The Cyber-Bio interface

Harvey Rubin, MD, PhD
University of Pennsylvania
NSF
Austin, Texas. October 17, 2006

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Goals

(a) clearly enumerate the fundamental limitations of today's cyber-physical systems,
(b) determine new cyber-physical applications and advances that can produce significant societal and economic impact,
(c) understand the core technical challenges that must be addressed to enable future cyber-physical systems,
(d) establish an overall architectural framework for cyber-physical systems, and
(e) identify new innovations and powerful cross-layer abstractions that will satisfy the challenging requirements of future cyber-physical systems.

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The four questions for cyber-bio systems

1. Can biological systems operationalize certain aspects of cyber systems so that we can understand and design advanced biological systems?
2. Can biological systems operationalize certain aspects of cyber systems so that we can understand and design advanced cyber systems?
3. Can cyber systems operationalize certain aspects of biological systems so that we can understand and design advanced biological systems?
4. Can cyber systems operationalize certain aspects of biological systems so that we can understand and design advanced cyber systems?

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Cyber-Bio comparisons: on the totally arbitrary and arguable scale of 1-5

	Cyber	Bio
Logic operations	5	1
Programmable	5	2
Parallel processing	3	5
Standardization	5	3
Abstraction	5	2
Modularity	5	5
Predictability of part	5	3
Predictability of part in system	4	2
Stable/durable in the natural environment	4	3
Stable/durable under stress and attack	2	4
Energy efficiency	2	5
Logically reversible	2	4
Thermodynamically reversible	2	4
Scalable	3	3
Evolvable	1	5
Self learning	1	5
Self repair	1	5
Self correcting	1	5
Self assembly	1	5
Self-Replicating (hardware)	0	5
Richness of user interface	2	4
Multi-agent communication	3	4
Aggregate data and predict outcomes	0-1	4
Solve the "inverse problem"	0-1	5
Impact on society	0-4	5

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1. Can biological systems operationalize certain aspects of cyber systems so that we can understand and design advanced biological systems?

Logic operations	5	1
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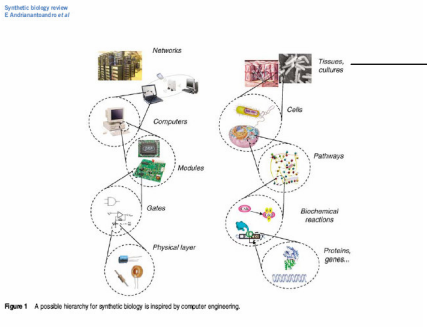

Figure 1 A possible hierarchy for synthetic biology is inspired by computer engineering.

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Answer to Question 1 –YES

up to the level of tissues and cultures, this is predominantly in the world of synthetic biology

- Cell cycle counter and cell division reporter
- Control metabolic pathways and switches
- Regulate intracellular communications
- Microbial fuel cells
- New therapies
- Biological sensors

National Science Advisory Board for Biosecurity (NSABB) subcommittee on synthetic biology

Roger Kornberg
Arthur Kornberg

Andrew Fire
Craig Mello

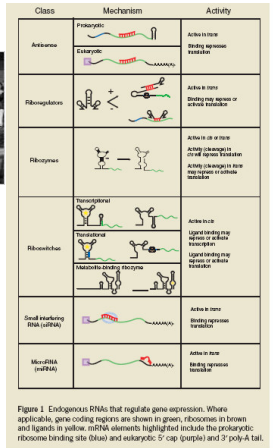

Figure 1 Endogenous RNAs that regulate gene expression. Where applicable, gene coding regions are shown in green, ribosomes in brown and ligands in yellow. mRNA elements highlighted include the prokaryotic ribosome binding site (blue) and eukaryotic 5′ cap (purple) and 3′ poly-A tail.

VOLUME 24 NUMBER 5 MAY 2006 NATURE BIOTECHNOLOGY

Isaacs, Dwyer, Collins

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Another example of best practices: recent publication of 1918 Pandemic Influenza Virus Papers

"The 1918 virus and recombinant H1N1 influenza viruses were generated using the previously described reverse genetics system (8, 14). All viruses containing one or more gene segments from the 1918 influenza virus were generated and handled under high-containment biosafety level 3 enhanced (BSL3) laboratory conditions in accordance with guidelines of the National Institutes of Health and the Centers for Disease Control and Prevention (15)."

