BIOGRAPHICAL SKETCH

(New NIH Style)

NAME: DOYLE, JOHN

eRA COMMONS USER NAME: DOYLEJC

POSITION TITLE: Jean-Lou Chameau Professor of Control and Dynamical Systems, Elect Eng, and Bioeng

EDUCATION/TRAINING

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	Completion Date MM/YYYY	FIELD OF STUDY
Massachusetts Institute of Technology	B.S. & M.S.	06/1977	Electrical Engineering
University of California at Berkeley	Ph.D.	12/1984	Mathematics

A. Personal Statement

My research is on developing a rigorous theoretical foundation and associated software tools for the study of complex networks in technology, biology, and medicine that integrates theory from control, computation, communication, optimization, statistics (e.g. Machine Learning, or ML), and physics. Illustrative case studies are recent breakthroughs in explaining heart rate variability (Li et al 2014), glycolytic oscillations (Chandra et al, 2011), and turbulence (Gayme et al, 2010, 2011). While vastly different in details, all 3 topics are paradigmatic and massively studied prototypes of scientific progress with extensive experiments and data, statistical analysis, and complex simulations, all in agreement. Yet our papers show that enormous, essential, and fundamental holes remained completely unresolved, and even the right questions were unasked until we supplied the answers. We showed that hard tradeoffs involving robustness and efficiency dominated each problem, and that new theory was needed to rigorously explain the consequences, including “universal laws” new to science (Doyle and Csete, 2011).

Our research impact goes back to the 1970s and our pioneering role in the origins of robust control theory (Doyle, 1978), culminating in the most prize-winning paper in the history of control and dynamical systems ((Doyle et al, 1989 *IEEE Trans. Auto. Control*) as well as the Matlab Robust Control Toolbox, the premier control design software in industry and academia, used by essentially every high tech aerospace, transportation, equipment, and industrial control organization. Beginning in the 90s we had similar impact on Internet, energy systems, biology, ecology, and multiscale physics, in addition to medicine. Additional details are below.

Educationally, the Control and Dynamical Systems (CDS) department at Caltech, which had its 20th anniversary in 2014, has had a huge impact despite its tiny size. Caltech CDS and the new CMS department are the recognized world leaders in the development of theory for analysis and design of complex networked control systems and applications to engineering and science. The top (London Times rankings of universities in the world overall and in engineering) THE world universities (i.e. Stanford, MIT, Princeton, Oxford, Berkeley, Harvard, Cambridge, Imperial, ETHZ, UCLA, Penn, Hopkins) have 15 tenured (12) or tenure track (3) professors who are former Doyle advisees (mostly PhDs, but a few postdocs). CDS has also promoted diversity, with 3 women out of the 4 most recent CDS alumni professors in the “THE top” and 7 women of 7 PhD graduates in 2013.

B. Positions and Honors

Positions and Employment

2014-	Jean-Lou Chameau Professor, CDS, EE, and BioE, Caltech
2004-2014	John G Braun Professor, CDS, EE, and BioE, Caltech
1991-	Professor, Control & Dynamical Systems and EE, Caltech
1986-1990	Associate Professor (with tenure), Electrical Eng, Caltech
1976-1990	Consultant, Honeywell Systems and Research Center, Minneapolis, MN
1974	Consultant, United Banks of Colorado and CIBAR, Inc.

Prize/Best Papers

2016 ACM Sigcomm Test of Time Award for “A First-Principles Approach… Router-level Topology”

2010 Best Writing on Mathematics 2010: “Mathematics and the internet”
2004 ACM Sigcomm: “A First-Principles Approach to Understanding the Internet's Router-level Topology “
1994 ACC Schuck Best Paper Award for “Behavioral Approach to Robustness Analysis”
1993 “State-space solutions…” in world top 10 “most important" papers in mathematics 1981-1993.
1990 IEEE Baker Prize (all IEEE publications) for “State-space…”
1989 IEEE Trans Auto Ctrl for “State-space solutions to standard H_2 and H_∞ optimal control problems”
1988 IEEE Trans on Automatic Control for “Robust control of ill-conditioned plants: high-purity distillation”

<u>Individual Awards</u>
2004 IEEE Control Systems Field Award
1987 NSF Presidential Young Investigator
1987 ONR Presidential Young Investigator
1984 IEEE Centennial Outstanding Young Engineer Award (One-time award).
1984 Bernard Friedman Thesis Award (UC Berkeley)
1983 American Automatic Control Council (AACC) Eckman Award
1977 IEEE Power and Energy Society Hickernell Award
19** World, national, and state records and championships in various sports

