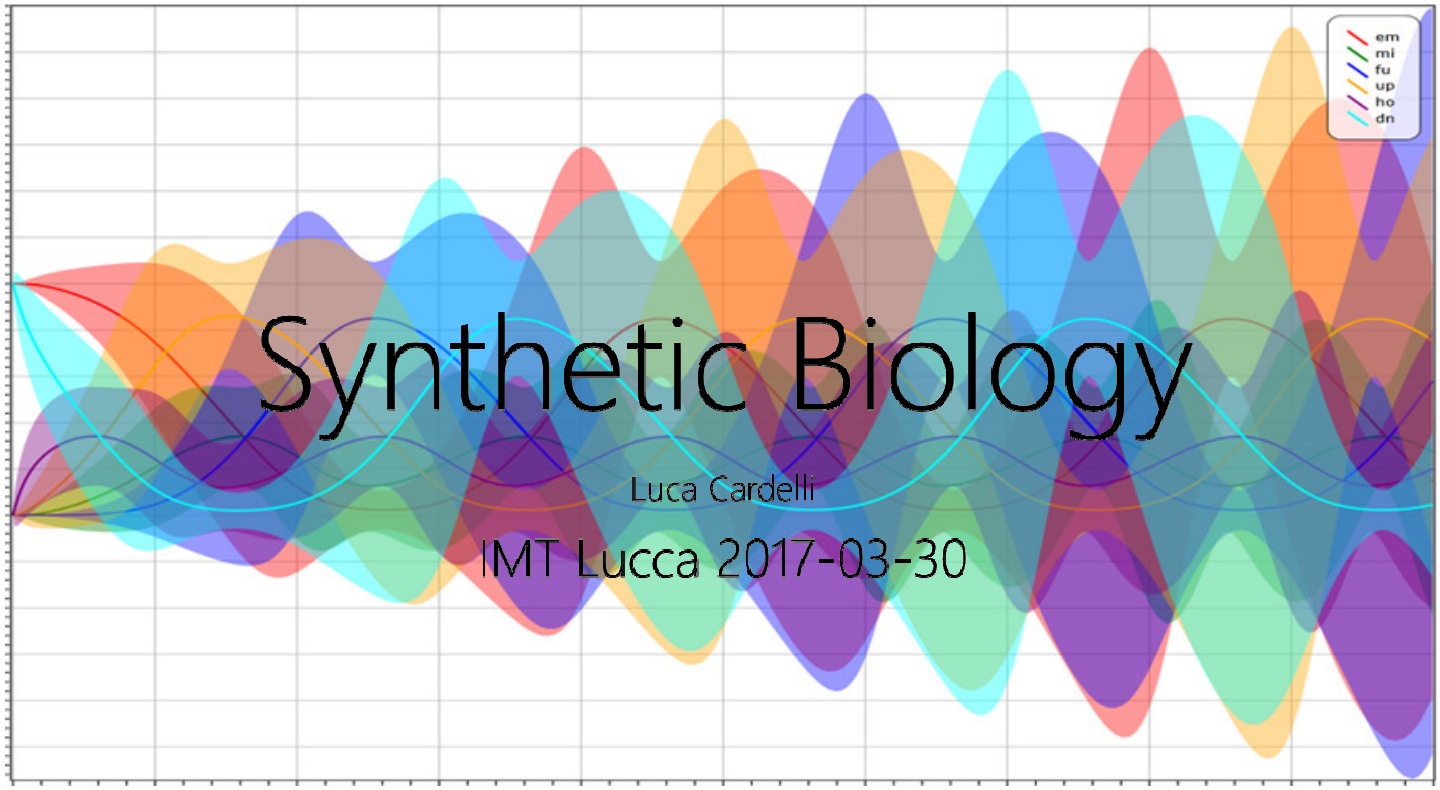


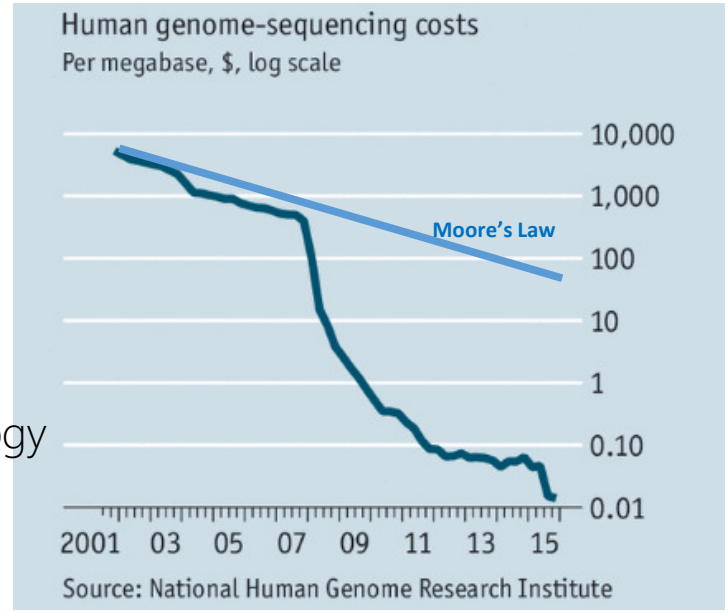
Synthetic Biology

Luca Cardelli

IMT Lucca 2017-03-30

Trends

- Technological Context
  - Moore's Law is approaching the single-molecule limit
  - Carlson's Curve is the new exponential growth in technology
  - In both cases, we are now down to *molecules*

