Biological Networks & Network Biology
and a Cancer Story

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Institute of Mathematical science, NUS, Singapore
8-12 JUNE, 2015
An ultimate goal of bioinformatics and systems biology is a complete computer representation of the cell and the organism, which will enable computational prediction of higher-level complexity, such as
• molecular interaction networks involving various cellular processes and
• phenotypes (morphological, physiological, and behavioral aspects) of entire organisms

from biological information

From: Prof. Kanehisa, Kyoto University
Co-founder of GenBank & Founder of KEGG databases
There are two types of Biological Information

- The **digital information**
- The **environmental information** that modifies the digital information.

```
CCAGAAAGGC CGAGGCTCTG CAGCGGGAGG
GCAGGGCACA GGGACAGCCC CCCTCCACAG
CCAGGAGGTT GCCCTTTCA GAGGCTTTTT
GCTCCAGCT GCTGTGAGTG CTGCACATTTC
CAGTTCTGCT GCCGCTCTTG GCCACAGCAA
GCCCTCTGGG GGGTCTAGTG GCTAGGCTAG
CAGCCAGTGG TTTGCCAGTG TTTGCCGTG
TTTGCTCGGC AGTGTGCGCC ACTTGTCCTT
GAAGTTGCAG GTCCCTCCAG GACAGTTGCG
```
Information Growth

Forecasts for global temperature and precipitation changes for 2100 (NASA). 12 TB of info.
BIG DATA

Why Big Data in Genomics Now?

- Better analytic tools
- More rapid development
- New data streams
- Need for precision medicine

Big Data – A Definition

“Big data is a term used to describe information assemblages that make conventional data, or databases, processing problematic due to any combination of their size (volume), frequency of update (velocity), or diversity (variety)”


Human Genome, in Numbers

- 6 billion DNA letters
- 22,000 GENES
- 46 CHROMOSOMES
- SIZE ON DISK
- COST TO SEQUENCE

Figure 1: Approximate Growth of Different Data Populations

Big Data in Biomedicine

- Genomics: A Big Data Challenge Impervious
  - Computation
  - Data Correlation
  - Network/Storage

Microarrays

- Genotyping
- Genomics Analysis
- Sequencing

Bioinformatics

- Big Data in Systems Biology
- Functional Genomics
- Metabolomics

Genome big data

- Association
- Pathway Analysis
- Functional Analysis
- Gene expression
- Pathway analysis
- Functional analysis
- Gene expression
- Pathway analysis
- Functional analysis
- Gene expression
Information Complexity

- Ecological Processes and Populations
- Tissue and Organismal Physiology
- Cellular & Developmental Processes
- Biochemical Pathways & Processes
- Complete Genomes
- Genes, Proteins, RNAs, and others
### Exhibit E3

**Estimated potential economic impact of technologies from sized applications in 2025, including consumer surplus**

$ trillion, annual

<table>
<thead>
<tr>
<th>Technology</th>
<th>Range of sized potential economic impacts</th>
<th>Impact from other potential applications (not sized)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mobile Internet</td>
<td>Low: 1.7–6.2; High: 3.7–10.8</td>
<td>X–Y</td>
</tr>
<tr>
<td>Automation of knowledge work</td>
<td>Low: 5.2–6.7; High: 9–11.7</td>
<td>X–Y</td>
</tr>
<tr>
<td>The Internet of Things</td>
<td>Low: 2.7–6.2; High: 4.4–7.2</td>
<td>X–Y</td>
</tr>
<tr>
<td>Cloud technology</td>
<td>Low: 1.7–6.2; High: 3.2–8.3</td>
<td>X–Y</td>
</tr>
<tr>
<td>Advanced robotics</td>
<td>Low: 1.7–4.5; High: 2.9–6.5</td>
<td>X–Y</td>
</tr>
<tr>
<td>Autonomous and near-autonomous vehicles</td>
<td>Low: 0.2–1.9; High: 0.7–1.6</td>
<td>X–Y</td>
</tr>
<tr>
<td>Energy storage</td>
<td>Low: 0.1–0.6; High: 0.3–0.9</td>
<td>X–Y</td>
</tr>
<tr>
<td>3D printing</td>
<td>Low: 0.2–0.6; High: 0.3–0.9</td>
<td>X–Y</td>
</tr>
<tr>
<td>Advanced materials</td>
<td>Low: 0.2–0.5; High: 0.4–0.8</td>
<td>X–Y</td>
</tr>
<tr>
<td>Advanced oil and gas exploration and recovery</td>
<td>Low: 0.1–0.5; High: 0.2–0.8</td>
<td>X–Y</td>
</tr>
<tr>
<td>Renewable energy</td>
<td>Low: 0.2–0.3; High: 0.4–0.6</td>
<td>X–Y</td>
</tr>
</tbody>
</table>