C. Contribution to Science

Glycolytic oscillation (GO) illustrates a classic challenge in **systems biology**. By 2010, GO was arguably the most deeply understood of any dynamic phenomena in biology. The feedbacks of autocatalysis and allosteric control of ATP on FPK were thought necessary and sufficient for GO, confirmed by detailed models, extensive simulations, and exhaustive experiments. Yet the deeper “why” questions went unasked, let alone answered, until we showed that the deep answer is that oscillations are natural and necessary side effects of robustness and efficiency tradeoffs (Chandra, 2011, Doyle, 2016). These are in turn special cases of universal mathematical “laws” that apply to all causal feedback systems. Here, the circuit must robustly maintain ATP concentrations despite fluctuations in supply and demand, while efficiently using ATP itself, including in enzyme concentrations, since protein biosynthesis is a major consumer of ATP. The role of additional allosteric control by ATP of PK was unclear, because without it oscillations still occurred in simulation. Our theory showed that ATP/PK feedback is essential for robust efficiency (not oscillations) as the circuit is implausibly fragile and wasteful without it. Control and dynamical systems theory played a pivotal role in showing that inevitable tradeoffs were constraints due to “universal laws” and not “accidents” of either evolution or our models.

In earlier work we applied CDS theory (Csete and Doyle, 2002, Stelling et al, 2004) to explain essential features of the control of bacterial chemotaxis (Yi et al, 2000) and heat shock (2005). Both were heavily studied and popular topics but had unresolved issues of robustness and efficiency tradeoffs involving feedback and dynamics. We also pioneered the development of the open source Systems Biology Markup Language (SBML) and the Systems Biology Workbench (SBW), which have become the central software infrastructures for systems biology (www.cds.caltech.edu/sbw). We have also released an analysis toolbox SOSTOOLS (www.cds.caltech.edu/sostools/) that has one of its main applications the robustness analysis of biological and technological networks.

More recently, in (Kempes et al, 2016) we consider how microbial metabolism and cellular composition change as cell size varies, using details about how much space a bacterium needs for its components—DNA, proteins, and the molecular factories called ribosomes—to function. We provide a comprehensive analysis of how cellular composition changes across the diversity of bacteria as connected with physiological function and metabolism, spanning five orders of magnitude in body size. We present an analysis of the trends with cell volume that covers shifts in genomic, protein, cellular envelope, RNA and ribosomal content. We show that trends in protein content are more complex than a simple proportionality with the overall genome size, and that the number of ribosomes is simply explained by cross-species shifts in biosynthesis requirements. Furthermore, we show that the largest and smallest bacteria are limited by physical space requirements. At the lower end of size, cell volume is dominated by DNA and protein content—the requirement for which predicts a lower limit on cell size that is in good agreement with the smallest observed bacteria. At the upper end of bacterial size, we have identified a point at which the number of ribosomes required for biosynthesis exceeds available cell volume. Between these limits we are able to discuss systematic and dramatic shifts in cellular composition. Much of our analysis is connected with the basic energetics of cells where we show that the scaling of metabolic rate is surprisingly superlinear with all cellular components.

1. Yi, Huang, Simon, **Doyle:** (2000) Robust perfect adaptation in bacterial chemotaxis through integral feedback control. *Proc. Natl. Acad. Sci*. 2000: Apr 25 97(9): 4649-53.
2. Csete M, **Doyle JC**: Reverse engineering of biological complexity. *Science* 2002: 295(5560): 1664-1669.
3. Hucka, Finney, Sauro, Bolouri, **Doyle**: The systems biology markup language (SBML): a medium for representation and exchange of biochemical network models, *Bioinformatics* 2003 19(4): 524-531.
4. Stelling, Sauer, Szallasi, Doyle III, **Doyle**: Robustness of cellular functions. *Cell* 2004: 118 (6) 675-685.
5. El-Samad, Kurata, **Doyle**, Gross, Khammash: Surviving Heat Shock: Control Strategies for Robustness and Performance, *PNAS* 2005: 102(8): Feb 22: 2736-2741.
6. Chandra, Buzi, **Doyle** JC (2011) Glycolytic oscillations and limits on robust efficiency. *Science*, Vol 333, pp 187-192.
7. Doyle (2016) Even Noisy Responses Can Be Perfect If Integrated Properly, *Cell Systems*
8. Kempes, Wang, Amend, **Doyle**, Hoehler (2016) Evolutionary tradeoffs in cellular composition across diverse bacteria, *The ISME Journal*, advance online publication 5 April 2016

Heart rate variability (HRV) and medicine: Our most complete, clinically relevant case study is a mechanistic explanation of well-known but cryptic changes in HRV with illness, aging, fatigue, etc. Reduction in human heart rate variability (HRV) is recognized in both clinical and athletic domains as a marker for stress or disease, but previous mathematical and clinical analyses have not explained the physiological mechanisms underlying the observed patterns of variability. Our analysis of HRV employing the tools of CDS mathematics reveals that the occurrence and magnitude of observed HRV is an inevitable outcome of a controlled system with known physiological constraints (Li et al, 2014). In addition to a deeper understanding of physiology, CDS analysis may lead to the development of timelier monitors that detect control system dysfunction, and more informative monitors that can associate HRV with specific underlying physiological causes.

