Biomedical Cyber-Physical Systems You Can Bet Your Life On

NSF CPS PI meeting 2011-08-01

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Outline

- Future-present robotics
  - Augmenting human skills, safety, and experiences
- Safety cases for robotic systems
  - Evidence-based certification for life-critical systems
- Future-present biology
  - Augmenting human health, productivity, and environment
- Safety cases for biological systems
  - Evidence-based certification for environment-critical biological systems

Future-Present Robotics

Augmenting human skills, safety, and experiences

Example: Telepresence Surgical Robotics

Origins of Remote Manipulation Robotics

- Leonardo da Vinci 1464
- Human-shape automaton
- Designed to raise arms, open visor, etc.
- Used cables and pullies to actuate
- Designs lost for 500 years
  - Rediscovered 1950

Origins

Remote manipulation of hazardous materials

- Robert Heinlein's 1942 science fiction "Waldo"
- Raymond Goertz (Argonne National Lab) and others developed Master-Slave Manipulators "Waldos" for radioactive handling in 1950s

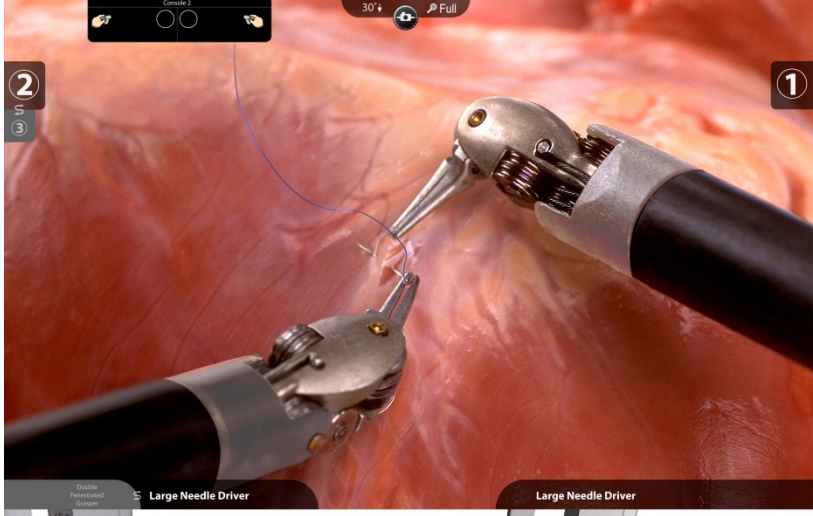
Teleoperation of Virtual Systems

- Brooks at University of North Carolina at Chapel Hill 1988, 1990

SRI Telepresence Surgery

- Phil Green's team at SRI created world's 1st complete telepresence surgical systems in 1980s and early 1990s
  - Primarily funded by DARPA for **remote military surgery**
  - Built on NIH funded experiments at SRI and Stanford University
  - Also built on NASA funding for remote teleoperation in space
    - NASA Flight Telerobotic Servicer (1980s)
  - Dexterous minimally invasive surgical tools
  - Intuitive user interface
- Successful demonstrations, though no long-range on-battlefield (let alone in-space) deployment
- SRI has many patents issued worldwide for the key components (now licensed to Intuitive Surgical)

The Basic Approach



- Human operator puts hands on master controllers
- Master system uses forward kinematics to compute desired pose of end effector
- Master computer communicates to slave control computer over a digital network
- Slave computer applies inverse kinematics to compute required robot arm and wrist angles
- Live stereo video is fed back to operator
- (optional) Sensed forces on slave effectors communicated back through similar system, providing haptic feedback

