BE440
Analysis of Biological Networks

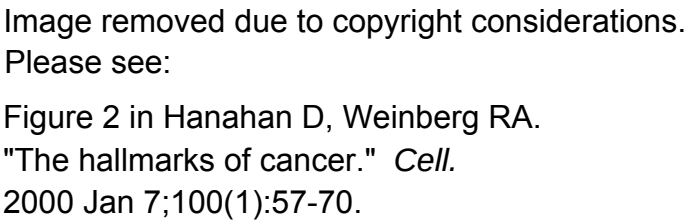


Image removed due to copyright considerations.
Please see:

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

BE440
Module 1: Information storage, evolution and transmission; Cytokine mediated signaling; Chemotaxis

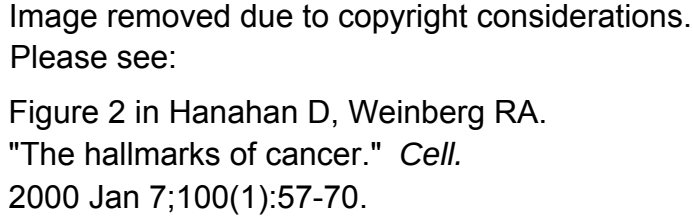


Image removed due to copyright considerations.
Please see:

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

Today

Storage, Replication, Evolution and Transmission of Biological Information

Why Start with a Refresher on Biochemistry and Molecular Biology?

- Last year we found that students had variable backgrounds
- We should have probed what they knew in order to know at what level to aim our lectures
- Some students "memorized" their way through biochemistry (retention of details was a problem)

Central "Dogma" of Molecular Biology

Image removed due to copyright considerations.

Typical Issues

- What does a sigma factor do in transcription? What are STATs?
- What is the structure at the 5' end of mRNA?
- How is it placed there?
- How is protein expression regulated at the translational level?
- How is protein expression positively and negatively regulated in procaryotes at the transcriptional level?

STATs

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.

Typical Issues

- What does a sigma factor do in transcription? What are STATs?
- What is the structure at the 5' end of mRNA?
- How is it placed there?
- How is protein expression regulated at the translational level?
- How is protein expression positively and negatively regulated in procaryotes at the transcriptional level?

Now, the Relevant Issues …

- What are the origins of really complex structures and functions?
- Why are there barriers to interspecies mating?
- Why is it a bad idea to mate with a sibling or parent?
- And, all of this will lead to a discussion of DNA replication and recombination

Image removed due to copyright considerations.

Please see:

Figure 2 in McAdams, Harley H. et al. "The evolution of genetic regulatory systems in bacteria." *Nature Reviews (Genetics),* vol. 5, March 2004, pp.1-9

What are the origins of really complex structures and functions?

Map of Interactions of 1,458 Yeast Proteins

Image removed due to copyright considerations.
Please see:

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

McAdams, Srinvasan and Arkin Paper

- What causes evolution? How does a gene mutate in concert with the other genes in an operon, to maintain network integrity?
  - "*The phylogeny of the catabolic genes is not congruent with that of the 16S genes of the corresponding host*." Arkin, 2004 (Box2) discussing horizontal gene transfer
  - Whew, that is heavy stuff …
  - What does this statement mean, scientifically?

Mutation Drives Evolution, But It Does So Ever So Slowly

- Rate of mutation is normally 0.003 errors per genome per generation (i.e., replication occurs with high fidelity) … Larry Loeb
- This rate is too slow to explain
  - The evolution of antibiotic resistance in a pathogenic bacterial population
  - The acquisition of drug resistance in a growing tumor
  - Evolution of drug resistant viral quasi-species in replication
- If normal replication is so error free, maybe there is some way to decrease fidelity, temporarily, to speed up evolution … Miroslav Radman; Myron Goodman

Arkin's Paradox

Image removed due to copyright considerations.

