The Ghost in our Genes

From the Past via the Present to the Future

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Intro (1/1)

Menu (Structural Levels):

- **Genetics** – a definition, a brief historical Overview
- **Properties of DNA**
  Genetic code, Chromosomes,
- **Cell**: Replication, Transcription, Mitosis, Meiosis;
- **Organism**: Mendelian Genetics, Mutagenicity,
- **Population**: Epigenetics

About myself:

- electronics engineer
- MSc in ecology
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12-06-13 Madl
The Basics
Lamarckism or Lamarckian evolution refers to the once widely accepted idea that an organism can pass on characteristics that it acquired during its lifetime to its offspring (also known as based on heritability of acquired characteristics or "soft inheritance"). It is named for the French biologist Jean-Baptiste Lamarck, who incorporated the action of soft inheritance into his evolutionary theories and is often incorrectly cited as the founder of soft inheritance.

It proposed that individual efforts during the lifetime of the organisms were the main mechanism driving species to adaptation, as they supposedly would acquire adaptive changes and pass them on to offspring. After publication of Charles Darwin's theory of natural selection, the importance of individual efforts in the generation of adaptation was considerably diminished. Later, Mendelian genetics supplanted the notion of inheritance of acquired traits, eventually leading to the development of the modern evolutionary synthesis, and the general abandonment of the Lamarckian theory of evolution in biology. In a wider context, soft inheritance is of use when examining the evolution of cultures and ideas, and is related to the theory of Memetics. While enormously popular during the early 19th century as an explanation for the complexity observed in living systems, the relevance of soft inheritance within the scientific community dwindled following the theories of August Weismann and the formation of the modern evolutionary synthesis.

Source: Vetsigian K., Woese C. Goldenfeld N., 2006; Collective evolution and the genetic code PNAS Vol. 103 no. 28
Evolution – The precursors:

- from 1815-1822 Jean Baptiste Lamarck (1744-1829) published his “Histoire naturelle des animaux sans vertèbres” (in seven volumes)
- in 1859 Charles Darwin (1809-1882) published “The Origin of Species”


Neo-Darwinism: …. The problem with this underemphasis on the environment is that it led to an overemphasis on "nature" in the form of genetic determinism - the belief that genes "control" biology …. When you are convinced that genes control your life and you know that you had no say in which genes you were saddled with at conception, you have a good excuse to consider yourself a victim of heredity …. The world is filled with people who live in constant fear that, …. they wait for cancer to explode in their lives as it exploded in the life of their mother or brother or sister or aunt or uncle. Millions of others attribute their failing health not to a combination of mental, physical, emotional and spiritual causes, but simply to the inadequacies of their body's biochemical mechanics ….

Evolution & Genetics:

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- in 1859 Charles Darwin (1809-1882) published “The Origin of Species”
- in 1889 Friedrich Leopold August Weismann (1834-1914) in his “Essays Upon Heredity” proved Lamarck wrong

Weismann barrier: Cutting off rat tails – a German developmental biologist, August Weismann, .... tried to test Lamarck’s theory .... He cut off the tails of male and female mice and mated them .... Weismann repeated the experiment for 21 more generations, but not one tail-less mouse was born, leading Weismann to conclude that Lamarck's notion of inheritance was wrong. But Weismann’s experiment was not a true test of Lamarck's theory. Lamarck suggested that such evolutionary changes could take “immense periods of time” .... Weismann's five-year experiment was clearly not long enough to test the theory ....

The idea that germline cells contain information that passes to each generation unaffected by experience and independent of the somatic (body) cells, came to be referred to as the Weismann barrier, and is frequently quoted as putting a temporary end to the theory of Lamarck and the inheritance of acquired characteristics. While Weisman based the idea on his limited knowledge of cells and his (largely wrong) theory of Germ Plasm, he is also widely quoted as having 'proved' the non-existence of Lamarckian inheritance by the experiment of chopping of the tails of fifteen hundred rats, repeatedly over 20 generations, and reporting that no rat was ever born in consequence without a tail. In fact he states that '901 young were produced by five generations of artificially mutilated parents and yet there was not a single example of a rudimentary tail or any other abnormality of the organ'.

http://en.wikipedia.org/wiki/Weismann,_August 
http://www.esp.org/books/weismann/essays/facsimile/
Discovery of the basic mechanism of inheritance in 1865 by *G. Mendel*:

- Genes as particles of inheritance
- Patterns of inheritance
- Genes come from both parents
- Forms of dominant genes (allele)
Genetics - an Overview:

• in 1865 Gregor Mendel (1822-1884) discovers the basics of inheritance
• in 1888 H.W. Waldeyer (1836-1921) observes the chromosomes
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His credo: Whether geneticists study at the molecular, cellular, organismal, familial, population, or evolutionary level, genes are always central to their studies.
History (7/10)

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• in 1953 J.Watson & F.Crick uncover the structure of DNA

im Jahr 1953 wird die Struktur der DNA von James Watson & Francis Crick erkannt;

They postulate the Central Dogma: Information flow is from DNA to RNA via the process of transcription, and hence to protein via translation. Transcription is the making of an RNA molecule off a DNA template. Translation is the construction of an amino acid sequence (polypeptide) from an RNA molecule. Although originally called dogma, this idea has been tested repeatedly with almost no exceptions to the rule being found (save retroviruses).

Source: http://www.emc.maricopa.edu/faculty/farabee/BIOBK/BioBookPROTSYn.html
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• 2000 HGP uncovers the human genome

im Jahr 2000 wird die Entschlüsselung des menschlichen genomes (human genome project) veröfentlicht;

i) 5 Jahre hat das HUGO gebraucht um dies zu schaffen

i) kostete US$ 6-E^9

i) zeitgleich arbeiteten daran die privaten Unternehmer Francis Collins (religioes motivier, Sprache Gottes) & Craig Venter (pragmatischer Geschaeftsmann – meint es sei der grösster Erfolg seit der Mondlandung)

i) 2008 erstellung eines humanen genomsatzes um ca US$ 1-E^3 innerhalb 3 tagen

The Human Genome Project … ‘provided the blueprint for life, but the epigenome will tell us how this whole thing gets executed’.

Genetics - an Overview:

HUGO aimed at finding genes for:
- addiction
- aggression
- anxiety
- depression
- homosexuality
- obesity, etc.

…. looked at DNA only, thus missed the associated proteins (nucleus contains approx. 50% DNA & 50% proteins)

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by George Howe Colt (Life Mag, 04,1998) 

It's not just brown eyes. your inheritance could also include insomnia, obesity and optimism. yet scientists are saying that genes are not--quite--destiny

Source:
Genetics - a fragmented science:

- **Genomics** is the study of the genomes of organisms. The field includes intensive efforts to determine the entire DNA sequence of organisms and fine-scale genetic mapping efforts. It focuses on genes at the molecular, cellular, organismal, familial, population, or evolutionary level.

- **EpiGenomics**: A field that refers to heritable changes in phenotype (appearance) or gene expression caused by mechanisms other than changes in the underlying DNA sequence (hence the name epi - "in addition to", "on top of" - genetics). These changes may remain through cell divisions for the remainder of the cell's life and may also last for multiple generations. However, there is no change in the underlying DNA sequence of the organism. Instead, non-genetic factors cause the organism's genes to behave (or "express themselves") differently. The best example of epigenetic changes in eukaryotic biology is the process of cellular differentiation. During morphogenesis, totipotent stem cells become the various pluripotent cell lines of the embryo which in turn become fully differentiated cells. In other words, a single fertilized egg cell - the zygote - changes into the many cell types including neurons, muscle cells, epithelium, blood vessels et cetera as it continues to divide. It does so by activating some genes while inhibiting others.

- **Transcriptomics** is the study of the transcriptome – i.e. the set of all messenger RNA (mRNA) molecules, or "transcripts," produced in one or a population of cells. The term can be applied to the total set of transcripts in a given organism, or to the specific subset of transcripts present in a particular cell type. Unlike the genome, which is roughly fixed for a given cell line (excluding mutations), the transcriptome can vary with external environmental conditions.

- **Proteomics** is the large-scale study of proteins, particularly their structures and functions. The proteome is the entire complement of proteins, including the modifications made to a particular set of proteins, produced by an organism or system. This will vary with time and distinct requirements, or stresses, that a cell or organism undergoes. The need to look directly at the Proteins that are made. Fragments can be identified by reference to the genome, if known, prediction. But needs powerful computers! BIOINFORMATICS

- **Metabolomics** is the study of metabolism, i.e. the set of chemical reactions that occur in living organisms in order to maintain life. These processes allow organisms to grow and reproduce, maintain their structures, and respond to their environments. Metabolism is usually divided into two categories.
  i) Catabolism breaks down organic matter, for example to harvest energy in cellular respiration.
  i) Anabolism, on the other hand, uses energy to construct components of cells such as proteins and nucleic acids.

p.xxi: schauen sie doch mal die landschaft an. Wenn heute jemand irgendwo als fysiker arbeitet, dann hat er ein spezielles gebiet .... Jeder hat so ein spezialgebiet und 99% der kollegen wären gar nicht in der lage die ganze problematik zu erfassen die ja von interdisziplinärer natur ist .... **Man darf gar keine fachdisziplin in den vordergrund stellen, sondern muss die fragstellung in den vordergrund rücken** (see D.Suzuki speaking in front of the Aussie museum society) ....

EpiGenetics - A definition:
(epi-, Gk. - “outside” or “above” the gene)

- The study of changes in gene expression
- The study of phenotypic variation w/o changing the genotype
- The spatio-temporal variations during growth
- The study of heritable changes in gene function; due to the environment - historicity of organism!
  e.g. how stressors influence offsprings

Conrad Hal Waddington (1905–1975) coined the term “epigenetics” in 1940

Conrad Waddington (1905-1975) is often credited with coining the term epigenetics in 1942 as “the branch of biology which studies the causal interactions between genes and their products, which bring the phenotype into being”. Epigenetics appears in the literature as far back as the mid 19th century, although the conceptual origins date back to Aristotle (384-322 BC). He believed in epigenesis: the development of individual organic form from the unformed. This controversial view was the main argument against our having developed from miniscule fully-formed bodies. Even today the extent to which we are preprogrammed versus environmentally shaped awaits universal consensus. The field of epigenetics has emerged to bridge the gap between nature and nurture. In the 21st century you will most commonly find epigenetics defined as ‘the study of heritable changes in genome function that occur without a change in DNA sequence’. But what do the scientists that work in this rapidly expanding research field have to say?

What is epigenetics?

i) epigenetics refers to changes in gene expression that are stable between cell divisions, and sometimes between generations ...  
i) processes involved in the genetic development of an organism, especially the activation and deactivation of genes ....  
i) heritable changes in gene function that occur without a change in the DNA sequence ....  
i) a factor that changes the phenotype without changing the genotype ....  
i) the study of inherited characteristics that lie outside of the genome in organisms (from the word epi-, meaning “outside” or “above”) ....  
i) relating to the appearance of new genetic phenomena not present at previous stages of development ....  
i) explaining the interactions of genes with their environment that bring the phenotype into being 

Source: http://www.metafilter.com/48343/Epigenetics
http://www.google.com/search?q=define:Epigenetics&ei=rGm5Sd_EAYOB_gpxciHBg&sa=X&oi=glossary_definition&ct=title
http://www.trwnews.net/Documents/Dioxin/Epigenetics%20-%20media%20coverage.htm
Epigenetics (1/4)

So what is EpiGenetics?

“Epigenetics has always been all the weird and wonderful things that can’t be explained by genetics” …. Denise Barlow (Vienna, Austria)

It seemed …. that any "epigenetic" changes …. could be mutable during the life of the organism, before it generates offspring. This is what 'epigenetic' means, as distinct from 'genetic'.

Phenotype: Epigenetic variation may explain such long-running mysteries as why identical twins are, in many ways, no such thing, including whether they have such supposedly genetic diseases as schizophrenia and cancer.

Spatial-temporal variation: Epigenetics may also help explain how the seeds of many adult diseases may be planted during fetal life. Studies suggest that the nutrition a fetus receives -- as indicated by birth weight -- might influence the risk of adult-onset diabetes, heart disease, hypertension and some cancers. The basis for such "fetal programming" has been largely an enigma, but epigenetics may be key.

Source: http://epigenome.eu/en/1,1,0
Epigenetics (2/4)

So what is EpiGenetics?

