Advanced Algorithms and Models for Computational Biology

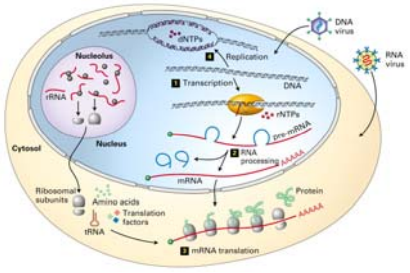
Introduction to cell biology, genomics, development, and probability

Eric Xing

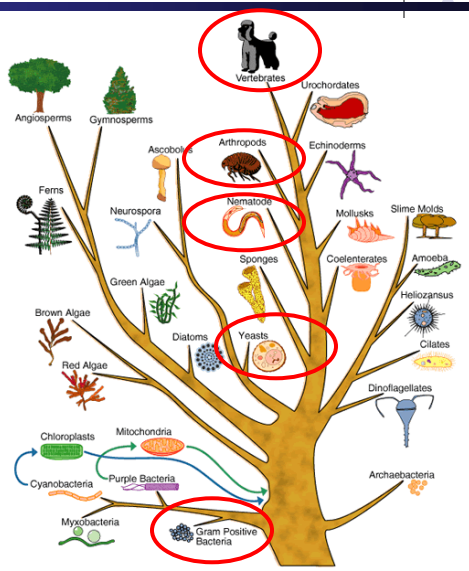
Lecture 2, January 23, 2006

Reading: Chap. 1, DTM book

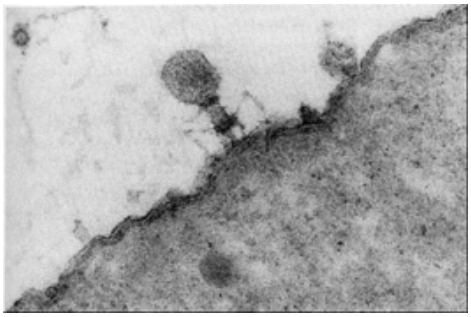
Introduction to cell biology, functional genomics, development, etc.

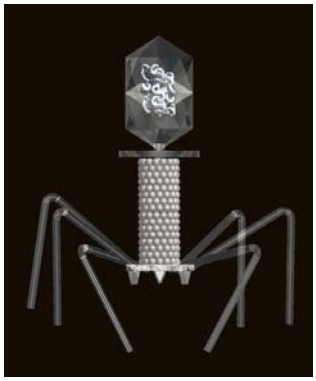


Model Organisms

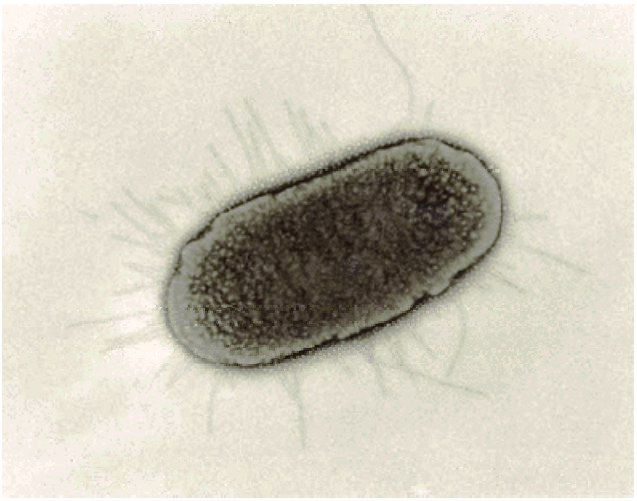


Bacterial Phage: T4

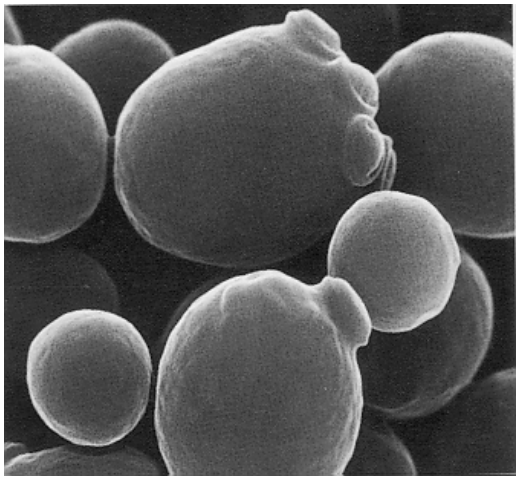




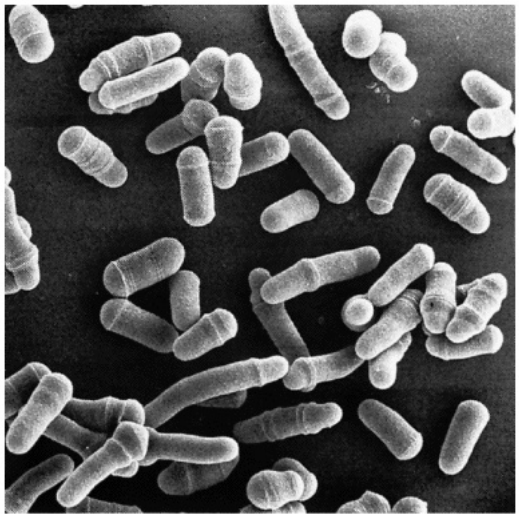
Bacteria: E. Coli



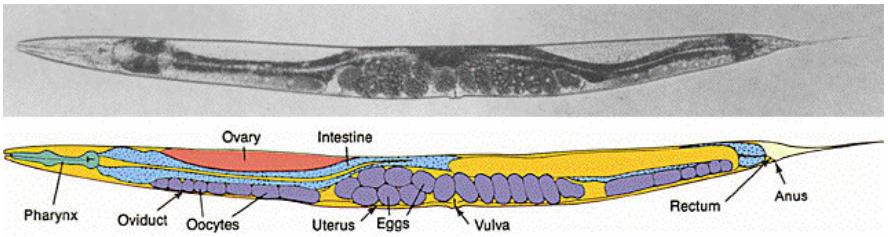
The Budding Yeast: *Saccharomyces cerevisiae*



