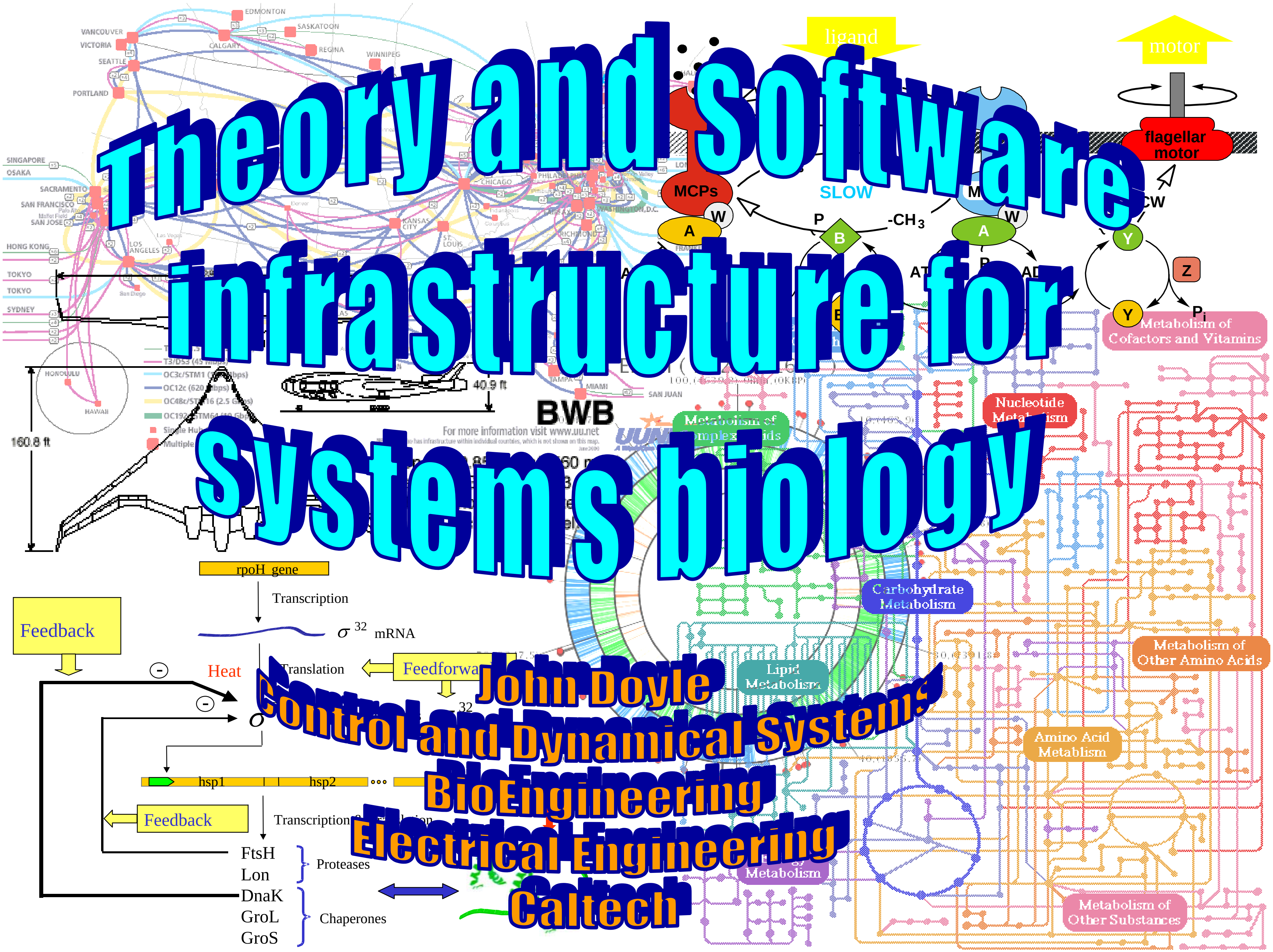


Theory and Software infrastructure for Systems biology

John Doyle

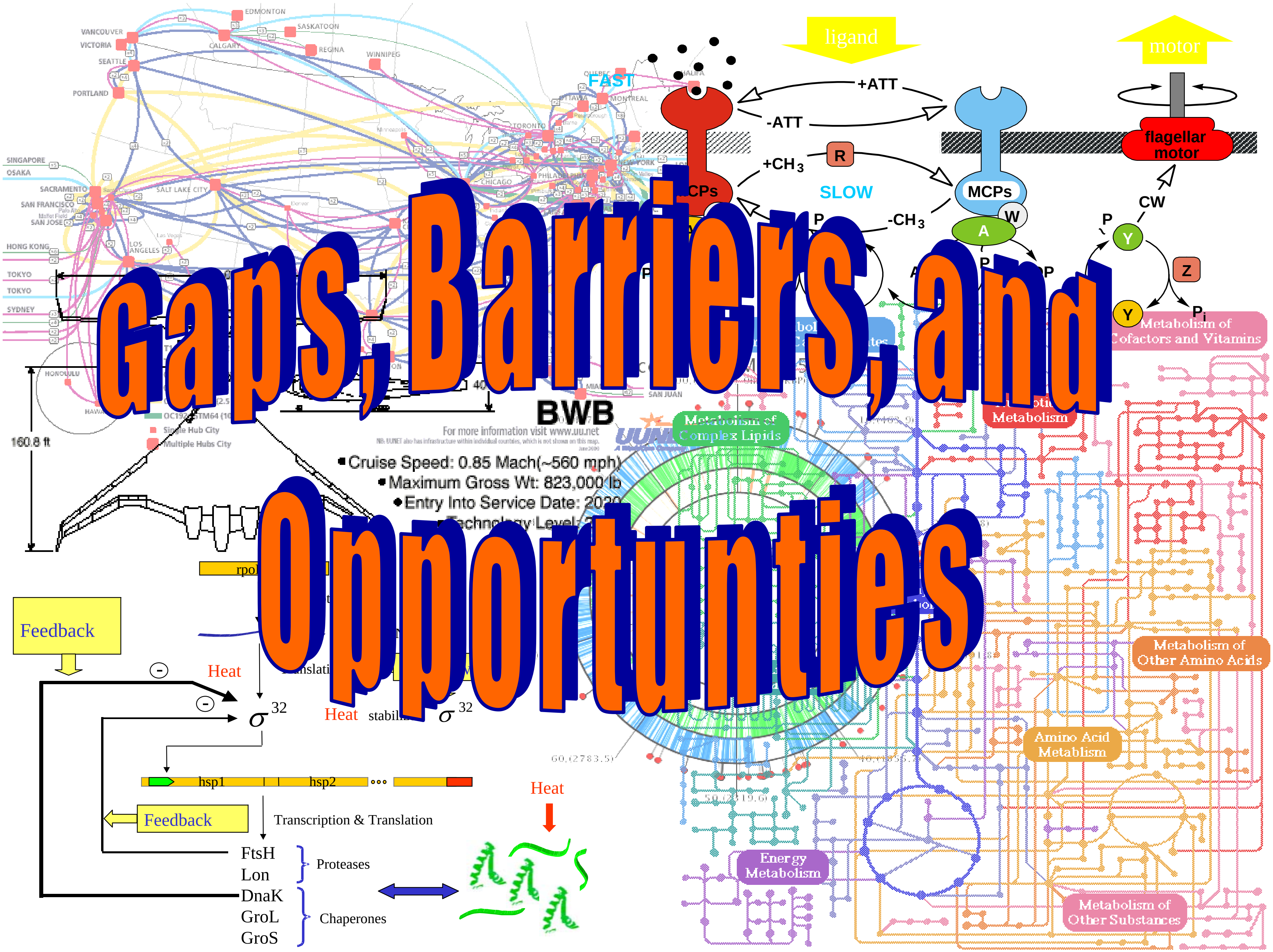
Control and Dynamical Systems

BioEngineering

Electrical Engineering

Caltech

Gaps, Barriers, and Opportunties



Collaborators and contributors (partial list)

Biology: Csete, Yi, Tanaka, Arkin, Savageau, Simon, AfCS, Kurata, Khammash, El-Samad, Gross, Bolouri, Kitano, Hucka, Sauro, Finney, …

Theory: Parrilo, Carlson, Paganini, Papachristodoulo, Prajna, Goncalves, Fazel, Lall, D'Andrea, Jadbabaie, many current and former students, …

Web/Internet: Low, Willinger, Vinnicombe, Kelly, Zhu, Yu, Wang, Chandy, Effros, …

Turbulence: Bamieh, Dahleh, Bobba, Gharib, Marsden, …

Physics: Mabuchi, Doherty, Barahona, Reynolds, Asimakapoulos, …

Engineering CAD: Ortiz, Murray, Schroder, Burdick, …

Disturbance ecology: Moritz, Carlson, Robert, …

Finance: Martinez, Primbs, Yamada, Giannelli, …

Caltech faculty

Other Caltech

Other

Thanks to

- Kitano ERATO Symbiotic systems 1997-2003
- AFOSR MURI “Uncertainty management in complex systems” 1995-2002
- NSF ITR 2004-?
- DARPA 2001-2003??? (See next talk.)
- AfCS (NIH+Pharma) 2000-?
- ARO Institute for Collaborative Biotechnologies
- Internet: NSF, DARPA, ARO

"GenBank is a false model" (Robbins)

- Think of the cell as an information processing system (a dangerous but temporarily useful metaphor)
- The genome is the cell's database, and thus lends itself to treatment via database methods.
- Thus GenBank is a good first step, but…
- 99% of silicon-based computers are ***embedded*** (hidden in other technologies, performing control functions)
- ???% of carbon-based computation is also doing control
- Control systems are very different than databases (and graph models give only cartoons of regulatory networks)

- > 150,000 components (many of which are complex subsystems),
- > 1,000 computers can automate nearly all functions
- During flight test, record > 100Mb per sec of data

- Global design network of >10,000 workstations
- >$1B in software infrastructure alone

- Is biology much simpler?

Key systems biology themes

1. Need new theoretical and software infrastructure for systems biology, beyond bioinformatics.
2. Multiscale (and large-scale) stochastic simulation is an essential technology.
3. Simulation alone is not scalable to larger network problems because complex, uncertain systems need an exponentially large number of simulations to answer biologically meaningful questions.
4. There are fundamental laws governing the organization of biological networks.
5. Tight coupling with experimental biology.

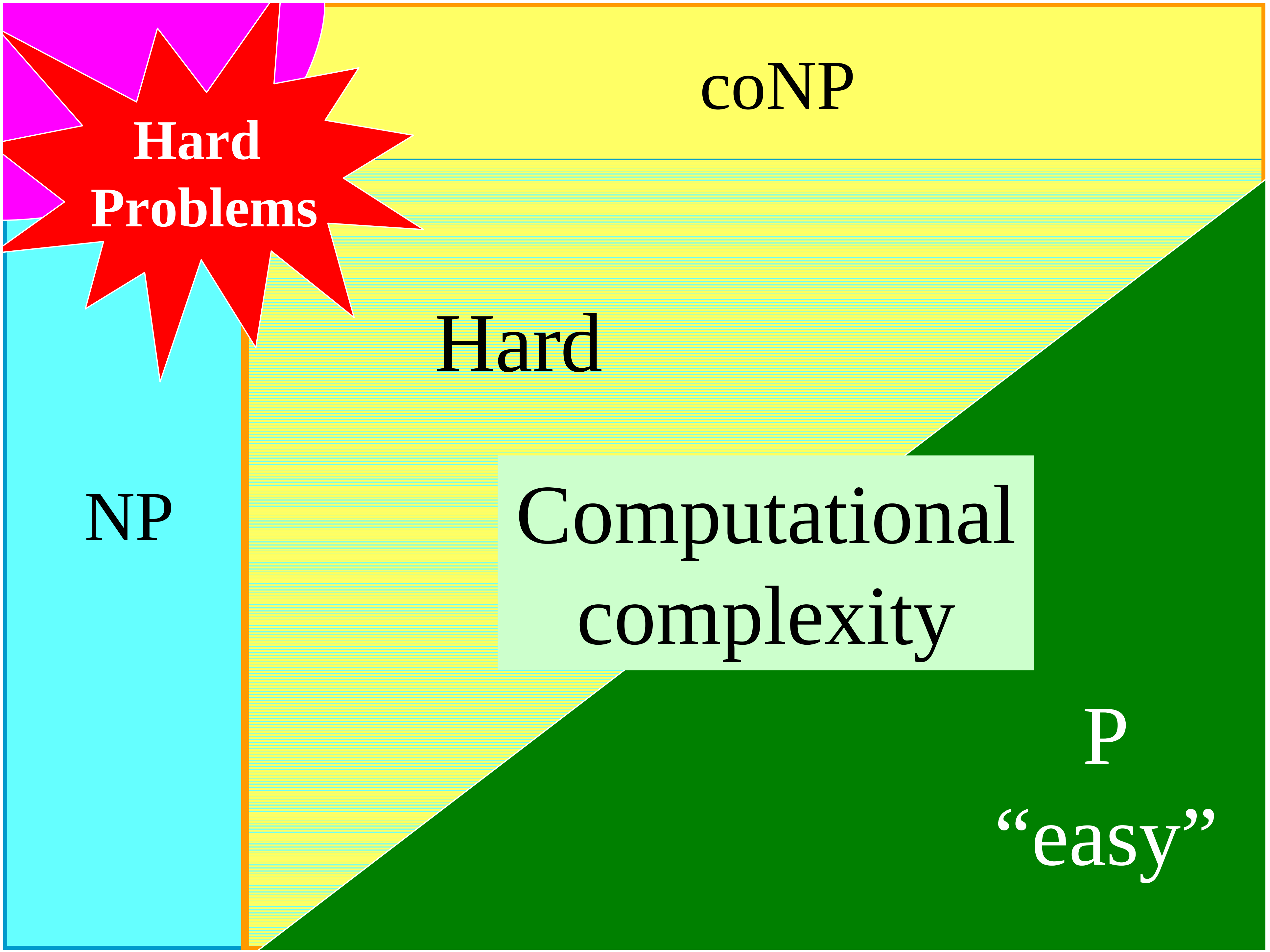
New algorithms and software

1. New software infrastructure.
   - SBML: Systems Biology Markup Language
   - SBW: Systems Biology Workbench
   - FAST: Fast AQM Scalable TCP (Internet protocols)
2. Stochastic simulation (+Gillespie/Petzold)
3. Beyond simulation.
   - SOStools: Sum-Of-Squares SemiDefinite Programming toolbox

Key themes

1. Need new theoretical and software infrastructure for systems (beyond purely molecular) biology.
2. Multisca… …tic simulation is an essent…
3. Simulati… … larger network problems… …ain systems need an exponentially large number of simulations to answer biologically meaningful questions.
4. There are fundamental laws governing the organization of biological networks.

Without exploiting these organizational laws, the complexity will be overwhelming.


Hard
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Computational
complexity
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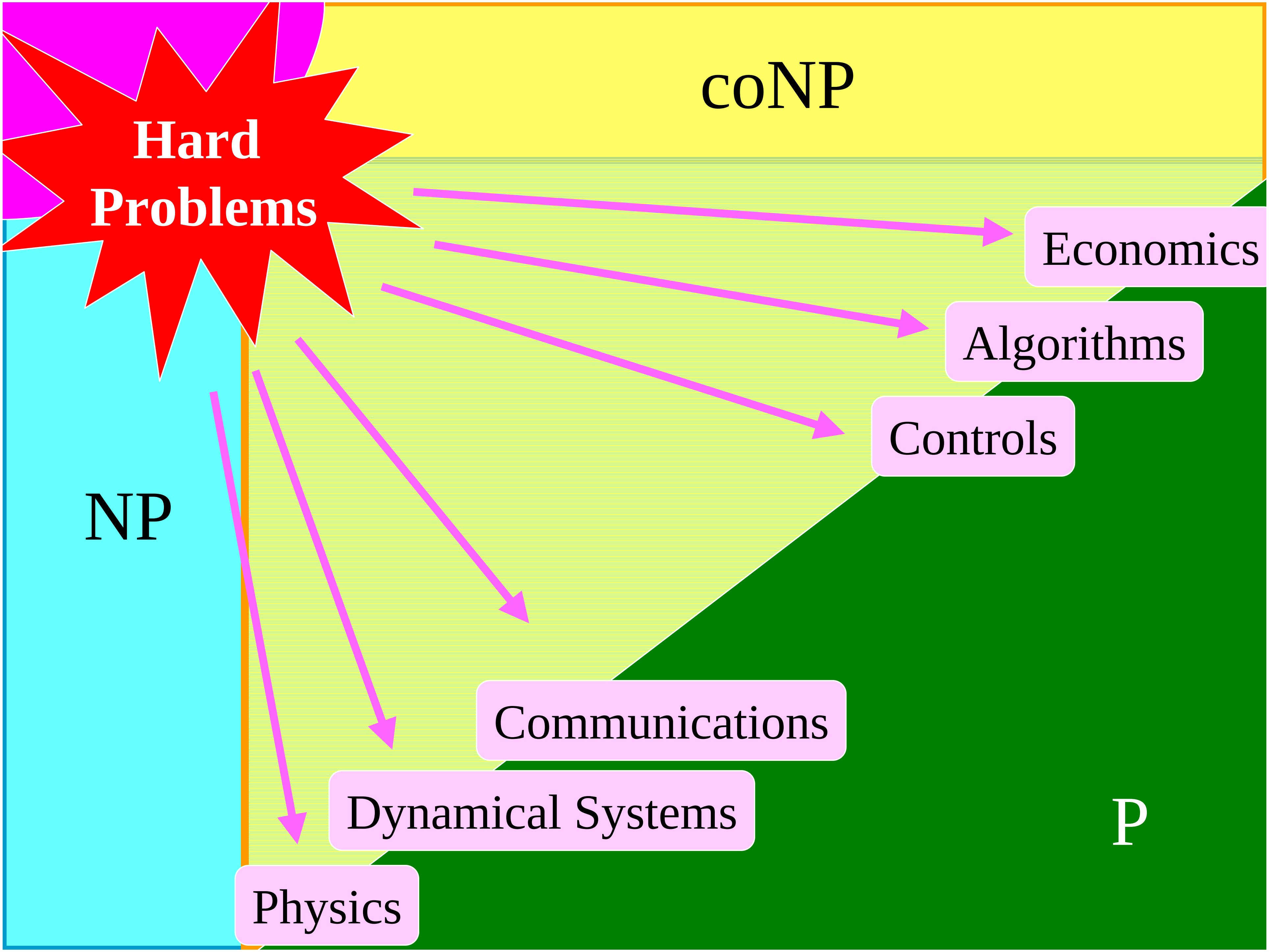
"easy"


Hard
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Controls
Communications
Dynamical Systems
Physics
P

- Domain-specific assumptions
- Enormously successful

- Handcrafted theories
- Incompatible assumptions

- Tower of Babel where even experts cannot communicate
- “Unified theories” failed
- New challenges unmet

