Reinventing Chemistry

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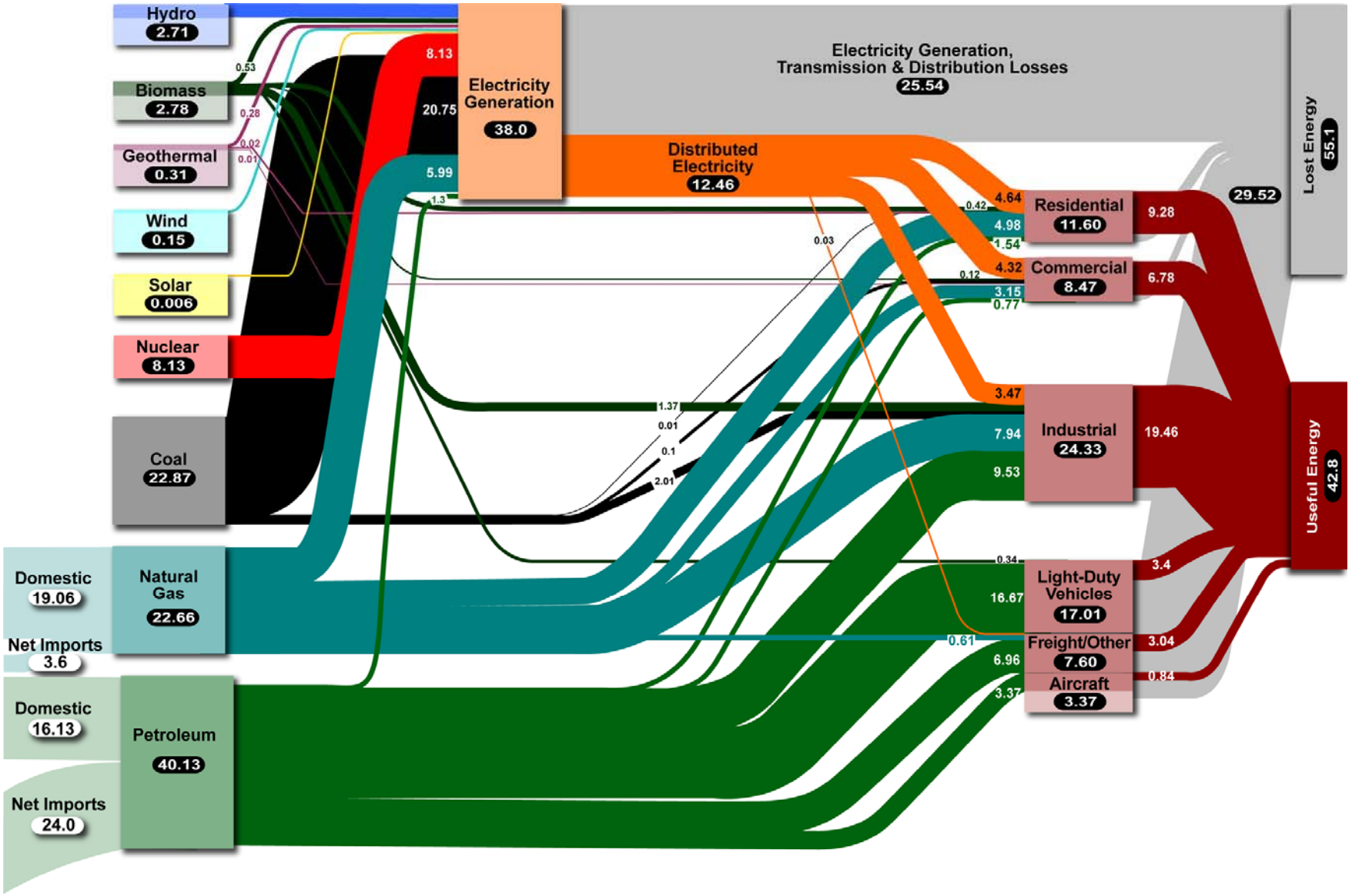
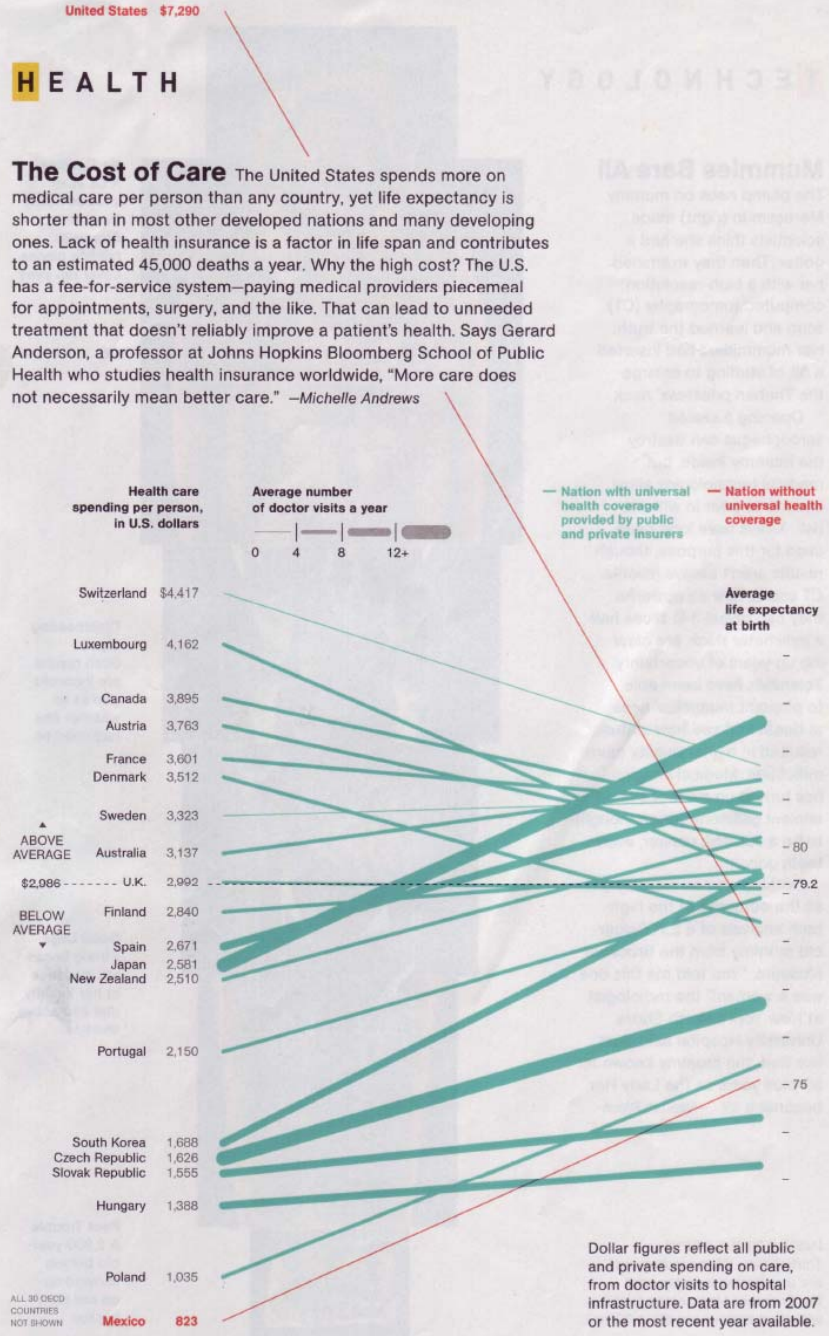

Hydro
2.71
Biomass
2.78
Geothermal
0.31
Wind
0.15
Solar
0.006
Nuclear
8.13
Coal
22.87
Domestic
19.06
Natural Gas
22.66
Net Imports
3.6
Domestic
16.13
Petroleum
40.13
Net Imports
24.0
Electricity Generation
38.0
Electricity Generation, Transmission & Distribution Losses
25.54
Distributed Electricity
12.46
Residential
11.60
Commercial
8.47
Industrial
24.33
Light-Duty Vehicles
17.01
Freight/Other
7.60
Aircraft
3.37
Lost Energy
55.1
Useful Energy
42.8
29.52
9.28
6.78
19.46
3.4
3.04
0.84
0.53
0.28
0.02
0.01
8.13
20.75
5.99
1.3
0.03
1.37
0.01
0.1
2.01
0.42
4.64
4.98
1.54
0.12
4.32
3.15
0.77
3.47
7.94
9.53
0.34
16.67
0.61
6.96
3.37

HEALTH

The Cost of Care

The United States spends more on medical care per person than any country, yet life expectancy is shorter than in most other developed nations and many developing ones. Lack of health insurance is a factor in life span and contributes to an estimated 45,000 deaths a year. Why the high cost? The U.S. has a fee-for-service system—paying medical providers piecemeal for appointments, surgery, and the like. That can lead to unneeded treatment that doesn't reliably improve a patient's health. Says Gerard Anderson, a professor at Johns Hopkins Bloomberg School of Public Health who studies health insurance worldwide, "More care does not necessarily mean better care." *–Michelle Andrews*



GRAPHIC: OLIVER UBERTI, NG STAFF. SOURCE: "OECD HEALTH DATA 2009," ORGANISATION FOR ECONOMIC CO-OPERATION AND DEVELOPMENT

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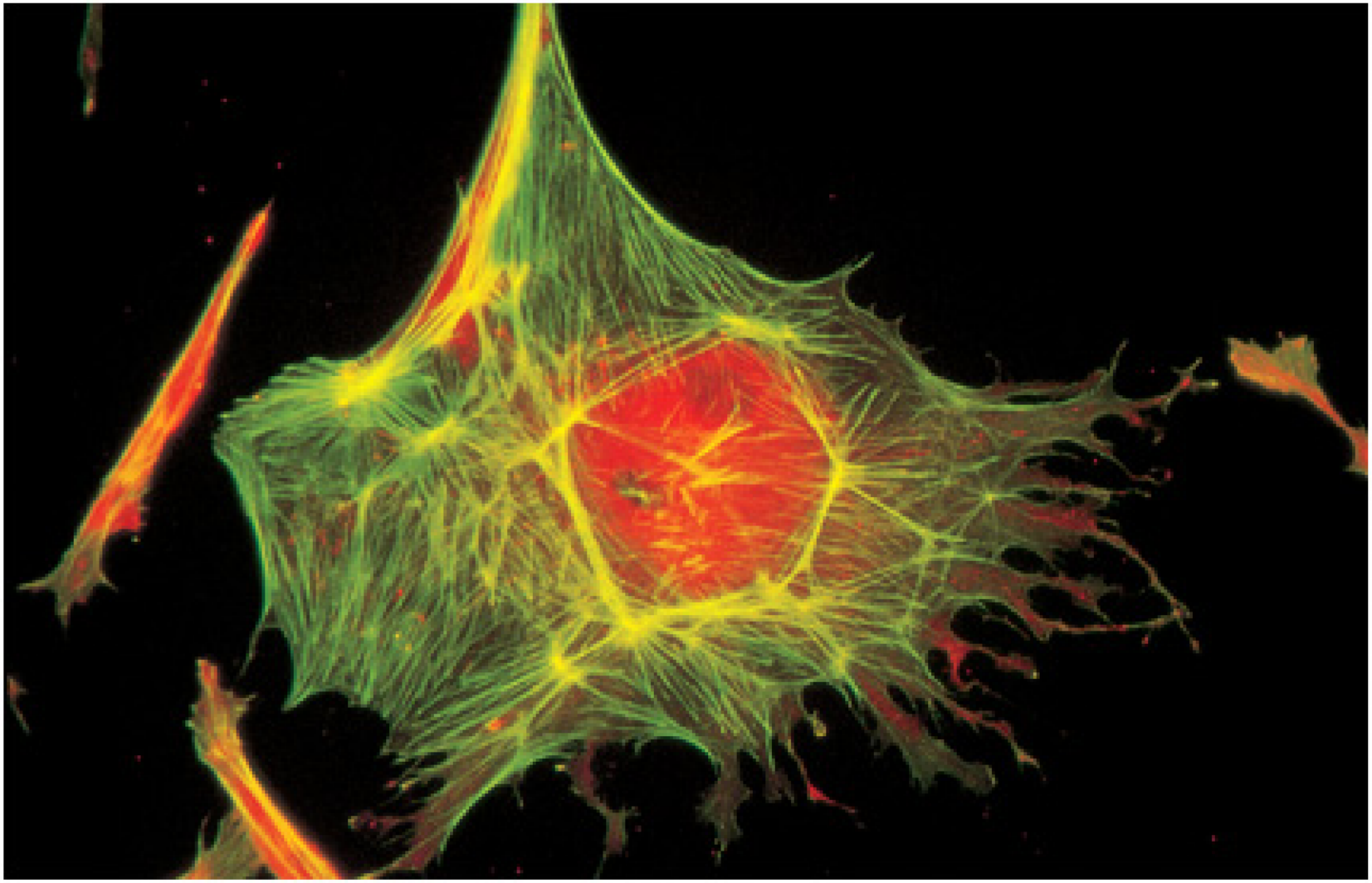
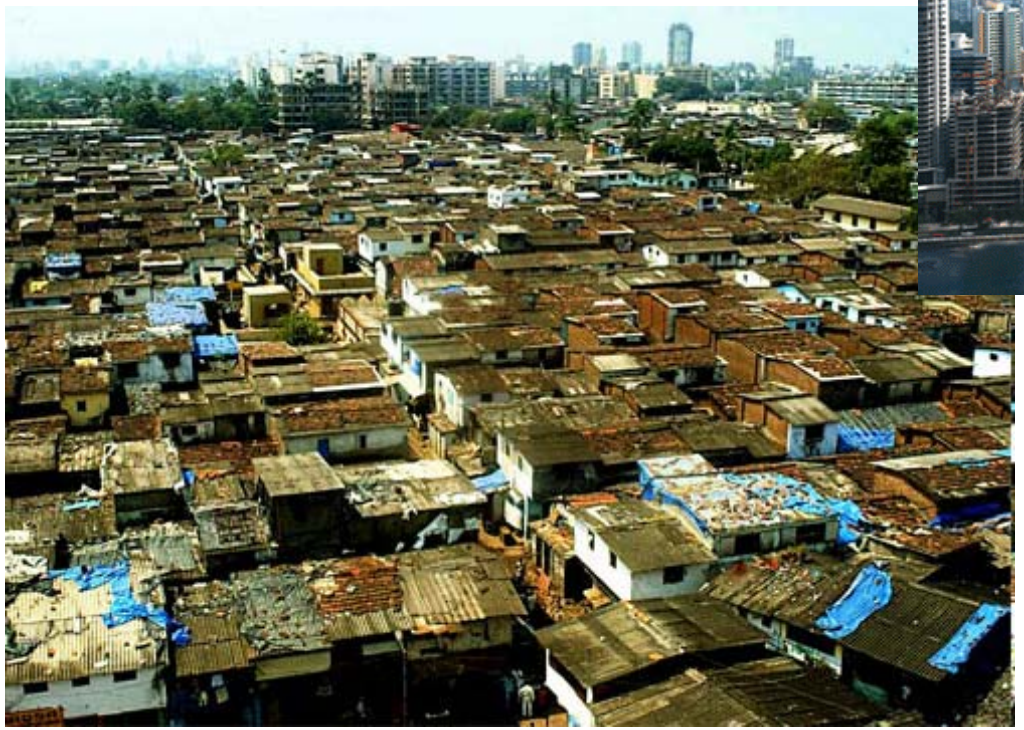