The Fission Yeast: *Schizosaccharomyces pombe*



The Nematode: *Caenorhabditis elegans*



- **SMALL: ~ 250 µm**
- **TRANSPARENT**
- **959 CELLS**
- **300 NEURONS**
- **SHORT GENERATION TIME**
- **SIMPLE GROWTH MEDIUM**
- **SELF- FERTILIZING HERMAPHRODITE**
- **RAPID ISOLATION AND CLONING OF MULTIPLE TYPES OF MUTANT ORGANISMS**

The Fruit Fly: Drosophila Melanogaster

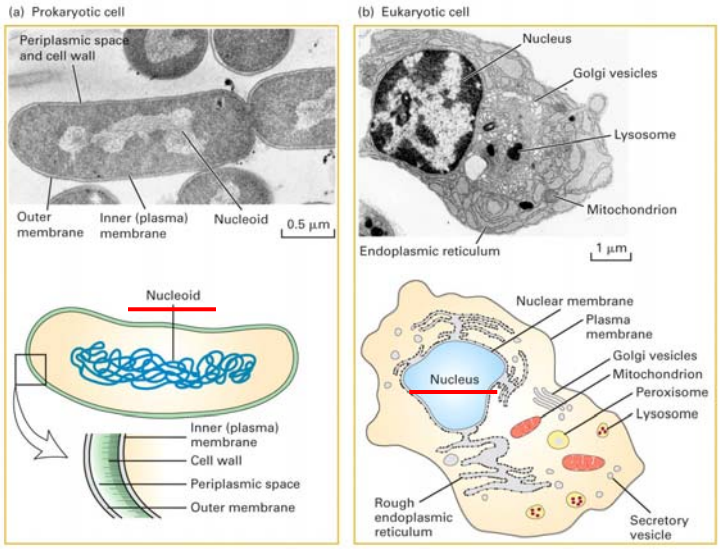
Normal

Ubx mutant

The Mouse

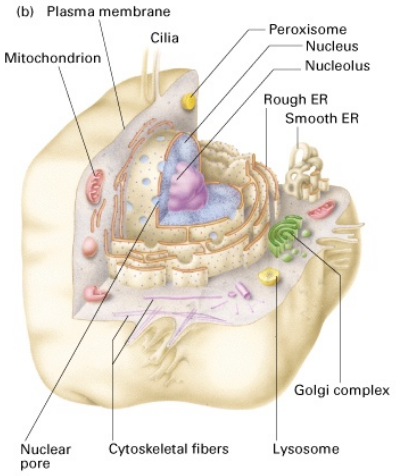
transgenic for human growth hormone

Prokaryotic and Eukaryotic Cells

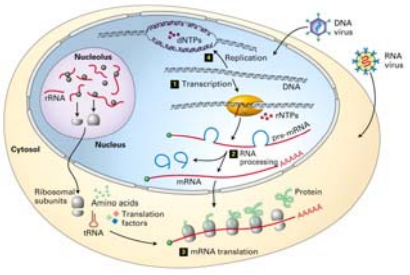


A Close Look of a Eukaryotic Cell

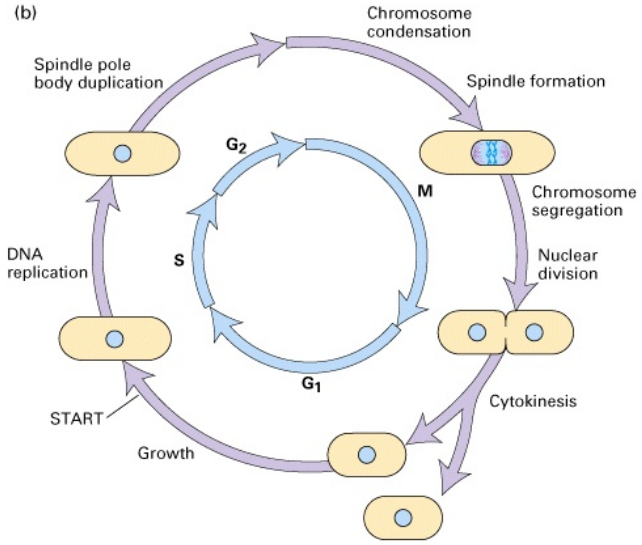
The structure:



The information flow:

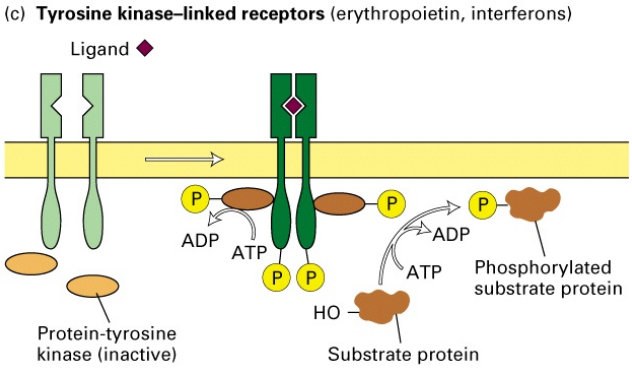


Cell Cycle

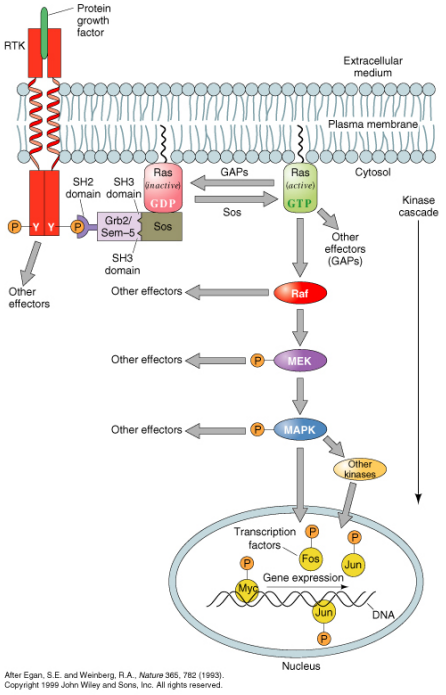


Signal Transduction

- **A variety of plasma membrane receptor proteins bind extracellular signaling molecules and transmit signals across the membrane to the cell interior**

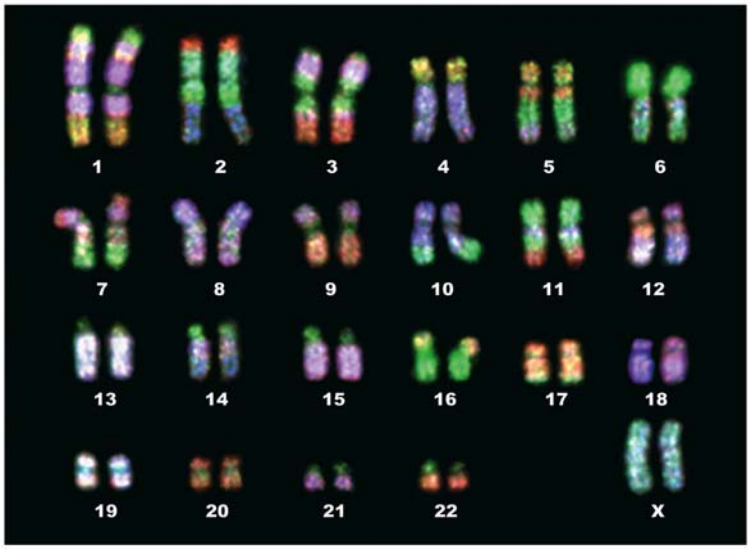


Signal Transduction Pathway

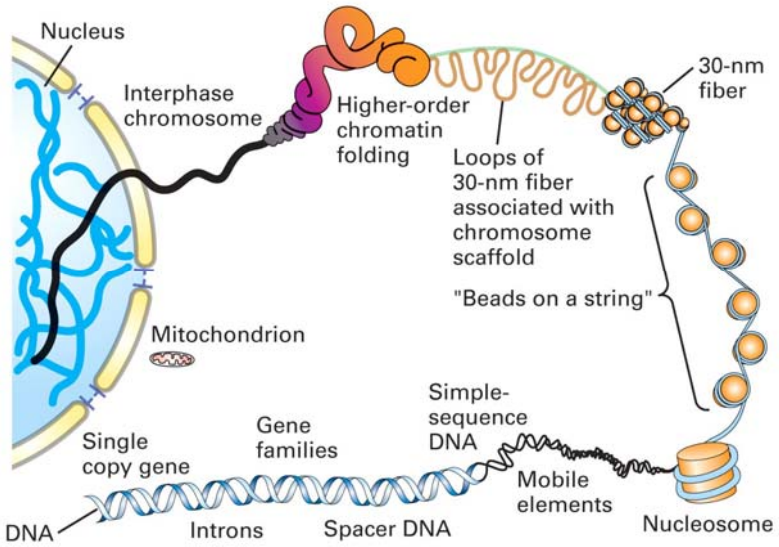


After Egan, S.E. and Weinberg, R.A., *Nature* 365, 782 (1993).

Functional Genomics and X-omics



A Multi-resolution View of the Chromosome



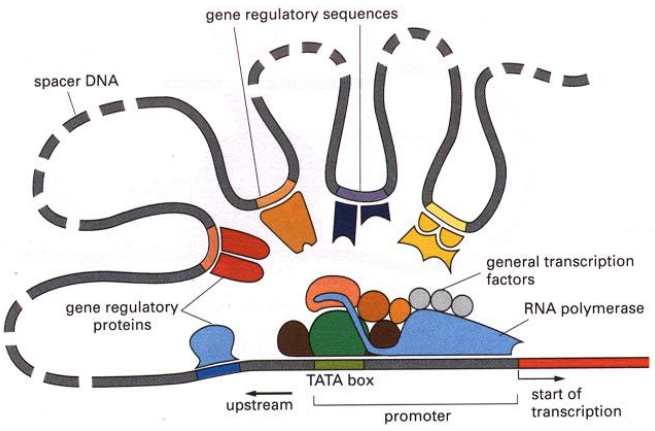
DNA Content of Representative Types of Cells

