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Seminar
Regulatory networks

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Autumn 2007, Fridays at 12:15, C220

Department of Computer Science

Outline for today

- Who are we?
- General seminar issues: How you get the credits
- The seminar book: Why this book and what is it about
- Topics for the presentations: What I have planned
- Scheduling: Who and when

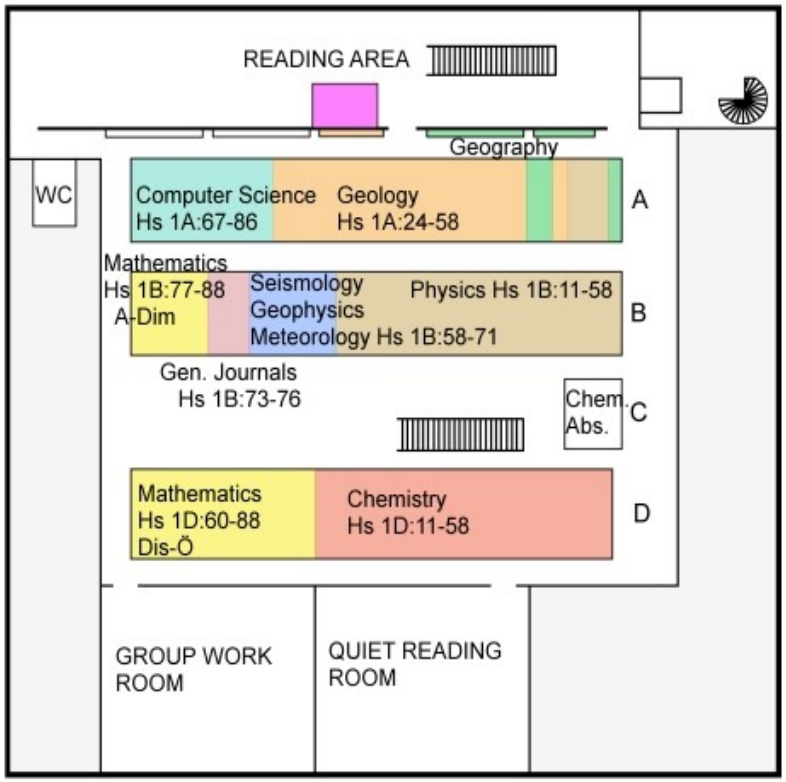
Seminar requirements (3cr) and evaluation

Study Guide: "*A seminar is usually based on presentations and discussions. Each student is required to prepare a* **report on a given topic**, *give an* ***oral presentation*** *and* **actively participate in discussions** *and other work. Seminars are evaluated on the presentation, on a written report and other participation. Students are required to* **be present during at least 3/4 of the regular weekly meetings**."

Specific requirements in this seminar

- A written summary on a given chapter of the seminar book, ready a week before oral representation
  - 5-6 pages, in English
  - Send to me by email (Teemu.Kivioja@helsinki.fi) and I will put it available for others at the seminar web page
- An oral presentation on the same chapter
  - Around 45 minutes, in English
  - A detailed presentation of the mathematics in one or two given sub chapters, “teach the other students (and us) the material”
- Active participation and attendance as normally (¾)
  - Read the summary before the seminar! Ask if you do not understand.
  - Comments utilizing your expertize

Seminar book: Uri Alon
An introduction to systems biology
Design principles of biological circuits



- 2 copies for the presenters
  - You get a copy at least a week before your written summary is due
- 1 copy in the Kumpula science library
  - Located in the group work room in the far corner of the first floor
  - Read your chapter well in advance so that there are no last minute suprises – for example the chapters are not independent!

Miscellaneous

- I am best available Fridays after the seminar
  - September 14 and September 21, office hour 13-14
  - Send an email if you want to see me some other time
- The time table of the seminar will be available on the web site

Why this book?

A simple answer

- The best book on systems biology I have seen
- Is a fascinating read

A longer answer

- In my opinion, the topic is important for anyone working on computational aspects of molecular biology in the future
- Unfortunately, the original literature is typically difficult for non-specialists and many beautiful results are not common knowledge even though they date back to 60's and 70's
- Fortunately for us, Alon presents the most important points in a very lucid and concise manner without getting lost in minute details