Megacities



Observation: Over 20 years, Jobs in Chemistry (US): -300,000

Avignon, 2007

- **What are the biggest ethical problems facing society…?**
- **Who is responsible for solving them?**
- **Obligations?**

Obligations to whom?

- **Industry: to stockholders/stakeholders**

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- **Research Universities:**
  - **To our fellow citizens?**
  - **To our profession? (peer review,…)**
  - **To ourselves (“unfettered curiosity”; personal advancement; …)**
  - **To students?**

Obligations to whom?

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  - **To students?**
- **“Curiosity driven” vs “Problem solving”**

Big Problems: Society and Science

- Climate Variability: ***global stewardship***
- **Water and Energy:** ***standard of living***
- Sustainability: ***obligations to the future***
- Health care: lowering costs, raising effectiveness, distributing benefits: ***equity and justice***
- Globalization: ***redistribution of opportunity and wealth***
- Developing Countries: ***equity and stability***
- Jobs: ***stabilizing societies, individual value***
- **Robotics; intelligent machines:** ***work and jobs***
- **Information:** ***privacy, equity, and access***

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- **Understanding:**
  - **Life, and its origins; the cell; sentience**
  - **Energy, water, the environment,**
  - **Complexity, emergence; simplicity**
  - **Societal needs: healthcare, sustainabilty, …**

Energy, Climate, Water, Sustainability

$$Wellbeing \approx \frac{Energy}{People}$$

Technology provides *options* to society

Options.

- *Generate more energy (in acceptable form: climate!)*
- *Conserve the energy we now generate.*
- *Have fewer people*

Five Opinions (Mine, but also Others')

The most important problems facing society, and the most interesting problems in science, belong to chemistry.

The cooperation in discovery between university and large industry has atrophied. Chemical industry does not rely on new products for growth; universities are doing more *development* and less *research*.

Society is no longer excited by what chemistry provides: "paint" vs. stem cells and Facebook.

Longer-term, curiosity-driven research is *more* important than in the past, but harder to justify.

Chemistry has forgotten about poetry

$0 \rightarrow 1$; $1 \rightarrow 10$; $10 \rightarrow 100$; $100 \rightarrow 10^6$

Science

Understanding

Engineering

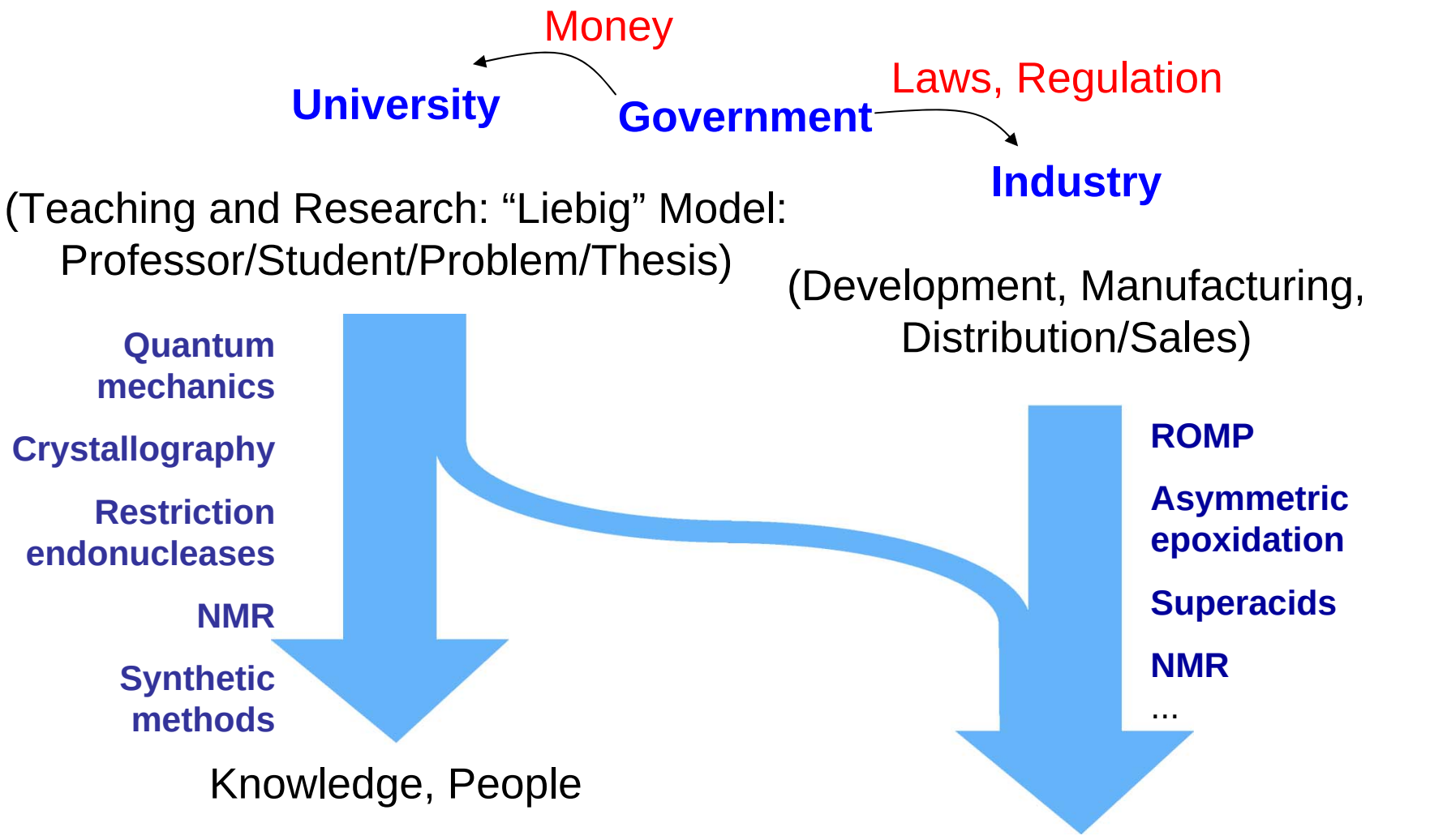
Solving defined problems

Invention/Discovery

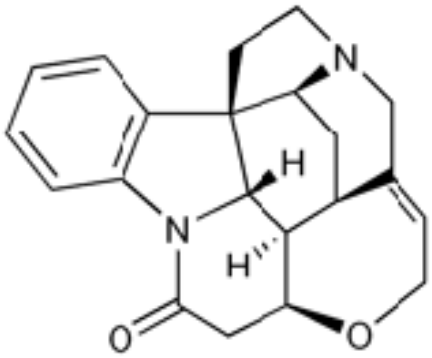
"What's that?"

"Can I ….?"

The Structure of Chemistry

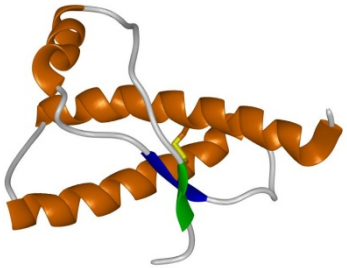


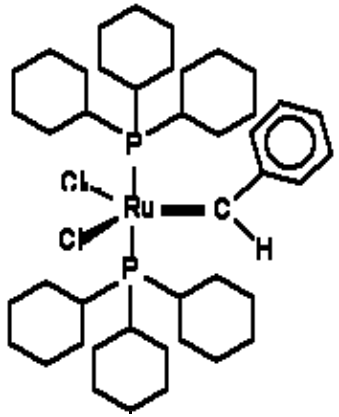
The Past 50 Years: Great Successes



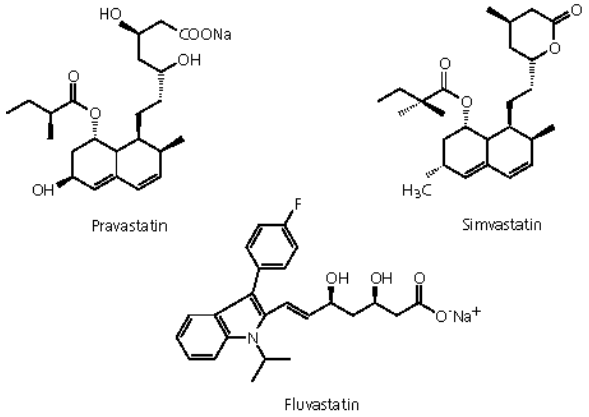
strychnine

protein NMR

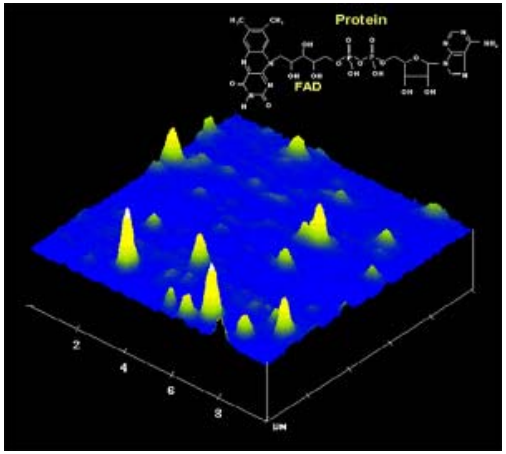




ROMP catalyst



statins



single-molecule spectroscopy

CH_y, NO_x ⟶ CO_2 + N_2

So: Why is there a Problem?

Is there a problem?

