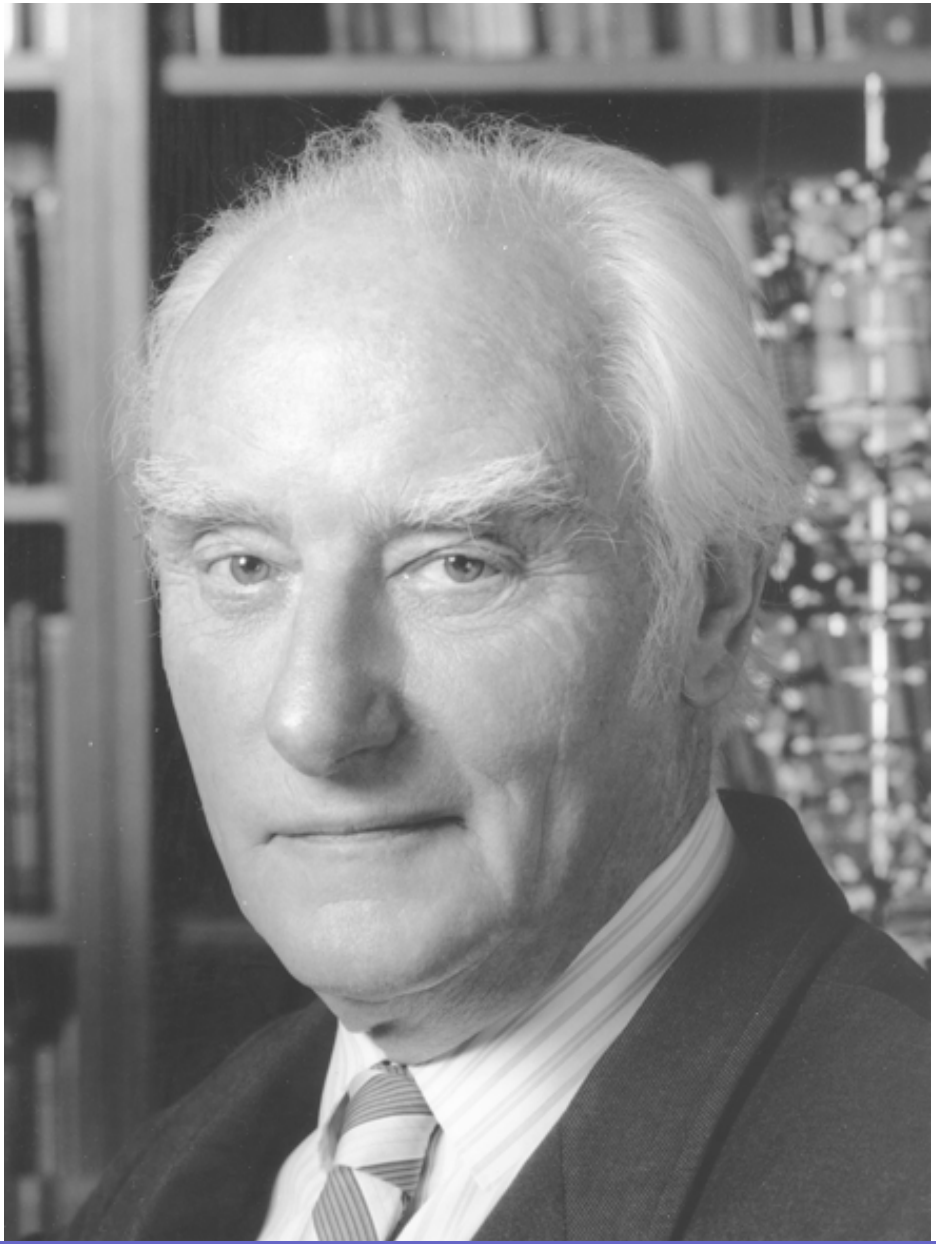
CS 6104: Systems Biology and Drug Discovery

T. M. Murali

August 26, 2004



51 Years Ago

equipment, and to Dr. G. E. R. Deacon and the captain and officers of R.R.S. *Discovery II* for their part in making the observations.

[1] Young, F. B., Gerrard, H., and Jevons, W., *Phil. Mag.*, **40**, 149 (1920).
[2] Longuet-Higgins, M. S., *Mon. Not. Roy. Astro. Soc., Geophys. Supp.*, **5**, 285 (1949).
[3] Von Arx, W. S., Woods Hole Papers in Phys. Oceanog. Meteor., **11** (3) (1956).
[4] Ekman, V. W., *Arkiv. Mat. Astron. Fysik. (Stockholm)*, **2** (11) (1905).

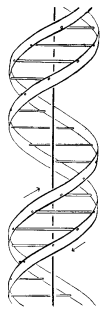
MOLECULAR STRUCTURE OF NUCLEIC ACIDS

A Structure for Deoxyribose Nucleic Acid

WE wish to suggest a structure for the salt of deoxyribose nucleic acid (D.N.A.). This structure has novel features which are of considerable biological interest.

A structure for nucleic acid has already been proposed by Pauling and Corey[1]. They kindly made their manuscript available to us in advance of publication. Their model consists of three intertwined chains, with the phosphates near the fibre axis, and the bases on the outside. In our opinion, this structure is unsatisfactory for two reasons: (1) We believe that the material which gives the X-ray diagrams is the salt, not the free acid. Without the acidic hydrogen atoms it is not clear what forces would hold the structure together, especially as the negatively charged phosphates near the axis will repel each other. (2) Some of the van der Waals distances appear to be too small.

Another three-chain structure has also been suggested by Fraser (in the press). In his model the phosphates are on the outside and the bases on the inside, linked together by hydrogen bonds. This structure as described is rather ill-defined, and for this reason we shall not comment on it.



This figure is purely diagrammatic. The two ribbons symbolize the two phosphate—sugar chains, and the horizontal rods the pairs of bases holding the chains together. The vertical line marks the fibre axis

We wish to put forward a radically different structure for the salt of deoxyribose nucleic acid. This structure has two helical chains each coiled round the same axis (see diagram). We have made the usual chemical assumptions, namely, that each chain consists of phosphate diester groups joining β-D-deoxyribofuranose residues with 3′,5′ linkages. The two chains (but not their bases) are related by a dyad perpendicular to the fibre axis. Both chains follow right-handed helices, but owing to the dyad the sequences of the atoms in the two chains run in opposite directions. Each chain loosely resembles Furberg's[2] model No. 1; that is, the bases are on the inside of the helix and the phosphates on the outside. The configuration of the sugar and the atoms near it is close to Furberg's 'standard configuration', the sugar being roughly perpendicular to the attached base. There is a residue on each chain every 3·4 A. in the *z*-direction. We have assumed an angle of 36° between adjacent residues in the same chain, so that the structure repeats after 10 residues on each chain, that is, after 34 A. The distance of a phosphorus atom from the fibre axis is 10 A. As the phosphates are on the outside, cations have easy access to them.