“Genetics vs. Epigenetics is comparable …. to the difference between writing and reading a book. Once a book is written, the text (DNA) will be the same in all the copies distributed. However, each individual reader of a given book may interpret the story slightly differently, with varying emotions and projections …. In a very similar manner, epigenetics would allow different interpretations of a fixed template (DNA) and result in different read-outs, dependent upon the variable conditions under which this template is interrogated.” Thomas Jenuwein (Vienna, Austria)

http://epigenome.eu/en/1,1,0

“The difference between genetics and epigenetics can probably be compared to the difference between writing and reading a book. Once a book is written, the text (the genes or DNA: stored information) will be the same in all the copies distributed to the interested audience. However, each individual reader of a given book may interpret the story slightly differently, with varying emotions and projections as they continue to unfold the chapters. In a very similar manner, epigenetics would allow different interpretations of a fixed template (the book or genetic code) and result in different read-outs, dependent upon the variable conditions under which this template is interrogated.” Thomas Jenuwein (Vienna, Austria)

Source: http://epigenome.eu/en/1,1,0
So what is EpiGenetics?

“\textit{Genes are only puppets}. Assorted proteins and RNAs pull the strings, telling the genes when and where to turn on or off”.

Pensisi, 2001, Science

So what is EpiGenetics?

Obviously ….

…. “The Genome is much more complex than the sum of the single parts”

• if not the DNA itself, who then controls gene activity?
• Waddington’s hypothesis pushed open the door to Quantum Biology

Waddington’s epigenetic landscape is a metaphor for a dynamical system, one in which the axes represent concentrations of all the substances, or all the gene products, in the cell. All the cells in the embryo would evolve according to the same laws, but because of the existence of inducing signals, cells in different regions would follow different pathways (‘chreodes’) and end up at different attractors, which can be elegantly associated with different states of terminal differentiation.

In certain simple physical systems, it is possible to predict the evolution of the system by computing the potential energy that is associated with it. In such cases, the system will evolve spontaneously to a local minimum of potential energy. René Thom in his ‘catastrophe theory’ proposed that it would be possible to compute a generalized ‘potential surface’ for any dynamical system. As these surfaces can be somewhat folded, movement ‘down’ the surface can lead to discontinuous changes in one or more of the system variables. This is a so-called ‘catastrophe’, representing an abrupt, discontinuous change in a system that is governed by smooth continuous dynamics.

**Epigenetics**: reversible heritable changes in gene function occur without a change in the sequence of nuclear DNA. Differentiating tissues/organs are inherently organized; such organization emerges from within the “epigenetic landscape” rather than from without. Complex networks of biological signalling pathways can arise from the interactions between simple pathways under local control. These networks exhibit emergent properties: there is integration of signals across multiple time scales; the generation of distinct outputs depend on input strength and duration; there are self-sustaining feedback loops.

Image:

top: “The path followed by the ball, corresponds to the developmental history of a particular organ.

bottom: Interacting network of signal transduction pathways. "The pegs in the ground represent genes; the strings leading from them represent the pathways initiated by gene expression. The slope of the epigenetic landscape is controlled by the pull of these numerous pathways which are ultimately anchored to the genes."


The “Nuclear” Level
Central Dogma (1/8)

Protein Synthesis:

- DNA ↓ (transcription)
- RNA ↓ (translation)
- Proteins

rooted on the belief that ...

.... life is controlled by genes

.... the belief that life is controlled by genes  .... Science mag: “macromolecular ballet” in nuclear dynamics – introduction .... Statement: For higher organisms the nucleus is the command center of the cell”


http://www.sciencemag.org/content/288/5470/1369.full
Central Dogma: a photocopy of the “recipe book” (genetic code)

- Information flow is from DNA to RNA via the process of transcription, and hence to protein via translation.
- Transcription is the making of an RNA molecule off a DNA template. Translation is the construction of an amino acid sequence (polypeptide) from an RNA molecule.
- Although originally called dogma, this idea has been tested repeatedly with almost no exceptions to the rule being found (however .... see retrovirus).

Source: http://www.emc.maricopa.edu/faculty/farabee/BIOBK/BioBookPROTSYN.html
Protein Synthesis in a **nutshell**:  
1. DNA replication, transcription and translation proceed rapidly in a hair follicle.  
2. In DNA replication DNA polymerase copies DNA strands using nucleotides that diffuse in and form base pairs with the DNA.  
3. In transcription, RNA polymerase copies a single strand of DNA into messenger RNA (mRNA).  
4. Newly made mRNA moves through a nuclear pore into the cell’s cytoplasm.  
5. In translation, at ribosomes, bonds form between amino acids (AA) which are alligned by tRNAs according to the nucleotide sequence in mRNA. The joined AA-sequence form a polypeptide.  
6. The main polypeptide synthesized in a hair follicle cell forms the protein keratin which makes long fibers.  
7. The fibers of keratin are about all that is left when the hair follicle cells die and become the hair.  

Central Dogma (4/8)

Reverse Transcriptase – breaking

The Central Dogma:

- RNA dependent DNA polymerase – transcribes single stranded RNA into single stranded DNA;
- telomerase rTST
- viral rTST (e.g. HIV)

Viral RNA is transcribed into DNA and inserted into the DNA of the host cell.

In biochemistry, a reverse transcriptase, also known as RNA-dependent DNA polymerase, is a DNA polymerase enzyme that transcribes single-stranded RNA into single-stranded DNA. Normal transcription involves the synthesis of RNA from DNA, hence reverse transcription is the reverse of this. Reverse transcriptase was discovered by Howard Temin at the University of Wisconsin-Madison, and independently by David Baltimore in 1970. The two shared the 1975 Nobel Prize in Physiology or Medicine with Renato Dulbecco for their discovery.

Commonly used examples of reverse transcriptases include:

- HIV-1 reverse transcriptase from the human immunodeficiency virus type 1 (PDB 1HMV).
- M-MLV reverse transcriptase from the Moloney murine leukemia virus.
- AMV reverse transcriptase from the avian myeloblastosis virus.
- Telomerase reverse transcriptase that maintains the telomeres of eukaryotic chromosomes

Conversion of the HIV RNA genome into DNA by viral reverse transcriptase (RT) is a key step in the early stages of the HIV life cycle, making the enzyme an ideal target for antiretroviral therapy. In the animation above, RT inhibitors are colored in orange. Two classes of reverse transcriptase inhibitors are commercially available: nucleos(t)ide reverse transcriptase inhibitors (NRTIs) and non-nucleoside reverse transcriptase inhibitors (NNRTIs). The NRTIs were the first antiretrovirals to be made available for the treatment of HIV. Based on their similarity to the natural nucleotide building blocks of DNA and RNA, NRTIs are incorporated into the growing DNA strand and terminate further strand elongation. On the other hand, NNRTIs are a chemically diverse class of drugs that bind to the same pocket near the active site of RT and as such inhibit the enzyme.

Source: http://en.wikipedia.org/wiki/Reverse_Transcriptase
Flexner C. 2007; HIV drug development: the next 25 years; Nature Reviews Drug Discovery;
Does Steele's main scientific claim contradict the Central Dogma?
The so-called 'Central Dogma of molecular biology' (Francis Crick) seems to forbid the inheritance of acquired characteristics:

DNA ---> RNA ---> protein

After the discovery of reverse transcription the Central Dogma, as it was known in the textbooks, needed a little modification:

DNA <--- RNA ---> protein

because reverse transcription produces DNA from RNA. However: "a sequence of amino acids in a protein can never act as a copying template for the reverse flow of protein sequence information into RNA." (Steele, p 42).

Does Steele's main scientific claim contradict the Central Dogma?

Genome studies reveal that we share about 95% of our DNA sequence with chimpanzees. This confirms something we have known for years: We are not solely the products of our genes, but of our genes interacting with each other and with the environment. The outcome is a prodigiously complicated chemical system that not only renders humans different from monkeys, but also makes each human being (and probably each cell of each human being) unique. In living cells, macromolecules, and especially proteins, exist in a myriad of forms. But how many of these molecular variants are accidental products of RNA splicing and posttranslational modification, and how many are genetically designed and of evolutionary significance? (Bray, 2003)

How do you get that sleeve off? You need an environmental signal to spur the "sleeve" protein to change shape, i.e. detach from the DNA’s double helix, allowing the gene to be read. Once the DNA is uncovered, the cell makes a copy of the exposed gene. As a result, the activity of the gene is "controlled" by the presence or absence of the ensleeving proteins, which are in turn controlled by environmental signals …. It is now clear that the Primacy of DNA chart described earlier is outmoded. The revised scheme of information flow should now be called the "Primacy of the Environment" …. (Lipton, 2005)

Image: http://danbartlett.co.uk/lipton_epigenetics.htm
A spider’s web ….

• is not the result of biochemical signal transduction cascade of a neuronal program ….

• is not even encoded in the genes ("Genes are only puppets ….") Pennisi, 2001)

• is nothing but the expression of a “spider-like” world-perception!

When Whitehead calls actual occasions “drops of experience” great care must be taken not to be mislead by his choice of language. Ordinarily we think of experience as something restricted to living and sentient beings. Experience here refers to the way a sentient (responsive) being receives the world. For Whitehead all entities are drops of experience. Whether we are speaking of a rock, a subatomic particle, or a human being, these actual occasions are drops of experience. Objectiles are drops of experience not for us, but for themselves. That is, just as a human being might be said to be the sum of their experiences, a rock is the sum of its experiences. “…In the becoming of an actual entity, the potential unity of many entities in disjunctive diversity… acquires the real unity of the one actual entity, so that the actual entity is the real concrescence of many potentials”

…. War früher die Interaktion eines Organismus mit seiner Umgebung eine Abfolge deterministischer biochemischer Abläufe, die im Lebewesen durch die Perzeption eines externen Stimulus ausgelöst werden, so wird nun dem organismischen Erfahrungsakt ein selbstorganisierendes Potential zugeschrieben. Der Bau des Netzes einer Spinne wäre deshalb nicht das Resultat eines mit Signalübertragungen gekoppelten neuronalen Programms, sondern der Ausdruck einer spinnenhaften Welterfahrung, aus der sowohl das Netz, als auch die Form einer Spinne in ihrem Stoffwechsel immer wieder von neuem hervorgeht.

…. our consciousness is delocalised throughout the liquid crystalline continuum of the body (including the brain), rather than being just localized to our brain, or to our heart. By consciousness, I include, at the minimum, the faculties of sentience (responsiveness), intercommunication, as well as memory ….

Falkner & Falkner (2009); Die Bedeutung der Philosophie von Alfred North Whitehead für eine neue Sichtweise in der Biologie
…. and the dead end of Neo-Darwinism

• is not the result mutation & selection
• …. This …. materialistic theory, is reduced to the …. description of the changes of the external relations b/w portions of matter. There is nothing to evolve …. one set of external relations is as good as any other set of external relations …. modified after Whitehead, 1926
• neo-Darwinism is a regression, an impoverishment of Darwin's own conceptions
    …. Stewart, 2001:11

The Genetic Code:

- **DNA**: double stranded macromolecule arranged in chromosomes (network of granules = nuclear chromatin).

- **RNA**: single stranded macromolecule, spherical, intranuclear structure(s) - nucleolus / nucleoli.

Nucleus:

- Genetic material of both eukaryotes and prokaryotes is DNA (deoxy-ribo-nucleic acid). Many viruses also have DNA, but some have RNA (ribo-nucleic acid) genomes instead.

- DNA has two chains, each made of nucleotides composed of a deoxy-ribose sugar, a phosphate group and a base. The chains form a double helix.
The Genetic Code:

- Code: AGC/T (U in RNA)
- Backbone (Phosphate Deoxy-Ribose chain)

Deoxyribose
- The base pairs are 0.34nm apart, and one full turn of the DNA helix takes 3.4nm, so there are 10 bp in a complete turn. The diameter of a dsDNA helix is 2nm.
- Because of the way the bases H-bond with each other, the opposite sugar-phosphate backbones are not equally spaced, resulting in a major and minor groove. This feature of DNA structure is important for protein binding.

