Computational Modeling and Analysis For Complex Systems

NSF Expedition in Computing

CMACS: An Overview

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Carnegie Mellon University

http://cmacs.cs.cmu.edu/

PI Meeting, University of Maryland

April 28, 2011

CMACS: An Overview

- Started in September 2009
- 8 institutions, 18 PIs, plus students & postdocs
- **Jet Propulsion Lab** joins CMACS in May 2011
  - Delay due to legal problems: ITAR regulations, ARRA (stimulus) funding restrictions

Significant Achievements & Impacts

- New computational methods for **cancer**
- New computational methods for **cardiac dynamics**
- New automated modeling and verification techniques for **complex embedded systems**
- Highly successful 2010 and 2011 **Undergraduate Workshops** on Pancreatic Cancer and Atrial Fibrillation for students from urban minority-serving institutions

CMACS: Whole > [Sum of Parts]

- Many breakthroughs due to **new**, **cross-institutional**, **cross-disciplinary** **collaborations**

- Typical example: Atrial Fibrillation Research

Stony Brook	Cornell	NYU
Bartocci (Computer Sci)	Cherry (Biomedical)	Le Guernic (Computer Sci)
Glimm (Applied Math)	Fenton (Physics)	
Grosu (Computer Sci)	Gilmour (Biomedical)	
Smolka (Computer Sci)		

CMACS: Whole > [Sum of Parts]

- Another example: Pancreatic Cancer Research

CMU	Pitt	UPMC
Clarke (Computer Sci)	Faeder (Sys. Biol.)	Lotze (Cancer Inst.)
Gong (Computer Sci)	Miskov-Z. (Sys. Biol.)	
Wang (Computer Sci)		
Zuliani (Computer Sci)		

- *Next week*: **Translational Genomics Research Institute**
  - CMU group visiting TGen (meeting Rich Posner and Daniel Von Hoff)

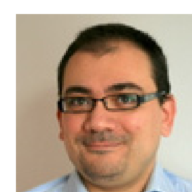
- Innovative educational program **would not have even been possible** without the CMACS Expedition

Collaboration

- CMACS PI review meetings:
  - Oct. 31 - Nov. 1, 2009. Kickoff meeting at CMU
  - Mar. 4-5, 2010. CMU
  - Oct. 28-29, 2010. NYU
- Teleconferences via Skype
- Our **wiki** http://wiki.cmacs.cs.cmu.edu
- **Webex** sessions
  - Research presentations
  - Management discussions, etc.

Collaboration

- CMACS seminar series at Carnegie Mellon
- **24 speakers** from top US and European institutions

12/10/2010, 2:00 PM **GHC-6501**	Ufuk Topcu California Institute of Technology, Department of Computing and Mathematical Sciences **Synthesis of Embedded Control Software** PDF slides	
12/03/2010, 2:00 PM **GHC-6501**	Christel Baier, Professor Technische Universität Dresden, Germany **On Model Checking Techniques for Randomized Distributed Systems** PDF slides	
11/19/2010, 2:00 PM **GHC-6501**	Mahesh Viswanathan, Associate Professor Department of Computer Science University of Illinois, Urbana-Champaign **Approximating Hybrid Systems** PDF slides	
11/12/2010 2:00 PM **GHC-6501**	Alessio Lomuscio Department of Computing, Imperial College, London, UK **Verification of multi-agent systems**	