Other Pioneers in Robotic Surgery

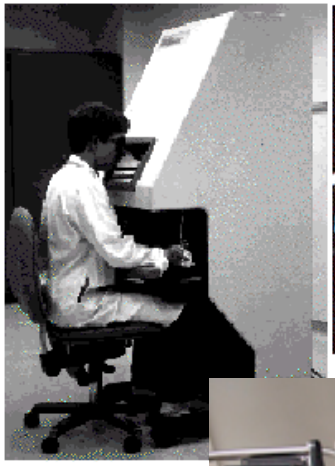
- Russel Taylor at IBM Watson Research Center and Mark Talamini at Johns Hopkins developed the Laparoscopic Assistant Robot
- Hari Das at JPL NASA-funded Robot Assisted Microsurgery (RAMS)
- Yulan Wang at UC Santa Barbara developed a robotic system Zues NASA-funded SBIR seeded Computer Motion Inc.
  - Computer Motion acquired by Intuitive Surgical in 2003
- Ken Salisbury at MIT developed innovative haptics systems
  - Later he joined Intuitive Surgical, now Stanford professor
- Brian Davies at Imperial College PROBOT
- Plus several other academic and industrial efforts

Intuitive Surgical

- Spun out from SRI in 1996
  - Large portfolio of SRI patents and prototypes
  - Entrepreneurs John Fruend, Dr. Frederick Moll, and Roberge Younge
  - Several SRI staff members, including current CEO Gary Guthart
  - Venture funding from Mayfield, Sierra, and Morgan Stanley

