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Editorial

Eric Davidson: Master of the universe

> "Development of Western science is based on two great achievements: the invention of the formal logical system (in Euclidean geometry) by the Greek philosophers and the discovery of the possibility to find out causal relationships by systematic experiment (during Renaissance)"
>
> Albert Einstein (1953).

1. Master of the universe

Eric Davidson was my closest friend, my most important scientific collaborator, and my mentor. As we will have to carry on without him now, essential lessons I learned from him come to mind. Eric taught us about the importance of focusing on scientific substance; advertising, packaging, selling were discarded as the preoccupations of a lesser intellect; substance defined as pressing unresolved technical problems that we are privileged to work on as part of our academic life. When we tarried on other topics, his urgent tone returned us to science. His toughness was legendary — Master of the Universe (MOTU) indeed – regarding focus, committing to getting things done at the highest possible technical level, spending time talking about important things — science, philosophy, behavior. Complaining was forbidden, and he had a flair for disarming it. "*Serious people do things seriously*," he wisely said. In his later years, mobility was a big problem; it was painful to see his legs fail him. These once were the legs of a muscular football player and gym enthusiast: *"use it or lose it"* he used to say, paraphrasing the dictum "form follows function." Ultimately, sadly, he could only move by scooter, yet not once did I hear him even mildly complain. His dexterity with stopping negativity in its tracks was a characteristic of his rock-solid confidence and optimism, expressed at times with an almost musical laugh, a dose of Eric-medicine accompanied by warmth and charm that cure all doubt. I miss Eric's laugh; that unique incredible, long, room-filling, equally spaced laugh of his. His toughness as a teacher enticed us, and we thought it our academic responsibility to speak up, to express our critical opinion, even if it made us uncomfortable; wasting time in the comfortable land of correctness is not what serious people do.

Our 15-year friendship spanned intense chapters in my life, including some of my most exciting scientific work, my life in private industry at Celera Genomics, my job search and transition from industry to academia via Eric's Lab at Caltech, and my first ten years at Brown University.

Eric was "embedded" throughout. Eric's search for sea urchin transcriptions factors gained excitement when he received the first assembly of the sea urchin genome done by my group at Celera, based on the low coverage genomic sequence reads publicly available in 2004. Then, with Applied Biosystems (AB)'s president Michael Hunkapiller, we presented a gift to Eric that made him very happy: the latest AB Sequencing Machine with reads about 800 DNA base pair long, the instrument that enabled the genome era. At the 2004 AB Retreat, Eric was the keynote speaker. During my job search after Celera folded, Eric's toughness and solid-gold advice was a source of strength through which I could recharge. Eric predicted in early Spring 2005 that I would end up at Brown. Again and again, unlike anyone else I knew, Eric demonstrated that he could predict the future.

2. Celera

I met Eric in Tokyo. It was in April 2000 and I was attending the RECOMB conference (International Annual Conference on Research in Computational Molecular Biology) just after joining Celera Genomics as its freshly minted Senior Director of Informatics Research. I carried "Uncle Craig Wants You!" posters — with the traditional Uncle Sam image — to help recruit bioinformaticians for the company. Eric was the conference's keynote lecturer. *"You are asking such good questions,"* Eric told me when, after his lecture, I met him to discuss cis-regulatory genomics. He mentioned that he wanted to talk to Craig Venter about the possibility of Celera sequencing and assembling the sea urchin genome, as he had no hope that the Human Genome Project (HGP) would ever do so. (To say that Eric had no kind words for the HGP leadership duo is an understatement.) The context of the genomic science events of that period, with its high highs and low lows, mirrors my own journey, and I was fortunate to feel the power of Eric's friendship throughout.

Eric's visit to Celera in the Fall of 2000 seeded plans for my visits to Caltech – about two a year for the next 15 years! During my earliest visits, Eric would give me full lectures on cis-regulatory genomics and developmental gene regulatory networks, about the experimental biology of cis-regulatory analysis, his mastery of the cause–effect inference through systematic experimental perturbations, where the Davidson Lab has been, most famously, the master of the universe of this experimental domain. His extraordinary tutelage – five years of lecture-learning and then wet-lab experiments – prepared me for writing our first collaborative paper.

Coincidental with Eric's visit at Celera, I had a graduate student intern, Vladimir Filkov (now professor at University of California, Davis), who was interested in "gene networks." I suggested that

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we pick an unresolved problem to work on, and we began to read through a pile nearly 20 papers high on my desk. One by one, Vladimir presented the papers to me, and one by one they were rejected as unexciting – until we reached the bottom nine, which were technically intimidating biology papers by Eric Davidson! I want to credit Vladimir, who was then a Stony Brook University graduate student in computer science who also had a strong background in chemistry: Our discussions on those papers were instrumental to my initial understanding of the Davidson papers and my sense of depth and excitement about them in an area totally new to me – experimental molecular biology.