Outreach

- CMACS website **http://cmacs.cs.cmu.edu**

Outreach

- CMACS is on **Facebook** and **Twitter**

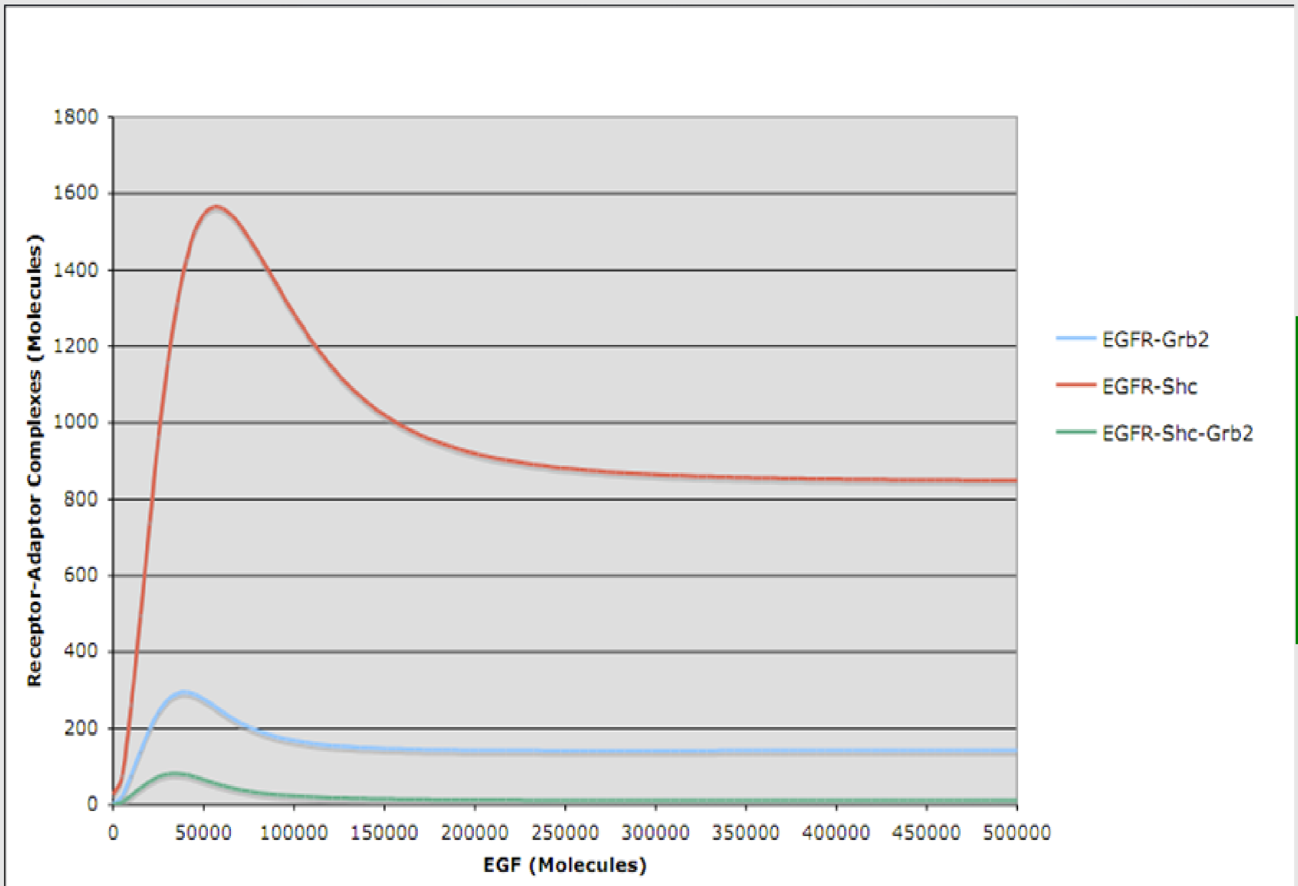
NSF-CMACS Annual Workshop Series

- Innovative educational program centered around annual workshops series which seeks to develop scientific interest & skills of students from urban, minority-serving institutions
- Each a **highly intensive 3-week workshop** held at Lehman College (part of CUNY) in the Bronx

Nancy Griffeth:
CMACS Educational
Program Director

Jan 2010: Workshop on Pancreatic Cancer

- Focus on mathematical and computational tools for modeling biological systems, esp. **EGFR** receptor and its role in PC