**Notes on sizing**

- These estimates of economic impact are not comprehensive and include potential direct impact of sized applications only.
- These estimates do not represent GDP or market size (revenue), but rather economic potential, including consumer surplus.
- Relative sizes of technology categories shown here cannot be considered a "ranking" because our sizing is not comprehensive.
- We do not quantify the split or transfer of surplus among or across companies or consumers. Such transfers would depend on future competitive dynamics and business models.
- These estimates are not directly additive due to partially overlapping applications and/or value drivers across technologies.
- These estimates are not fully risk- or probability-adjusted.

**SOURCE:** McKinsey Global Institute analysis
## Exhibit E3
Estimated potential economic impact of technologies from sized applications in 2025, including consumer surplus

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<td></td>
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</tr>
<tr>
<td>Next-generation genomics</td>
<td>0.7–1.6</td>
<td></td>
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</tr>
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**SOURCE:** McKinsey Global Institute analysis
$5 million vs. $400
Price of the fastest supercomputer in 1975 and an iPhone 4 with equal performance

230+ million
Knowledge workers in 2012

$2.7 billion, 13 years
Cost and duration of the Human Genome Project, completed in 2003

300,000+
Miles driven by Google’s autonomous cars with only one accident (human error)
2–3 billion
More people with access to the Internet in 2025

$5–7 trillion
Potential economic impact by 2025 of automation of knowledge work

$100, 1 hour
Cost and time to sequence a human genome in the next decade

1.5 million
Driver-caused deaths from car accidents in 2025, potentially addressable by autonomous vehicles
Genomics, Bioinformatics & Systems Biology


Genomics

Bioinformatics

Systems Biology

Synthetics Biology
What is Systems Biology?

The study of the mechanisms underlying complex biological processes as integrated systems of many interacting components. First described in 1999 by Leroy Hood

David Baltimore (2005)
“a new science, a critical science of the future that seeks to understand the integration of the pieces to form biological systems.”
Some thoughts about “Systems”

Manner in which components interact to achieve the output of a system

Wiring diagrams reflect the logic of a system, and may sometimes be more relevant than the individual components, considered one at-a-time

Direct physical interaction is part of wiring, but not all interactions occur at this level

Components

Circuits

Machines
Systems biology

Manner in which gene products interact to achieve the output of a system.

Wiring diagrams reflect the logic of a system, and may sometimes be more relevant than the individual gene products, considered one at-a-time.

Direct physical interaction is part of wiring, but not all interactions occur at this level.

Components

Networks?

Organisms
Essence of living systems is flow of mass, energy, and information in space and time.

The flow occurs along specific pathways.

- Flow of mass and energy (metabolic pathways)
- Flow of information involving DNA (transcriptional regulation pathways)
- Flow of information not involving DNA (signaling pathways)
How to Describe a System As a Whole?

Networks - The Language of Complex Systems
Network?

Network is a mathematical structure composed of points connected by lines.

Network Theory <-> Graph Theory

Network <-> Graph
Nodes <-> Vertices (points)
Links <-> Edges (Lines)

A network can be built for any system the elements of which interact with each other.
Biological Networks

- **Node**
  
gene, protein, metabolite, enzyme, ...

- **Edges**

  interactions, regulations, reactions, transformations, activation, inhibitions, ...
The Protein Network of Drosophila

CuraGen Corporation
Science, 2003
Signaling Pathway
Internet
Airline routes
Other Networks

X → Y represents

transcription network

gene x

gene y

neuron synaptic connection network

ecological food web

X

Eat

Y
Common Biological Networks

Proteins
Metabolites
Metabolism
Gene regulation
Cell signaling
PPIs

A
m_1
m_2

B
m_3

C

D

E

F
Common Properties

- Small world
- Scale free
- Modular
- Robust
Properties of large biological networks

- **Global network properties**
  - Degree distribution
  - Average clustering coefficient
  - Clustering spectrum
  - Average Diameter
  - Spectrum of shortest path lengths
  - Centralities
  - ...