The structure is an open one, and its water content is rather high. At lower water contents we would expect the bases to tilt so that the structure could become more compact.

The novel feature of the structure is the manner in which the two chains are held together by the purine and pyrimidine bases. The planes of the bases are perpendicular to the fibre axis. They are joined together in pairs, a single base from one chain being hydrogen-bonded to a single base from the other chain, so that the two lie side by side with identical *z*-co-ordinates. One of the pair must be a purine and the other a pyrimidine for bonding to occur. The hydrogen bonds are made as follows: purine position 1 to pyrimidine position 1; purine position 6 to pyrimidine position 6.

If it is assumed that the bases only occur in the structure in the most plausible tautomeric forms (that is, with the keto rather than the enol configurations) it is found that only specific pairs of bases can bond together. These pairs are: adenine (purine) with thymine (pyrimidine), and guanine (purine) with cytosine (pyrimidine).

In other words, if an adenine forms one member of a pair, on either chain, then on these assumptions the other member must be thymine; similarly for guanine and cytosine. The sequence of bases on a single chain does not appear to be restricted in any way. However, if only specific pairs of bases can be formed, it follows that if the sequence of bases on one chain is given, then the sequence on the other chain is automatically determined.

It has been found experimentally[3,4] that the ratio of the amounts of adenine to thymine, and the ratio of guanine to cytosine, are always very close to unity for deoxyribose nucleic acid.

It is probably impossible to build this structure with a ribose sugar in place of the deoxyribose, as the extra oxygen atom would make too close a van der Waals contact.

The previously published X-ray data[5,6] on deoxyribose nucleic acid are insufficient for a rigorous test of our structure. So far as we can tell, it is roughly compatible with the experimental data, but it must be regarded as unproved until it has been checked against more exact results. Some of these are given in the following communications. We were not aware of the details of the results presented there when we devised our structure, which rests mainly though not entirely on published experimental data and stereochemical arguments.

It has not escaped our notice that the specific pairing we have postulated immediately suggests a possible copying mechanism for the genetic material.

Full details of the structure, including the conditions assumed in building it, together with a set of co-ordinates for the atoms, will be published elsewhere.

We are much indebted to Dr. Jerry Donohue for constant advice and criticism, especially on interatomic distances. We have also been stimulated by a knowledge of the general nature of the unpublished experimental results and ideas of Dr. M. H. F. Wilkins, Dr. R. E. Franklin and their co-workers at

King's College, London. One of us (J. D. W.) has been aided by a fellowship from the National Foundation for Infantile Paralysis.

J. D. Watson
F. H. C. Crick
Medical Research Council Unit for the Study of the Molecular Structure of Biological Systems,
Cavendish Laboratory, Cambridge.
April 2.

[1] Pauling, L., and Corey, R. B., *Nature*, **171**, 346 (1953); *Proc. U.S. Nat. Acad. Sci.*, **39**, 84 (1953).
[2] Furberg, S., *Acta Chem. Scand.*, **6**, 634 (1952).
[3] Chargaff, E., for references see Zamenhof, S., Brawerman, G., and Chargaff, E., *Biochim. et Biophys. Acta*, **9**, 402 (1952).
[4] Wyatt, G. R., *J. Gen. Physiol.*, **36**, 201 (1952).
[5] Astbury, W. T., Symp. Soc. Exp. Biol. 1, Nucleic Acid, 66 (Camb. Univ. Press, 1947).
[6] Wilkins, M. H. F., and Randall, J. T., *Biochim. et Biophys. Acta*, **10**, 192 (1953).

Molecular Structure of Deoxypentose Nucleic Acids

WHILE the biological properties of deoxypentose nucleic acid suggest a molecular structure containing great complexity, X-ray diffraction studies described here (cf. Astbury[1]) show the basic molecular configuration has great simplicity. The purpose of this communication is to describe, in a preliminary way, some of the experimental evidence for the polynucleotide chain configuration being helical, and existing in this form when in the natural state. A fuller account of the work will be published shortly.

The structure of deoxypentose nucleic acid is the same in all species (although the nitrogen base ratios alter considerably) in nucleoprotein, extracted or in cells, and in purified nucleate. The same linear group of polynucleotide chains may pack together parallel in different ways to give crystalline[1–3], semi-crystalline or paracrystalline material. In all cases the X-ray diffraction photograph consists of two regions, one determined largely by the regular spacing of nucleotides along the chain, and the other by the longer spacings of the chain configuration. The sequence of different nitrogen bases along the chain is not made visible.

Oriented paracrystalline deoxypentose nucleic acid ('structure *B*' in the following communication by Franklin and Gosling) gives a fibre diagram as shown in Fig. 1 (cf. ref. 4). Astbury suggested that the strong 3·4-A. reflexion corresponded to the internucleotide repeat along the fibre axis. The ~ 34 A. layer lines, however, are not due to a repeat of a polynucleotide composition, but to the chain configuration repeat, which causes strong diffraction as the nucleotide chains have higher density than the interstitial water. The absence of reflexions on or near the meridian immediately suggests a helical structure with axis parallel to fibre length.

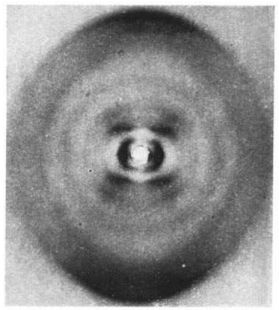


Fig. 1. Fibre diagram of deoxypentose nucleic acid from *B. coli*. Fibre axis vertical

Diffraction by Helices

It may be shown[5] (also Stokes, unpublished) that the intensity distribution in the diffraction pattern of a series of points equally spaced along a helix is given by the squares of Bessel functions. A uniform continuous helix gives a series of layer lines of spacing corresponding to the helix pitch, the intensity distribution along the *n*th layer line being proportional to the square of J_n, the *n*th order Bessel function. A straight line may be drawn approximately through the innermost maxima of each Bessel function and the origin. The angle this line makes with the equator is roughly equal to the angle between an element of the helix and the helix axis. If a unit repeats *n* times along the helix there will be a meridional reflexion (J_n^2) on the *n*th layer line. The helical configuration produces side-bands on this fundamental frequency, the effect[5] being to reproduce the intensity distribution about the origin around the new origin, on the *n*th layer line, corresponding to *C* in Fig. 2.