Bill Bryson, "A Short History of Nearly Everything", Random House, 2003

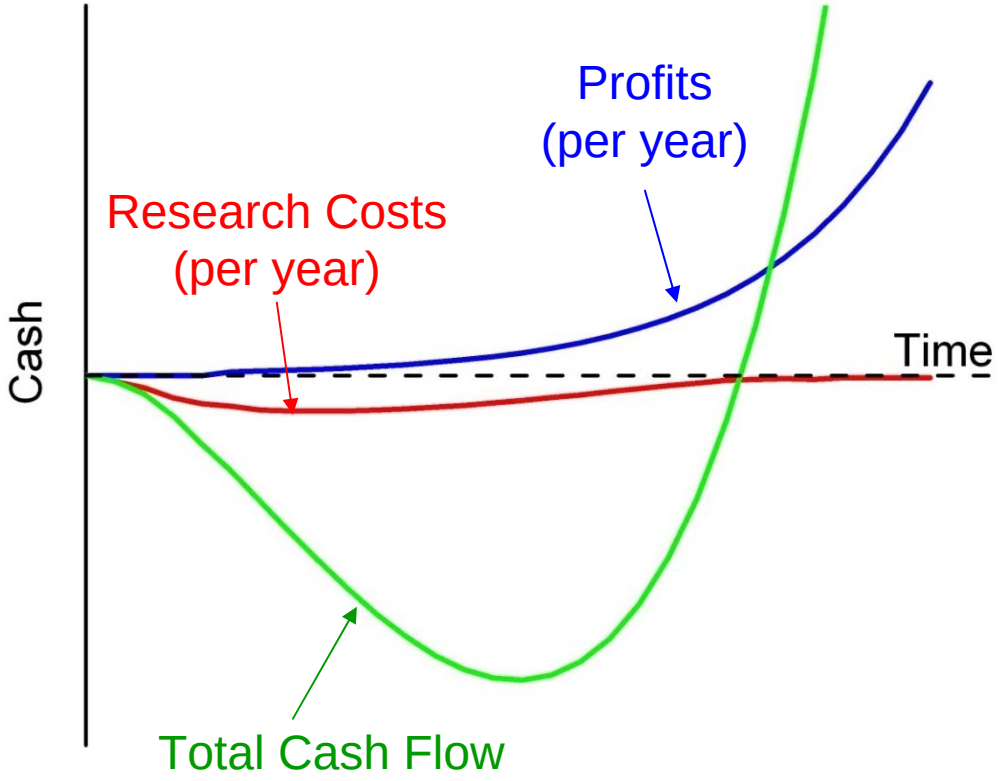
p. 137:

Physicists are notoriously scornful of scientists from other fields. When the wife of the great Austrian physicist Wolfgang Pauli left him for a chemist, he was staggered with disbelief. "Had she taken a bullfighter I would have understood," he remarked in wonder to a friend. "But a *chemist*. . ."

Broad Issues

- **Capitalism**
  - **Recognizes financial return, not strategic value or social/societal return.**
  - **Assigns little value to long-term research**
  - **Centers of wealth are shifting (from US, Europe, Japan to China, Russia, middle east)**
- **Globalization**
  - **Lowest-cost provider wins …**
- **Information**
  - **IT (computers, www, . . .) has changed everything.**
- **Workforce**
  - **Cost; Work ethic; Education; Transnational flows**

Money: *Time- and Risk-Discounted Cash Flow*



Is there *any* economic model that justifies long-term/non-product related research? *(Option theory?)*

If it takes a long time, it's hard to justify!

Business Development

"The principal applications of any sufficiently new and innovative technology always has been—and will continue to be—applications created by that technology.

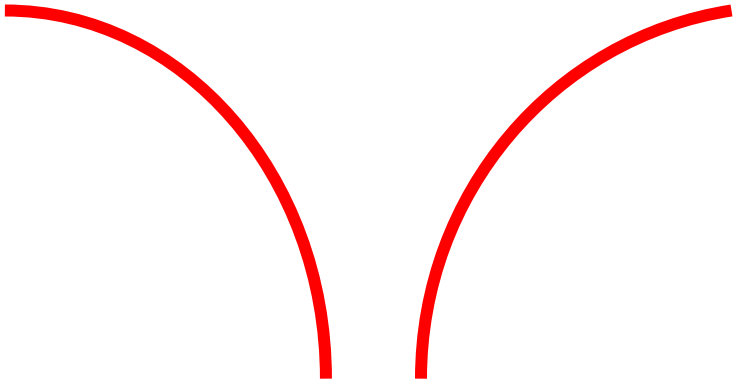
Herbert Kroemer (2000 Nobel, Physics)

High Technology: the Pharmaceutical Industry

Hit
Lead

ADME/
Tox/PK

Clinicals:
Phase I
II
III



Cost of capital > Return on Invested capital?

In the past, the pharmaceutical industry:

**** supplied the problem to the universities, and***

**** measured the function.***

Now, much harder (targets, safety, clinical failure) and less familiar to universities

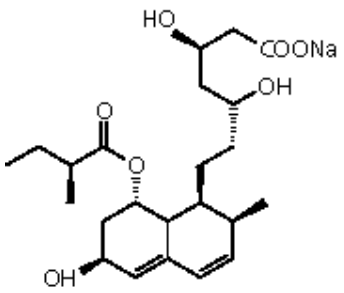
Research Universities

- **“Liebig:” Research in Universities**
- ***Research* Universities: A US invention after WW II.**
- **Designed to provide technical capability for national security, but…now: two views:**
  - **“Leave us alone. Remember quantum mechanics!”**
  - **“Playtime is over!”**
- **Vannevar Bush “The Endless Frontier”**
  - **Jobs**
  - **Health**
  - **National Security**

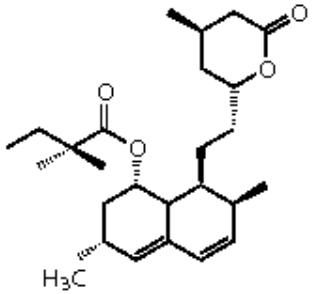
Research Universities: Now

- **Incentives reward conservatism.**
- **Peer review is democratic and rewards average ideas. Invention and scholarship are elitist.**
- **Many pressures to be “relevant” and politically correct.**
- **Connections to financially oriented capitalism are complicated.**
- **Growth, dependence on government money has grown a robust bureaucracy.**

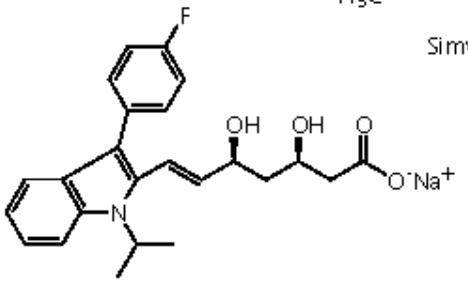
Poetry



Pravastatin



Simvastatin



Fluvastatin

- Statins block HMGA-CoA reductase and act as antiinflammatories. They are a major source of sales for the pharmaceutical industry.

Poetry

- **Statins change the way we die.**

Identity: What does field…“X”… do?

- **Biology and Biomedicine**
  - **Cures disease, understands the nature of life, the brain,…**
- **Physics and Astronomy**
  - **Studies exploding stars, quarks, energy, matter, and all that; makes the internet, cellphones, and nuclear weapons; does nanotechnology and quantum whatever**
- **Chemistry**
  - **?...**

Is Chemistry Scientifically Mature? Can We...

… *really* understand molecules / reactions?

… engineer function?

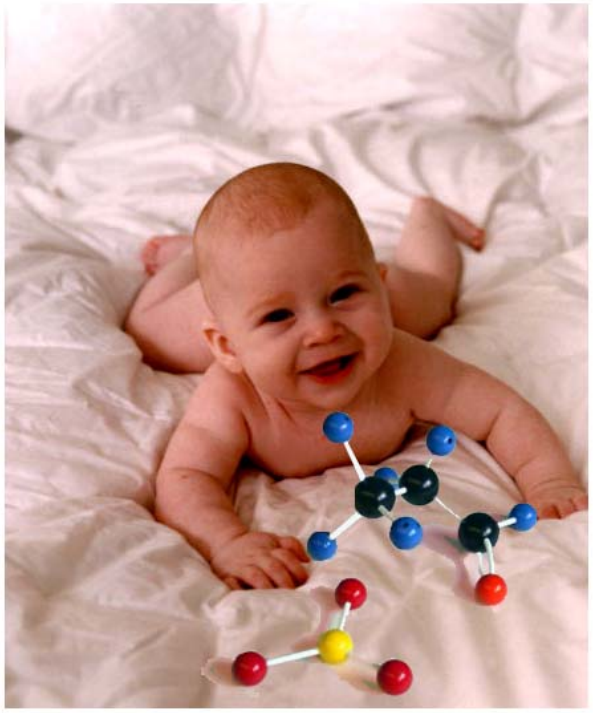
…model the environment?

…manage CO_2

… design drugs?

… make materials by design?

… rationalize the origin of life?



Chemistry is still in its infancy!

History: Will Chemistry Reinvent Itself, or Evaporate? Scientific Revolutions

- **Newtonian Physics ⇨ Quantum Physics (1905-1925)**
- **Naturalists ⇨ Molecular Biology (1953→)**

- **High Energy Physics ⇨? (Astrophysics and superstrings)**
- **Chemistry ⇨ ?**

- **Religion**
- **Farming**

Are there signs of a revolution in chemistry?

The Structure of Scientific Revolutions: Two Theories—"Necessity" and "Tools"

- **Intellectual Necessity**
  - **Discontinuities follow accumulating incompatibilities with theory**
  - ***Problems* vs. *Puzzles***
  - **Business-as-Usual vs. Revolutions**

- **Tools**

  NMR/IR/MS and synthesis; PCR and molecular biology; STM and nanotechnology

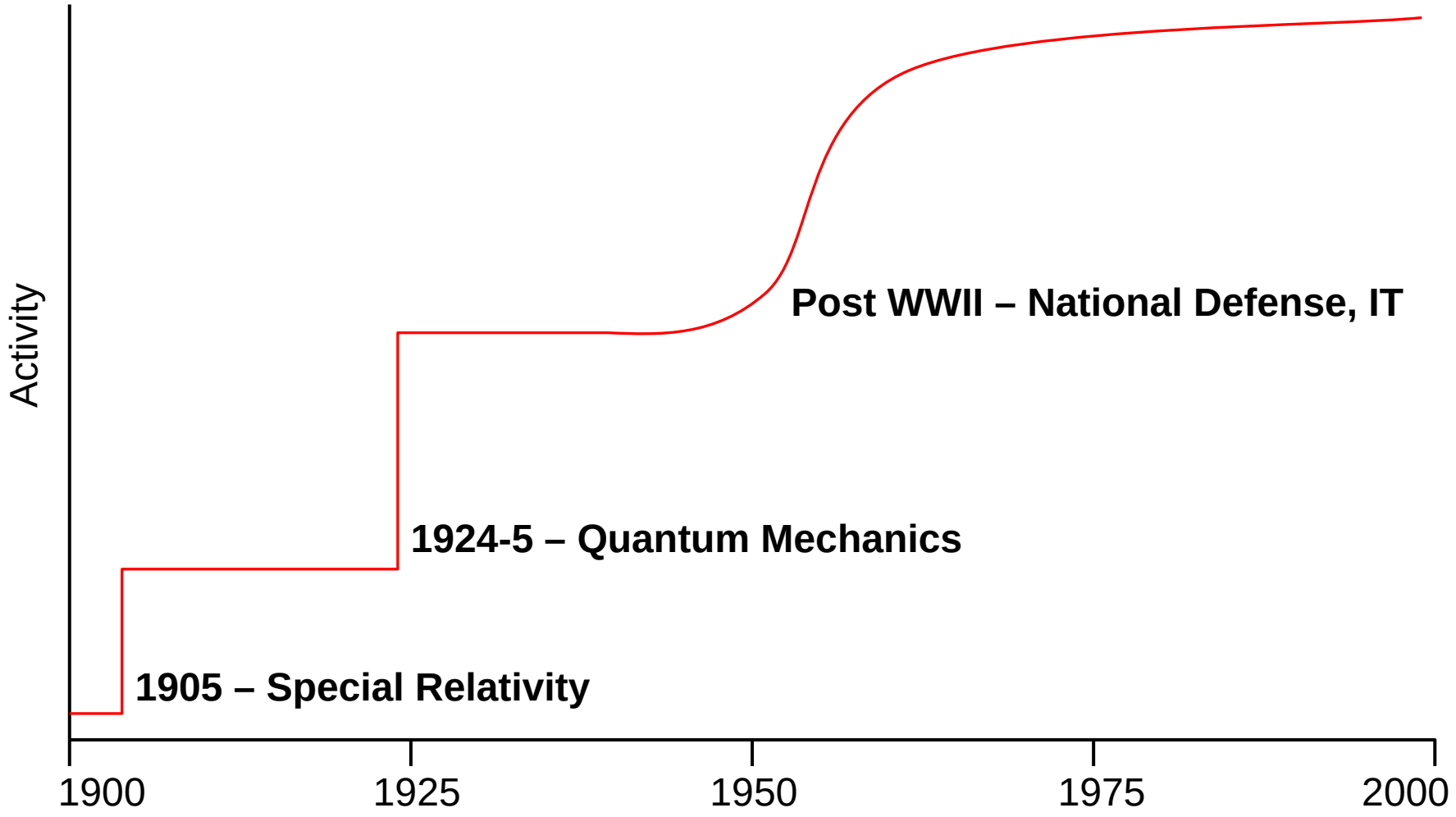
Kuhn, Popper, Feyerabend, Dyson, Garrison, others

Thomas Kuhn: “The Structure of Scientific Revolutions”