HRV is a heavily studied area, with huge data bases of physiological data, an endless variety of moderately detailed physiological models, and roughly 10,000 papers/yr applying every conceivable ML and signal processing algorithm to establish a steady stream of correlations. Yet before our work there was little deep mechanistic understanding beyond the proximal role of autonomic tone. Using human subject experiments, data analysis, modeling, and CDS theory we showed that HRV in healthy subjects is due to robust efficiency tradeoffs between metabolic efficiency in muscles with homeostatic maintenance of cerebral blood perfusion pressure. Using mathematical tools from control theory, we combine mechanistic models of basic physiology with experimental exercise data from healthy human subjects to explain causal relationships among states of stress vs. health, HR control, and HRV, and more importantly, the physiologic requirements and constraints underlying these relationships. Nonlinear dynamics play an important explanatory role--most fundamentally in the actuator saturations arising from unavoidable tradeoffs in robust homeostasis and metabolic efficiency.

These results are grounded in domain-specific mechanisms, tradeoffs, and constraints, but they also illustrate important, universal properties of complex systems. We show that the study of complex biological phenomena like HRV requires a framework which facilitates inclusion of diverse domain specifics (e.g. due to physiology, evolution, and measurement technology) in addition to general theories of efficiency, robustness, feedback, dynamics, and supporting mathematical tools. Two crucial elements combined for insight into mechanisms underlying HRV: “black box fits” as in ML to establish causal dependencies between key variables, and explaining these with mechanistic mathematical descriptions of physiology. This illustrates the power of collaborations between math/computation and physician-scientists, which we have been engaged in for more than 15 years.

9. Csete, Doyle (2004), Bow ties, metabolism, and disease, *Trends in Biotechnology*, Vol 22, Issue 9
10. Doyle, Csete (2011) Architecture, Constraints, and Behavior, *PNAS*, vol. 108, Sup 3 15624-15630
11. Namas, Zamora, An, Doyle, et al, (2012) Sepsis: Something old, something new, and a systems view, *Journal Of Critical Care* Volume: 27 Issue: 3
12. Li, Cruz, Chien, Sojoudi, Recht, Stone, Csete, Bahmiller, Doyle (2014) Robust efficiency and actuator saturation explain healthy heart rate control and variability, *P Natl Acad Sci USA* 2014 111 (33) E3476-E3485

Turbulence is a classic challenge in **physics** and engineering. By 2010, laser Doppler particle imaging velocimetry (DPIV) provided almost arbitrarily fine spatial and temporal resolution of turbulent flow fields (very “big data”), and massive “direct” supercomputer simulations of Navier-Stokes PDEs (DNS) could match these data. This near perfect and detailed match of measurement, modeling, and simulation is a paradigmatic modern scientific success story. Yet the most important and central mysteries remained almost completely unresolved: the mechanism of the blunting of the turbulent profile that causes increased drag (costing > $100B /yr), and the role of the large coherent structures present even in fully developed turbulence. More importantly, there was little hint of how to control these flows. This is of biological interest as dolphins and sharks reduce drag by controlling turbulence. This story is now utterly changed because of our research (Gayme et al, 2010, 2011), using methods from control engineering. We have also made fundamental contributions to understanding wildfire dynamics and ecosystems (Moritz et al, 2005 and Bowman et al, 2009) as well as statistics of earthquakes (Page et al 2011). Both our wildfire and ecology work corrected and clarified widespread errors and confusion regarding the "power laws" in the data, and provided new explanations for the mechanisms involved in the large "tail events."

11. Moritz, Morais, Summerell, Carlson, Doyle (2005), Wildfires, complexity, and highly optimized tolerance, *PNAS*
12. Bowman, Balch, Artaxo, Bond, Carlson, Cochrane, D'Antonio, DeFries, **Doyle**, et al. (2009) Fire in the Earth System. Science 2009: 324(5926): 481-484. PMID: 19390038.
13. Gayme, McKeon, Papachristodoulou, Bamieh, **Doyle (2010)**: A streamwise constant model of turbulence in plane Couette flow, J Fluid Mech 2010: 665: 99-111.
14. Gayme, McKeon, Bamieh, Papachristodoulou, **Doyle** (2011) Amplification and Nonlinear Mechanisms in Plane Couette Flow, *Physics of Fluids*, V23, Issue 6
15. Page, Alderson, **Doyle** (2011) The magnitude distribution of earthquakes near Southern California faults, *J. Geophys. Res* 2011: 116, B12309. doi: 10.1029/2010JB007933.

