mutations; and we analyzed tens of thousands of two-mutation recombinants derived from each progenitor. We observed frequent interactions between mutations (epistasis) including many cases of synergistic epistasis, but we saw no excess synergism relative to the alternative. In short, the results were qualitatively consistent with what Santiago and I had reported two years earlier for *E. coli*—but with the far greater replication and precision that Avida provided.

In the meantime, Charles, Chris, and I were discussing possible experiments to address other questions, and as implied by the reference above to "our proposal" we were thinking about how to support an expanding research program. I had also been working with Charles (and behind the scenes) to see whether we could get him to MSU after he finished his Ph.D. at Caltech.

1.6 Dollars and Sense

On January 14, 1999, the NSF—under the leadership of Rita Colwell, a distinguished microbial ecologist—issued a call for proposals:

> As a first step in a longer-term effort to understand the nature and dynamics of biocomplexity, NSF announces a special competition to support integrated research on the functional interrelationships between microorganisms ... and the biological, chemical, geological, physical, and/or social systems that jointly comprise complex environmental systems.

So that afternoon, I wrote Chris and Charles:

> There might be something here for us, say a series of expts comparing avida and ecoli under a variety of evolutionary scenarios ... Notice that multi-institutional collaborations are favored, with a focus on "biocomplexity" and microorganisms.

A pre-proposal would be due in mid-March. Charles wrote back on February 6:

> I finally had time to sit down (and grab Chris!) and really go through the Biocomplexity program announcement. As Chris put it, they've only come one step away from actually writing our names in there! ... Obviously we should play off of the three approaches we take. You do experimental work in actual biological systems, I model those systems allowing much easier statistical study, and Chris applies a theoretical approach using statistical mechanics and the like. So we can all come at the same problem from very different perspectives and really work off each other. Especially nice is the fact that they're looking for

> collaborations from more than one university, and from more than one field ... I can't afford to take off too much time at this point though. Speaking of which, FYI, my thesis defense is set for May 13th ...

As a graduate student, Charles wasn't eligible to be co-PI on the proposal, though he was listed as a key participant. Also, I thought we needed more microbiological expertise. So I contacted Margaret (Peg) Riley, a talented molecular evolutionist (then at Yale, now at the University of Massachusetts, Amherst), about teaming up with Chris and me as a third co-PI. Her lab would sequence some genes from the LTEE bacteria to get a handle on the rate of genome evolution (this was many years before it was affordable to sequence a set of complete genomes). Peg was interested, and Chris sent around a "draft of a draft" of the pre-proposal on March 1. After an intense week of back and forth about the science, we submitted the pre-proposal on March 8, a full week early. On April 19, we heard that the NSF invited us to submit a full proposal, which would be due in mid-June. In the meantime, our paper using Avida to study genetic interactions had been accepted by *Nature*, so we could cite it as "in press" in the full proposal, and Charles defended his dissertation at Caltech.

After overcoming a bug or two in NSF's online submission system, we submitted the full proposal on June 11. Charles moved to MSU in early August to begin a postdoc, and on September 8 we got the news that our biocomplexity project would be funded. One of the first orders of business for Charles was to purchase and configure a Beowulf cluster, so that we could scale up our Avida experiments. That cluster was placed in the basement of the Plant and Soil Sciences Building, which is the building where my lab was then. I look back on the biocomplexity grant as a sort of dry run for BEACON, albeit on a smaller scale. It had interdisciplinary research, multiple institutions, proven collaborations, and lots of ideas for moving forward along with intense competition to get there. Many of the ideas panned out, too, as evidenced by exciting papers including, on the Avida side, demonstrating the survival of the flattest [19] and the evolutionary origin of complex features [12], and on the bacterial front, identifying beneficial mutations [6] and starting to characterize the rate of genome evolution [14] in the LTEE. Two other important developments during that period were Rob Pennock (who I had just met at the ALife VII meeting in Portland) moving to MSU in 2000, and Charles becoming a tenure-track faculty member in computer science in 2002.

1.7 Best Lunch Deal Ever

In 2003, the NSF issued a call for Science and Technology Centers (STCs), which they do only every few years. I had moved from UC-Irvine to MSU to join one of the first STCs: the Center for Microbial Ecology (CME), directed by the amazing Jim Tiedje. On March 15, I wrote Charles:

> I think you should consider going after an NSF Science & Technology Center – that's what got the CME going at MSU and thus scientifically why I came here. With you [and others] defining a field of, say, digital evolution or genetic programming – and by also pulling

> some additional players on the biology side including me [and others] – I think you'd have a reasonable shot at a very important center-level grant ... The tie-in between the basic science and industry would be very appealing to both MSU and NSF. I suggest you think seriously about this, and pull together a group of your colleagues to see if they are interested. You'd probably want someone a bit more senior to be the director – Erik G strikes me as one possibility.