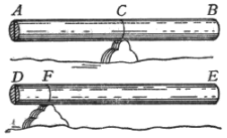


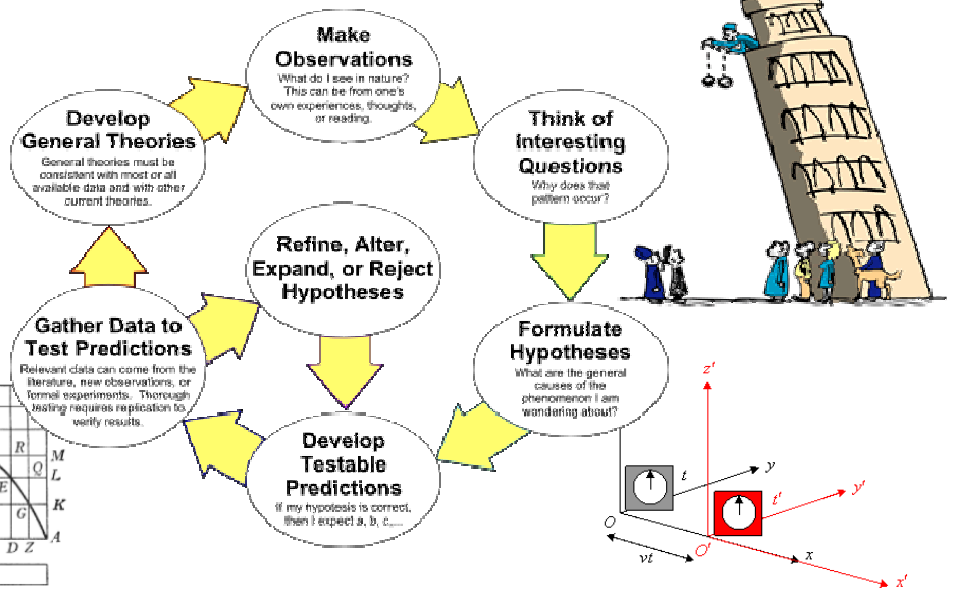
- Automating the discovery and synthesis of molecular systems
  - Unambiguous descriptions of molecular systems
  - Computational analysis of scientific models
  - Performance evaluation of experimental protocols
  - Make physical matter as programmable as software