Economics

Algorithms

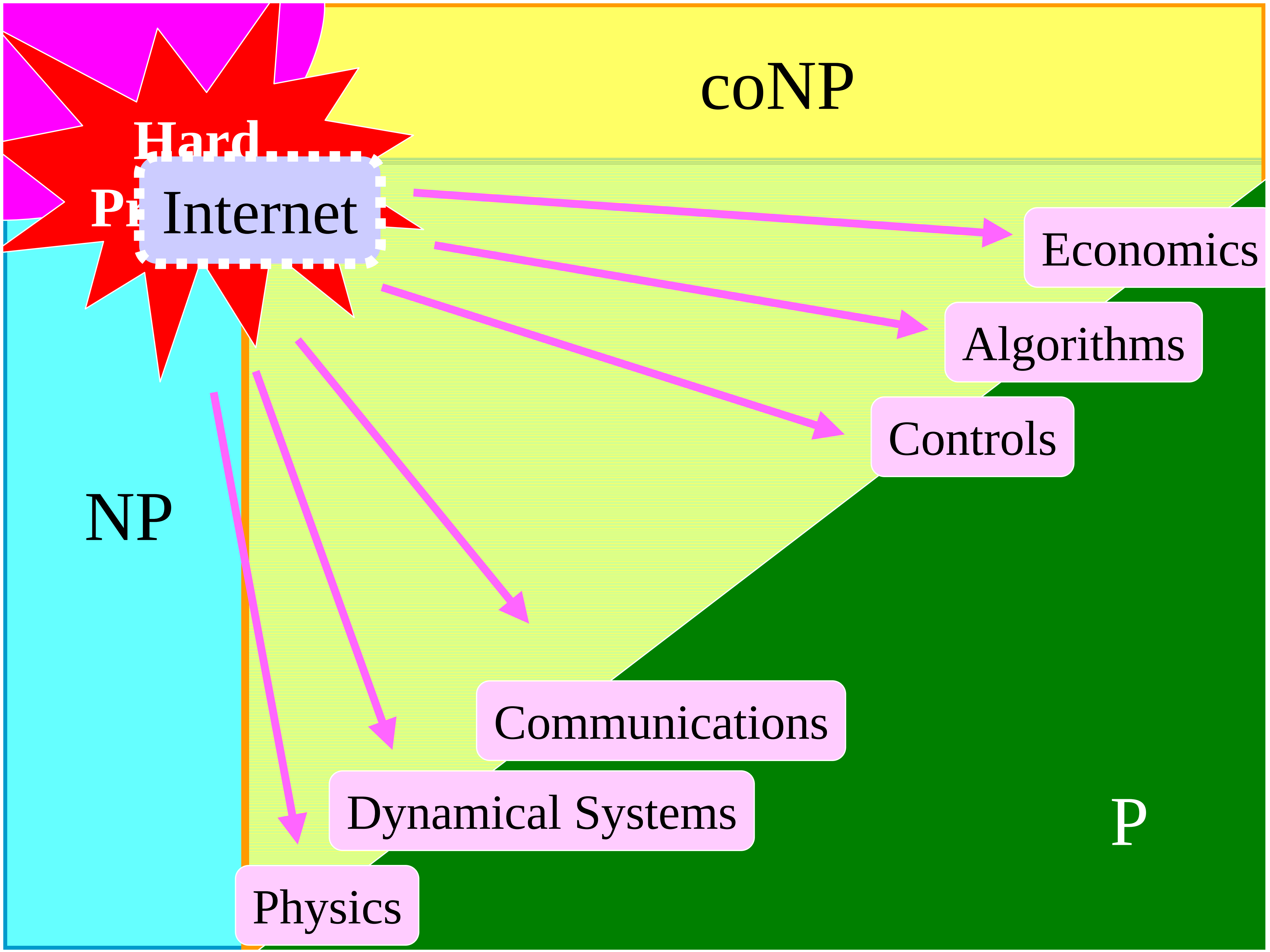
Controls

Communications

Dynamical Systems

Physics

P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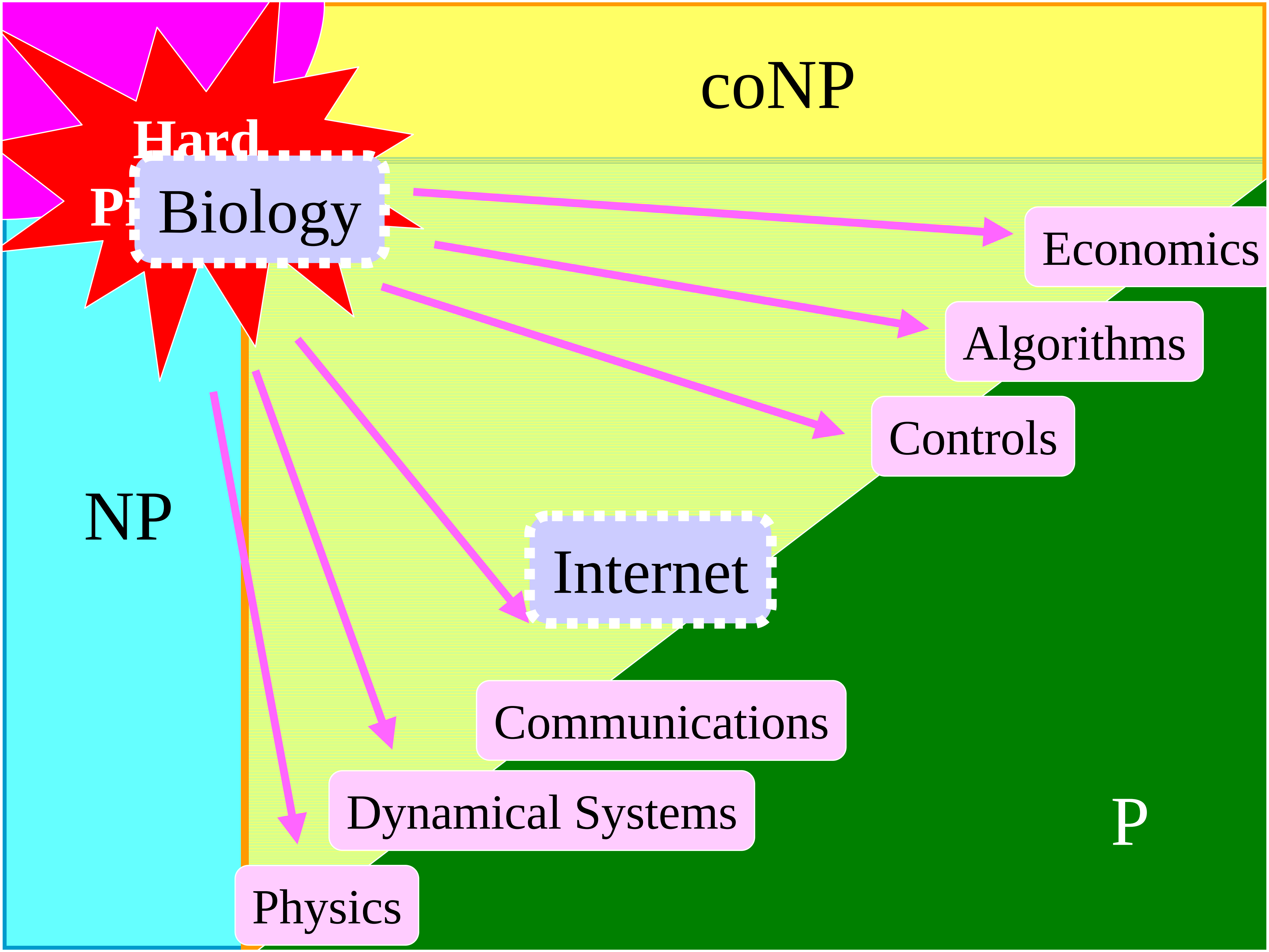
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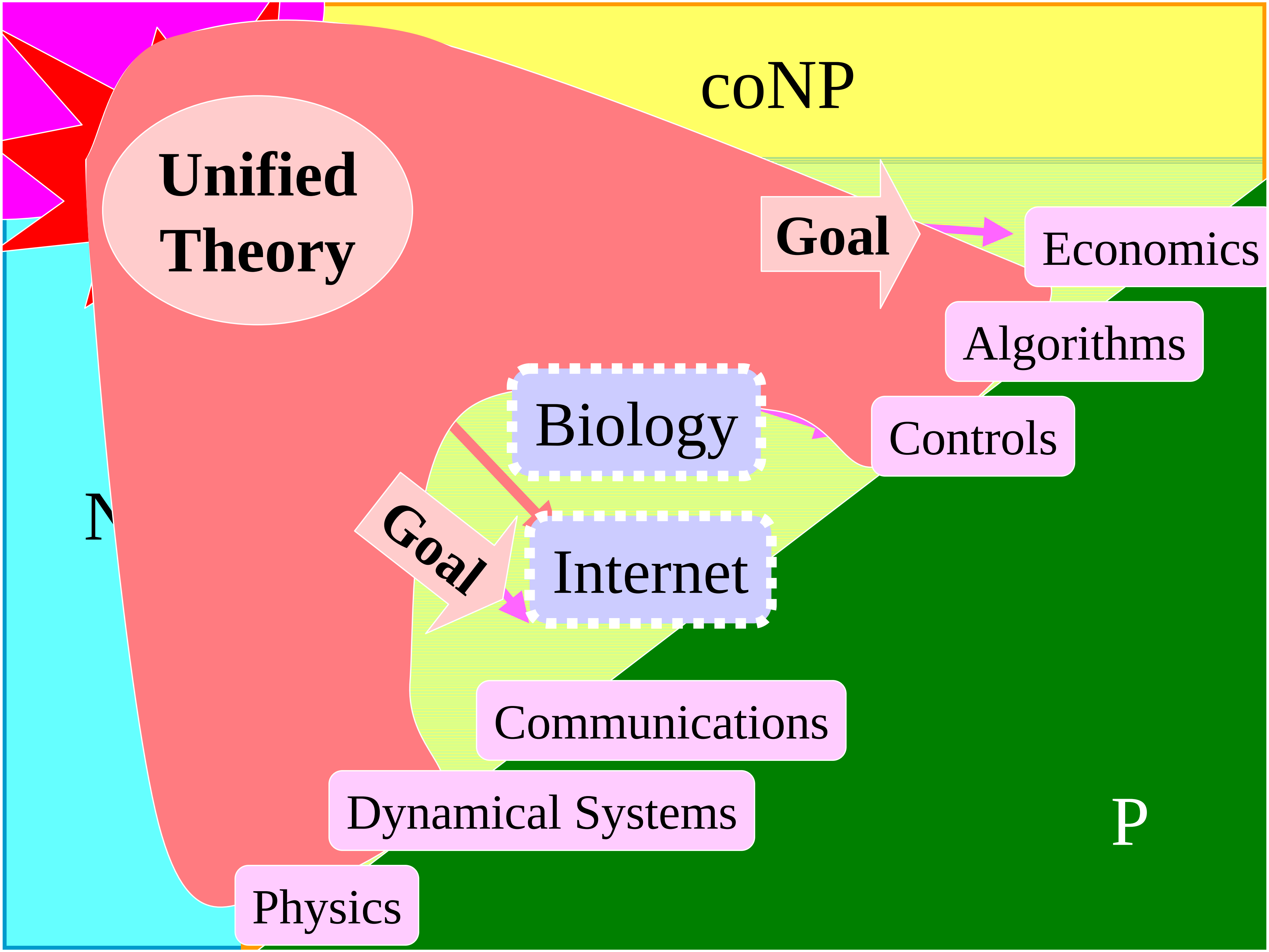
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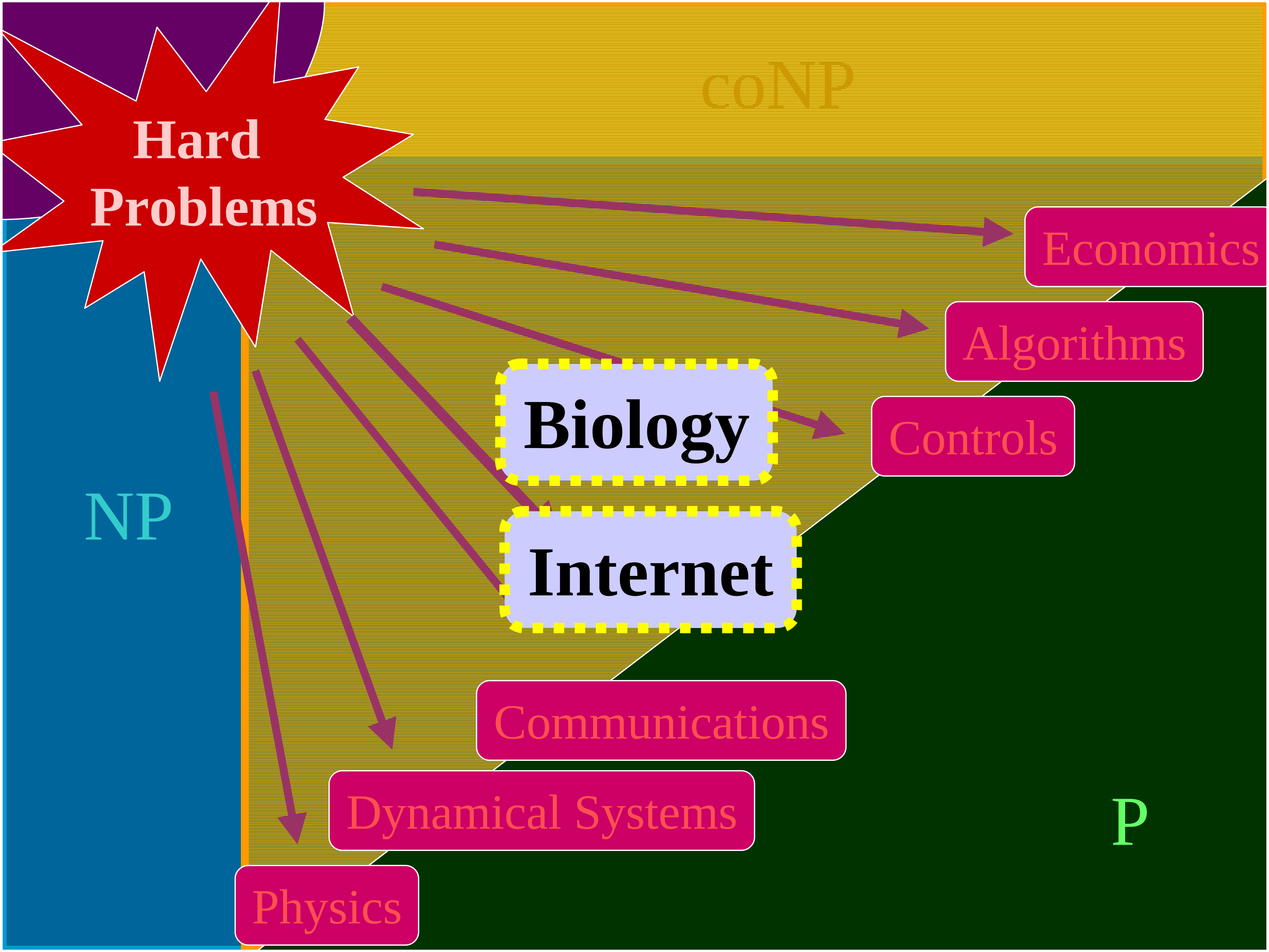
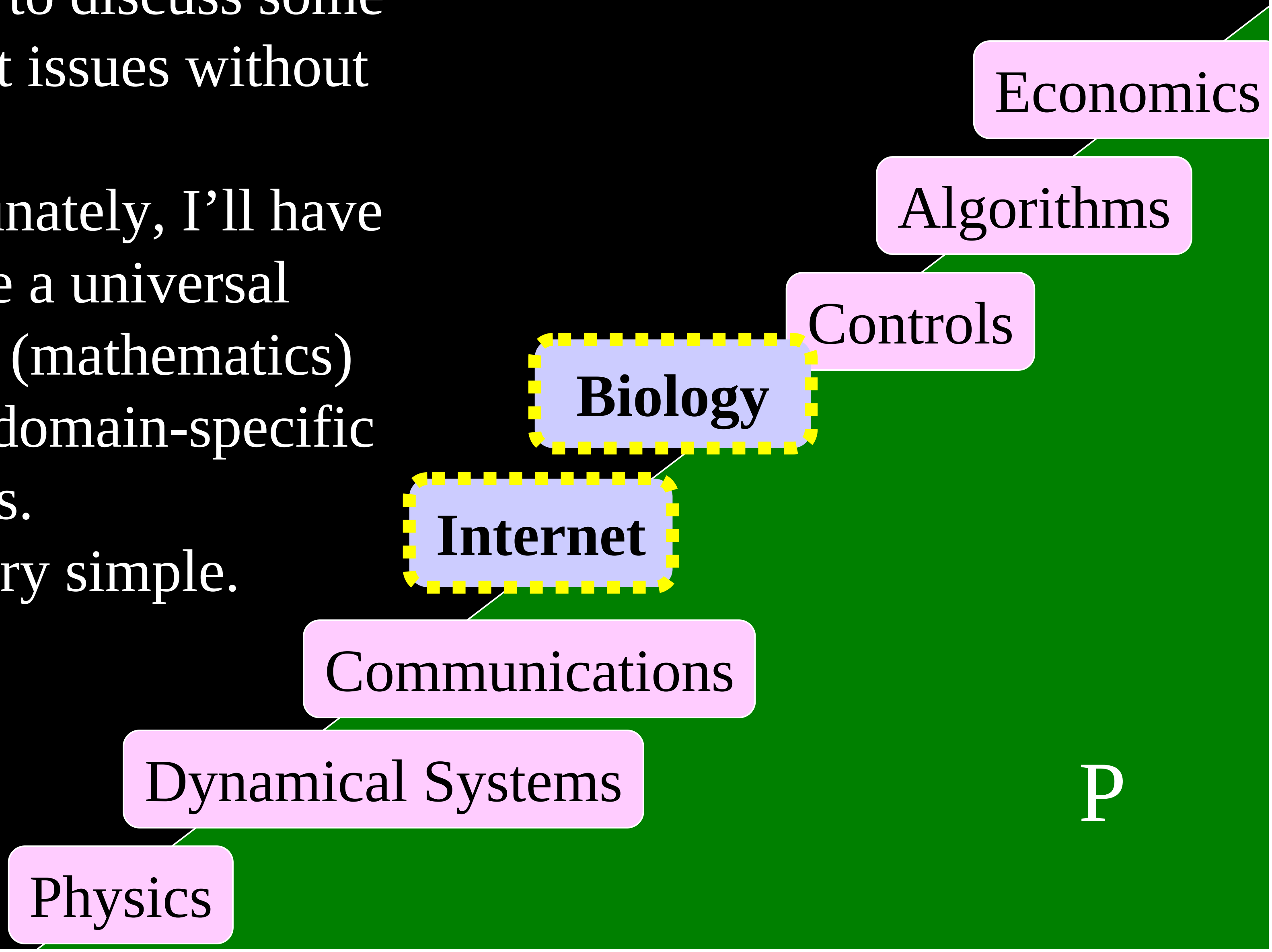


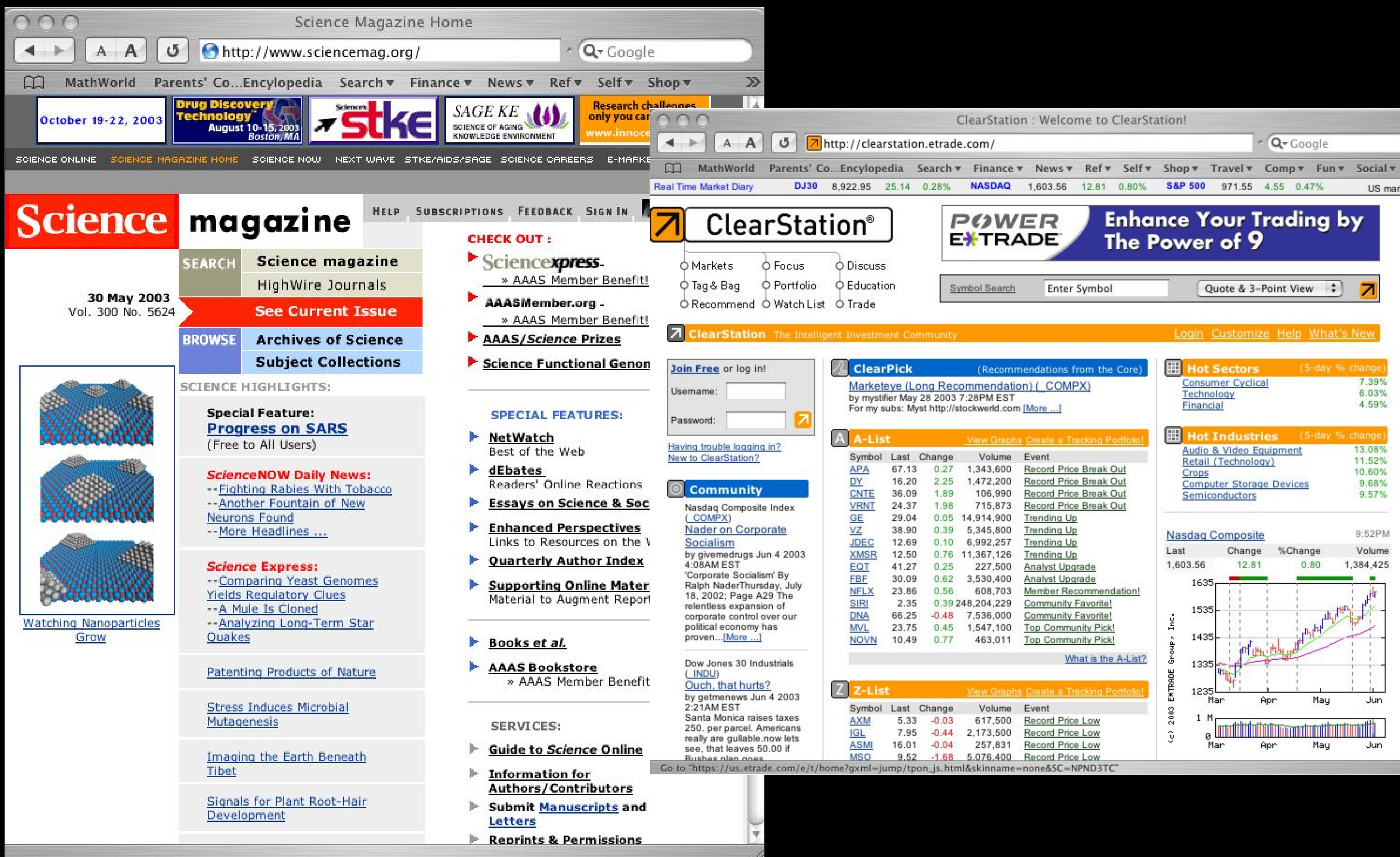
coNP
Hard Problems
Economics
Algorithms
Biology
Controls
Internet
NP
Communications
Dynamical Systems
P
Physics

Challenge

- The unifying language is (new) mathematics
- I'll aim to discuss some important issues without math
- Unfortunately, I'll have to replace a universal language (mathematics) with the domain-specific languages.
- Start very simple.



HTML: Lingua Franca of the Web



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  </tr>
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Cessation and Gender</a></td
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<tr valign="top">
    <td><img src="http://www
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Breast Cancer Treatment</a><
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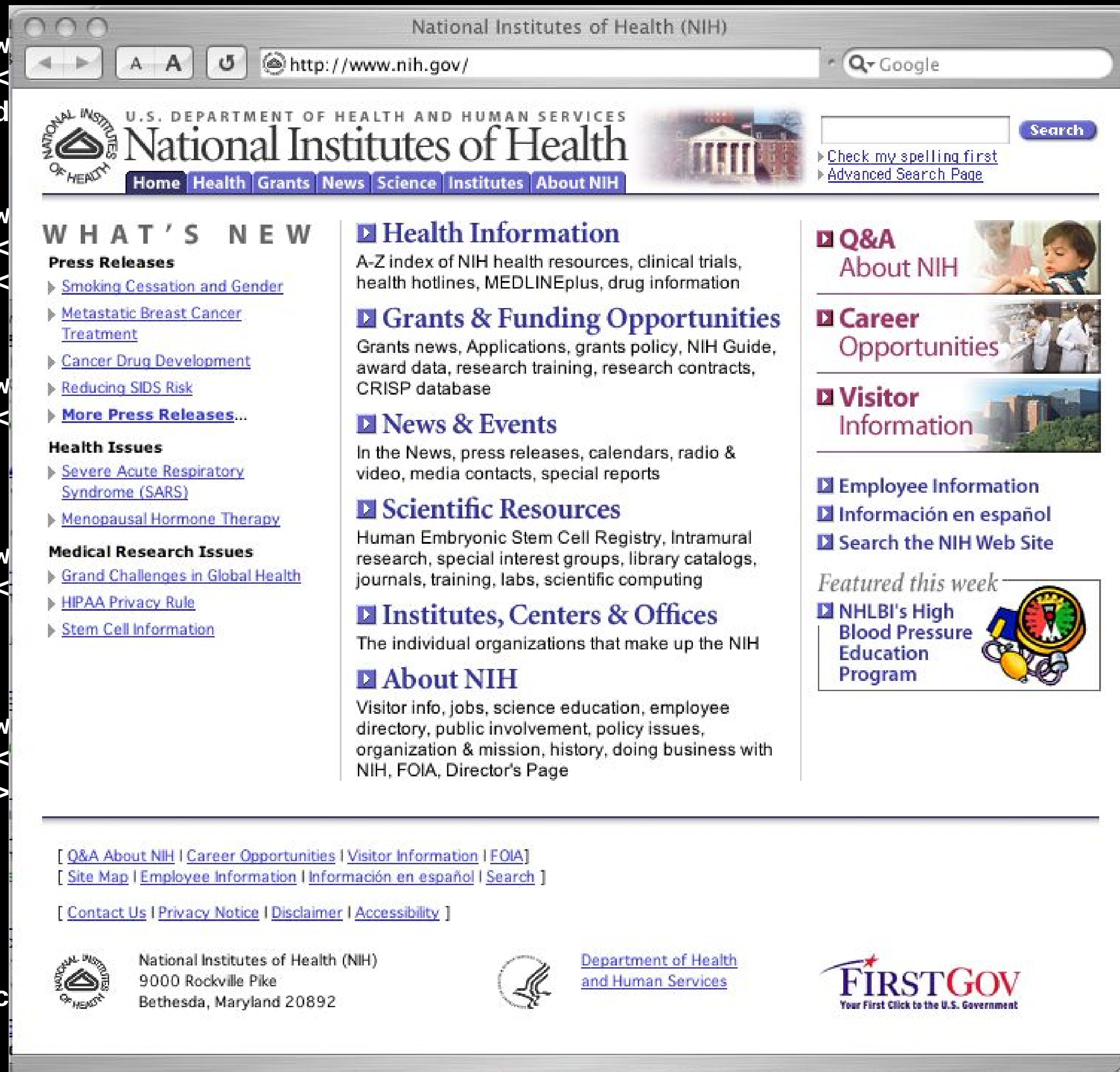

HTML: Lingua Franca of the Web

Web needed agreement on a common format

- HTML (caution: a rather ugly hack)
- *But users never need to see this side*

Common format allows unprecedented capabilities for information exchange

- Makes it possible for a program to interpret content written by wide variety of other programs
- Enables all kinds of applications
- May seem boring, but important to get right

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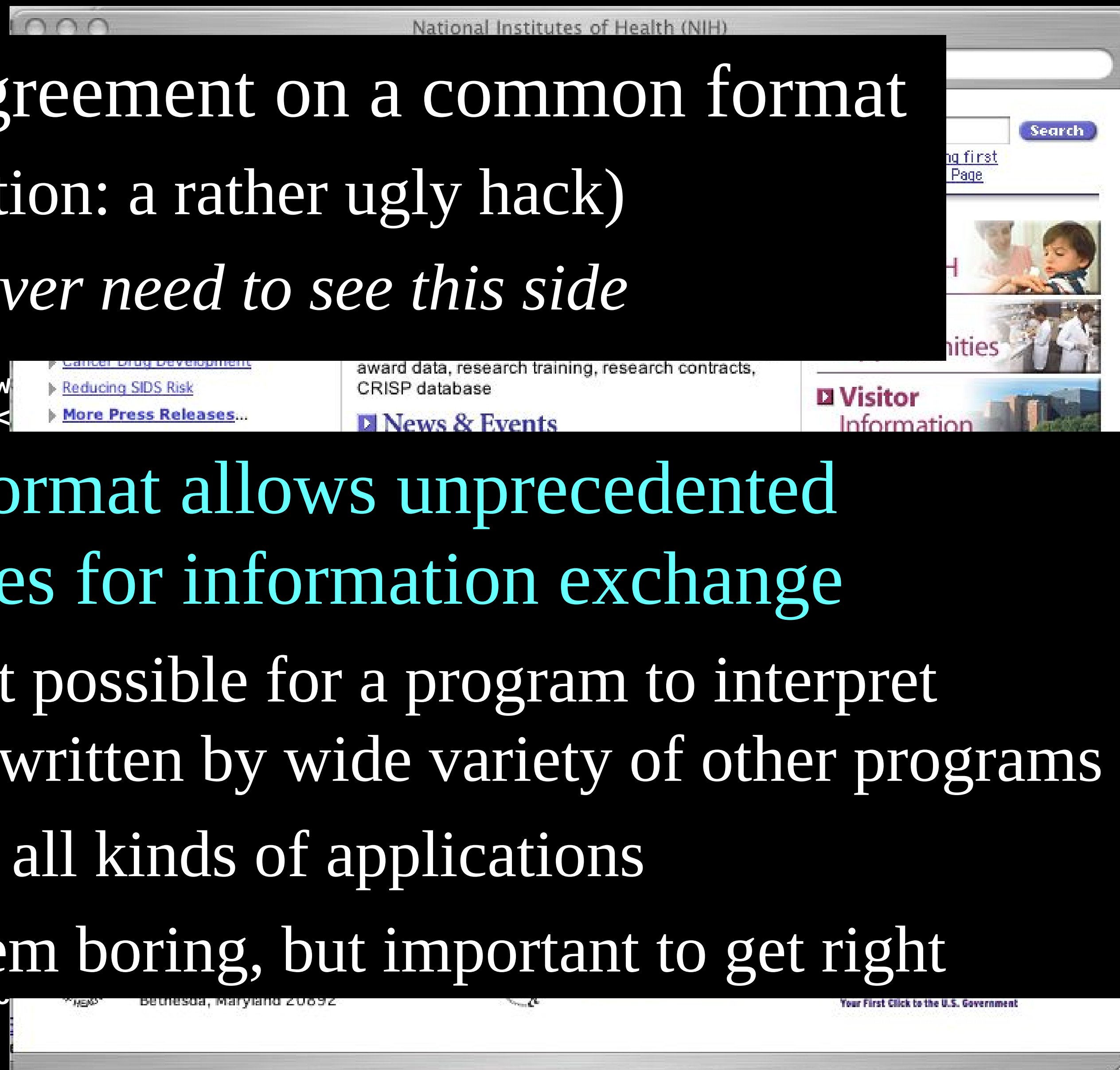

HTML: Lingua Franca of the Web

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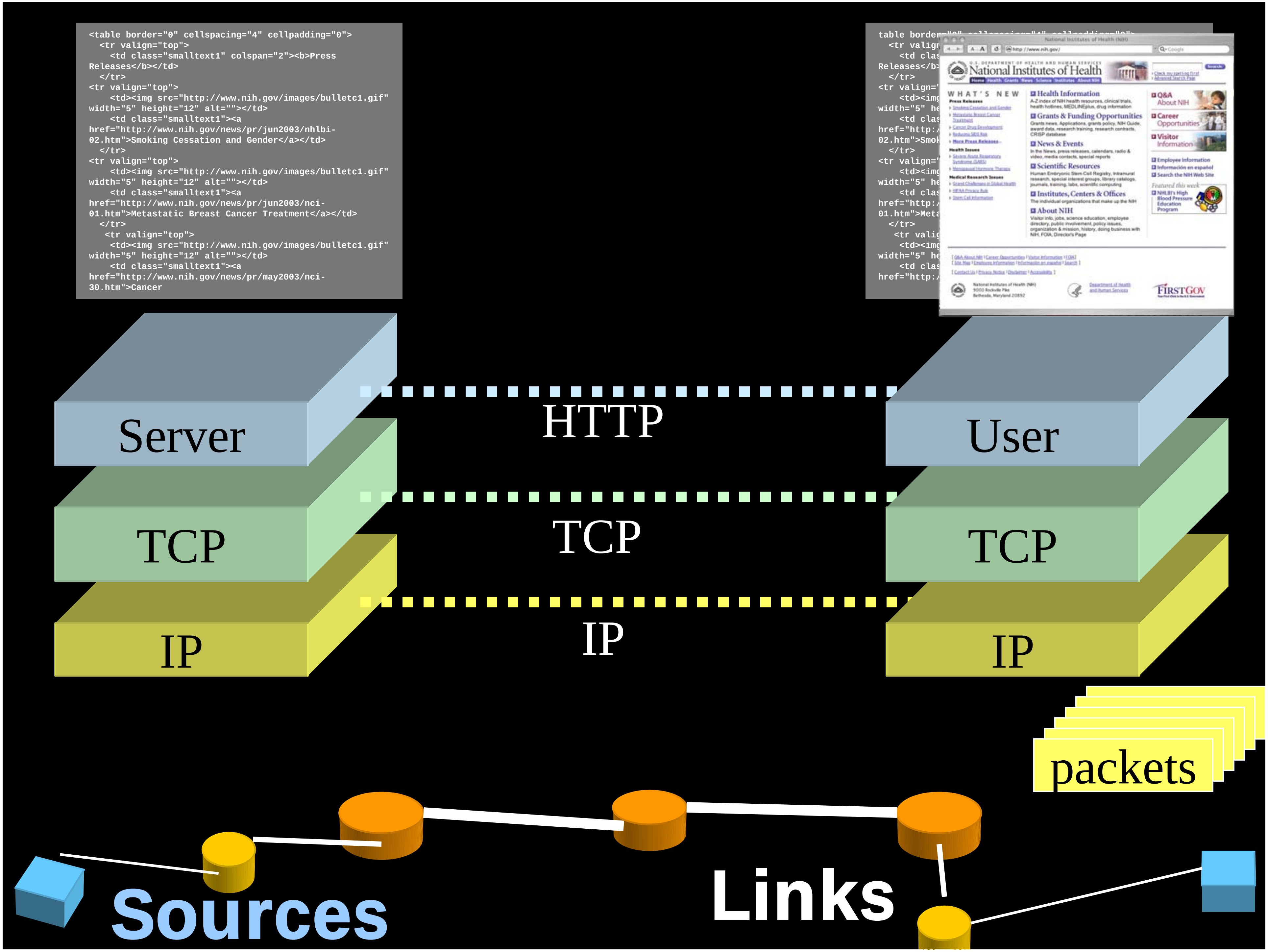
  - *But users never need to see this side*
- Common format allows unprecedented capabilities for information exchange
  - Makes it possible for a program to interpret content written by wide variety of other programs
  - Enables all kinds of applications
  - May seem boring, but important to get right

It’s *important* to have a *boring* trip home.

