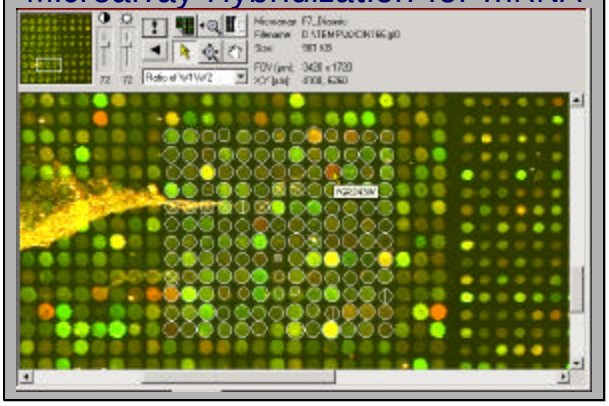
20 Epigenetics

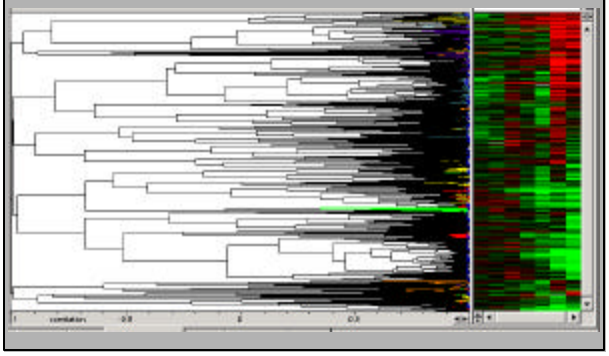
http://www.landesbioscience.com/journals/epigenetics/

Microarray Hybridization for mRNA

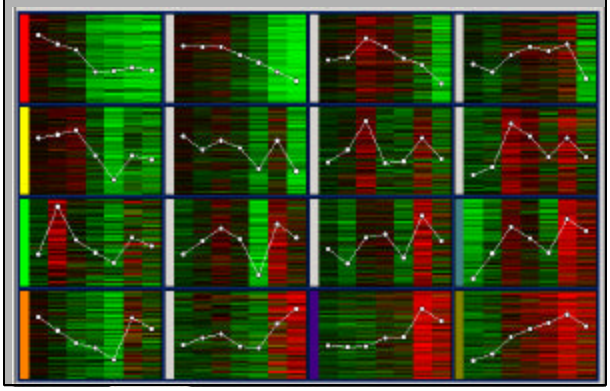


mRNA Identity ?