Genetic Code (sequence of AT & GC):
- Purines (double-ring, nine-membered structures) include adenine (A) and guanine (G).
- The code corresponds to the structure of the DNA and regulates cell functions by way of directing the synthesis of cell proteins;
- The code is transmitted to new cells during cell division;
- The coded messages are contained in the chromosomes;
The Genetic Code:

- **Deoxyribose**
- **Phosphate**
- **4 Bases:**
  - Adenine (Purine)
  - Guanine (Purine)
  - Cytosine (Pyrimidine)
  - Thymine (Pyrimidine)
  - Uracil (in RNA)

Genetic Code:
- A series of messages contained in the chromosomes;
- This code regulates cell functions by way of directing the synthesis of cell proteins;
- The code corresponds to the structure of the DNA;
- The code is transmitted to new cells during cell division;

The basic unit is the **nucleotide**: it consists of a
- phosphate group
- deoxy-ribose sugar

There are two classes of nitrogenous bases:
- a. Purines (double-ring, nine-membered structures) include adenine (A) and guanine (G).
- b. Pyrimidines (one-ring, six-membered structures) include cytosine (C), thymine (T) in DNA and uracil (U) in RNA.

The sequence of bases determines the genetic information. Genes are specific sequences of nucleotides that pass traits from parents to offspring.
The Genetic Code:

- **Base pairing**
  H-bonding

- **Chargaff’s law**
  equal numbers of bases
  A & T;
  equal numbers of bases
  G & C;

The bases of the two strands are held together by hydrogen bonds between complementary bases (two for A-T pairs and three for G-C pairs). Individual H-bonds are relatively weak and so the strands can be separated (by heating, for example). Complementary base pairing means that the sequence of one strand dictates the sequence of the other strand.

Chargaff’s Law:

- 1<sup>st</sup>: In human DNA, for example, the four bases are present in these percentages: A=30.9% and T=29.4%; G=19.9% and C=19.8%. This strongly hinted towards the base pair makeup of the DNA, although Chargaff was not able to make this connection himself.

- 2<sup>nd</sup>: is that the composition of DNA varies from one species to another, in particular in the relative amounts of A, G, T, and C bases. Such evidence of molecular diversity, which had been presumed absent from DNA, made DNA a more credible candidate for the genetic material than protein.
Eukaryotic chromosomes are linear dsDNA, and by weight contain about twice as much protein as DNA (50% is protein) – in humans it is a 2m long thread of DNA packed into the nucleus. The DNA-protein complex is called chromatin, and it is highly conserved in all eukaryotes.

1. Both histones and non-histones are involved in physical structure of the chromosome.
2. Histones are abundant, small proteins with a net (+) charge. The five main types are H1, H2A, H2B, H3 and H4. By weight, chromosomes have equal amounts of DNA and histones.
3. Histones are highly conserved between species (H1 less than the others).
4. Non-histone is a general name for other proteins associated with DNA. This is a big group, with some structural proteins, and some that bind only transiently. Non-histone proteins vary widely, even in different cells from the same organism. Most have a net (-) charge, and bind by attaching to histones. HMG (high mobility group) proteins are a well-studied example of non-histone proteins.
5. Chromatin formation involves histones, and condenses the DNA so it will fit into the cell. Chromatin formation has two components:
   Two molecules each of histones H2A, H2B, H3 and H4 associate to form a nucleosome core, and DNA wraps around it 1 \(\frac{3}{4}\) times for a 7-fold condensation factor. Nucleosome cores are about 11 nm in diameter.
   H1 serves as the linker histone, connecting nucleosomes to create chromatin with a diameter of 30 nm, for an additional 6-fold condensation. The exact mechanism used by H1 is unknown.
6. Chromatin is arranged in looped domains of DNA similar to those formed in prokaryotic chromosomes. Loops are anchored to the nuclear matrix at DNA sequences called MARs (matrix attachment regions). An average human chromosome has about 2,000 looped domains. Loop domains may be important in regulating transcription and replication.
Eukaryotes have multiple linear chromosomes in a number characteristic of the species. Most have two versions of each chromosome, and so are diploid (2N).

a. Diploid cells are produced by haploid (N) gametes that fuse to form a zygote. The zygote then undergoes development, forming a new individual.

b. Examples of diploid organisms are humans (23 pairs) and *Drosophila melanogaster* (4 pairs). The yeast *Saccharomyces cerevisiae* is haploid (16 chromosomes).

### Chromosome: Genetic material in cells is organized into chromosomes (literally “colored body” because it stains with biological dyes).

a. Prokaryotes generally have one circular chromosome.

b. Eukaryotes generally have:

i. Linear chromosomes in their nuclei, with different species having different numbers of chromosomes.

ii. DNA in organelles (e.g., mitochondria and chloroplasts) that is usually a circular molecule.

### Chromatid: Paired chromosomes, before mitosis, the DNA chains duplicate to form new chromosome material. The duplicated chromosomes lie side by side = chromatid. During Mitosis = the process by which chromatids separate into chromosomes.

Genes occur in pairs on homologous chromosomes, one from each parent;

Different effects of gene whether ♀ or ♂;

Genes modified during gametogenesis;

Gene imprinting: additional methyl groups added to DNA molecules;

Basic structure identical; in some diseases different expression (behavior) depending on parent of origin - hereditary disease as a result of imprinting;
First looked through a microscope. Later Fluorescence In Situ Hybridization produces chromosome bands. Genetic map grew to 5000 markers (places where distinctive variation occurs, like those used in DNA fingerprinting).

The image shows Ch.No 4, with about 186 million bases. Order of the markers determined by studying family inheritance of variations. Studies also led to the identification of genes associated with some diseases:

- Huntington’s disease (HD), is a rare inherited neurological disorder affecting up to approximately 10 people per 100,000 people of Western European descent and 0.1 out of 100,000 in people of Asian and African descent. HD is caused by a trinucleotide repeat expansion in the Huntington (Htt) gene and is one of several polyglutamine (or PolyQ) diseases. This expansion produces an altered form of the Htt protein, mutant Huntington (mHtt), which results in neuronal cell death in select areas of the brain. Huntington's disease is a terminal illness. HD's most obvious symptoms are abnormal body movements called chorea and a lack of coordination, but it also affects a number of mental abilities and some aspects of personality. These physical symptoms occur in a large range of ages, with a mean occurrence a person's late forties/early fifties. If the age of onset is below 20 years then it is known as juvenile HD. As there is currently no proven cure, symptoms are managed with various medications and care methods. Age at onset in Huntington's disease (HD) is variable and is influenced by parental sex, paternal age, and genetic background. We show here that methylation at D4S95, a locus tightly linked to the HD gene, is highly variable. Older persons tend to have lower levels of methylation at this locus. This observation is of interest with regard to studies that show an effect of paternal age, or more generally of 'ageing genes', on age at onset in HD (Reik et al.)


http://en.wikipedia.org/wiki/Chromosome_4
HD = Huntington’s disease gene. First success of RFLP (restriction fragment length polymorphism) mapping. Found linkage in 1983 before the first RFLP map was even constructed. Disease claimed Woody Guthrie. Nancy Wexler, whose mother had died of the disease, became director of the Huntington’s commission (congressional) and of NIH project. Collected family data in Venezuela. “Lucky Jim” Gusella found a link between HD and one of the first RFLP markers he tested. Took another 10 years to actually locate the gene. Takes seconds on the browser.

Source: Human Genome Project @ Phoenix Eagleshadow, UC Santa Cruz (2004)
Chromosome (5/8)

…. to the single gene level …. 

HGP @ UCSC, 2004
…. to the single exon level …. HGP @ UCSC, 2004
A gene is the basic unit of heredity in a living organism. All living things depend on genes. Genes hold the information to build and maintain their cells and pass genetic traits to offspring. In general terms, a gene is a segment of nucleic acid that, taken as a whole, specifies a trait. The colloquial usage of the term gene often refers to the scientific concept of an allele.

In technical terms, a gene is a locatable region of genomic sequence, corresponding to a unit of inheritance, and is associated with regulatory regions, transcribed regions and/or other functional sequence regions. The physical development and phenotype of organisms can be thought of as a product of genes interacting with each other and with the environment.

Source: http://en.wikipedia.org/wiki/Gene
Human Genome (HG):

Karyotype (22 + 1)
- 22 chromosomes
- plus sex chromosome
  - X chromosome
  - Y chromosome

Postlethwait & Houspon, 1995

**Chromosome** (8/8)

Karyotype shows the complete set of chromosomes in a cell (diploid). Metaphase chromosomes are used because they are easiest to see under the microscope after staining. The karyotype is species-specific.

a. The karyotype for a normal human male has 22 pairs of autosomes, and 1 each of X and Y; one sex has a matched pair (e.g., human females with XX) and the other has an unmatched pair (human male with XY). Female (22+XX), male (22+XY), altogether 23 chromosome-pairs for a human being;

b. Human chromosomes are numbered from largest (1) to smallest (although 21 is actually smaller than 22).

c. Human chromosomes with similar morphologies are grouped (A through G).

d. Staining produces bands on the chromosomes, allowing easier identification. G banding is an example.

i. Chromosomes are partially digested with proteolytic enzymes or treated with mild heat, and then stained with Giemsa stain. The dark bands produced are G bands.

ii. In humans, metaphase chromosomes show about 300 G bands, while about 2,000 can be distinguished in prophase.

iii. Drawings (ideograms) show the G banding pattern of human chromosomes.

The Human Genome Landmarks poster is a 24" by 36" wall poster that lists selected genes, traits, and disorders associated with each of the 24 different human chromosomes. Request a free print copy of this poster online.

Source: http://www.ornl.gov/sci/techresources/Human_Genome/posters/chromosome/
Human Genome (HG):

- $3 \times 10^9$ base pairs;
- $35 \times 10^3$ genes (10% of HG);
- 85% of them are known;
- 15% are unknown (inactive);
- of the 85% only 1/5 are known what they accomplish.

The Human Genome is the sum total of all genes contained in a cell’s chromosomes:

- approx. 27,000 genes (humans and mice have about the same number of genes. But we are so different from each other, how is this possible? One human gene can make many different proteins while a mouse gene can only make a few!
- Genes = 10% of human genome
- Exons: parts of the DNA chain that code for specific proteins
- Introns: the parts in-between the exons that are excised later on after transcription
- Both exons and introns are transcribed but only the exons are translated (introns are removed from mRNA before leaving nucleus)

There are a relatively small number of human genes, less than 30,000, but they have a complex architecture that we are only beginning to understand and appreciate.

- We know where 85% of genes are in the sequence.
- We don’t know where the other 15% are because we haven’t seen them “on” (they may only be expressed during fetal development).
- We only know what about 20% of our genes do so far.

So it is relatively easy to locate genes in the genome, but it is hard to figure out what they do.

As the finishing touches were being applied to the sequencing of the human genome (completed in April 2003), unaccountable anomalies kept creeping in, strangely reminiscent of the quarks and dark matter and sundry weird forces that keep muddying the waters of theoretical physics. Scientific American (Nov. & Dec. 2003 issues) summarizes: Only 2% of our DNA - via RNA - codes for proteins. Until very recently, the rest was considered "junk," the byproduct of millions of years of evolution. Now scientists are discovering that some of this junk DNA switches on RNA that may do the work of proteins and interact with other genetic material. "Malfunctions in RNA-only genes, can inflict serious damage."
Human Genome (HG):

…. still some challenges left: …. 

• how to pack this into the nucleus?
• why are there only 35·E3 genes?
  i) a mouse has about the same,
  i) DNA of apes & humans = 98%
• there are some 100·E3 proteins, hence: 1 gene ≠ 1 protein!

A typical eukaryotic cell is about 25 μm in diameter, but this average hides a large range of sizes. The smallest cell is a type of green algae, *Ostreococcus tauri*, with a diameter of only 0.8 micrometers, about the size of a typical bacterium. The human sperm is about 4 μm wide, but 40 μm long, while the egg is about 100 μm in diameter. Single neurons can be a meter or more in length. While schematic diagrams often picture cells as simple cubes or spheres, most cells have highly individual shapes. Human red blood cells are flattened disks indented on either side; muscle cells are highly elongated; neurons are long and thin with many branches on each end; and white blood cells constantly change their shapes as they crawl through the body.

The nucleus is the largest organelle in the cell (approx. 10μm in diameter).