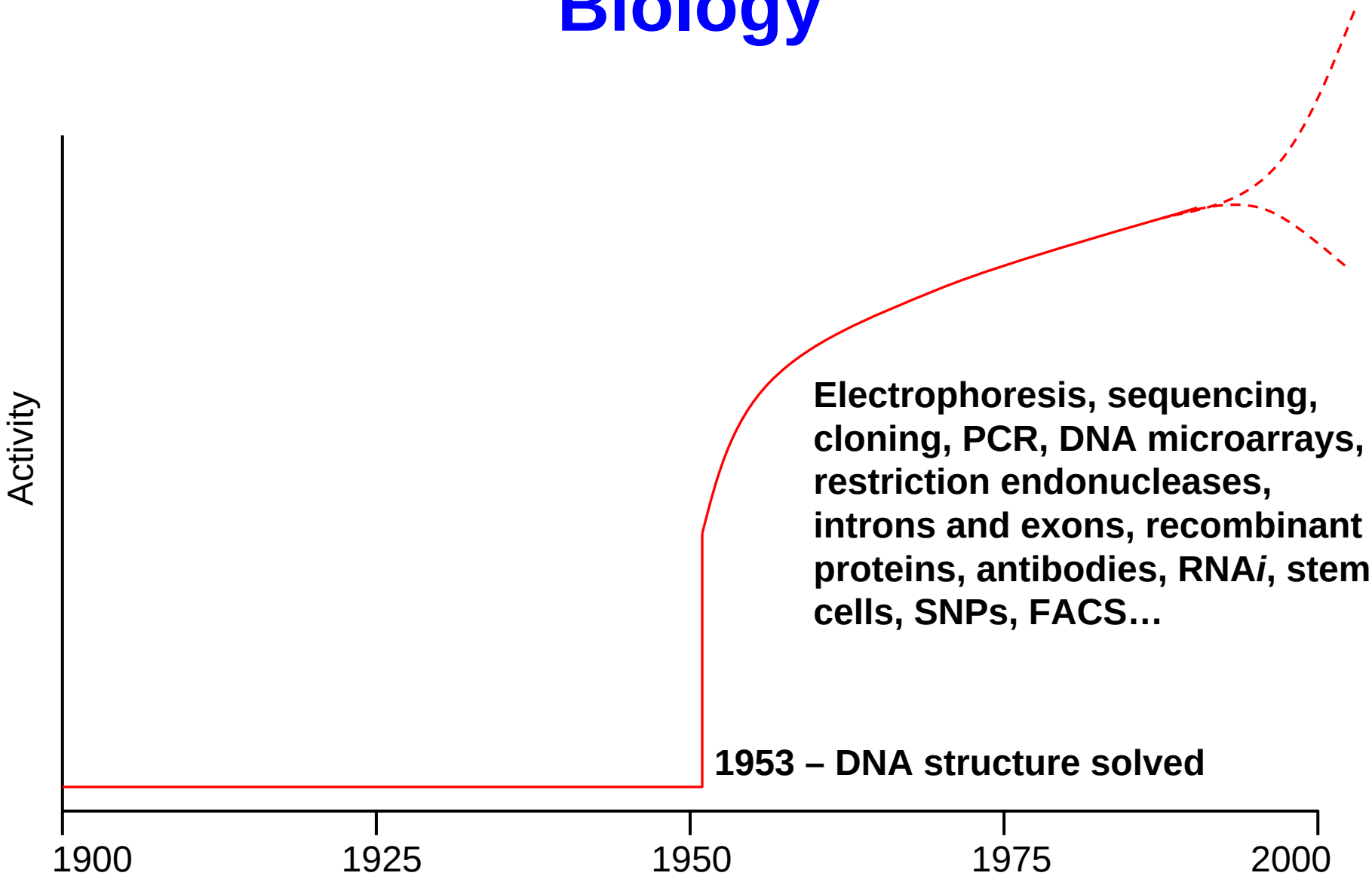
- **Puzzle:** ***“Though its outcome can be anticipated, often in detail so great that what remains to be known is itself uninteresting, the way to achieve that outcome remains very much in doubt.”***

- **Problem:** ***“The really pressing problems, e.g., a cure for cancer or the design of a lasting peace, are often not puzzles at all, largely because they may not have any solution.”***

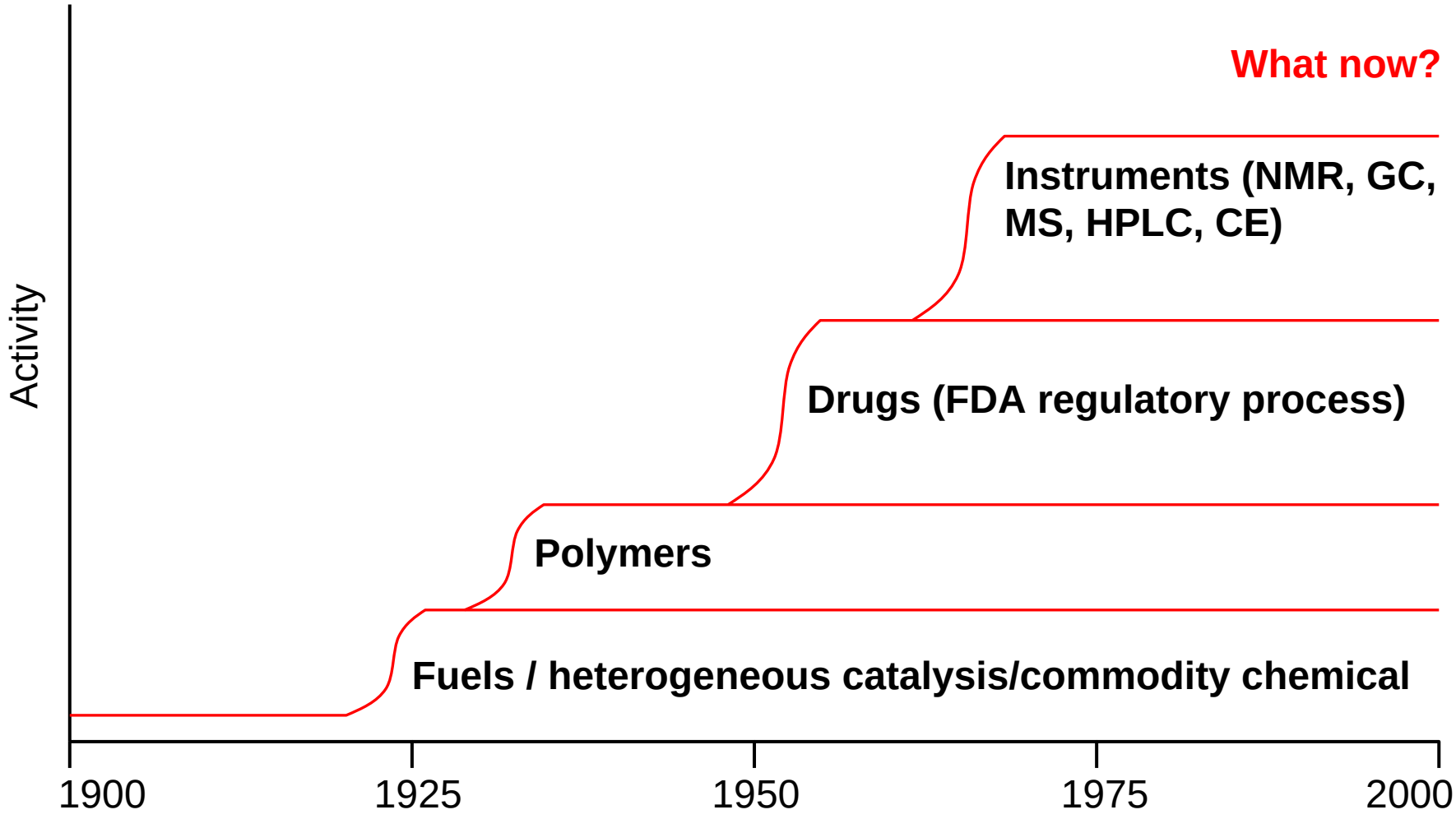
Physics


Activity
Post WWII – National Defense, IT
1924-5 – Quantum Mechanics
1905 – Special Relativity
1900
1925
1950
1975
2000

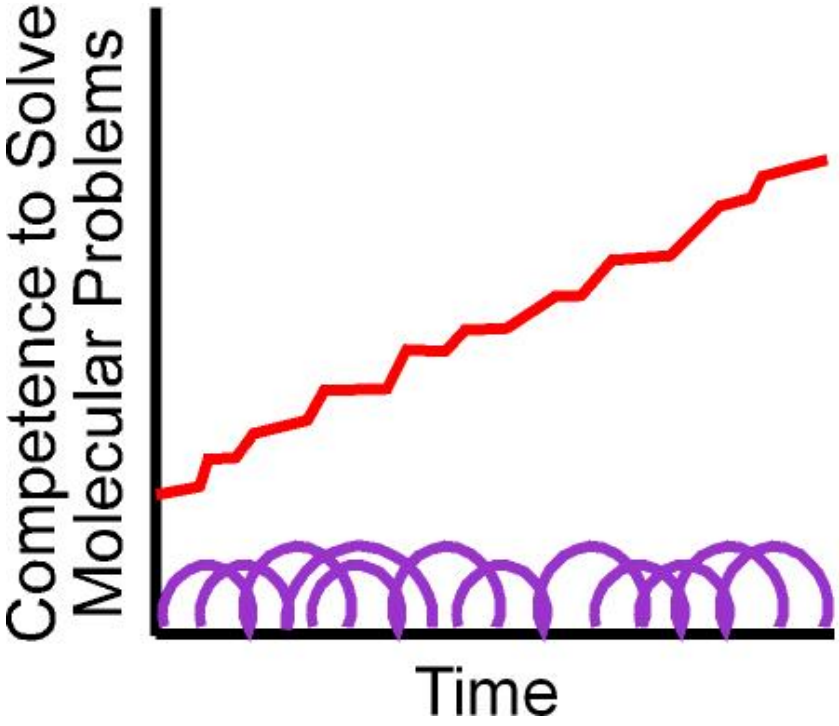
Biology


Activity
Electrophoresis, sequencing, cloning, PCR, DNA microarrays, restriction endonucleases, introns and exons, recombinant proteins, antibodies, RNA*i*, stem cells, SNPs, FACS…
1953 – DNA structure solved
1900
1925
1950
1975
2000

Chemistry


What now?
Instruments (NMR, GC, MS, HPLC, CE)
Drugs (FDA regulatory process)
Polymers
Fuels / heterogeneous catalysis/commodity chemical
Activity
1900
1925
1950
1975
2000

Chemistry at Finer Granularity

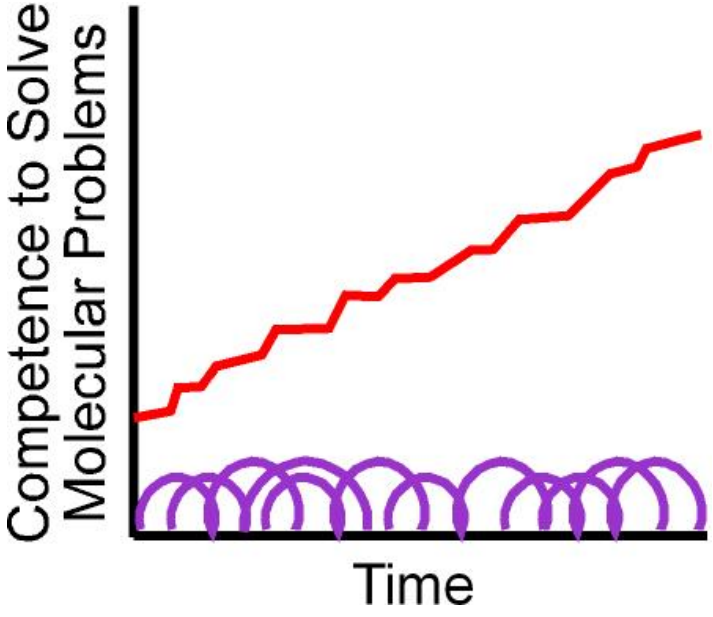


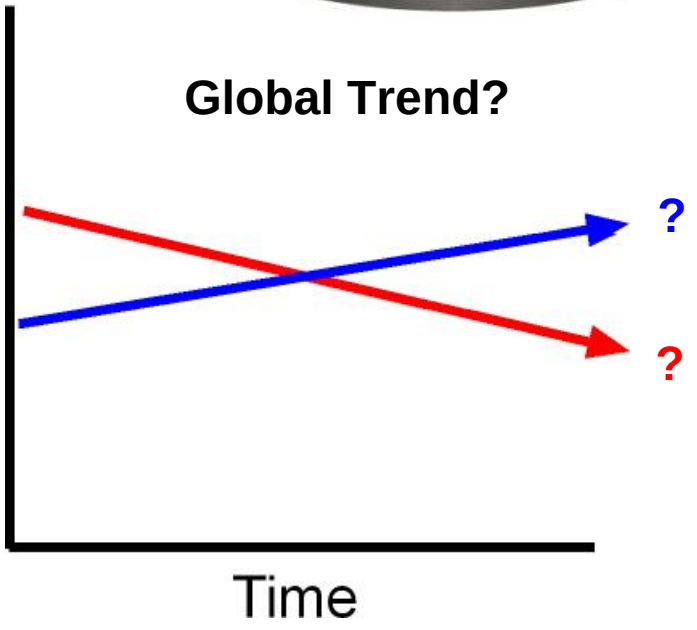
- *Enzymatic mechanisms*
- *Nonclassical carbonium ions*
- *Enzymatic in organic synthesis*
- *Structure by NMR*
- *Asymmetric synthesis*
- *Complex synthesis*
- *Single-molecule spectroscopy*
- *Natural products*
- *High vacuum surface science*
- *DNA synthesis*
- *Reactive intermediates*
- *SAMs*
- *Combinatorial chemistry*
- *Nano*
- *Buckyballs/tubes*
- *Synthons*
- *New reagents*
- *Molecular recognition*
- *Molecular beams*
- *Heterogeneous catalysis*
- *Separations*
- *Fluorescence*
- *Homogeneous catalysis*