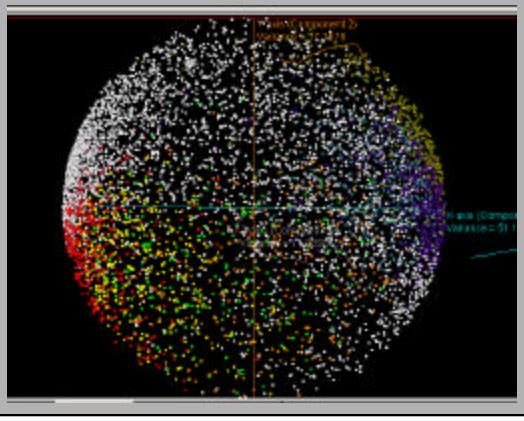
Cluster Analysis for functional groups



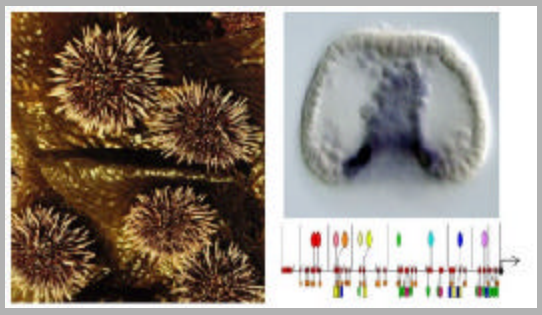
Group Expression Dynamics



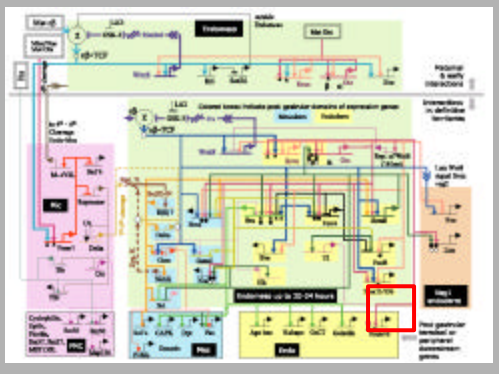
Genomic Network Structure



Development & Gene Expression Networks

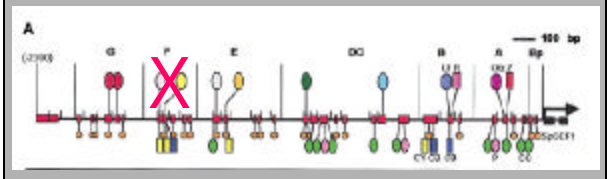


Developmental Regulatory Network



Davidson et al., 2002, Science

Network Variance ?



> Sea Urchin genome has been sequenced and the final contig assembly is almost ready for release.

So just how important are all these regulatory domains? How redundant are they?

Genetic Basis of Natural Variation . . . .

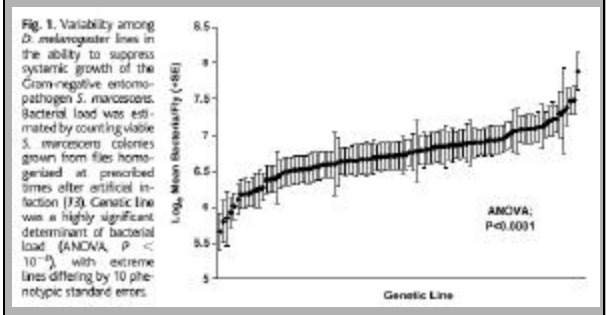


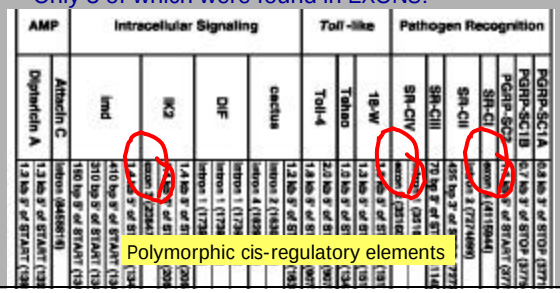
Fig. 1. Variability among *D. melanogaster* lines in the ability to suppress systemic growth of the Gram-negative entomopathogen *S. marcescens*. Bacterial load was estimated by counting viable *S. marcescens* colonies grown from flies homogenized at prescribed times after artificial infection (13). Genetic line was a highly significant determinant of bacterial load (ANOVA, $P < 10^{-6}$), with extreme lines differing by 10 phenotypic standard errors.

> Note Normal Distribution ?

- Lazzaro et al., 2004, Science (19 March)

Polymorphic sites

- 30 polymorphic sites in 16 genes at which allelic state was significantly associated with variation in systemic pathogen load
- Only 3 of which were found in EXONS!



Adaptive Networks

- The necessity of maintaining recombinatorial diversity across generations suggests that a network associations are more likely to be probabilistic than deterministic
- Natural selection operates at the level of a population by determining the degree of phenotypic variance that is permissible in any trait.
- *Variances* in network topologies are just as likely to experience selective pressures as any other phenotypic trait

Conrad H. Waddington (1905-1975),

- Conrad H. Waddington (1905-1975), developmental biologist known as the inventor of the term *epigenetics*
- Waddington suggested that *epigenesis* + *genetics* = *epigenetics*, refering to the debate on epigenesis versus "preformationism" in neoclassical embryology
- Trained as a geologist, he did not respect the traditional boundaries established between genetics, embryology, and evolutionary biology.