With the sequencing of the sea urchin genome, the reads were made available on the Baylor University website, and Eric was eager to start his search for transcription factors. My Informatics Research group was the leading industry group in genome assembly technology at that time, so we used the Celera Assembler to construct a first sea urchin genome assembly for Eric to look at. Two years later, in 2006, with significantly more coverage, the first high-quality genome assembly of sea urchin was done at Baylor and the paper describing this landmark achievement was published in *Science*. Eric Davidson was the chief scientist of the project, and his collaborators, including myself, were among the 270 coauthors. In the same issue of *Science*, we also published one of the first complete animal transcriptome papers, "The transcriptome of the Sea Urchin embryo." This was a six-author paper; my Brown University Lab provided one-third of the funding.

The Celera experience was without question the most exciting scientific time in my career. The confidence two presidents, Venter and Hunkapiller, had in me and my delight in working closely with them left me feeling as though I had graduated from their "leadership schools." Throughout my ups and downs at Celera, Eric, with his characteristic rock-solid confidence, remained close. Together we observed the twilight of the private company that went from unprecedented height – Venter being celebrated by President Clinton at the White House for "The Sequence of the Human Genome," considered the best scientific achievement in 25 years – to the disintegration of the corporate structure that began with Craig's departure. Then, Hunkapillar, President of Celera's corporate sister Applied Biosystems, took my Informatics Research group under his wing. Hunkapillar was a famous Caltech graduate who co-invented the sequencing machine that was instrumental to ushering in the genome era. The winds of change next blew through Applied Biosystems when its unapologetic CEO who fired Venter, replaced Hunkapiller, a most able president, with an unqualified outsider from another industry.

Eric's knowledge of history was impressive (I believe he could have taught classes in a history department), so he easily recognized the signs of dictator-like power in private industry as well as in the Public Republic of Genomics. Firing people at will without regard for their impressive qualifications, and retaining full control through clever stratagems for almost two decades are signature actions of dictatorial leadership. Coming from Romania, I, too, knew a dictatorship duo when I saw one.

With Eric's inexhaustible guidance, I began to transition from private industry to academia. Caltech/Davidson Lab, where I had a visiting position as senior associate in the Division of Biology, became my base of operations.

3. Caltech

My office was in the "pain room," a lab in the large Davidson Laboratory in the basement of the Kerckhoff building. Fully emerged into the experimental setting, the room has a number of large instruments as well as a lab technician's desk. I tried to bribe Eric to swap "my office" with one next to his, used just to store old computers. But Eric, my best friend, did not give in, for long ago it was the office of Eric's mentor, Nobel laureate Max Delbruck, renowned physicist and pioneer in the laws of quantitative molecular biology.

During my visits to Caltech, we would always dine one evening at Celentino's, a favorite of Eric's. Almost always we were joined by Ellen Rothenberg; other times Jane Rigg would join us. The brilliant Ellen was always a charming partner in the passionate intellectual arguments we would have. Eric tells stories at such dinners. One time I got worried: Eric had an extraordinary memory. He knew my cell phone number without looking it up, and there was never a time when he said "I am busy now, I have to call you back" and failed to call back. I am hopeless in such matters. With his Lab — its 20–30 scientists, students, faculty, technicians, managers and results streaming in constantly from more than 10 major concurrent projects — I guess one needs to evolve a good system for memory and recording. I admired his.

At one such dinner, the unexpected happened: he repeated a story about Delbruck. One day Delbruck said "Eric you need to learn some math." Eric responded (I am sure, with his MOTU confidence), "I know mathematics!" Delbruck said, "I will have my postdoc teach you some math." Eric then said "OK." End of the story. The next morning, after much reflection on my part about the two servings of Delbruck at dinner, I told him: "OK, Eric. I take the Delbruck–Davidson challenge." With that, Eric instructed two of his senior lab people to start teaching me experimental molecular biology. Chiou-Hwa (Cathy) Yuh, at that time senior postdoc in the lab (recognized as the most able experimental postdoc in the Lab history, now professor at the National Health Research Institutes, Institute of Molecular and Genomic Medicine, Taiwan) introduced me to PCR and in-situ hybridization. Under her supervision I began doing week-long experiments, starting with fertilization and followed by gene expression measurements of a dozen genes. Andy Ransick, the Lab's senior experimental scientist, taught me microscopy and basic experimental tasks, including building the glass tube mouthpiece – a basic tool of every wet lab scientist – used to catch sea urchin embryos, about 200 at a time, and depositing them in tubes. Discussions with Andy Cameron, the senior bioinformatician scientist in the Lab, rounded out my Davidson Lab experience within its complex palette of databases of genomic information. Eric wanted to grade my PCR results at the end of the week. Only once did he give me an A.