Creeping Normalcy

"Perhaps the commonest circumstance under which societies fail to perceive a problem is when it takes the form of a slow trend concealed by wide up-and-down fluctuations. Politicians use the term 'creeping normalcy'…

-Jared Diamond



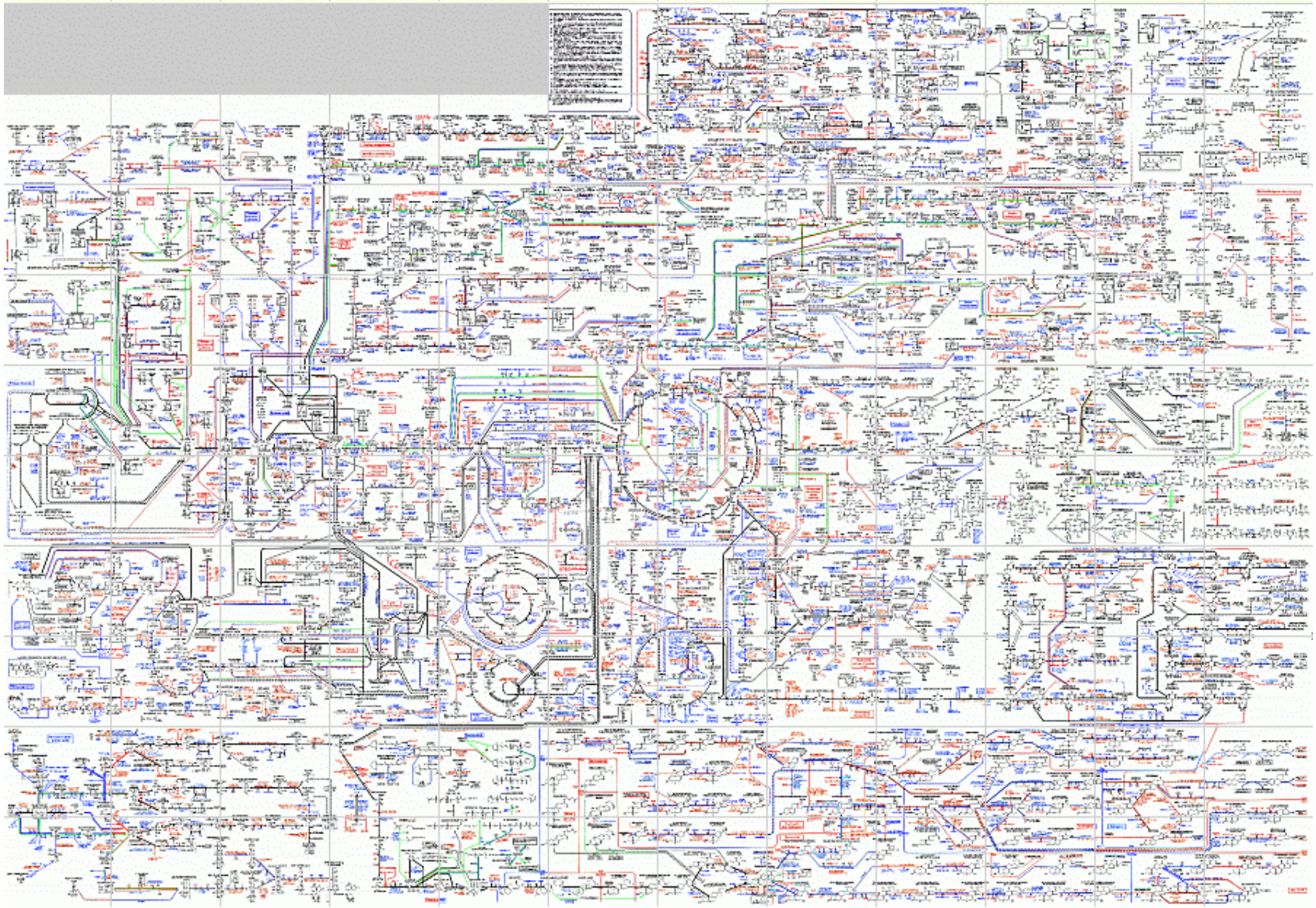


So: Is there a revolution in the future of chemistry?

- **Understanding**
  - **Molecular Recognition**
  - **Origin of Life**
  - **Sentience**
- **Engineering**
  - **CO_2, H_2O, O_2, CH_4, Pu, Th, Energy**
  - **Healthcare Cost Reduction; “Public Health”**
  - **The Developing World**
  - **Megacities**

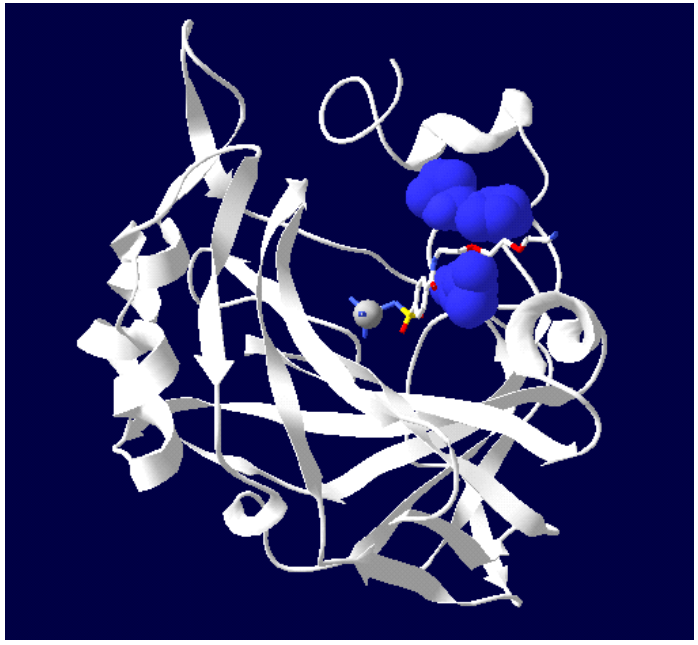
The Umbrella Theory of Scientific Managment

Systems: “What is life?”

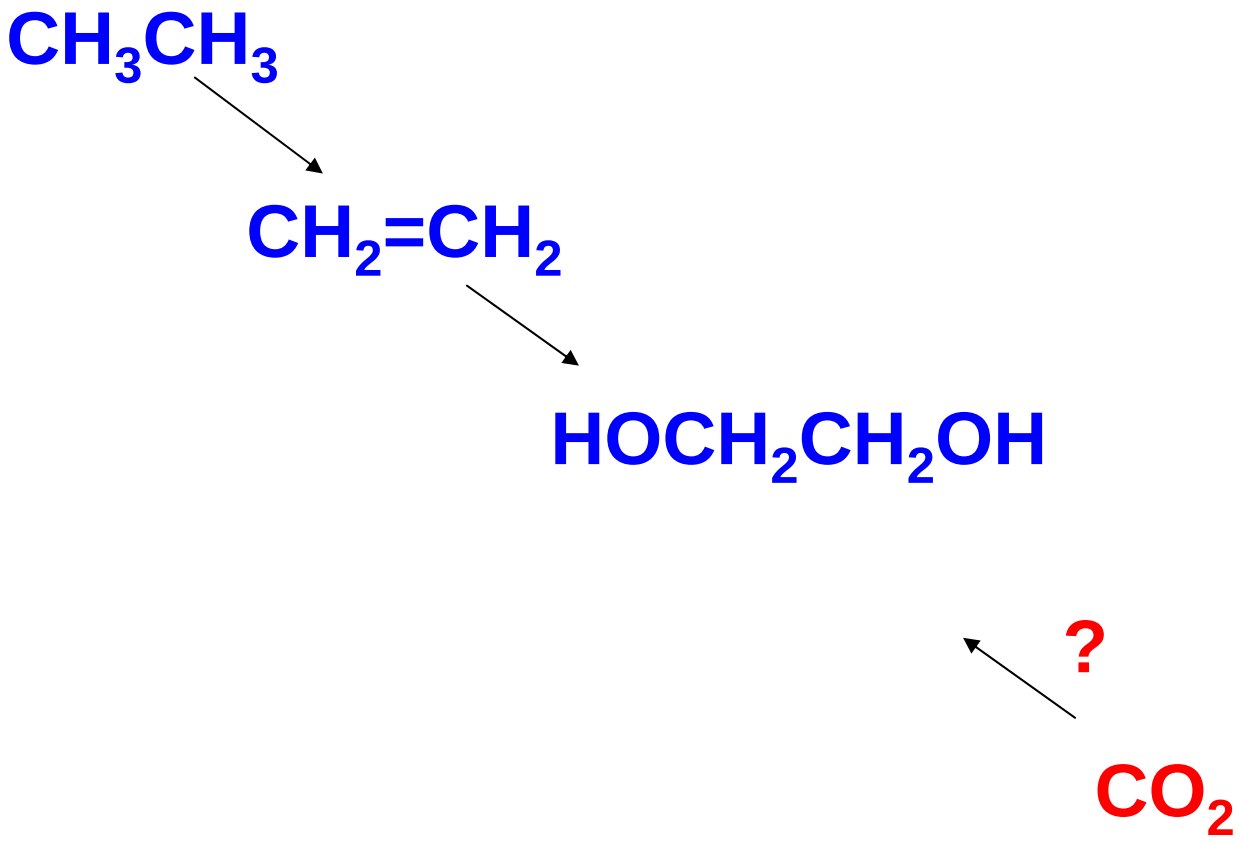


Molecular Recognition in Water: Protein-Ligand Interactions

- **Water**
- **Protein Plasticity**
- **Entropy/enthalpy *and* compensation**
- **What is the best “sloppy fit”?**
- **Potential Functions**

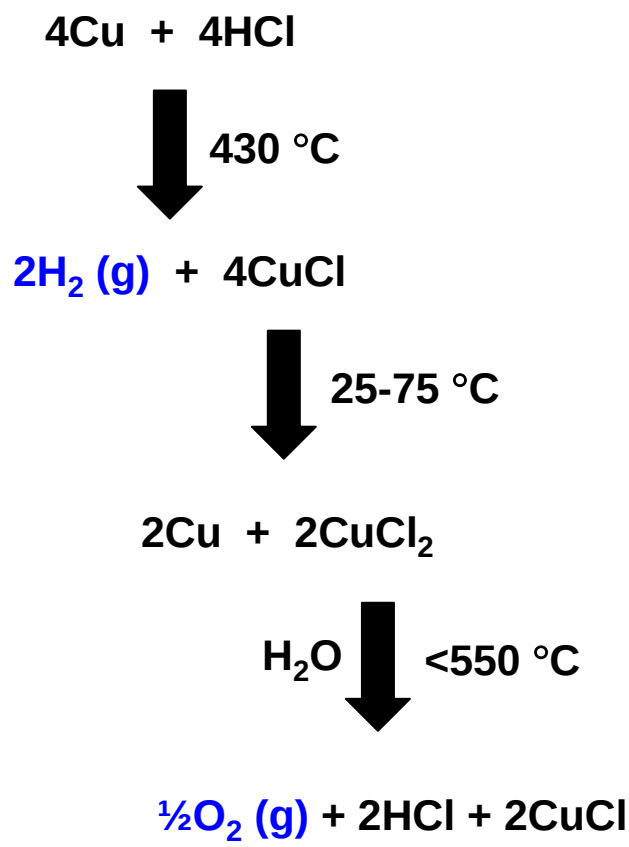


Reinventing Commodity Chemistry



Energy: Thermal hydrogen cycles

* **Copper-chlorine Cycle**



Net reaction: $H_2O \longrightarrow H_2\,(g) + \frac{1}{2}O_2\,(g)$

An Hour Examination:

1. **(60%) Recreate the world of chemicals and derived materials using only CO_2, H_2, heat, and e^-**
2. **(20%) Trace a mechanistic pathway from ions and neurotransmitters to the Brahms *Requiem*. Explain the reaction of the audience.**
3. **(20%) Sequester unlimited quantities of CO_2, and provide unlimited power and water, with a guaranteed 20% after-tax return on investment. Use no equipment not readily available in Haiti and Somalia.**

What to do?