What do you think all those computers are doing?



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<td class="smalltext1">Smoking Cessation and Gender</td>
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<td class="smalltext1">Metastatic Breast Cancer Treatment</td>
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<td class="smalltext1"><a href="http://www.nih.gov/news/pr/may2003/nci-30.htm">Cancer
National Institutes of Health
Server
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National Institutes of Health
Home Health Grants News Science Institutes About NIH
Search
Check my spelling first
Advanced Search Page
WHAT'S NEW
Press Releases
Smoking Cessation and Gender
Metastatic Breast Cancer Treatment
Cancer Drug Development
Reducing SIDS Risk
More Press Releases...
Health Issues
Severe Acute Respiratory Syndrome (SARS)
Menopausal Hormone Therapy
Medical Research Issues
Grand Challenges in Global Health
HIPAA Privacy Rule
Stem Cell Information
Health Information
A-Z index of NIH health resources, clinical trials, health hotlines, MEDLINEplus, drug information
Grants & Funding Opportunities
Grants news, Applications, grants policy, NIH Guide, award data, research training, research contracts, CRISP database
News & Events
In the News, press releases, calendars, radio & video, media contacts, special reports
Scientific Resources
Human Embryonic Stem Cell Registry, Intramural research, special interest groups, library catalogs, journals, training, labs, scientific computing
Institutes, Centers & Offices
The individual organizations that make up the NIH
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Visitor info, jobs, science education, employee directory, public involvement, policy issues, organization & mission, history, doing business with NIH, FOIA, Director's Page
Q&A About NIH
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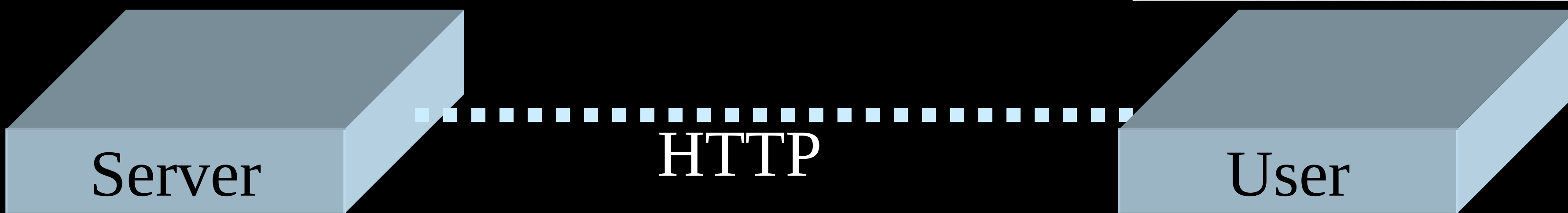
National Institutes of Health (NIH)
9000 Rockville Pike
Bethesda, Maryland 20892
Department of Health and Human Services
FIRSTGOV
Your First Click to the U.S. Government
Server
TCP
IP
User
TCP
IP
TCP
IP
Hidden from the user
Sources

HTTP: HyperText
Transfer Protocol

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    <td class="smalltext1"><a
href="http://www.nih.gov/news/pr/may2003/nci-
30.htm">Cancer
```

HTML: HyperText
Markup Language

SBML: A Lingua Franca for Models in Systems Biology

- A lot like HTML (but hopefully not an ugly hack)
  - But for computing, not (just) displaying on screen
- Provides a common machine-readable format for models of networks of biochemical reactions
  - A + B —> C, C + D —> E, etc.
- Components in SBML are conceptually simple
  - Chemical species
  - Reactions
  - Parameters
  - etc.

- To learn more: http://www.sbml.org

The Systems Biology Markup Language (SBML): a medium for representation and exchange of biochemical network models

M. Hucka, A. Finney, H. M. Sauro, H. Bolouri, J. C. Doyle, H. Kitano, *and the rest of the SBML Forum*: A. P. Arkin, B. J. Bornstein, D. Bray, A. Cornish-Bowden, A. A. Cuellar, S. Dronov, E. D. Gilles, M. Ginkel, V. Gor, I. I. Goryanin, W. J. Hedley, T. C. Hodgman, J.-H. Hofmeyr, P. J. Hunter, N. S. Juty, J. L. Kasberger, A. Kremling, U. Kummer, N. Le Novere, L. M. Loew, D. Lucio, P. Mendes, E. Minch, E. D. Mjolsness, Y. Nakayama, M. R. Nelson, P. F. Nielsen, T. Sakurada, J. C. Schaff, B. E. Shapiro, T. S. Shimizu, H. D. Spence, J. Stelling, K. Takahashi, M. Tomita, J. Wagner and J. Wang

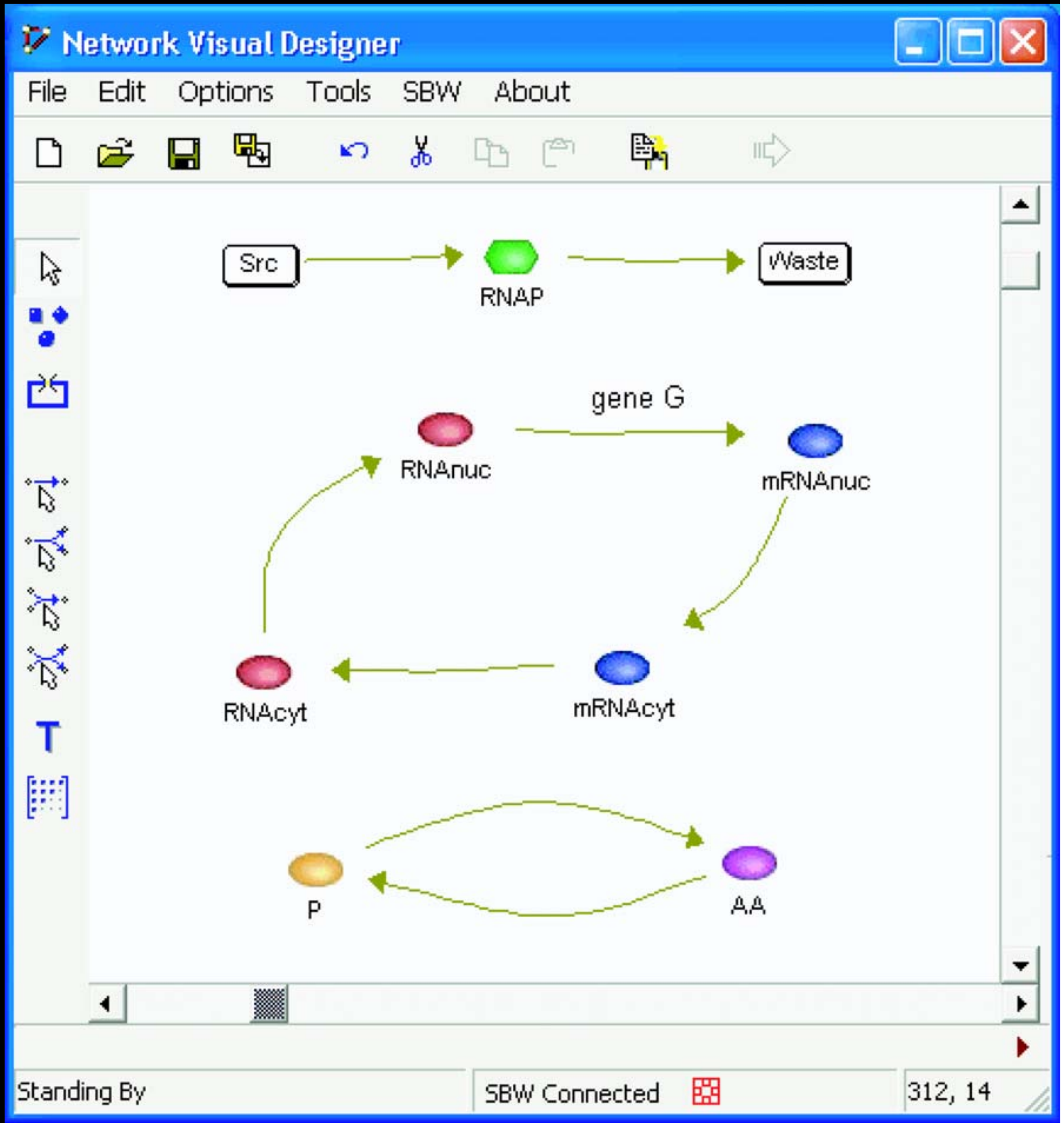
Bioinformatics 19(4): 524-531, 2003

What Are Example Uses of SBML?

- Example scenario #1:
  1. User develops a model of a biological process in an editing/capture tool
  2. User simulates the model in a simulation package to produce predictions. Common examples of simulation approaches include:
     - Differential equations
     - Stochastic systems
     - Boolean logic

- Example scenario #1:

User develops a model of a biological process in an editing/capture tool.



- Example scenario #1:
  1. User develops a model of a biological process in an editing/capture tool
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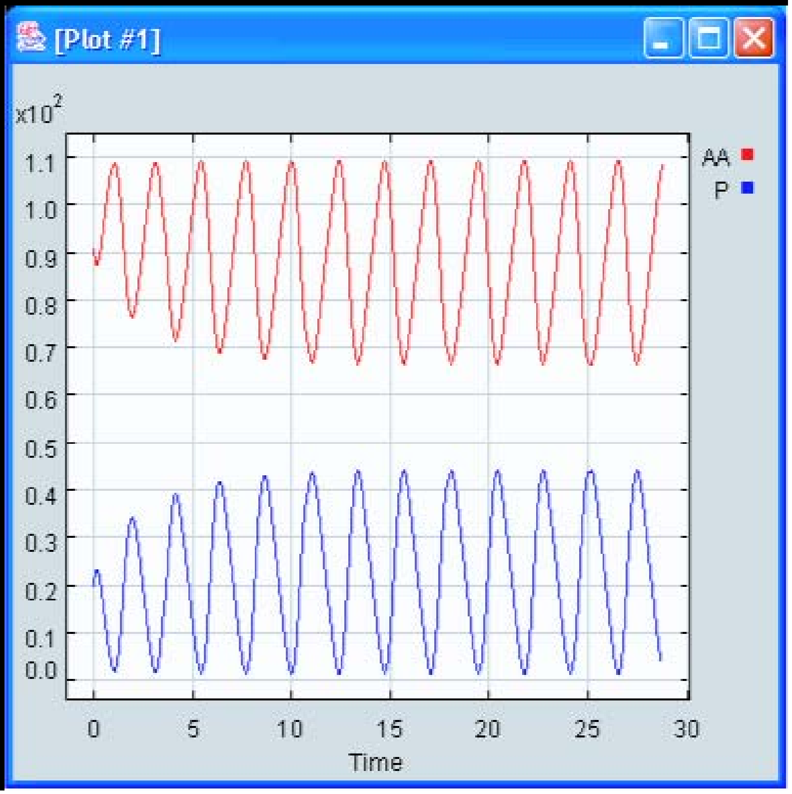
  3. User visualizes the results as time-series data plots



What Are Example Uses of SBML?

- Example scenario #1:

SBML

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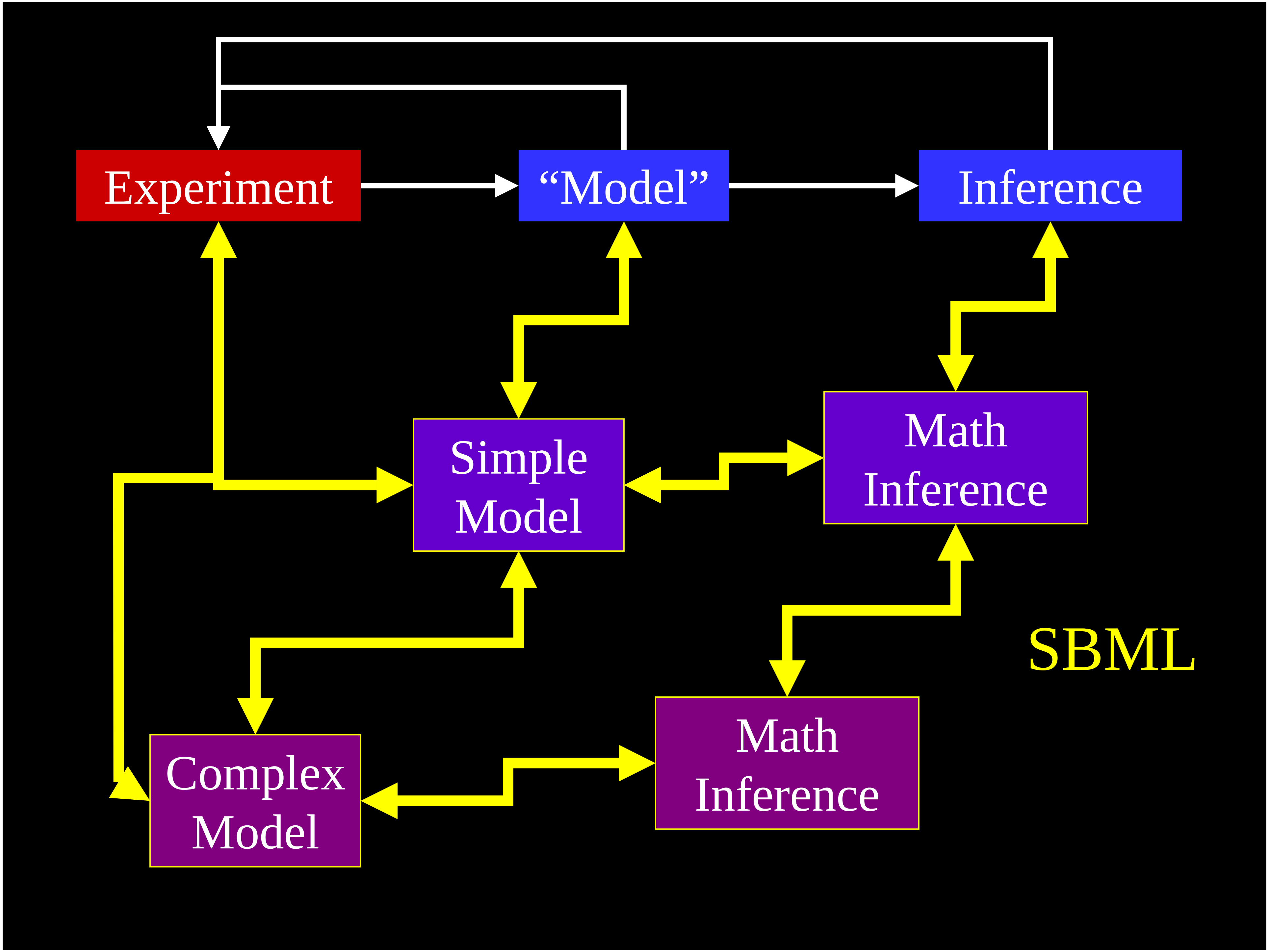
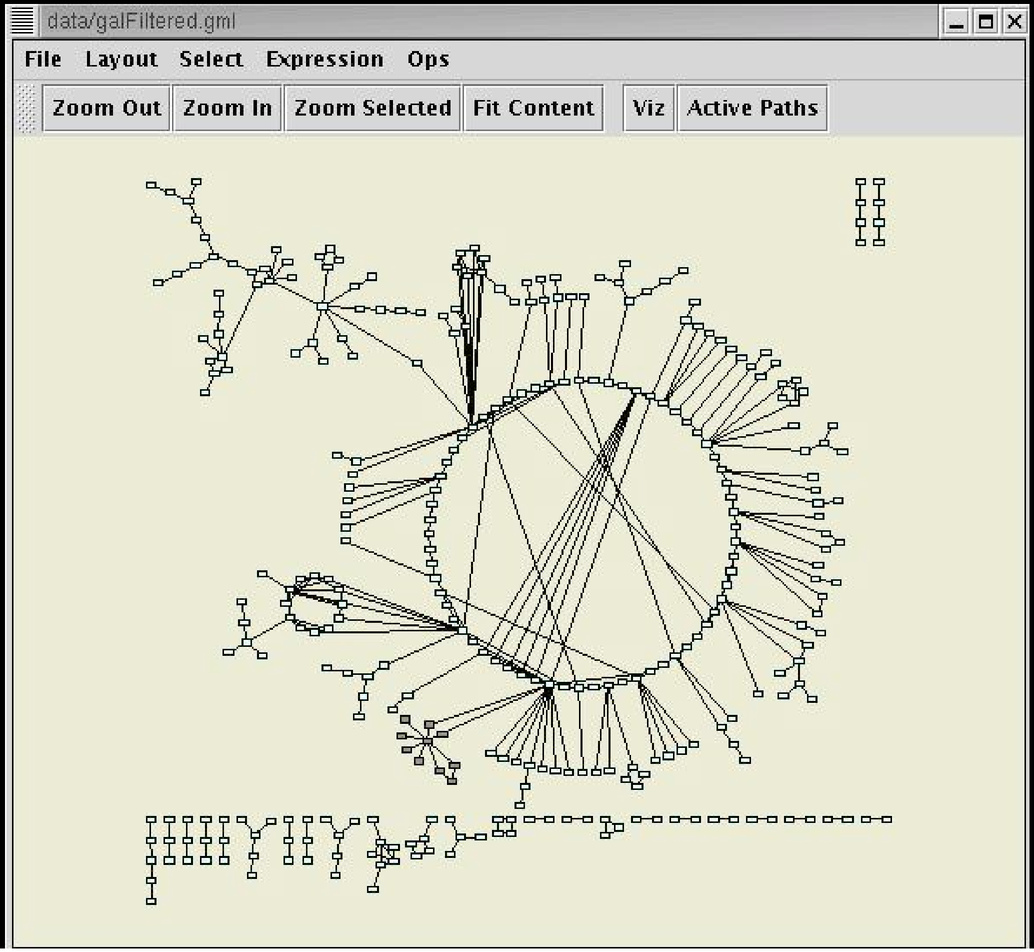

Experiment
“Model”
Inference
Simple Model
Math Inference
Complex Model
Math Inference
SBML

- Example scenario #2:
  1. User employs a database query tool to search for pathways involving a specific protein

- Example scenario #2:
  1. User employs a database query tool to search for pathways involving a specific protein
  2. User sends the output to a network graphing tool

SBML



- DARPA BioSPICE MDL standardized on SBML
- International E. coli Alliance has adopted SBML
- Software supporting SBML today:
  - Cellerator — NASA JPL & University of California Irvine
  - Cytoscape — Institute for Systems Biology & MIT
  - Gepasi — Virginia Tech
  - Jarnac — Keck Graduate Institute
  - JDesigner — Keck Graduate Institute
  - JigCell — Virginia Tech
  - BioSketchPad — BBN technologies & UPenn
  - NetBuilder — University of Hertfordshire
  - SBedit — ERATO-Kitano
  - SigPath — Mount Sinai
  - StochSim — Cambridge University
  - Virtual Cell — University of Connecticut Health Center

Structure of Models Expressed in SBML

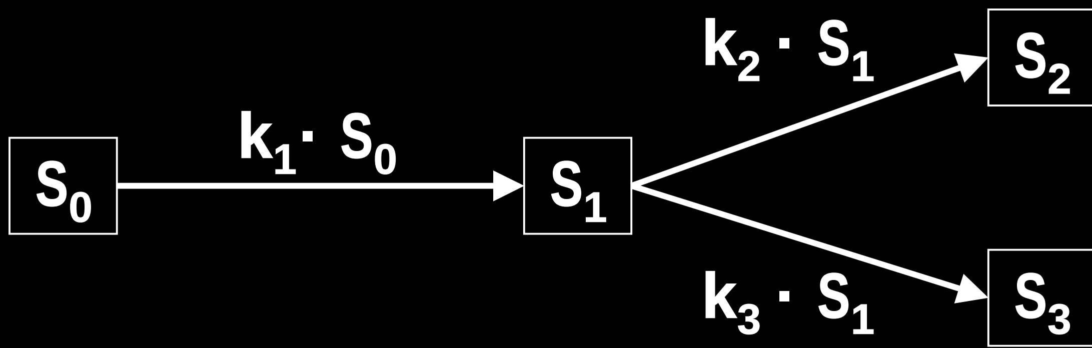
- Reaction networks described by list of components:
  - Beginning of SBML model definition
    - List of function definitions (new in Level 2)
    - List of unit definitions
    - List of compartments
    - List of species
    - List of parameters
    - List of rules
    - List of reactions
    - List of events (new in Level 2)
  - End of SBML model definition
- Software tools write SBML—humans don't!

Notes to reviewers

- Software tools write SBML—humans don't!
- It's all open source.

- These points are so obvious that we typically only mention them 1000 times in proposals, apparently not enough.

Example



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                        initialAmount="0"/>
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                     boundaryCondition="true"
                        initialAmount="0"/>
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    </listOfSpecies>
```

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                         initialAmount="0"/>
      <species name=”S1" compartment="c1"
                    boundaryCondition="true"
                         initialAmount="0"/>
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                         initialAmount="0.23"/>
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```

