

Analysis of Biological Networks

Professors

Ram Sasisekharan

John M. Essigmann

Systems Approach to Biological Problems

Image removed due to
copyright considerations.

8th Sept, 2004
Ram Sasisekharan

Image removed due to copyright considerations..

Retinopathy

- Diabetic retinopathy, Macular degeneration and 10 other indications
- Over 500,000 patients per year
- Unmet medical condition
- Current treatment - laser surgery and this procedure has > 60% relapse < 3 months

Central Dogma of Molecular Biology

Image removed due to copyright considerations.

Proteins

Image removed due to copyright considerations.

Post-genomic challenges

- Newer tools and more sophisticated technology to push the field forward in the post genomic age
- Genomics, proteomics, glycomics and others
-enter cell, tissue organ level mechanisms
- A '**systems approach**' to understand the complex biological system

Linking molecular & cellular events *with physiological function*

Image removed due to copyright considerations

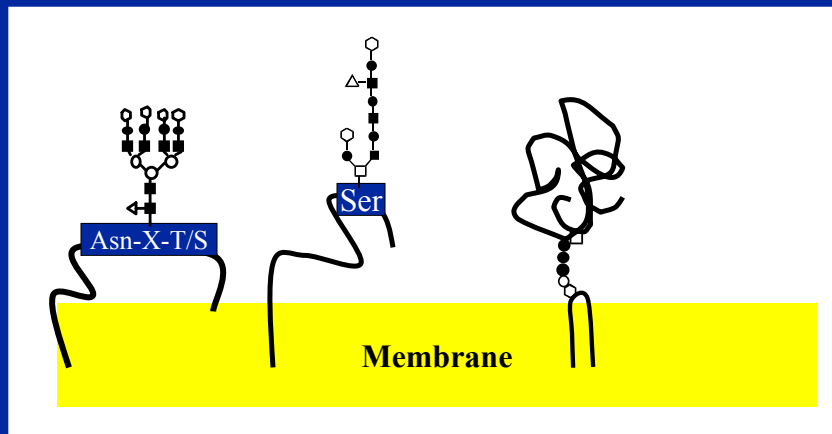
Please see:

Figure 2a in Hunter, Peter J. and Borg, Thomas K.
"Integration from proteins to organs: The Physiome
Project." *Nature Reviews*, vol. 4, March 2003, pp. 237-243.

Protein Post-translational Modification *Signal Transduction*

Image removed due to copyright considerations.

Protein Post-translational Modification *Glycoprotein*



Scale and components

Image removed due to copyright considerations.

Example I



Image removed due to copyright considerations.



Image removed due to copyright considerations.

Retina and fine structure

Image removed due to copyright considerations

Please see:

<http://www.arts.uwaterloo.ca/~bfleming/psych261/image19.gif>

Circulatory system

- Unicellular - multicellular transition
- Supply of oxygen and nutrients
- Major Constraints on growth: surface to volume ratio
- Area changes as $L^2 \propto (4\pi r^2)$ and volume as L^3 ($\frac{4}{3}\pi r^3$)
- Diffusion from outside versus inside- solutions: flat, hollow tubes and invagination
- Circulation: problem of size: effective transport (large) diffusion small vessels, also, decrease size increase resistance

Hierarchical View

- Tissue level: endothelium/ECM/pericytes
- Cellular level: endothelial cells
- Cellular and molecular level: signal transduction and growth factors
- Molecular level