Organism	Number of base pairs (millions)	Number of encoded proteins	Number of chromosomes
PROKARYOTIC			
Mycoplasma genitalum (Bacterium)	0.58	470	1
Helicobacter pylori (Bacterium)	1.67	1590	1
Haemophilus influenza (Bacterium)	1.83	1743	1
EUKARYOTIC			
Saccharomyces cerevisiae (yeast)	12	5885	17
Drosophila melanogaster (insect)	165	13,601	4
Caenorhabditis elegans (worm)	97	19,099	6
Homo sapiens (human)	2900	30,000 TO 40,000	23
Arabidopsis thaliana (plant)	125	25,498	10

Functional Genomics

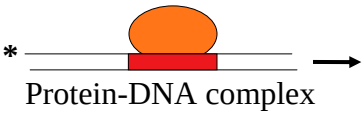
- The various **genome projects** have yielded the complete DNA sequences of many organisms.
  - E.g. human, mouse, yeast, fruitfly, etc.
  - Human: 3 billion base-pairs, 30-40 thousand genes.
- Challenge: **go from sequence to function**,
  - i.e., define the role of each gene and understand how the genome functions as a whole.

Regulatory Machinery of Gene Expression

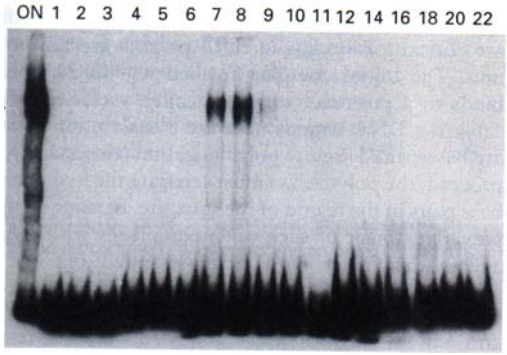


Classical Analysis of Transcription Regulation Interactions

"Gel shift": electorphoretic mobility shift assay ("EMSA") for DNA-binding proteins



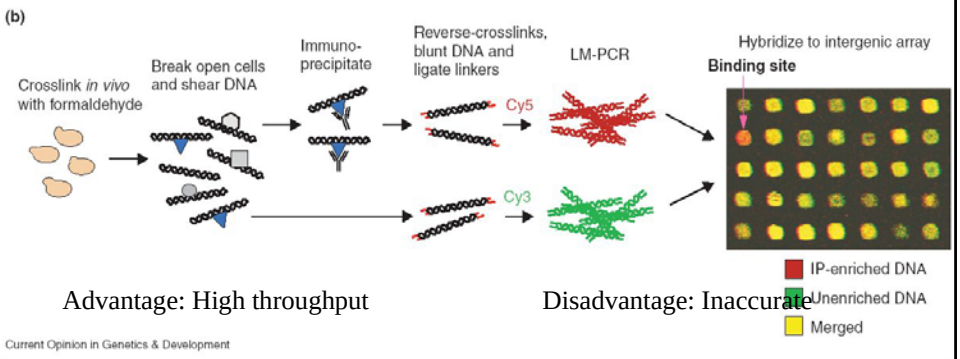
Advantage: sensitive



Disadvantage: requires stable complex; little "structural" information about which protein is binding

Modern Analysis of Transcription Regulation Interactions

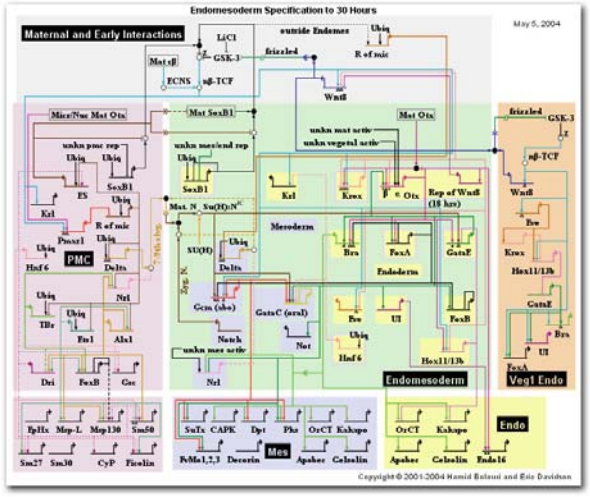
- **Genome-wide Location Analysis (ChIP-chip)**



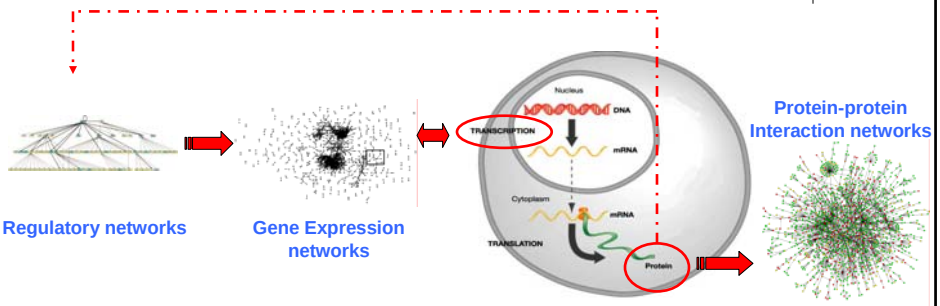
Advantage: High throughput

Disadvantage: Inaccurate

Gene Regulatory Network



Biological Networks and Systems Biology



Regulatory networks

Gene Expression networks

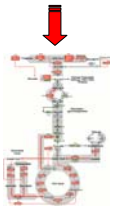
Protein-protein Interaction networks

Systems Biology:

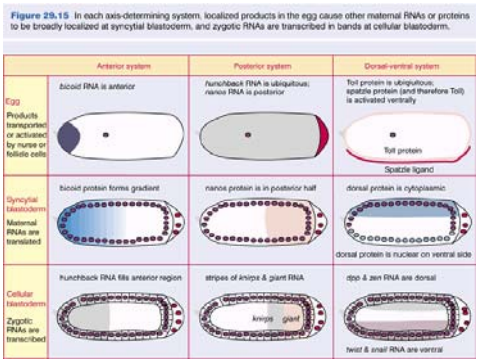
understanding cellular event under a system-level context

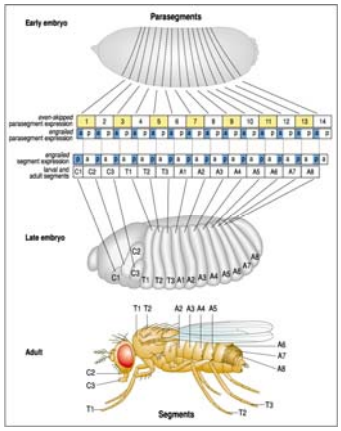
Genome + proteome + lipome + …

Metabolic networks

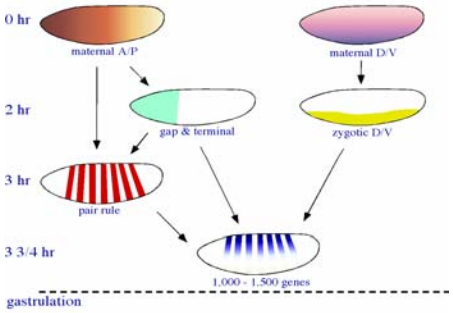


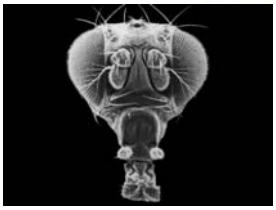
Gene Regulatory Functions in Development

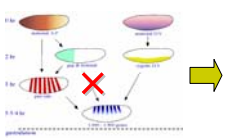




Temporal-spatial Gene Regulation and Regulatory Artifacts



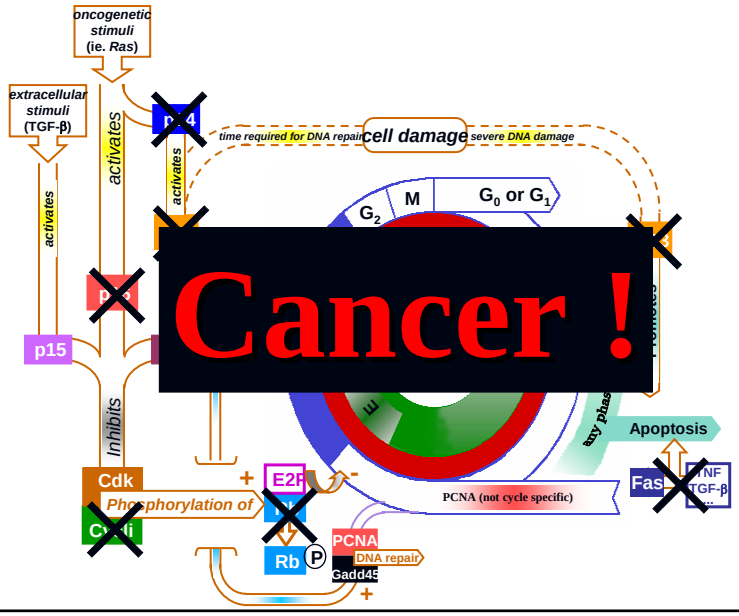




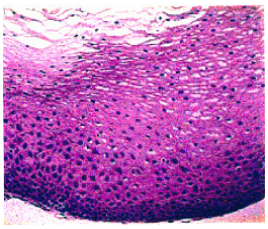
A normal fly

Hopeful monster?

