Computational Modeling and Analysis for Complex Systems (CMACS)

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Carnegie Mellon University

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

Carnegie Mellon | Stony Brook State University of New York | NASA | Cornell University Founded A.D. 1865 | NYU New York University

Lehman College | University of Maryland | University of Pittsburgh

Our Vision

To gain fundamental new insights into the **emergent behaviors** of complex biological and embedded systems through the use of **revolutionary**, highly **scalable**, and fully **automated** modeling and analysis techniques.

Our Goals

Scientific

Next-Generation Methodology for Analyzing Complex Systems

Model Checking

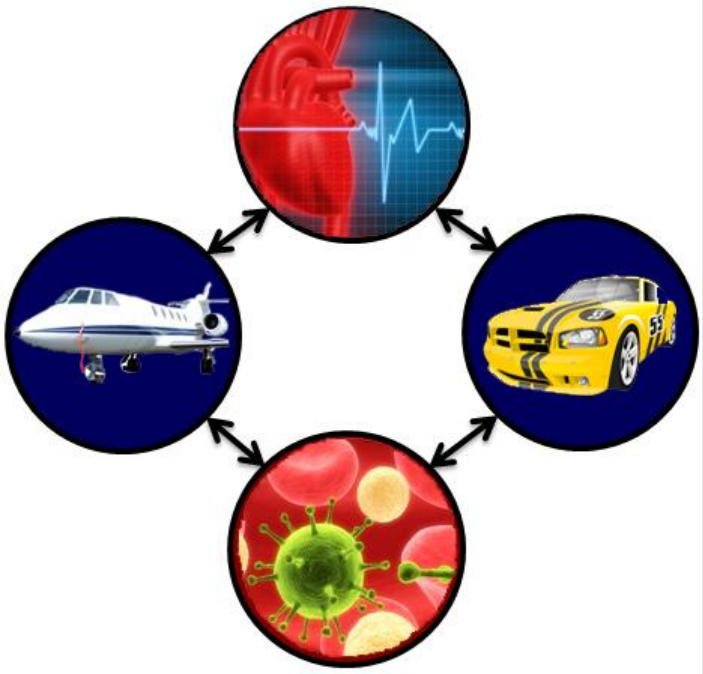
Abstract Interpretation

Societal

Tackle Challenge Problems in Systems Biology and Embedded systems

Education & Outreach

Programs for research and knowledge transfer



Model Checking

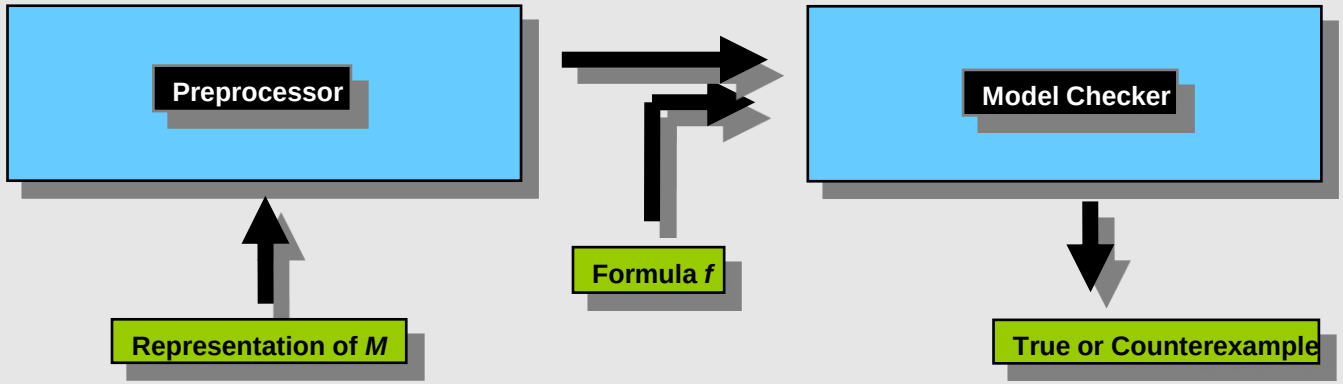
The **Model Checking Problem** (**Clarke**, Emerson, Sifakis '81):