We will now briefly analyse in physical terms some of the effects of the shape and size of the repeat unit or nucleotide on the diffraction pattern. First, if the nucleotide consists of a unit having circular symmetry about an axis parallel to the helix axis, the whole diffraction pattern is modified by the form factor of the nucleotide. Second, if the nucleotide consists of a series of points on a radius at right-angles to the helix axis, the phases of radiation scattered by the helices of different diameter passing through each point are the same. Summation of the corresponding Bessel functions gives reinforcement for the inner-

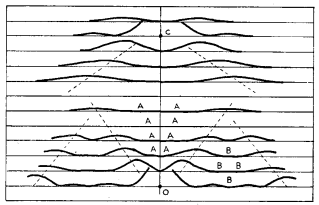
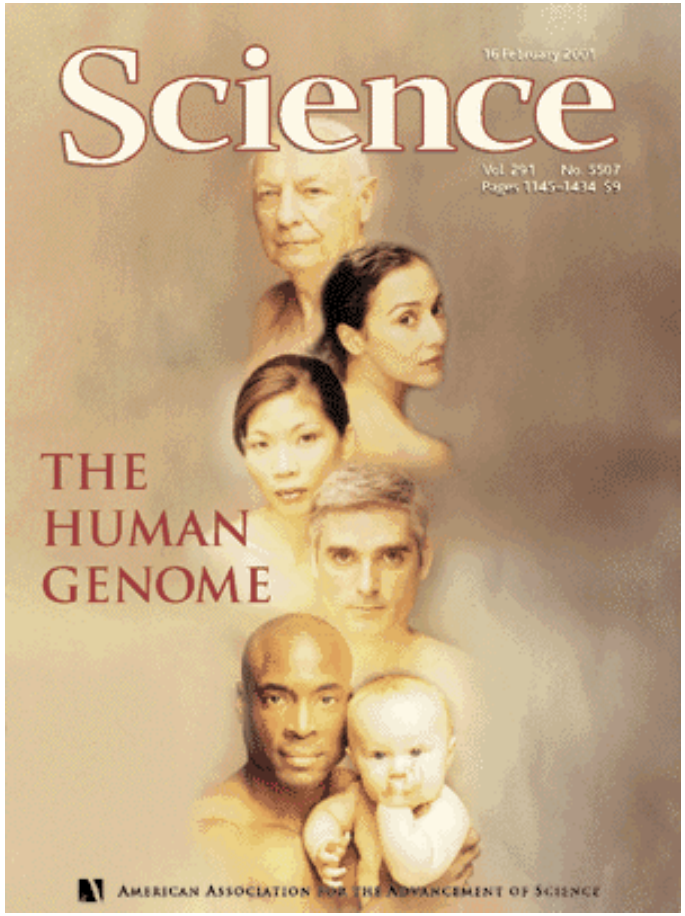


Fig. 2. Diffraction pattern of system of helices corresponding to structure of deoxypentose nucleic acid. The squares of Bessel functions are plotted about O on the equator and on the first, second, third and fifth layer lines for half of the nucleotide mass at 20 A. diameter and remainder distributed along a radius, the mass at a given radius being proportional to the radius. About *C* on the tenth layer line similar functions are plotted for an outer diameter of 12 A.

The Human Genome Project



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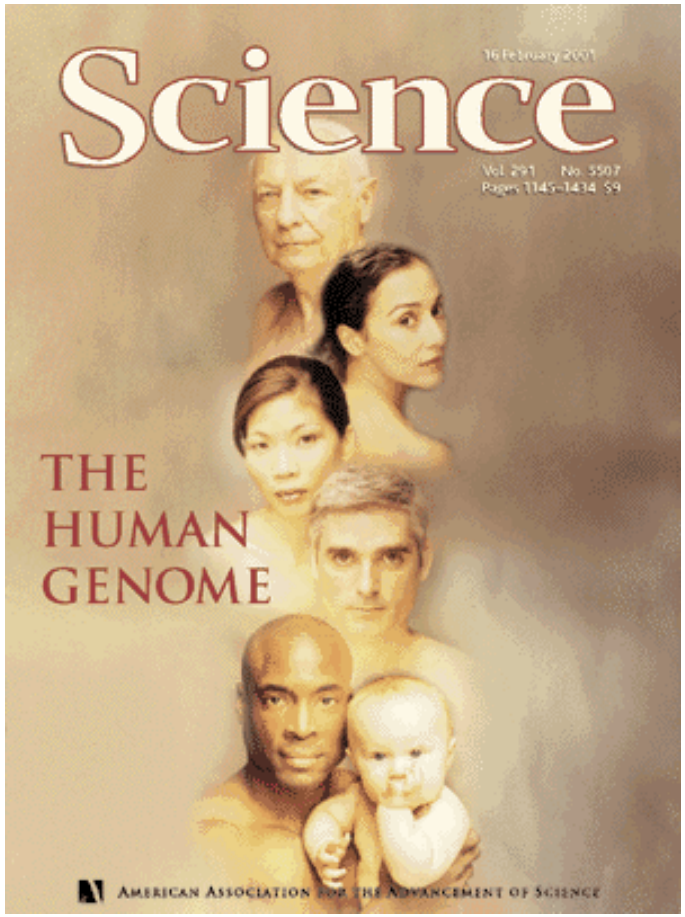
Before: human genome has about 100,000 genes.



The Human Genome Project

Before: human genome has about 100,000 genes.

After: human genome has about 30,000 genes.

Shock and Dismay

- The New York Times: **Genome Analysis Shows Humans Survive on Low Number of Genes** The two teams report that there are far fewer human genes than thought—probably a mere 30,000 or so—only a third more than those found in the roundworm. . . . The impact on human pride is another matter.