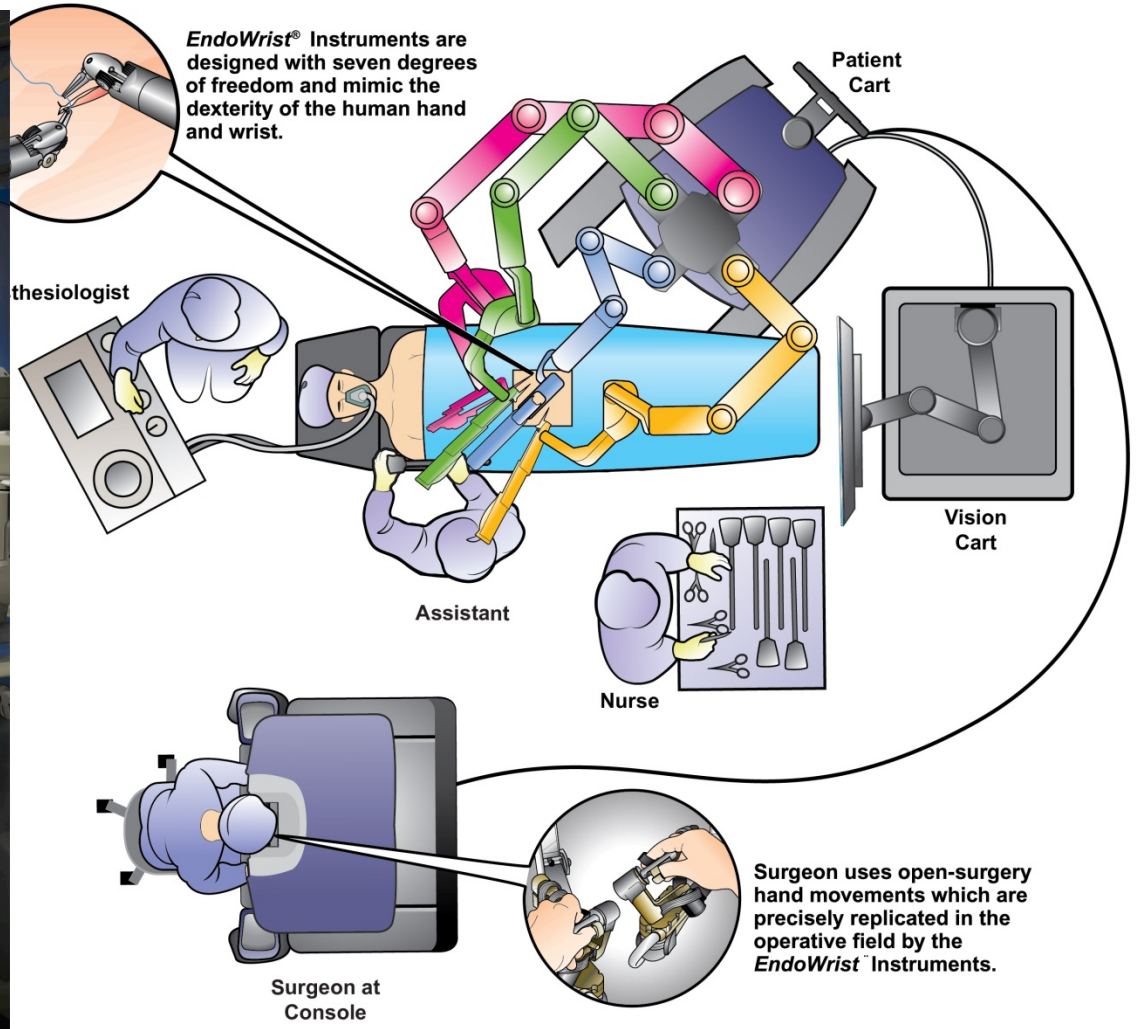
Forming a Venture: Intuitive Surgical

- SRI spun out Intuitive Surgical in 1996
- ISRG Refined SRI system into "Lenny" 1997
- Created daVinci robot 1998
- First robotic-assisted heart bypass 1998
- First beating-heart robotic-assisted heart bypass 1999
- IPO in April 2000
- FDA approval in 2003
- ISRG market cap today: $15B




Concept of Operations

Nurses at bedside, surgeon a few steps away



Impact of Telepresence Surgery

- Many types of surgery improved:
  - Urology, Gynecology, Cardiothoracic, General Surgery, Colorectal, Head & Neck, Pediatric
- ~2,000 installed daVinci robots installed
- Nearing one million surgeries total

  #1 treatment option for prostate and gynecological cancer
- Direct benefits:

  + Reduced risk of infection
  + Less pain and scarring
  + Less blood loss and less need for blood transfusions
  + Shorter hospital stay (2-5 days less for cardiac)
  + Faster recovery and return to normal activities
  - Note: Capital cost $1+M per robot, $1+K consumables

Example Impact on Cardio Bypass

- No sternotomy
- No 8-10” cut through chest
- No cuts through sternum
- No cracking of ribs
- Shorter time on table
- Shorter recovery time
- Less blood loss
- Less pain and scarring
- Quicker return to normal activities
- Less morbidity

Abstraction Enables

Putting a computer between surgeon and patient enables certain advantages

- Scaling up or down
- Virtually altering or stopping motion

Safety cases for robotic systems

Evidence-based certification for life-critical systems

Next Question: How Assured?

- Original system used unreliable transport network
- Software and hardware originally constructed using standard engineering practices
  - Not bad, but not perfect

- Engineering cannot aim for perfection

  99% yes. 99.999% yes. 100% no.
- What level of assurance is appropriate for this type of system?

FDA Approvals and Clearances

See: Medical Devices and Public Health, 2011

- Approvals require extensive documentation, laborious testing, rigorous science, expert review.
  This enables principled approval of new things
  - For drugs, not devices
- Medical devices are cleared, not approved, through the 510(k) process
  - 510(k) arises from 1976 congressional authorizing legislation
  - Main topic of 510(k): "substantial equivalence" to existing "predicate" devices

Definition of Substantial Equivalence in 1990 Safe Medical Device Amendments

A. For purposes of determinations of substantial equivalence . . . the term "substantially equivalent" or "substantial equivalence" means, with respect to a device being compared to a predicate device, that the device has the same intended use as the predicate device and that [FDA] by order has found that the device –

(i) has the same technological characteristics as the predicate device, or

(ii) has different technological characteristics and the information submitted that the device is substantially equivalent to the predicate device contains information, including clinical data if deemed necessary by FDA, that demonstrates that the device is as safe and effective as a legally marketed device and **does not raise different questions of safety and efficacy** than the predicate device.