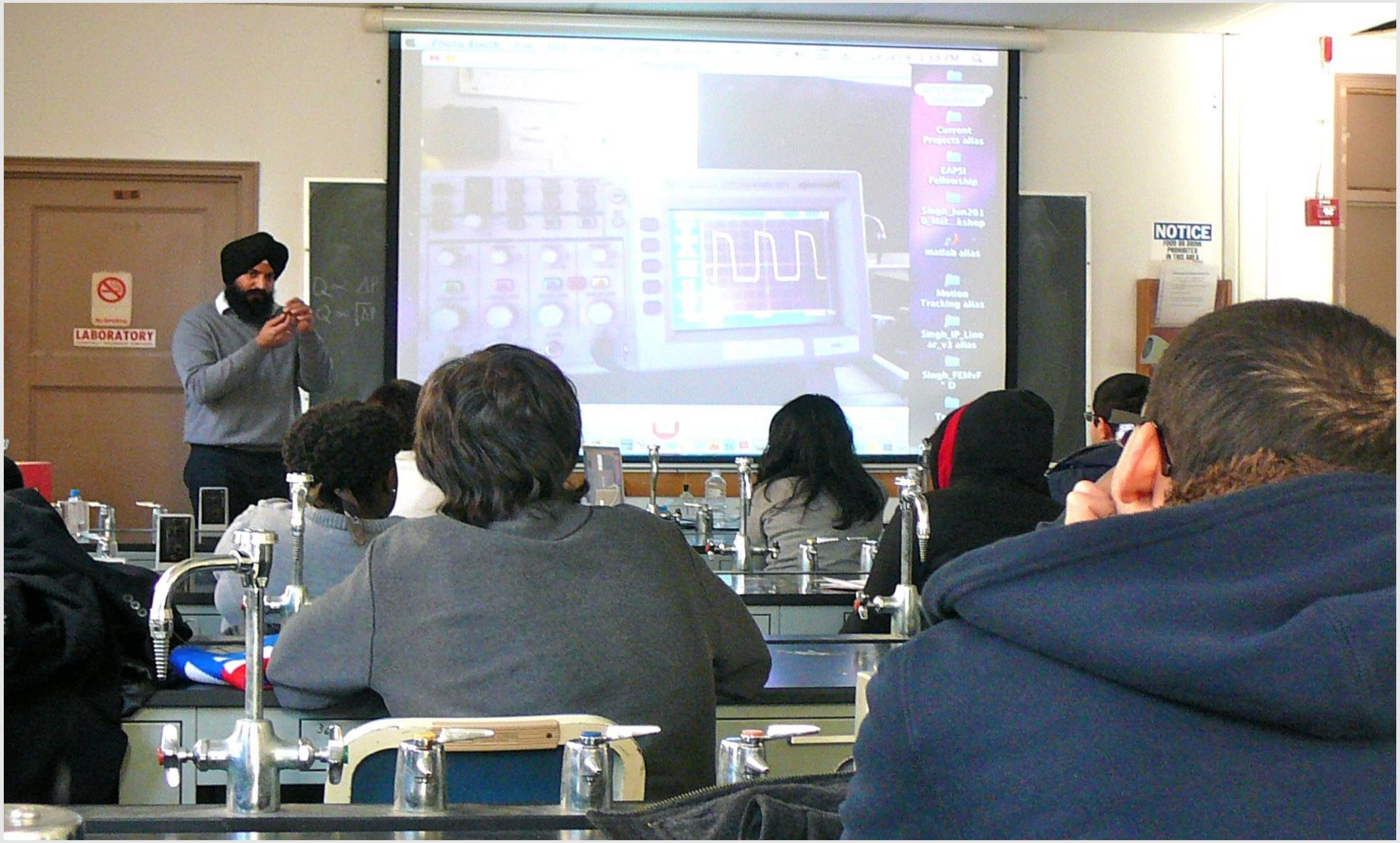


By Ilya Korsunsky et al. Ilya now Junior Research Fellow in Bud Mishra's group

Jan 2011: Workshop on Atrial Fibrillation

- Fifteen CUNY undergraduates, including five women, three African Americans, and three Hispanics