Of my five papers coauthored with Eric, the most meaningful in my emotional bank acount, with just the two of us as co-authors, was our first – "Logic functions of the genomic cis-regulatory code" (Istrail and Davidson, 2005). Eric forcefully brought to biology "logic" as in Boolean logic laws, and the evolutionary acquisition of higher order logic as we move up to higher order animals. I was lucky to be one of Eric's three logician sidekicks, following Hamid Bolouri and continuing with the brilliant Isabelle Peter. With Eric's writing clarity, here is the message of our first paper:

"Comparatively speaking, the diversity or complexity of the genomic regulatory code is going to be greatly less than the diversity of the biochemical operations that execute each type of function (that is why it is properly referred to as a code)… Tackling the genomic regulatory code head on is liable to be a more direct avenue to learning what it says than by dissection of the particular biochemistry operative in every different CRM. To reverse the argument, the mechanistic biochemical exploration of cis-regulatory function will indeed be much facilitated if it can be couched in terms of an elemental functional CRM repertoire."

My search for employment as a full professor of computer science started in the summer of 2004. With the Celera feather in my hat, I was a highly ranked candidate who was greeted with anticipation, and at times a university official would express high

admiration for Celera. Yet though I had a number of interviews at great universities, no offers were forthcoming by fall. I came to the realization that transitioning from private industry to academia was no trivial matter, and I was having difficulty adjusting to what was expected.

I talked with Eric about my blues. *"If you want to feel sorry for yourself go back to your pain room,"* he said, then suggested that I hone my interview skills with members of his Lab. The members of the Davidson Lab were a delight: the cool-under-fire, extraordinarily resourceful laboratory manager Jane Rigg, who provided great help to all of us; the doctoral and postdoctoral students of exceptional talent, academic brothers and sisters of Davidson lineage indeed, all nurtured by Eric; the managers, system administrators and laboratory technicians, including "my office" mate in the pain room, Jina Yun – all great friends to have.

Eric, Mike Waterman, and Pavel Pevzner, awakened me to the realization that my interviews, with their industry-style focus on multiple problems using more than 100 Powerpoint slides, bombed on an academic audience. Pavel put it best: "Just one topic; go in depth and show that you can teach. All slides should have the same font, all aligned. All perfect. The Perfect Talk!"

I took their critique to heart and camped out for a month in my basement, working on my Perfect Talk. And perfect it was: Each interview in winter and spring yielded an offer, including one from Brown, as Eric predicted. Brown University was Sea Urchin country indeed, due to professor Gary Wessell sea urchin laboratory. We celebrated my success in the coffee room of Eric's Lab. The first champagne cork hit the ceiling; my name was inscribed next to the mark it made – a Davidson Lab tradition to celebrate the many biological discoveries and successes launched there, a place where the sky's the limit.

4. Brown

Having successfully transitioned to academia, my years of research collaborations with Eric reached the fruitful stage of publications. I coauthored four papers with Eric – two in *Science* (Worley et al., 2006; Samanta et al., 2006), one in *Developmental Biology* (Istrail et al., 2007), and one in *Proceedings of the National Academy of Sciences* (Nam et al., 2010). Our research flourished and our discussions broadened to include teaching, grant writing, and philosophy of life, academic and otherwise (Fig. 1).

Fig. 1. Eric Davidson and Sorin Istrail, 2005.

The first grant proposal emerged from many discussions with Eric about a clear bioinformatics agenda for my Lab at Brown. I had hoped that the proposal would enable us to collaborate as academic peers, and that my Lab would function as a bioinformatics arm for his. As always, the challenges Eric formulated were of a technical difficulty and elegance that defined him. He was a very tough, critical scientist, the most such person I had the pleasure to work with. He could articulate at a glance a bottleneck and a longstanding difficulty that required new mathematics or algorithmic advances to overcome. I love hard computational problems, but his were difficult in dimensions that were different than my usual computer science and mathematics, an exciting form of Eric-energy for my creativity.

4.1. The CYRENE Project

My work at Brown has been funded by the National Science Foundation, starting with a 5-year grant "The cisGRN Browser and Database: cis-Regulatory Information Behind the Network." Eric wanted me to work on the construction of a database of causality-inferred DNA regulatory regions structure of genes, validated by the most stringent experimental test, the cis-regulatory analysis. This experimental technology became known in my group as the "Davidson criteria," and is defined, in short, as DNA mutagenesis followed by loss of function in vivo. The (parts of the) regulatory regions of genes that were validated by Davidson criteria were to be included in the cis-Lexicon database of genomic cis-regulatory architectures. These cis-regulatory architectures of DNA regulatory regions of genes are published in research journals through experimental papers that describe cis-regulatory analysis experiments and report the DNA regulatory sequence content as well. Eric's challenge to me in 2005 was to create the first such database of cis-regulatory architectures, *as complete as possible.* And so the CYRENE Project was started and funded by NSF a year later. It funded the full five years of the Ph.D. thesis of Ryan Tarpine, and a small army of annotators – 25 Brown biology and computer science undergraduates — and enabled the teaching of four generations of the CYRENE project gene annotators by the biology leaders in the group — Kyle Shutter (now an entrepreneur in Kenya), James Hart (now graduate student at Berkeley) and Tim Johnstone (now graduate student at Yale). Seven years later, my Lab has cataloged over 600 genes with resolved genomic cis-regulatory architectures in eight species: human, sea urchin, mouse, rat, fruit fly, worm, chicken, and zebra fish. To understand intuitively the scale and magnitude of the project and the nature of bioinformatics challenges involved, I would start by examining a problem familiar to all of us, from Apple and Google.