Please see:

Figure 1 in McAdams, Harley H. et al. "The evolution of genetic regulatory systems in bacteria." *Nature Reviews (Genetics)*, vol. 5, March 2004, pp.1-9

- A mutation leading to a fitter offspring is unlikely
- But it is easy to see how a more fit gene product could be evolved, and selected under pressure
- It is more difficult to see how a whole pathway or a complex structure (chemotaxis or flagellar motor) could evolve

Radman's Possible Solution to the Arkin Paradox

- Cell lowers barriers to inter-species mating by inactivating mismatch repair (MMR)
- This creates a hyper-Rec phenotype
- Recombination brings in massive genetic elements
- Lack of MMR creates a favorable environment for tweaking codon preferences
- Then, find a new MMR gene cluster and cut and paste it into the recipient genome

Mismatch Repair Proteins Maintain Genomic Integrity by Correcting Replication Errors

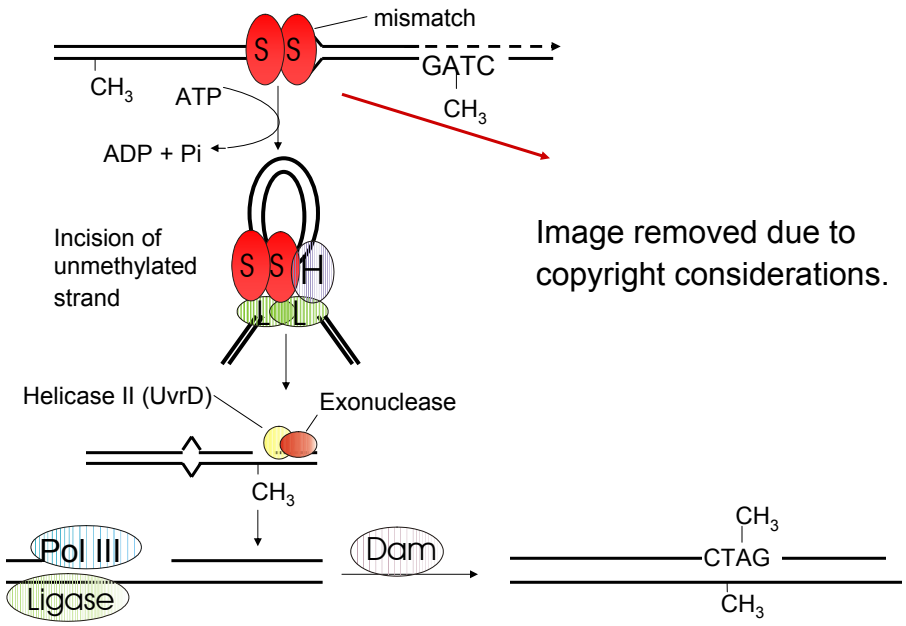
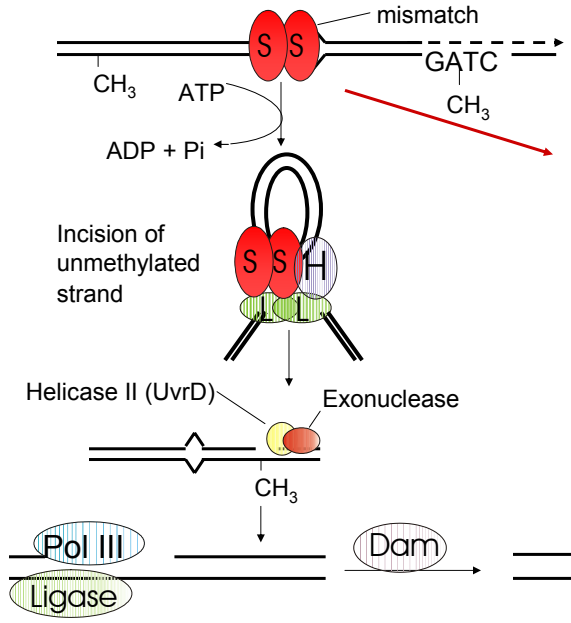


Image removed due to copyright considerations.

Mismatch Repair Proteins Maintain Genomic Integrity by Correcting Replication Errors **and by Regulating Recombination**



Grant Proposal: MMR defects lead to resistance to apoptosis

Image removed due to copyright considerations.