- **Local network properties**
  - Network motifs
  - Graphlets
  - ...

Tijana Milenković, Graph-theoretical approaches for studying biological networks, 2008. The university of California
Biological Networks for diseases & Cancer

Human genes ~25,000

Essential genes (1,565)
Essential non-disease genes (1,267)

Disease genes (1,777)
Essential disease genes (398)
Non-essential disease genes (1,379)

Biological Networks for diseases

Topological module

Functional module

Disease module

- Topologically close genes (or products)
- Functionally similar genes (or products)
- Disease genes (or products)
- Undirectional interactions
- Directional interactions

Biological Networks for diseases

Metabolic disease network

Review

Metabolic Cancer Biology: Structural-based analysis of cancer as a metabolic disease, new sights and opportunities for disease treatment

Ali Masoudi-Nejad *, Yazdan Asgari

Laboratory of Systems Biology and Bioinformatics (LBB), Institute of Biochemistry and Biophysics, University of Tehran, Tehran, Iran

Alterations in cancer cell metabolism: The Warburg effect and metabolic adaptation

Yazdan Asgari a, Zahra Zabihinpour a, Ali Salehzadeh-Yazdi a, Falk Schreiber b,c,*, Ali Masoudi-Nejad a,***

Controllability in Cancer Metabolic Networks According to Drug Targets as Driver Nodes

Metabolism and Cancer

Otto Heinrich Warburg
1883-1970

Nobel prize in Physiology and Medicine for his Warburg effect in 1931
The "Warburg effect" asserts that even when oxygen is plentiful, cancer cells continue to use glycolysis followed by lactic acid fermentation, rather than through oxidative phosphorylation in the mitochondria.

Lopez-Lazaro M (2008), Anticancer Agents Med Chem 8: 305-312
With the emergence of systems biology and High-Throughput technology, many attempts were performed to revise the Warburg effect.
Metabolic Networks Modeling Approaches

- **Qualitative Models**
  - Topological Analysis
    - Static description
    - No kinetic parameters
    - Topological properties
  - Flux Balance Analysis
    - Static description
    - No kinetic parameters
    - Quantitative predictions

- **Quantitative Models**
  - Structural Kinetic Models
    - Dynamic description
    - No kinetic parameters
    - Bifurcation structure
  - Kinetic Models
    - Dynamic description
    - Kinetic parameters
    - Differential equations

Size of System

Level of Detail
Goal:
Can the Warburg effect be observed by topological analysis?

Strategy:
Comparison of normal and cancer cells by topological analysis
Input: Metabolic Network in SBML format

SBML: Systems Biology Markup Language
Metabolic Network as a Graph

Rogier Braakman and Eric Smith 2013 *Phys. Biol.* **10** 011001
Metabolites and enzymes as network
Structural Cobra Add-oN (SCAN) for metabolic networks
Structural Cobra Add-oN (SCAN) for metabolic networks
Cytoscape
<table>
<thead>
<tr>
<th>Cancerous cell</th>
<th>Normal cell</th>
</tr>
</thead>
<tbody>
<tr>
<td>Breast</td>
<td>Breast Glandular</td>
</tr>
<tr>
<td>Cervical</td>
<td>Cervix squamous</td>
</tr>
<tr>
<td>Colorectal</td>
<td>Colon Glandular</td>
</tr>
<tr>
<td>Endometrial</td>
<td>Copus Endometrial-Copus Glandular</td>
</tr>
<tr>
<td>Renal</td>
<td>Kidney Glomeruli-Kidney Tubules</td>
</tr>
<tr>
<td>Liver</td>
<td>Liver Hepatocyt</td>
</tr>
<tr>
<td>Lung</td>
<td>Lung Alveolar</td>
</tr>
<tr>
<td>Ovarian</td>
<td>Ovary Stromal</td>
</tr>
<tr>
<td>Pancreatic</td>
<td>Pancreas Islet</td>
</tr>
<tr>
<td>Prostate</td>
<td>Prostate Glandualr</td>
</tr>
<tr>
<td>Skin</td>
<td>Skin Epidermal</td>
</tr>
<tr>
<td>Stomach</td>
<td>Stomach Glandular (I&amp;II)</td>
</tr>
<tr>
<td>Testis</td>
<td>Testis Leydig</td>
</tr>
<tr>
<td>Thyroid</td>
<td>Thyroid Glandular</td>
</tr>
<tr>
<td>Urotheial</td>
<td>Urinary Bladder</td>
</tr>
</tbody>
</table>