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  stoichiometry="1"/>
       </listOfReactants>
       <listOfProducts>
          <speciesReference species=“S1"
  stoichiometry="1"/>
       </listOfProducs>
       <kineticLaw>
         <math
  xmlns="http://www.w3.org/1998/Math/MathML">
            <apply>
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                  <ci> k1 </ci>
                  <ci> S0 </ci>
            </apply>
         </math>
          <listOfParameters>
             <parameter name="k1" value=”2.07"/>
          </listOfParameters>
       </kineticLaw>
    </reaction>
```

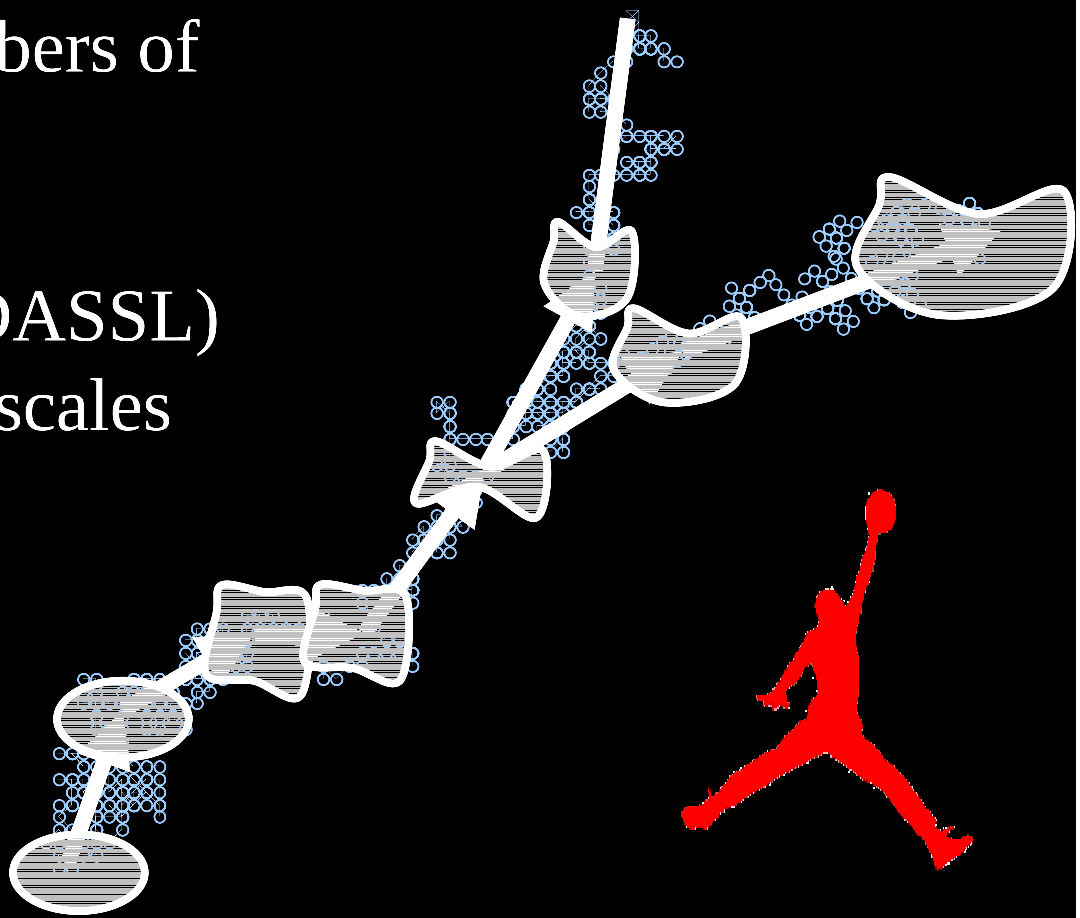
Stochastic simulation issues

Stochastics (Gillespie)

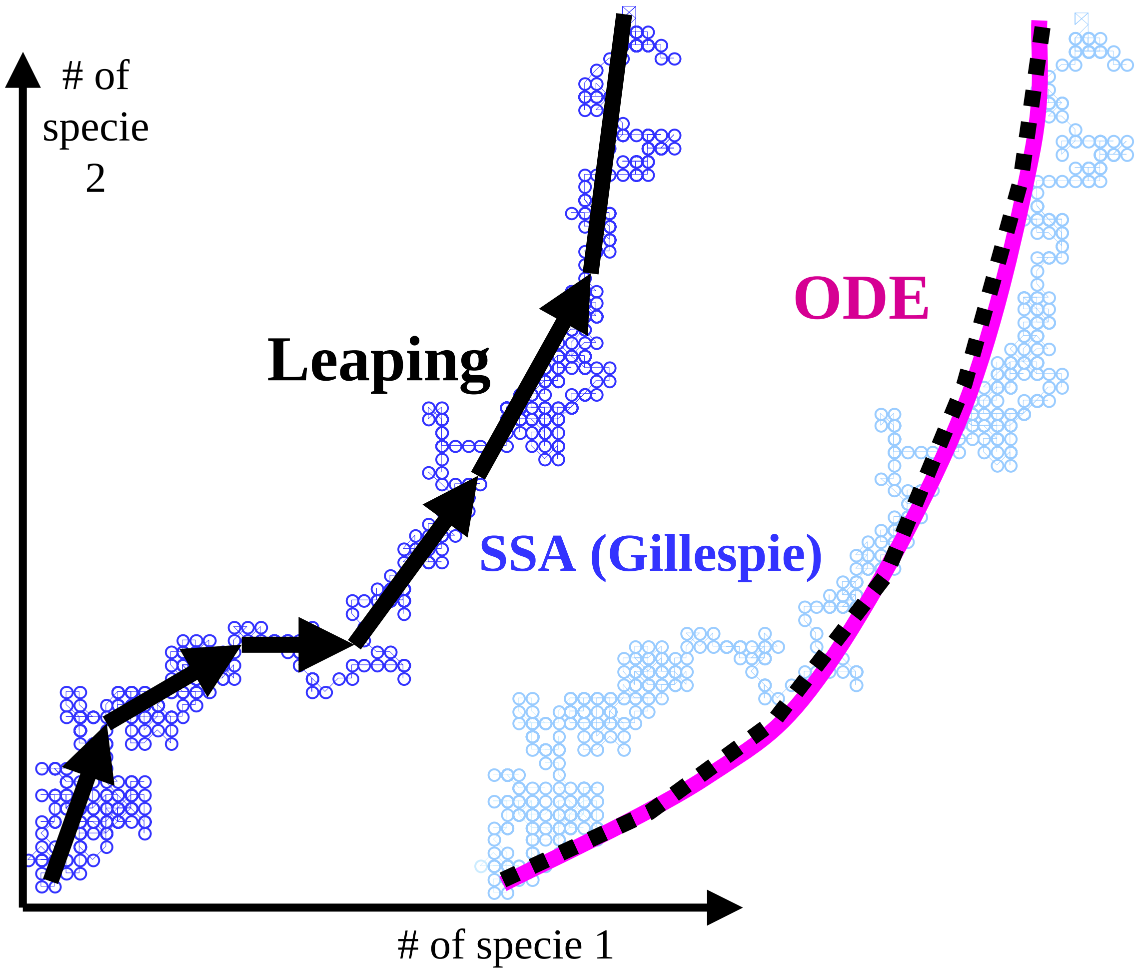
• Widely different numbers of molecules coexisting

Stiffness (Petzold, eg DASSL)

• Widely different timescales coexisting



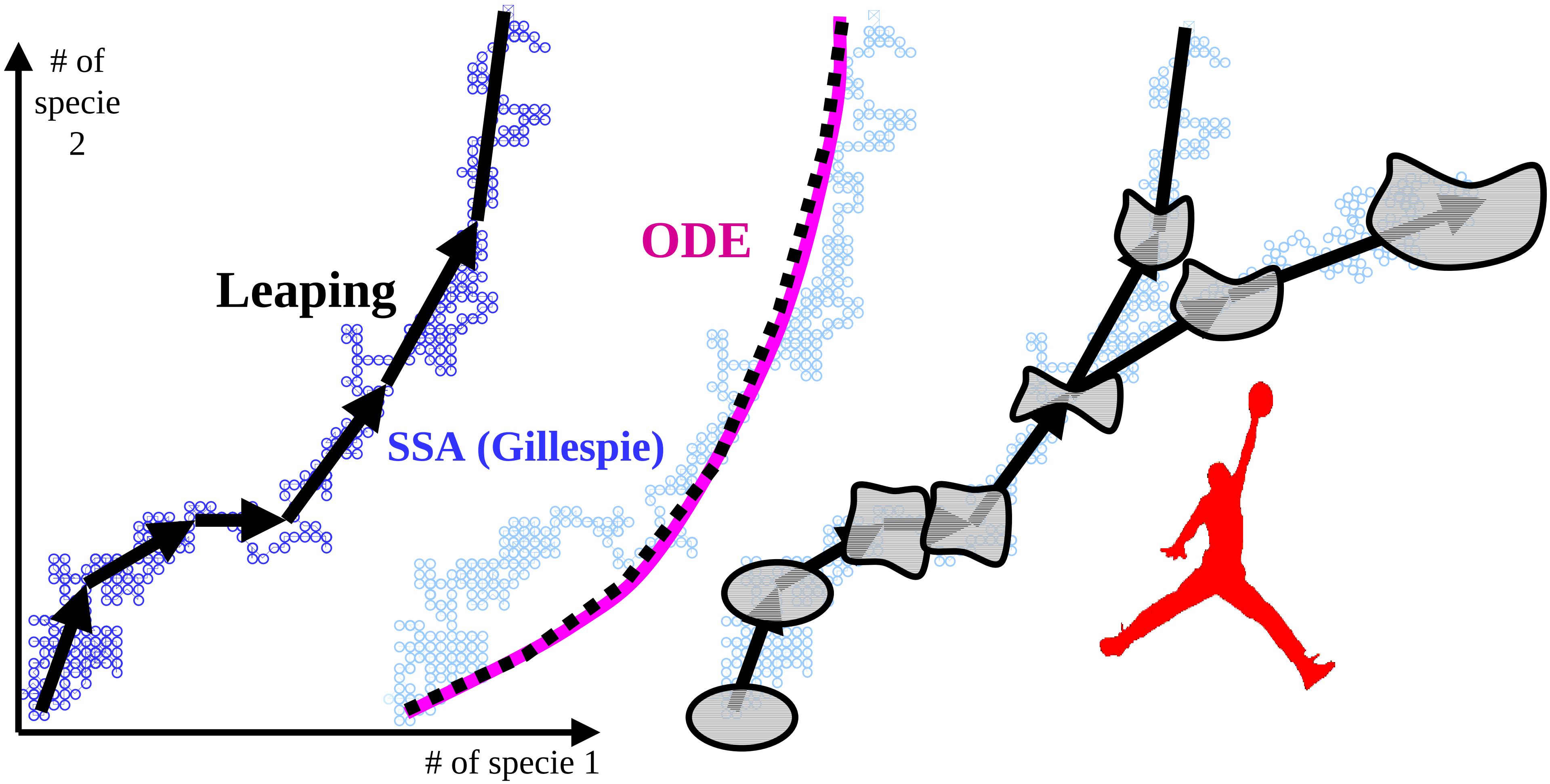
Stochastic simulation

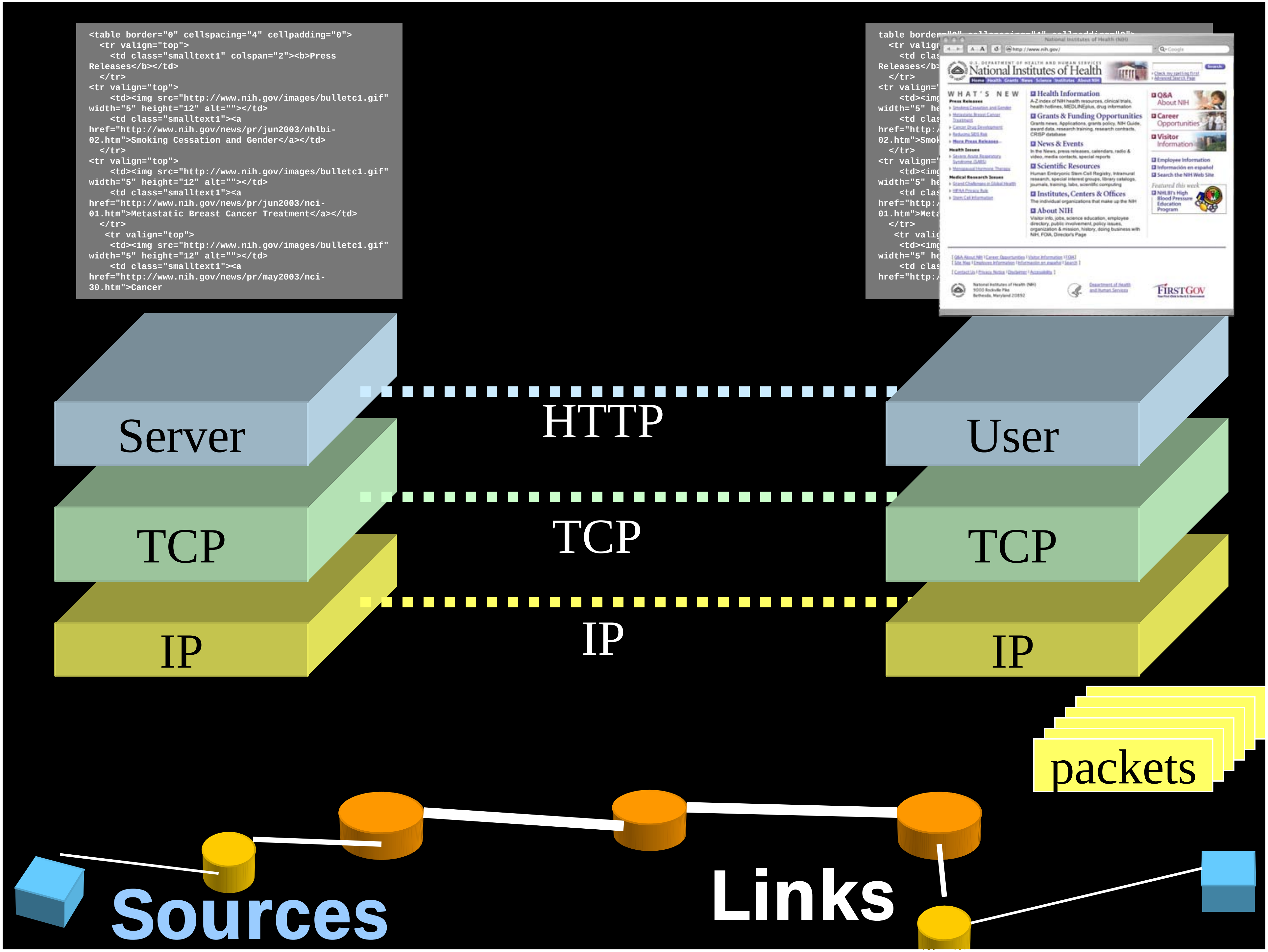


Stochastic simulation

Ultimate leaping:

• (Naïve “hybrid” combinations don’t work)
• Adaptive step size
• Estimated statistics
• Higher order methods

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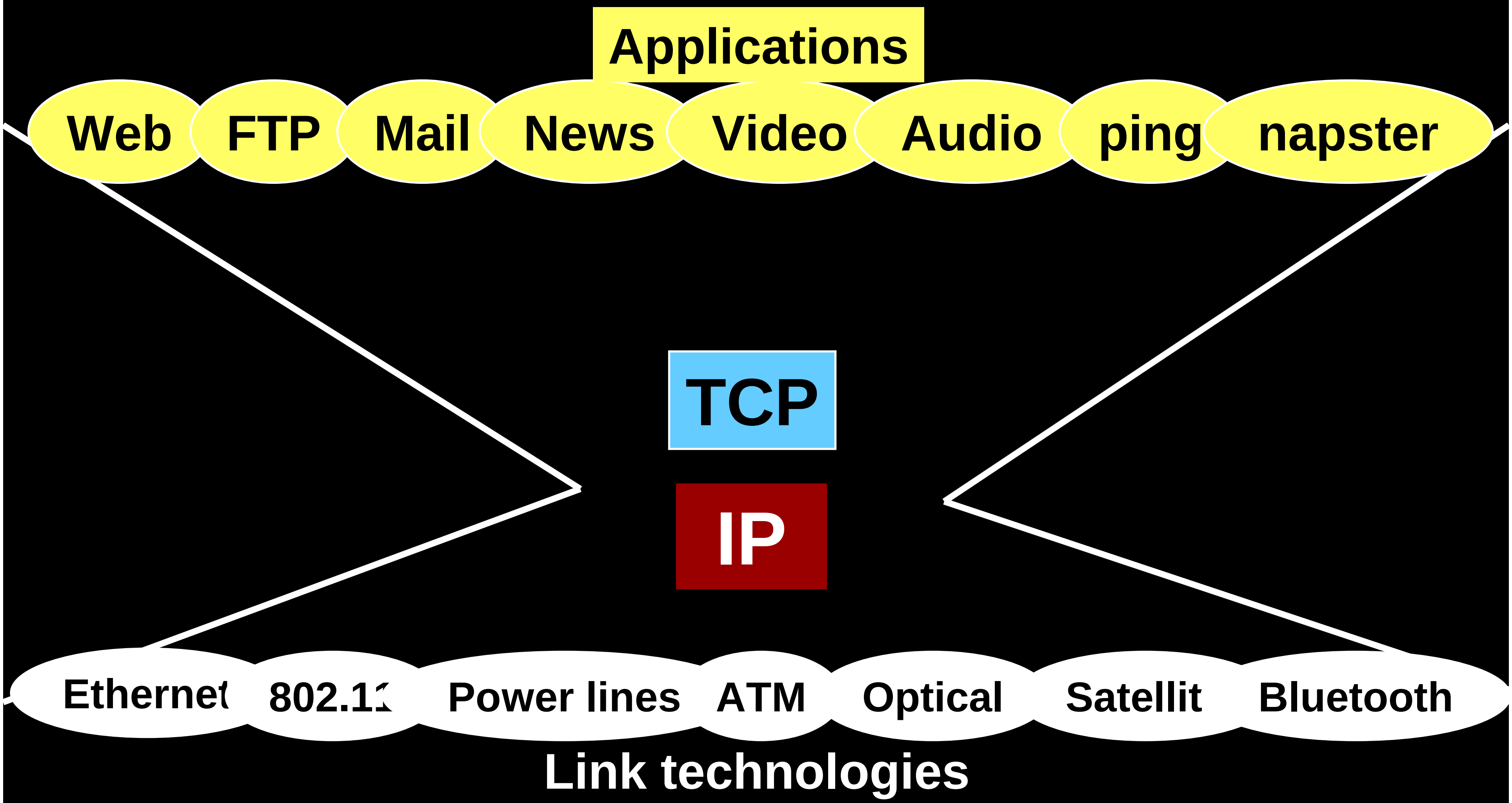
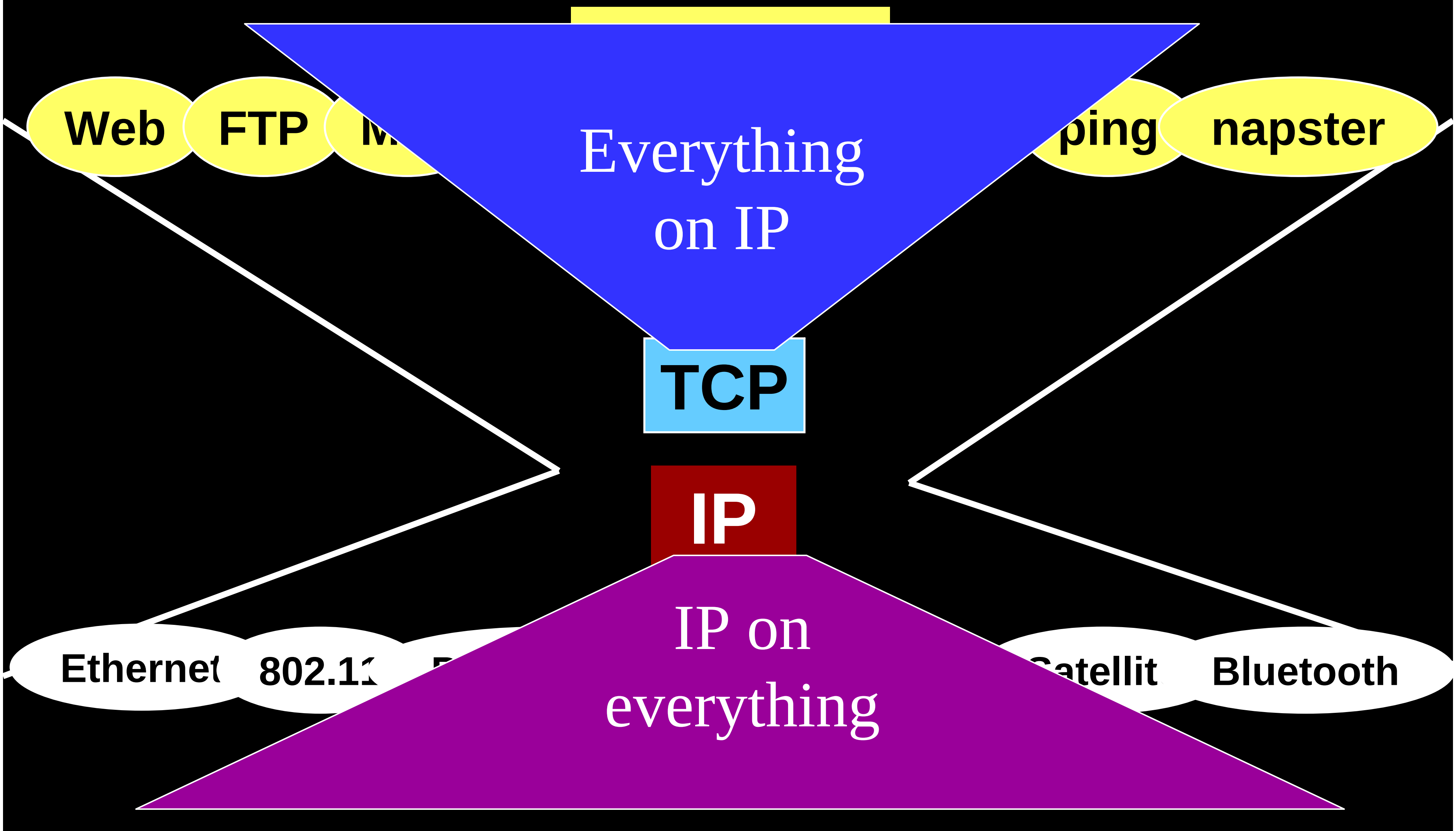
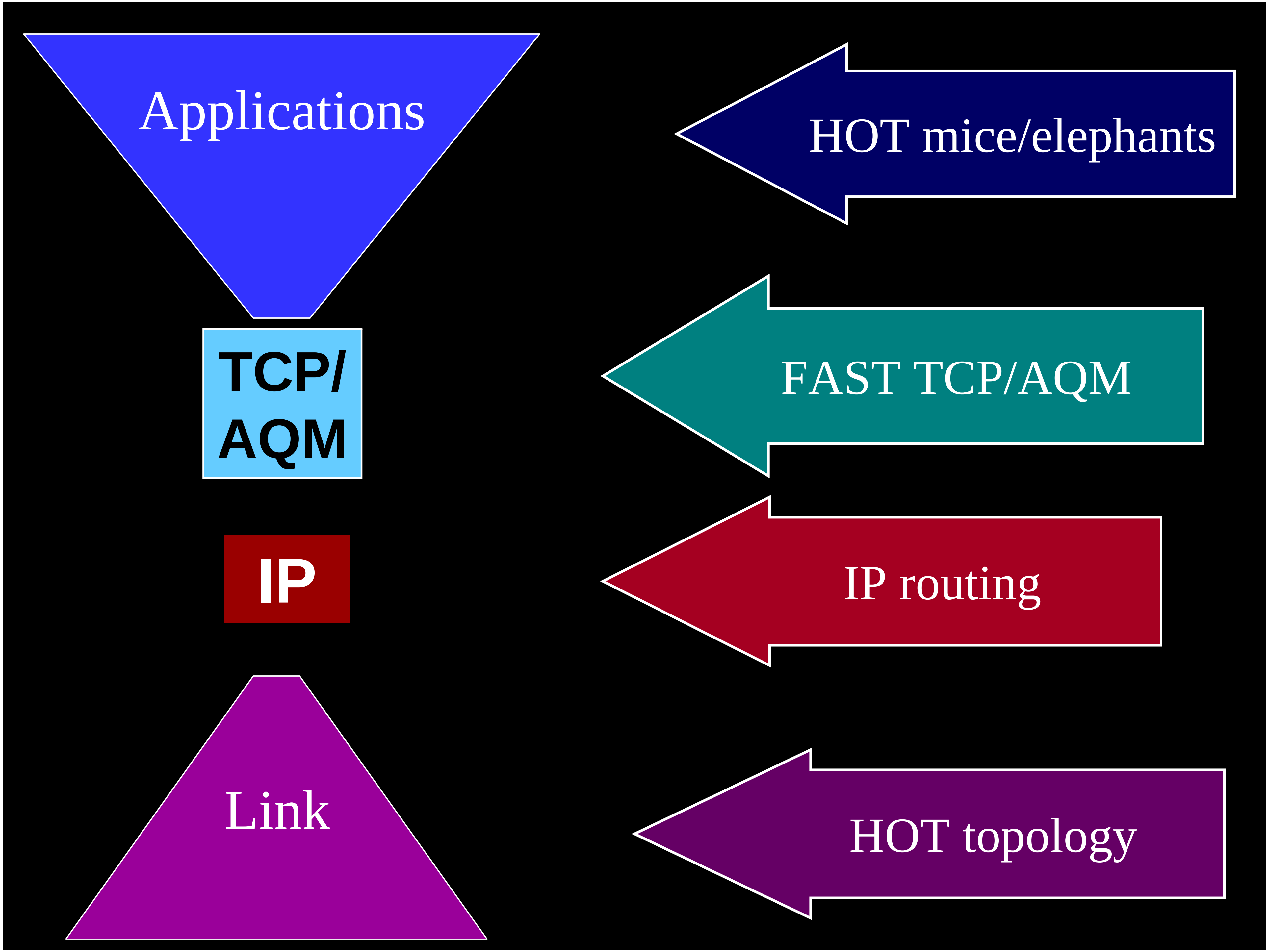
<tr valign="top">
<td><img src="http://www.nih.gov/images/bulletc1.gif" width="5" height="12" alt=""></td>
<td class="smalltext1">Metastatic Breast Cancer Treatment</td>
</tr>
<tr valign="top">
<td><img src="http://www.nih.gov/images/bulletc1.gif" width="5" height="12" alt=""></td>
<td class="smalltext1"><a href="http://www.nih.gov/news/pr/may2003/nci-30.htm">Cancer
National Institutes of Health
Server
HTTP
User
TCP
TCP
TCP
IP
IP
IP
packets
Sources
Links

The Internet hourglass

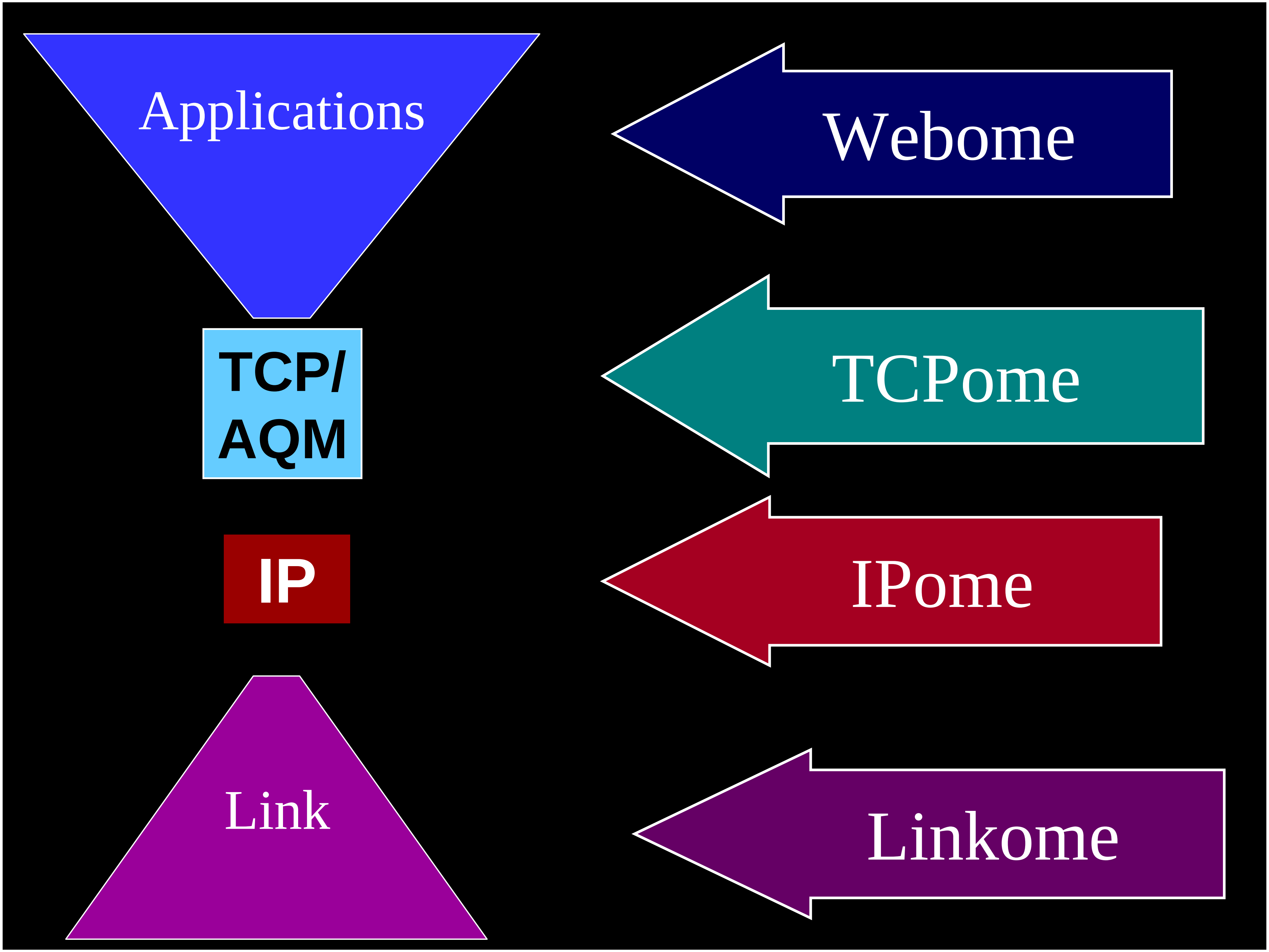


The Internet hourglass



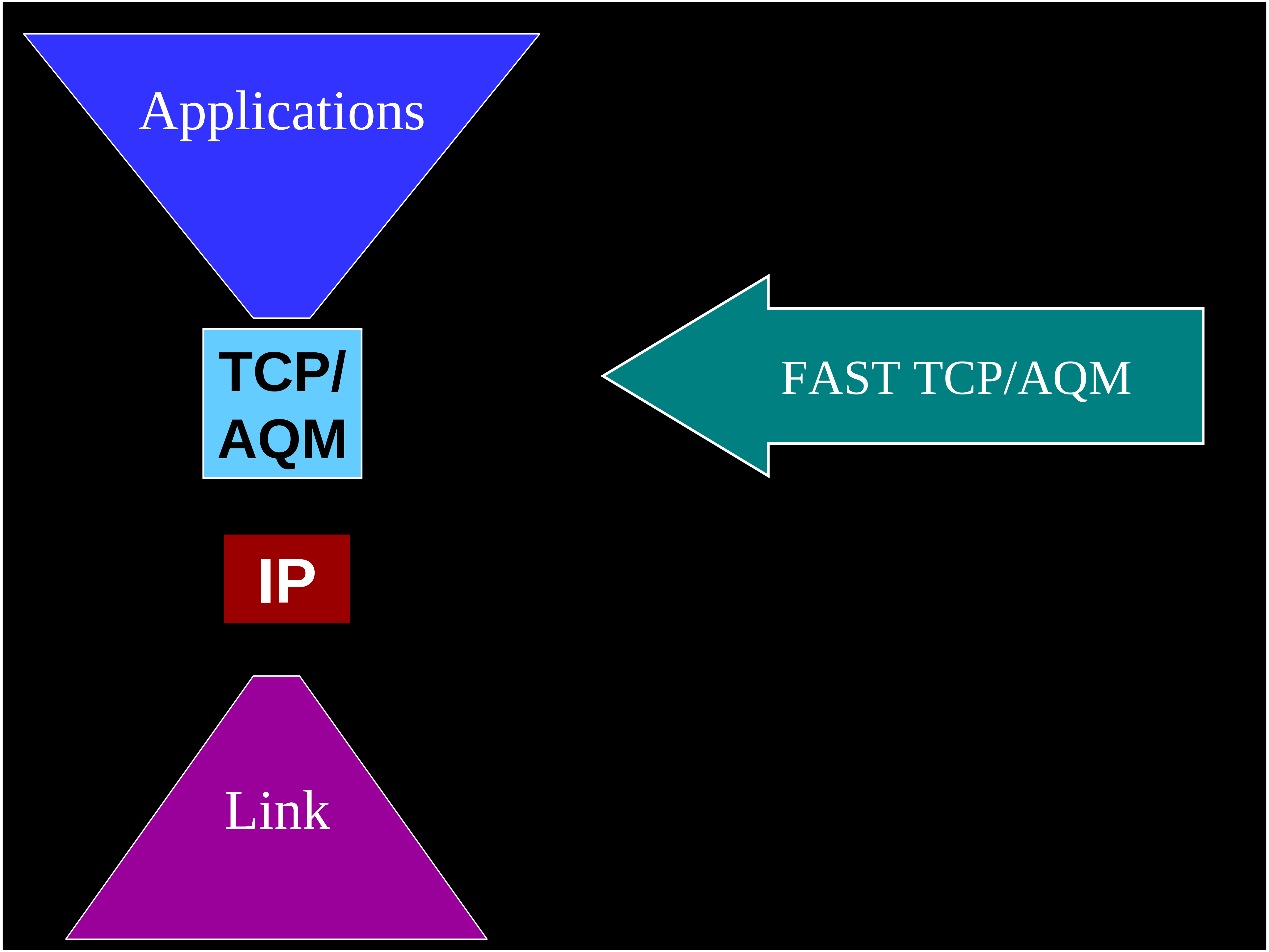