Universities must lead the change

Industry

- **Must live with capitalism**
- **Has the job of *exploiting* knowledge**

Government

- **Competing agents / interests**
- **Requires relevance to national needs**
- **Responds primarily to political necessity**

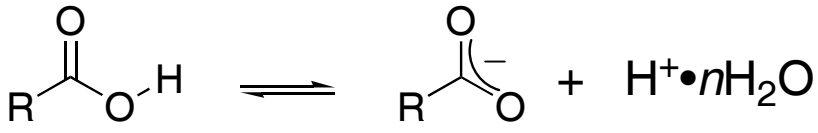
University

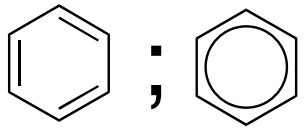
- **The only participant with some flexibility**
- **Problems, not puzzles**

Teaching and Education

- ***Archaic***
- ***Often wrong***
- ***Non-demanding***
- ***Not very relevant***

Resonance





Solutions and “intrinsic reactivity”: S_N2

- ***Textbooks are designed to sell, not to help students learn to do creative research; replace them with the web.***

$I^- > Br^- > Cl^- > F^-$

or

$F^- > Cl^- > Br^- > I^-$

The Research University and "Fundamental Research"

- **History: Utilitarian.**
  - **Vannevar Bush: "The Endless Frontier"-- defense, jobs, and health.**
- ***How much research done in universities is truly "creative" and "fundamental"?***
- **The peer review system is a recipe for scientific democracy.**

The Research University:
Is there a change in the social contract?

From

Do fundamental research

(and someone will solve social problems)

To

Solve societal problems

(and, by the way, if you want to do some fundamental research, that's OK)

…but what about quantum mechanics?

Chemistry as an Art Form: The “Ballet” Test.

The Saalfelt Criterion:

Assume:

- **Unlimited Resources**
- **Unlimited Success**

Answer the question:

- ***“Who cares?”***

A Strategy for Change

- **Connect to Big, Recognizable Problems**

  Use them to shelter curiosity-driven research

- **Pick areas where Chemistry brings unique skills**

  Molecules and Molecular Synthesis: materials, molecular biology, non-covalent aggregates, …

  Complex (kinetic) systems: systems biology, environment, energy (global stewardship)

  Catalysis

  Water, energy sustainability, developing economies

- **Emphasize *Function,* not *Structure.***

Reinvent the Process for Product Innovation from the Bottom Up

- **Assume "Big Chemical Industry" will be primarily developer/producer/distributor.**
- **Universities Lead in Invention:**
  - **Entrepreneurial Students (MIT/Stanford model),**
  - **(Perhaps) Venture capital and/or investment banking**
- **Universities, Industry, and Government Cooperate in Innovation.**

- **The template will have to be new: *not what* worked for biotech or information.**
  - **Small companies bring agility**
  - **Large companies bring low cost of capital**

Reinvent Education

- Replace textbooks with the web.
- Reduce/eliminate specialization.
- Emphasize intellectually “difficult” subjects.
- Stop “dumbing it down”
  - Solvation
  - Thermodynamics
  - Applied mathematics
  - Systems and complexity
  - Information
  - Organismic biochemistry

Dismantle the Apprentice System

- ***…teach, don't use***

JOBS

- **Big industry provides employment and improves existing products, but does not create new technologies**
- **Universities (ideally) generate new possibilities/options, but almost never products**
- **The venture community is essentially dead, outside of low-cost technologies such as IT (and IT arguably does not create jobs!)**
- ***Solution: (re)invent entrepreneurship!***

Conclusions

The most important problems now facing society depend on chemistry

The most interesting and important problems in science depend on chemistry.

***New* chemistry is essential, and the field is therefore essential.**

Chemistry is intellectually risk-averse

Financial return defines what industry can do.

Teaching focuses on the past rather than the future, and on technical competence rather than creativity.

Solutions require:

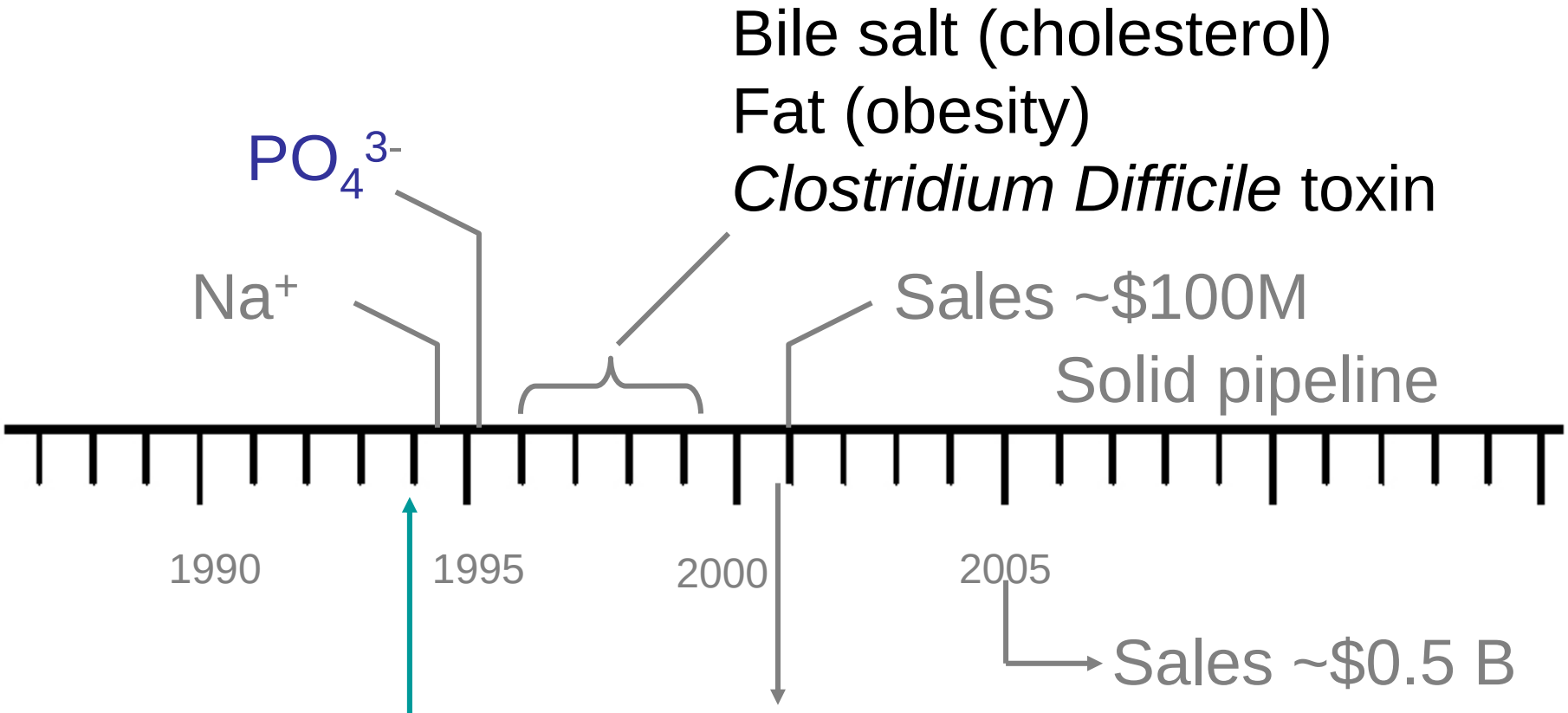
- **Aggressively broadening the definition of what chemistry is and does**
- **Redrawing the map of university, industry, government, and society.**
- **Teaching for breadth and creativity rather than for technical competence.**
- **Allowing old fields to retire, and new ones to grow**
- **Making collaborative research and development the norm, rather than the exception.**
- **Putting some of the poetry back!**

One Final Thought: *Risk*

	Successful?	
Problem?	**Yes**	**No**
Important	**+ + +**	**+**
Unimportant	**-**	**- - -**


Micropneumatic Gripper
Harvard University. Whitesides group.

Geltex: Timeline



An Example: Geltex

- Technology: Non-adsorbed organic polymers to adsorb ions/molecules from the gut. **(Poly(acrylamide)-based, phosphate-selective, ion-exchange resins).**
- Strategy: High safety; low costs; fast to market
- Market: Renal dialysis patients, chronic health care

Reinventing Long-Term Research

The 3 stages of a research problem

1	2	3
Identifying/ Defining the problem	Solving the problem	Selling the “solution” (The more original the result the more difficult to sell)

And the fourth stage = getting the money

Something has to change, and the research organizations (universities, Max Plancks, national labs, …) are the only game in town.


Boston Dynamics

Ethics

Kantianism

Utilitarianism

Social Contract Theory

Virtue Theory

Religion

Languages

Money

Science

Ethics

Ethics, Choice, Rewards, Incentives

- **Self-interest**
- **Institutional loyalty**

  Survival of our local environment
- **National competitiveness**

  Jobs for our children
- **National/global stabilization**

  1st/2nd/3rd World; Globalization; Sustainability
- **“Puzzle” vs. “Problem”**

  ***We* (and close friends) are interested, or *others* are interested.**

Back to Basics

- **Emphasize function**
- **Take control of the systems**
- **Reengineer the transition from university to industry; generate a “new chemical industry”**
- **Reinvent teaching / objectives**
- **Consider the balance between single investigator and collaborative research**
- **Modify/supplement peer review**
- **Focus resources on change**

Research Universities

Past ➡ Future

Physical organic

Applied quantum theory

Organic synthesis

Organometallic and catalysis

Analytical Tools

⋮

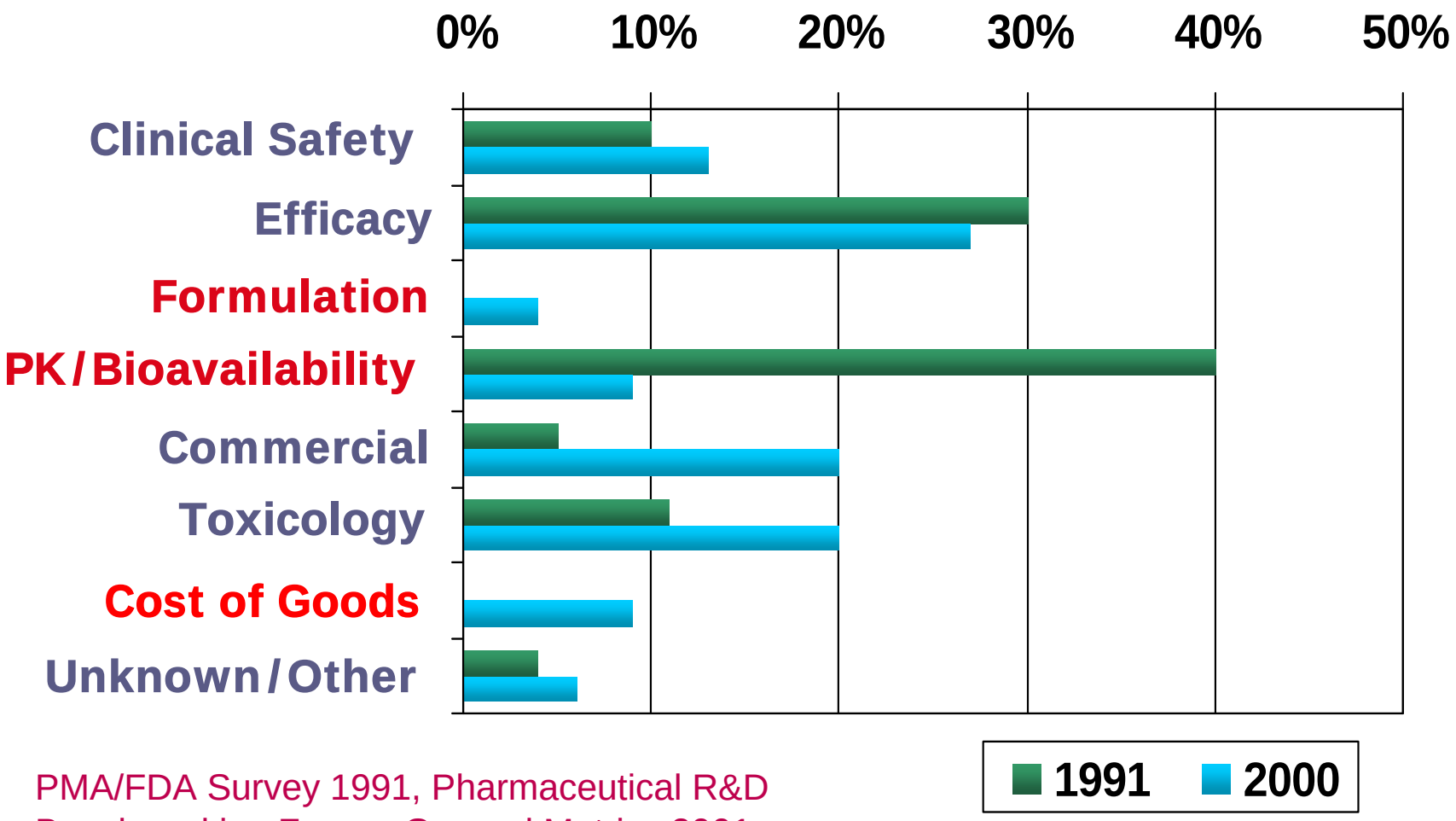
➡

Biochemistry/ Biology

Materials Science

(… but as leader or follower?)