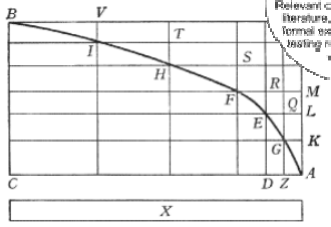
State of the Art Yesterday - Discovery

- The Scientific Method ~ 1638

- 1 Guy







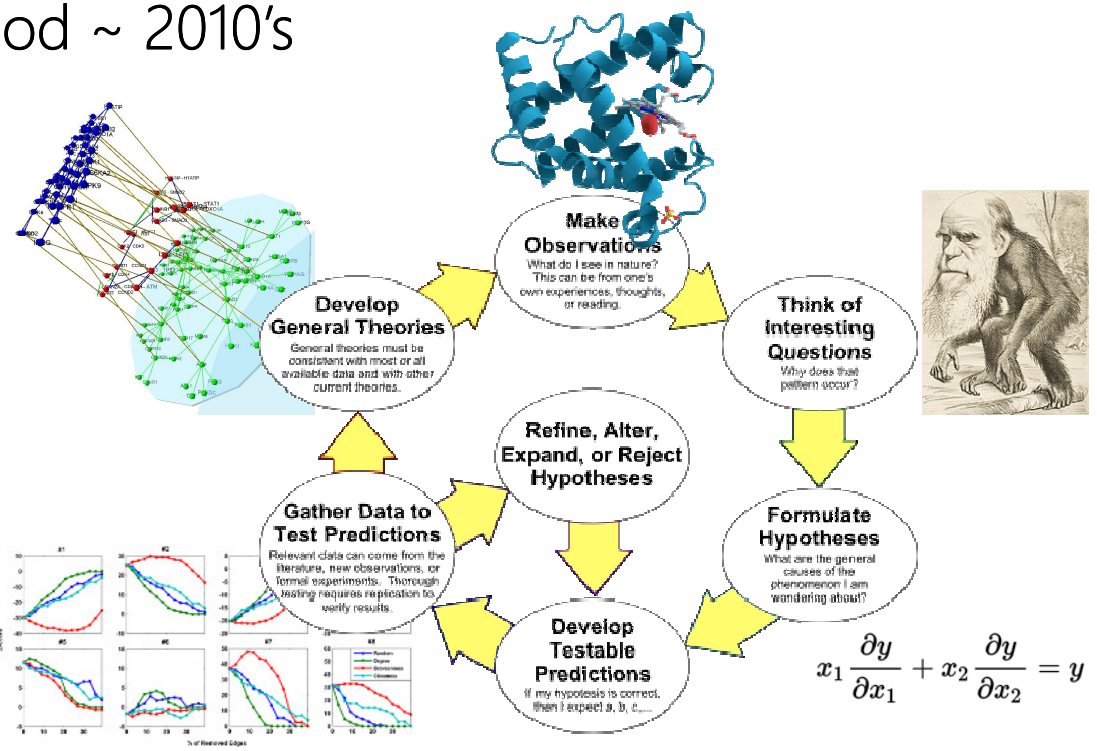
State of the Art Today - Discovery

- The Scientific Method ~ 2010's

• 1 Lab

1 protein = 30 people / 30 years

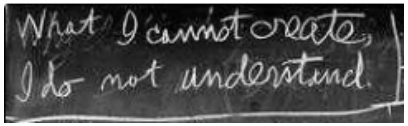
Humans have >250,000 proteins ☹



New Approach – Discovery + Synthesis

- The Scientific Method ~ 2020's

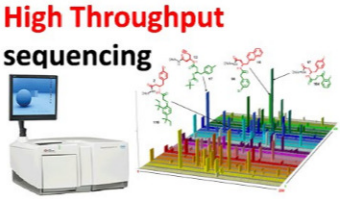
- 1 Software

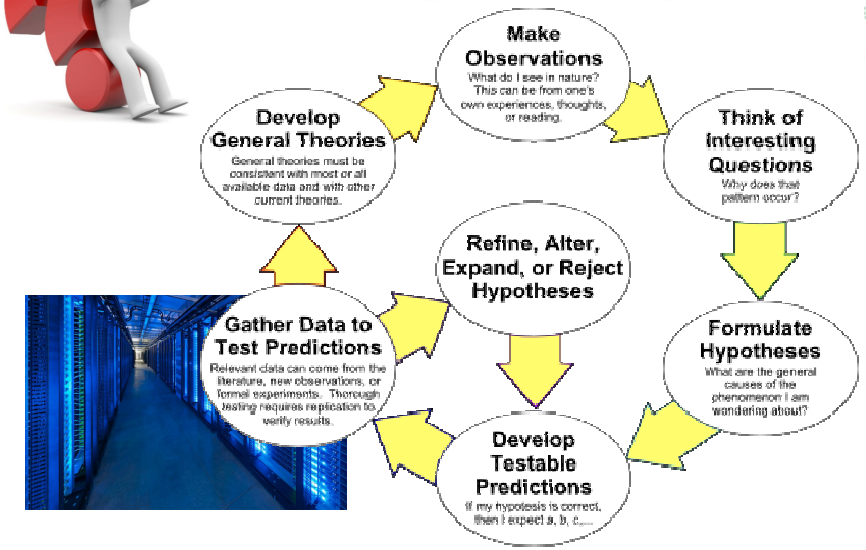


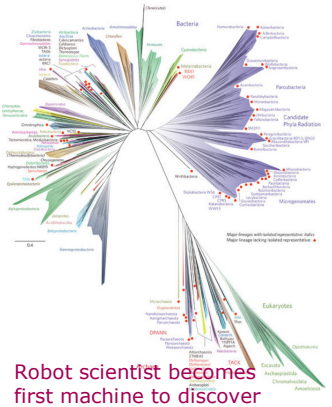
Falsification + Verification

Discovery in complex systems requires increased intervention - synthesis

Read nature, but also write nature.







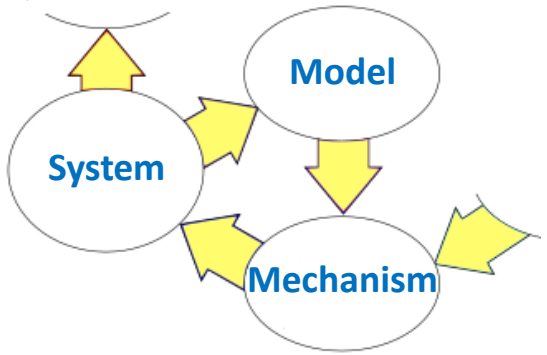
Robot scientist becomes first machine to discover new scientific knowledge

Ross King

New Approach – The Inner Loop

- A *model* is refined by testing *mechanisms* within *systems*
- Today: publication does not accurately reflect execution