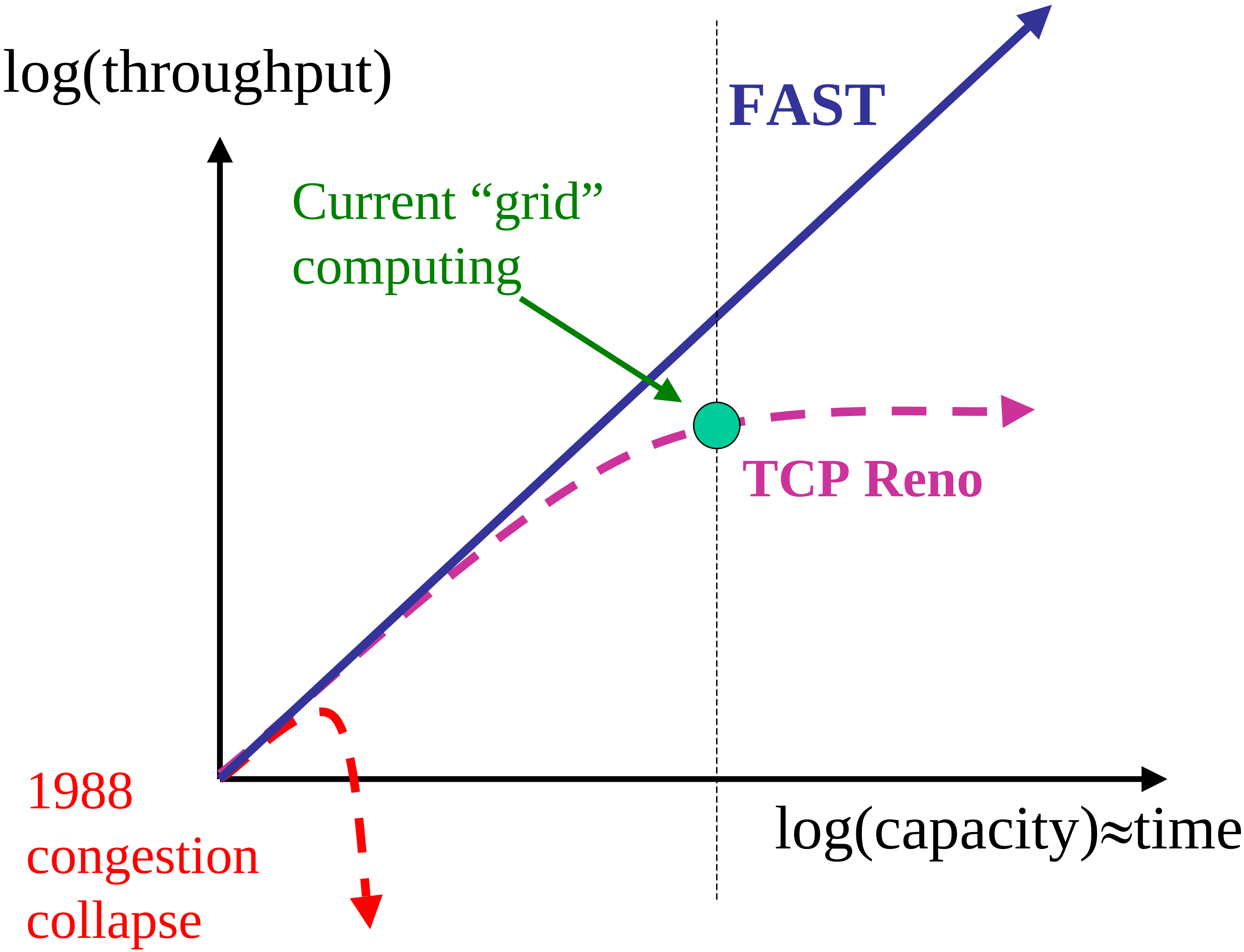
Applications
TCP/
AQM
IP
Link
HOT mice/elephants
FAST TCP/AQM
IP routing
HOT topology


Applications
TCP/
AQM
IP
Link
Webome
TCPome
IPome
Linkome

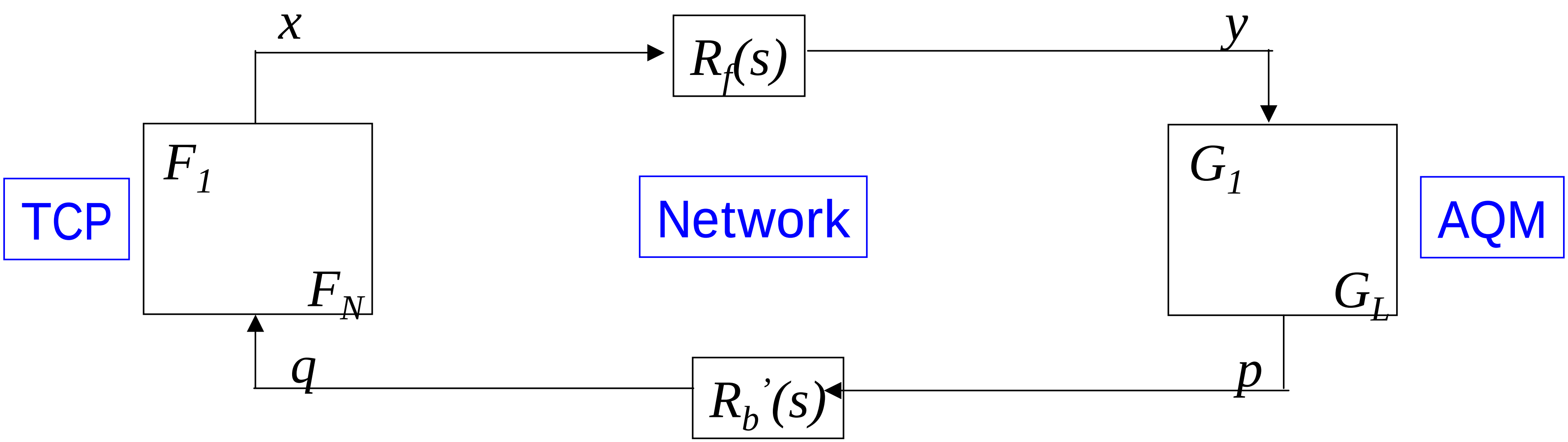
"Aeronomics"

We already have the entire parts list!!!


Applications
TCP/
AQM
IP
Link
FAST TCP/AQM


log(throughput)
FAST
Current “grid”
computing
TCP Reno
1988
congestion
collapse
log(capacity)≈time

Stability: scalable control



$$x_i(t) = \bar{x}_i \, e^{-\frac{\alpha_i}{\tau_i m_i} q_i(t)}$$

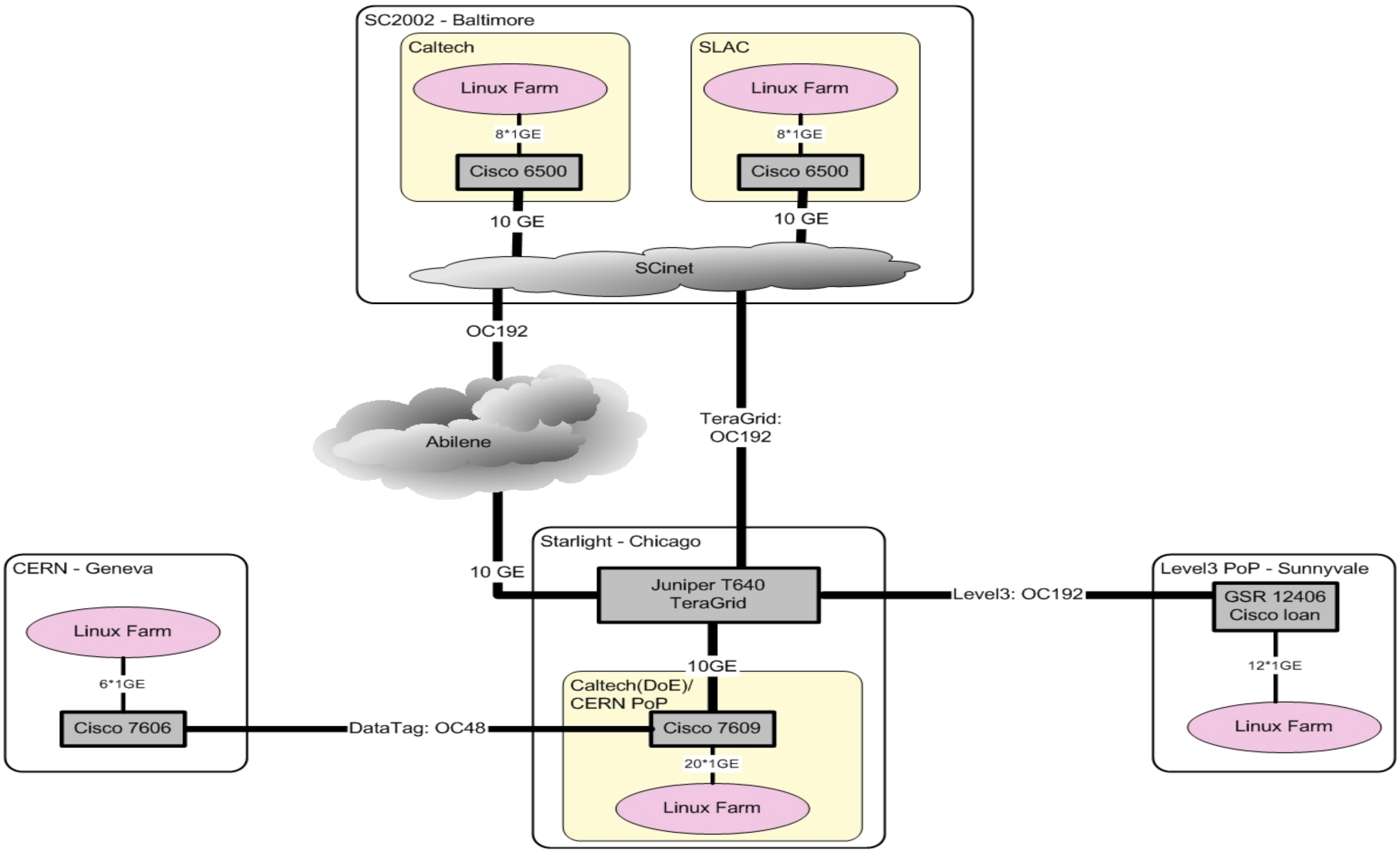
$$\dot{p}_l(t) = \frac{1}{c_l}\left(y_l(t) - c_l\right)$$

<u>Theorem</u> (Paganini, Doyle, Low, CDC'01) Provided *R* is full rank, feedback loop is locally stable for arbitrary delay, capacity, load and topology.

- Modeling and simulation alone is a limited tool because it isn't scalable.
- Simulation produce examples, never proofs. (NP, not coNP)
- Theory can prove cases too complex for simulation.
- This will be critical for the future of both advanced technology and systems biology.
- Needs new mathematics and software infrastructure

Theorem (Paganini, Doyle, Low, CDC'01) Provided R is full rank, feedback loop is locally stable for arbitrary delay, capacity, load and topology.

Initial Test Network Deployment

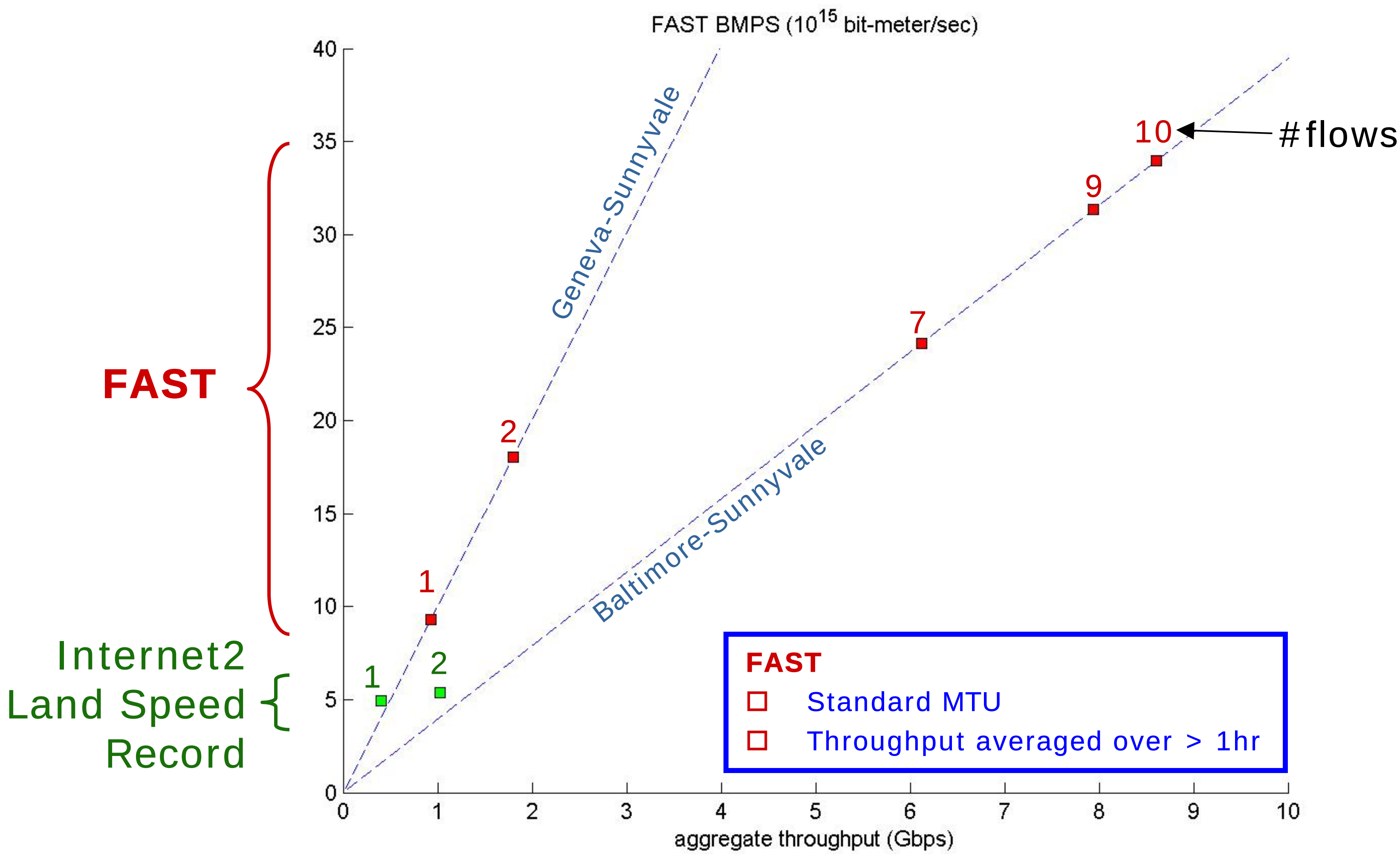


(Sylvain Ravot, caltech/CERN)

Network

(Sylvain Ravot, caltech/CERN)

FAST BMPS

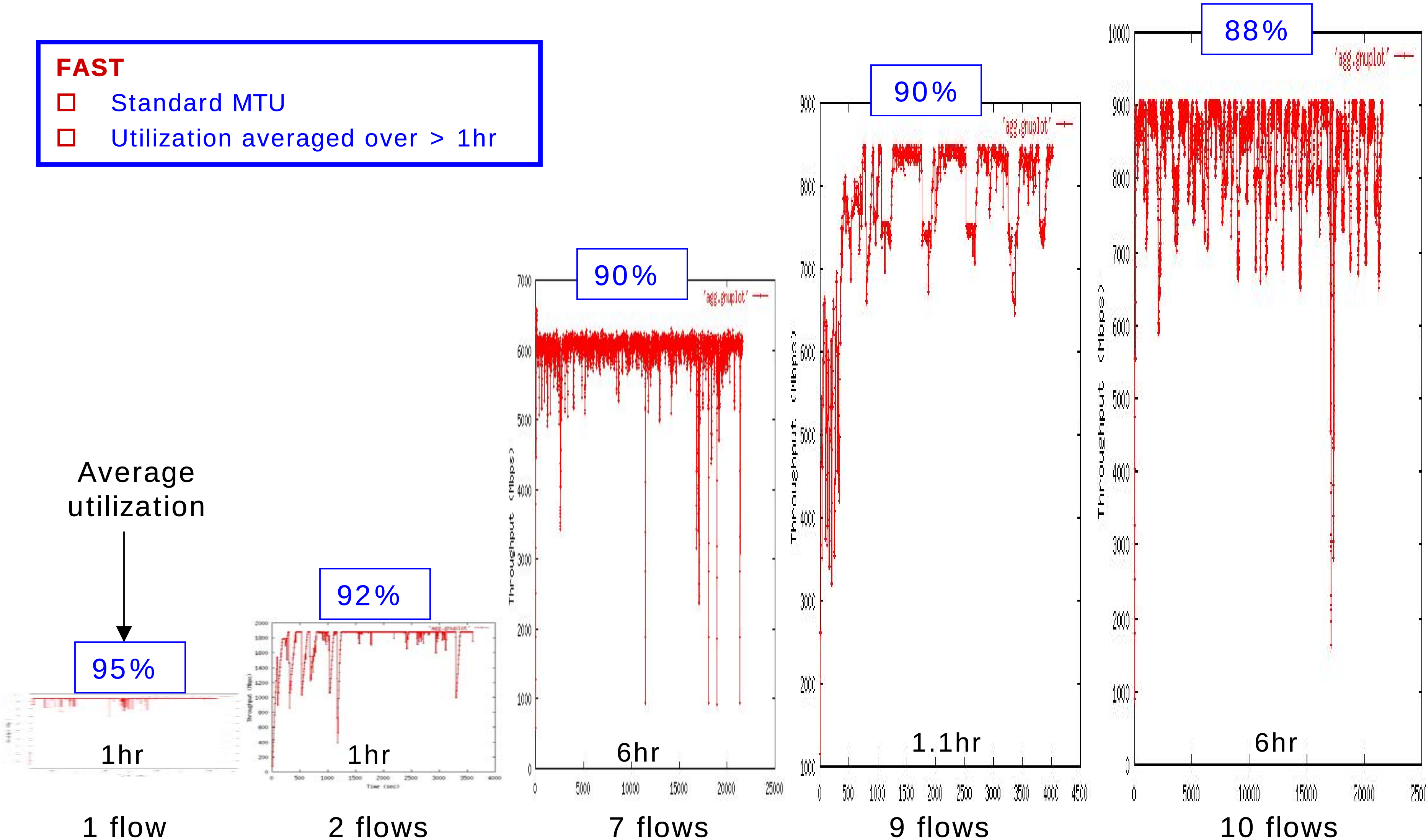


FAST BMPS (10^{15} bit-meter/sec)
40
35
30
25
20
15
10
5
0
0
1
2
3
4
5
6
7
8
9
10
aggregate throughput (Gbps)
Geneva-Sunnyvale
Baltimore-Sunnyvale
1
2
7
9
10
#flows
FAST
Internet2
Land Speed
Record
1
2
FAST
Standard MTU
Throughput averaged over > 1hr

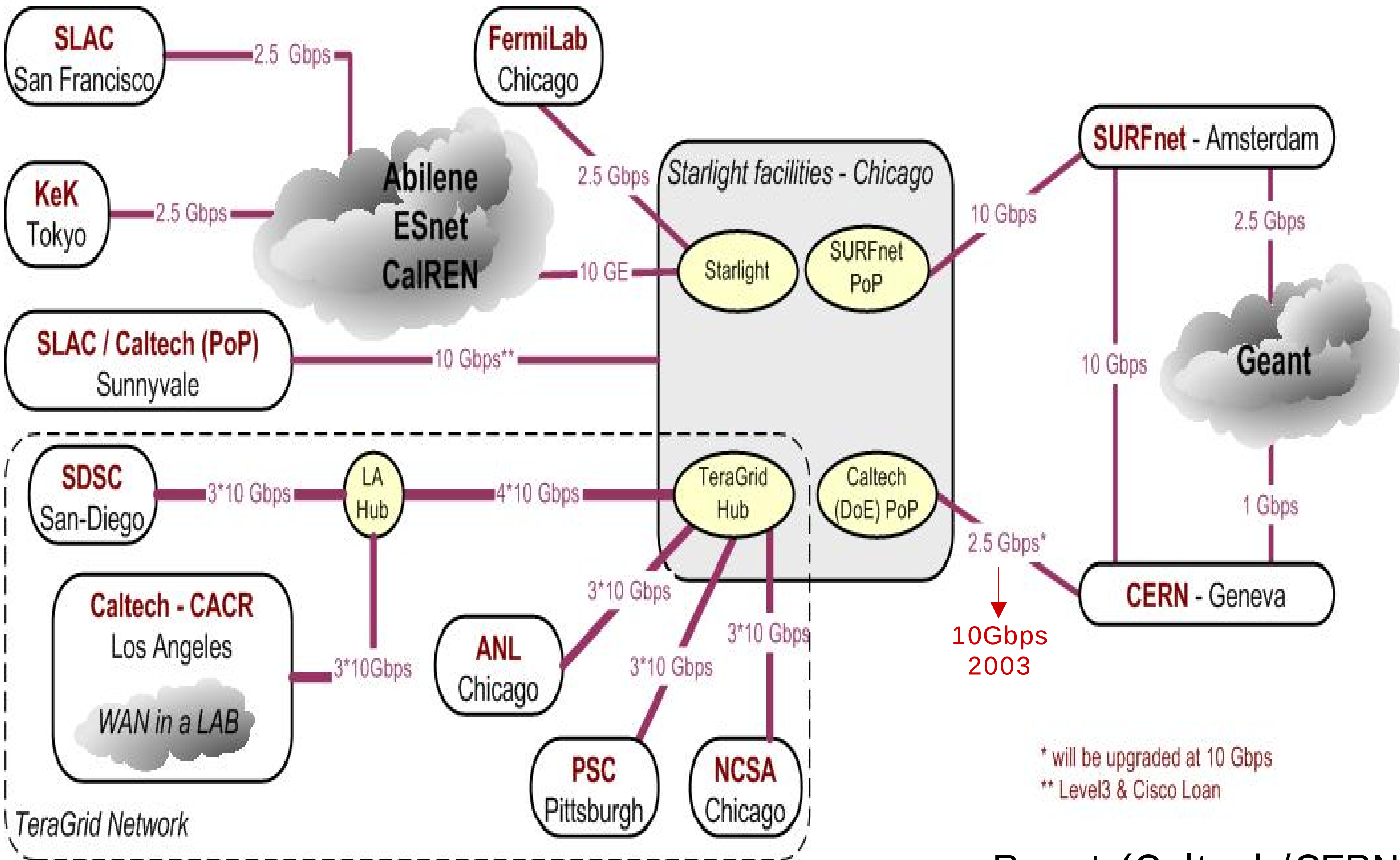
Aggregate throughput

FAST

- Standard MTU
- Utilization averaged over > 1hr



Global testbed plans

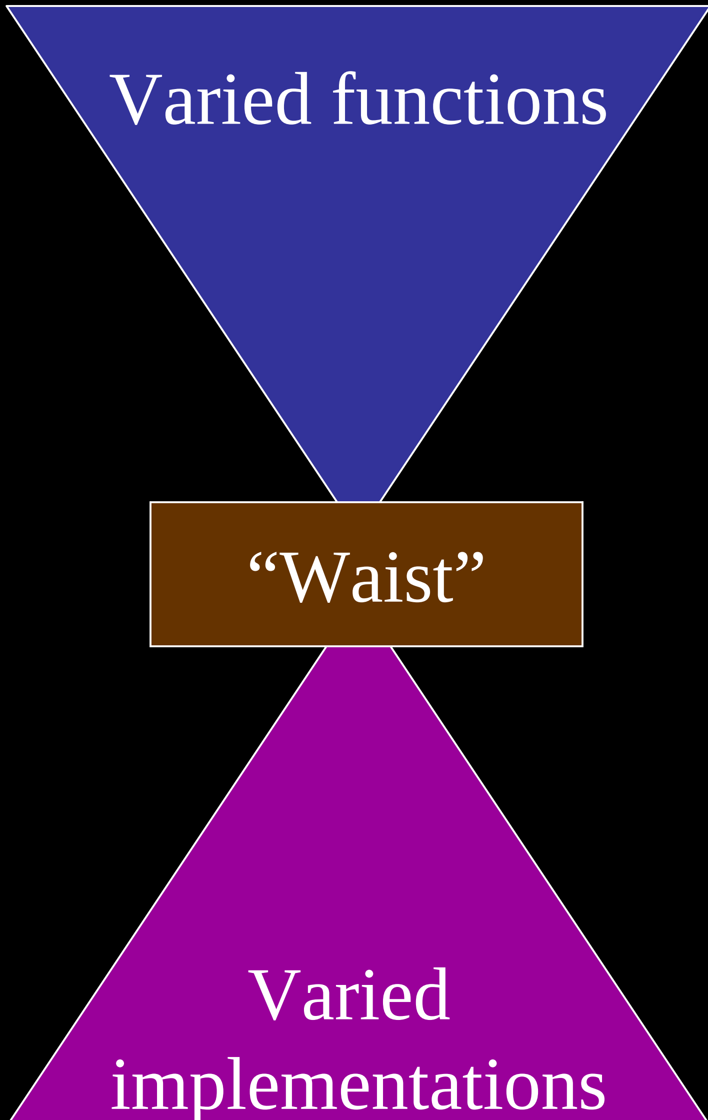