B. For purposes of subparagraph (A), the term "different technological characteristics" means, with respect to a device being compared to a predicate device, that there is a significant change in the materials,…

Ensuring Safety and Effectiveness vs. Promoting New Innovative Medical Devices

- 1997 FDA Modernization act
  - Directs FDA to require "least burdensome" level of scientific evidence for manufacturers to assert substantial equivalence

- FDA attempting to foster innovation, but balance need for safety and evidence of effectiveness

Mathematician's Issues With 510(k)

- **Base case**: no reason to assume everything used before 1976 is safe and effective
- **Induction case**: broad definition of substantially equivalent may mean devices with really new, novel technology cleared without rigorous evidence of safety and effectiveness

Example Challenges in Verification that CPS biomedical systems meet their requirements

- Ethical testing of the unproven on human subjects
- Interoperable devices, inter-device interference
- Composability
- Lifecycle and maintenance issues
- Metrics and measurement
- Malicious attack
- Hybrid (discrete and analog) control
- Regulatory staffing (vs peer review)

Current FDA efforts are making progress on some of these challenges, such as assurance case frameworks

A Way Forward, How You Can Help

- Create new approval procedure for de novo medical devices, and for new technologies for equivalents
  + Evidence-based medicine, formal methods
  + Expand # of applications that cite clinical evidence
- Like the safety cases for avionics and other industries, enable reasonable procedures and practices based on rigorous scientific principles
  + Many in the Cyber-Physical-Systems community could be very helpful to this process
- Enable post-market monitoring of safety and effectiveness
  + Many in the HCSS / CyberTrust communities could be helpful in ensuring privacy and security

Looking to Other Industries: Consider Fly-By-Wire

- What computer would you feel comfortable putting between the pilot and the wings of the aircraft you will fly home on?
  - Digital fly-by-wire avionics is now commonplace
- Classic goal of nine-nines in avionics
  - One system failure in a billion hours of use
  - Practically untestable: >1000 planes flying >100 years
  - What evidence other than testing should be gathered for a new aircraft type?
  - Led by NASA and FAA, standards and practices for safety cases exist and are in regular use

Can We Show Medical Robots Operate Within Specified Parameters Despite Faults?

- Latency, Speed, Responsiveness, Accuracy, etc.

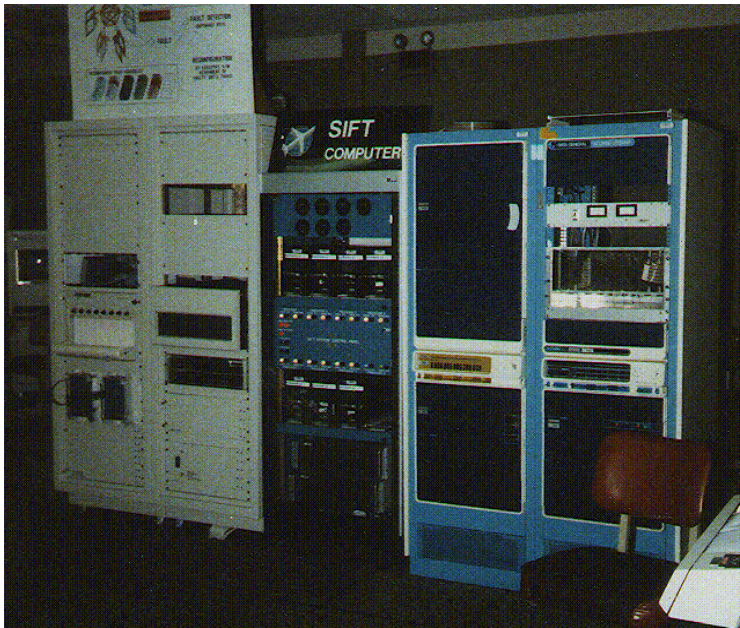
Leverage ancient history of high-assurance machines

- Byzantine fault-tolerance machines: NASA and SRI's SIFT, Allied's MAFT, Draper's FTP, Vienna MARS, AIPS
- Fundamental academic work in distributed systems

And their formal analysis

- Reduction of questions of interest to symbolic calculation: EHDM, PVS, ACL

Much high-quality research and development in academia and industry, including much performed or funded by speakers and attendees here at the NSF CPS meeting



Practicality of Assured Surgical Robotics?