Epigenetics

- ***What is epigenetics?***
  Epigenetics, literally "on" genes, refers to all modifications to genes other than changes in the DNA sequence itself. Epigenetic modifications include addition of molecules, like methyl groups, to the DNA backbone. Adding these groups changes the appearance and structure of DNA, altering how a gene can interact with important interpreting (transcribing) molecules in the cell's nucleus.

Epigenetic Regulation: Covalent modifications of DNA to alter expressed phenotypes

Most plants, animals and fungi utilize:

- Acetylation
- Methylation
- Phosphorylation
- ADP-ribosylation

for control of gene expression

Covalent modifications of DNA: 1. Acetylation of histones

Acetylation/De-acetylation

- Hypoacetylation of *Lys* residues
  - Heterochromatin & Silenced euchromatic genes
- Hyperacetylation of *Lys* residues
  - Euchromatin and Inducible genes
  - HS regions

Covalent modifications of DNA: 2. Methylation of histones

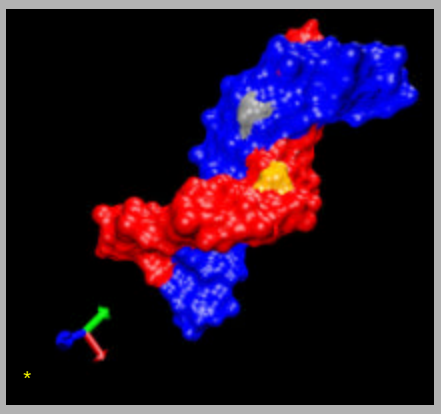
H3 methylation at Lysine 9 (H3-m*Lys*9)

- Characteristic of the heterchromatic state
- Predominantly in pericentric DNA and repetitive DNA sites
- Absent in areas flanking silent genes
- Also associated with silencing of euchromatic genes

Covalent modifications of DNA: 3. Methylation of DNA

5'-Cytosine methylation (5mC)

- Most common form of DNA modification in eukaryotes
- Contributes to the stability of pericentromeric heterochromatin
- Maintains epigenetic expression states
- Silencing of imprinted genes

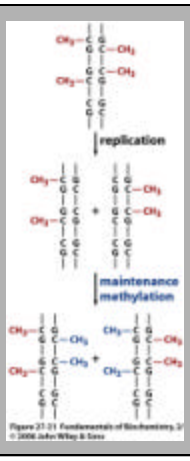


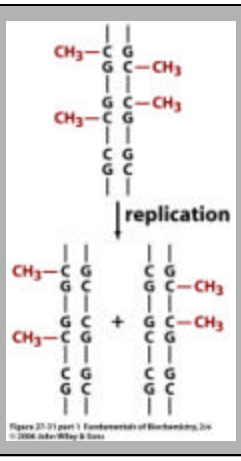
K.Stierhoff

CpG islands: common methylation sites

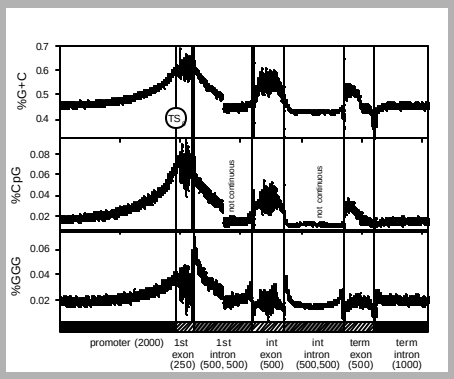
- Segments rich in repeating C+G dinucleotides
- Strong promoter regions and potential replication origins
- Targeted by DNA methyl transferases (DNMTs) for methylation
- Serve as a mechanism for recognition of genes to be silenced

http://www.pagangraphics.com/vue/Islands.jpg





Gene Fine-Structure: motifs



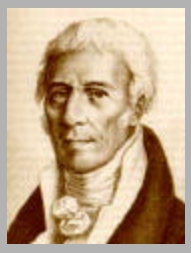
Majewski & Ott, 2002, Genome Research, 12:1827-1836