Let ***M*** be a **state-transition graph**

Let ***f*** be a **formula of temporal logic**

e.g., a U b means "**a** holds true Until **b** becomes true"

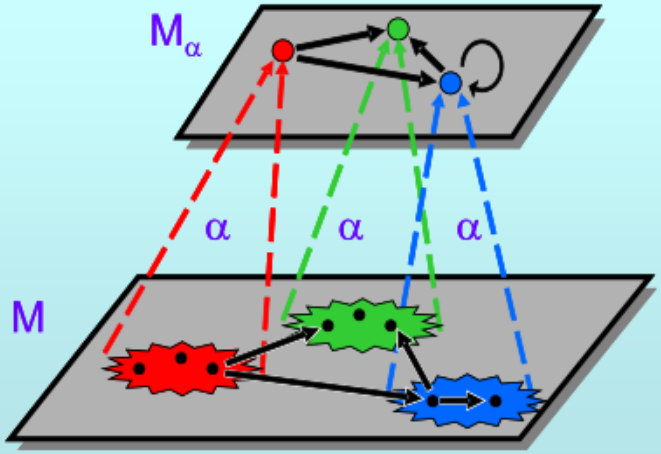
Does ***f*** hold along all paths that start at initial state of ***M*** ?



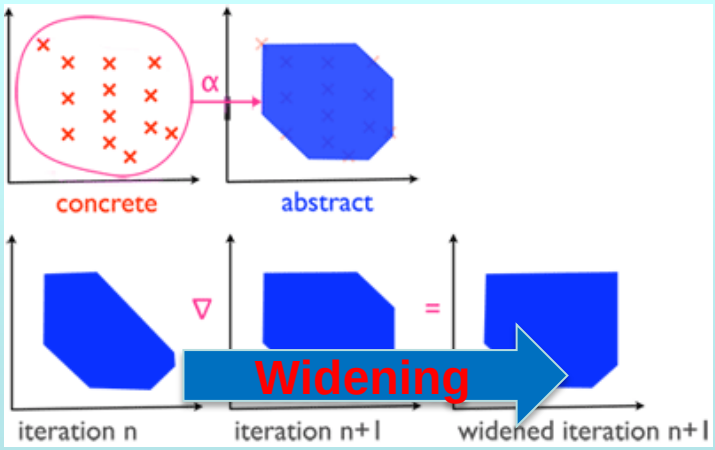
Abstract Interpretation

- Abstracts the **concrete semantics** of a system into a simpler **abstract semantics**
  - Crucial for Analyzing Complex Systems
  - Mature Methodology since [**Cousot** & Cousot 1977]

Control Abstraction



Data Abstraction



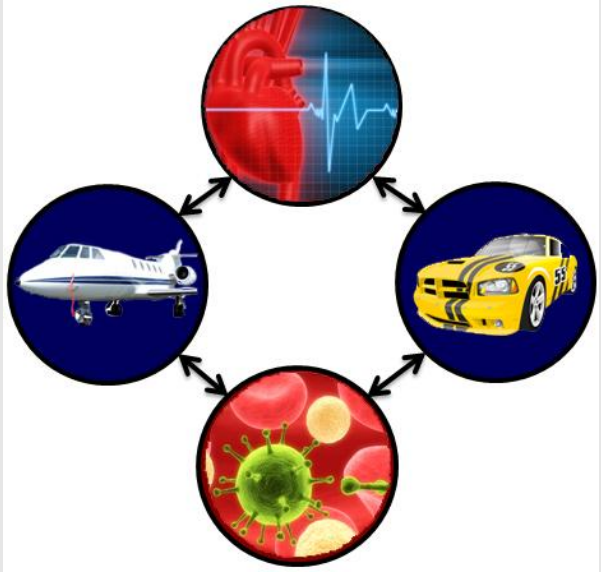
CMACS

- **Rethink and develop** an **integration** of Model Checking and Abstract Interpretation
- Driven by the **centrality of computational modeling** in science & engineering
- Focus on complex **biological** and **embedded** systems
- **Cross-pollinate:** same techniques applicable in one domain **transfer to the other** and beyond