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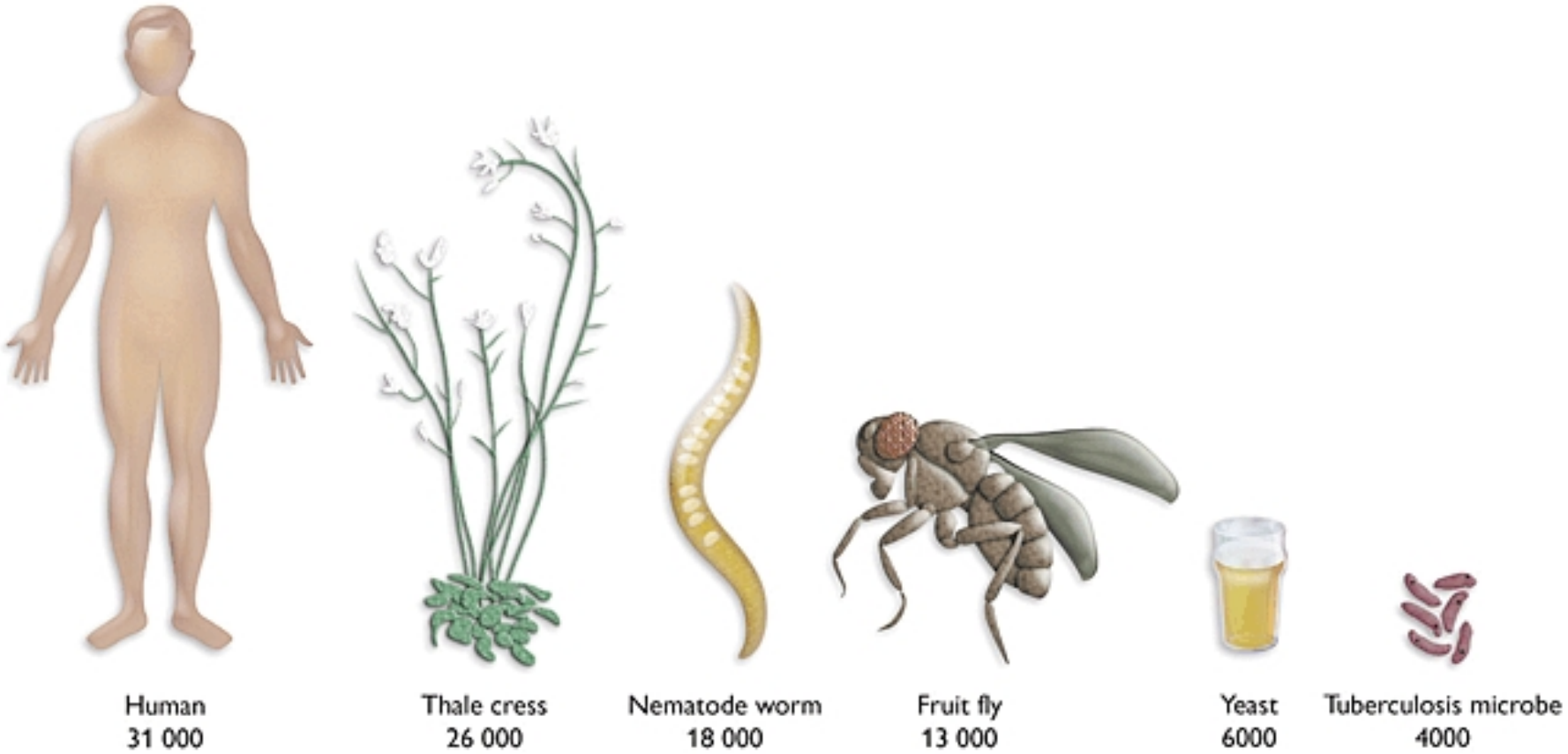
- The New York Times (Aug 24, 2001): **Human Genome Now Appears More Complicated After All** After a humiliating deflation this February, human dignity is on the recovery path, at least as measured by the number of genes in the human genome.

Relative Genome Sizes



Chimps vs. Humans

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Chimp and human genome are only about 1.2% different!

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- We need to understand how genes, proteins, and other molecules interact with other in different cell states and under different external conditions.
- Study only of individual elements is unlikely to reveal higher-order principles.

Enter Systems Biology

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- What are the structures and modules that make up cellular networks?
- How do these modules interact with each other over time and in different situations?
- How can we interrogate the cell and iteratively refine our models of the cell?

Characteristics of Systems Biology

- Modular cell biology (rather than molecular).
- Discovery-driven *and* hypothesis-driven.
- Driven by high-throughput and accurate biological measurements.
- Uses and needs sophisticated computational, mathematical, and statistical ideas.
- Requires close collaboration between biologists and quantitative scientists.

Promises of Human Genome Project

- Identify numerous novel targets for drug therapy.
- Determine the physiological functions of many proteins.
- Enhance knowledge of the genetic basis of various complex diseases.
- Knowledge of all human genes and haplotypes will lead to a better understanding of individual drug responses.

Challenges in Achieving these Promises

- What are the pathways and genetic programmes that cause diseases?
- What are the functions of human genes and how are they involved in disease processes?
- What are the effects of administering a drug "downstream" of the drug target?
- What genetic and environmental factors cause differences in an individual's susceptibility to a disease or response to a drug?

Systems Biology and Drug Discovery

By assembling a comprehensive understanding of cellular networks and pathways, systems biology helps in:

1. Target identification: drug developed to target a specific molecule or interaction in a pathway.
2. Predicting the molecular mechanism-of-action of a drug (with known therapeutic effects).
3. Predicting drug toxicity.

Course Structure

Discuss state-of-the-art research papers.

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- Class participation
- Final project

Grading

- Presentation: 20%
- Class participation: 30%
- Final project: 50%
- Homeworks: 0–10%.

Student Groups

- Each group has 2-3 members.
- You can form your own groups.
- Try to form groups with students with different backgrounds.

Group Presentations

- Number of papers: the group and I mutually decide a set of 2–3 papers. You can either present one paper in detail (and summarise others) or give equal importance to all papers.
- Time: present for 1.5–2 hours and expect 0.5–1 hours of questions and discussion. Be prepared for some discussions to take over your presentation.
- Please give me PDF/PostScript/LaTeX copies of slides (no Microsoft PowerPoint).

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- Class Participation is very important.

Suggestions on Reading and Presenting Papers

- Be sceptical/critical: even papers in Nature, Science, or PNAS have errors or invalid thinking.

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- Algorithmic/computational papers:
  - Are the biological assumptions valid?
  - Is the algorithm good and computational efficient? Can you improve the technique?
  - Can you mathematically describe the output of the algorithm?
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- Read supplementary information. Often has details about the assumptions, the techniques, and the results.

Final Software Project

- Software + analysis project.
- We will define a project inspired by the papers you present.
- I will discuss list of projects in the next class.
- You can propose a project to me.
- I will meet each group once a week to monitor progress.
- You can use Perl, C, C++, Java, Python, R ...

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- The software has to run on Linux!
- If a life science student is part of a software project, biological analysis of the results must play a major role.

Course Times

- Is the Thursday 5–7:45pm time slot fine with everybody?
- Office hours: 10am-12pm Wednesdays and by appointment.