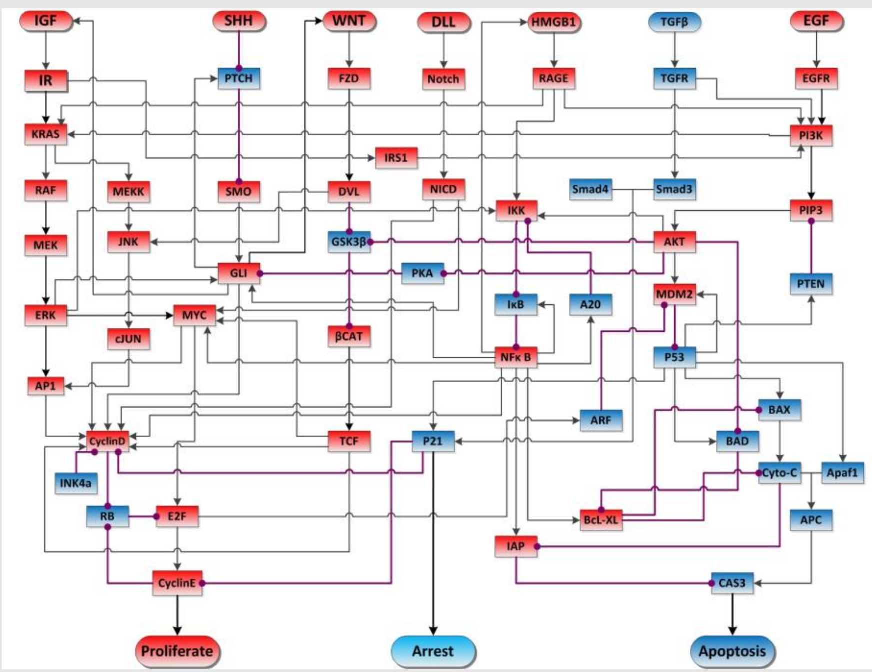
Jan 2011: Workshop on Atrial Fibrillation



- Student co-authored paper submitted to journal *Advances in Physiology Education*

Understanding Pancreatic Cancer through Computational Models

- CMACS researchers from CMU, Pitt & UPMC developed models & automated techniques for analysis of dynamic behavior of key biochemical processes in pancreatic cancer
- Potential applications in understanding the evolution of pancreatic cancer, and in drug design

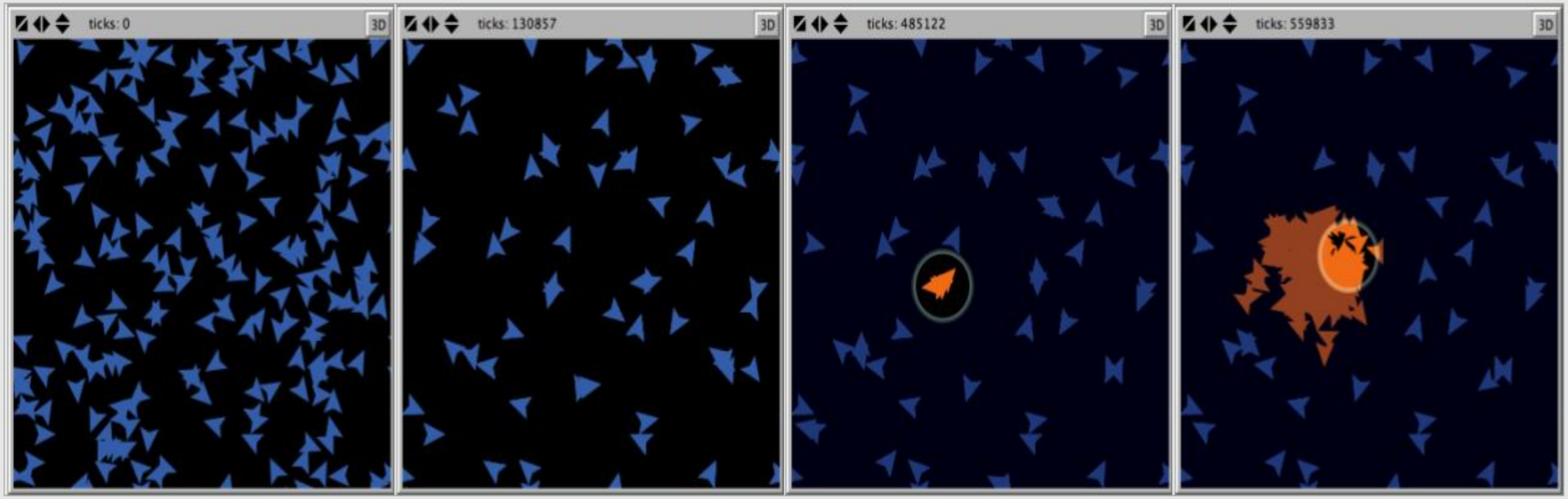


Computational Model of PC Cell

Blue Nodes: tumor supressors
Red Nodes: oncoproteins/lipids
→ : activation
—● : inhibition