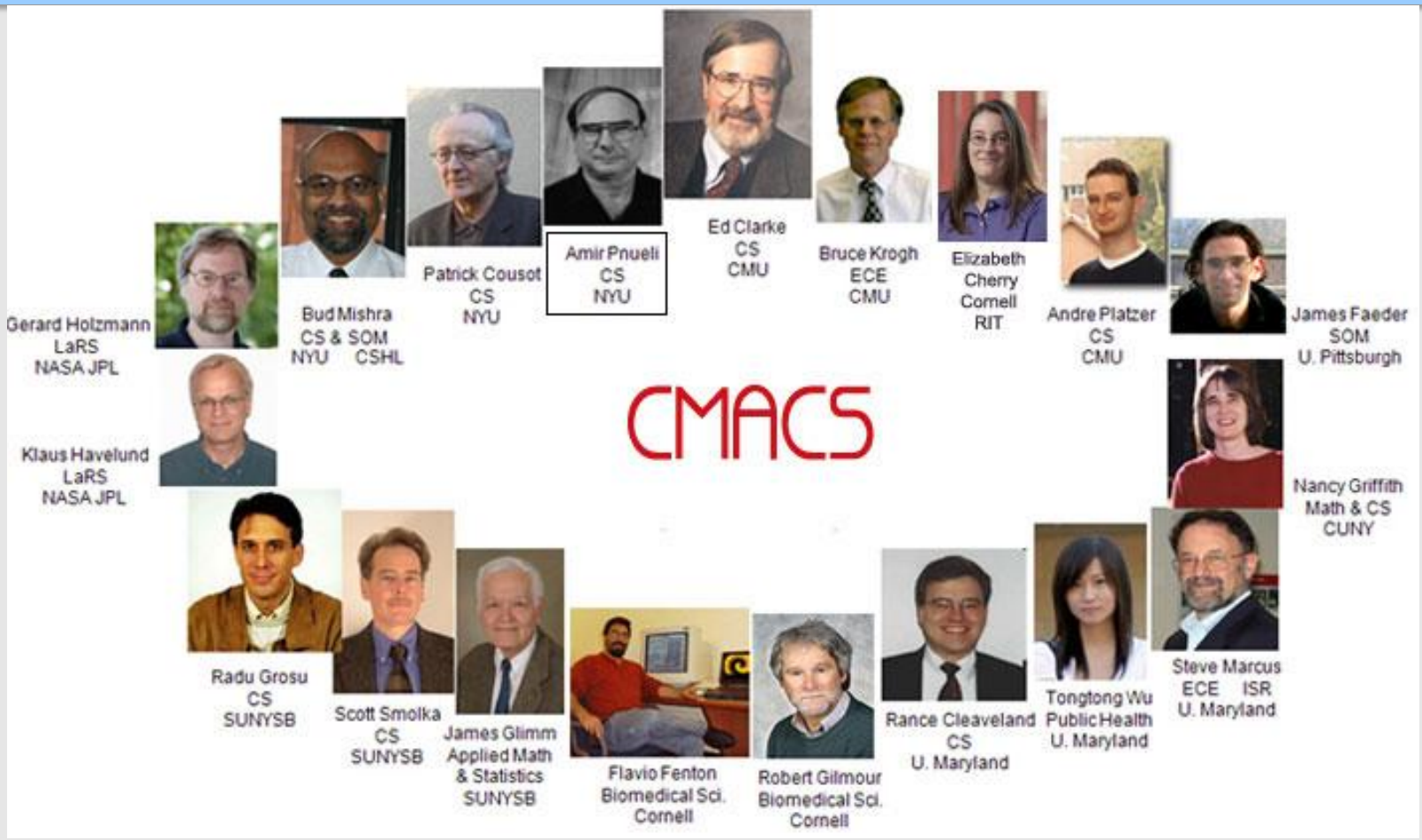
Challenge of Complex Systems

Real-World Biological & Embedded Systems can exhibit any combination of the following features