- Recent advances in formal methods make practical the analysis of complex CPS systems such as medical robots
- Example project: SimCheck
  - Safety, Reliability, and Resilience of M7 slave unit
  - Matlab Simulink models of robot and control system
  - PVS and Yices used to analyze properties of models
  - **Natarajan Shankar**, John Rushby, Sam Owre, Bruno Dutertre
  - Supported by NASA Cooperative Agreement NNX08AY53A and NSF Grant CSR-EHCS(CPS)-0834810
- Other example projects at Berkeley, UPenn, MIT,…
  - Including speakers today

Next Steps

- Can the lessons learned here and tools developed help analyze infusion pumps, insulin pumps, heart monitors, pacemakers, and other new medical devices?
- Can we build a tool bus to integrate many analysis engines for designing high-assurance cyber-physical biomedical systems?
- What kind of assurance case can we build for such devices?
- What kind of architecture (with software health management) yields the strongest assurance case?

Future-Present Biology

Augmenting human health, productivity, and environment

Future Directions for Biomedical CPS

- Small assays
- Fast assays
- Precise biochemical actuation (Synthetic Biology)

Future Directions for Biomedical CPS
Extremely Small Assays

- Today many assays are performed on large populations of cells, averages are reported
- Move to single cell assays
  - Flow cytometry (Herzenbergs, Stanford)
    - 15-color cell sorter
  - Nanoliter PCR (Farris, SRI)
    - Single-cell-content PCR
  - Nanowire voltmeter (Lieber, Harvard)
    - 30 simultaneous electrical readings on single cell

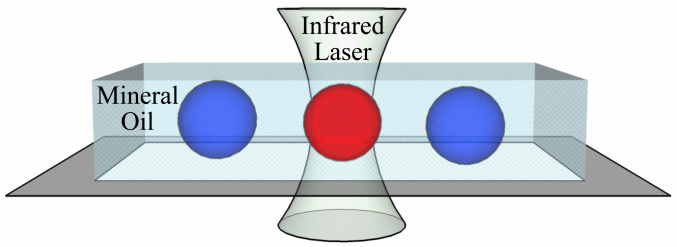
Future Directions for Biomedical CPS Extremely Fast Assays

- Today assays are performed over hours or days
- Tomorrow can we move to real-time assays?
  - Real-time (outpatient in clinic) blood assays
    - Can we tell if patient was exposed to pathogen, toxin, or radiation from a blood sample, before they leave the clinic?
  - Dialysis-like control systems
    - Can we enable more sensing and tighter controls, enabling dialysis-like treatment of sepsis, rapidly mitigate shock, etc?
  - Embedded medical devices
    - Can we enable long-term implantable medical devices to sense and actuate to improve health and wellness?
    - Insulin pumps, pacemakers, and others

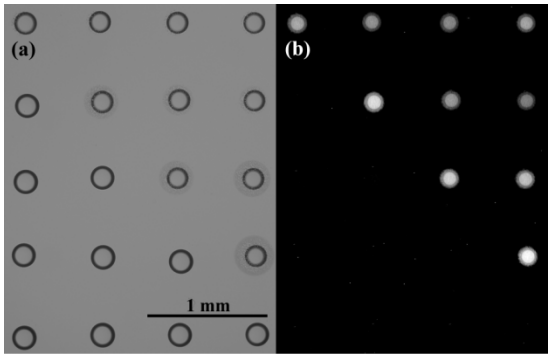
Example Enabler: Really Really Rapid PCR

Greg Faris, SRI

- Laser heating of nanoliter droplets allows extremely fast polymerase chain reaction (PCR) amplification of DNA and RNA
- One of fastest PCR methods
  >1000 PCR-base-pair cycles per minute
  40 amplification cycles of a 186 base pair amplicon in 370 s
- Amplification of the contents of **single cell** demonstrated