Cancer Modeling for Diagnosis, Prognosis, and Therapy

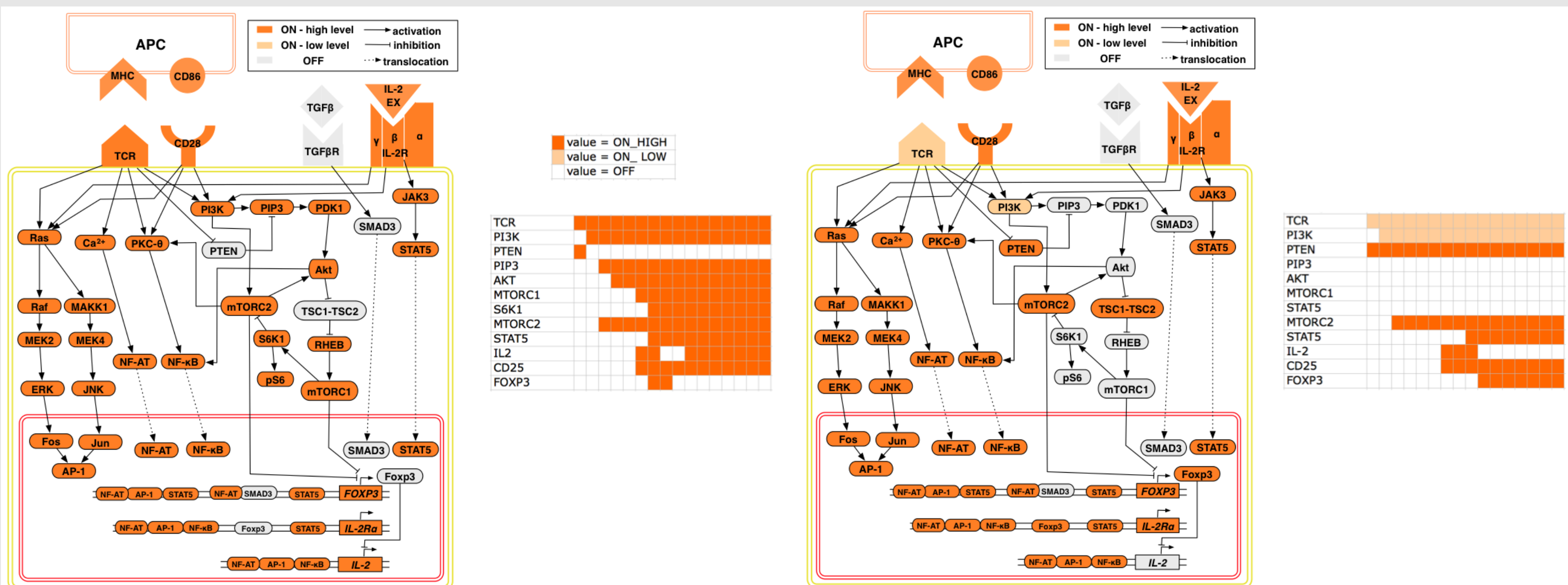
- NYU CMACS researchers created framework that formally represents existing progression models from cancer biology
- **Cancer Hallmark automaton** can be used for automatic generation of appropriate treatment plans



Simulation illustrating how mutation causes local aberrant growth in a previously homeostatic monoclonal cell population

Boolean Modeling and Analysis of Peripheral T Cell Differentiation

- Pitt CMACS researchers developed model that reproduces important experimental observations re: T Cell differentiation
- Its construction helped clarify relationships among molecular inputs at key control points in T Cell differentiation process



T cell interactions might be one way to eliminate antigen-specific Treg cells and thus decrease or even reverse immune suppression in cancer

Cancer Subtype Classification based on High-Dimensional Genetic Data

- Tongtong Wu (Maryland) has developed a simple, accurate, stable, and fast method for systematic cancer diagnosis based on patients' **gene expression profiles**
- Cancer diagnostic procedure simplified as only **small subset of genes** needs to be examined
- Method can be used for classification and dimension reduction in other areas; e.g. to detect gastrointestinal (GI) disease using optical coherence tomography (OCT) images