There is something extraordinary concerning Siri, the automatic assistant feature for the iPhone. The speed with which a question, expressed in full sentences, is answered by Siri is just ridiculous, a "spooky action at a distance" kind of thing. You've barely finished pronouncing (with your Romanian accent or not) the last phonemes of your question yet Siri already has the answer. How is this possible? Google does something else to be that fast, not parsing words and calling programs accordingly, but what?

Let us ask a type of question that Eric would ask. How about if we have *the database of all the questions and queries* ever asked on Google, together with their answers? Then instead of doing the parse-and-call-subroutines approach, you map your question to questions already asked and give the answer recorded with it that way. This approach involved a magnitude of vision that only brave thinkers such as Eric would have: the set of all questions ever asked on Google. Obviously, people ask the same questions again and again, and therefore it is conceivably easier to get the repeated answer faster. Rooted in enormous computer memory and computation speed, this makes Siri look *Twilight Zone* fast.

There are parallels between the database of all questions ever asked on Google and the cis-Lexicon database of our Cyrene Project. Here were Eric's fundamental questions.

Question 1. What is the size of the cis-regulatory universe of all the published papers that present the cis-regulatory architectures of genes that are validated by cis-regulatory analysis (Davidson criterion)?" We call such papers "gold-standard" Cyrene papers, as they describe the cis-regulatory analysis of the regulatory architecture of a gene, giving its DNA content detail of that structure.

Question 2. Can you design a software system to analyze the text of a paper to find out whether it belongs to the cis-regulatory universe described in Question 1? That is, to analyze the paper title, abstract, key words, full text and images, to find out if the paper is a gold-standard Cyrene paper?

This would require the text analysis of all articles in all journals that publish such molecular biology experimental papers in order to discover which papers describe cis-regulatory analysis and publish the DNA sequence data validated that way. It took us only five years to solve this problem. The exciting solution came from the solution of the "Cloning of Professor Davidson" problem, i.e., to automate through software the way Eric would read/scan a paper to find out whether it is a gold-standard Cyrene paper. CLOSE, the cis-Lexicon Ontology Search Engine provided the software package solution for identifying the gold-standard Cyrene papers.

Question 3. Can you construct the solution to the Translation Table Problem? Namely, to find all known pairs of homolog genes from a pair of species, both with solved cis-regulatory architectures.

Question 4. Can you construct a software browser, the cis-Browser, a full genome browser dedicated to the regulatory genome?

All these questions were answered, over a period of seven years of collaborative work, at the level Eric expected, and in my last visit with Eric, we planned the writing of our paper containing the results. *"We cannot publish until we solve the completeness problem: what is the size of the genes cis-reg resolved universe, and what percentage of the genes we have?"*

Like for the founders of Mathematical Logic, Kurt Godel and John von Neumann, the Completeness Problem was for Eric, the Biologist-Logician, a life-long quest, and their solutions to the problem become a defining pillar of their fame, most revered, demi-god results of their scientific disciplines. For Mathematics, the analytical might of revolutionary innovation of their solutions finds the complete the set of axioms (principles) for mathematical theories that capture the complete "truth. " For Biology, Causality-inferred principles play the role of axioms in the experimental universe. The Completeness Problem: "Have we identified the complete set the genes that capture the complete "truth" (all causal relationships) for Gene Regulatory Networks?" was solved by the lifetime achievement of Eric's experimental might of revolutionary innovation.

After several years of work, Ryan's CLOSE search engine gave the solution after "cloning Eric": The optimum software automatic capture was achieved for 95% of the gold standard Cyrene genes papers, together with the remaining 25,000 "promising" papers in the ocean of literature outside the Cyrene island, papers not yet annotated by my small army of annotators. With random samples of several hundred such promising papers at one time, analyzed by our annotators, the estimate was that about 1% of them would end up as gold-standard Cyrene papers yielding new genes in the cis-Lexicon database. The conclusion was that the size of the universe, at that time, was about 800, so our 600+ Cyrene genes would give the cis-Lexicon about 70–75% completeness! Eric was really excited. "*I did not believe that this would be possible. Ryan, this is really very useful. You did a great job.*"