Source: http://www.bookrags.com/research/cell-eukaryotic-gen-01/

If we compare a human DNA with the DNA of the great apes, the gorillas, the orang-utans, and chimpanzees, 98% of our DNA is identical. They are our closest relatives. And if you compare our DNA with the DNA of a snake, of an insect, of a fish, or of a bird, or a tree, vast tracks of our DNA are still identical. We are all related, because we are all descendents from one original cell some 3 and a half billion years ago. And if you begin to recognize that other species are our relatives, our kin, than as Willson and Ehrlich point out, surely the goodness, we would treat them with greater respect and care than if we simply look at them as commodities or resources.

D. Suzuki - speaking at the Australian Museum Society in Sydney AUS - 1992 (wisdom of the elders)
Human Genome (HG):

…. still some challenges left: ….

Eu- vs. Hetero-Chromatin
1. Nature of DNA sequence
2. mRNA or dsRNA expression
3. Spatial organization within the nucleus (nucleoplasm vs. nuclear matrix, or distinct nuclear domains).

The distinction between euchromatin and heterochromatin

Euchromatin:
* active” chromatin
* largely coding sequences
* less than 4% of the mammalian genome
* “open” (decompacted), nuclease-sensitive state
* complexed with transcription/chromatin machineries

Heterochromatin:
* historically less well studied
* important in the organization and proper functioning of eukaryotic genomes
* “closed”, or “locked-down” state
* centromeres & telomeres: constitutive heterochromatin
* defense mechanism
* heterochromatin serves important genome maintenance functions

DNA-Faltung (supercoiling) – rund 2m langer DNA-faden ist im Nucleus verpackt. Die Gen-Expression kann aber nur stattfinden wenn die DNA “ausgewickelt” ist (Euchromatin), nur so koennen Abschnitte abgelesen werden um eine mRNA-Kopie zu erstellen;

HUGO (4/5)

Human Genome (HG):

…. still some challenges left: …. 

• so, what is a gene then?

i) a gene is a union of genomic sequences encoding a coherent set of potentially overlapping functional products,

i) coding portion that determines what can be done and a non-coding portion that determines when the “doing” is active (expressed)

i) phenotype can be thought of as a product of genes interacting with each other and with the environment (epigenitics!)

Not so long ago, it was assumed that a gene is the basic unit of heredity in a living organism. All living things depend on genes. Genes hold the information to build and maintain their cells and pass genetic traits to offspring. In general terms, a gene is a segment of nucleic acid that, taken as a whole, specifies a trait. The colloquial usage of the term gene often refers to the scientific concept of an allele … In cells, a gene is a portion of DNA that contains both "coding" sequences that determine what the gene does, and "non-coding" sequences that determine when the gene is active (expressed). When a gene is active, the coding and non-coding sequences are copied in a process called transcription, producing an RNA copy of the gene's information.

A concise definition of a gene, taking into account complex patterns of regulation and transcription, genic conservation and non-coding RNA genes, has been proposed by Gerstein et al.: "A gene is a union of genomic sequences encoding a coherent set of potentially overlapping functional products".

The classical view of a gene as a unit of hereditary information aligned along a chromosome, each coding for one protein, has changed dramatically over the past century. To quote Falk (1986), "... the gene is ... neither discrete ... nor continuous ..., nor does it have a constant location ..., nor a clear-cut function ..., not even constant sequences ... nor definite borderlines.

Our definition .... argues .... that final, functional gene products (rather than intermediate transcripts) should be used to group together entities associated with a single gene. It also manifests how integral the concept of biological function is in defining genes.

Another issue: in forensic science we are now able to work out a pretty refined picture of a criminal by using DNA-samples to deduct eye & skin & hair color, body stature etc. (Ballantyne & Kayser). However, we are not able to explain why there are eyes, ears, etc in the first place!

Source: http://en.wikipedia.org/wiki/Gene


... Hence ....

- each gene give rise to several proteins by alternative splicing;
- genes should be seen as one long **continuum**;
- each protein is modified in multiple ways by **epigenetic modulation**
- these modified proteins further take part in different **protein complexes**.

**Yeast** (clone & 5 - 6·E³ genes)  **Human**: (~ 33·E³ genes for ~200 cell types)

Geneticists experienced a comparable shock when, contrary to their expectations of over 120,000 genes, they found that the entire human genome consists of approximately 33,000 genes [Pennisi 2003a and 2003b; Pearson 2003; Goodman 2003] of which 19,000 are protein coding [www.genenames.org]. ... Now that the Human Genome Project has toppled the one-gene for one-protein concept, our current theories of how life works have to be scrapped .... There are simply not enough genes to account for the complexity of human life or of human disease ....

We can no longer use genes to explain why humans are at the top of the evolutionary ladder. It turns out there is not much difference in the total number of genes found in humans and those found in primitive organisms. Let's take a look at three of the most studied animal models in genetic research, a microscopic nematode roundworm known as *Caenorhabditis elegans*, the fruit fly and the laboratory mouse (humans are not at the top of the pyramid of creationist thinking) ....

*Caenorhabditis* .... has a precisely patterned body comprised of exactly 969 cells and a simple brain of about 302 cells .... The *Caenorhabditis* genome consists of approximately 24,000 genes [Blaxter 2003]. The human body, comprised of over 80 trillion cells, contains only 1,500 more genes than the lowly, spineless, thousand-celled microscopic worm.

**Yeast**: no differentiation - clonal, repetitive “immortal”; 5-6·E³ genes for metabolism & cell division;

**Human**: ~27,000 genes for ~200 cell types;

Further observations: Genome size vs. gene numbers
i) Coding sequences vs. noncoding & repetitive sequences (yeast has almost no non-coding; human has 96% non-coding+repeats)
ii) Larger transcriptional units in higher eukaryotes (30-200 kb for human)
iii) Factors contributing to different epigenetic regulatory pathways:
   - Larger genomic size, more extensive epigenetic silencing mechanisms
   - Multicellularity: how to maintain multiple cell types (cellular identity)
iv) Non-protein RNA considered “Junk genes” (Steve Jones) with 50% of the human genome consisting of “transposons” (transposable elements, themselves being internalised viruses (Villareal))

Source: http://en.wikipedia.org/wiki/Chromosome
Epigenetics
Epigenetics (epi = on or over the genetic information).
Reversible changes in DNA function, without changing the DNA sequence.

Hence, at least 2 forms of info:
• Genetic information (genotype)
• Epigenetic information (phenotype modulated via environmental signals)

The effect of every gene depends both upon the environment, and upon other genes. A gene does not act alone, it gives instructions for the manufacture of a protein. Proteins act with other proteins, with substrates, etc... All genes interact with the environment to some extent. Sometimes the contribution of the environment is small, sometimes it is very significant.

• Genetic information provides the building block for the manufacture of all proteins needed for the cell functional activity;
• Epigenetic information provides additional instruction on how, when and where these information should be used.
Epigenetics in multicellular organisms is not only limited to cell-differentiation, epigenetic patterns have been observed in transgenerational epigenetic inheritance. Although most of these multigenerational epigenetic traits are gradually lost over several generations, the possibility remains that multigenerational epigenetics could be another aspect to evolution and adaptation.

• **Bookmarking** is a biological phenomenon believed to function as an epigenetic mechanism for transmitting cellular memory of the pattern of gene expression in a cell, throughout mitosis, to its daughter cells. This is vital for maintaining the phenotype in a lineage of cells so that, for example, liver cells divide into liver cells and not some other cell type.

• **Paramutation** is a phenomenon whereby the characteristic of a gene is "remembered" and seen in later generations, even if that particular version of the gene is no longer present. It is an interaction between two alleles of a single locus, resulting in a heritable change of one allele that is induced by the other allele. **What may be transmitted in such a case are RNAs such as piRNAs, siRNAs, miRNAs or other regulatory RNAs.** These are packaged in egg or sperm and cause paramutation upon transmission to the next generation. This means that RNA is a molecule of inheritance, just like DNA.

Pruitt and his co-workers’ analysis shows … plants had replaced the abnormal DNA sequence with the regular code possessed by earlier generations … It definitely changes the view of inheritance … **Here we show that Arabidopsis plants homozygous for recessive mutant alleles of the organ fusion gene HOTHED5 (HTH) can inherit allele-specific DNA sequence information that was not present in the chromosomal genome of their parents but was present in previous generations. **… We postulate that these genetic restoration events are the result of a template directed process that makes use of an ancestral RNA-sequence cache.

Image: mutant DNA in Arabidopsis may be ‘corrected’ by inherited backup-copies of RNA.

**Bookmarking** (during one’s life):

1. activation gene promoters (in transcription)
2. cellular memory (through mitosis)

- phenotypic changes during a life span
- is an aspect of health and disease
- ectodermal cell layer associated to skin & CNS (= brain!)

**Bookmarking** is a biological phenomenon believed to function as an epigenetic mechanism for transmitting cellular memory of the pattern of gene expression in a cell, throughout mitosis, to its daughter cells. This is vital for maintaining the phenotype in a lineage of cells so that, for example, liver cells divide into liver cells and not some other cell type.

It is characterized by non-compaction of some gene promoters during mitosis. In terms of mechanism, it is believed that:

- at some point prior to the onset of mitosis, the promoters of genes that exist in a transcription-competent state become "marked" in some way,
- that this "mark" persists both during and after mitosis,
- and that the marking transmits gene expression memory by preventing the mitotic compaction of DNA at this locus, or by facilitating reassembly of transcription complexes on the promoter, or both.

In some cases, bookmarking is mediated by binding of specific factors to the promoter prior to onset of mitosis, but in other cases could be mediated by patterns of histone modification or presence of histone variants that are characteristic of active genes, and which are believed to persist throughout mitosis.

In the case of specific genes, for example, the stress-inducible hsp70 gene, bookmarking may also function as a mechanism for ensuring that the gene can be transcribed early in G1 phase if a stress were to occur at that time. If this gene promoter were compacted it would take time to de-compact in G1, during which time the cell would be unable to transcribe this cytoprotective gene, leaving it vulnerable to stress-induced cell death. In this case, bookmarking appears to be important for cell survival.

Source: http://en.wikipedia.org/wiki/Bookmarking
http://www.epigenetics.co.kr/epigenetics.htm
**Paramutation** (cross-generations):
(par-a, Gk, “a quasi” mutation)

1. gene silencing
2. genomic imprinting
3. transvection

- refers to inheritance over several generations
- violates G.Mendel’s 1st law and
- is another aspect to evolution and adaptation

Mondin & Gardingo, 2005

**Paramutation** is a phenomenon whereby the characteristic of a gene is "remembered" and seen in later generations, even if that particular version of the gene is no longer present. It is an interaction between two alleles of a single locus, resulting in a heritable change of one allele that is induced by the other allele …. In paramutation an allele in one generation heritably affects the other allele in future generations, even if the allele causing the change is itself not transmitted. What may be transmitted in such a case are RNAs such as piRNAs, siRNAs, miRNAs or other regulatory RNAs. These are packaged in egg or sperm and cause paramutation upon transmission to the next generation. This means that RNA is a molecule of inheritance, just like DNA.

- **Gene silencing** is a general term describing epigenetic processes of gene regulation. The term gene silencing is generally used to describe the "switching off" of a gene by a mechanism other than genetic modification. That is, a gene which would be expressed (turned on) under normal circumstances is switched off by machinery in the cell. Genes are regulated at either the transcriptional or post-transcriptional level.

- **Genomic imprinting** is a genetic phenomenon by which certain genes are expressed in a parent-of-origin-specific manner. It is an inheritance process independent of the classical Mendelian inheritance. Imprinted genes are either expressed only from the allele inherited from the mother (eg. H19 or CDKN1C), or in other instances from the allele inherited from the father (eg. IGF2).

- **Transvection** is an epigenetic phenomenon that results from an interaction between an allele on one chromosome and its homologous chromosome. It can lead to either gene activation or repression. Formally, it can also occur between non-allelic regions of the genome as well as regions of the genome that are not transcribed.

Image: Segregating ears showing paramutation phenotypes in the pericarp. The arrows indicate kernels that contain paramutation events in the locus p and r.


Gene Silencing (1/2)

Transposons (TE) – jumping genes

- Class-I RNA Retro-transposon (copy & paste)
- Class-II DNA transposon (cut & paste)

**e.g. Mosaicisms**
- cell with two different genotypes;
- originates from a reversible mutation during development;

McClintock B., 1948

Transposons are sequences of DNA that can move around to different positions within the genome of a cell, (=transposition, transposons are also called “jumping genes”, examples of mobile genetic elements). In this process, they can cause mutations and change the amount of DNA in the genome. Insertion of a transposon into a gene can disrupt that gene's function in a reversible manner; transposase-mediated excision of the transposon restores gene function. This produces plants in which neighboring cells have different genotypes.