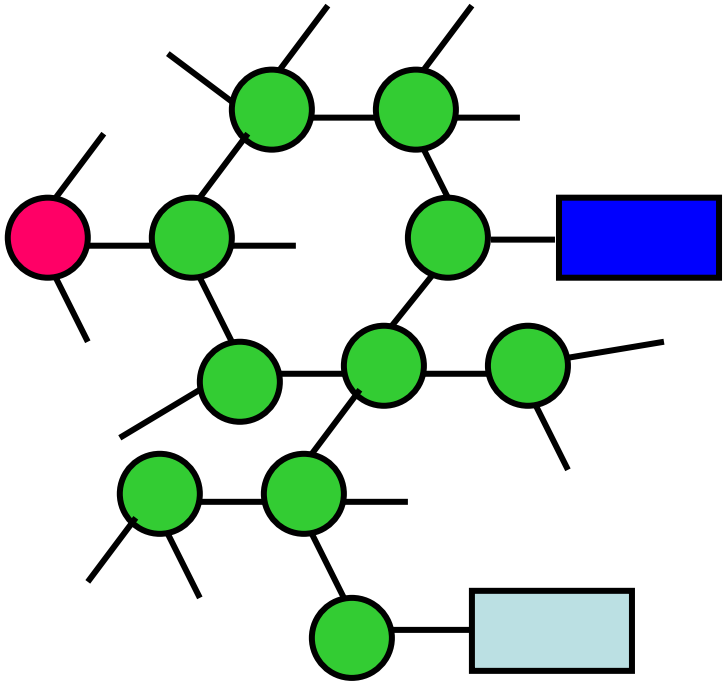
Reasons for Failure of Drug Candidates



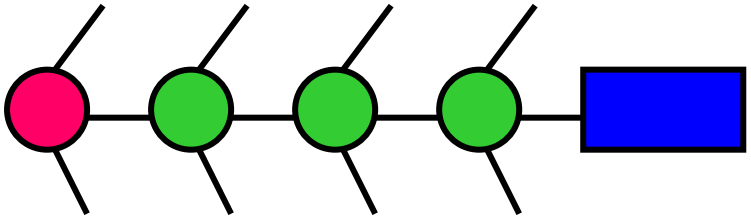
PMA/FDA Survey 1991, Pharmaceutical R&D Benchmarking Forum, General Metrics 2001

Coupling University and Industry

Old model
- *Fractal*

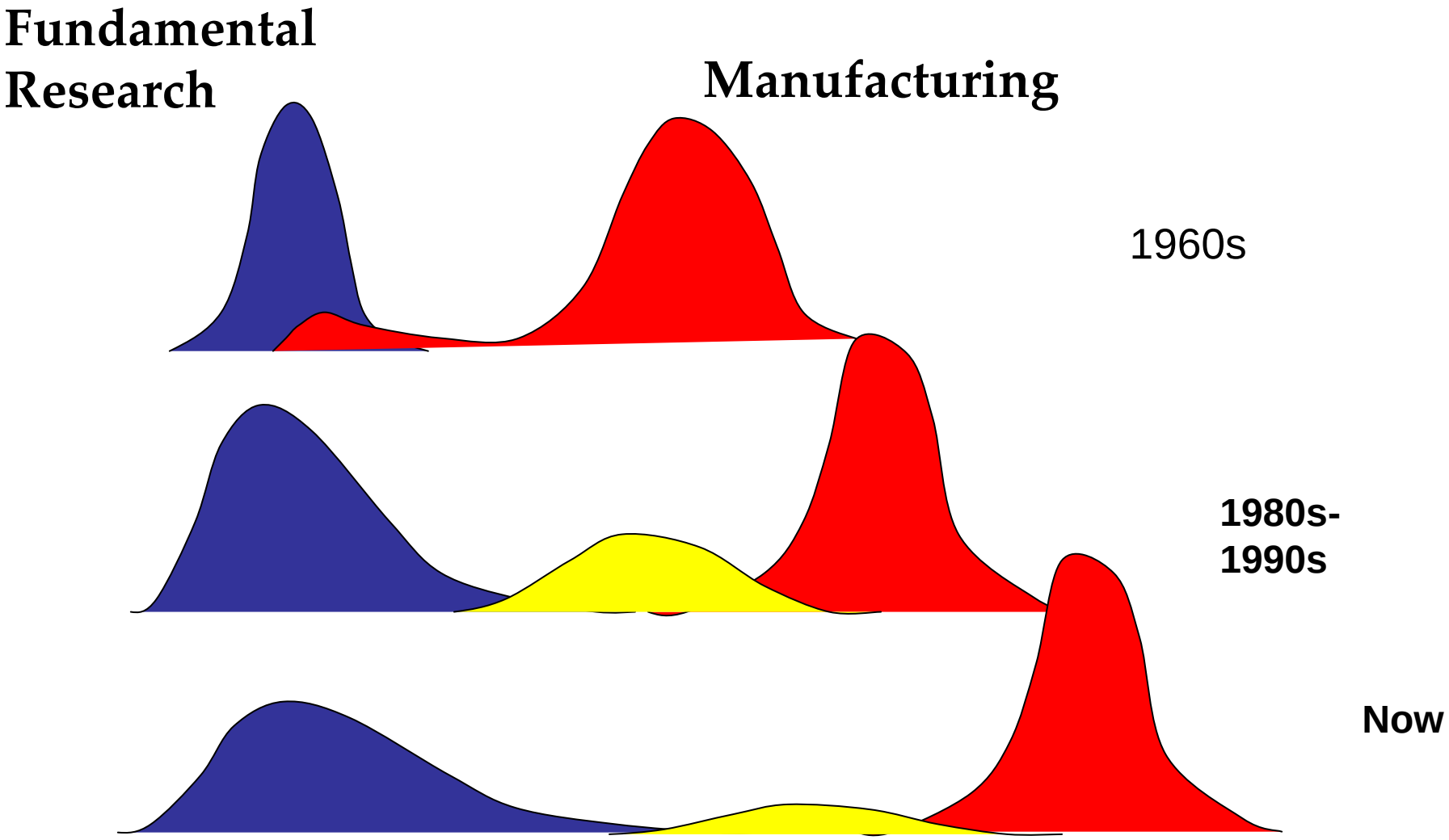


New Model
- *Directed*



“Let a thousand flowers bloom”

Industry, Venture, and University Interactions



And! *Many* Interesting and Important Problems Waiting to be Solved

Fundamental **and** ***Applied***

Liquids and Solutions

Catalysis/Materials by design

Systems biology/ biochemistry

Molecular recognition; "ligands-by-design

New energy technologies

Water

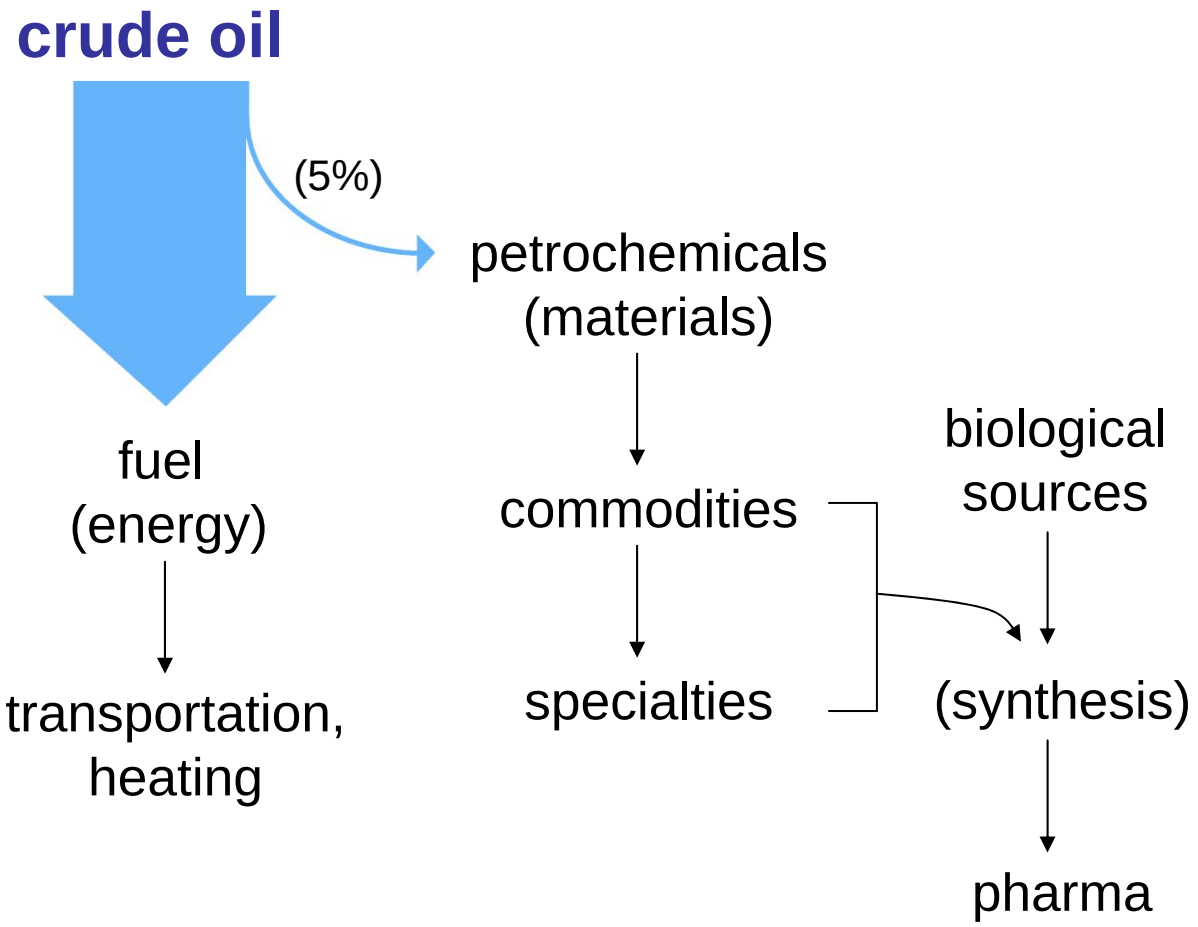
Nutrition

Disease/aging

Globalization

Sustainability

The Chemical Industry



<u>Assertion:</u> The industrial chemical industry no longer includes invention (innovation) in its business model.

Research Universities

Past → Future

Physical organic

Applied quantum theory

Organic synthesis

Organometallic and catalysis

Analytical Tools

⋮

→

Materials Science

Biochemistry/ Biology

Medicine/Public Health

Environment

Energy

In These New Problems and New Fields, Is Chemistry:

– Composer, conductor, or musician?

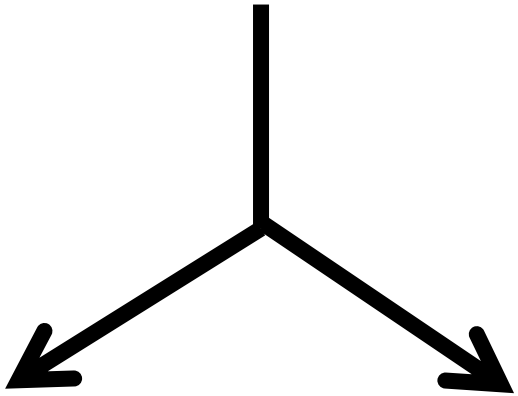
–“Integrator” or “supplier”?

So: Does the World Need Chemistry?

- Of course it does!
  - Health
  - Energy / water / food (both production and conservation)
  - Population Control
  - Information Technology (convergence, ubiquity, low cost)
  - Global environmental stability
  - $2^{nd}/3^{rd}$ World assistance and needs
  - National security
  - Reinventing the supply chain (Hydrocarbons → CO_2
  - *And understanding the living and material, and information-based worlds.*

Chemistry will and must change

Chemistry
(the profession)



Reinvention
New Problems

Absorption/
Evaporation into
Biology
Materials
Energy/Environment
???