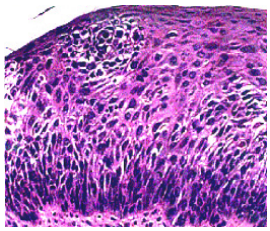
Gene Regulation and Carcinogenesis



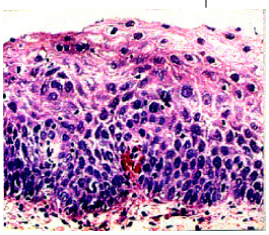
The Pathogenesis of Cancer



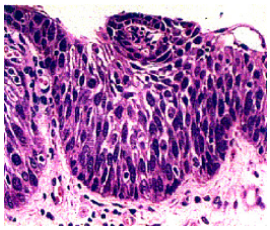
Normal



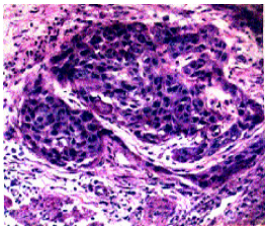
BCH



DYS



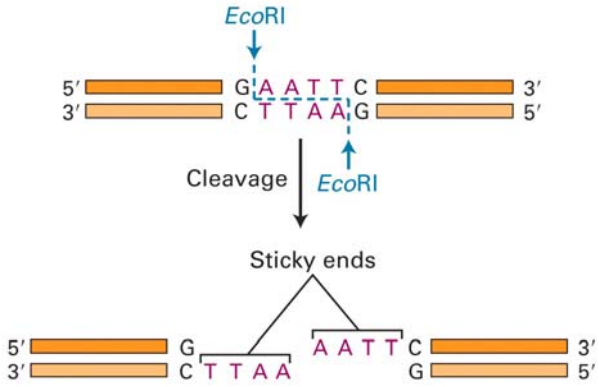
CIS



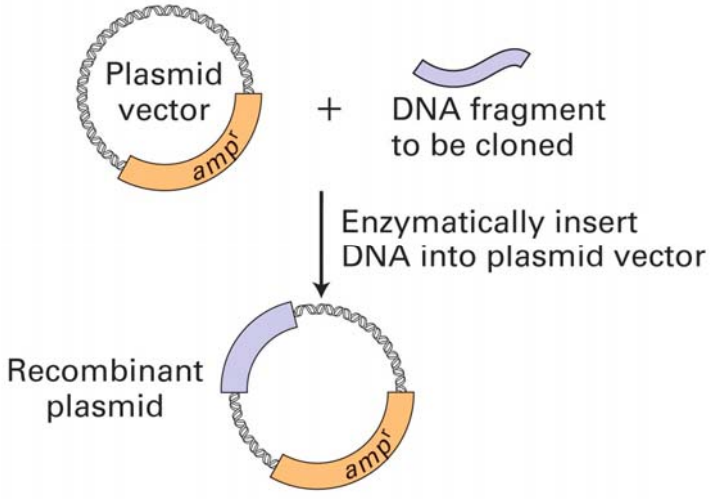
SCC

Genetic Engineering: Manipulating the Genome

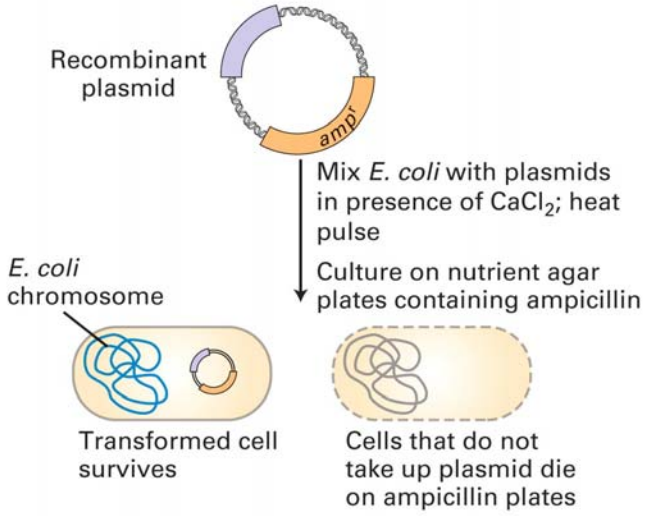
- Restriction Enzymes, naturally occurring in bacteria, that cut DNA at very specific places.



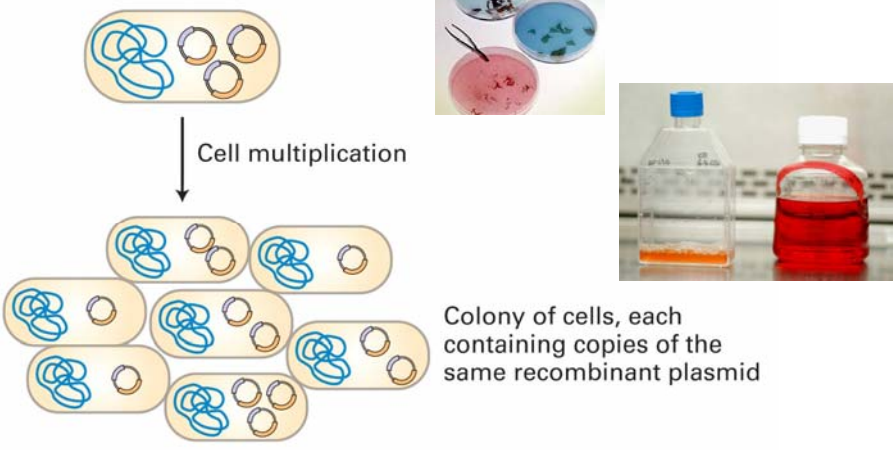
Recombinant DNA



Transformation

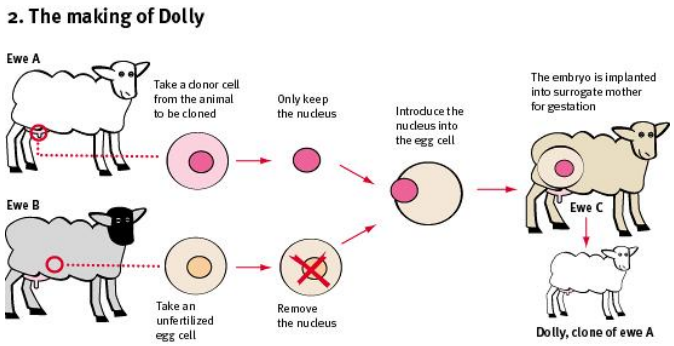


Formation of Cell Colony



How was Dolly cloned?

- Dolly is an exact genetic replica of another sheep.