Construction of metabolite- and enzyme-centric networks based on SBML files of normal and cancer cells
Workflow

(SCAN toolbox)

Topological analysis
(Cytoscape)

GSMM of normal cell
(INIT algorithm)

GSMM of cancer cell
(INIT algorithm)
Purpose of study:
to check any structural differences between metabolite- and enzyme-centric of normal and cancer networks.

Software:
Network Analysis.

Parameters for directed networks:
in-degree, out-degree, Clustering Coefficient, connected components, network diameter, characteristic path length, average number of neighbors, number of nodes, isolated node, multi-edge node pairs.

Parameters for undirected networks:
degree, Clustering Coefficient, connected components, network diameter, network centralization, characteristic path length, average number of neighbors, total number of nodes, network density, network heterogeneity, isolated node.
• **Purpose of study:**
to check difference between highly connected nodes of normal and cancer networks.

• **Networks Types:**
directed and undirected networks.

• **Software:**
cytoHubba plug-in in Cytoscape.

• **Centrality Indices:**
Maximal Clique Centrality (MCC), Density of Maximum Neighborhood Component (DMNC), Maximum Neighborhood Component (MNC), Degree, Edge Percolated Component (EPC), Bottleneck, Eccentricity, Closeness, Radiability, Betweenness, Stress, Clustering Coefficient
• **Purpose of study:**
  to check any differences between metabolite- and enzyme-centric of normal and cancer networks.

• **Networks Types:**
  directed metabolite-centric network and directed enzyme-centric network.

• **Software:**
  Quatexelero algorithm.

• **Parameters:**
  Motif of size 3 (13 types).
Network Motif discovery

QuateXelero: An Accelerated Exact Network Motif Detection Algorithm


MODA: an efficient algorithm for network motif discovery in biological networks.
Omidis S, Schreiber F, Masoudi-Nejad A.
• **Purpose of study:**
  to check any differences between number of clusters in normal and cancer networks.

• **Networks Types:**
directed and undirected networks.

• **Software:**
MCODE plugin in Cytoscape.

• **Parameters:**
degree cutoff = 2, without loops, node score cutoff = 0.2, K-core = 2, Max. Depth = 100, Include haircut, without fluff.
Results: Topological analysis

- All networks have scale-free property.
- No significant differences found in first top 100 centrality indices.
- No significant difference found in number of motif 3.
- No significant difference found in number of clusters.

Barabási, Oltvai,, NATURE REVIEWS GENETICS, 2004
Goal:
- Can the Warburg effect be observed by constraint-based modeling?

Strategy:
- Integration of gene expression into the GEM (Recon-1) for construction of cancer GEMs by the E-FLUX method.
- Gene expression analysis of different cancer cells by geWorkbench.
Workflow

Flux Balance Analysis (COBRA Toolbox)

Gene Expression Analysis (geWorkbench)

Integration of gene expression data in genome-scale metabolic network

Recon1
genome-scale metabolic model

Gene expression data

Gene expression data
<table>
<thead>
<tr>
<th>Gene</th>
<th>Reaction</th>
<th>P-value</th>
<th>Fold change</th>
</tr>
</thead>
<tbody>
<tr>
<td>Q0130</td>
<td>r_0226</td>
<td>0.002</td>
<td>-2.4</td>
</tr>
<tr>
<td>YNL268W</td>
<td>r_1213</td>
<td>0.004</td>
<td>-1.2</td>
</tr>
<tr>
<td>YEL063C</td>
<td>r_1184</td>
<td>0.001</td>
<td>-1.1</td>
</tr>
<tr>
<td></td>
<td>r_1238</td>
<td></td>
<td></td>
</tr>
<tr>
<td>YML008C</td>
<td>r_0986</td>
<td>0.003</td>
<td>-0.65</td>
</tr>
<tr>
<td>YBL076C</td>
<td>r_0665</td>
<td>0.009</td>
<td>-0.48</td>
</tr>
</tbody>
</table>
\[ D - Glc + ATP \xrightarrow{HK} D - G6P + ADP \]