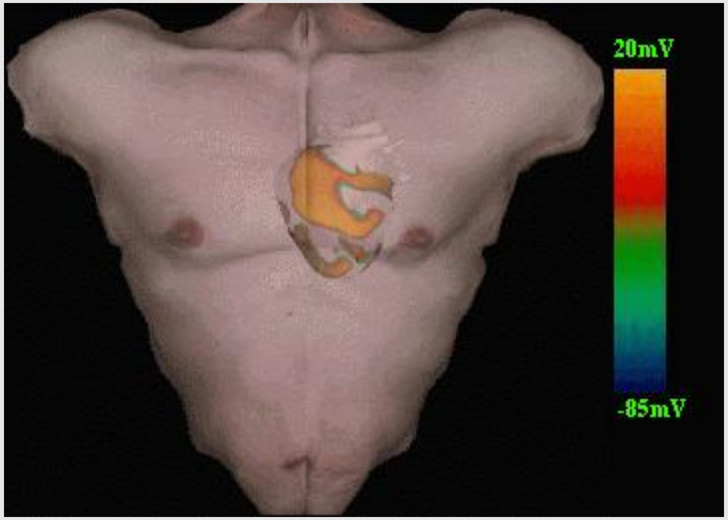
GWAS for Pancreatic Cancer Survival

- Tongtong Wu, Haijun Gong, and Ed Clarke have identified an **8-gene signature** for **pancreatic cancer survival** out of 43,376 candidate genes through Lasso-penalized Cox regression
- No previous studies on gene signatures that are directly related to pancreatic cancer survival

Gene Name	Protein Name	Gene Function
GTPBP5	GTP binding protein 5 (putative)	Act as molecular switch, regulate protein synthesis
BRIP1	Fanconi anemia group J protein	Repair broken strands of DNA
PPARD	peroxisome proliferator-activated receptor delta	Function as a transcription factor, regulate the cellular differentiation, development, metabolism & tumorigenesis.
PTP4A2	protein tyrosine phosphatase type IVA, member 2	Cell signaling proteins which regulate many cellular processes
CCR5	chemokine (C-C motif) receptor 5	Predominantly expressed on T cells, macrophages etc, associated with inflammation.
TXNL4B	thioredoxin-like 4B	Required in cell cycle progression for S/G(2) transition
HIST3H2BB	histone cluster 3, H2bb	Nuclear Protein, upregulated in head and neck squamous cell cancer
ITGAV	integrin, alpha V	Signal transduction and cell to cell interaction

Toward Real-Time Simulation of Cardiac Dynamics

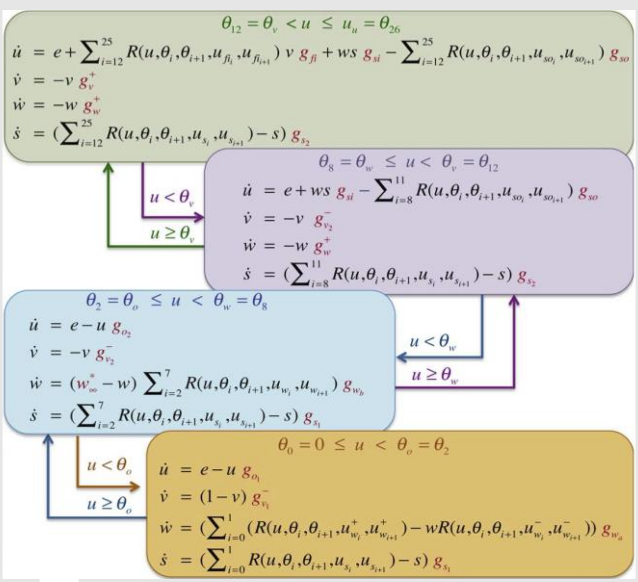
- Stony Brook & Cornell researchers have made novel use of GPUs & associated CUDA parallel architecture to achieve **near-real-time simulations** of detailed cardiac models, previously possible only on large supercomputers
- Expected to accelerate scientific research on cardiac arrhythmias such as atrial fibrillation



Complicated spatiotemporal organization of electrical activity during ventricular fibrillation (cause of sudden cardiac death)

First Automated Formal Analysis of Realistic Cardiac Cell Model

- CMACS researchers from Stony Brook, Cornell & NYU succeeded in carrying out the first automated formal analysis of a realistic cardiac cell model
- Determined parameter ranges that lead to **loss of excitability**, a precursor to e.g. ventricular fibrillation