Angiogenesis

Matrix degradation

Release of transient molecules

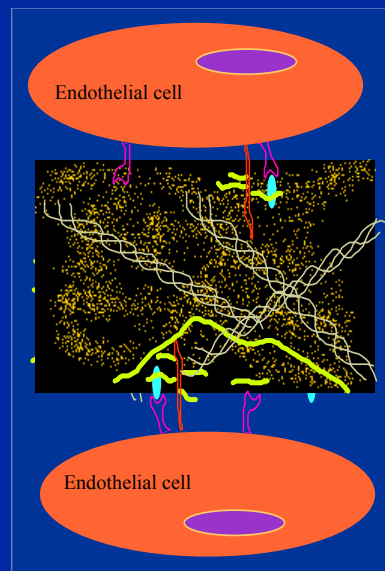
Cell migration

Promotion by angiogenic factors

Cell proliferation

Other matrix molecules

Capillary formation



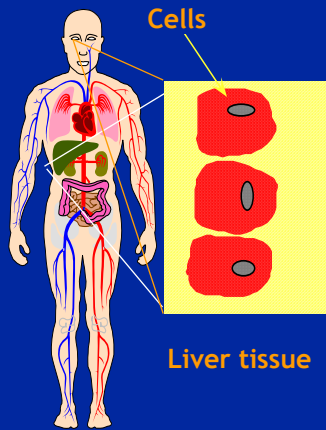
Single Cell

- Basic house keeping
 - energy,
 - multiplication
- Cell cycle
- Genotype - phenotype
- Signaling pathways

Division, Differentiation or Death

Image removed due to copyright considerations.

Extracellular Matrix



ECM critical path between cell and outside

Cell volume 3-5 % in tissue, rest is ECM

ECM	Water	(~ 70-80 %)
	Protein	(~ 20-10 %)
	Polysaccharide	(~ 8-10 %)

Scaffold for cells to form tissue

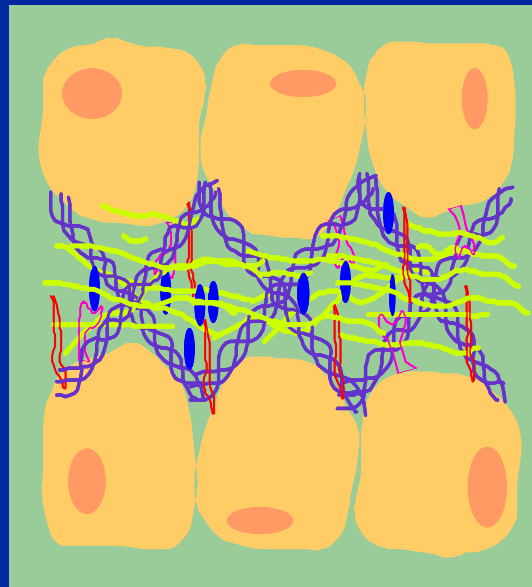
Sponge bringing water and food to cells

ECM

collagen

polysaccharide

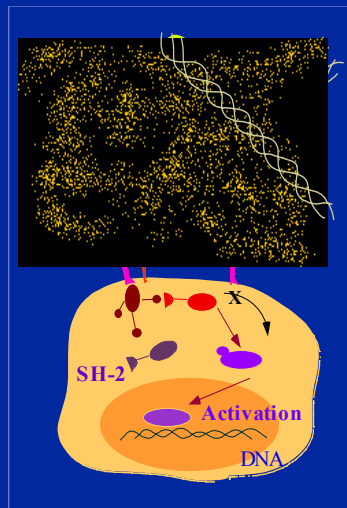
cytokines



Properties of ECM

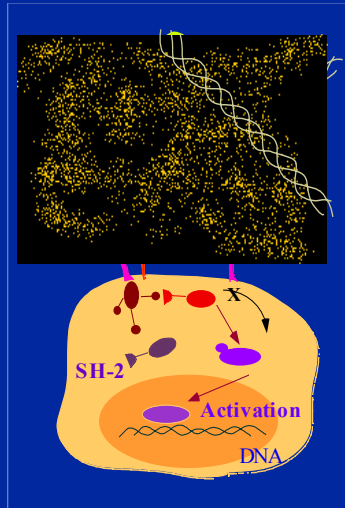
- ECM is bi-phasic $\begin{cases} \text{insoluble (mechanical)} \\ \text{soluble (chemical)} \end{cases}$
- ECM influences $\begin{cases} \text{hydration and ionic strength} \\ \text{permeability, diffusion and transport} \\ \text{mechanical strength} \end{cases}$
- Passive physico-chemical properties $\begin{cases} \text{binding (enthalpic)} \\ \text{excluded volume (entropic)} \end{cases}$
- ECM highly heterogeneous (varying ratios and chemical composition)