- Class-I **Retrotransposons** work by copying themselves and pasting copies back into the genome in multiple places. Initially retrotransposons copy themselves to RNA (transcription) but, in addition to being transcribed, the RNA is copied into DNA by a reverse transcriptase (often coded by the transposon itself) and inserted back into the genome (copy & paste) ….. The duplications at the target site can result in gene duplication and this is supposed to play an important role in evolution. Retrotransposons behave very similarly to retroviruses, such as HIV, giving a clue to the possible evolutionary origins of such viruses.

- Class-II **DNA transposons** does not involve an RNA intermediate. Usually move by a mechanism analogous to cut and paste using the transposase enzyme. Some transposase can bind to any part of the DNA molecule, and the target site can therefore be anywhere, while others bind to specific sequences. Transposase makes a staggered cut at the target site producing sticky ends (a staggered cut in the target DNA filled by DNA polymerase) followed by inverted repeats (which are important for the transposon excision by transposase).

The first transposons were discovered in maize (Zea mays), by Barbara McClintock in 1948. She noticed insertions, deletions, and translocations, caused by these transposons. These changes in the genome lead to a change in the color of corn kernels. About 60% of the total genome of maize consists of transposons. The Ac/Ds system McClintock described are class II transposons (unstable inheritance of mosaicism).

Image: the relationship of Ac/Ds in the control of the elements and mosaic color of maize. The seed in 10 is colorless, there is no Ac element present and Ds inhibits the synthesis of colored pigments called anthocyanins. In 11 to 13, one copy of Ac is present. Ds can move and some anthocyanin is produced, creating a mosaic pattern. In the kernel in panel 14 there are two Ac elements and in 15 there are three.

Gene Silencing (2/2)

Transposons (TE) – jumping genes

<table>
<thead>
<tr>
<th>Species</th>
<th>(common name)</th>
<th>Genome size [Gb]</th>
<th>TE [%]</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Rana esculenta</em></td>
<td>Frog</td>
<td>5,6–8,0</td>
<td>77</td>
</tr>
<tr>
<td><em>Zea mays</em></td>
<td>Mais</td>
<td>5,0</td>
<td>60</td>
</tr>
<tr>
<td><em>Homo sapiens</em></td>
<td>Human</td>
<td>3,5</td>
<td>45 (!)</td>
</tr>
<tr>
<td><em>Mus musculus</em></td>
<td>Mouse</td>
<td>3,4</td>
<td>40</td>
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<tr>
<td><em>D. melanogaster</em></td>
<td>Fruitfly</td>
<td>0,18</td>
<td>15-22</td>
</tr>
<tr>
<td><em>C. elegans</em></td>
<td>Worm</td>
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<td>12</td>
</tr>
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<td>Yeast</td>
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<td>3-5</td>
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<tr>
<td><em>E. coli</em></td>
<td>Bacter</td>
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<td>0,3</td>
</tr>
</tbody>
</table>

Boeke & Corces, 1989

The first transposons were discovered in maize (*Zea mays*), by Barbara McClintock in 1948. She noticed insertions, deletions, and translocations, caused by these transposons. These changes in the genome lead to a change in the color of corn kernels. About 60% of the total genome of maize consists of transposons. The Ac/Ds system McClintock described are class II transposons (unstable inheritance of mosaicism).

This isn't just about yellow and brown mice. "About 45% of the human genome is transposons," notes Prof. Jirtle.

Source: http://de.wikipedia.org/wiki/Transposon
Imprinting (1/5)

Various modes of **Epigenetic** imprinting

1. DNA methylation (-CH$_3$)
2. 

Genomic imprinting is parent-of-origin-specific allele silencing. It is maintained, in part, by differentially methylated regions and it is normally reprogrammed in the germline. Methylation is nature's way of allowing environmental factors to tweak gene expression without making permanent mutations, Dr. Jirtle said.

**DNA modification**: Stretches of DNA can be inactivated by covalently attaching methyl groups, which can interfere with the binding of transcriptional enzymes, and can also be signals to recruit enzymes that modify associated histones. Cells have enzymes called methyltransferases that bind to specific dinucleotides (a cytosine adjacent to a guanine) and attach a methyl group to the cytosine. Methylated DNA is silent DNA.

**DNA Methylation**: (addition of a methyl-group, CH$_3$). It is the covalent addition of methyl group to 5$^{th}$ Position of cytosine with in CPG di-nucleotides which are frequently located in the promoter region of genes. It is a complex process catalyzed by DNA methyl transferase. The addition of the methyl group from the universal methyl Donor s-adenosyl L -methionine. Methylated DNA-sequences are silenced (inactivated, off).

Heute kennt man rund 28·E$^6$ methylisierbare gen-positionen in der DNA. Prinzipiell wird in den keimzellen fast die gesamte methylierung geloescht (ausnahmen)!

Imprinting (2/5)

Various modes of Epigenetic imprinting

1. DNA methylation (-CH₃)
2. histone modifications
3. 

Histone modification. Those roughly spherical histone complexes also have dangling N-terminal tails that can also be covalently modified by acetylation, phosphorylation, ubiquitination, or methylation. These changes affect how tightly packed the chromatin will be: in loosely packed chromatin, called euchromatin, the DNA is more accessible and more active, while in tightly packed chromatin (heterochromatin), the DNA is more inactive.⁸

• Histone variants. All histones are not alike! Some variants are more permissive of transcription, while others facilitate tighter packing. Activity in a region of DNA can be modulated by the kinds of histones used.⁸

• Histone Methylation: The process is carried out by an enzyme histone methyl transferase which directs site-specific methylation of amino-acid residues such as lys. 4&9 in the tail of the histone H3. Methylation of lysine 9 in histone H3 directs the binding of non-coding RNA, histone deacetylase to control chromatin structure and gene expression.

Image: The figure illustrates nucleosome models and major posttranslational modifications which play essential roles in gene expression and regulation and disease processes.

Small Image: The dynamic nature of epigenetic modifications. The modifications that occur on histone N-terminal tails and on DNA are shown together with the enzymes that lay down and remove the marks. Deregulation of any of these enzymes has the potential to be oncogenic.⁹

Source: http://chemistry.gsu.edu/faculty/Zheng/research.html
Chromatin reshaping seems to underlie healthy adaptations such as learning and memory as well as disease processes—including cancer, seizures, schizophrenia, and depression. Even social stress turned on a particular gene in the brains of mice through chromatin remodeling, a long-lasting change that corresponded with a behavioral indicator of depression. Antidepressant medication reversed both the behavioral sign of depression and the elevated gene activity, underscoring a key point about the modifications: experience and chemical agents can alter gene expression through chromatin remodeling, but such changes are reversible.

Image (L): Nucleosomes consist of DNA (black line) wrapped around histone octomers (purple). Post-translational modification of histone tails by methylation (Me), phosphorylation (P) or acetylation (Ac) can alter the higher-order nucleosome structure. Nucleosome structure can be regulated by ATP-dependent chromatin remodellers (yellow cylinders), and the opposing actions of histone acetyltransferases (HATs) and histone deacetylases (HDACs). Methyl-binding proteins, such as the methyl-CpG-binding protein (MECP2), target methylated DNA (yellow) and recruit HDACs. a | DNA methylation and histone deacetylation induce a closed-chromatin configuration and transcriptional repression. b | Histone acetylation and demethylation of DNA relaxes chromatin, and allows transcriptional activation (Johnstone).

Image (R): The figure shows a schematic pair of imprinted alleles. Hallmarks of imprinted genes such as CpG islands and repeats (arrows) are indicated. The enlarged region below the chromosomes highlights the allele-specific epigenetic changes, such as nucleosomal condensation through deacetylation, and methylation (allele 1) and opening of the chromatin by acetylation and demethylation (allele 2). The transcriptional competence of allele 2 is indicated by the binding of a transcription complex (Reik & Walter).

Various modes of **Epigenetic imprinting**

1. DNA methylation (-CH$_3$)
2. histone modifications
3. mRNA silencing

Images: Cells can inhibit the expression of individual genes (stop proteins from being made) by interfering with a mRNA being transcribed. This is done via a small double-stranded RNA. An enzyme named DICER snips short interfering RNAs (siRNA) from longer double stranded RNAs made by (A) self-copying gene sequences, (B) by replicating viruses, or (C) regulatory RNA sequences known as microRNAs. All the RNAs (A, B, & C) are cleaved by DICER enzyme into short siRNA pieces that can suppress gene expression.

The short siRNA pieces (A, B, & C above image) unwind into single strand RNAs, which then combine with proteins to form a complex called RNA-Induced Silencing Complex (RISC). The RISC then captures a native mRNA molecule that complements the short siRNA sequence. If the pairing (native mRNA and siRNA piece) is essentially perfect, the native mRNA is cut into useless RNA fragments that aren’t translated into AA-sequences. If however, the pairing is less than perfect then the RISC complex binds to the mRNA and blocks ribosome movement along the native mRNA also halting translation. The net effect is NO PROTEIN IS MADE.

In diverse organisms, small RNAs derived from cleavage of double-stranded RNA can trigger epigenetic gene silencing in the cytoplasm and at the genome level. Small RNAs can guide posttranscriptional degradation of complementary mRNA and (at least in plants) induce methylation of homologous DNA sequences. RNA silencing can counteract foreign sequences (like retroviruses and transposons) and is probably involved in development (Matzke et al.).


http://porpax.bio.miami.edu/~cmallery/150/gene/how_siRNA_works.htm
http://porpax.bio.miami.edu/~cmallery/150/gene/siRNA.htm
Imprinting (5/5)

Various modes of **Epigenetic** imprinting

1. DNA methylation (-CH₃)
2. histone modifications
3. mRNA silencing

.... Video-clip ....

Brown, 2006

Epigenetics & Imprinting:

- Parents have enzymes which add methyl groups to gamete’s genes.
- Methylation of DNA messes up the grooves to which the regulatory proteins bind. Regulatory proteins usually have domains (zinc fingers, leucine zippers, or helix-turn-helix) which will fit into the smooth double-helix grooves. But adding methyl (CH₃) puts bumps in the grooves.
- Histones can also bind to the TATA box so that the promotor site on the DNA is hidden or exposed.

Source: http://www.rci.rutgers.edu/~wmbrown/

Legastenie video 03:30-04:48
Properties of the Genome:

- **Hologram**
- **Recipe book**
  1 recipe book = 1 genome
  1 recipe = 1 gene(-products)
  1 word = 1 codon (3 letters)
  1 letter = 1 base (A, T, G & C)

**Hologram - Top:** This is how a photographic image would appear if you look at it with magnifying glasses of increasing strength. If you were to cut away the pieces of the picture that are outside the frame shown, the pixels containing the information would be lost and the image could not be reconstructed. **Below:** The principle of information storage in the hologram. The actual image would not be visible on the film, but the smaller sections of the film still contain the information about the complete object. If you cut it in half or even smaller pieces, you can still use each of the pieces to create a projection of the whole kitten.

**Recipe book:** Inside this giant instruction book's 23 chapters (23 pairs of chromosomes grouped into one genome), one finds all the recipes (approx. 25,000 genes) for cooking up 100s of thousands of proteins that make and maintain our body. By determining which genes we inherit from your parents, chance may play a role. However, “genes themselves need instructions for what to do, and where and when to do it.” These additional instructions are not in DNA, but on it, in an array of chemical markers and switches, known collectively as the epigenome, that lie along the length of the double helix. These epigenetic switches and markers in turn help switch on or off the expression of particular genes (critical to the healthy development of organisms). These can be dramatically tweaked by exposure to a vitamin, a toxin or even mothering, altering “the software of our genes in ways that affect an individual’s body and brain for life.” .... Thus we are not simply product of our genes, but rather that of our experiences, our surroundings, and only to a minimal extent by chance.

23 chapters = 23 pairs of chromosomes, hold all our recipes. Chromosomes are tightly bundled threads of DNA and protein. They're wrapped up like balls of string in the nucleus of a cell.