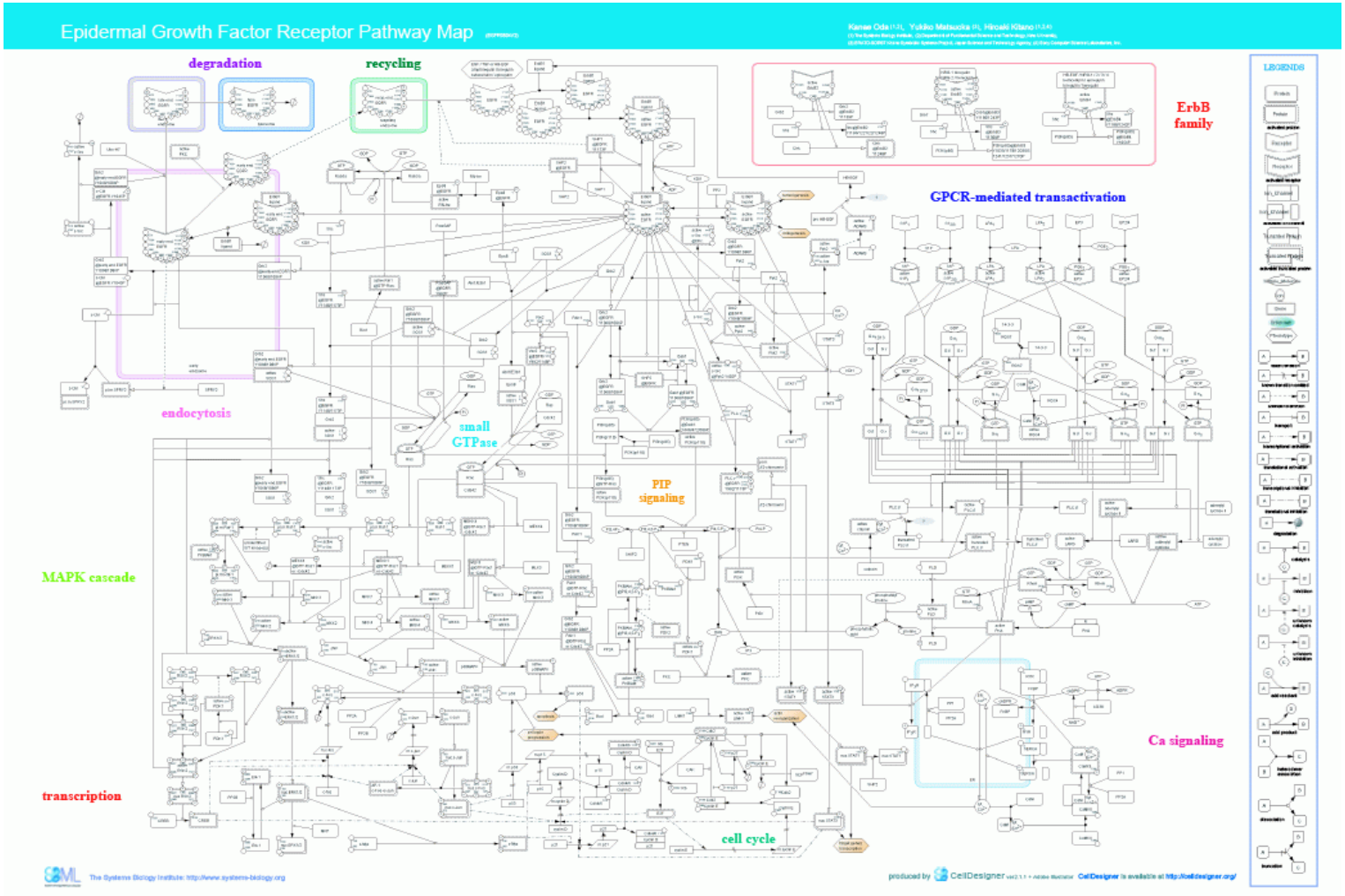
Who is Uri Alon?

- A physicist by training
- Combines computational models with lab experiments
- One of the few people in molecular biology that are known on both sides of the field: experimental and computational
- Done a lot of work in the area that the book covers but...
- The book is not based only on his own work but covers old and new work by many people

Topic of the seminar and the book: Understanding regulatory networks

- A cell of a living organism has be able to respond to diverse changes in its environment
  - rise in temperature, lack of nutrients, signals from other cells...
- Cells do complex information processing to integrate
  - different signals (input) to an
  - internal description of the environment (state) and to produce
  - appropriate response (output).
- This control system is implemented in the cell by thousands of interacting genes and proteins
  - The system is usually formalized as a network where nodes are genes or proteins and edges are interactions between them
- As their parts, the structures of the networks are also products of evolution

An example of the complexity: Pathway map of EGFR signaling in mammals



Oda et al. Molecular Systems Biology 1:2005.0010

Understanding regulatory networks: Fundamental questions of systems biology

- How does the information processing capabilities of the cell emerge from the individual interactions?
- Why is the structure of the network as it is? Are there immense number of networks that would produce similar properties?
- How have these network evolved?
- Is it even possible to understand these networks beyond building vast catalogs describing individual systems?