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"1918 Flu and Responsible Science"

"I firmly believe that allowing the publication of this information was the correct decision in terms of both national security and public health."

***Science* Editorial**
Vol. 310, 7 October 2005
Philip A. Sharp

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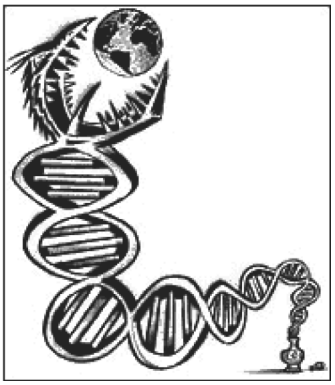
"The 1918 flu genome: Recipe for Destruction"



"This is extremely foolish. The genome is essentially the design of a weapon of mass destruction."

***New York Times* Op-Ed**
October 17, 2005
Ray Kurzweil and Bill Joy

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A new idea that specifically addresses an enormous societal problem *if* bio systems can operationalize cyber systems to design more advanced bio systems

(a) clearly enumerate the fundamental limitations of today's cyber-physical systems

(b) determine new cyber-physical applications and advances that can produce significant societal and economic impact

(c) understand the core technical challenges that must be addressed to enable future cyber-physical systems

(d) establish an overall architectural framework for cyber-physical systems

(e) identify new innovations and powerful cross-layer abstractions that will satisfy the challenging requirements of future cyber-physical systems

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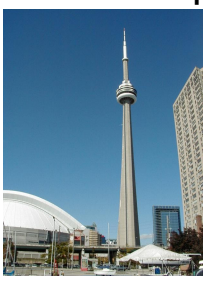
THE NEW ARMS RACE:

Making the Case for a Comprehensive International Compact for Infectious Diseases



Harvey Rubin, MD, PhD
Plenary Address
Infectious Disease Society of America
Toronto, October 12, 2006

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The problem

Recognizing the impact of infectious diseases on national and international health, economic development and security, can a truly comprehensive agreement between states be developed that will limit and control known, newly discovered or deliberately created infectious diseases?

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The need is well documented

- *Emerging Infections: Microbial Threats to Health in the United States* 1992, 2003, Institute of Medicine
- *The Global Infectious Disease Threat and Its Implications for the United States"* 2000, unclassified report from the National Intelligence Council
- *The Darker Bioweapons Future* 2003, unclassified CIA document analyzed the many benefits of modern molecular biology weighed against the danger that "the effects of engineered biological agents could be worse than any disease known to man."
- *National Security Strategy*: 2006, "Public health challenges like pandemics (HIV/AIDS, avian influenza) ... recognize no borders. The risks to social order are so great that traditional public health approaches may be inadequate, *necessitating new strategies and responses. ..."* (italics added).

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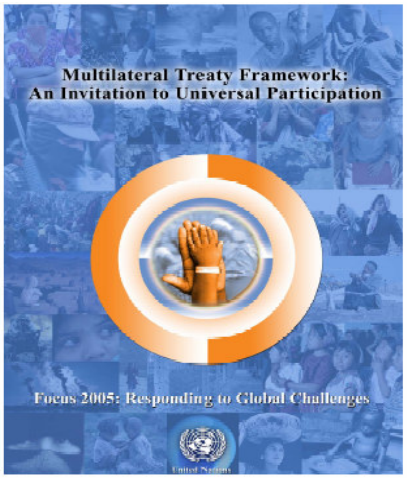
Dangerous assumption that an agreement exists



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Human Rights

1. International Covenant on Economic, Social and Cultural Rights (New York, 1966)
2. International Covenant on Civil and Political Rights (New York, 1966)
3. Optional Protocol to the International Covenant on Civil and Political Rights (New York, 1966)
4. Convention on the Prevention and Punishment of the Crime of Genocide (New York, 1948)
5. Convention against Torture and Other Cruel, Inhuman or Degrading Treatment or Punishment (New York, 1984)
6. Optional Protocol to the Convention against Torture and Other Cruel, Inhuman or Degrading Treatment or Punishment (New York, 2002)
7. International Convention on the Protection of the Rights of All Migrant Workers and Members of their Families (New York, 1990)
8. Optional Protocol to the Convention on the Rights of the Child on the involvement of children in armed conflict (New York, 2000)
9. Optional Protocol to the Convention on the Rights of the Child on the sale of children, child prostitution and child pornography (New York, 2000)