Ravot (Caltech/CERN)

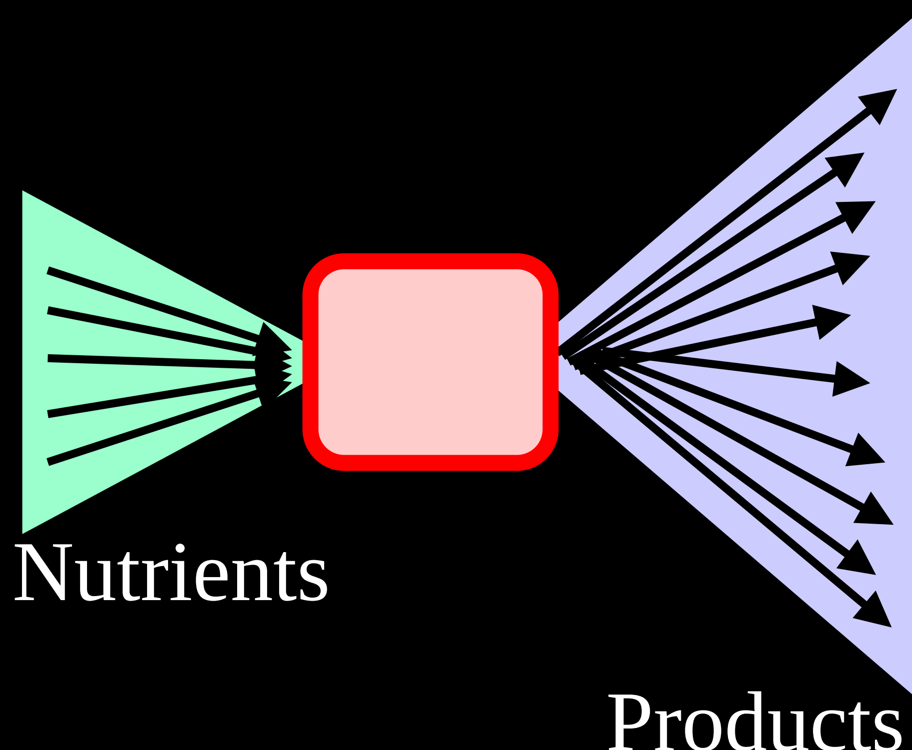
What are the most significant
and challenging

Gaps,
Barriers, and
Opportunities

regarding standards and protocols?



What are the “standards” and “protocols” that cells use to organize their networks?

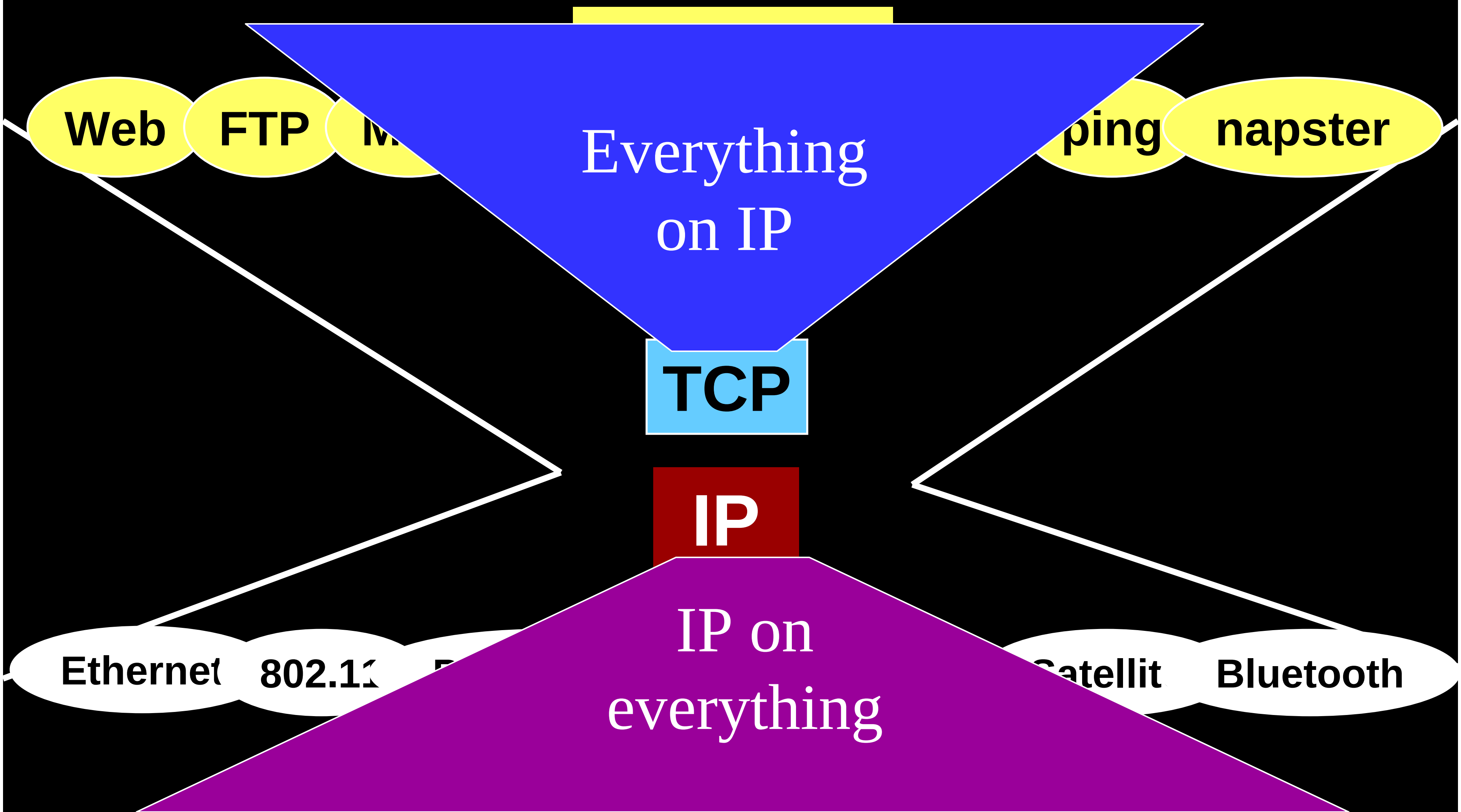


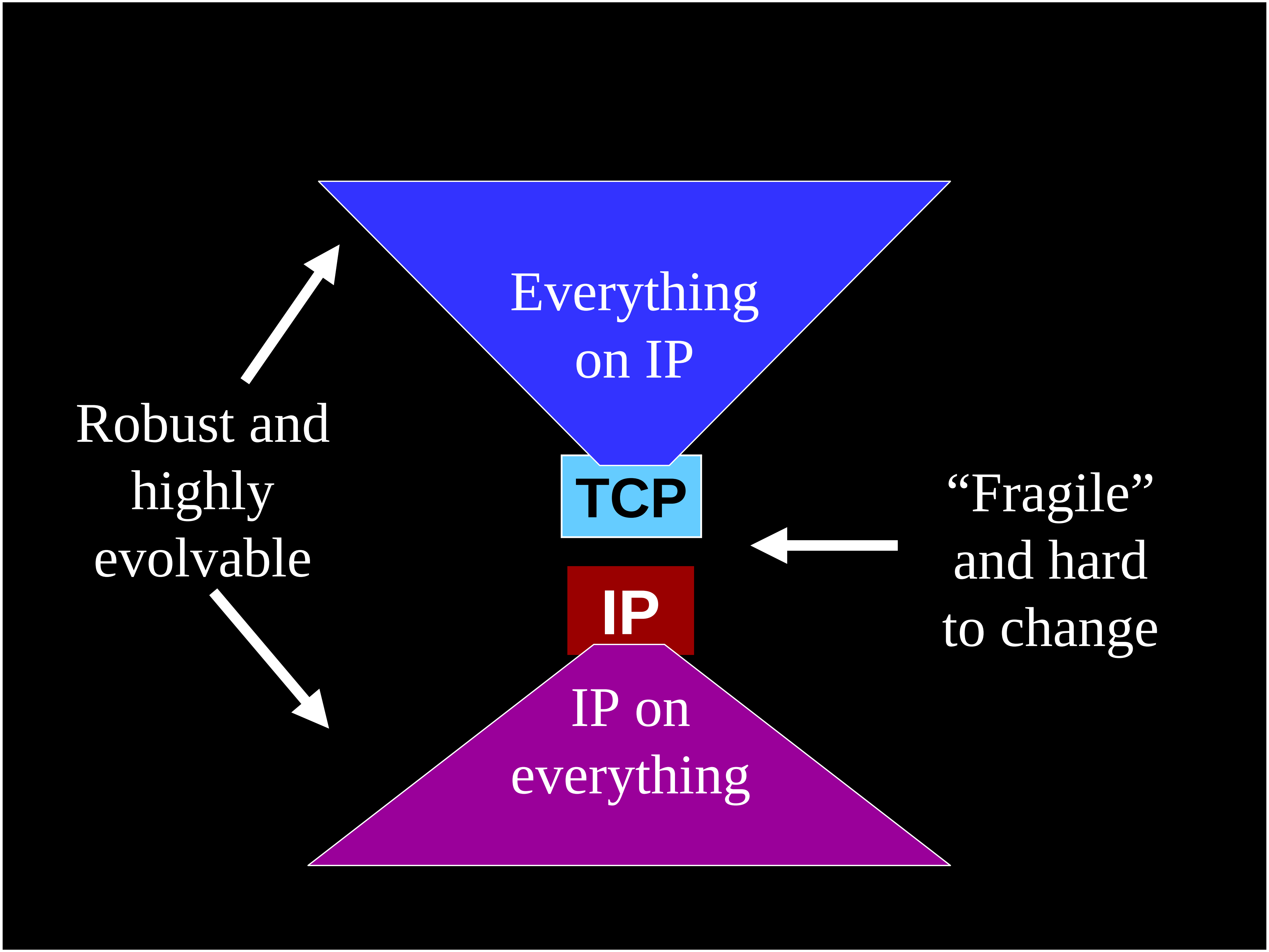
Key themes

1. Need new theoretical and software infrastructure for systems (beyond purely molecular) biology.
2. Multisca tic simulation is an essent
3. Simulati larger network problems ain systems need an exponentially large number of simulations to answer biologically meaningful questions.
4. There are fundamental laws governing the organization of biological networks.

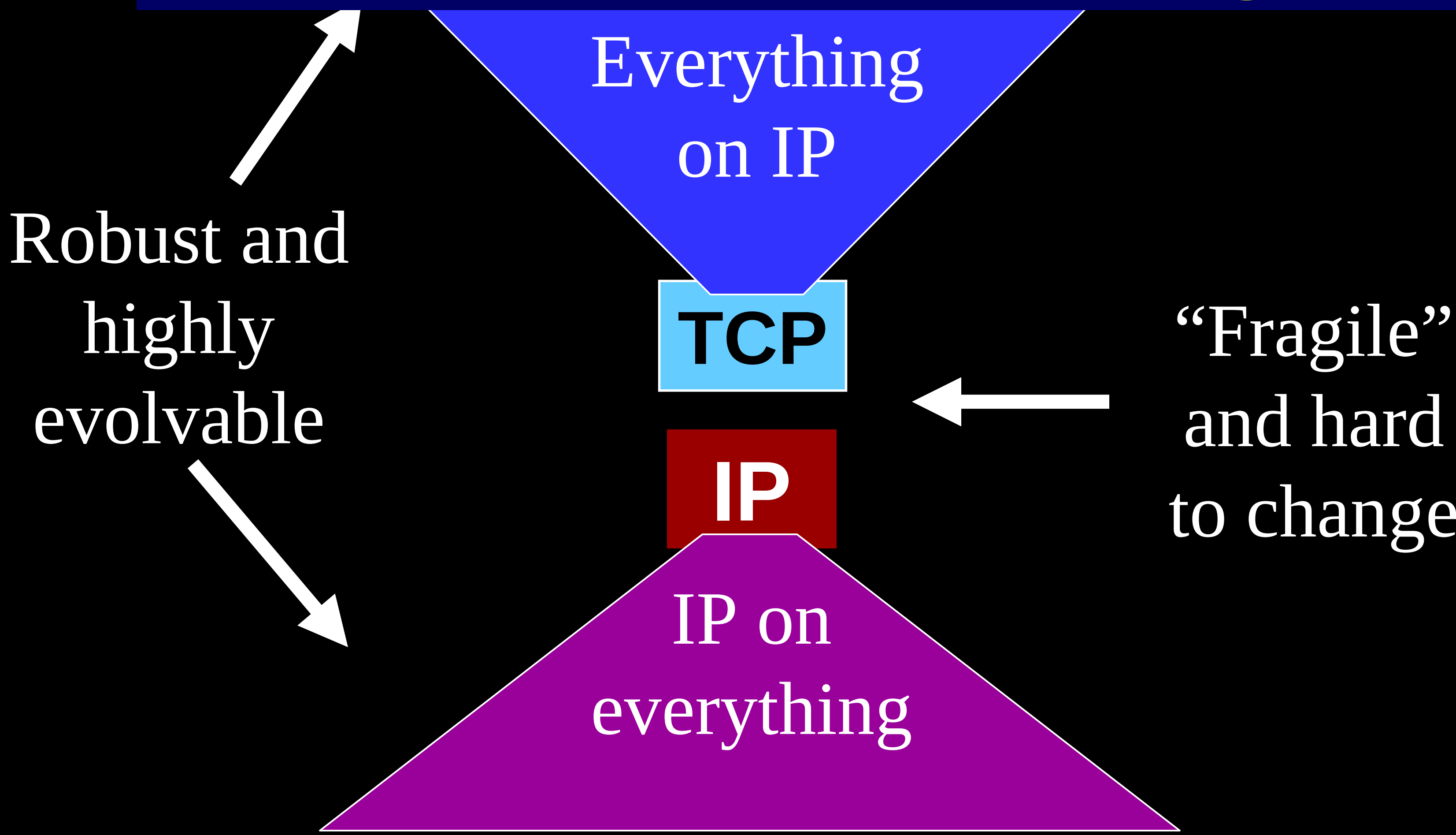
Without exploiting these organizational laws, the complexity will be overwhelming.

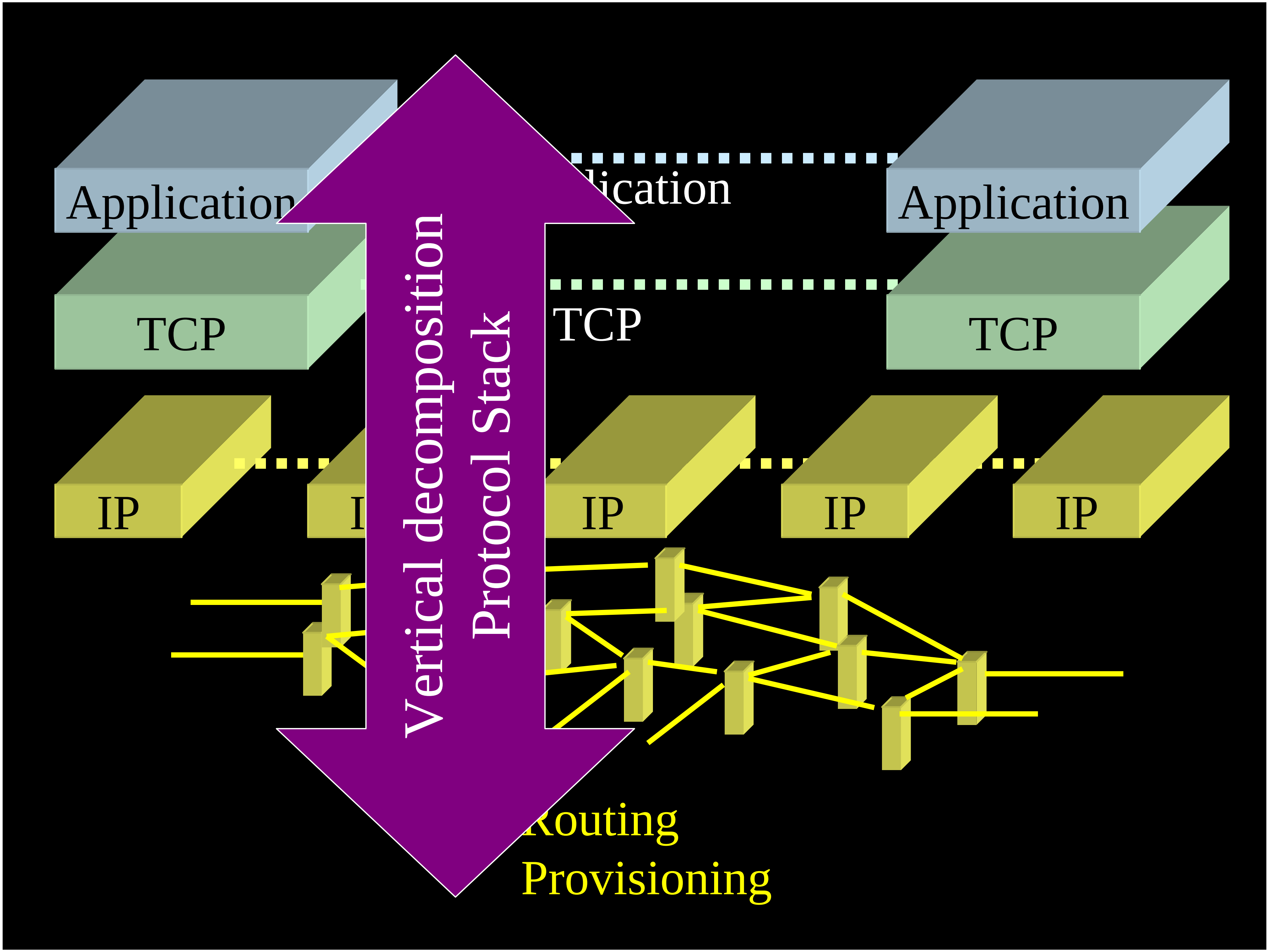
The Internet hourglass

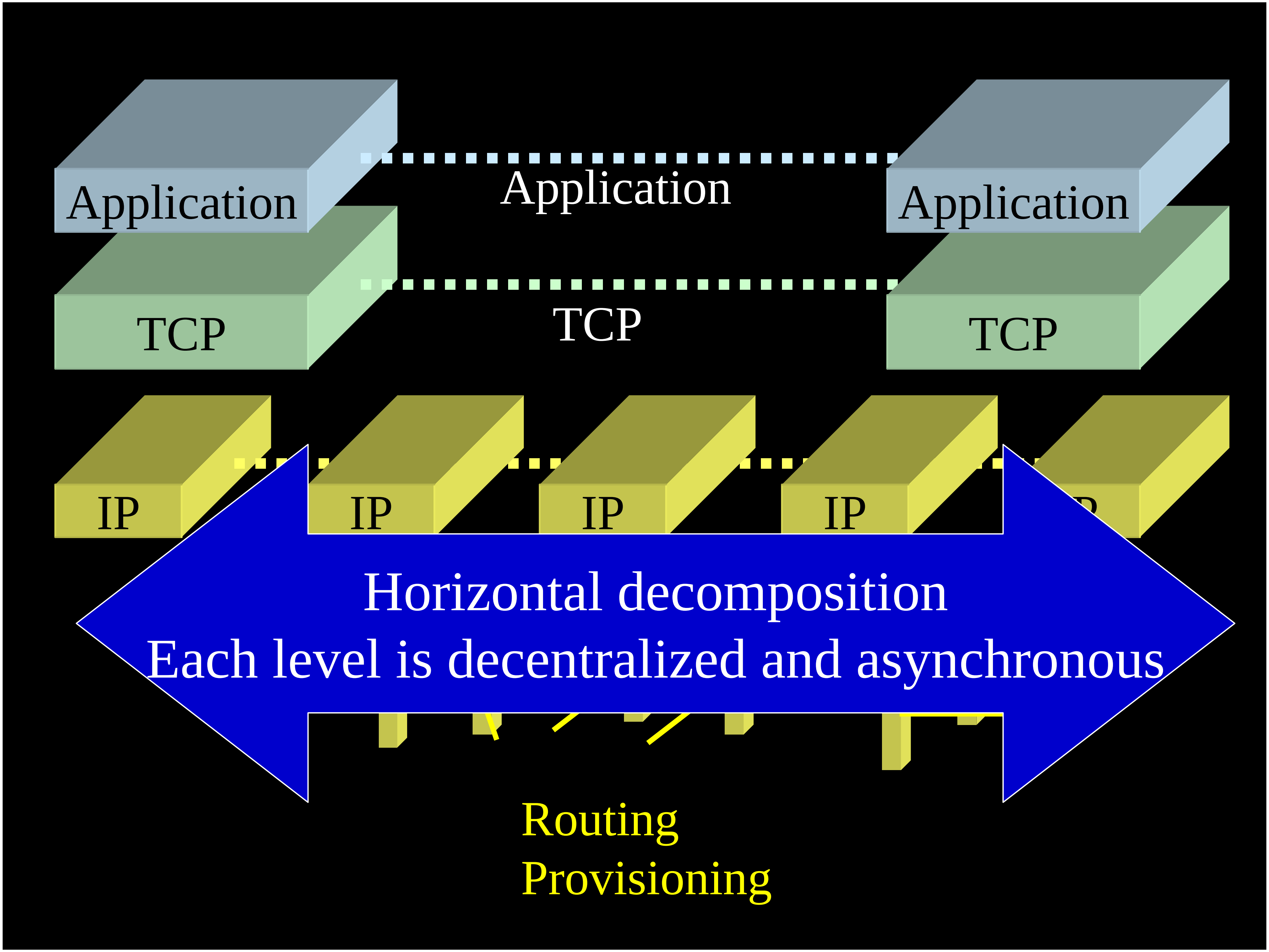


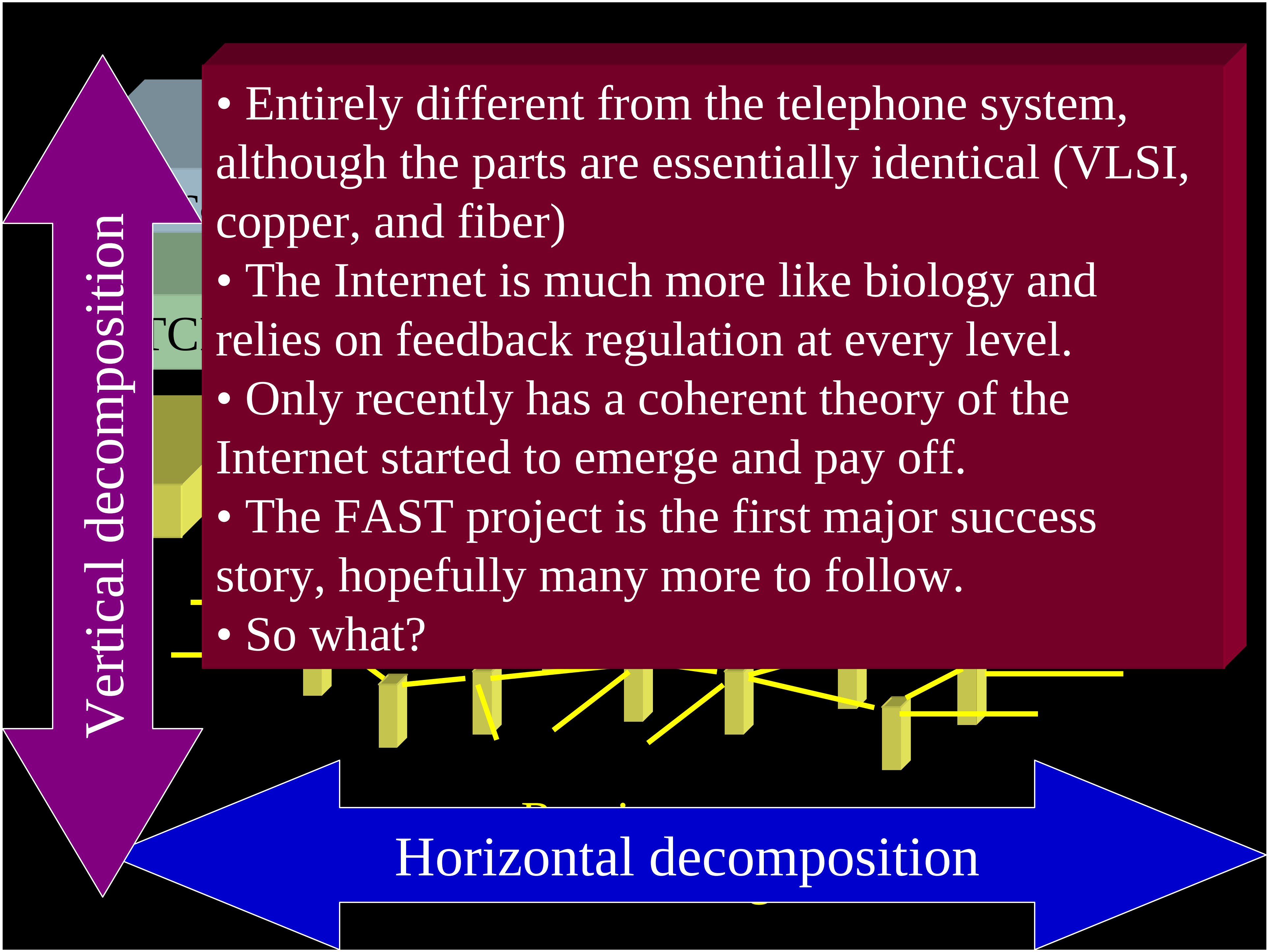

Everything
on IP
TCP
IP
IP on
everything
Robust and
highly
evolvable
"Fragile"
and hard
to change

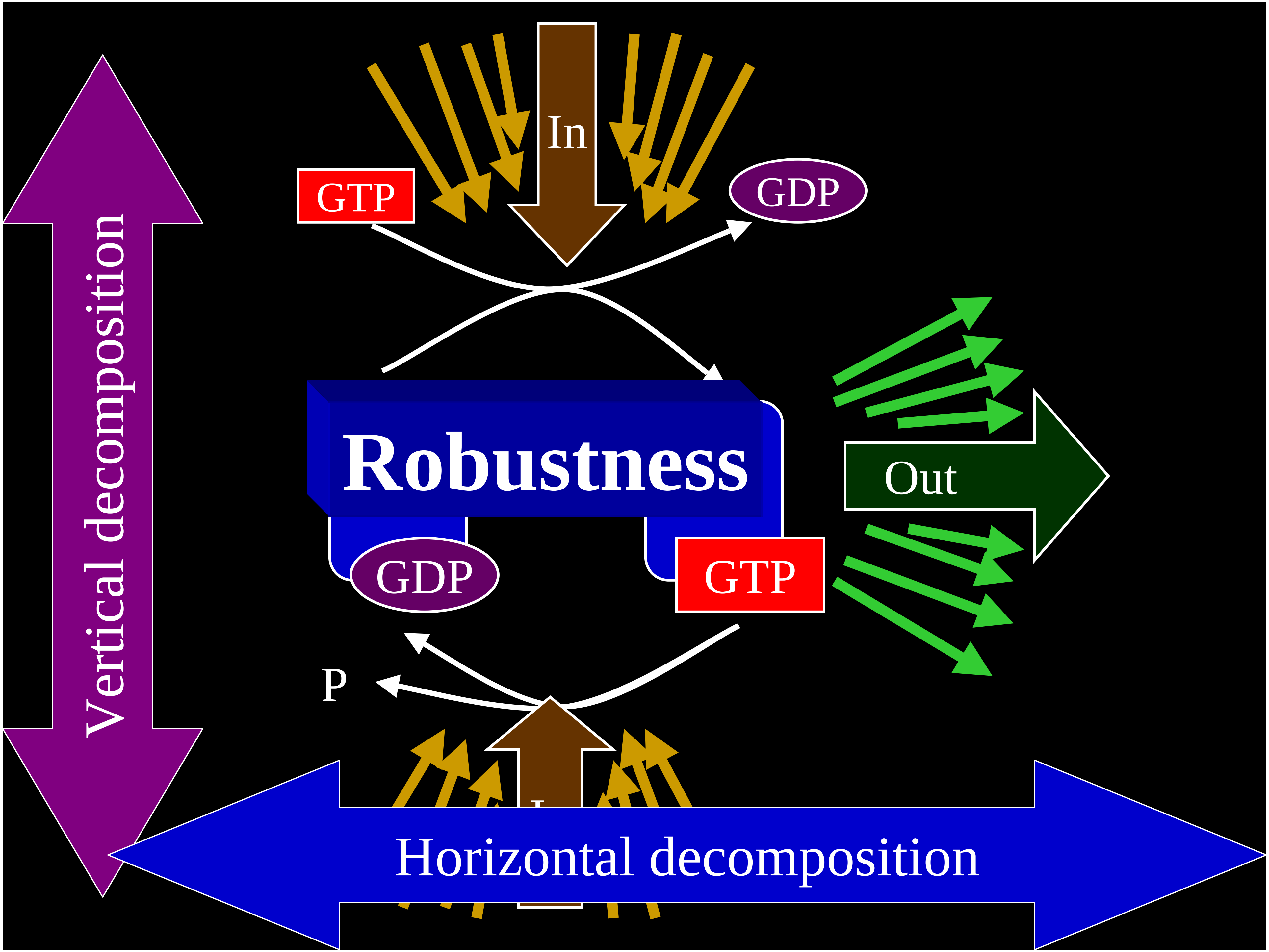
Caution: Fragility/robustness is very subtle here. Many popular accounts are wildly wrong.

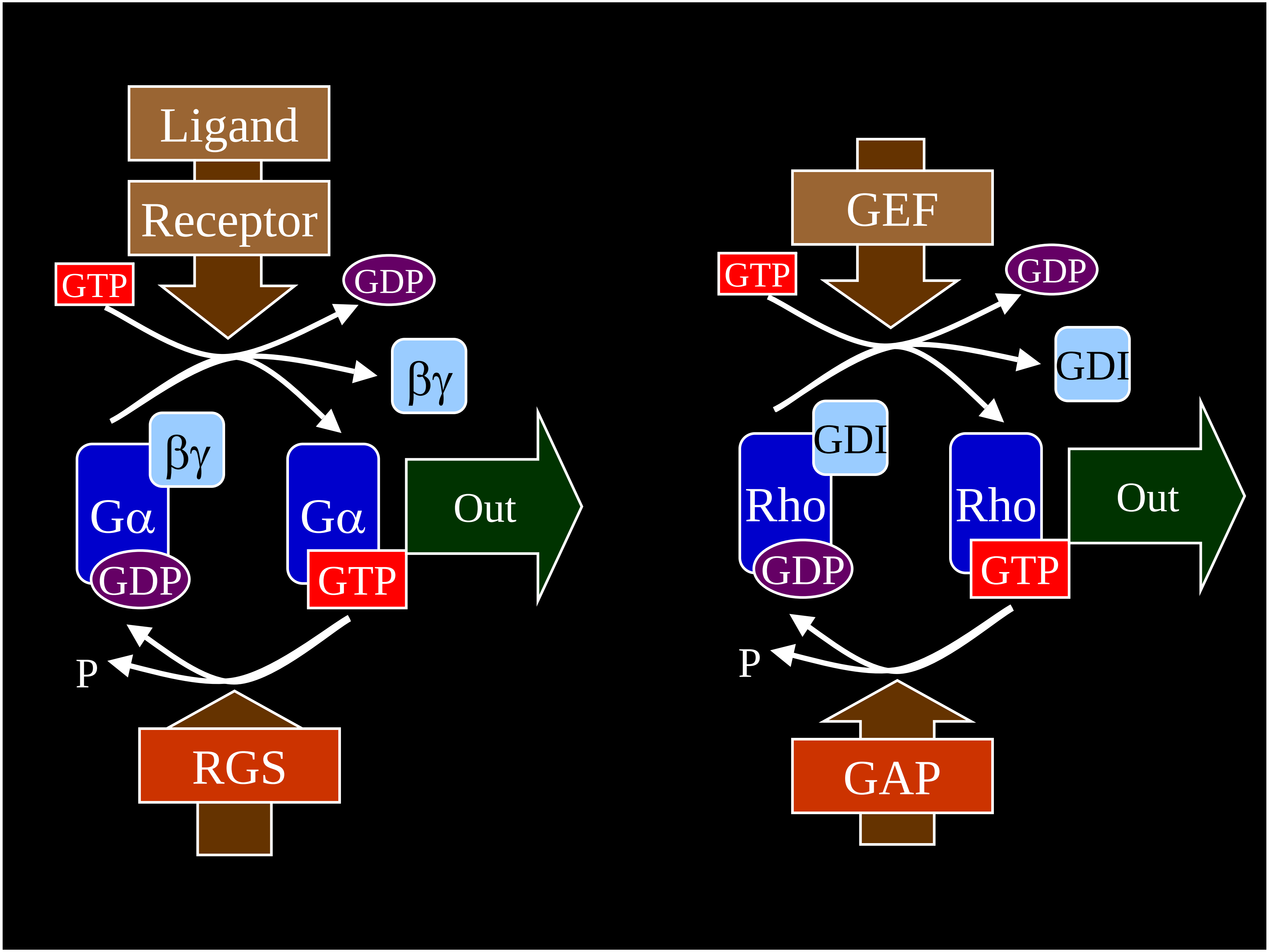


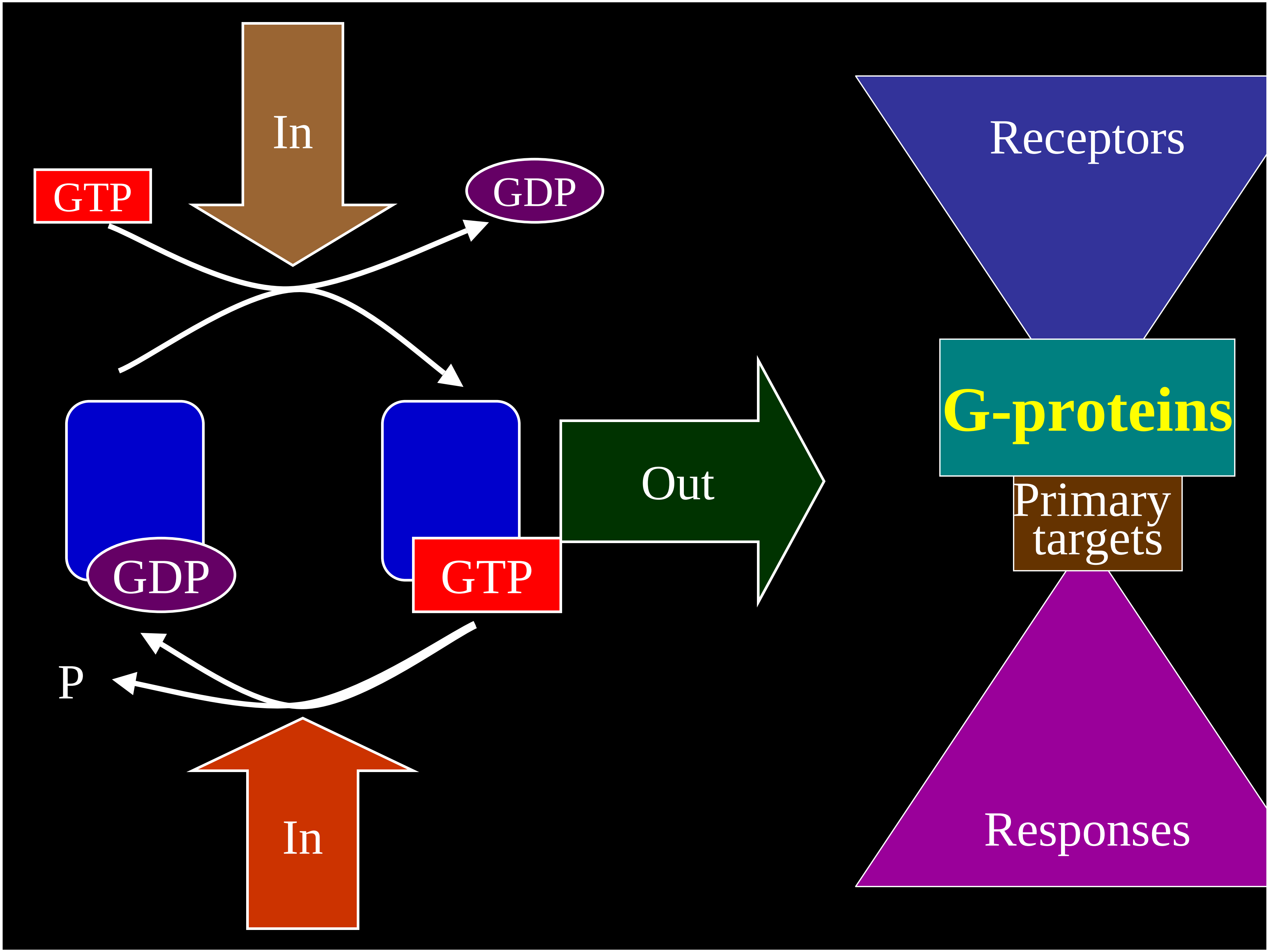

Application
Application
Application
TCP
TCP
TCP
IP
IP
IP
IP
IP
Vertical decomposition
Protocol Stack
Routing
Provisioning


Application
Application
Application
TCP
TCP
TCP
IP
IP
IP
IP
Horizontal decomposition
Each level is decentralized and asynchronous
Routing
Provisioning

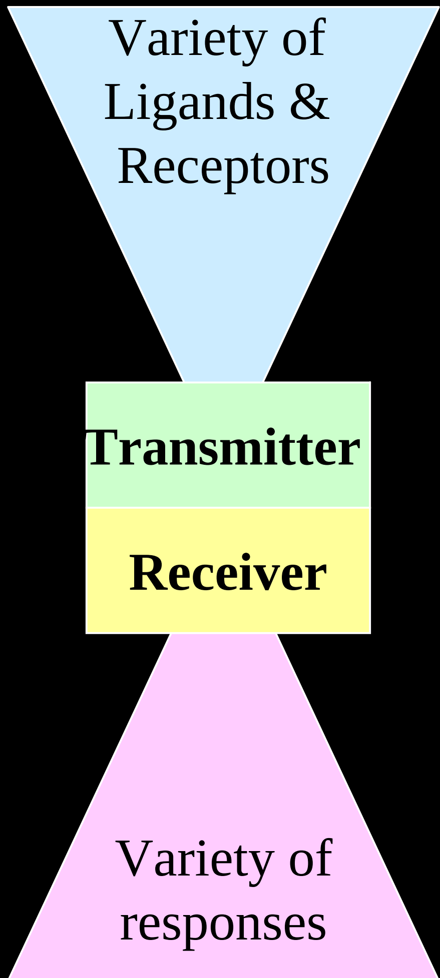

• Entirely different from the telephone system, although the parts are essentially identical (VLSI, copper, and fiber)
• The Internet is much more like biology and relies on feedback regulation at every level.
• Only recently has a coherent theory of the Internet started to emerge and pay off.