- **1 recipe = 1 gene(-products).** Some genes contain the recipe for a single protein; other genes can make more than one protein. A gene is a section of DNA on a chromosome.
- **1 word = 1 codon** is spelled by a sequence of three bases, such as TCG, along one side of the DNA ladder. Each three-letter word is called a codon.
- **1 letter = 1 base.** Four bases-A, T, G, and C-make up the rungs of the DNA ladder (A connects to T, G connects to C). Our entire genome contains about 3 billion rungs.

Source - hologram: receipe: http://genome.pfizer.com/station2-4.cfm
http://dangerousintersection.org
Chromosome pairs in diploid organisms are homologous chromosomes. One member of each pair (homolog) is inherited from each parent. Chromosomes that have different genes and do not pair are nonhomologous chromosomes.

Eukaryotes have multiple linear chromosomes in a number characteristic of the species. Most have two versions of each chromosome, and so are diploid (2N).

a. Diploid cells are produced by haploid (N) gametes that fuse to form a zygote. The zygote then undergoes development, forming a new individual.

b. Examples of diploid organisms are humans (23 pairs) and Drosophila melanogaster (4 pairs). The yeast Saccharomyces cerevisiae is haploid (16 chromosomes).

c. Cells within multicellular organisms can be functionally divided into two major compartments (at embryogenesis): *Based on differentiation potency
   - Germ cells: totipotent (infinite proliferation potential) Ex. mammalian oocytes (40 years)
   - Somatic cells: differentiated also include stem cells (multipotent);

   (stem cells can be activated by mitogenic signals to enter restricted number of cell divisions);

Animals and some plants have male and female cells with distinct chromosome sets, due to sex chromosomes. One sex has a matched pair (e.g., human females with XX) and the other has an unmatched pair (human male with XY). Autosomes are chromosomes other than sex chromosomes.

Chromosomes differ in size and morphology. Each has a constriction called a centromere that is used in segregation during mitosis and meiosis. The centromere location is useful for identifying chromosomes.

a. Metacentric means the centromere is approx. in the center, producing two equal arms.

b. Submetacentric means one arm is somewhat longer than the other.

c. Acrocentric have one long arm and a short stalk and often a bulb (satellite) as the other arm.

d. Telocentric chromosomes have only one arm, because the centromere is at the end.
Meiosis:

1st meiotic division: duplication of chromosomes;
- Prophase of meiosis: synapse & crossover.
- Metaphase: paired arrangement of chromosomes;
- Anaphase: migration of homologous chromosomes;
- Telophase: new progeny cells;

2nd meiotic division: halving of chromosomes (2n → n + n)

In biology or life science, meiosis is a process of reductive division in which the number of chromosomes per cell is halved. In animals, meiosis always results in the formation of gametes, while in other organisms it can give rise to spores. As with mitosis, before meiosis begins, the DNA in the original cell is replicated during S-phase of the cell cycle. Two cell divisions separate the replicated chromosomes into four haploid gametes or spores.

Meiosis is essential for sexual reproduction and therefore occurs in all eukaryotes (including single-celled organisms) that reproduce sexually. A few eukaryotes, notably the Bdelloid rotifers, have lost the ability to carry out meiosis and have acquired the ability to reproduce by parthenogenesis. Meiosis does not occur in archaea or bacteria, which reproduce via asexual processes such as binary fission.

Meiosis is two successive divisions of a diploid nucleus (2n) after only one DNA replication cycle. The result is haploid (n) gametes (animals) or meiospores (plants). The two rounds of division in meiosis are meiosis I and meiosis II, each with a series of stages. Cytokinesis usually accompanies meiosis, producing four haploid cells from a single diploid cell.

First meiotic division: duplication of chromosomes to form chromatids (2N)
- Prophase of meiosis: homologous chromosomes lie side by side over entire length = synapse.
  - Interchange of segments of homologous chromosomes = crossover.
  - 2 Xs side by side just like the autosomes.
  - X and Y end to end – no crossover.
- Metaphase: paired chromosomes arrange in middle of cell;
- Anaphase: homologous chromosomes migrate to opposite poles of the cell; each chromosome is composed of two chromatids, the chromatids are not separated
- Telophase: two new daughter cells form; each contains half the chromosome number = reduction of chromosomes by half; interchange of genetic material occurred during synapse;

Second meiotic division = mitotic division
- 2 chromatids separate, 2 new daughter cells are formed with half the normal number of chromosomes (N)
Gametogenesis formation of haploid cells (n) during meiosis:

- **Oocytes** formed before birth (arrested prophase - up to 4 decades!);
- Spermatocytes continuous formation (fresh);

Gametogenesis:

**Oocytes**: formed before birth - prolonged prophase of first meiotic division until ovulation – more frequent congenital abnormalities in ova of older women (longer exposure to potentially harmful environmental influences until meiotic division resumes at ovulation);

ii. In females, oogenesis produces eggs (oocytes) in the ovary.

1. Primordial germ cells (primary oogonia) undergo mitosis to produce secondary oogonia.
2. Secondary oogonia transform into primary oocytes, which grow until the end of oogenesis.
3. Primary oocytes undergo meiosis I and unequal cytokinesis, producing a large secondary oocyte, and a small cell called the first polar body.
4. The secondary oocyte produces two haploid cells in meiosis II. One is a very small cell, the second polar body, and the other rapidly matures into an ovum.
5. The first polar body may or may not divide during meiosis I. Polar bodies have no function in most species and degenerate, so that a round of meiosis produces only one viable gamete, the ovum. Human oocytes form in the fetus, completing meiosis only after fertilization.

**Spermatocytes**: continuously formed ('fresh' sperm)

i. In males, spermatogenesis produces spermatozoa within the testes.

1. Primordial germ cells (primary spermatogonia) undergo mitosis to produce secondary spermatogonia.
2. Secondary spermatogonia transform into primary spermatocytes (meiocytes) which undergo meiosis I, giving rise to two secondary spermatocytes.
3. Each secondary spermatocyte undergoes meiosis II, producing haploid spermatids that differentiate into spermatozoa.
Meiosis (germ line):
- Segregation
- Assortment
- Potential gametes: $2^N$
- Linkage
- Crossing-over (rare in mitosis)

1. **Segregation**: Diploid organisms must form haploid gametes via the process of meiosis. They therefore start with two copies of every gene, but produce gametes with only one copy of each gene. Segregation is the process by which the different alleles of a diploid organism are packaged into separate gametes. 

   **Example**: A heterozygote for the albino gene, for example, would produce two types of gametes, $a$ and $A$. This process occurs at every locus, and is a result of the separation of homologous chromosomes during meiosis. **Segregation** applies to ONE LOCUS. Segregation of alleles is 2:2. Rarely, 3:1 or 1:3 ratios are seen, due to gene conversion.

2. **Independent Assortment** describes the process of segregation occurring at multiple loci simultaneously: The segregation of alleles into gametes follows the laws of probability: therefore an Aa individual would produce 50% $A$ gametes and 50% $a$ gametes. If genes are on different chromosomes, alleles assort independently of each other. This is called independent assortment. The chance of an allele at one locus being in a particular gamete is independent for each locus.

3. **Number of potential gametes**: The number of potential, different, gametes a parent can produce is equal to $2^n$, where $n$ is the number of loci assorting. Thus, a heterozygote for three loci: $AaBbCc$ could form EIGHT different gametes; e.g. $ABC$, $ABo$, $AbC$, $AbO$, $aBC$, $aBo$, $abc$, $abc$. By contrast, $AA BB Cc$ can form only two different gametes, $ABC$ and $ABC$, because only one locus is assorting. For $n$ independently assorting loci, there are $2^n$ different gametes that can be created. If they are truly assorting independently, they will be present in equal numbers.

4. **Linkage**: Departures from independent assortment are most often caused by **LINKAGE**, when two loci are close to each other on the same chromosome. Linkage causes certain combinations of alleles to be over-represented in the gametes.

   i. During meiosis alleles of some genes assort together because they are near each other on the same chromosome.

   ii. Recombination occurs when genes are exchanged between the X chromosomes of the F1 females.

   e. Some relevant terminology:

   i. A chiasma (plural chiasmata) is the site on the homologous chromosomes where crossover occurs.

   ii. Crossing-over is the reciprocal exchange of homologous chromatid segments, involving the breaking and rejoining of DNA.

   iii. Crossing-over is also the event leading to genetic recombination between linked genes in both prokaryotes and eukaryotes.

   f. Crossing-over occurs at the four-chromatid stage of prophase I in meiosis. Each crossover event involves two of the four chromatids. All chromatids may be involved in crossing-over, as chiasmata form along the aligned chromosomes.

   g. For genes on different chromosomes, crossover is not involved. PD and NPD tetrads are produced with equal frequency; and no T tetrads are expected.
In eukaryotes, chromosomes are enormously long, linear molecules. Each chromosome encompasses many genes, arranged linearly, and interspersed with stretches of DNA that do not code for anything.

- a locus (plural, loci) describes a precise location (site) on a chromosome. Since the chromosomes exist in pairs, genes are also paired;
- **Allele**: alternate forms of a gene can occupy the same locus (homo, hetero);
- **Recessive / dominant gene**: recessive expressed only when homozygous; dominant can be homo- or hetero- or co-;
- **Sex-linked gene**: X, recessive, hemi

Genes are arranged on linear chromosomes: Frequently, geneticists use the terms gene and loci interchangeably, because genes are small relative to chromosomes and seem to occupy pinpoint locations. We speak of loci having different alleles (polymorphic), or only one allele (monomorphic).

**Phenotype vs. Genotype**: An organism heterozygous for a recessive allele, such as albinism, would exhibit the dominant trait, yet would possess the heterozygous genotype.

An organism’s PHENOTYPE is its observable characteristics.

An organism’s GENOTYPE is its genetic composition of alleles.

Another issue: in forensic science we are now able to work out a pretty refined picture of a criminal by using DNA-samples to deduce eye & skin & hair color, body stature etc. (Ballantyne & Kayser). However, we are not able to explain why there are eyes, ears, etc in the first place!

**Do all loci have multiple alleles?** No, only a small percentage of loci have multiple alleles, perhaps 1-5% or less, depending upon the species (again, this is a rough estimate, scientists don’t really know and gene-hunters frequently ignore variation).

**Epistasis** occurs when a gene at one locus alters the expression of a gene at another locus.

Chromosomal crossover is the process by which two chromosomes pair up and exchange sections of their DNA. This occurs often during prophase 1 of meiosis in a process called synopsis.

**Crossover** usually occurs when matching regions on matching chromosomes break and then reconnect to the other chromosome. The result of this process is an exchange of genes, called genetic recombination. Chromosomal crossovers also occur in asexual organisms and in somatic cells, since they are important in some forms of DNA repair. Although crossovers typically occur between homologous regions of matching chromosomes, similarities in sequence can result in mismatched alignments. These processes are called unbalanced recombination. Unbalanced recombination is fairly rare compared to normal recombination, but severe problems can arise if a gamete containing unbalanced recombinants becomes part of a zygote. The result can be a local duplication of genes on one chromosome and a deletion of these on the other, a translocation of part of one chromosome onto a different one, or an inversion.

Image: Meiotic exchange is not distributed randomly along eukaryotic chromosomes. Meiotic recombination is generally suppressed across the centromere of eukaryotic chromosomes. The most pronounced departure from uniformity is observed near centromeres and telomeres in a wide variety of plant and animal genomes. The centromere exerts a negative effect on recombination activity both within itself and in proximal regions. The figure shows the recombination activity in the juxtacentromeric region of chromosome 21 in CEPH reference families. Recombination rate per physical unit (cM/Mb) in female (black dots, solid line) and in male (white dots, dashed line) have been deduced from segregation data of 24 markers delineating intervals of known physical size, up to 6.6 Mb away from the alphoid centromeric block (hatched box).

Mutations, non-epigenetic disorders: Chromosomal aberrations are disruptions in the normal chromosomal content of a cell, and are a major cause of genetic conditions in humans. Some chromosome abnormalities do not cause disease in carriers, such as translocations, or chromosomal inversions, although they may lead to a higher chance of birthing a child with a chromosome disorder. Abnormal numbers of chromosomes or chromosome sets, aneuploidy, may be lethal or give rise to genetic disorders. Genetic counseling is offered for families that may carry a chromosome rearrangement. The gain or loss of chromosome material can lead to a variety of genetic disorders.

Chromosomal mutations produce changes in whole chromosomes (more than one gene) or in the number of chromosomes present.