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Refugees

10. Convention Relating to the Status of Refugees (Geneva, 1951)
11. Protocol Relating to the Status of Refugees (New York, 1967)

Penal Matters

12. Rome Statute of the International Criminal Court (Rome, 1998)
13. Agreement on the Privileges and Immunities of the International Criminal Court (New York, 2002)
14. Convention on the Safety of United Nations and Associated Personnel (New York, 1994)

Terrorism

15. International Convention for the Suppression of Terrorist Bombings (New York, 1997)
16. International Convention for the Suppression of the Financing of Terrorism (New York,1999)
17. International Convention for the Suppression of Acts of Nuclear Terrorism (New York, 2005)

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Organized Crime and Corruption

18. United Nations Convention against Transnational Organized Crime (New York, 2000)
19. Protocol to Prevent, Suppress and Punish Trafficking in Persons, Especially Women and Children, supplementing the United Nations Convention against Transnational Organized Crime (New York, 2000)
20. Protocol against the Smuggling of Migrants by Land, Sea and Air, supplementing the United Nations Convention against Transnational Organized Crime (New York, 2000)
21. Protocol against the Illicit Manufacturing of and Trafficking in Firearms, Their Parts and Components and Ammunition, supplementing the United Nations Convention against Transnational Organized Crime (New York, 2001)
22. United Nations Convention against Corruption (New York, 2003)

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Environment

23. Kyoto Protocol to the United Nations Framework Convention on Climate Change (Kyoto, 1997)
24. Rotterdam Convention on the Prior Informed Consent Procedure for Certain Hazardous Chemicals and Pesticides in International Trade (Rotterdam, 1998)
25. Stockholm Convention on Persistent Organic Pollutants (Stockholm, 2001)
26. Cartagena Protocol on Biosafety to the Convention on Biological Diversity (Montreal 2000)

Law of the Sea

27. United Nations Convention on the Law of the Sea (Montego Bay, 1982) and Agreement relating to the implementation of Part XI of the United Nations Convention on the Law of the Sea of 10 December 1982 (New York, 1994)

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Disarmament
28. Comprehensive Nuclear-Test-Ban Treaty (New York, 1996)
29. Convention on the Prohibition of the Use, Stockpiling, Production and Transfer of Anti-Personnel Mines and on their Destruction (Oslo, 1997)

Law of Treaties
30. Vienna Convention on the Law of Treaties (Vienna, 1969)

Health
31. WHO Framework Convention on Tobacco Control (Geneva, 21 May 2003)

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BUT NO COMPREHENSIVE PROGRAM FOR INFECTIOUS DISEASES

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The 4 parts of the Compact

1. Establish, maintain and monitor international standards for surveillance and reporting of infectious diseases using advanced information technology to ensure timeliness, interoperability and security
2. Establish, maintain and monitor international standards for best laboratory practices
3. Expand capabilities for the production of vaccines and therapeutics expressly for emerging and reemerging infections
4. Establish, maintain and monitor a network of international research centers for microbial threats.

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Part 1
Establish, maintain and monitor international standards for surveillance and reporting of infectious diseases

- States parties to the Compact would set up standard, secure computer architectures for biosurveillance information systems
- Parties would define and continuously refine criteria for surveillance and reporting as the environment changes

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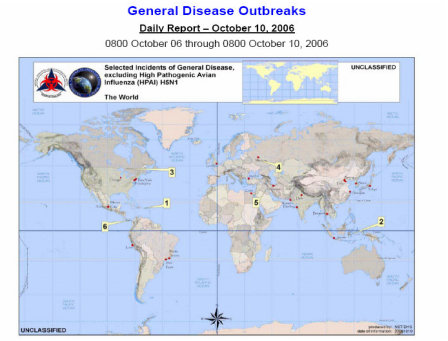
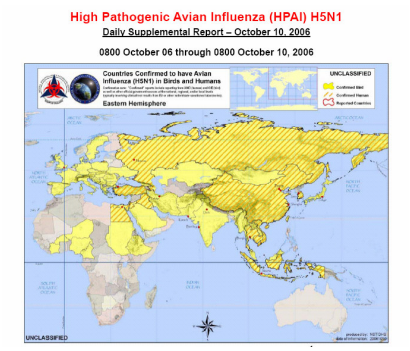
The problem is global and dynamic





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Challenges and roadmap for systems solutions (1)