Stoichiometric Constants

\[
\begin{array}{cccc}
Glc & ATP & G6P & ADP \\
-1 & -1 & +1 & +1 \\
\end{array}
\]
An outline of the major steps involved in FBA

FBA: Flux Balance Analysis

Raman and Chandra (2009) BRIEFINGS IN BIOINFORMATICS
• **Purpose of study:**
  Assessment of the Warburg effect.

• **Networks Types:**
  Constructed GEMs by the E-FLUX method.

• **Software:**
  SCAN-Tolbox
  COBRA toolbox

• **Objective function:**
  Human biomass

• **Parameters:**
  Metabolic fluxes in all reactions.

<table>
<thead>
<tr>
<th>Tissue</th>
<th>Tumor Type</th>
<th>Tumor Samples</th>
<th>Normal Samples</th>
<th>GEO Accession Number</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adrenal</td>
<td>Adrenocortical carcinoma</td>
<td>33</td>
<td>10</td>
<td>GSE10927</td>
</tr>
<tr>
<td>Breast</td>
<td>Ductal carcinoma</td>
<td>5</td>
<td>10</td>
<td>GSE5764</td>
</tr>
<tr>
<td></td>
<td>Lobular carcinoma</td>
<td>5</td>
<td>10</td>
<td>GSE5764</td>
</tr>
<tr>
<td>Cervix</td>
<td>Squamous cell carcinoma</td>
<td>20</td>
<td>8</td>
<td>GSE6791</td>
</tr>
<tr>
<td>Colon</td>
<td>Colorectal carcinoma</td>
<td>12</td>
<td>10</td>
<td>GSE4107</td>
</tr>
<tr>
<td>Head and Neck</td>
<td>Squamous cell carcinoma</td>
<td>26</td>
<td>12</td>
<td>GSE9844</td>
</tr>
<tr>
<td>Leukemia</td>
<td>Acute myeloid leukemia</td>
<td>9</td>
<td>4</td>
<td>GSE17054</td>
</tr>
<tr>
<td>Liver</td>
<td>Hepatocellular carcinoma</td>
<td></td>
<td></td>
<td>GSE6764</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Very early</td>
<td>8</td>
<td>10</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Early</td>
<td>10</td>
<td>10</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Advanced</td>
<td>7</td>
<td>10</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Very Advanced</td>
<td>10</td>
<td>10</td>
</tr>
<tr>
<td>Lung</td>
<td>Pulmonary adenocarcinoma</td>
<td></td>
<td></td>
<td>GSE10799</td>
</tr>
<tr>
<td></td>
<td>Bone Marrow Positive</td>
<td>7</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Bone Marrow Negative</td>
<td>9</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>Ovary</td>
<td>Serous carcinoma</td>
<td>13</td>
<td>12</td>
<td>GSE10971</td>
</tr>
<tr>
<td>Pancreas</td>
<td>Ductal adenocarcinoma</td>
<td>39</td>
<td>39</td>
<td>GSE15471</td>
</tr>
<tr>
<td>Prostate</td>
<td>Adenocarcinoma</td>
<td>17</td>
<td>7</td>
<td>GSE7307</td>
</tr>
<tr>
<td>Stomach</td>
<td>Gastric carcinoma</td>
<td>38</td>
<td>31</td>
<td>GSE13911</td>
</tr>
<tr>
<td>Thyroid</td>
<td>Papillary carcinoma</td>
<td>7</td>
<td>7</td>
<td>GSE3678</td>
</tr>
</tbody>
</table>
Now, there are more than 70 plug-ins available supporting:

- The visualization
- Analysis of gene expression
- Analysis of sequence data

## Number of significant metabolic genes and number of their affected reactions

<table>
<thead>
<tr>
<th>Cancer type</th>
<th>Number of significant metabolic genes</th>
<th>Number of up-regulated genes</th>
<th>Number of down-regulated genes</th>
<th>Number of affected reactions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adrenal</td>
<td>23</td>
<td>12</td>
<td>11</td>
<td>46</td>
</tr>
<tr>
<td>Breast-ductal</td>
<td>3</td>
<td>0</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>Breast-lobular</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Cervix</td>
<td>39</td>
<td>27</td>
<td>12</td>
<td>65</td>
</tr>
<tr>
<td>Colon</td>
<td>10</td>
<td>5</td>
<td>5</td>
<td>22</td>
</tr>
<tr>
<td>Head &amp; neck</td>
<td>13</td>
<td>2</td>
<td>11</td>
<td>25</td>
</tr>
<tr>
<td>Leukemia</td>
<td>5</td>
<td>4</td>
<td>1</td>
<td>8</td>
</tr>
<tr>
<td>Liver-very early</td>
<td>7</td>
<td>5</td>
<td>2</td>
<td>22</td>
</tr>
<tr>
<td>Liver-early</td>
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<td>Number of subsystems</td>
<td>Decreased flux</td>
<td>Number of subsystems</td>
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</tbody>
</table>
Conclusion

- Flux analysis suggests that the Warburg effect could be a result of biochemical adaptation.

- Different fluxes in metabolic could be used as a metabolic biomarker or drug target in different cancers.

- Elaborated experimental design is needed to support these findings.
• **Liu model.**
  Their approach is based on the identification of a subset of nodes (called **driver nodes**) in a directed network that can control the dynamics of the system.

• **Nacher model.**
  Introduced a new approach which investigated the dependence of the size of the **minimum dominating set (MDS)** of nodes on topological features of directed real networks for the purposes of control design.

Nacher J, Akutsu T (2012), *New Journal of Physics*
**Assumption:** Anticancer metabolic drugs and their targets as driver nodes

<table>
<thead>
<tr>
<th>Drug Target</th>
<th>Metabolic target function</th>
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<tbody>
<tr>
<td>DHFR</td>
<td>Dihydrofolate reductase</td>
</tr>
<tr>
<td>TYMS</td>
<td>Thymidylate synthase</td>
</tr>
<tr>
<td>GART</td>
<td>Trifunctional purine biosynthetic protein adenosine-3</td>
</tr>
<tr>
<td>IMPDH2</td>
<td>Inosine-5'-monophosphate dehydrogenase 2</td>
</tr>
<tr>
<td>HPRT1</td>
<td>Hypoxanthine-guanine phosphoribosyltransferase</td>
</tr>
<tr>
<td>GMPR</td>
<td>GMP reductase 1</td>
</tr>
<tr>
<td>GMPR2</td>
<td>GMP reductase 2</td>
</tr>
<tr>
<td>ADSL</td>
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<td>GMP synthase</td>
</tr>
<tr>
<td>AMPD1</td>
<td>AMP deaminase 1</td>
</tr>
<tr>
<td>AMPD3</td>
<td>AMP deaminase 3</td>
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<tr>
<td>PPAT</td>
<td>Amidophosphoribosyltransferase</td>
</tr>
<tr>
<td>ADA</td>
<td>Adenosine deaminase</td>
</tr>
<tr>
<td>PNP</td>
<td>Purine nucleoside phosphorylase</td>
</tr>
<tr>
<td>RRM1</td>
<td>Ribonucleoside-diphosphate reductase large subunit</td>
</tr>
<tr>
<td>CMPK1</td>
<td>UMP-CMP kinase</td>
</tr>
</tbody>
</table>
| DPYD        | Dihydropyrimidine dehydrogenase [NADP(+)]
| ALAD        | Delta-aminolevulinic acid dehydratase |

<table>
<thead>
<tr>
<th>Metabolic targets</th>
</tr>
</thead>
<tbody>
<tr>
<td>DHFR</td>
</tr>
<tr>
<td>TYMS</td>
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<tr>
<td>GART-DHFR-GART-TYMS</td>
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<tr>
<td>IMPDH2-HPRT1-GMPR-GMPR2-ADSL-IMPDH1-AMPD2-GMPS-AMPD1-AMPD3-PPAT</td>
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<td>ADA-RRM1</td>
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<tr>
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<td>TYMS</td>
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<tr>
<td>TYMS-CMPK1-RRM1</td>
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<td>DPYD-TYMS</td>
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<tr>
<td>ALAD</td>
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<tr>
<td>RRM1</td>
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</table>
Conclusion: Distributed Controllability

We investigated the distribution of drug targets in all topological parameters, and found that drugs didn’t affect the central nodes and motifs. Instead, they just affected the metabolism of cancer cells through clusters.