- Deletion - loss of part of a chromosome
- Duplication - extra copies of a part of a chromosome
- Inversion - reverse the direction of a part of a chromosome
- Translocation - part of a chromosome breaks off and attaches to another chromosome

Most mutations are neutral - have little or no effect

Source: http://en.wikipedia.org/wiki/Chromosome
Chromosome mutations:  
(non-epigenetic!)

Genetic disorders include:

- Cri du chat,
- Wolf-Hirschhorn syndrome,
- Down's syndrome
- Edwards syndrome
- Patau Syndrome
- Isodicentric 15
- Jacobsen syndrome
- Klinefelter's syndrome (XXY)
- Turner syndrome (X only)
- XYY syndrome.
- Triple-X syndrome (XXX).
- Pallister-Killian syndrome.

Cri du chat, which is caused by the deletion of part of the short arm of chromosome 5. "Cri du chat" means "cry of the cat" in French, and the condition was so-named because affected babies make high-pitched cries that sound like those of a cat. Affected individuals have wide-set eyes, a small head and jaw, and are moderately to severely mentally retarded and very short.

Wolf-Hirschhorn syndrome, which is caused by partial deletion of the short arm of chromosome 4. It is characterized by severe growth retardation and severe to profound mental retardation.

Down's syndrome, usually is caused by an extra copy of chromosome 21 (trisomy 21). Characteristics include decreased muscle tone, stockier build, asymmetrical skull, slanting eyes and mild to moderate mental retardation.[41]

Edwards syndrome, which is the second-most-common trisomy (after Down syndrome). It is a trisomy of chromosome 18. Symptoms include mental and motor retardation and numerous congenital anomalies causing serious health problems. Ninety percent die in infancy; however, those that live past their first birthday usually are quite healthy thereafter. They have a characteristic clenched hands and overlapping fingers.

Patau Syndrome, also called D-Syndrome or trisomy-13. Symptoms are somewhat similar to those of trisomy-18, but they do not have the characteristic hand shape.

Isodicentric 15 on chromosome 15; also called the following names due to various researches, but they all mean the same; IDIC(15), Inverted duplication 15, Inv dup 15, partial tetrasomy 15

Jacobsen syndrome, also called the terminal 11q deletion disorder.[42] This is a very rare disorder. Those affected have normal intelligence or mild mental retardation, with poor expressive language skills. Most have a bleeding disorder called Paris-Trousseau syndrome.

Klinefelter's syndrome (XXY). Men with Klinefelter syndrome are usually sterile, and tend to have longer arms and legs and to be taller than their peers. Boys with the syndrome are often shy and quiet, and have a higher incidence of speech delay and dyslexia. During puberty, without testosterone treatment, some of them may develop gynecomastia.

Turner syndrome (X instead of XX or XY). In Turner syndrome, female sexual characteristics are present but underdeveloped. People with Turner syndrome often have a short stature, low hairline, abnormal eye features and bone development and a "caved-in" appearance to the chest.

XYY syndrome. XYY boys are usually taller than their siblings. Like XXY boys and XXX girls, they are somewhat more likely to have learning difficulties.

Triple-X syndrome (XXX). XXX girls tend to be tall and thin. They have a higher incidence of dyslexia.

Small supernumerary marker chromosome is an extra, abnormal chromosome. Features depend on the origin of the extra genetic material. Cat-eye syndrome and isodicentric chromosome 15 syndrome (or Idic15) are both caused by a supernumerary marker chromosome, as is Pallister-Killian syndrome.

Source: http://en.wikipedia.org/wiki/Chromosome
http://www.ornl.gov/sci/techresources/Human_Genome/posters/chromosome/
Sickle Cell Anemia: J. Herrick (1910) first described sickle-cell anemia, finding that red blood cells (RBCs) change shape (form a sickle) under low O2 tension. Sickled RBCs are fragile, hence the anemia. They are less flexible than normal RBCs, and form blocks in capillaries, resulting in tissue damage downstream. Effects are pleiotropic, including damage to extremities, heart, lungs, brain, kidneys, GI tract, muscles and joints. Results include heart failure, pneumonia, paralysis, kidney failure, abdominal pain and rheumatism. Heterozygous individuals have sickle-cell trait, a much milder form of the disease. V.M. Ingram (1956) found that the 6th amino acid of the β chain in sickle-cell hemoglobin is valine (no electrical charge) rather than the negatively charged glutamic acid in the β chain of normal hemoglobin. Outline of the genetics and gene products involved in sickle-cell anemia and trait:

Wild-type β chain allele is βA, which is codominant with βS.

Hemoglobin of βA/βA individuals has normal β subunits, while hemoglobin of those with the genotype βS/βS has β subunits that sickle at low O2 tension.

Hemoglobin of βA/βS individuals is ½ normal, and ½ sickling form. (The two β chains of an individual hemoglobin molecule will be of the same type, rather than mixed.) These heterozygotes may experience sickle-cell symptoms after a sharp drop in the oxygen content of their environment.

People with one sickle hemoglobin gene and one normal hemoglobin gene (sickle cell trait) are somewhat more resistant to malaria than people with two normal hemoglobin genes. The widely accepted theory is that Hb S offers selective protection against falciparum malaria probably because of induction of sickling even at physiological oxygen tension by *P. falciparum* followed by sequestration of parasitized red cells deep with in reticulo-endothelial system where microenvironment is hostile for parasite growth. Thus people with sickle cell trait would have a better chance of surviving an outbreak of malaria and passing their genes (sickle and normal hemoglobin) to the next generation when they have children.


OMIM (online mendelian inheritance in man) mit ca. \( 18 \times 10^3 \) Eintragungen hat gezeigt dass fänotypische Krankheitserscheinungen nur in ca. 2,3% der Fälle auch eine genotypischen Grundlage haben! Alle anderen korrelieren nur insofern als dass es ein Risikofaktor darstellt an dieser oder jener Krankheit zu leiden: z.B. cystic fibrosis (CF).

But single-gene disorders affect less than two percent of the population; the vast majority of people come into this world with genes that should enable them to live a happy and healthy life. The diseases that are today's scourges - diabetes, heart disease and cancer - short circuit a happy and healthy life. These diseases, however, are not the result of a single gene, but of complex interactions among multiple genes and environmental factors. What about all those headlines trumpeting the discovery of a gene for everything from depression to schizophrenia? Scientists have rarely found that one gene causes a trait or a disease.

In fact, only 5% of cancer and cardiovascular patients can attribute their disease to heredity (Willett 2002). While the media made a big hoopla over the discovery of the BRCA1 and BRCA2 breast cancer genes, they failed to emphasize that ninety-five percent of breast cancers are not due to inherited genes. The malignancies in a significant number of cancer patients are derived from environmentally-induced epigenetic alterations and not defective genes (Kling 2003; Jones 2001; Seppa 2000; Baylin 1997).


Preventable diseases:
- diet and life-style, both contribute to
  - cardiovascular disease,
  - cancers
  - and other causes of death

Evidence indicate that environmental factors are most important.

In fact, only 5% of cancer and cardiovascular patients can attribute their disease to heredity [Willett 2002]. While the media made a big hoopla over the discovery of the BRCA1 and BRCA2 breast cancer genes, they failed to emphasize that ninety-five percent of breast cancers are not due to inherited genes. The malignancies in a significant number of cancer patients are derived from environmentally-induced epigenetic alterations and not defective genes [Kling 2003; Jones 2001; Seppa 2000; Baylin 1997]....

Genetic and environmental factors, including diet and life-style, both contribute to cardiovascular disease, cancers, and other major causes of mortality, but various lines of evidence indicate that environmental factors are most important. Overly enthusiastic expectations regarding the benefits of genetic research for disease prevention have the potential to distort research priorities and spending for health. However, integration of new genetic information into epidemiologic studies can help clarify causal relations between both life-style and genetic factors and risks of disease. Thus, a balanced approach should provide the best data to make informed choices about the most effective means to prevent disease (Willett).

Image: Percentage of colon cancer, stroke, coronary heart disease, and type 2 diabetes that is potentially preventable by life-style modifications. For colon cancer, the low-risk definition includes body mass index <25 kg/m², physical activity equivalent to >30 min per day of brisk walking, folic acid supplement of 100 mg per day or more, less than three alcoholic drinks per day, lifetime nonsmoking, and fewer than three servings of red meat per week. For stroke (unpublished data) and coronary heart disease, the low-risk definition includes nonsmoking, a good diet (incorporating low intake of saturated and trans fat and glycemic load and adequate intake of polyunsaturated fat, N-3 fatty acids, cereal fiber, and folate), body mass index <25 kg/m², physical activity equivalent to >30 min per day of brisk walking, and moderate alcohol consumption. For diabetes, the low-risk definition was similar to that for coronary heart disease except that the dietary score did not include folic acid or N-3 fatty acids.

... Yet ...

• focus still on genes (e.g. SNP in forensic science)
• we keep finding disease-associated genes
• in polygenic inherited diseases only 30% probability of phenotypic expression
• evidence assign epigenetics a far more significant role

that’s why the EU has launched
• EPIGENOME (follow-up project);
• overall costs: 5.3·E6 [€]

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**Single-nucleotide Polymorphism**: Epigenetic markers and patterns are so important that researchers are rallying to begin a project to create an elaborate human epigenome project to map out the entire human epigenome.


Small Image: **Multifaktorielle Ursachen für eine Krankheit**: Das folgende Beispiel soll eine Krankheit zeigen, die einerseits polygenisch verursacht und andererseits von Umweltfaktoren beeinflusst ist. In epidemiologischen Studien wurde das Vorkommen der vier für diese Krankheit verantwortlichen Genvarianten in der kranken Bevölkerungsgruppe bestimmt. Die Abbildung zeigt, dass nebst der genetischen Prädisposition noch weitere Faktoren (Umwelt/Lebensstil) einen Einfluss haben, damit eine Krankheit ausbricht. Im weiteren wird deutlich, dass Varianten des Gens A den grössten Einfluss auf die Krankheit zu haben scheinen, sie jedoch nicht hinreichend erklären können.

Source: http://www.embryology.ch/allemand/kchromaber/genom01.html
A hereditary mix of:

- **Classical genetics** - passing on the recipes of the parent genome
- **Epi-Genetics - Paramutation** (contradicts Mendel’s 1st law)
- **is initiated by Meiosis** i.e. life cycle via gametes, reproduction of haploid cells, (n)


Epigenetic Reprogramming in the Murine Egg and Early Embryo: Once ovulated, the terminally differentiated mammalian oocyte will die if it does not bind and fuse with a sperm. If fertilization occurs, however, maternal gene products orchestrate the transformation of the egg into a totipotent zygote within hours. The mammalian egg is endowed with factors capable of reprogramming terminally-differentiated, transcriptionally-inactive, germ cell nuclei into totipotent embryonic nuclei within a short time period. In the course of differentiation processes cells change their gene expression profiles drastically.

Source: http://www.med.cornell.edu/dgm/coonrod-lab.html
http://www.fz-borstel.de/cms/index.php?id=170&L=1
Gametogenesis & Methylation:

- Methylation in the germ line
- Methylation in preimplantation embryos

Reik et al., 2001

In mammalian embryos there are two major cycles of epigenetic reprogramming of the genome: during preimplantation development and during germ cell development. Reprogramming in germ cells is necessary for imprinting; reprogramming in preimplantation embryos paradoxically can interfere with imprinting and has shaped imprinting mechanisms. It is possible that both demethylation cycles involve active demethylation, and it is crucial to identify the mechanisms. Reprogramming mechanisms in preimplantation embryos affect epigenetic modifications and genome function of cloned embryos. Sequences that escape reprogramming may be involved in epigenetic inheritance. It is important to examine whether in addition to germ cells and early embryos, reprogramming is also involved in stem cell differentiation.

Image:
(A) Methylation reprogramming in the germ line. Primordial germ cells (PGCs) in the mouse become demethylated early in development. Remethylation begins in prospermatogonia on E16 in male germ cells, and after birth in growing oocytes. Some stages of germ cell development are shown [modified from (29)].

(B) Methylation reprogramming in preimplantation embryos (used for preimplantation genetic diagnosis – see below). The paternal genome (blue) is demethylated by an active mechanism immediately after fertilization. The maternal genome (red) is demethylated by a passive mechanism that depends on DNA replication. Both are remethylated around the time of implantation to different extents in embryonic (EM) and extraembryonic (EX) lineages. Methylated imprinted genes and some repeat sequences (dashed line) do not become demethylated. Unmethylated imprinted genes (dashed line) do not become methylated.