• The FAST project is the first major success story, hopefully many more to follow.
• So what?
Vertical decomposition
Horizontal decomposition


In
GTP
GDP
Robustness
Out
GDP
GTP
P
Vertical decomposition
Horizontal decomposition

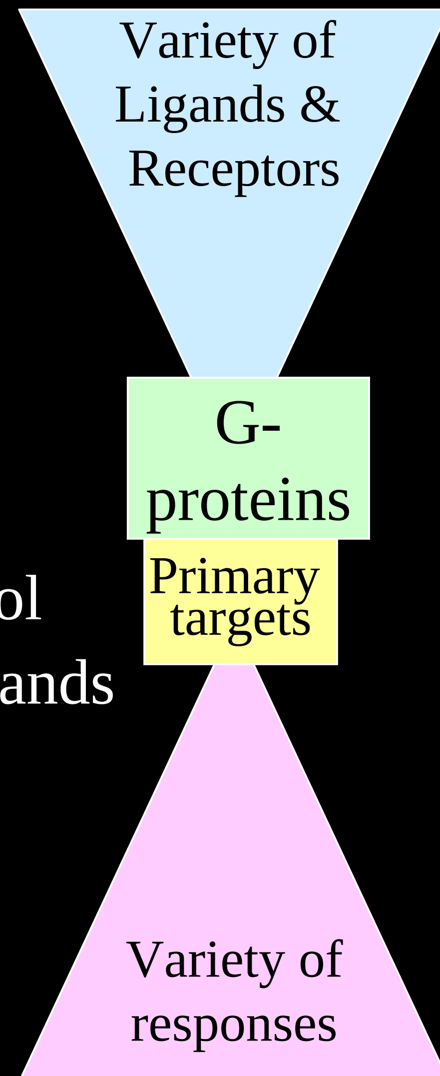

Ligand
Receptor
GTP
GDP
βγ
βγ
Gα
GDP
Gα
GTP
Out
P
RGS
GEF
GTP
GDP
GDI
GDI
Rho
GDP
Rho
GTP
Out
P
GAP


In
GTP
GDP
Receptors
G-proteins
Out
Primary targets
GDP
GTP
P
In
Responses

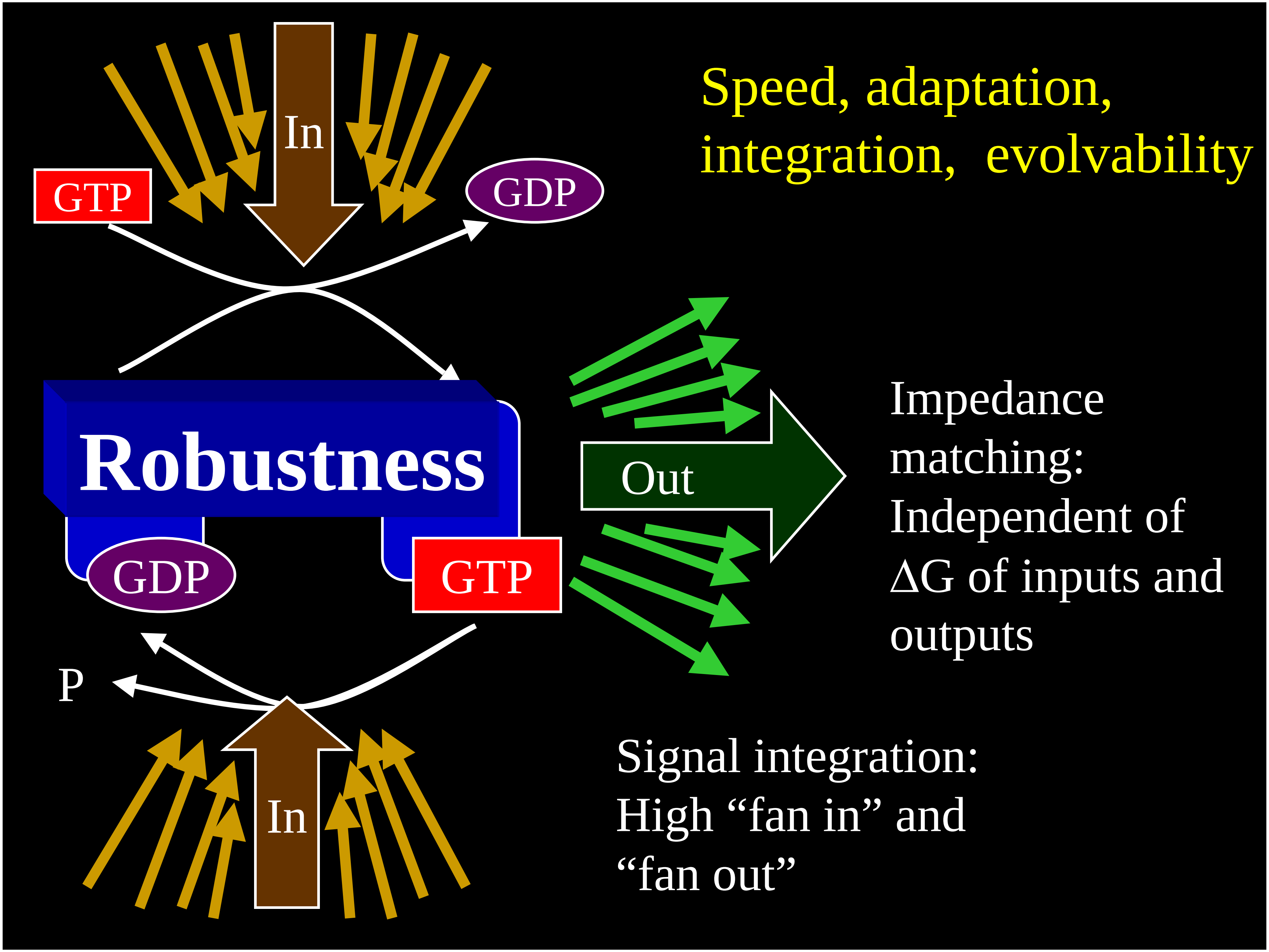
Signal transduction



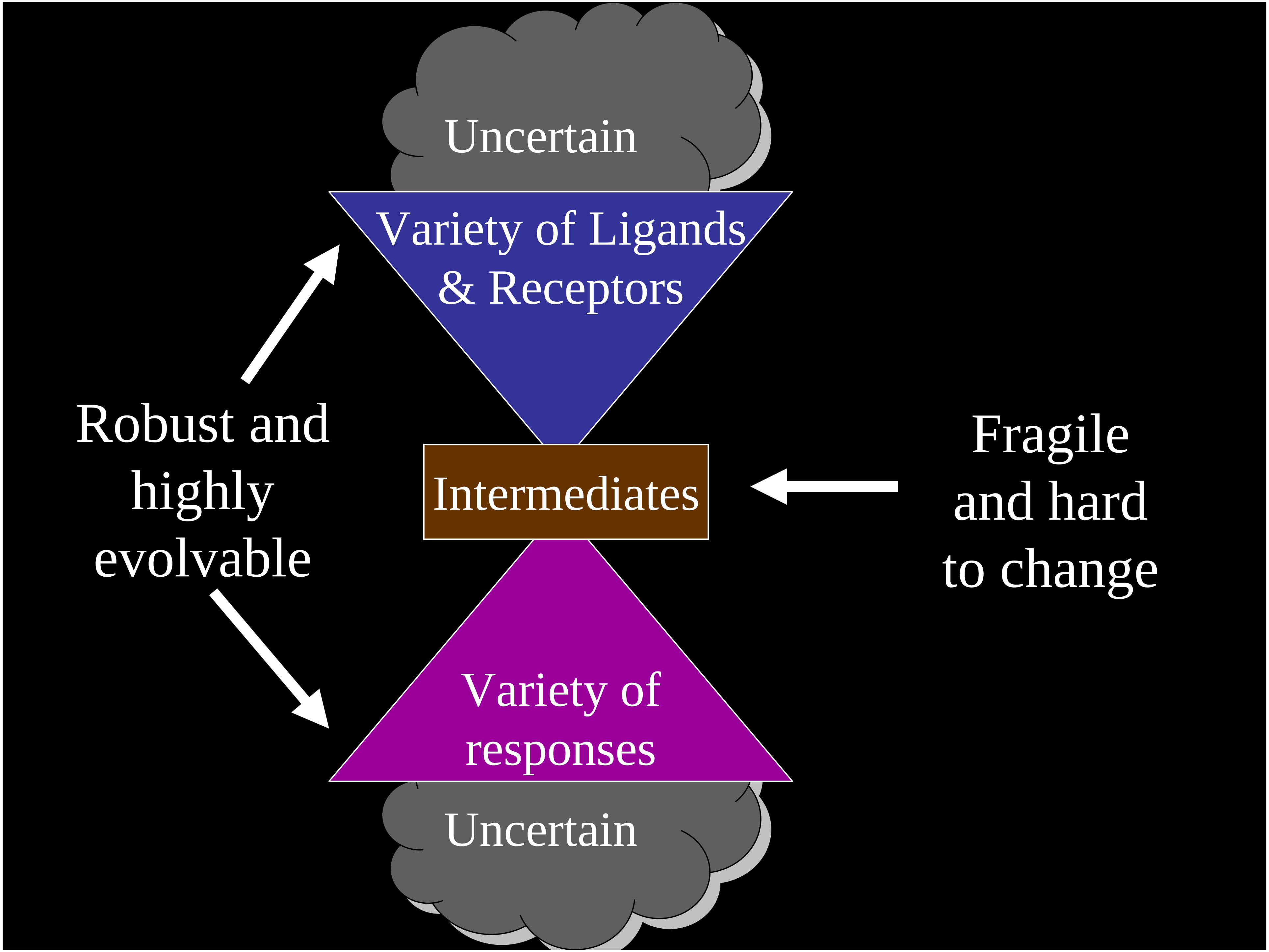
- ≈50 such "two component" systems in *E. Coli*
- All use the same protocol
  - Histidine autokinase transmitter
  - Aspartyl phospho-acceptor receiver
- Huge variety of receptors and responses



- Ubiquitous eukaryote protocol
- Huge variety of receptors/ligands
- Large number of G-proteins grouped into similar classes
- Handful of primary targets
- Huge variety of downstream responses



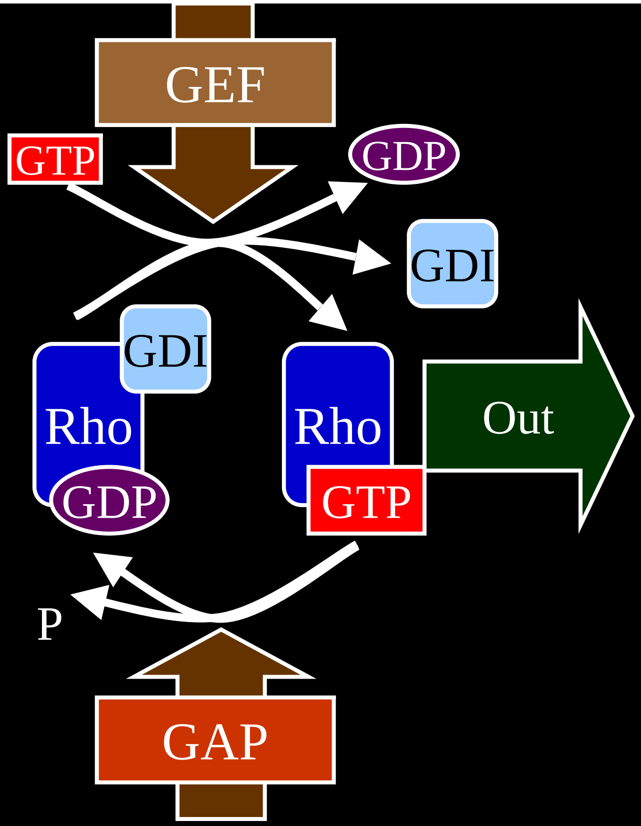
In
GTP
GDP
Robustness
GDP
GTP
Out
P
In
Speed, adaptation, integration, evolvability
Impedance matching: Independent of ΔG of inputs and outputs
Signal integration: High “fan in” and “fan out”

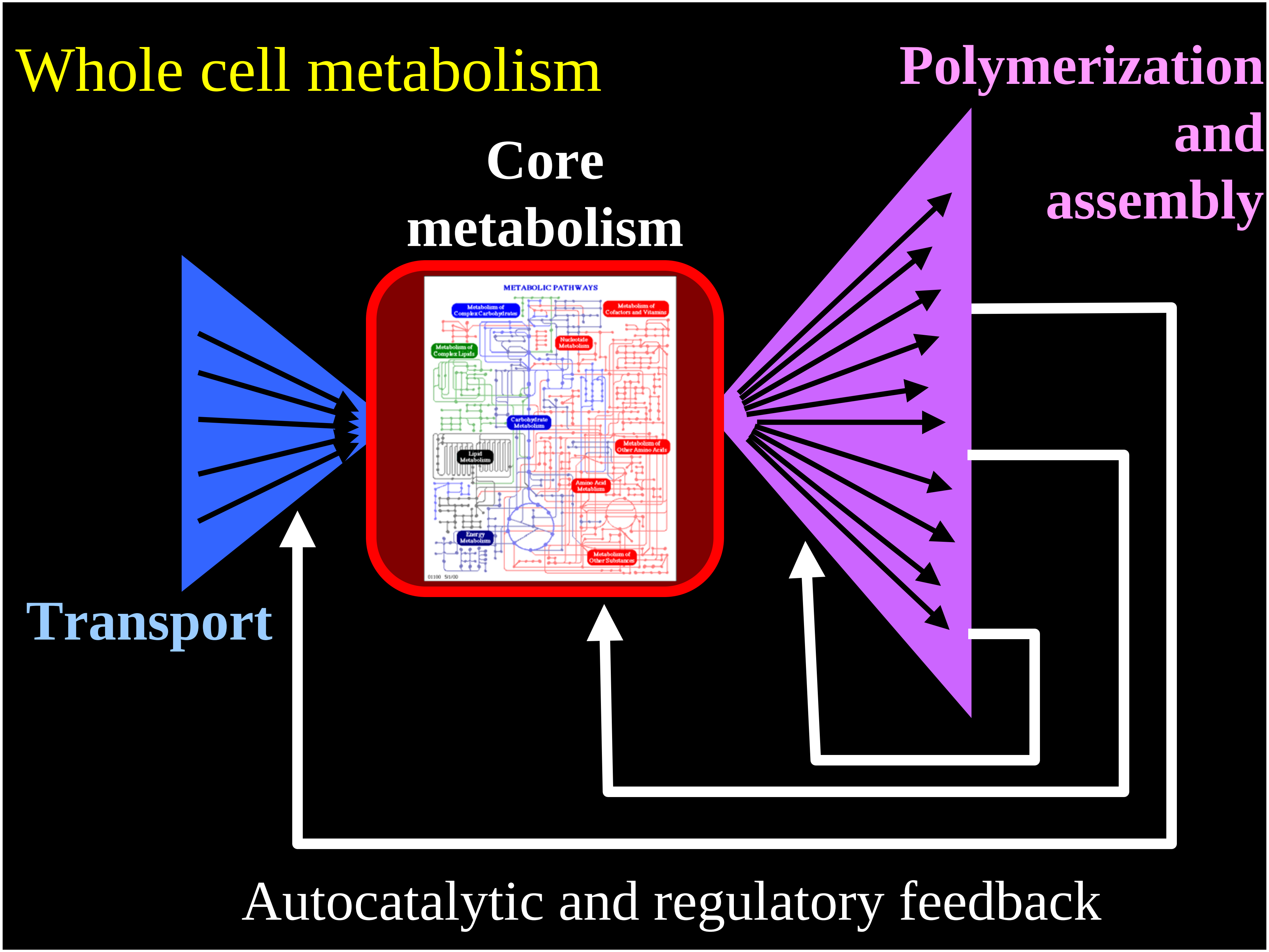

Uncertain
Variety of Ligands & Receptors
Robust and highly evolvable
Intermediates
Fragile and hard to change
Variety of responses
Uncertain

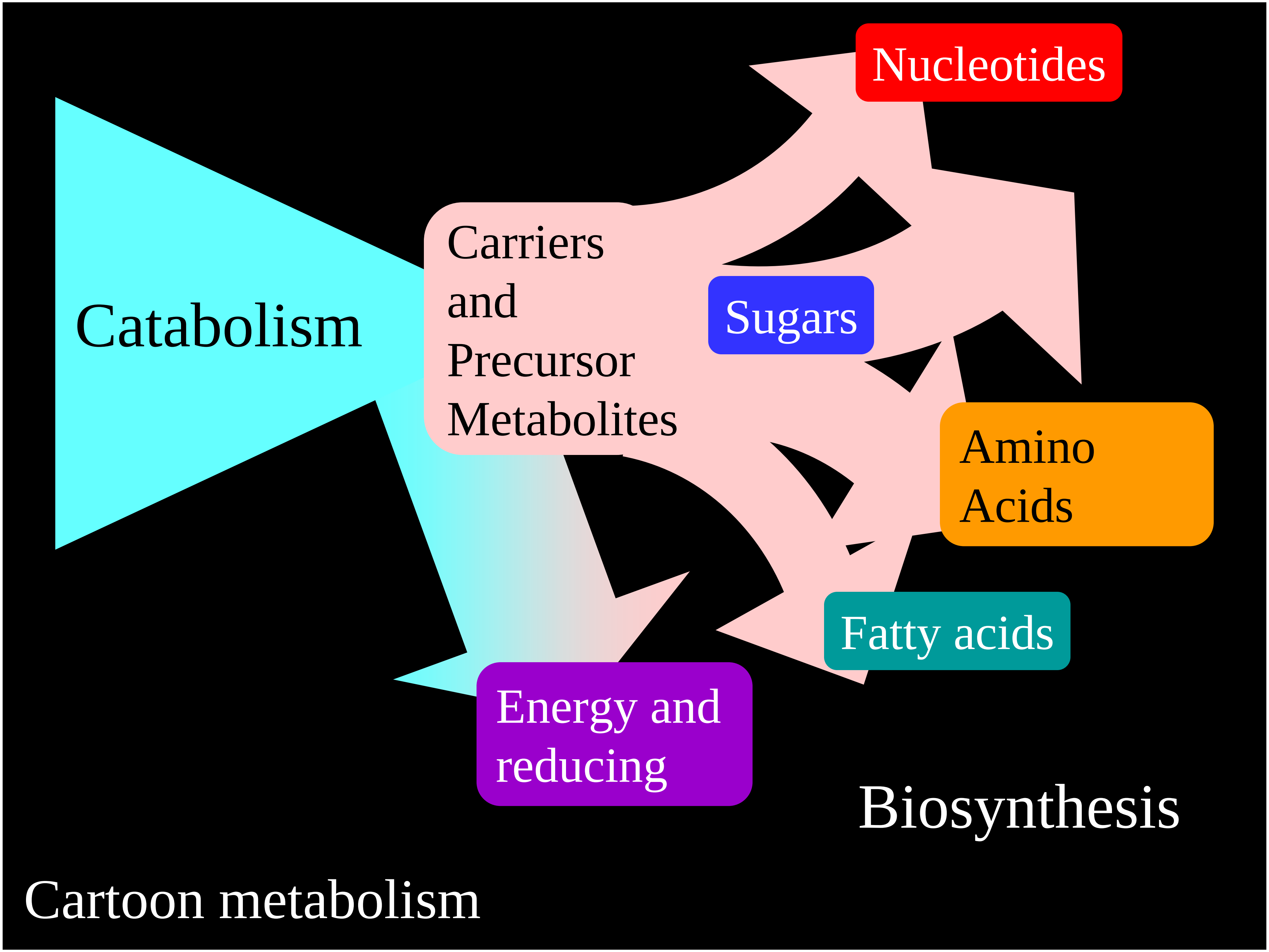
Fragility?

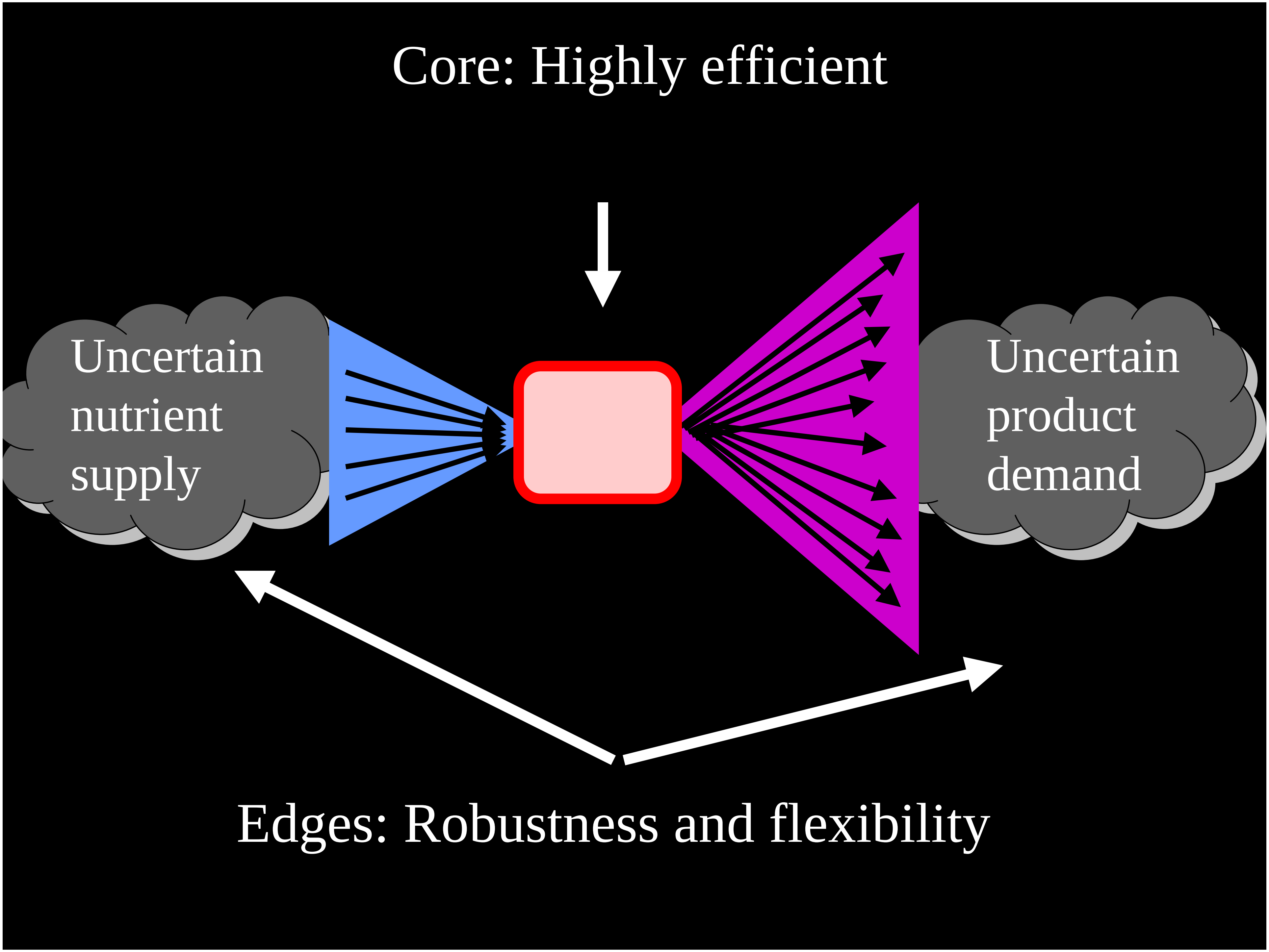
- A huge variety of pathogens attack and manipulate GTPases.
- A huge variety of cancers are associated with altered GTPase pathways.

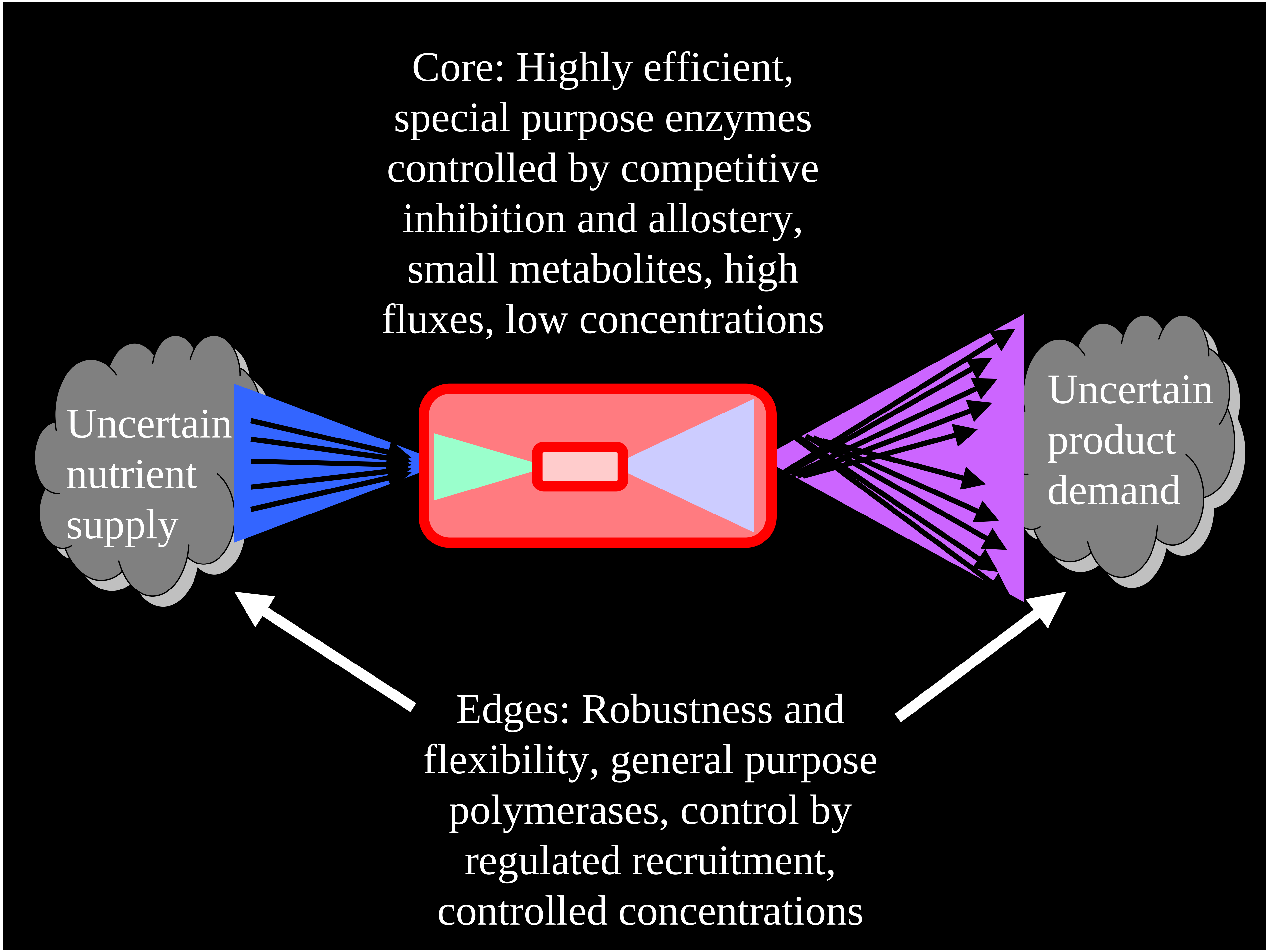
- The GTPases may be the least evolvable elements in signaling pathways, in part because they facilitate evolvability elsewhere

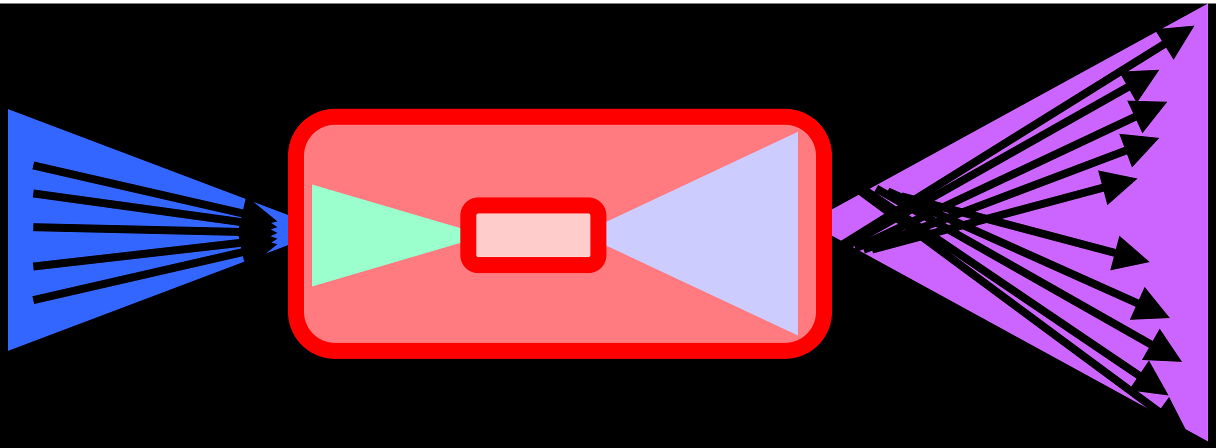



Whole cell metabolism
Polymerization and assembly
Core metabolism
METABOLIC PATHWAYS