- **Highly Nonlinear**
- **Very High Dimensions**
- **Hybrid Behavior (Continuous+ Discrete)**
- **Safety Critical**
- **Sensitive to Perturbations**
- **Spatial Distribution**
- **Stochastic Behavior**



CMACS: Research Team



Carnegie Mellon University

LEHMAN COLLEGE

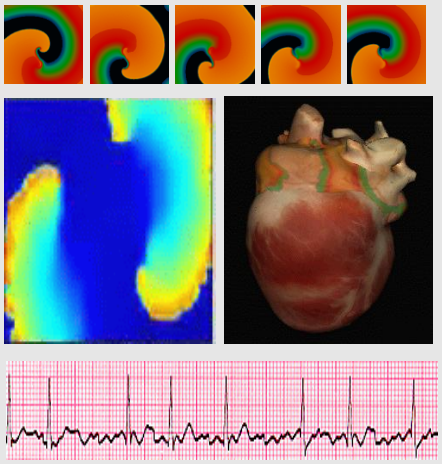
STONY BROOK UNIVERSITY

NASA

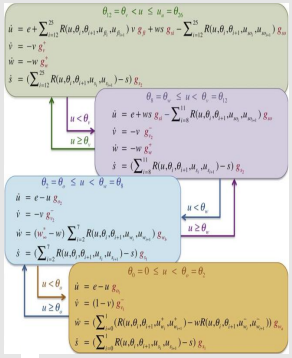
NEW YORK UNIVERSITY

Most Significant Contribution to Date

- **Atrial Fibrillation Challenge Problem:** multi-disciplinary, multi-institutional, high-impact research
  - Increases stroke, heart failure, mortality
  - Afflicted Americans:12 million by 2050
  - 2011 *Nature* paper on Low-Energy Defibrillation
  - First automated formal analysis

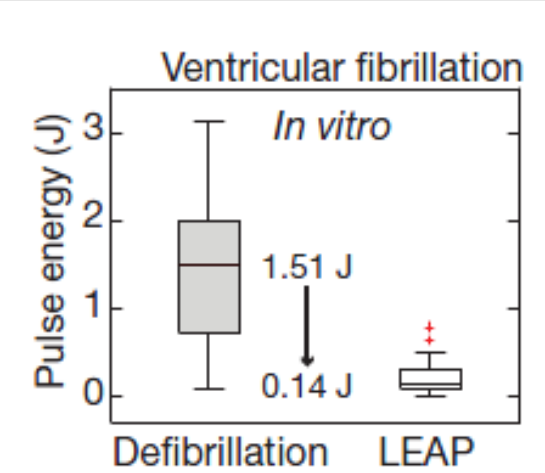


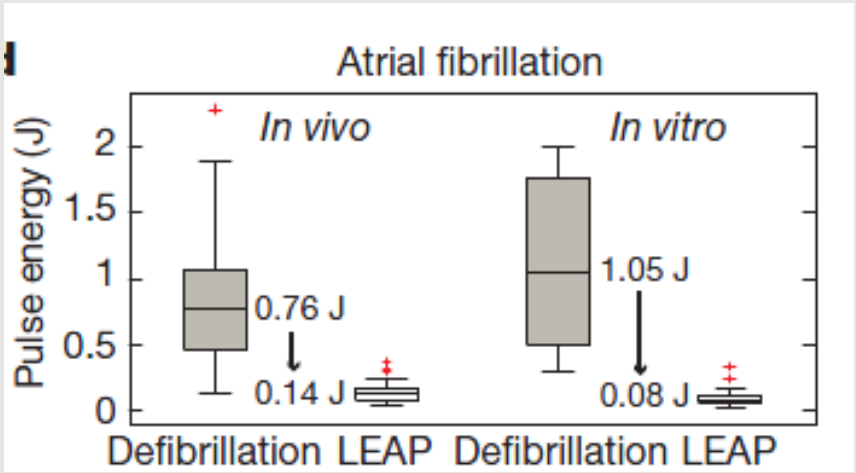
- **Delta-Reachability:** breakthrough theory and techniques for verifying hybrid systems
  - Scalable model checking for nonlinear hybrid systems
  - Successfully applied to the Atrial Fibrillation models, and many other realistic biological and cyber-physical systems