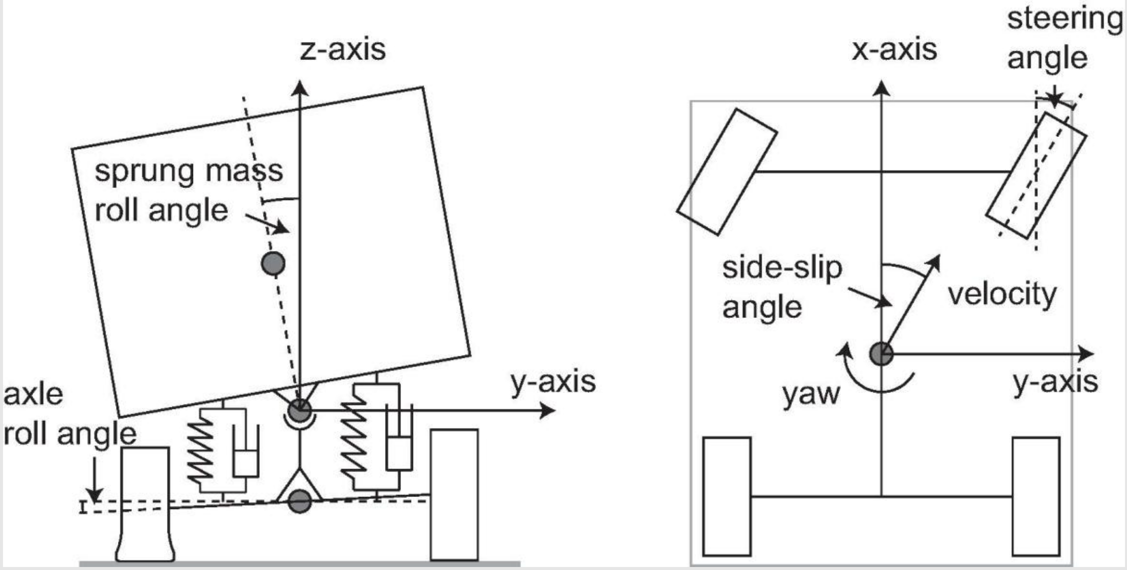


Multiaffine Hybrid Automaton model of Fenton et al.'s Minimal Cardiac Cell model

Such automata commonly used in the analysis of Genetic Regulatory Networks

Efficient Verification of Nonlinear and Hybrid Dynamic Systems

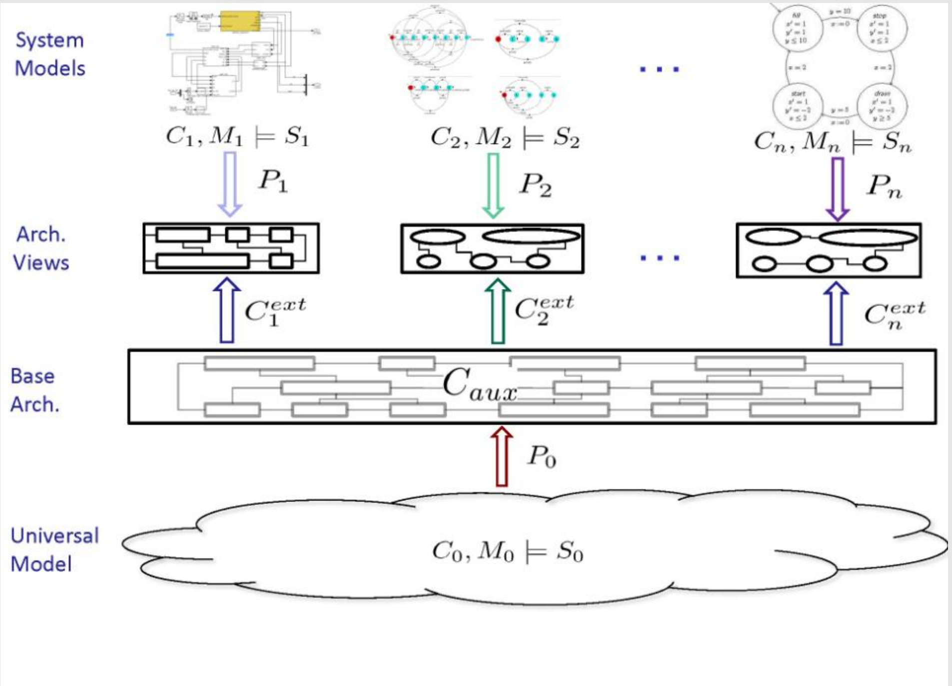
- Matthias Althoff, Colas Le Geurnic, and Bruce Krogh have developed a new method for evaluating all possible behaviors of complex dynamic systems
- Will **reduce significantly time required** to verify that embedded control designs for automobiles and aircraft satisfy stringent environmental and safety requirements