Metabolism of Complex Carbohydrates
Metabolism of Cofactors and Vitamins
Metabolism of Complex Lipids
Nucleotide Metabolism
Carbohydrate Metabolism
Lipid Metabolism
Metabolism of Other Amino Acids
Amino Acid Metabolism
Energy Metabolism
Metabolism of Other Substances
01100 5/1/00
Transport
Autocatalytic and regulatory feedback


Nucleotides
Catabolism
Carriers
and
Precursor
Metabolites
Sugars
Amino
Acids
Fatty acids
Energy and
reducing
Biosynthesis
Cartoon metabolism


Core: Highly efficient
Uncertain nutrient supply
Uncertain product demand
Edges: Robustness and flexibility


Core: Highly efficient, special purpose enzymes controlled by competitive inhibition and allostery, small metabolites, high fluxes, low concentrations
Uncertain nutrient supply
Uncertain product demand
Edges: Robustness and flexibility, general purpose polymerases, control by regulated recruitment, controlled concentrations



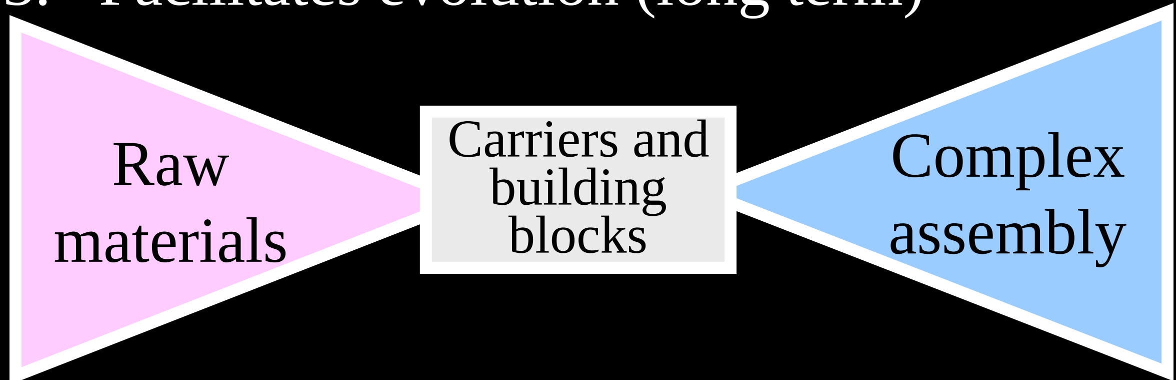
Universally shared bowtie protocol suites facilitate regulation on multiple time scales:

1. Fast: metabolite fluxes and concentrations via enzyme rates using allostery
2. Slower: concentrations of enzymes using transcriptional regulation (by regulated recruitment)
3. Even slower: transfer of genes
4. Even slower: copying and evolution of genes by accumulation of point mutations

Universal structures

Core is preserved by selection on three levels:

1. Fragile to change (short term)
2. Facilitates robustness elsewhere (short term)
3. Facilitates evolution (long term)



All advanced technologies have bowtie/hourglass architectures:

Manufacturing: Wide variety of raw materials and products with a few intermediate building blocks

Electricity: Wide variety of sources and uses all linked with a 60 Hz AC electric common carrier

Internet: Wide variety of applications and hardware technologies, all using TCP/IP as the universal protocol