Another paper I especially enjoyed writing with Eric was one in which I could teach him a few things about my hero-in-chief, mathematician John von Neumann. Our paper "The Regulatory Genome and the Computer" (Istrail et al., 2007) was written in homage of the 50th anniversary of "The Computer and the Brain" (von Neumann, 1958), von Neumann's last book/publication. Written in the style of von Neumann's book, the article describes the parallel of the most decisive information processing components in the electronic computer versus the corresponding ones in the cis-regulatory gene networks and systems, known in our paper as the "genomic computer." Here is, in Eric's authoritative voice, the paper's "survival of the computational most fit" message:

"The definitive feature of the many thousand cis-regulatory control modules in an animal genome is their information processing capability … In summary, a view of the evolutionary process leading to complex animals is that the essential properties of the genomic computer discussed in this essay were the condition for, and predate, complex animal forms: first came the properties of the genomic computer, including logic processing CRMs and regulatory network subcircuits, and then came programs for development built on these properties, and hence the animals."

4.2. Causality

Causality in molecular biology, especially cis-regulatory genomics, was one of Eric's most important research themes. Almost all of our work together touched upon causally-inferred DNA regions of regulatory architectures and the algorithmic challenges around them. Eric's passion for the topic was contagious. This level of molecular biology science, cataloged in Eric's 400+ papers and six books, with final versions written by himself in his uniquely eloquent style, was the defining characteristic of the Davidson Lab. I articulated the topic with critical energy in my review of his 2006 book *The Regulatory Genome* which was excerpted by the publishers to appear on the back of the book cover (Istrail, 2006). I wrote: "The foremost experimentalist of regulatory genomics, Eric Davidson, with his new book, *The Regulatory Genome*, is delivering a compelling proof that after the availability of the Human Genome in 2001, the next major event in Molecular Biology has been the availability of the developmental gene regulatory networks. Like his mentor Max Delbruck, and with the sea urchin genome in hand, Eric Davidson is today the leading liberator of quantitative principles of cell regulation, trapped in the qualitative, descriptive world of biology without genomic sequence.

"With the notorious elegance of his writing, Davidson forcefully reminds us that in the scientific method causality is everything; all other approaches are just distractions. Such 'posterior Biology' approaches, too impatiently employed today – 'measure first' expression of thousands of genes, 'and then, computationally infer Biology,' receive in the book, by contrast, a devastating criticism. The luminaries of mathematical statistics of the last century taught us in no uncertain terms that causality cannot be inferred from statistical tables. Aligned with them, Davidson adds to the argument a practical dose of reality. The exquisite regulatory mechanisms, "*locked down by evolution*," can only be revealed through systematic experimental perturbations. In the absence of the ocean deep 'prior Biology' knowledge, no amount of clustering statistics, or other skinny deep dives, would be able infer 'Biology.'"

In that regard, I once compared Eric to President John F. Kennedy. During an academic meeting, someone was overhyping in recent personal papers the biological impact of "disease-cured-already" "gene network" research. I had just hosted software

developer Bill Longabaugh, a close collaborator of Eric, at Brown for two full days of lecturing about the Davidson Lab's Biotapestry gene network inference system. Compared with that, the shallow research might as well have been a 3-year-old's drawing sitting next to a Rembrandt. Taking liberties with the well-known line from the 1988 vice-presidential debate, I said, "I worked with the MOTU of gene networks. I know him. He is a friend of mine. You are no 'gene network' researcher!"

4.3. Genomic control process: development and evolution

This 2015 book by Isabelle Peter and Eric Davidson (Peter and Davidson, 2015) is indeed a defining event in Eric's life in science. This was his sixth book, the only one co-authored. It provided the most comprehensive monograph on the regulatory genome and its information processing systems. Isabelle was first his postdoctoral student and then his lab scientist; he took great joy in her premier research talent, and serving as her mentor thrilled him. Their extraordinary collaboration provided several seminal papers, including the breathtaking "Network Equations" paper (Peter et al., 2012).

The paper "A New Software Package for Predictive Gene Regulatory Network Modeling and Redesign" by Emmanuel Faure, Isabelle S. Peter, and Eric H. Davidson turned out to be a landmark publication in the Journal of Computational Biology (2013) (Faure et al., 2013). The paper is an extraordinary exemplification of Eric-the-teacher-master-of-the-interdisciplinary-universe with his focus on innovation in the teaching arena, especially at the interdisciplinary crosstalk between disciplines. The Journal of Computational Biology, with focus on innovation on rigorous analytical computational and mathematical sciences methods, started a new series of articles "Bioinformatics Software Tools and Systems," with Eric's paper as the flagship paper. Honoring Eric's teaching eloquence exemplified, by his software tools model paper, the Journal encourages authors of analytically advanced methods to present their genomic software tools in ways that meet high standards of rigor, accuracy and didactical innovation best suited to educate and entice the user community to apply the the new tools towards new discoveries.

Over the years, I also had the pleasure to work with Isabelle and Eric on research themes related to the mathematical modeling of the cis-regulatory architectures. Like Eric, I became a big admirer of Isabelle's talent and her insights of experimental and computational import, intertwined perfectly.