Public and Government Perception of Chemistry

Chemistry is invisible to the public

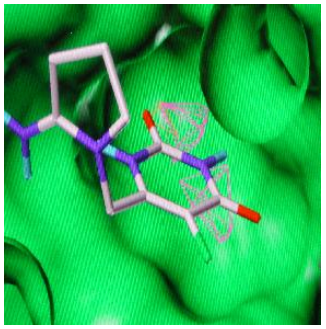
Chemistry is considered “mature” economically

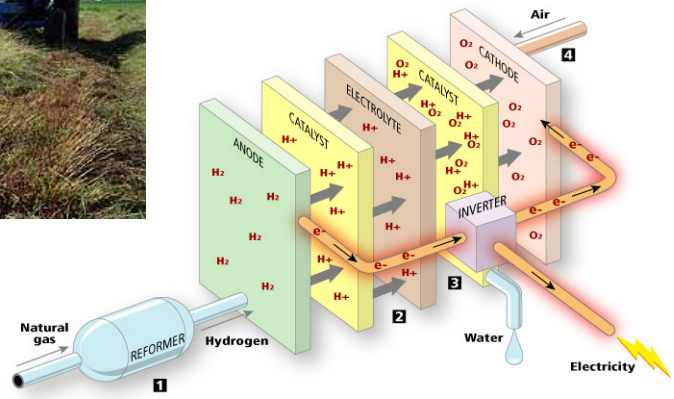
Chemistry is associated with pollution/global warming

“Good” and “Bad” are not balanced in perceptions of chemistry

More *Applied* Problems

- Rational *Drug* Design
- Biomass
- H_2 economy
- Alternative feedstocks
- O_2 electrode
- 3^{rd} world / 1^{st} world
- Sustainability
- Counterterrorism





Reinventing the Chain: The chemical economies

petroleum

fuel

transportation,
heating

petrochemicals

commodities

specialties

fermentation

natural products

pharmaceuticals

nuclear

heat

electricity

H_2

? H_2 thermal cycles

? Electrocatalysis

? "Hydrogenochemicals"

? Fuel cells

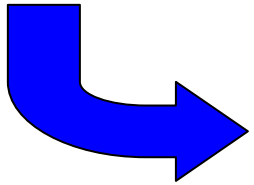
? Materials

Similarly, what are the chemical economies for: *CH_4*, *coal*, and *biomass*?

Examine the models

- **Is the “Liebig Model” obsolete?**

  Systems! Collaborations
- **Is the current model of the university (“a collection of semi-isolated experts”) still workable?**
- **Is “molecular synthesis/molecular structure” still king?**
- **Can curiosity-driven research survive?**
- **Chemistry as an art-form.**



Excellence; The ballet problem

Emphasize Tools and Functional Assays

How do you tell where to go, and if you have succeeded?

Functional Assays Are Overwhelmingly Important!

No Longer “what is it?”, but “what does it do?”

- **Measurement guides science**
- **Assays for function are key to success**

Reengineer Education: Content (1)

- Molecule vs. Molecule + Solvent
- Thermo/stat mech
- ADME/Tox/PK/PD
- Systems analysis
- Complexity vs. Simplicity
- The difficult subject of “difficult” subjects
  - Statistical mechanics
  - Electricity and Magnetism
  - Applied mathematics
  - Thermodynamics

Reengineer Education: Throughput (2)

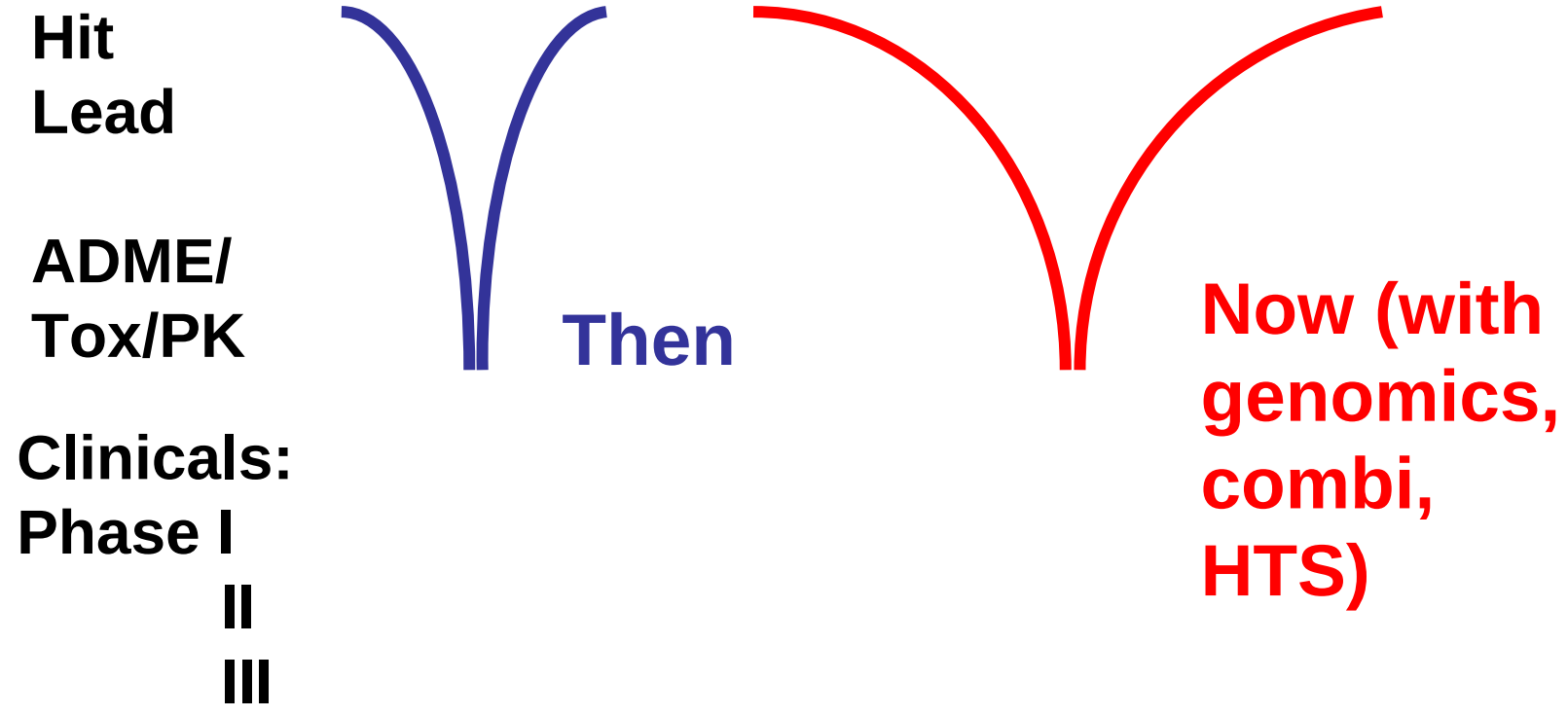
- **What are the opportunities for our students?**
  - **too many students,**
  - **too narrowly trained (and educated),**
  - **ill-equipped for globalization**
  - **backwards rather than forwards looking**
- **Fewer PhD programs? Broader training?**
- **Make education an expert business?**

  IT makes information free.

Reengineer Education: Breadth and Style (3)

- Macroeconomics
- Accounting (language of capitalism)
- Corporate governance
- Systems integration
- Chem / Chem E / Biol / Materials
- Globalization

Special Case: the Pharmaceutical Industry



In the past, the pharmaceutical industry:

** supplied the problem to the universities, and*

** measured the function.*

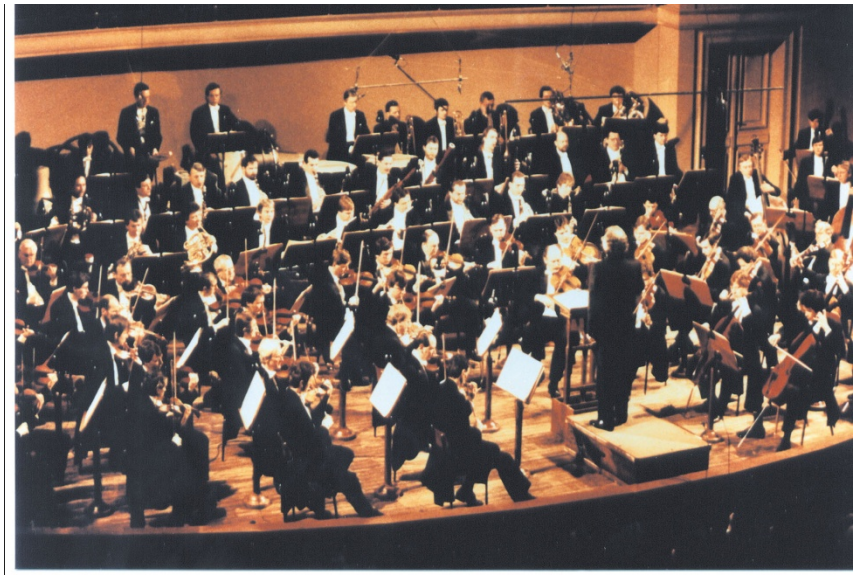
Now, the process is much harder (targets, safety, clinical failure) and less familiar to universities

So: Does the world *need* "chemistry?"

Is chemistry the composer, conductor, orchestra, or ticket taker?

- a supplier of useful technologies, or an distinct intellectual contributor?

Do we know the chemistry required to solve the really big problems?



A Second View of Revolutions: "Tools" vs. "Science-Enabled-by-Tools"

NMR and IR	Organic structure
Lasers	Spectroscopy
PCR	Genomics
STM/AFM	Nanoscience
Mass Spectroscopy	Proteomics
Photolithography	Microelectronics, MEMS
Computers	Everything
X-ray Diffraction	Protein Chemistry

Fundamental Problems; Examples

- **Simple-molecule chemistry**
  - **CO_2, H_2, H_2O, CH_4, NO_x, O_2**
- **Energy Production and Conservation**
- **Understanding Earth: Global Stewardship**
- **"Impossible Materials"**
  - **GMR, Negative Index of Refraction, High T_c, ultra-high index of refraction, self-healing materials,….**
- **Complex Systems**
  - **Systems "Biology" (really "Chemistry")**
  - **The global environment (atmospheres, oceans, land),**
  - **The Cell**
- **Origin of Life**
- **The Chemical Basis of Thought and Self-Awareness**

Energy: Thermal hydrogen cycles

* **Copper-chlorine Cycle**

$4Cu + 4HCl$

↓ 430 °C

$2H_2$ (g) $+ 4CuCl$

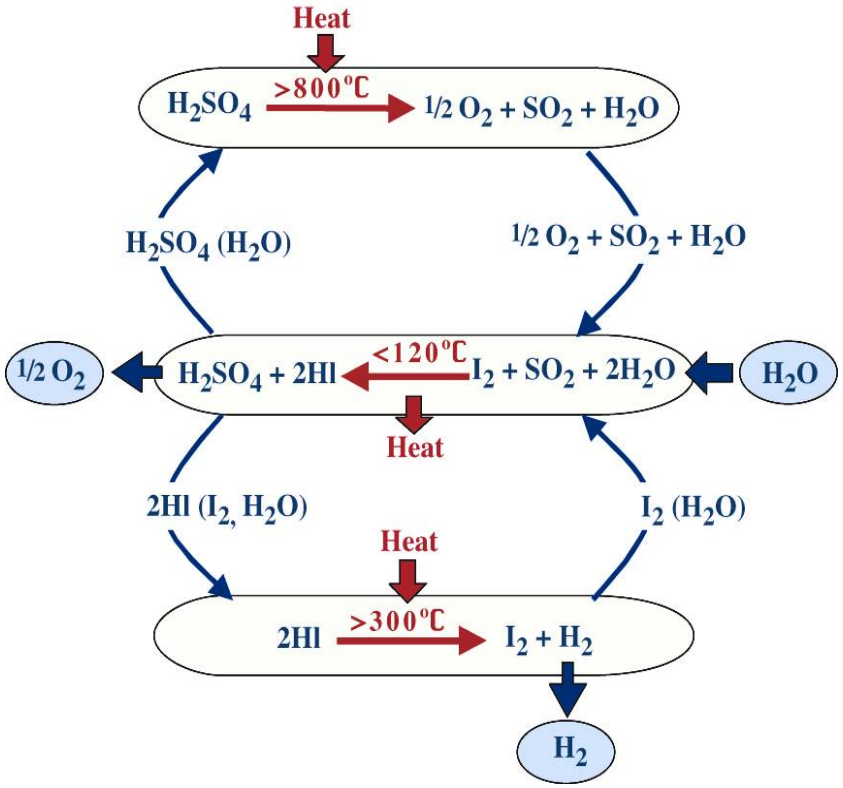
↓ 25-75 °C

$2Cu + 2CuCl_2$

H_2O ↓ <550 °C

$½O_2$ (g) $+ 2HCl + 2CuCl$

* **Sulfur-iodine Cycle**



Net reaction: $H_2O \longrightarrow H_2$ (g) $+ ½O_2$ (g)