- trust between signatory nations and a willingness to share biosurveillance data
- developing incentives to share data
- creation of a common architecture for information systems requires common ontologies
- developing and validating new algorithms and models of disease spread
- consequences of non-reporting, or significantly under-reporting the incidence of communicable diseases

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challenges and roadmap (2)

- integrate current initiatives into national health IT strategies and federal architectures to reduce the risk of duplicative efforts
- develop and adopt consistent interoperability standards
- create enough flexibility to bring together disparate underlying IT languages and technologies to provide a common operating picture
- generate the ability to accept multiple data formats used by agencies that provide the bio-surveillance information

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challenges and roadmap (3)

- generate the ability to feed information back to the originating agencies providing bio-surveillance information in a format each agency can accept
- identify data flows that will evolve during the developmental process
- allow the methods of analysis to evolve and adapt as new data become available or existing data sets are improved
- know and evaluate the effectiveness of the current underlying algorithms, methods, and structures for biosurveillance data analysis.

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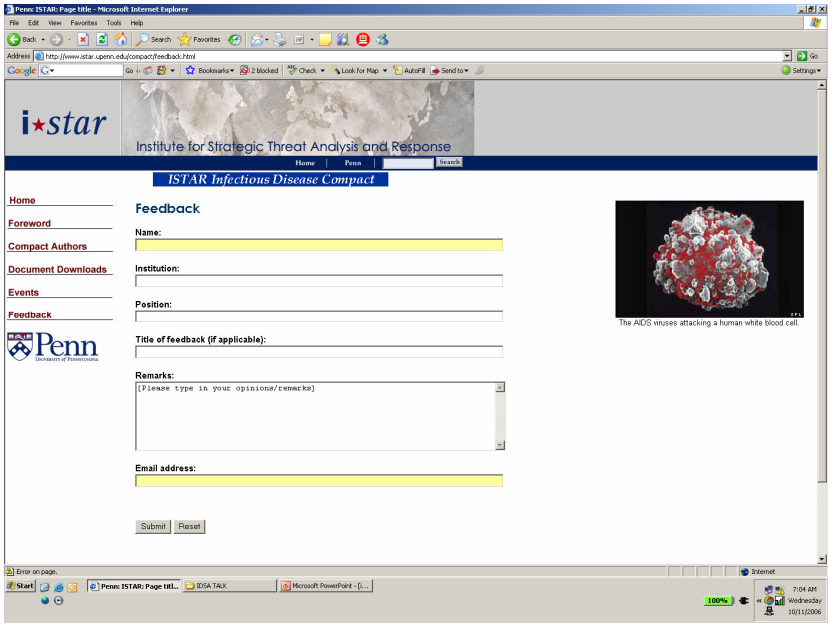
Next steps

1. Feedback and suggestions from international community: www.istar.upenn.edu/compact

2. Draft the legal, business and research cases engaging
   - the pharmaceutical industry
   - the information technology industry
   - NGOs
   - Academia

3. Present plans to the appropriate national and international governmental agencies



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2. Can biological systems operationalize certain aspects of cyber systems so that we can understand and design advanced cyber systems?

	Cyber	Bio
Logic operations	5	1
Programmable	5	2
Parallel processing	3	5

Len Adelman DNA computation papers—highly parallel, solve NP problems

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Physical Limitations of DNA Computing

Hamiltonian path problem
25 nodes…..
1 kilogram of DNA needed
70 nodes…..
1000 kilograms of DNA needed

Decryption
10^{1233} strands of DNA
at 0.17 uM------->10^{1216} liters!

From Cox, Cohen,& Ellington

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Adleman reported in a meeting that
he solved a 20 variable SAT problem using DNA

"It is not remarkable that the bear dances well--

It is that the bear dances at all"

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Not particularly interested in dancing bears, we decided to see if DNA computing had anything to say about some of the fundamental limits of computation

	Cyber	Bio
Energy efficiency	2	5
Logically reversible	2	4
Thermodynamically reversible	2	4

The Fundamental Physical Limits of Computation
What constraints govern the physical process of computing? Is a minimum amount of energy required, for example, per logic step? There seems to be no minimum., but some other questions are open
by Charles H. Bennett and Rolf Landauer
Scientific American **253**(1):48-56 (July, 1985).

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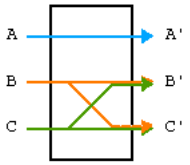
A Fredkin Gate: Logically reversible with no energy limit on the computation

A.