5. Not so easy pieces

Eric's writing was uniquely eloquent, not only in dealing with deep technical or academic life problems but difficult ones as well. Here are three pieces, in the Master's words, on family, collaboration, and grants.

5.1. "You can't go home again"

After I returned from a visit to Iasi, Romania, where I was lecturing at my alma mater, I sent Eric a fascinating essay by Simcha Jocobovici (Jacobovich, 2014) about the meaning of the song "Somewhere Over the Rainbow" and its 75th anniversary celebrated at the 2014 Oscars. Discussions with Eric about his upbringing were always fascinating and in these exchanges he revealed captivating details about his ancestry.

On Thursday, October 31, 2013 at 7:15 PM, Davidson, Eric H. < davidson@caltech.edu > wrote:

"Dear Sorin,

I am very curious to hear your impressions on returning to the site of your earlier life on the other side of the world and the other side of the Iron Curtain. There was a famous American novel by Tom Wolfe titled "You can't go home again," which I have always found so true myself….Now of course there's no one left that belongs to what was my original home…."

From: Istrail, Sorin [mailto:sorin_istrail@brown.edu]
Sent: Saturday, March 15, 2014 3:09 PM
To: Rothenberg, Ellen; Davidson, Eric H.
Subject: Fwd: "Somewhere Over the Rainbow"
song- background

Dear Ellen and Eric, What a moving essay about our search for meaning and … the Jews and "Somewhere Over the Rainbow," the 75th anniversary of the song and Pink's performance at the 2014 Oscars …

Sorin
Forwarded message
From: Davidson, Eric H. < davidson@caltech.edu >
Date: Sunday, March 16, 2014 at 3:40 PM
Subject: RE: "Somewhere Over the Rainbow" song- background
To: "Istrail, Sorin" < sorin_istrail@brown.edu >

Dear Sorin,

As you know Jewish experience is not my usual subject of contemplation, Ellen is very much closer to that than am I. My Old Man was essentially an apostate, who could not stand anything cultural, linguistic, culinary or religious that was redolent of his 19th century Eastern European Jewish ancestors (he was born here in 1898). He grew up in a Baltimore slum, escaped forever, and became first a New York painter and then an international artist; I myself was never once in my life taken to a synagogue (and cannot say I have ever been in a synagogue even still, except the ruins of the historic one in Berlin), and I really knew only one boy of Jewish extraction growing up until I went to college (I think I really learned about American Jewish people from marvelous girl friends in Provincetown in the summers). So the subject of what you sent is much more remote to me, except as a matter of fascinating history. Thank you for sending it. Nonetheless, I think that piece is indeed a remarkably moving and intelligent and interesting essay, even though very unfortunately I don't know anything about movies or Hollywood either. … Nonetheless, this will not stop me from going back to Israel for the fourth time in five years for another wonderful symposium this coming Fall…

Best always
Eric
Forwarded message
From: Davidson, Eric H. < davidson@caltech.edu >
Date: Thursday, November 21, 2013 at 12:52 AM
Subject: RE: call
To: "Istrail, Sorin" < sorin_istrail@brown.edu >

"Dear Sorin,

… I am here with Ellen and it is her family not mine with roots in Iasi. Her father's father grew up in Iasi. His father was an émigré from up the coast of the Black Sea, Odessa, but when he moved to Iasi (1880?) he met and married a woman whose family was said (by them) to have lived in Iasi for 900 years. That would bring their arrival back to the time of Alexis Comnenus or so, when the Byzantines occupied that area. On my mother's side it is true that one side of her father's family was from Odessa, whence they continued to see relatives after they came to America in 1888 (such as my mother's childhood piano teacher Sonia) and there was a legend that they also had Romanian connections; since Iasi is just down the water road from Odessa probably this was common. The other three fourths of my ancestors were of the less civilized sort, from Lithuania, however, from the Northern, Baltic end of Catherine's Pale of Settlement. As you know, virtually every Lithuanian Jew was on orders murdered by uniformed Wermacht and Police Brigade machine gunners in the year 1942, when I was 5 in Piermont new York, including whatever remote relatives I might have had."

5.2. One Britten

When Roy Britten, Eric's collaborator for 25 years, passed away, I wrote to Eric to express my sorrow. I proposed a measure for long-term transformative scientific collaborative Duos, calling the unit 1 Britten. I would now reduce the time of the unit to 15 years instead of 25 so that I can proudly say that I also had the fortune in my life to have a 1 Britten–Davidson collaboration.

From: Istrail, Sorin [mailto:sorin_istrail@brown.edu] Sent: Wednesday, January 25, 2012 9:09 AM To: Davidson, Eric H. Subject: Re: [lab] sad news

Dear Eric, I am so sorry to hear the sad news about Roy. I understand how much long-term intellectual collaboration of most excitement type change you in so wonderful ways. Is this where epigenomics contributes to the memory mechanism? I hope that you will find a way to carry on, and that you are strong, as always, a model for all of us.

