Computational Systems Biology: Biology X

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L#1:(September-13-2010)
Cancer and Signals

Outline

Cancer's a Funny Thing:
I wish I had the voice of Homer
To sing of rectal carcinoma,
This kills a lot more chaps, in fact,
Than were bumped off when Troy was sacked....

–JBS Haldane, *The Enchantress of Florence*, 2008.

Outline

1. Administrivia
2. Theme

Administrivia

- **Instructor:** Bud Mishra
- Room 1002, 715 Broadway
- email: mishra@nyu.edu
- phone: 212-998-3464
- Office Hours: Mondays 1:30 pm - 2:30 pm (and by appt)

Administrivia

- BIOLOGY X
- **Course Details:** G22.3033-002
  || Bioinformatics
- **Time and Place:** Monday, 5:00 PM - 6:50 PM EST
  || Room 1221, 719 Broadway
- **Number of Credits:** 3 credits
- **Course Work:** Software Project, Analyzing Genetics Data, Review Articles
- **Languages of Choice:** R (May be Python, Matlab, Mathematica — But no Perl please)

Some Ideas

- Signaling is a well-studied phenomenon both in evolutionary game theory and in cell biology.
- In game theory, signaling frameworks have been used to study the evolution of such fundamental phenomena as conventions and cooperation, while in biology, signal transduction has been extensively studied as a basic ingredient to multicellularity, enabling cells to communicate and coordinate.
- However, approaches that span both fields are scarce.

- In this course, we explore the idea of viewing multicellular organisms as signaling systems in the game-theoretic sense, attempting to unify these two perspectives on signaling.
- A multicellular organism corresponds to a population of cells in a cooperative state, with a working signaling system in place.
- We will discuss how the evolution of such a system may be modeled. Then, we will in particular be interested in the breakdown of cooperation, leading to an interpretation of cancer as a disease of multicellularity.
- The course will be as self-contained as possible and include introductions to evolutionary game theory and signaling systems, signal transduction in cell biology, and the biology of cancer.

Text Books

- **Required Textbook (1)**: *Signals: Evolution, Learning, and Information* || Brian Skyrms || Oxford University Press || 2010.
- **Required Textbook (2)**: *Biology of Cancer* || Robert A. Weinberg || Garland Science, 2006.
  - **Recommended textbook (1):** *Game Theory Evolving* || Herbert Gintis || Princeton University Press || 2000
  - **Recommended textbook (2):** *Computational Biology of Cancer* || Dominik Wodarz and Natalia L. Komarova || World Scientific Publishing Company || 2005
  - **Recommended textbook (3):** *Information Theory, Inference & Learning Algorithms* || David J. C. MacKay || Cambridge University Press || 2002

Outline

Cancer and Signals

- **Main Thesis**
- Cancer is a complex disease.
  1. *It is associated with the natural somatic* **evolution***.*
  2. *It has its origin in* **multicellularity***.*
  3. *It makes use of every* **mechanism in biology***.*

Areas we wish to touch on...

- *Bioinformatics to study Mechanisms in Biology*: Genomics, Transcriptomics (c- and ncRNA), Proteomics, Metabolomics and Signaling
- *Structure of Multicellularity*: Signaling and Signaling Games; Multicellularity, Information Theory and Rate Distortion Theory
- *Evolutionary Structure of Somatic Modifications*: Repeated Games, Signaling Games and Neologism

Let us think about these inter-connected questions from a single global perspective...

A Tentative Syllabus

I would like to focus this course on three basic questions...

1. **Biology** of **cancer**
2. **Signaling** game models of multicellular **biology**
3. **Information** theoretic utility functions in **signaling** games

Possible Sets of Lectures

- **Lecture 1:** Causes of Cancer
- **Lecture 2:** A Very Brief Introduction to Game Theory
- **Lecture 3:** Introduction to Biology
- **Lecture 4:** The Nature of Cancer
- **Lecture 5:** Growth Factors, Receptors and Cancer
- **Lecture 6:** Cytoplasmic Signaling Circuitry
- **Lecture 7:** Game Theory: Signaling Games

Possible Sets of Lectures (Contd.)

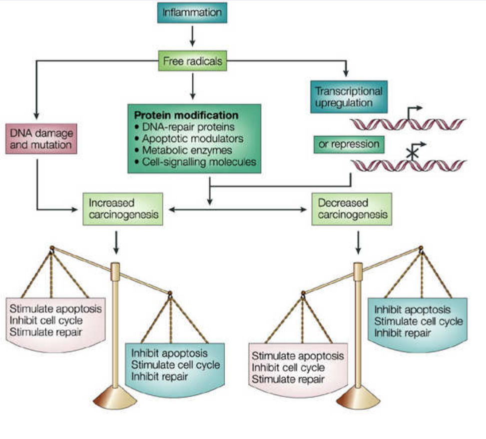
- **Lecture 8:** Repeated Games and Evolutionary Dynamics
- **Lecture 9:** Probability and Information Theory
- **Lecture 10:** Rate-Distortion Theory and Game Utility
- **Lecture 11:** Cancer Models: Genomics
- **Lecture 12:** Cancer Models: Signaling
- **Lecture 13:** Cancer Models: Genetics
- **Lecture 14:** Cancer Models: Therapeutics
- **Lecture 15:** The Future Challenges

Cancer

- **What "causes" cancer?**
  1. Cancer as a disease of the genome;
  2. Cancer as a somatic evolutionary process;
  3. Cancer as a price of symbiosis (mitochondrial);
  4. Cancer as a response to multi-cellularity;
  5. Cancer as a price of repair/regeneration (stem cells);
  6. Cancer as a consequence of energy consumption (Anaerobic Glycolysis); *Warburg Effect*.
  7. Cancer as a response to external stress; and
  8. Cancer as a response to the micro-environment (hyper- and hypo-methylation).