A	B	C	->	A'	B'	C'
1	1	1		1	1	1
1	1	0		1	0	1
1	0	1		1	1	0
1	0	0		1	0	0
0	1	1		0	1	1
0	1	0		0	1	0
0	0	1		0	0	1
0	0	0		0	0	0



CAB is a piece of DNA that we can synthesize

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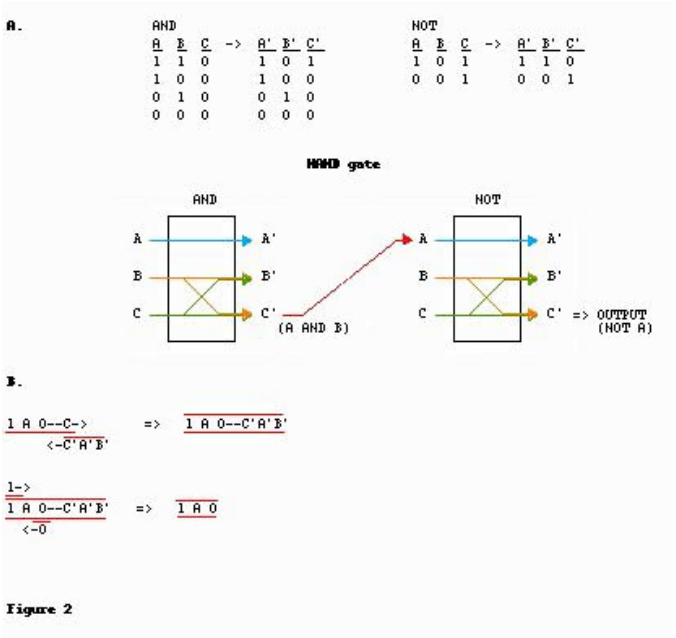
a NAND gate



A.

AND

A	B	C	->	A'	B'	C'
1	1	0		1	0	1
1	0	0		1	0	0
0	1	0		0	1	0
0	0	0		0	0	0

NOT

A	B	C	->	A'	B'	C'
1	0	1		1	1	0
0	0	1		0	0	1

B.

1 A 0--C-> => 1 A 0--C'A'B'

<-C'A'B'

1->

1 A 0--C'A'B' => 1 A 0

<-0

Figure 2

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Why reversible?

Minimal energy expense

Detection and correction of intrusion

Error checking by reversing computation to recreate inputs

Bidirectional debugging

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In principle it can take minimal energy to go through a biochemical gate

$DNA_n + dNTP \Longleftrightarrow DNA_{n+1} + PPi$

$\Delta G = kt \ln[dNTP/PPi]$

If dNTPs are just 1% over the equilibrium value:
$\Delta G = kt \ln[10.1/10]$ or about 0.01kT

a modification of an idea in Bennett and Landaur's Sci. Am paper—suggested using RNA

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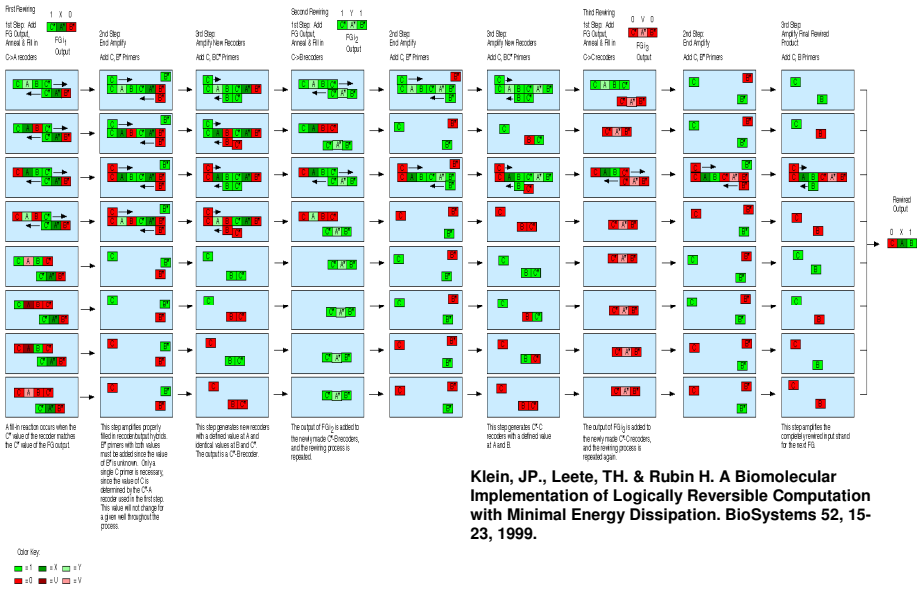
We synthsized the oligonucleotides and ran the reactions



Klein, JP., Leete, TH. & Rubin H. A Biomolecular Implementation of Logically Reversible Computation with Minimal Energy Dissipation. BioSystems 52, 15-23, 1999.