Charles was too early in his career to direct an STC, and I didn't like the idea of being an STC director myself—how Jim Tiedje could simultaneously direct a successful STC and run an extraordinarily productive lab was beyond my understanding.

So Charles and I began to make plans. He responded with a proposed center name of "Experimental and Applied Evolution." I was concerned that the proposed center be seen as sufficiently distinct from the CME:

> I think you should consider an explicit focus on the computational side of things, rather than experimental evolution in the broader context. My reasoning is that NSF likes to spread things around and things that come too close to the CME – such as including microbial evolution – might actually get in the way of success. So definitely have ties to biologists, and to biological systems, but make computer science the focus. "Genetic programming and digital evolution" might be the title ...

But Charles wisely pushed back against my suggestion to narrow the center's focus:

> Erik sounds quite keen on the STC idea and would like to meet (possibly for lunch) to talk more about it. Would you be interested/available to join us some time this week? Also, I do see your point about not wanting to choose something too close to the CME, but I think that as long as microbes aren't the focal point ... the rewards will be worth it.

So Erik, Charles, and I went to Sindhu's restaurant for lunch, and we had a great discussion. Charles and I proposed to Erik that he would be the director of the hoped-for STC. Erik was interested, but he said he needed some time to think about it. After just a few days, Charles told me Erik had said yes, so that was the best lunch deal ever!

1.8 Sunken Treasure

Before he could firmly commit to being director, Erik had to meet with MSU administrators about disclosures and recusals related to his company, Red Cedar Technology. It took a few weeks to get meetings with all of the higher-ups, but everything worked out. Meanwhile, it was time to make plans and build a team. On April 11, Charles wrote with a proposed set of thrust areas for the center:

> 1. The Universal Foundations of Evolution. The goal of this area is to understand general principles that govern all evolving systems, primarily through controlled experiments. Much of the work being done in Avida or E. coli would fall here ...
> 2. Tools and Methods for Directed Evolution. In this area, we would be harnessing the principles that we discover in the first area in order to create tools that will make things evolve in directions that we want ... A lot of Erik Goodman's work on multi-level GAs would fit here ...

> 3. Applications of Evolution to Real World Problems. Here, we take the tools constructed in area two, and actually do something useful with them. Be it building parts of cars as Erik does, or evolving proteins ...
> 4. Bringing Evolution to the Masses. Okay, this one needs a better title, but basically it's the education component. I think that the education portion of this project is so strong, that it warrants being brought front and center with its own thrust area ... I think we could put together multiple courses, but in a modular fashion where they could be mixed and matched as needed ...

In late April, though, we ran into a problem. The NSF deadline for submitting the pre-proposal was June 3, but MSU announced they would need a draft by May 7 for an internal review, because each institution could submit a maximum of five pre-proposals to the NSF and the number of interested groups at MSU exceeded that limit. The days that followed were hectic but productive: writing text that would dovetail our ideas with the NSF goals, drafting budgets, identifying partners and participants, collecting bio-sketches, preparing an organizational chart, and assembling it all. I realized what a superb leader Erik was—dedicated, organized, even-handed, timely, and a funny and nice guy on top of all that! In the wee morning hours of May 7, Erik sent a revised org chart and text, along with these words:

> Going to bed ... coffee has worn off and my tail is draggin'.

That afternoon Erik submitted our pre-pre-proposal to the MSU administration.

On Thursday, May 15, we were told that our pre-pre-proposal was selected to move forward, so we had to get back to work in order to submit a pre-proposal to NSF in a little over two weeks. By Sunday, Erik was sending around a section on industry involvement, having already lined up several companies interested in becoming affiliates. The next couple of weeks were a blur of meetings, emails, writing, editing, and polishing. Decisions had to be made about font size, and what points would have to be cut in order to squeeze into the allotted page limit. In the evening of Saturday, May 31, Erik sent an email with the subject "Shrunken summary attached." We were coming down to the wire. Emails and attachments with names reflecting the various sections of the proposal were flying among us every day and almost around the clock, including an edited summary from Rob Pennock on the morning of June 3, the due date at NSF. That afternoon, it was submitted. We would have to wait until October to hear whether we were invited to submit a full proposal for our center, which we'd named the Center for Applied Evolutionary Dynamics and Computation.

The NSF's decision arrived on October 17:

> Review panels of experts met recently at the National Science Foundation to evaluate preproposals submitted to the above referenced Program Solicitation. I regret to inform you that your preproposal was not among those invited to submit a full proposal.

I wrote Erik some words of solace:

> Well, the good news is that we don't need to do all that additional work! Reviewer #2 got it right, by the way, so read that one to feel better ... I'm sure there was terrific competition, and we probably didn't fit into any easily definable area ... I want to thank you personally for your tremendous leadership on this project ... And I look forward to working with you in other ways to develop our vision further!