Sources of Information

- **There is no textbook for the course.**
- Useful/related books:
  - *Computational Modeling of Genetic and Biochemical Networks*, James M. Bower and Hamid Bolouri, MIT Press
  - *Microarrys for an Integrative Genomics*, Isaac S. Kohane, Atul J. Butte, and Alvin Kho, MIT Press.
- Conferences: ICSB, RECOMB, ISMB, PSB, KDD, machine learning conferences, discrete algorithms conferences.
- Journals (CS-oriented): Bioinformatics, Journal of Computational Biology, BMC Bioinformatics, TCBB, TKDE.
- Journals (biology-oriented) Nature, Science, Nature Reviews Drug Discovery, Nature Biotechnology, Nature Reviews Cancer, Drug Discovery Today, PNAS, NAR, Genome Biology, Genome Research.
- Discussions on the listserv: `CS6104_91493@listserv.vt.edu`

Topics

- Disease classification using gene expression data.
  - Computational and statistical techniques.
  - Application to various diseases, primarily cancer.
- Prediction of disease outcome.
- Personalised medicine, genome variation and disease.
- Whole-genome functional annotation of genes.
- Chemical genomics and pharmacogenomics.
- RNA interference to probe gene function.
- Comparative systems biology.
- Proteomics and disease.
- Literature mining (gene-disease association databases).

Other Possible Topics

- Cancer biology.
- Malaria (possible invited lecture).
- Data integration techniques.
- Designing novel proteins.

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- Literature, Computation, Databases
  - Transcriptional regulators (TRANSFAC)
  - Protein-protein interactions (DIP, GRID, Predictome, MIPS)
  - Metabolic networks (KEGG, EcoCyC, BioCarta, GenMAPP)
  - Functional annotations (GO, MIPS, species-specific databases)

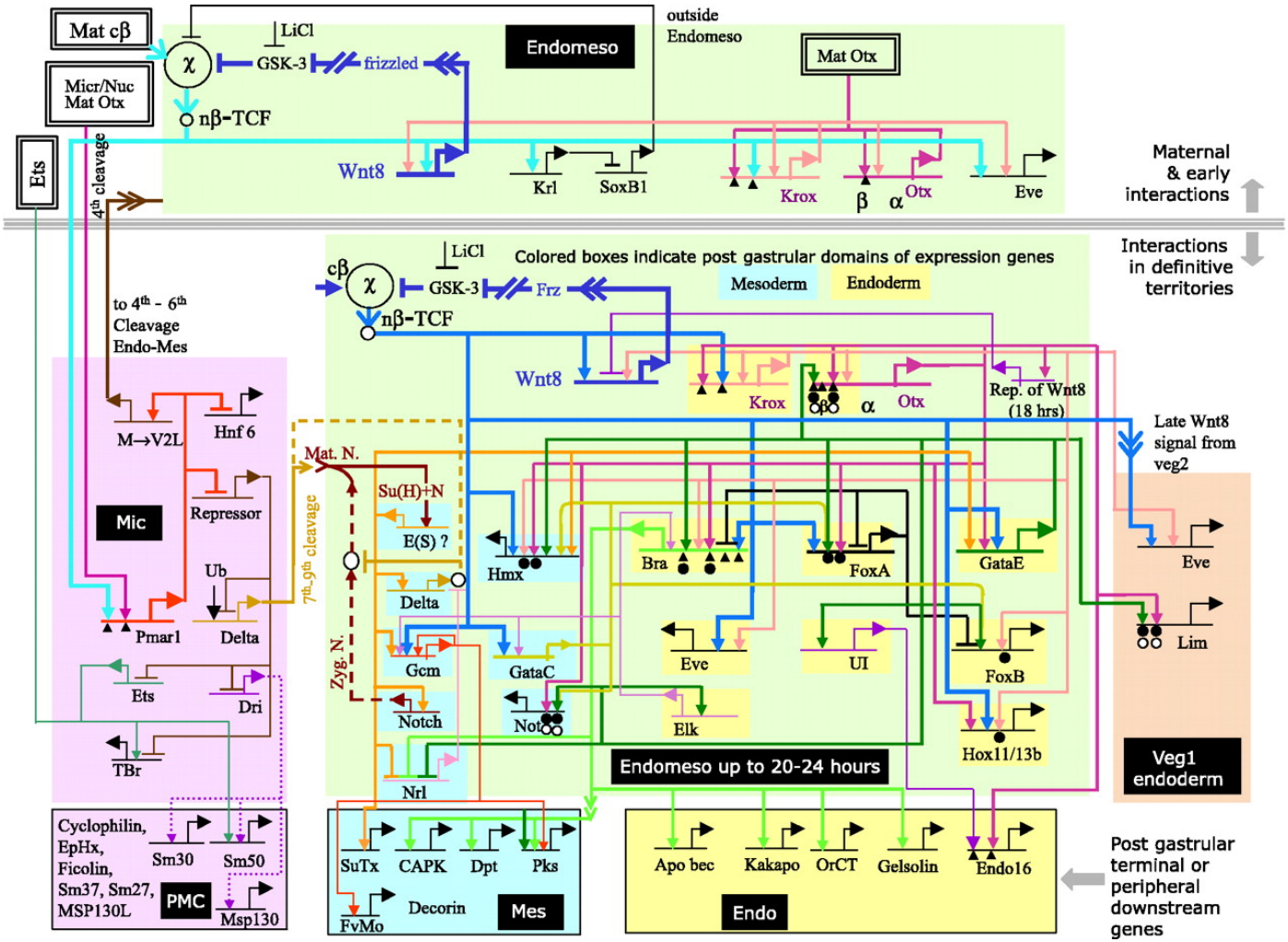
Computational Systems Biology (Fall 2003)

- Fundamental computational ideas and techniques used in systems biology.
- Biotechnological breakthroughs that make systems biology possible.
- Studied research that improves our basic understanding of biology.