The gate works in the lab

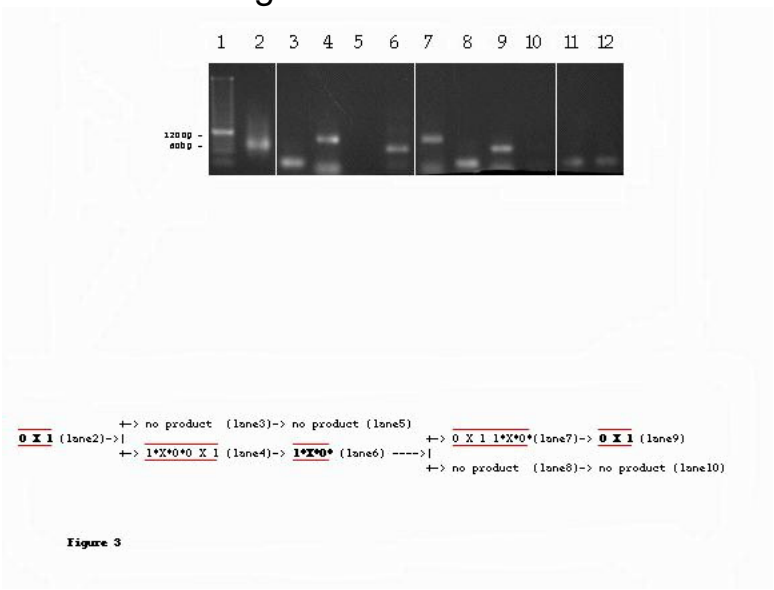


Figure 3

How fast is the gate?

$t_{1/2}$ annealing:	3 sec.
DNA polymerization rate:	15 bases/sec
For 60 bases pair input:	10 sec

2. Can biological systems operationalize certain aspects of cyber systems so that we can understand and design advanced cyber systems?

---**NO**

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3. Can cyber systems operationalize certain aspects of biological systems so that we can understand and design advanced biological systems?

- Nano-bio
- Medical devices
- Lab on a chip
- NSF workshop on high confidence medical devices and software systems last year
- Subject of Tele-Physical services and applications working group at this meeting
- > $3 billion invested already

2007 NSTI Nanotechnology Conference and Trade Show – May 2007 - Santa Clara

Life Sciences & Medicine
Bio-nano Materials & Tissues
Bio Sensors & Diagnostics
Biomarkers & Nanoparticles
Cancer Nanotechnology
Cellular & Molecular Dynamics
Drug Delivery & Therapeutics
Imaging
Nano Medicine
Nanotech to Neurology

Answer to Question 3--YES

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4. Can cyber systems operationalize certain aspects of biological systems so that we can understand and design advanced cyber systems?

	Cyber	Bio
Evolvable	1	5
Self learning	1	5
Self repair	1	5
Self correcting	1	5
Self assembly	1	5
Self-Replicating (hardware)	0	5
Richness of user interface	2	4
Multi-agent communication	3	4
Aggregate data and predict outcomes	0-1	4
Solve the "inverse problem"	0-1	5
Impact on society	0-4	5

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Can cyber systems operationalize certain aspects of biological systems so that we can understand and design advanced cyber systems?

examples abound from molecular level to societal level

- Persistence in bacteria as hedge strategy against attack
- Cellular metabolism- metabolome:metabolic flux models
  - supply chain
- Swarm behavior
  - Autonomous mobile robots
  - Inverse problem
- Markets
  - Data aggregation
  - Event prediction

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Prediction markets

- buy and sale of contracts to predict future events
- value of the contracts depends on the outcome of the event
- contract traders have special information about the event
- to profit, traders will use their information to buy contracts that they consider undervalued and sell contracts that are overvalued.
- the trade price reflects an aggregated consensus about the future value, i.e. a prediction of the future event.
- the Iowa Electronic Market (IEM): election predictions, interest rate decisions of the Federal Reserve, currency and stock prices, movie box office receipts, IPOs, congressional approval of legislation, the future sale of Harry Potter Books

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prediction markets support decisions

- markets give continuously updated dynamic forecasts.
- thru the price formation process, markets aggregate information across traders, solving complex aggregation problems.
- markets give unbiased, relatively accurate forecasts in advance of outcomes
- forecasts can outperform existing alternatives
- markets can be designed to forecast a variety of issues
- markets are generally the best available mechanism for gathering and aggregating dispersed information from private, self-interested economic agents.