  - Model: poorly-maintained matlab script
  - Mechanism : poorly-described manual protocols in the lab
  - System: poorly-characterized and hardly "resettable"
  - ⇒ Crisis in biology: experiments are done once and are hard to reproduce

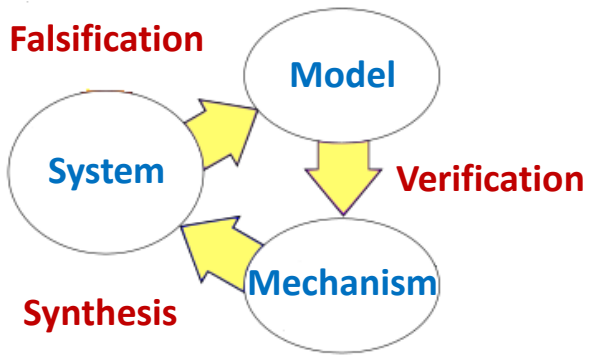
    http://www.nature.com/news/reproducibility-1.17552



New Approach – The Inner Loop

- Tomorrow, automation

Nodes
- Model: unambiguous (mathematical) description (CompBio)
- Mechanism: standardized (engineered) parts and protocols (SynthBio)
- System: characterized (biological) organism and foundries (SysBio)



Arcs
- Verification: simulation / analysis / model checking / theorem proving
- Synthesis: exponential technological growth – sit back and enjoy
- Falsification: lab automation / statistical inference / model reduction

Lifecycle
- Performance evaluation/optimization: of model+protocol+system combined
- Management: version control, equipment monitoring, data storage