The Internet is a canonical case study in large complex engineering networks, but until recently had very little theoretical basis, which our research fundamentally changed. We first developed a coherent framework for analyzing and synthesizing congestion control protocols, which evolved into a full mathematical theory for layered network architecture (Chiang et al 2007). Network protocols in layered architectures had historically been obtained on an ad hoc basis. Now network protocol stacks may instead be holistically analyzed and systematically designed as distributed solutions to some global optimization problems. The overall communication network is modeled by a generalized network utility maximization problem, each layer corresponds to a decomposed subproblem, and the interfaces among layers are quantified as functions of the optimization variables coordinating the subproblems. Through numerous case studies, we illustrated how "Layering as Optimization Decomposition" provides a common language to think about modularization in the face of complex, networked interactions, a unifying, top-down approach to design protocol stacks, and a mathematical theory of network architectures.

We also clarified the structure of the router level topology (Doyle et al, 2005), that had been mistakenly claimed to be "scale-free," whereas nothing could be further from the truth. These various theoretical and mathematical results are reviewed and summarized in (Willinger et al, 2009) which was selected as among the "Best Writing on Mathematics 2010." The most exciting opportunity for use of our methods, however, is in more "clean slate" architectures, where CDS theory could play an integral role at the outset, rather than patch a leaky architecture when problems (e.g. congestion collapse) arise. Thus we are working with engineers in academia and industry to rethink the engineering network architectures (e.g. the TCP/IP protocol stack) that were the primary motivation for the development of the theory over the last decade. A crucial element of our recent theoretical progress that applies to neuroscience as well as the Internet is a more integrated theory of distributed control that unifies previously fragmented control, computation, and communication theories (Matni et al, 2015, 2016).

15. Low, Paganini, **Doyle** (2002) Internet congestion control, *IEEE Contr Syst Mag* 22 (1)
16. **Doyle** et al: The "Robust Yet Fragile" Nature of the Internet, PNAS 2005 102(41): 1497-14502
17. Chiang, Low, Calderbank, **Doyle**: Layering As Optimization Decomposition: A Mathematical Theory of Network Architecture, Proc of the IEEE 2007: 95(1): 255-312.
18. Willinger, Alderson, **Doyle**: Mathematics and the internet: A source of enormous confusion and great potential. Notices Amer Math Soc 2009: 56:586-59
19. Matni, Tang, **Doyle**, A case study in network architecture tradeoffs, ACM Sigcomm Symposium on SDN Research (SOSR), 2015.
20. Matni, Doyle, A Theory of Dynamics, Control and Optimization in Layered Architectures, *IEEE American Control Conference*, 2016. Accepted.

Robust control theory, along with optimization, statistics, and dynamical systems, is the foundation of our current framework for complex networks. Most of today's robust control concepts and mathematical foundations explained in textbooks, taught in courses, implemented in software packages and applied in industry, are due to Doyle, his group, and collaborators. The debunking of the robustness "conjectures" of the then dominant LQG framework (Doyle, 1978), based on work started as an undergraduate, is one of the key starting points for robust control. In the following years he introduced structured singular values and mu-synthesis (Doyle, 1982, the most cited paper in *IEE Control Systems* history), solved the general H-infinity optimal control problem (Doyle et al, 1989, the most award winning paper in the history of CDS), and contributed to a wide variety of applications directly and indirectly through software, e.g. Matlab Robust Control Toolbox (RCT) and SOSTOOLS. Early applications were in diverse aerospace (e.g. X-29, F-16XL, F-15 SMTP, B-2,757, Shuttle Orbiter, many other aircraft and helicopters) and other commercial fields (e.g. backhoe, active suspension, CD players). RCT is now used routinely at thousands of locations worldwide.

19. **Doyle**, Guaranteed Margins for LQG Regulators, *IEEE Trans Auto Control* 1978: 23(4): 756-757.
20. **Doyle** (1982) Analysis of Feedback-Systems with Structured Uncertainties, *IEE Proceedings-D Control Theory and Applications* Volume: 129 Issue: 6
21. Zhou, **Doyle**, Glover (1996), *Robust and Optimal Control,* Prentice Hall
22. Robust control toolbox (Matlab)
23. **Doyle**, Glover, Khargonekar, and Francis (1989) State-space solutions to standard H_2 and H_∞ optimal control problems, *IEEE Trans. Auto. Control,* August, 1989