Information Systems Frontiers 5:1, 79–93, 2003
Prediction Markets as Decision Support Systems
J.E. Berg, T.A. Rietz University of Iowa

Personal knowledge-search engines---"trade" --- aggregate---predict–autonomously reconfigure

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Bio-systems under potential attack
Persistence in bacteria

- microorganisms often encounter an environment with limited nutrients or certain other stress related stimuli
- they enter a dramatically slowed growth state until a new equilibrium is established

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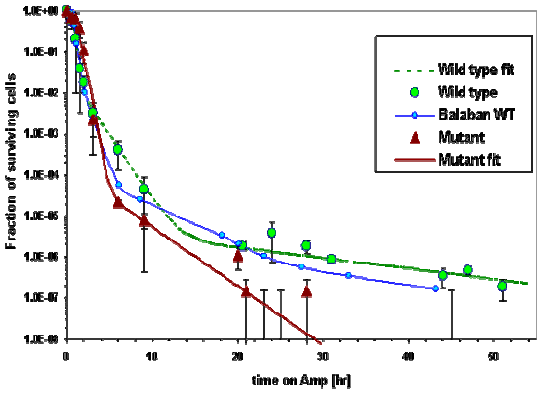
Persistence in bacteria



Kill curves in the presence of ampicillin

***E. COLI* PERSISTENCE LINKED TO (p)ppGpp BY A MIXED STOCHASTIC AND DETERMINISTIC MECHANISM**
Halász, Buckstein, Imieliński, Marjanovich, Teh, Kumar, Rubin

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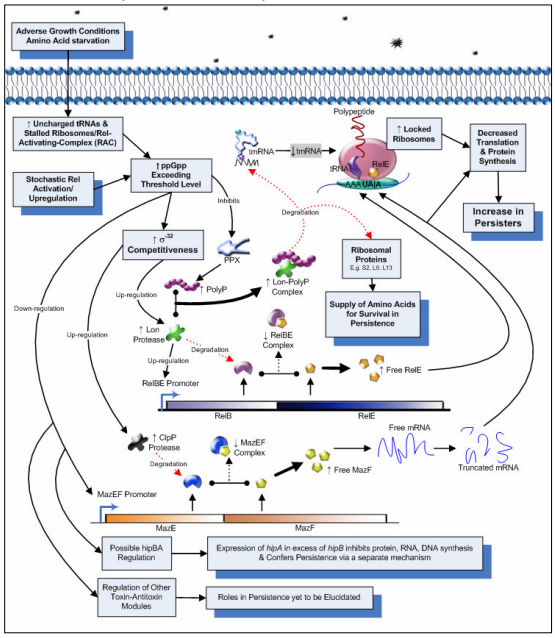
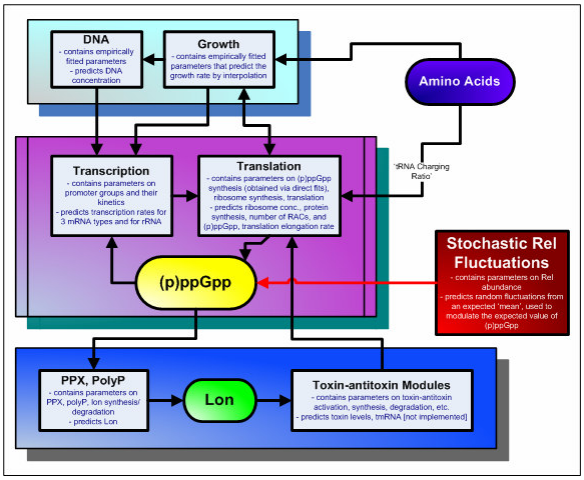
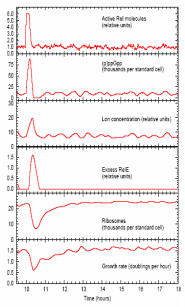
Molecular components of persistence in bacteria