This could suggest using distributed controllability concept for cancer metabolic networks.
FDG PET/CT images of a 33-year-old woman with infiltrating locally advanced ductal carcinoma before (left) and 19 days after (right) beginning of therapy with Lapatinib (anti-HER2) and Paclitaxel. A marked reduction of glucose consumption in the nodule (white arrows) is evident after medical therapy. After PET, the patient underwent mastectomy.
<table>
<thead>
<tr>
<th>Mechanism of action</th>
<th>Target gene</th>
<th>Inhibitor(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reduction of glucose entry into the cell</td>
<td>GLUT1</td>
<td>Imatinib, 2-DG, Phloretin, Fasentin</td>
</tr>
<tr>
<td>Inhibition of phosphorylation of glucose</td>
<td>HK</td>
<td>LND, 3-BrPA, Mannheptulose</td>
</tr>
<tr>
<td>Inhibition of fructose-6-PO₄ to fructose-1, 6-bisphosphate</td>
<td>PFK1</td>
<td>Methyl jasmonate, 3-PO</td>
</tr>
<tr>
<td>Inhibition of phosphoenolpyruvate to pyruvate</td>
<td>PKM2</td>
<td>TT-232, Flourophosphates, creatine phosphate oxalate, L-phospholactate, Oxythiamine, 6-AN</td>
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<tr>
<td>Suppression of pentose phosphate pathway</td>
<td>TKTL1, G6PD</td>
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<tr>
<td>Promotion of pyruvate entry into mitochondria</td>
<td>PDK1</td>
<td>DCA</td>
</tr>
<tr>
<td>Reduction of HIF-1 activity</td>
<td>HIF-1α</td>
<td>Topotecan&lt;br&gt;Digoxin&lt;br&gt;YC-1&lt;br&gt;GA&lt;br&gt;2ME2&lt;br&gt;PX-478&lt;br&gt;Echinomycin</td>
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</tbody>
</table>

Abbreviations: 2-DG, 2-deoxyglucose; LND, lonidamine; 3-BrPA, 3-bromopyruvate; 3-PO, 3-(3-pyridinyl)-1-(4-pyridinyl)-2-propen-1-one; 6-AN, 6-aminonicotinamide; DCA, dichloroacetate; GA, geldanamycin; 2ME2, 2-methoxyestradiol; PX-478, S-2-amino-3-[4'-N,N-bis(2-chloroethyl)amino]phenyl propionic acid N-oxide dihydrochloride.
Several companies pipeline drug candidates that should interfere with cancer metabolism:

- **Dynamix has drug programs targeting Pyruvate Kinase M2 (PKM2), a key enzyme in the metabolism of glucose. PKM2 is overexpressed in the cancer cells, leading to an increase in the production of lactate and the creation of the Warburg effect.**

- **Myrexis, Inc. compound, MPC-9528 is nicotinamide phosphoribosyl transferase (NAMPT) inhibitor. NAMPT catalyzes the formation of nicotinamide adenine dinucleotide (NAD). Depletion of NAD inhibits cell metabolism, DNA repair, and other processes. Human trials are expected in 2011.**

- **Warburg Glycomed GmbH is developing butanoic acid derivatives which have been shown to reprogram cancer cell aerobic glucose metabolism and anti-cancer effects.**

- **Tavargenix GmbH is developing inhibitors of Transketolase like 1 (TKTL1). TKTL1, which is high in certain tumors (such as head and neck), promotes glucose to lactate conversion; inhibition of TKL1 results in inhibition of cancer cell proliferation and tumors in animal models.**

- **Synta Pharmaceuticals' Elesclomol is in early trials for ovarian cancer and in acute myeloid leukemia. It targets cancer cell energy production by interfering with the electron transfer chain in the mitochondria.**
Acknowledgement
Thank You
Structural and Functional Brain Mapping Based On Message Passing Between Networks
A Systems Biology Approach to Study Response to Anti-Cancer Therapy
Systems biology approach for reconstruction and simulation of Airway remodeling pathway