Epigenetics

- **At the heart of this new field is a simple but contentious idea – that genes have a 'memory'. That the lives of your grandparents – the air they breathed, the food they ate, even the things they saw – can directly affect you, decades later, despite your never experiencing these things yourself. And that what you do in your lifetime could in turn affect your grandchildren.**

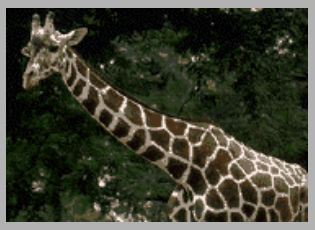
http://www.bbc.co.uk/sn/tvradio/programmes /horizon/ghostgenes.shtml

Jean-Baptiste Lamarck (1744-1829)

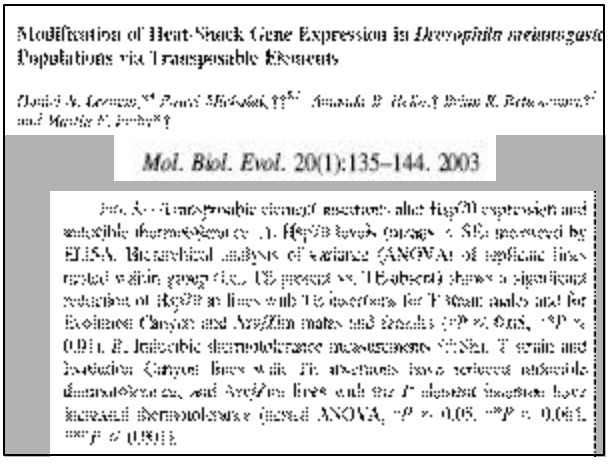


- "Lamarck was the first man whose conclusions on the subject excited much attention. This justly celebrated naturalist first published his views in 1801. . . he first did the eminent service of arousing attention to the probability of all changes in the organic, as well as in the inorganic world, being the result of law, and not of miraculous interposition." *(Darwin, 1861)*

Vitalism

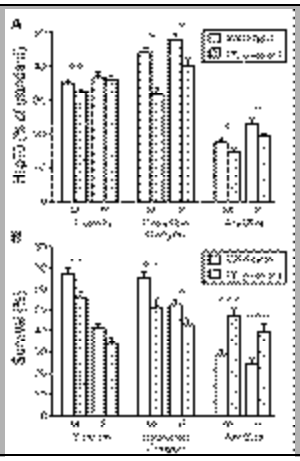


- Lamarck is credited with making the first large advance toward modern evolutionary theory by being the first to propose a mechanism by which the gradual change of species might take place.



Modification of Heat-Shock Gene Expression in *Drosophila melanogaster* Populations via Transposable Elements

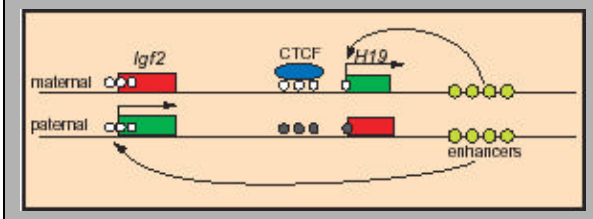
Mol. Biol. Evol. 20(1):135–144. 2003



Gene Imprinting

What is "imprinting?"
"Imprinted genes" don't rely on traditional laws of Mendelian genetics, which describe the inheritance of traits as either dominant or recessive. In Mendelian genetics, both parental copies are equally likely to contribute to the outcome. The impact of an imprinted gene copy, however, depends only on which parent it was inherited from. For some imprinted genes, the cell only uses the copy from the mother to make proteins, and for others only that from the father.