Getting around the inner loop

Nodes

- Models (mathematical): [Oxford]
  - We work on understanding the intrinsic computational capability of matter, as expressed by the "language" of chemical reaction networks
- Mechanisms (technological): [Oxford Physics, MSRC] [previously: Caltech, UW]
  - We engineer nanotechnology constructs that perform computation and control
- Systems (biological): [King's College, MSRC]
  - We search for computational mechanisms in natural systems

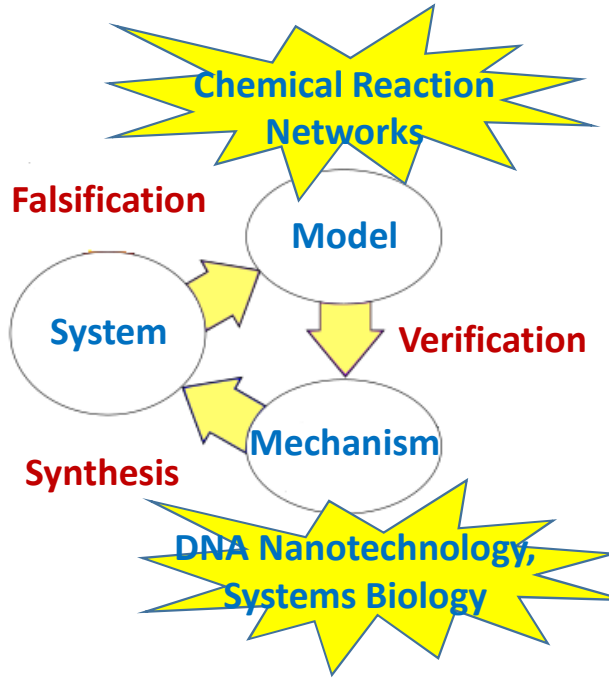
Arcs

- Verification: [Oxford, MSRC]
  - We develop software tools and algorithms for the analysis and simulation of biochemical models.
  - We integrate new algorithms and model classes into our (MSRC) tool suites.
- Synthesis: [Oxford Physics, MSRC] [previously: Caltech, UW] [MSR, Technion?]
  - We develop techniques to "compile" chemical programs into (e.g. DNA) molecules.
- Falsification: [IMT Lucca]
  - We work on advanced algorithms for model reduction of very complex data sets

Lifecycle

- Performance evaluation/optimization: [Oxford, MSRC]
  - We plan to apply hybrid (probabilistic+continuous) modelchecking techniques that we are developing, to verify properties and error bounds of integrated models + lab protocols

Opportunistic



Collaborators

Oxford University - Computer Science



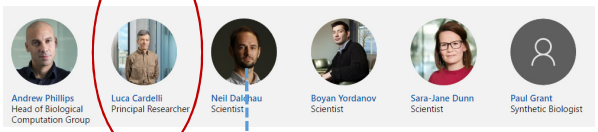
Marta Kwiatkowska
Professor

Luca Laurenti
Royal Society PhD Student

Max Whitby
PhD Student

What/how can we compute with chemical networks and DNA?
How can we verify the properties of engineered molecular systems?
CMSB'15 CMSB'16 QEST'16 DNA'16 DNA'16 HSCC'17 BioSystems'17

MSR Cambridge - Biological Computation



Algorithms & Tools

King's College London - Biology


Attila Csikász-Nagy
Senior Lecturer

Rosa Hernansaiz Ballesteros
MSR PhD Scholarship '15

How do biological switches and oscillators work?
What are the algorithms and how did they evolve?
ScientificReports'16, PLoS'17

Oxford University - Physics


Andrew Turberfield
Professor

Michael Boemo
Postdoc

How can we perform logic with DNA walkers?
ACS SynthBio'16 PhD'16

Lucca Institute for Advanced Studies



Mirco Tribastone
Associate Professor

Andrea Vandin
Assistant Professor

Max Tschaikowski
Assistant Professor

How can we automatically simplify large molecular networks, natural or synthetic, exactly or approximately?
CONCUR'15 POPL'16 LICS'16 TACAS'16 TACAS'17

MSR Redmond / Technion Israel



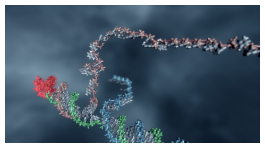
Karin Strauss
Researcher

Zohar Yakhini
Visiting Faculty

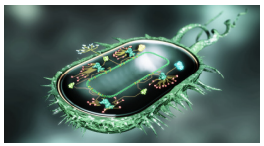
Leon Anavy
MSR PhD Scholarship '17

How can we efficiently store data in DNA?