CSB 2003: Topics in Analysis of Gene Expression Data

- Simple DNA microarray clustering
- Biclustering of DNA microarray data

CSB 2003: Transcriptional Regulatory Networks



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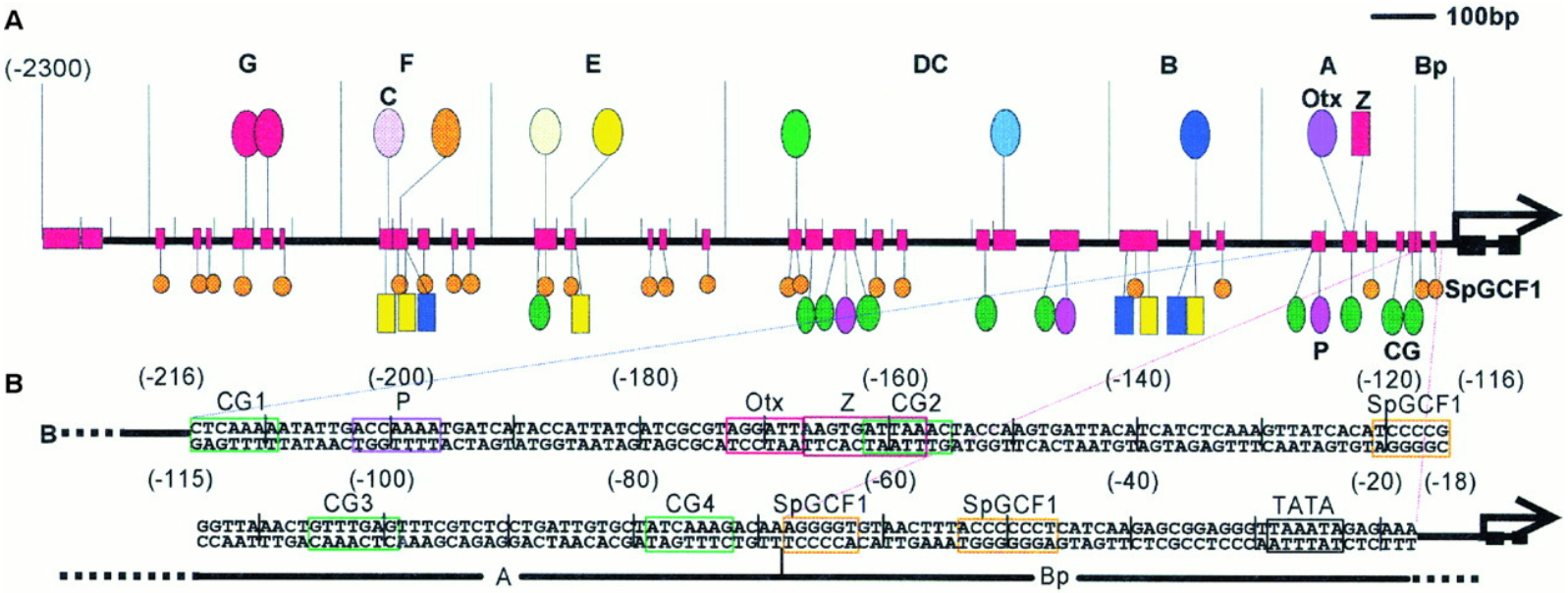


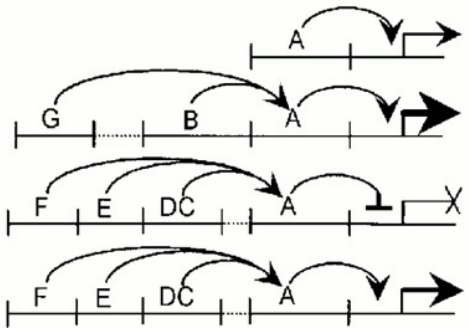
C Module A functions:

Vegetal plate expression in early development:

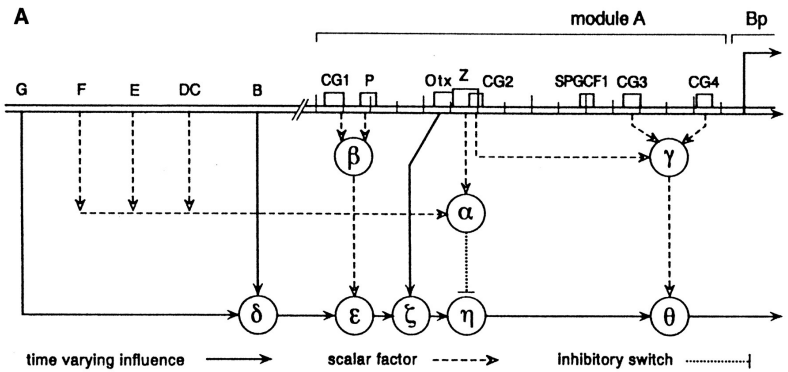
Synergism with modules B and G enhancing endoderm expression in later development:

Repression in ectoderm (modules E and F) and skeletogenic mesenchyme (module DC):

Modules E, F and DC with LiCl treatment:



CSB 2003: Transcriptional Regulatory Networks



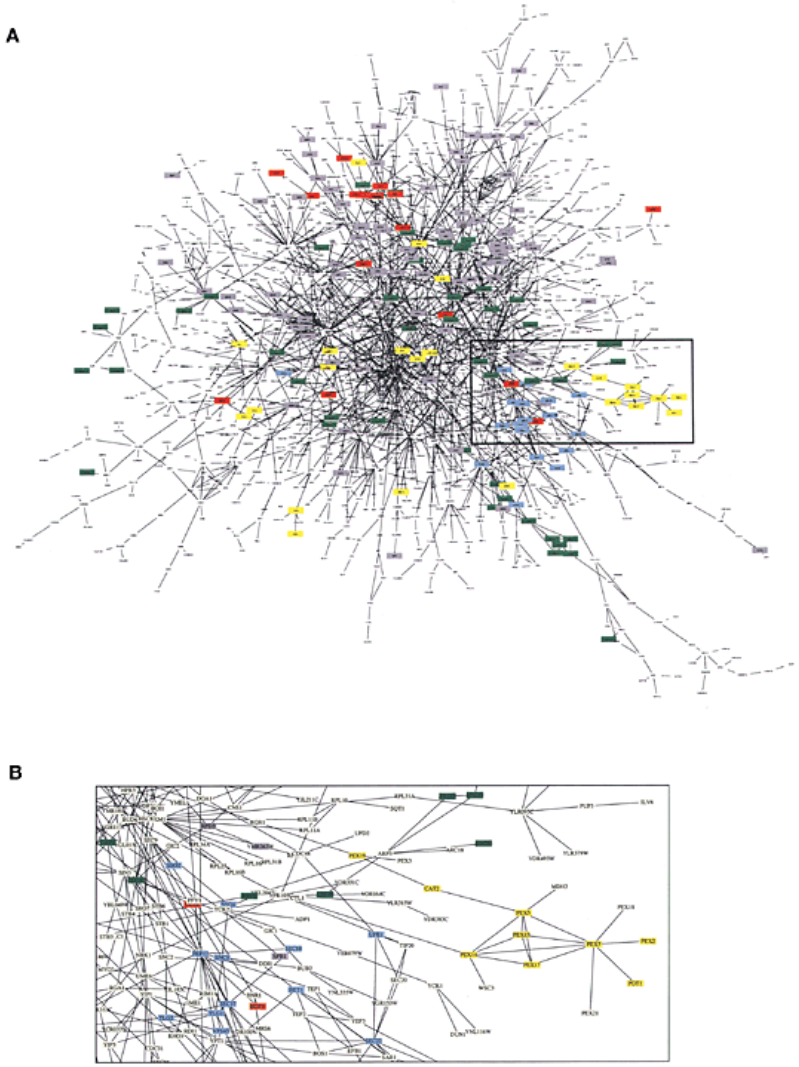
B

if (F = 1 or E = 1 or CD = 1) and (Z = 1)	Repression functions of modules F, E, and DC mediated by Z site
$\alpha = 1$	
else $\alpha = 0$	
if ($P = 1$ and $CG_1 = 1$)	Both P and CG_1 needed for synergistic link with module B
$\beta = 2$	
else $\beta = 0$	
if ($CG_2 = 1$ and $CG_3 = 1$ and $CG_4 = 1$)	Final step up of system output
$\gamma = 2$	
else $\gamma = 1$	
$\delta(t) = B(t) + G(t)$	Positive input from modules B and G
$\varepsilon(t) = \beta * \delta(t)$	Synergistic amplification of module B output by CG_1-P subsystem
if ($\varepsilon(t) = 0$)	Switch determining whether Otx site in module A, or upstream modules (i.e., mainly module B), will control level of activity
$\xi(t) = Otx(t)$	
else $\xi(t) = \varepsilon(t)$	
if ($\alpha = 1$)	Repression function inoperative in endoderm but blocks activity elsewhere
$\eta(t) = 0$	
else $\eta(t) = \xi(t)$	
$\Theta(t) = \gamma * \eta(t)$	Final output communicated to BTA

CSB 2003: Topics in Transcriptional Regulatory Networks

- Extracting them from DNA microarray data.
- Finding genes that are regulated together under specific conditions.
- Developmental regulatory networks.
- Modular organisation and network motifs.

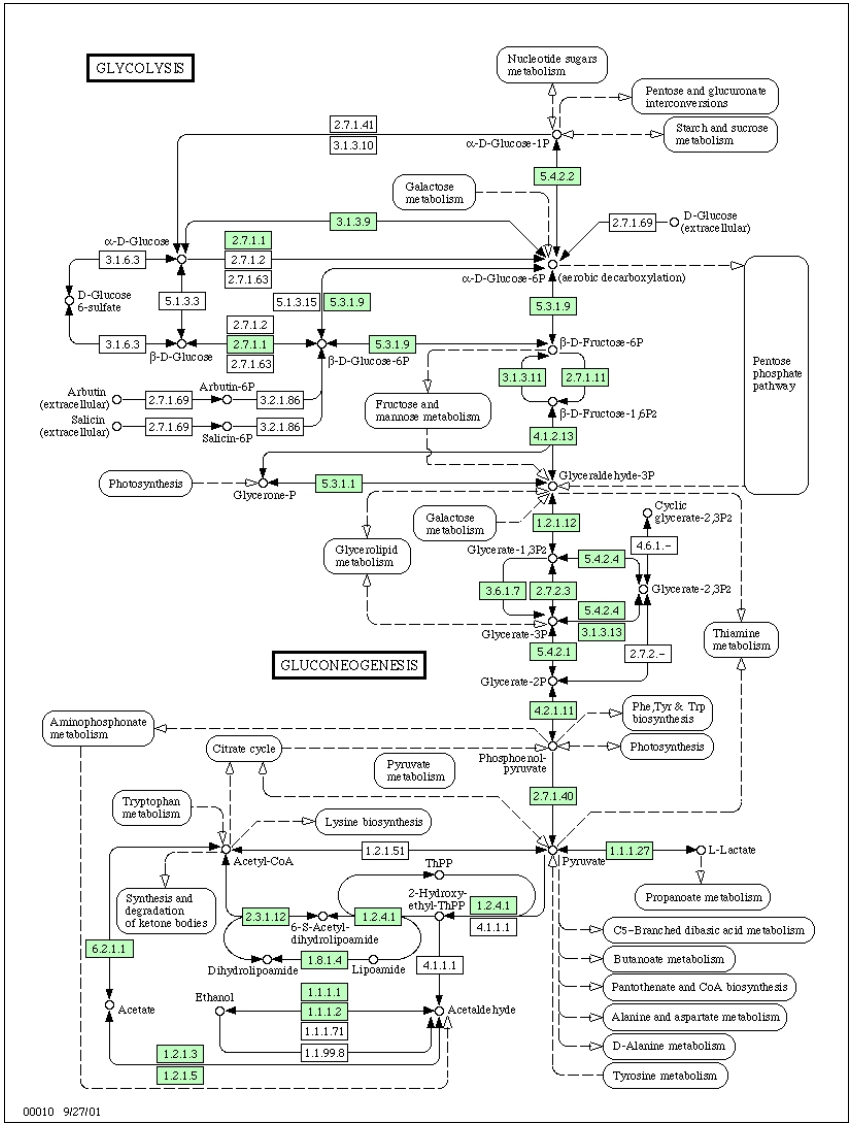
CSB 2003: Protein-Protein Interaction Networks