Control and Termination of Arrhythmias with Low-Energy Defibrillation

Low-Energy Defibrillation (LEAP) tested for VF *in vitro* and for AF *in vitro* and *in vivo* (canine hearts).





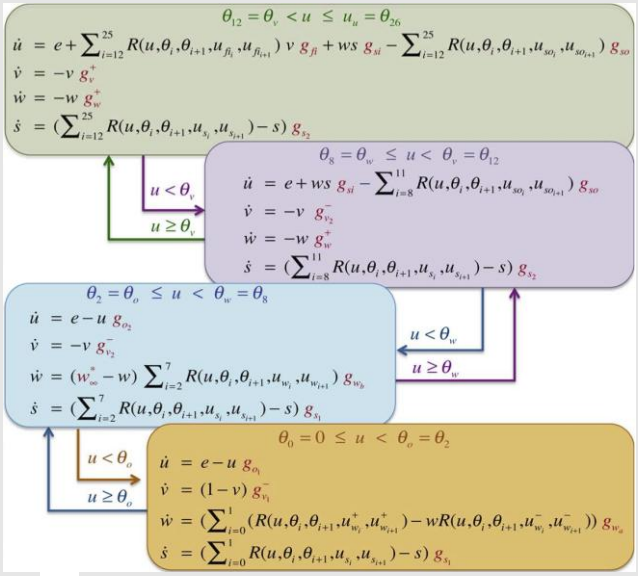
For both AF and VF we found successful defibrillation with LEAP using about 10% of the energy required by the standard 1-shock defibrillation protocol

Furthermore, using high-resolution mCT we obtained detail vessel distribution of the heart and found a scaling law which was used to obtain a theory that explains the mechanism behind LEAP.

These results appeared in *Nature* 475: 235-239; 2011.

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 **[CAV 2011]**
- 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

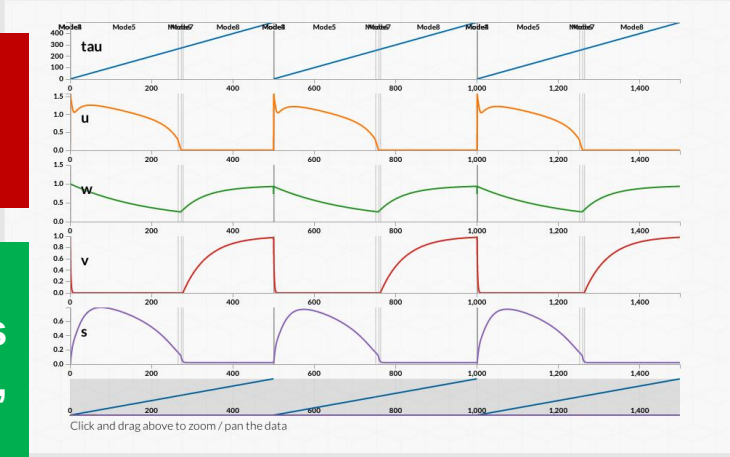
Delta-Reachability http://dreal.cs.cmu.edu