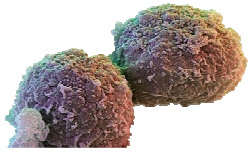
A platform for programming biology



Programming DNA
(Nature Nanotechnology 2013)



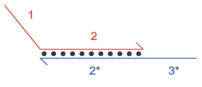
Programming Genetic Devices
(Molecular Systems Biology 2016)



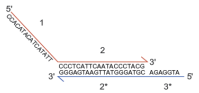
Reprogramming Cells
(Science 2014)

Domain Specific Languages

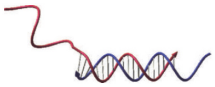
DNA Domains



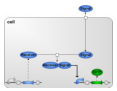
DNA Sequences



DNA Biophysics

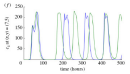


Genetic Circuit

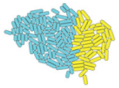


Chemical Reaction Network

Ordinary Differential Equations



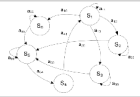
Cell Biophysics



Partial Differential Equations

Symbolic Regulatory Network

Labelled Transition System



Continuous Time Markov Chain

Abstractions, Compilers, Verification

Biological experiments as programs SYNTHACE

Bayesian Inference; Machine Learning

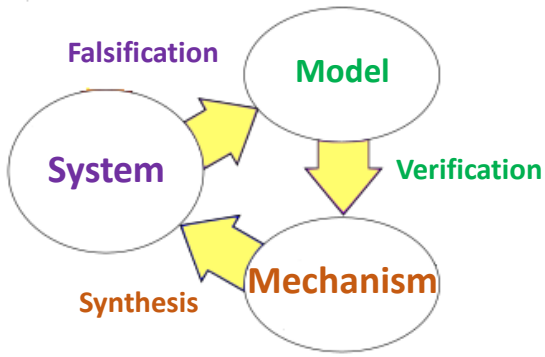
Automation & Analytics

Lab robotics

Microsoft Azure

Infrastructure

Appendix



Key papers from some years back

- **The Cell Cycle Switch Computes Approximate Majority** (Scientific Reports'12)
- **Programmable chemical controllers made from DNA** (Nature Nanotech'13)
- **Morphisms of Reaction Networks that Couple Structure to Function** (BMC Systems Biology'14)

- Biological Algorithms
- Nanotechnology
- Model reduction

Color Coded

Recent papers

- **Efficient Switches in Biology and Computer Science** (PLOS Computational Biology'17)
- **ERODE: A Tool for the Evaluation and Reduction of Ordinary Differential Equations** (TACAS'17)
- **Noise Reduction in Complex Biological Switches** (Scientific Reports'16)
- **Chemical Reaction Network Designs for Asynchronous Logic Circuits** (DNA22 '16)
- **The Formal Language and Design Principles of Autonomous DNA Walker Circuits** (ACS Synthetic Biology'16)
- **A Stochastic Hybrid Approximation for Chemical Kinetics Based on the Linear Noise Approximation** (CMSB'15, BioSystems'16)
- **Comparing Chemical Reaction Networks: A Categorical and Algorithmic Perspective** (LICS'16)
- **Programming Discrete Distributions with Chemical Reaction Networks** (DNA22 '16)
- **Approximation of Probabilistic Reachability for Chemical Reaction Networks.** (QEST'16)
- **Efficient Syntax-Driven Lumping of Differential Equations** (TACAS'16)
- **Symbolic Computation of Differential Equivalences** (POPL'16)

http://lucacardelli.name/