Cell- ECM Interactions



- Cells make the matrix - matrix tells cells what to do
- Cells can rapidly change matrix components
- Matrix is the signature of cellular phenotype or states
- Direct link between ECM-Cell surface- Nucleus
- Generation of signal versus signal processing
- Stored, latent and activation
- Signal amplification

Signal Transduction



Extracellular
signal sensor



Protein
phosphorylation



transcriptional
activator

- Signal amplification and regulation
- Transmembrane G protein
- Tyrosine or Ser/Thr kinases
- many second messengers
- Transcriptional regulation

Cell-ECM Interactions

Image removed due to copyright considerations.

- Integrin clustering
- multiple pathways

Coupled-signaling

Image removed due to
copyright considerations.

Important Principles

- Signal processing rather than signal generation
- Information flow between cells and the ECM is both dynamic and reciprocal
- Physical connections between ECM - cell surface - cytoskeleton-nucleus occur along a structural continuum
- Architectural scaffold upon which biochemical pathways overlaid
- ECM context, accessory factors, and the milieu impinge a template

Angiogenesis

Matrix degradation

Release of transient molecules

Cell migration

Promotion by angiogenic factors

Cell proliferation

Other matrix molecules

Capillary formation

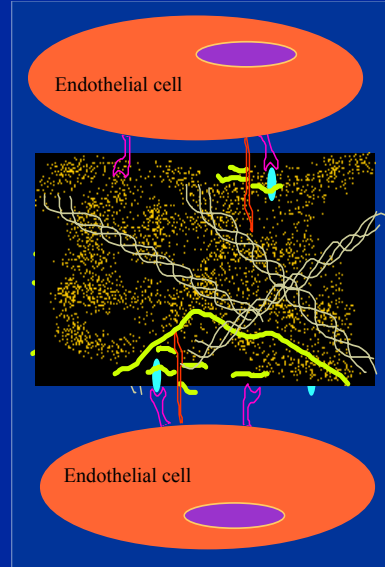


Image removed due to copyright considerations.

Example II

Cellular - Molecular II

Image removed due to copyright considerations

Please see:

Figure 2 in Hanahan D, Weinberg RA.
"The hallmarks of cancer." *Cell*. 2000 Jan 7;100(1):57-70.

Image removed due to copyright considerations

Please see:

Figure 1 in H. Jeong, S. P. Mason, A.-L. Barabási,
Z. N. Oltvai. "Lethality and centrality in protein networks."
Nature 411, 41 - 42 (03 May 2001).

Molecular/Cellular System as a "Circuit"

Image removed due to copyright considerations.

Map of Boston

Image removed due to copyright considerations.

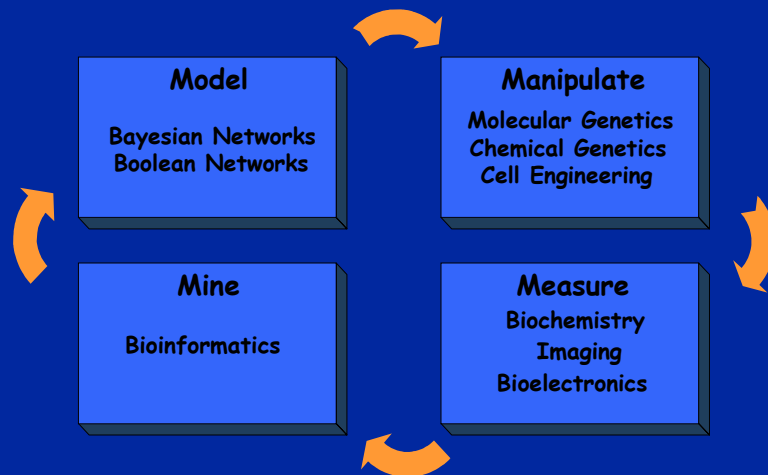
Map of Boston with all hotels

Image removed due to copyright considerations.