Alon's claim: There are simplifying principles that make biological systems understandable

- There are small **recurring interaction patterns** in the networks that Alon calls **motifs**: a subnetworks/circuits made by a couple of genes/proteins with defined relationships
- Each motif can perform specific **information processing functions**
- Motifs are basic building blocks that can help us to understand the structure and information processing capabilities of the networks

Alons tool: Toy models that describe the motifs

- Simplified “Toy models” that
  - Capture the essential properties in simple equations. Do not try to faithfully describe the details of any real system. Approximations used heavily.
  - Are still quantitative, mathematical models whose predictions can be compared with the experimental data
  - Play essential part in physics, not so much in biology or computer science
- Here a toy model of a motif (or other regulatory interaction)
  - Describes how information processing function of a motif emerges from interactions of couple of genes or proteins
  - Is usually formalized using simple differential equation

Remember in your summary and presentation

- Describe the biological background:
  - What is the function of this subsystem? Who are the players?
  - What are the essential properties of the system that need to be explained by the model?
- Describe the model
  - In your presentation go through the mathematics of the sub chapter(s) step-by-step in detail, “teach”
  - Remember: that this is difficult stuff for most of us and we have different backgrounds!
- What experimental evidence there is to support the model?
- Do you find the model helpful? What are the shortcomings? Are you convinced?
- Use original papers if needed, pictures etc.

Topics for presentations

2 Basic concepts of transcription networks

- Sensory transcription networks
- Basics of transcriptional regulation: the interaction of transcription factors and genes their regulate
- Logic approximation: Integrating multiple inputs to a gene to single output

2.4 Dynamics and response time for simple gene regulation

- Understanding how the concentration of a protein depends on the degradation and dilution rates
- Relating one edge in the network to the biochemistry of the cell

3 Negative autoregulation: A network motif

- Sensory transcription networks
- Basics of network motifs
- How to show that a pattern occurs more often than expected?

3.4-3.5 Negative autoregulation speeds the response time and promotes robustness

- Why is negative autoregulation so common?
  Understanding the function of negative autoregulation

Appendix C: Graph properties of transcription networks

4.1 - 4.6 The Feed-forward loop network motif

- Sensory transcription networks
- What is feed-forward loop motif?

4.6 The C1-FFL is a sign sensitive delay element

- Understanding the information processing of one type of feed-forward loop motif using a toy model

5 Temporal programs and the global structure of transcription networks

- Sensory transcription networks
- How to produce temporal programs of expression: genes activated one by one in a defined order
- Understanding the global network structure with the help of motifs, *E. coli*

5.5 The multi-output FFL can produce FIFO temporal order

- *E. coli* flagella (motor) construction
- A descriptive model, no equations

6.1 - 6.4 Network motifs in developmental and signal transduction networks

- Developmental transcription networks: what kind of motifs according to Alon
- Signal transduction networks: Basics

6.4 Information processing using multi-layer perceptrons

- Toy models to understand the complex protein kinase cascades
- Linked to neural networks in artificial intelligence
  - a critical view?

8 Robust patterning in development

- Developmental networks
- Basics of morphogens
- How is robust development is possible despite fluctuations of the biochemical parameters from cell to cell?

8.2-8.3 Exponential morphogen profiles are not robust / Increased robustness by self-enhanced morphogen degradation

- A toy model for one morphogen

9 Kinetic proofreading

- How is specific recognition of molecules almost without errors possible in the cell despite many similar molecules?

9.3 Recognizing self and non-self by the immune system

- Some basics of immune system
- How T-cells recognize a specific foreign protein almost without errors
- No differential equations

10 Optimal gene circuit design

- How do gene networks evolve?
- What is the fitness of a gene network?
- Are networks optimal?

10.2 Optimal expression level of a protein under constant conditions

- Fitness function for the lactose system in *E. coli*
- Cost vs. benefit of producing one enzyme
- Comparison to chemostat cultures

Guest lecture by Kimmo Palin: Transcriptional regulation in mammals

- ?

Topics, dates, and presenters (7.9-12.10, 2.11-7.12)

Bombino Sari
Cheng Lu
Juvonen Jaakko
Karinen Sirkku
Sipilä Sanna
(Wang Hao)
Vera Mönter
Thekla Hemstedt

2 Basic concepts of transcription networks, Sept. 28

3 Negative autoregulation: A network motif, Oct. 5

4.1 - 4.6 The feed-forward loop network motif, Oct. 12

(5 Temporal programs and the global structure of transcription networks, Nov. 2) Open?

6.1 - 6.4 Network motifs in developmental and signal transduction networks, Nov. 9

8 Robust patterning in development, Nov. 16

9 Kinetic Proofreading, Nov. 23

10 Optimal gene circuit design, Nov. 30

Open, Dec 7?

(7 Bacterial chemotaxis - a bit more complex)

(6.6 Network motifs in the neuronal network of *C. Elegans* – a bit thin, additional material?)