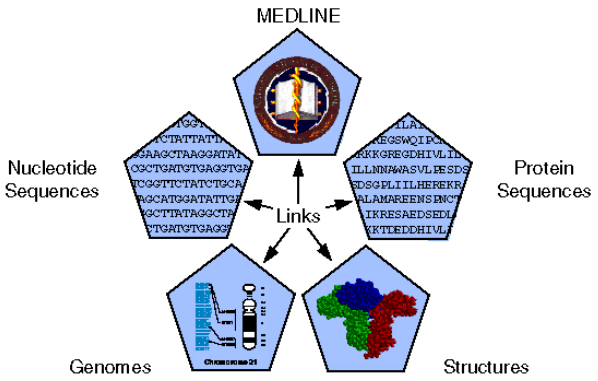
Definitions

- Recombinant DNA: Two or more segments of DNA that have been combined by humans into a sequence that does not exist in nature.
- Cloning: Making an exact genetic copy. A **clone** is one of the exact genetic copies.
- Cloning vector: Self-replicating agents that serve as vehicles to transfer and replicate genetic material.

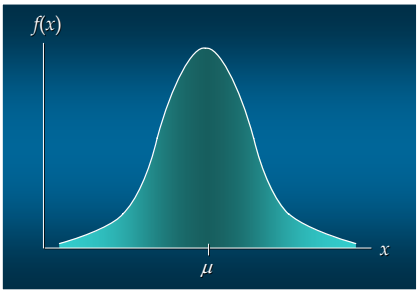
Software and Databases

- NCBI/NLM Databases Genbank, PubMed, PDB
  - DNA
  - Protein
  - Protein 3D
  - Literature

Entrez

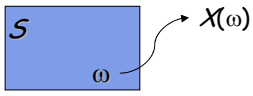


Introduction to Probability



Basic Probability Theory Concepts

- A *sample space* $\mathcal{S}$ is the set of all possible outcomes of a conceptual or physical, repeatable experiment. ($\mathcal{S}$ can be finite or infinite.)
  - E.g., $\mathcal{S}$ may be the set of all possible nucleotides of a DNA site: $\mathcal{S} \equiv \{A, T, C, G\}$
- A *random variable* is a function that associates a unique numerical value (a token) with every outcome of an experiment. (The value of the r.v. will vary from trial to trial as the experiment is repeated)
  - E.g., seeing an "A" at a site $\Rightarrow X$=1, o/w X=0.
  - This describes the true or false outcome a random *event*.
  - Can we describe richer outcomes in the same way? (i.e., X=1, 2, 3, 4, for being A, C, G, T) --- think about what would happen if we take expectation of X.



- Unit-Base Random vector
  - $X_i=[X_{iA}, X_{iT}, X_{iG}, X_{iC}]^T$, $X_i=[0,0,1,0]^T \Rightarrow$ seeing a "G" at site i

Basic Prob. Theory Concepts, ctd

- (In the discrete case), a probability distribution P on $\mathcal{S}$ (and hence on the domain of X) is an assignment of a non-negative real number $P(s)$ to each $s \in \mathcal{S}$ (or each valid value of x) such that $\Sigma_{s \in \mathcal{S}} P(s)=1$. ($0 \le P(s) \le 1$)
  - intuitively, $P(s)$ corresponds to the *frequency* (or the likelihood) of getting s in the experiments, if repeated many times
  - call $\theta_s = P(s)$ the *parameters* in a discrete probability distribution
- A probability distribution on a sample space is sometimes called a *probability model*, in particular if several different distributions are under consideration
  - write models as M_1, M_2, probabilities as $P(X|M_1)$, $P(X|M_2)$
  - e.g., M_1 may be the appropriate prob. dist. if X is from "splice site", M_2 is for the "background".
  - M is usually a two-tuple of {dist. family, dist. parameters}

Discrete Distributions

- Bernoulli distribution: Ber(p)

$$P(x) = \begin{cases} 1-p & \text{for } x = 0 \\ p & \text{for } x = 1 \end{cases} \quad \Rightarrow \quad P(x) = p^x (1-p)^{1-x}$$

- Multinomial distribution: Mult(1, θ)
  - Multinomial (indicator) variable: $X = \begin{bmatrix} X_A \\ X_C \\ X_G \\ X_T \end{bmatrix}$, where $X_j = [0,1]$, and $\sum_{j \in \{A,C,G,T\}} X_j = 1$

    $X_j = 1$ w.p. θ_j, $\sum_{j \in \{A,C,G,T\}} \theta_j = 1$.

$$p(x(j)) = P(\{X_j = 1, \text{where } j \text{ index the observed nucleotide}\})$$
$$= \theta_j = \theta_A^{x_A} \times \theta_C^{x_C} \times \theta_G^{x_G} \times \theta_T^{x_T} = \prod_k \theta_k^{x_k} = \theta^x$$

- Multinomial distribution: Mult(n, θ)
  - Count variable: $X = \begin{bmatrix} x_1 \\ \vdots \\ x_K \end{bmatrix}$, where $\sum_j x_j = n$

$$p(x) = \frac{n!}{x_1! x_2! \cdots x_K!} \theta_1^{x_1} \theta_2^{x_2} \cdots \theta_K^{x_K} = \frac{n!}{x_1! x_2! \cdots x_K!} \theta^x$$