We need a measure of highest scientific collaborative Duos, of lasting scientific value of in increments 25 years. 1 Britten? Well, my friend, you have had 2+ Brittens!

With my best wishes,

Sorin

Forwarded message

From: Davidson, Eric H. < davidson@caltech.edu >

Date: Thursday, January 26, 2012 at 4:07 AM

Subject: RE: [lab] sad news

To: "Istrail, Sorin" < sorin_istrail@brown.edu >

Dear Sorin,

You are very wise and I respect very deeply your philosophical intuitions. So I have to ask you, exactly what you meant…. Who is the second Roy? I think I know exactly what you meant, because neither Isabelle nor you could ever occur more than once in a lifetime in science, and I am 74 years old, and curiously, am still entirely aware, and I know, integrating over time, what I am talking about….

You and I have our fates secure. If we care about anything outside our current events, we need to care about those who will carry the brilliant torch forward. Isabelle is the best bet; as you call her, Isabelle the Logician. Logic Rules!! We need to somehow make sure Isabelle survives and is given the opportunity to flower, as she will, unless the dull, political, status-dominated, stupid, anti-intellectual world kills her first. Which it could, as surely as cancer killed Roy …

Eric

5.3. *"'tis an ill wind that bloweth no good"*

"Two weeks hence all my main funding is up for review, As we say, 'tis an ill wind that bloweth no good; perhaps I will finally get enough time to get our book finished!

6. Criticism

Eric was a beacon of critical discourse. We celebrated this component of his academic legacy at the Brown University 250th Anniversary Symposium: The Next 250 Years, held in May 2015 (Brown University 250th Anniversary Symposium, 2015). The Symposium featured 14 John von Neumann lectures on computer science, economics, physics and neuroscience, unified by John von Neumann's vision of "Computation as a Scientific Lens." Each lecture was followed by a tough Q&A session with the speaker, a so-called Sweatbox session, concept inspired by Eric. The distinguished lecturers, including three Nobel Laureates and one Turing Award winner: Ken Arrow (Stanford), Leon Cooper (Brown), Frank Wiczek (MIT), Leslie Valiant (Harvard), Nima Arkani-Hamed (Institute for Advanced Studies), David Berson (Brown), Patricia Chirchland (USCD), Vincent Crawford (Oxford), Freeman Dyson (Institute for Advanced Studies), Michael Jordan (Berkeley), Tom Leighton (MIT), Christos Papadimitriou (Berkeley), Mark Satterthwaite (Northwestern), and Susanne Schennach (Brown) were each questioned in the Davidson–Sweatbox style. In the preceding 2010 Symposium, Eric delivered the John von Neumann Lecture on Biology.

From the 2015 Symposium poster (https://cs.brown.edu/media/filer_public/a7/f3/a7f35838-9dac-4269-886d-5b1bb1aea167/2015_poster_final.pdf):

"History of the Sweatbox Concept.

Funded by the National Science Foundation as a workshop called "Q&A Boot Camp at Brown University: Asking Tough Scientific Questions," the "Sweatbox" session as a didactic concept was inspired by the famous 8-week "Summer Course/Boot Camp on Embryology" at the Marine Biological Laboratory, Woods Hall, MA and the director of the course for 15 years, Professor Eric Davidson of the Division of Biology at California Institute of Technology. The story goes that invited speakers at this course would talk in the laboratory's Warm Room and would be subjected there to tough scientific questions about their scientific findings and their claims. Professor Davidson, professor-in-chief of developmental gene regulatory network biology and a beacon of critical discourse, has mentored about 300 Ph.D.s, postdocs and faculty in his laboratory. Basing his work on causality-focused and genomics-based systems, and with insights from experimental biology, biochemistry, physics and engineering, he has been bringing together all us biologists, physicists, biochemists, engineers, mathematicians, statisticians and computer scientists in a renaissance research quest for the functional meaning of DNA. The resulting symbiosis of insights is von Neumannesque in spirit and fits well with von Neumann's unfinished research towards a new logical and computational model for the biological cell by unifying continuous and discrete mathematics via a concept of thermodynamic error. Our "Sweatbox" is so named to honor Professor Davidson's academic legacy."

7. Eric's April phone call

Eric called me in April. Whenever he called, I felt a sense of excitement, manifested in my response. "Eric," I would shout, almost as if he were far away and I needed to make sure he could hear me. His first words were almost always *"How are you man?"* This time, for the first time, Eric – the tower of strength, the rock-solid one you could hold when you need your balance – was different. He told me that the doctors found a growth on his spine and had suggested surgery to replace the affected vertebras with metal parts. *"Forget it, I am not going to do it,"* he said. And then he told me that Jane was also very sick. Such news was hard to bear. I asked him to think some more about his doctor's advice. *"Forget about it,"* he said, and he simply refused to discuss it further. He brightened a bit when I asked to come visit in June, and immediately noted that he was working on a big funding proposal and might need a letter from me. The phone call scared me. His tone was different, discouraged, empty of his usual shining energy. I should have told him "things would improve" or "be strong," but I was speechless, overwhelmed by the news. I called him the following day to reiterate the discussion about his doctor's advice, only to be told *"Forget about it. Not worth talking about."* A few weeks later, when we spoke on the phone, he gave me a positive progress report: things were much better, and, that he just published a new PNAS paper and that I should check it out.