Gene Imprinting: Growth Regulation



IGF2/H19 alternate transcripts. CTCF = "CCCTC binding factor"
> CTCF binds to methylated promotor domains.

Regulation is not encoded in DNA:
Epigenetic determination

Imprinting: "non-genetic" inheritance

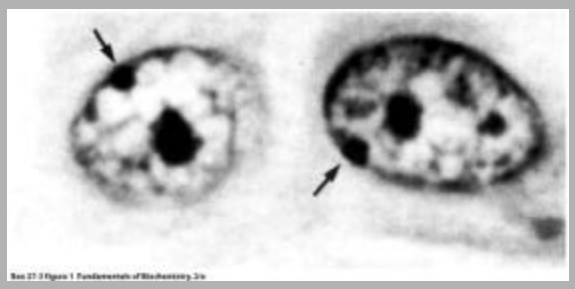
Parents matter. Hybrid of a horse and donkey, the hinny (foreground) differs from the mule because of parent-of-origin effects.

male horse x female donkey = hinny
female horse x male donkey = mule

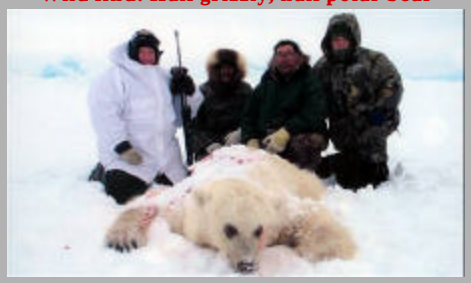
Cloning alters imprinting

Gene Silencing

Barr Bodies



Wild find: Half grizzly, half polar bear



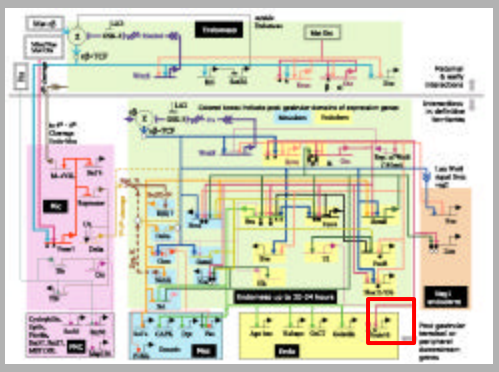
What defines a species? A Genome? A pattern of Gene Regulation?

11MAY06; http://msnbc.msn.com/id/12738644/

King and Wilson, 1975

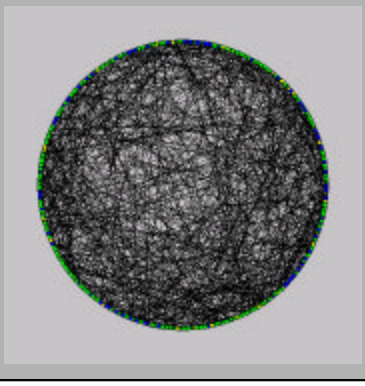
- ". . . all the biochemical methods agree that the genetic distance between humans and the chimpanzee is probably too small to account for their substantial organismal differences . . ."
- "We suggest that evolutionary changes in anatomy and way of life are more often based on changes in the mechanisms controlling the expression of genes than on the sequence changes in proteins."

Science is Beautiful

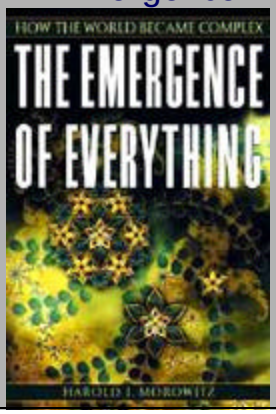


Davidson et al., 2002, Science

But LIFE isn't pretty . . .



Emergence



Life isn't pretty