Reachability analysis for verifying maneuver stability for a vehicle with gain-scheduled yaw control

Embedded Control System Design and Verification using Heterogeneous Models

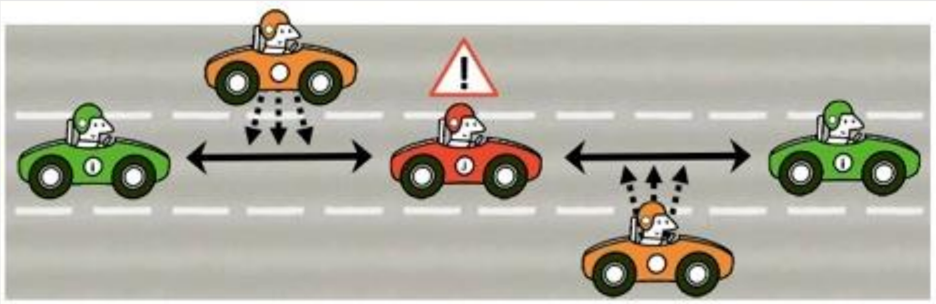
- Bruce Krogh & André Platzer (with Akshay Rajhans, Ajinkya Bhave, Sarah Loos, and David Garlan) have developed novel **inter-model constraint verification process**
- Makes it possible to verify a level of consistency across widely varying tools and techniques



Logical foundation for guaranteeing system-level requirements early in the design process

How to Avoid Bugs while Driving on the Highway

- André Platzer, Sarah Loos, and Ligia Nistor have developed a protocol for **distributed adaptive cruise control** for highway traffic.
- Has further developed verification technology with which he can **prove** that protocol will successfully prevent collisions



Automated cars driving on the highway

Requirement Reconstruction via Machine Learning for Automotive Software

- Rance Cleaveland & PhD student Sam Huang have devised strategy ***in conjunction with researchers at Fraunhofer & Robert Bosch*** to use machine learning on testing results to **uncover requirements** that may have been implemented but not documented

- Using this approach, part of a production automotive control system was analyzed, and **two crucial yet undocumented requirements were uncovered**

- Offers solution to vexing problem of long-standing: **what does a piece of software actually do** (as opposed to what the requirements document states that it does)?

Automated Verification of Large-Scale Avionics Software

- Patrick Cousot has developed a framework based on Abstract Interpretation for the **static analysis and verification of aerospace software**
- Help ensure that industry will be able to cope with requirements (e.g. **DO-178C**) that certification authorities will impose on commercial software-based aerospace systems

Unifying Logical and Algebraic Abstractions for Verification

- Patrick Cousot has proposed a breakthrough method to **combine logical and algebraic abstractions for verification**
- Results in a new way of understanding the verification problem and paves the way for a **unification of two visions** that have developed largely independently during the last two decades

Future Work: What Do the Next 3.5 Years Hold?

- Discovery of **more detailed, realistic & probing computational models** of the biological & embedded systems we are so invested in studying

- Development of even **more efficient verification technology**, allowing us to tackle more expressive **properties** and more sophisticated **systems** (e.g. 2D & even 3D cell structures)

- Building off of **JPL's expertise**, become the leading authority on aerospace & automotive software verification

Future Work (contd.)

- Studying **multi-cellular** cancer models:
  - modeling the tumor microenvironment for pancreatic cancer
  - increasingly important (“Hallmarks of Cancer: The Next Generation”)

- More & wider cross-institutional & cross-disciplinary **collaborations**; e.g.
  - apply UMD classification & dimension-reduction technology to NYU cancer models
  - apply CMU statistical model checking to SB+Cornell 2D & 3D cardiac models