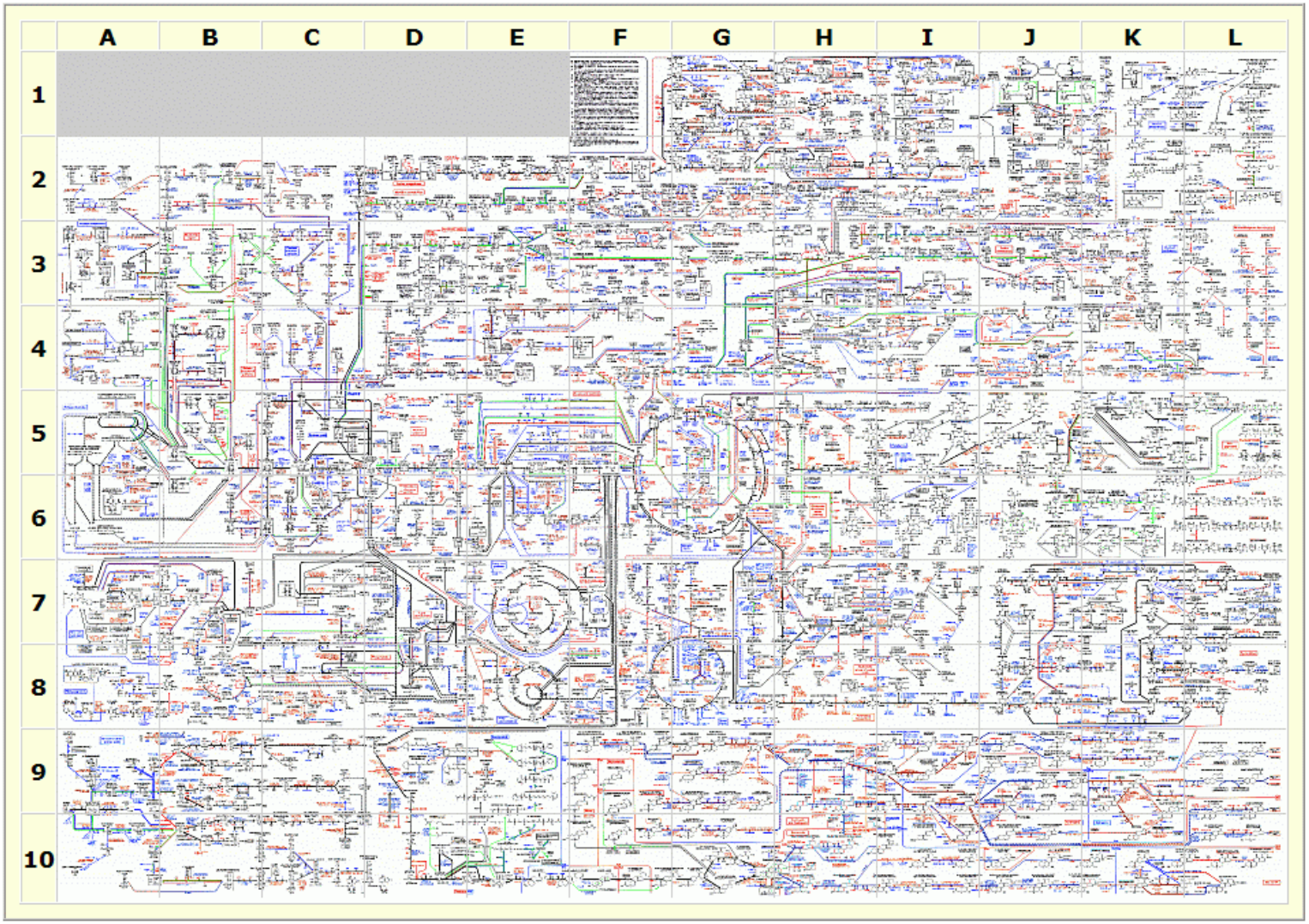
CSB 2003: Topics in PPI networks

- Experimental and computational techniques for determining protein-protein interactions.
- Assessing and improving their reliability.
- Functional annotation using PPI networks (by integrating different sources of evidence).

CSB 2003: Metabolic Networks



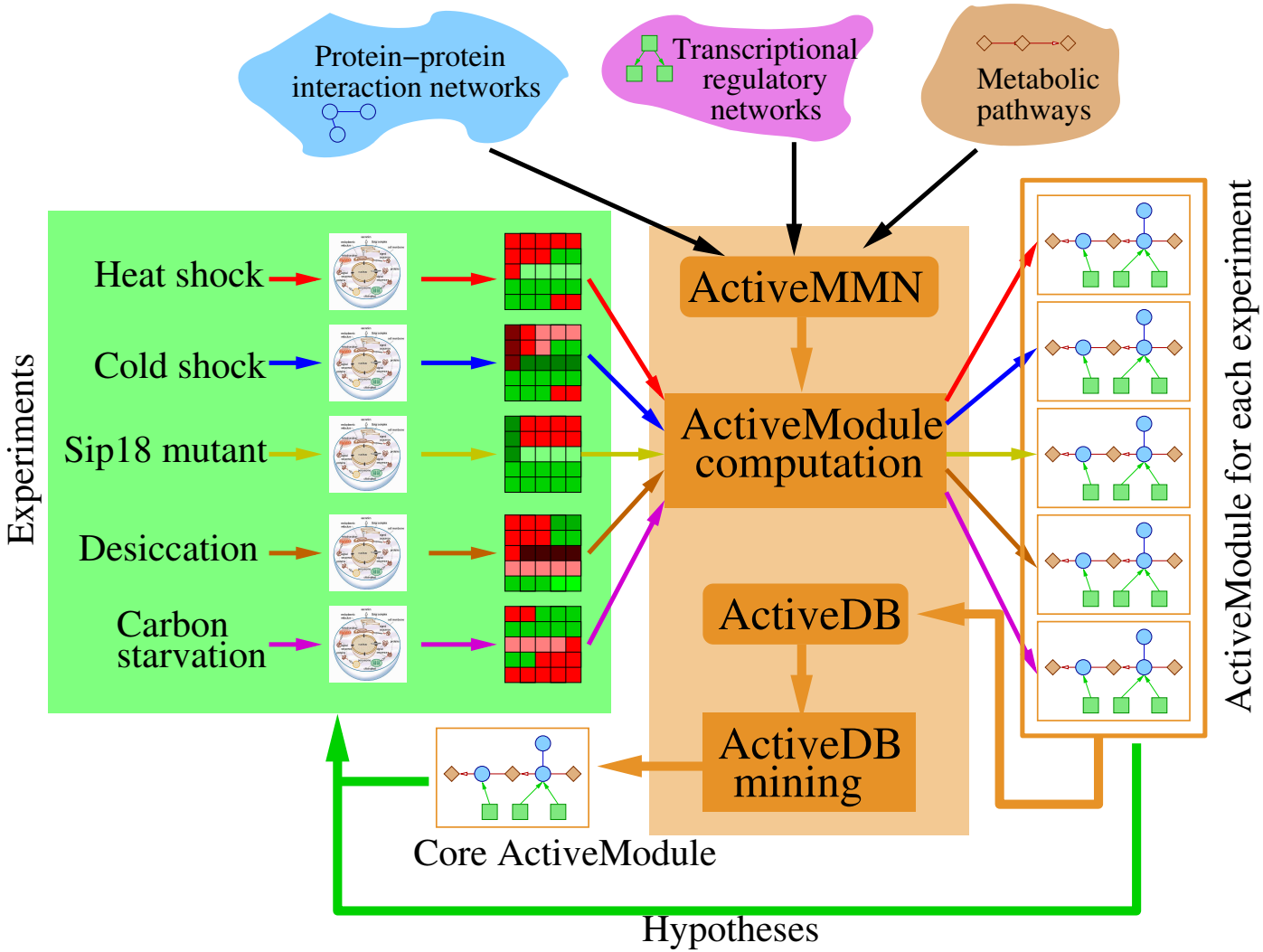
CSB 2003: Metabolic Networks



CSB 2003: Topics in Metabolic Networks

- High-level structural properties.
- Modelling and reconstruction.
- Modelling and simulation of cellular networks.

Example Project: ActiveNetworks



Example Project: ActiveNetworks