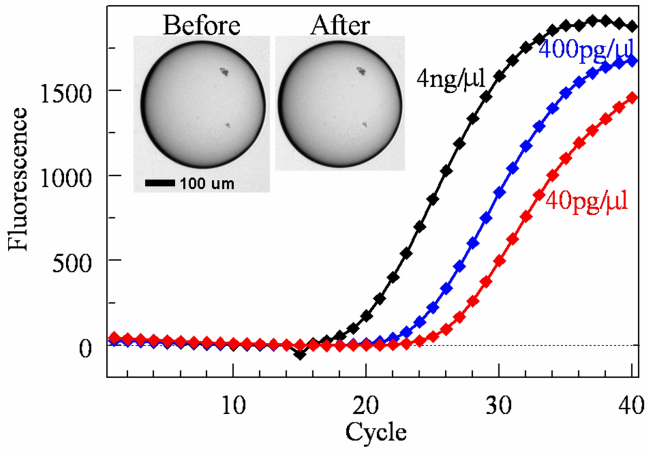


Laser Heating of Droplet



PCR Products in Droplet Array

Real Time PCR in Single Droplet



H. Kim, S. Dixit, C. J. Green, and G. W. Faris, "Nanodroplet real-time PCR system with laser assisted heating," Opt. Express 17, 218-227 (2009).

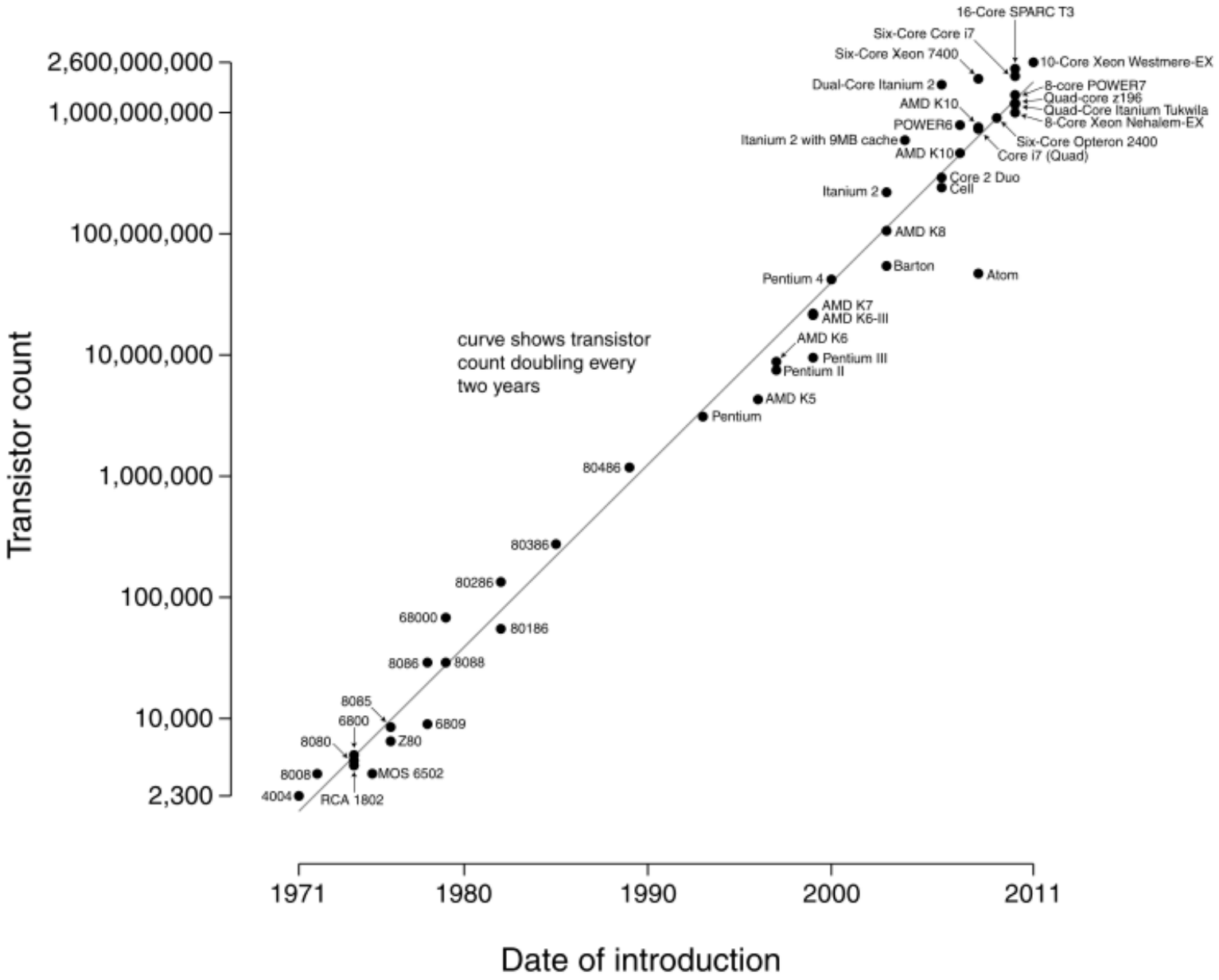
H. Kim, S. Vishniakou, and G. W. Faris, "Petri dish PCR: laser-heated reactions in nanoliter droplet arrays," Lab Chip 9, 1230-1235 (2009).