Fig. 2. Sorin Istrail, Eric Davidson and Ellen Rothenberg, June 2015.

8. The last visit

We used my June visit to work on our seven years in the making paper, including the meta-analysis of the cis-Lexicon code, which would turn out to be our last, as yet unpublished. Derek Aguiar, my former Ph.D. student and now a postdoc in computer science at Princeton University, joined us by Skype. Eric was impressed by Derek's valuable contributions, and we decided to combine all four components of the CYRENE Project, work done over almost seven years, into one major publication containing four components: (1) the cis-Lexicon database consisting of 600+ cis-regulatory architectures in eight organisms, human, sea urchin, mouse, rat, fruit fly, worm, chicken, zebra fish, validated by the most stringent experimental technology, the Davidson criteria; (2) the cis-Browser the software system for the cis-Lexicon database and for genomic navigation of the regulatory genome; (3) the Translation Table of pairs of homolog genes from a pair of species both with solved cis-regulatory architectures; and (4) CLOSE (cis-Lexicon ontology search engine) the software server system for identifying the gold standard Cyrene papers describing genes and their DNA regulatory sequence that are resolved there in terms of their cis-regulatory architecture. At the end of our final working session, Eric said: *"Next you need to do the paper outline."* With Derek on the phone, Eric clicked on the translation table links that Derek's web software presented, and saw the mysterious short mnemonic peculiar names of genes, those with solved cis-regulatory architecture across homolog domains; a notoriously adhoc bioinformatically bottlenecked problem, that took us years to overcome for the cis domain, the "gene naming problem." *"This is great, very useful,"* he said. *"Derek you did a great job."* (Fig. 2).

In the evening, we were joined by Ellen at Celentino's, where Eric was always treated like the VIP he was. The servers and the manager all love Eric, and his return to the restaurant was an event. They would make room at his favorite table, clearing space for his scooter. In years previous, we would go together – either in his car or my rental. A few years back he drove me the Eric way – with great speed – to the Davidson lab retreat in Corona del Mar, Newport Beach, at Caltech's Kerckhoff Marine Laboratory, in his spaceship-like new Acura. At that time, my car was an older model Acura. And yes, my new car I bought in 2010 was exactly the Acura TL model that Eric had. Yes, I wanted to be like Eric: Like Eric the driver, like Eric the great scientist, like Eric the great teacher, like Eric the intellectual so versed in other intellectual domains including musician and singer of songs of old-time America, banjo player and concert performer and recording artist with his band, Iron Mountain String Band – a true renaissance man.

At that night's dinner, Eric noted that Caltech was hiring in the bioinformatics area and that he preferred a junior faculty hiring. The opening for an assistant professor had not even been posted, but Eric expressed an interest in encouraging Derek to apply. He told me exactly how Derek should formulate his letter. In that moment, I wrote email to Derek from the restaurant: "Eric and Caltech want you!" and described to him what Eric said. It was wonderful to see Eric so energetic at dinner. The three of us had our usual conversations on topics of intellectual and life import, and Eric drank his usual whisky. Like with everything else, Eric was serious about his whisky. For his 75th birthday, I told him I would like to replenish his whisky reserves. *"Go to #82 Mission Liquor on Washington; bourbon section; top shelf; must have old age e.g. 10 years old, and over 95 proof. Rowan's Creek, 100.1, 15 years; Black Maple Hill 95, min 4 years; and Willet 137.2,17 years."* At our last dinner, the Eric, Ellen and I toasted for a bright future.

Dear Eric,

Thank you for everything, my dear friend. We will carry on!

Yours ever,

Sorin

9. Eric Davidson's Axioms

Axiom 1. "*Serious people do things seriously*"

Axiom 2. "*The answer to how to recognize the right place to crawl through the wall of thorns lies in the shape of the mental triangle composed of intuition, current knowledge, and logic*"

Axiom 3. "*Logic Rules!*"

Axiom 4. "*If we care about anything outside our current events, we need to care about those who will carry the brilliant torch forward*"

Axiom 5. "*Life is short: Let's keep in touch!*"

Axiom 6. "*Use it or lose it*"

Axiom 7. "*Have inexhaustible optimism, inexhaustible curiosity, inexhaustible energy and inexhaustible honesty!*" (Davidson, 2012)

Axiom 8. And in the end, the love you take is equal to the love you make.

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