Basic Prob. Theory Concepts, ctd

- A continuous random variable X can assume any value in an interval on the real line or in a region in a high dimensional space
  - X usually corresponds to a real-valued measurements of some property, e.g., length, position, …
  - It is not possible to talk about the probability of the random variable assuming a particular value --- $P(x) = 0$
  - Instead, we talk about the probability of the random variable assuming a value within a given interval, or half interval
    - $P(X \in [x_1, x_2])$, $P(X < x) = P(X \in [-\infty, x])$
- The probability of the random variable assuming a value within some given interval from x_1 to x_2 is defined to be the area under the graph of the probability density function between x_1 and x_2.
  - Probability mass: $P(X \in [x_1, x_2]) = \int_{x_1}^{x_2} p(x)dx$, note that $\int_{-\infty}^{+\infty} p(x)dx = 1$.
  - Cumulative distribution function (CDF): $P(x) = P(X < x) = \int_{-\infty}^{x} p(x')dx'$
  - Probability density function (PDF): $p(x) = \frac{d}{dx} P(x)$

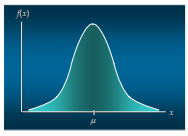
Continuous Distributions

- Uniform Probability Density Function

$$p(x) = 1/(b-a) \quad \text{for } a \le x \le b$$
$$= 0 \quad \text{elsewhere}$$

- Normal Probability Density Function

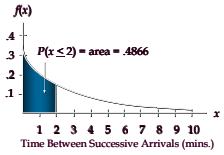
$$p(x) = \frac{1}{\sqrt{2\pi}\sigma} e^{-(x-\mu)^2/2\sigma^2}$$



  - The distribution is symmetric, and is often illustrated as a bell-shaped curve.
  - Two parameters, μ (mean) and σ (standard deviation), determine the location and shape of the distribution.
  - The highest point on the normal curve is at the mean, which is also the median and mode.
  - The mean can be any numerical value: negative, zero, or positive.

- Exponential Probability Distribution

density: $p(x) = \frac{1}{\mu} e^{-x/\mu}$, CDF: $P(x \le x_0) = 1 - e^{-x_0/\mu}$



Statistical Characterizations

- **Expectation:** the center of mass, mean value, first moment):

$$E(X) = \begin{cases} \sum_{i \in S} x_i p(x_i) & \text{discrete} \\ \int_{-\infty}^{\infty} x p(x) dx & \text{continuous} \end{cases}$$

  - Sample mean: $\mu = \frac{1}{N} \sum_{i=1}^{N} x_i$

- **Variance:** the spreadness, second moment:

$$Var(X) = \begin{cases} \sum_{x \in S} [x_i - E(X)]^2 p(x_i) & \text{discrete} \\ \int_{-\infty}^{\infty} [x - E(X)]^2 p(x) dx & \text{continuous} \end{cases}$$

  - Sample variance $\sigma^2 = \frac{1}{N-1} \sum_{i=1}^{N} (x_i - \mu)^2$

Basic Prob. Theory Concepts, ctd

- Joint probability:
  - For events E (i.e. $X=x$) and H (say, $Y=y$), the probability of both events are true:

$$P(E \text{ and } H) := P(x,y)$$

- Conditional probability
  - The probability of E is true given outcome of H

$$P(E \text{ and } H) := P(x \mid y)$$

- Marginal probability
  - The probability of E is true regardless of the outcome of H

$$P(E) := P(x)=\Sigma_x P(x,y)$$

- Putting everything together:

$$P(x \mid y) = P(x,y)/P(y)$$

Independence and Conditional Independence

- Recall that for events E (i.e. $X=x$) and H (say, $Y=y$), the conditional probability of E given H, written as $P(E|H)$, is

$$P(E \text{ and } H)/P(H)$$

(= the probability of both E and H are true, given H is true)

- E and H are (statistically) independent if

$$P(E) = P(E|H)$$

(i.e., prob. E is true doesn't depend on whether H is true); or equivalently

$$P(E \text{ and } H)=P(E)P(H).$$

- E and F are *conditionally* independent given H if

$$P(E|H,F) = P(E|H)$$

or equivalently

$$P(E,F|H) = P(E|H)P(F|H)$$

Representing multivariate dist.

- Joint probability dist. on multiple variables:

$$P(X_1, X_2, X_3, X_4, X_5, X_6)$$
$$= P(X_1)P(X_2 \mid X_1)P(X_3 \mid X_1, X_2)P(X_4 \mid X_1, X_2, X_3)P(X_5 \mid X_1, X_2, X_3, X_4)P(X_6 \mid X_1, X_2, X_3, X_4, X_5)$$

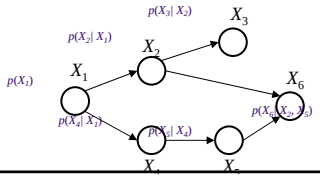
- If X_i's are independent: ($P(X_i|\cdot)= P(X_i)$)

$$P(X_1, X_2, X_3, X_4, X_5, X_6)$$
$$= P(X_1)P(X_2)P(X_3)P(X_4)P(X_5)P(X_6) = \prod_i P(X_i)$$

- If X_i's are conditionally independent, the joint can be factored to simpler products, e.g.,

$$P(X_1, X_2, X_3, X_4, X_5, X_6) = P(X_1)\, P(X_2|\, X_1)\, P(X_3|\, X_2)\, P(X_4|\, X_1)\, P(X_5|\, X_4)\, P(X_6|\, X_2, X_5)$$

- The *Graphical Model* representation



The Bayesian Theory

- The Bayesian Theory: (e.g., for date *D* and model *M*)

$$P(M|D) = P(D|M)P(M)/P(D)$$

  - the **posterior** equals to the **likelihood** times the **prior**, up to a constant.

- This allows us to capture uncertainty about the model in a principled way