Precise Biological Actuation: Synthetic Biology

Definition of Synthetic Biology:
the design and construction of new biological parts, devices, and systems, and the re-design of existing, natural biological systems for useful purposes

Synthetic Biology is a new approach to engineering biology, with an emphasis on technologies to write DNA. Foundational work, including the standardization of DNA-encoded parts and devices, enables them to be combined to create programs to control cells.

Microprocessor Transistor Counts 1971-2011 & Moore's Law



Costs of Synthetic Biology

- The longest synthesized DNA sequence has been growing on a rapid exponential curve
  - It will likely slow as the utility of many megabase sequence synthesis is limited by design tools
- More importantly, the cost of DNA sequencing is now low and continues to drop exponentially
- Also, the cost of DNA synthesis continues to drop, though somewhat more slowly

Moore's Law & Carlson Curves
The Cost of Fablines

- The cost of production for chips (especially the capital required for a fab) is rising
  - Though not rising as fast as in the past
  - Astounding capital commitment is required (>$5B)
- The cost of production for biology is falling

Emerging Synthetic Biology Community

- Synthetic Biology 1.0, 2.0, 3.0, 4.0, 5.0
  - Led by Tom Knight, Drew Endy, and Randy Rhetberg
- Growing the community from the bottom up
  - Already great international interest

Safety cases for biological systems

- Evidence-based certification for environment-critical biological systems

Assessing Risks of Synthetic Biology

- Presidential Commission for the Study of Bioethical Issues recommendation:
  - Risk Assessment Prior to Field Release
  - See: "NEW DIRECTIONS The Ethics of Synthetic Biology and Emerging Technologies" December 2010
- Risk Assessment Prior to Field Release
  - Reasonable risk assessment should be carried out, under the National Environmental Policy Act or other applicable law, prior to field release of research organisms or commercial products involving synthetic biology technology. This assessment should include, as appropriate, plans for staging introduction or release from contained laboratory settings. Exceptions in limited cases could be considered, for example, in emergency circumstances or following a finding of **substantial equivalence to approved products**

Risk Assessment Prior to Field Release and Substantial Equivalence Determination

- How do we go about this?
- Living systems are wickedly complicated
- Our knowledge is extremely limited
- Our ability to accurately model and predict behaviors of a given organism is extremely limited
- Our ability to accurately predict changes in systems, such as DNA mutation, is extremely limited

Rigorous Abstract Methods Are Needed To:

- Accommodate conventional types of discrete reasoning based on experimentation
- Unambiguously define a model and allowable reasoning steps
- Provide predictive power for generating testable hypotheses

A Way Forward, How You Can Help

- Create new analysis methods for de novo biological devices, and for new technologies for equivalents
  + Evidence-based synthetic biology, formal methods, pathway logic, pathway tools
- Like the safety cases for avionics and other industries, enable reasonable procedures and practices based on rigorous scientific principles
  + Can we close the gap that exists in design tools in this domain?
  + Many in the Cyber-Physical-Systems community could be very helpful to this process
- Enable post-release monitoring of genetically modified and synthetic organisms
  + Many in the HCSS / CyberTrust communities could be helpful in ensuring privacy and security

The End