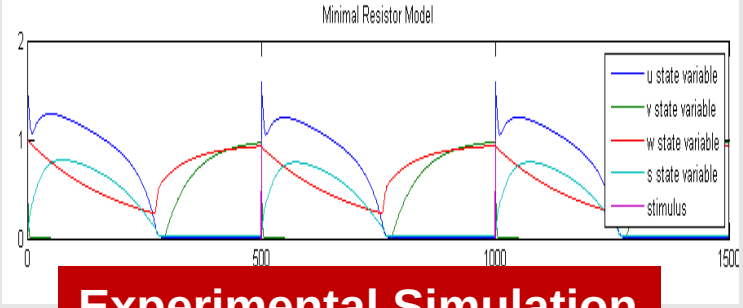
- Significant **breakthrough** in unifying **logical reasoning** and **numerical methods** [Gao et al. LICS'12, IJCAR'12, PhD Thesis, CADE'13]
- Theory and tools to perform model checking & parameter synthesis on **highly nonlinear hybrid systems**
- Successfully applied on **Atrial Filbrillation models** and many others

Counterexamples from **model checking** confirmed by experimental simulations**. Highly nonlinear** model without simplification.

Witness trace from Model Checking

Depth 24
1500 time units
(size: 96 ODEs, 240 variables)





Experimental Simulation

Workshops on Atrial Fibrillation and Pancreatic Cancer

- 2011 and 2013: Highly intensive **3-week workshops on Atrial Fribrillation** at Lehman College (Bronx, NY), organized by **Nancy Griffeth**
  - Develop scientific interest and skills for students from minority-serving institutions
  - Next workshop in 2014
- 2010 and 2012: Workshops on signaling pathways and pancreatic cancer
- Students co-authored in *Advances in Physiology Education*
- 66 students attended; several students went on to PhD programs

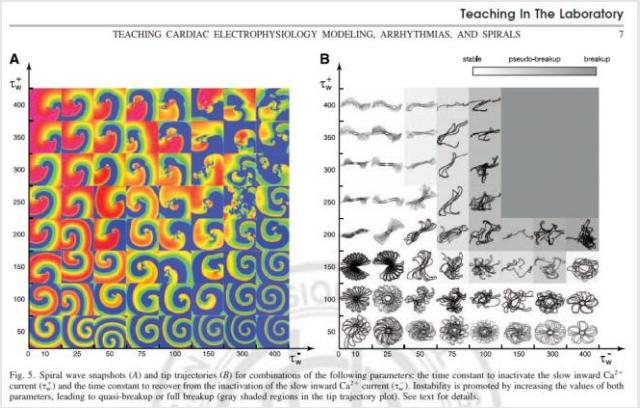
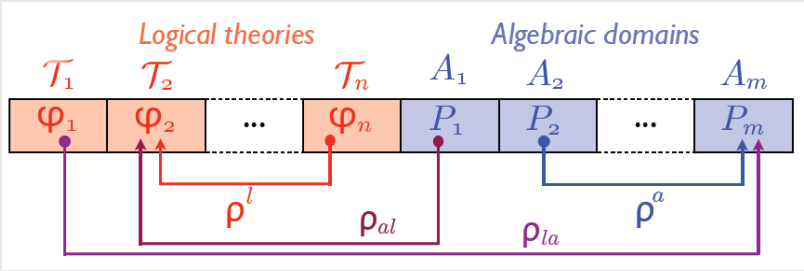


Fig. 5. Spiral wave snapshots (*A*) and tip trajectories (*B*) for combinations of the following parameters: the time constant to inactivate the slow inward Ca^{2+} current (τ_w^+) and the time constant to recover from the inactivation of the slow inward Ca^{2+} current (τ_w^-). Instability is promoted by increasing the values of both parameters, leading to quasi-breakup or full breakup (gray shaded regions in the tip trajectory plot). See text for details.