Processes involved in Cancer

- Coordination of processes in cancer progression
  1. Inflammation
  2. Autophagy and mitophagy
  3. Apoptosis
  4. Hypoxia
  5. Anaerobic glycolysis
  6. Fibrosis
  7. Signaling


Inflammation
Free radicals
DNA damage and mutation
Protein modification
• DNA-repair proteins
• Apoptotic modulators
• Metabolic enzymes
• Cell-signalling molecules
Transcriptional upregulation
or repression
Increased carcinogenesis
Decreased carcinogenesis
Stimulate apoptosis
Inhibit cell cycle
Stimulate repair
Inhibit apoptosis
Stimulate cell cycle
Inhibit repair
Stimulate apoptosis
Inhibit cell cycle
Stimulate repair
Inhibit apoptosis
Stimulate cell cycle
Inhibit repair

Information Bottleneck

- The computational principles to create a Kripke model (with states and state transitions)
- It uses Information Bottleneck Theory (a special case of RDT)

Data

- $D_i =$ The random variable; Samples are the rows in submatrix of D_i

States

- **States** Cluster $D_i =$; effectively identifying the state variable X_i such that the mutual information between D_i and X_i is minimized

$$\min I(D_i; X_i) \qquad \text{subj DISTORTION}$$

Transitions

- **State-Transitions** Preserve "ontologies"... Relate the conditional distribution $P(O|X_i)$ with

$$\begin{array}{lll} & P(O|X_{i+1}) & (1 \leq i < k) \\ \& & P(O|X_{i-1}) & (1 < i \leq k) \end{array}$$

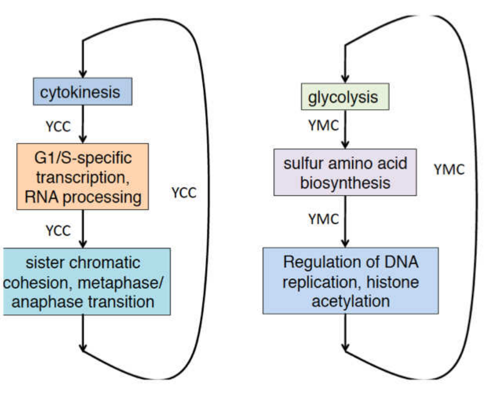
  Measure distortions using Kullback-Liebler Distances.

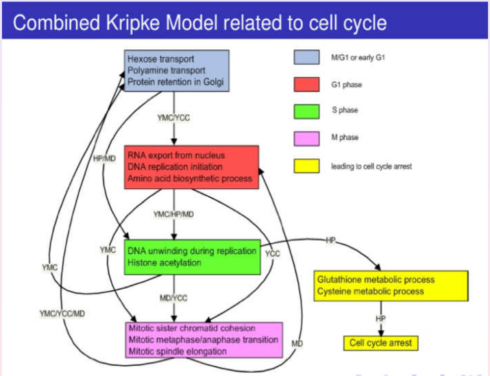
Algorithm

- Cluster the data over time as well as gene sets...
- Cluster and cluster-edges optimize the mutual information terms

$$
\begin{aligned}
& I(D_i; X_i) \\
& - \quad \beta_+ D_{KL}(O|X_i \| O|X_{i+1}) \\
& - \quad \beta_- D_{KL}(O|X_i \| O|X_{i-1})
\end{aligned}
$$

Measure distortions using Kullback-Liebler Distances.


cytokinesis
YCC
G1/S-specific transcription, RNA processing
YCC
sister chromatic cohesion, metaphase/ anaphase transition
YCC
glycolysis
YMC
sulfur amino acid biosynthesis
YMC
Regulation of DNA replication, histone acetylation
YMC


Combined Kripke Model related to cell cycle
Hexose transport
Polyamine transport
Protein retention in Golgi
YMC/YCC
RNA export from nucleus
DNA replication initiation
Amino acid biosynthetic process
HP/MD
YMC/HP/MD
DNA unwinding during replication
Histone acetylation
YMC
YCC
YMC
HP
Glutathione metabolic process
Cysteine metabolic process
MD/YCC
YMC/YCC/MD
HP
Mitotic sister chromatid cohesion
Mitotic metaphase/anaphase transition
Mitotic spindle elongation
MD
Cell cycle arrest
M/G1 or early G1
G1 phase
S phase
M phase
leading to cell cycle arrest

CAN THESE ALGORITHMS BE USED TO UNDERSTAND ALL THE PROCESSES INVOLVED IN CANCER????

Questions???

Heated Discussions on the Suggested Topics...
Resulting in a New and Better Syllabus...
That EVERYONE Loves!

Projects

- Agent-Based Models of Cancer
- Mathematical Models (ODE and PDE) of Cancer
- Copy-Number Variation Analysis of Cancer Genomics
- Systems Biology of Cancer: Temporal, transcriptomic data
- PPI Networks and Cancer
- Progression in Pancreatic Cancer, Therapeutics (Abraxane + Gem)
- Cancer Genetics Model
- Biological Lab Projects (Single Cell analysis of tumors, Tumor heterogeneity, Tumorigenesis, Dedifferentiation)

[End of Lecture #1]