Systems Biology

Large 'Glue' Programs

Systems Biology



New Research Models for Post Genomics Science,
- the Glue Grants

- **Alliance for Cellular Signaling (AfCS):** To understand as completely as possible the relationships between sets of inputs and outputs in signaling cells that vary both temporally and spatially, *i.e.* how cells interpret signals in a context-dependent manner
- **Cell Migration Consortium:** To accelerate progress in cell migration-related research by fostering interdisciplinary research activities and producing novel reagents and information
- **Consortium for Functional Glycomics:** Define the paradigms by which carbohydrate binding proteins function in cellular communication
- **Inflammation and Host Response Consortium:** It is designed to acquire new scientific knowledge about the biological basis for different outcomes in injured patients.

Consortium for Functional Glycomics

Image removed due to copyright considerations.

Highlights of CFG

- **Data Acquisition Interface**
 - Core D: **251 Synthetic Glycan Structures** have been deposited
 - Core E: **20 Experiments and 260 Samples** deposited
 - Core F: **Information on all 24 mouse strains** in web site have been uploaded in database
 - Core G: Database of over **5000 mice** have been transferred to Core B and is being updated on monthly basis; **73 Experiments from 4 SubCores, for 7 Strains** deposited
- **Data Dissemination Interface for Consortium Database**
 - **List, View, Search and Download** features implemented for all Core data
- **GBP and Glycoenzyme Molecule Page Interface**
 - **Prototype Interfaces for 160 GBPs** have been implemented
- **Glycan Structures Database and Interfaces**
 - **Created seed database of 1751 glycan structures** (1500[Glycominds] + 251 from Core D and Glycan Array)

Molecule Page Interface

Home - Molecule Pages - Glycan Binding Proteins - Galectin-3 (human)

General	Resources	References	Genomes	Proteomes	Glycomes	Biologys
Galectin-3 (human)						
CFG ID	cbo_num_galact_00086					
CBP Name	Galectin-3					
Category	Galectin Family					
Other names	IMAC-2 antigen, CBP-35, mL34, L-29, N-31, epsilon BP, IgE-binding protein					
Species	Human					
Summary	<p>Galectin-3 contains a carboxyl-terminal lectin domain and an amino-terminal non-lectin part consisting primarily of short tandem repeats. It is widely distributed in tissues and found in epithelial cells, fibroblasts, dendritic cells, and inflammatory cells. In many cell types studied, galectin-3 is present diffusely in the cytoplasm, but is also localized to the nucleus and subcellular structures, such as mitochondria, phagosomes and exosomes, under specific conditions. It is secreted by various cell types, including monocytes, macrophages, and epithelial cells, and the extracellular protein can bind to a large number of different glycoconjugates on the cell surfaces and extracellular matrices.</p> <p>Galectin-3 can form dimers through intermolecular interactions that involve the N-terminal domain and can function bivalently. It thus has the potential to cross-link cell surface glycoproteins of various cells, causing cell activation (such as mediator release and superoxide production). It is also suited for mediating cell-cell and cell-extracellular matrix adhesion (including homotypic cell aggregation by serving as a bridge to bind cells together or cells to extracellular matrix proteins). Moreover, it can induce migration of a number of different cell types, including monocytes, macrophages, and endothelial cells, possibly through binding to and activating a G-protein-coupled receptor. Galectin-3 is present on the cell surface. Cell surface galectin-3 on T cells can form multivalent complexes with ligands on TCR and thereby restrains the lateral mobility of TCR complexes and suppress TCR-mediated signal transduction.</p> <p>Galectin-3 is also abundantly present inside the cells and has been shown to play important roles in some biological responses through its intracellular actions. It has been identified as a regulator of the cell cycle, apoptosis, and angiogenesis. The mechanisms underlying these functions have not been elucidated, but they probably involve the</p>					

Automated Acquisition

Data from Public databases, links to Public resources

Data from Cores

Links to Resource and Data IDs for viewing Consortium resources

PI entry

Filling out fields as experts on the molecule

Integration of data from different components

Image removed due to copyright considerations.