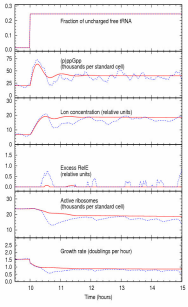


Model simulation results

A

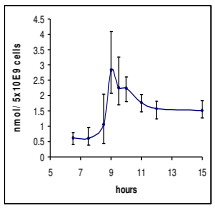


B



A: The stringent response triggered by a transient fluctuation of (p)ppGpp. B: The stringent response following a mild downshift in nutrient availability, C: Experimentally determined (p)ppGpp level in *E. coli* grown in 0.4% glucose MOPS with 10 µg/mL thiamine. This tracing should be compared with (p)ppGpp in panel B above showing very similar results to calculated (p)ppGpp.

C



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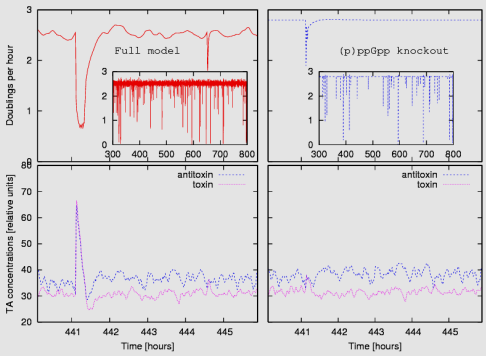
Simulation results illustrating the shutdown mechanism and the cumulative effect of many shutdown episodes on the survival properties of a colony.

A



B

C

Lines marked "(p)ppGpp knockout" were obtained by turning off the (p)ppGpp production mechanism and setting the (p)ppGpp concentration to its basal level, effectively zero. (A) timecourses of instantaneous growth rate (top) and of the toxin and antitoxin concentrations during one shutdown event. The shutdown is missed in the knockout because of a larger average difference between the toxin and antitoxin concentrations. The same fluctuation leads to a smaller slowdown event.

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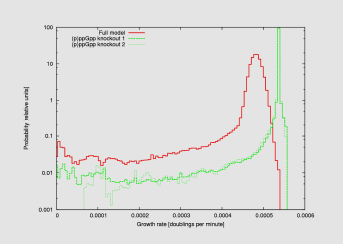
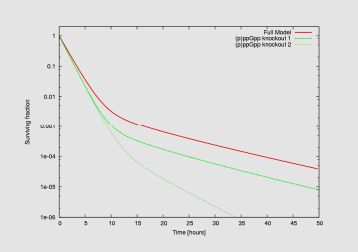


(B) Histograms obtained by sampling the growth rates of one single-cell simulation over approximately 1000 hours. The thin line marked "(p)ppGpp knockout 2" corresponds to a shorter sampling period which does not include a large shutdown event.



(C) Kill curves derived from the growth rate histograms. Both versions of the knockout exhibit fewer persisters.

Bio-systems under potential attack
Persistence in bacteria

- Persistence emerges when the stringent response mechanism is randomly engaged generating a very small population of slow-growing bacteria that revert to normal growth rates only when the necessary protein synthesis machinery re-accumulates.
- The proposed model of persistence has only a *single* stable steady state.
- In this model, stochastic fluctuations trigger a fast growing cell to dramatically slow its growth, which then deterministically rebounds to its original fast growing state.
- On a population level, this model predicts the existence of a continuous distribution of growth rates that includes a substantial “tail” of slow growing cells. In the presence of a bactericidal antibiotic, which preferentially kills fast growing cells, this model reproduces the phenomenon of persistence and closely matches *in vivo* kill curve data.
- Can this mechanism be operationalized by cyber systems as hedge against attack?

Research program:
Can cyber systems operationalize certain aspects of biological systems so that we can understand and design advanced cyber systems?

	Cyber	Bio
Evolvable	1	5
Self learning	1	5
Self repair	1	5
Self correcting	1	5
Self assembly	1	5
Self-Replicating (hardware)	0	5
Richness of user interface	2	4
Multi-agent communication	3	4
Aggregate data and predict outcomes	0-1	4
Solve the "inverse problem"	0-1	5
Impact on society	0-4	5

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" We choose to go to the moon in this decade and do the other things, not because they are easy, but because they are hard, because that goal will serve to organize and measure the best of our energies and skills, because that challenge is one that we are willing to accept, one we are unwilling to postpone, and one which we intend to win…"

John F. Kennedy Rice University September 12, 1962

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