Other Significant Contributions

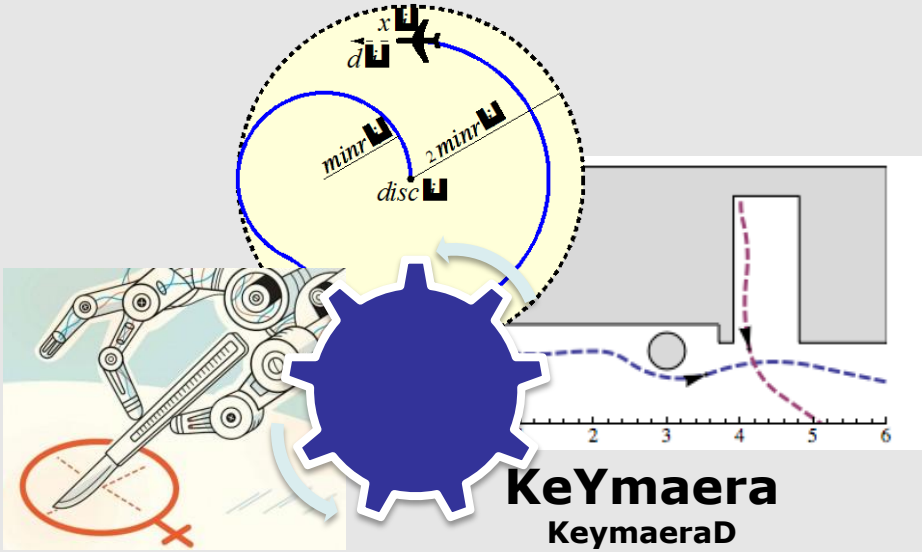
- G. Holzmann & K. Havelund performed formal analysis of complex software in **Curiosity Rover**

- P. Cousot has developed **liveness analysis of unbounded systems** [POPL 2012] and **combining algebraic and logical domains** [JACM 2012]

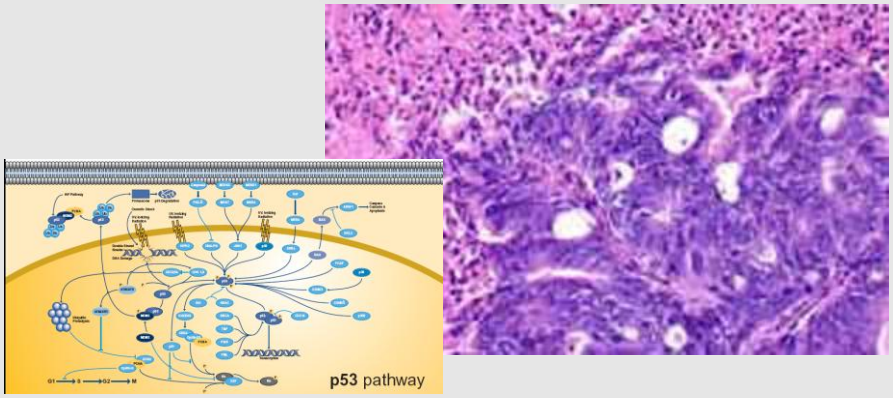


Other Significant Contributions

- A. Platzer's group have used **KeYmaera** Theorem Prover to formally verify the **Safety of Autonomous Robots** [RSS 2013], **Distributed Aircraft Controllers** and **Surgical Robots** [HSCC 2013]



- T.T. Wu, H. Gong and E. M. Clarke have identified **12-gene signature for PC survival** through Lasso-penalized Cox regression [*J. Bioinformatics & Computational Biology*. To appear]



Achievements Made Possible by EXP

- Many breakthroughs are coming from **new**, **cross-institutional**, **cross-disciplinary collaborations**

Atrial Fibrillation

Stony Brook

(Computer Sci)
Bartocci, Grosu
Smolka, Glimm

Georgia Tech/RIT

(Physics)
Fenton
(Biomedical)
Cherry, Climour

CMU

(Computer Sci)
Clarke, Gao
Kong, Liu

NYU

(Computer Sci)
Le Guernic

Pancreatic Cancer

CMU

(Computer Sci)
Clarke, Gong
Wang, Zuliani

Pitt

(Sys Biol)
Faeder
Miskov-Z

UMD

(Public Health)
Wu

UPMC

(Cancer Inst)
Lotze

Future Work:
The Next 15 Months and Beyond

- More **detailed, realistic & probing computational models** of the biological & embedded systems
- More **scalable formal analysis technology**
- More sophisticated **systems and** expressive **properties**
- Continue our outstanding **Education & Outreach** program

- Start planning for follow-up projects.