(C) preimplantation genetic diagnosis (PGD) is a form of genetic diagnosis performed prior to implantation. This implies that the patient’s oocytes should be fertilized in vitro and the embryos kept in culture until the diagnosis is established …. (preimplantation embryos is used forPGD also known as embryo screening, PIG) - (see wikipedia)

Methylation reprogramming in the germ line and embryo. The figure shows the level of methylation in methylated (black) and non-methylated (grey) imprinted genes and non-imprinted sequences (red = maternal; blue = paternal) during germ-cell and early embryonic development. The horizontal time axis and the vertical axis indicating the relative methylation levels are not to scale. (E, embryonic day.)

In the imprinted region on human chromosome 15, small deletions were found in patients with Prader–Willi syndrome (PWS) in the promoter region of SNURF–SNRPN, and a few kilobases upstream of this, deletions were found in patients with Angelman syndrome (AS). PWS requires paternal transmission of the deletion, whereas AS requires maternal transmission. The intriguing feature of these deletions is that they lead to altered expression and altered methylation patterns of many of the imprinted genes in the region, even if the genes are separated from the deletions by several megabases. This is defined as ‘EPIGENOTYPE spreading’. In the PWS deletions, when paternally transmitted, otherwise paternally expressed genes are silenced and methylated. In the AS deletions with maternal transmission, genes that are otherwise repressed are now demethylated and expressed.

Independent of primary gene sequence, there are genomic modifications that can be passed on from the parental environment – “Epigenetic marks. Both of these genetic disorders are caused by deletion of up to 4Mb on chr.15. Primary genes affected are: SNRPN (small nuclear ribonucleoprotein polypeptide N), NDN (necdin), MKRN3 (makorin), IPWS (imprinted in Prader-Willi syndrome).

Prader-Willi Syndrome (abnormal father copy) del-15q11.2-13

Angelman Syndrome (abnormal mother copy) del-15q11.2-13

Deletions account for ~70%, and always of the paternal chromosome. 28% are uniparental disomy*, always maternal, with NO genomic deletion. 2% are small mutations on the paternal side, affecting the whole region (*usually follows trisomic rescue – 47 chromosomes in fertilised ovum, one lost on cell division - correction by two mistakes).

However, the syndromes differ:

Prader-Willi Syndrome (PWS): obesity, muscular hypotonia, mental retardation, short stature, hypogonadism, small limbs.

Angelman Syndrome (AS): uncontrollable laughter, jerky movements, and other motor and mental symptoms.

Life Cycle (2d/6)

PW-AM-Syndrome:

- *in vitro* fertilisation by intracytoplasmic sperm injection: girls maintained paternal imprint
- 9% of all IVF compared to 4.2% naturally conceived

Gene de-/activation by exposure to light and artificial environment (petri dish)


The risk of major birth defects after intracytoplasmic sperm injection and *in vitro* fertilization

Following

ICS, 26/301 (8.6%) ICS = intracytoplasmic sperm injection
and
IVF, 75/837 (9.0%) have major birth defects

compared with 168/4000 naturally-conceived infants (4.2%)

Assisted reproductive technology (ART) often required for sperm malfunction, but Angelman (for example) which has increased incidence following IVF/ICS is a result of loss of maternal methylation? Increased risk more a reflection of *in vitro* culture effects?
Gametes:

- **Haploid spermatocyte**
  (4 x 40µm)

- **Halpoid oocyte**
  (≈100µm)

Once ovulated, the terminally differentiated mammalian oocyte will die if it does not bind and fuse with a sperm.
Fertilization:

- fusion of **haploid** gametes
- **diploid** zygote (2n)

If fertilization occurs, however, maternal gene products orchestrate the transformation of the egg into a totipotent zygote within hours.
Fertilization:

- fusion of **haploid** gametes
- **diploid** zygote (2n)

… most important
- Zygote is **totipotent** (!)
Organizer & Inducer during Individuation:

1. Blastomere stage
2. Induction of central axis
3. Hensen’s graft experiment
   and Waddingtons deduction of the Organizer

Waddington showed that the grafting of a duck node onto an early chick embryo (at the blastoderm stage) could induce the formation of a second body axis. The most celebrated of his experiments was one on duck embryos in which he joined two blastoderms face to face and showed that each Hensen's node induced another primitive streak in the adjoining blastoderm …. Although, in his day, it was difficult to distinguish the graft from the host and hence determine exactly which parts had been induced, this could be done to some extent on the basis of the size of cells from the different species used. Waddington's conclusions on the organizer-like role of Hensen's node proved essentially correct, but in my view he was not credited sufficiently when interest in this question was re-awakened in the 1990s.

The modern equivalent of 'individuation' is the formation of many specified regions in response to a concentration gradient of the inducer, to which the responding tissue has several threshold responses (Dalcq & Pasteels, 1937) …. In the case of Waddington and the Needhams, it was later found that the neural-inducing activity ('the evocator') are related to steroids …. growth factors, present in picomolar concentrations.

Image: Top - Graft of a duck node (indicated by an arrowhead) onto a chick blastoderm. The original embryo body is on the left, and the induced secondary embryo is on the right. Bottom - The neural tube of the secondary embryo — a cylindrical structure that runs through the midline of the embryo — can be seen clearly in the section on the right.

Omnipotence of the totipotent zygote in embryonic development of the frog *Xenopus laevis*

long-distance communication of MFG in developmental biology

De Robertis, 2006

The entire early embryo constitutes a self-differentiating **morphogenetic field**, in which cells communicate with each other over great distances. This is demonstrated by experiments such as the one shown here, in which an African clawed frog (*Xenopus laevis*) embryo was cut into two halves at the blastula stage. If it is ensured that both halves contain part of the dorsal organizer region, two perfect identical twins are obtained (an intact sibling is shown at the top of the figure). In humans, identical twins are found in 3 out of 1,000 live births, and arise most frequently by the spontaneous separation of the inner cell mass of the mammalian blastula into two, followed by self-regulation. The ultimate example of self-regulation is provided by another mammal, the nine-banded armadillo, in which every blastocyst gives rise to four genetically identical siblings. Note that each twin is longer than just half the length of the intact sibling, which represents yet another effort to regulate towards the normal pattern. Both half-embryos shown here are derived from the same blastula.

The movie starts with photos of Hans Spemann and Hilde Mangold circa 1924. Next, it shows the author at the dissection microscope. Two embryos can be seen, one of which has the dorsal blastopore lip, the Spemann's organizer, clearly visible as a crescent. With the help of a tungsten needle and forceps, a square of organizer tissue is excised — the operation is done free-hand. The organizer is pushed into the ventral side of a recipient gastrula with an eyebrow hair. One hour after transplantation, the graft has, almost miraculously, healed into the host embryo. Two days later, a Siamese twin has developed with two perfect body axes. The Spemann's organizer graft induced complete central nervous systems and mesodermal somites in tissues of the host that would otherwise have become ventral tissue.

Source: De Robertis E.M.; 2006; Spemann's organizer and self-regulation in amphibian embryos; Nature Reviews Molecular Cell Biology 7, 296-302;

http://www.nature.com/nrm/journal/v7/n4/fig_tab/nrm1855_F1.html
Fertilization:
• the totipotent zygote
• dedifferentiation into the 3 main dermal layers (ecto-, meso-, endo-) and germ line
• and their associated specialized somatic cells (environment makes sure that liver cells are produced where liver cells are needed)

Epigenetic Reprogramming in the Murine Egg and Early Embryo: maternal gene products orchestrate the transformation of the egg into a totipotent zygote within hours.
The mammalian egg is endowed with factors capable of reprogramming terminally-differentiated, transcriptionally-inactive, germ cell nuclei into totipotent embryonic nuclei within a short time period. In the course of differentiation processes cells change their gene expression profiles drastically.

The central Dogma: a photocopy of the “recipe book” (genetic code) – every cell of a body has a complete set of this code (holographic memory), only the environment determines which pages of this code are read for the appropriate function (liver cell has to express liver-associated function, proteins, etc, not muscle associated information).

• a specialized cell will only activate the appropriate information of this recipe book (i.e. chapter of the liver);
• a stem-cell can specialize into any cell – therefore is pluri-potential;

Das genom einer jeden Zelle ist im gesamten Organismus identisch – nur wird lokal ein kleiner Anteil davon zum Fenotypus exprimiert (Hautzelle – hautrelevante Gene, Leberzelle - leberrelevante Gene, etc.)

Source: http://www.med.cornell.edu/dgm/coonrod-lab.html
http://www.fz-borstel.de/cms/index.php?id=170&L=1
Imprints are 'established' during the development of germ cells into sperm or eggs. After fertilization, they are 'maintained' as chromosomes duplicate and segregate in the developing organism. In the germ cells of the new organism, imprints are 'erased' at an early stage (but later on re-established!). This is followed by establishment again at a later stage of germ-cell development, thus completing the imprinting cycle. In somatic cells, imprints are maintained and are modified during development. For example, methylation may spread from an IC into the promoter. The imprints are eventually read, resulting in parent-specific gene expression.

Image: Life cycle of methylation imprints. Erasure, establishment and maintenance of methylation imprints at imprinting centres during germ cell and embryonic development. Imprinting control elements 1 (IC1) and IC2 are shown as examples (see chromosome 11p15.5 in FIG.1). Grey indicates modification and white indicates no modification at the corresponding alleles. Parental chromosomes are marked according to their sex in blue (male) or red (female). The reading (transcriptional interpretation of the primary imprints) in the developing embryo is indicated by arrows.

Particular attention is applied to understand how variations in genetic instructions result in human disease and to discover inheritable changes in gene expression patterns that are not due to changes in DNA sequence. Such epigenetic regulations are important mechanisms that organisms use to change gene expression patterns and directly correlate with disease occurrence.

So far, more than 40 imprinted genes have been found; about half are expressed when they come from the father and half when they come from the mother. Among these are a number of disease genes, including the necdin and UBE3A genes on chromosome 15 that are involved in Prader-Willi and Angelman syndromes, and possibly p73, a tumor suppressor gene involved in the brain cancer neuroblastoma. Seven, including Peg3 and Igf2, affect embryonic growth or are expressed in the placenta.

Image: Genome-wide distribution of imprinted genes proved (filled triangles) or predicted with high confidence (unfilled triangles) to be imprinted. Red downward triangles, blue upward triangles, and black dots indicate genes predicted to be maternally, paternally, or bi-allelically expressed, respectively. Light blue bars highlight a 3-Mb region centered on the linkage regions presented in Supplemental Table 6.

The Eukaryotic Cell:

- Plant vs. Animal

again: every cell possesses an entire copy of the genome (holographic principle) – only the closer environment determines fate of cell.

Generalized features of higher plant and animal cells are:

a. A plasma membrane encloses the cytoplasm in both.
b. Plant cells have a rigid cell wall.
c. In both, the nucleus contains DNA complexed with proteins and organized into chromosomes.
d. The nuclear envelope is two layers of semipermeable membrane with pores that allow movement of materials (e.g., ribosomes) between nucleoplasm and cytoplasm.
e. The cytoplasm contains many materials and organelles. Important in genetics are:
   i. Centrioles (basal bodies) are in cytoplasm of nearly all animals, but not in most plants. In animals, a pair of centrioles is associated with the centrosome region of the cytoplasm where spindle fibers are organized in mitosis or meiosis.
   ii. The endoplasmic reticulum (ER) is a double membrane system that runs through the cell. ER with ribosomes attached collects proteins that will be secreted from the cell or localized to an organelle.
   iii. Ribosomes synthesize proteins, either free in the cytoplasm or attached to the cytoplasmic side of the ER.
   iv. Mitochondria are large organelles surrounded by double membrane that play a key role in energy processing for the cell. They contain their own DNA encoding some mitochondrial proteins, tRNAs and rRNAs.
   v. Chloroplasts are photosynthetic structures that occur in plants. The organelle has a triple membrane layer, and includes a genome encoding some of the genes needed for organelle functions.

Every cell possesses an entire copy of the genome (holographic principle) – only those genes according to the environmental context are expressed.
Genes are only **puppets**.
Assorted proteins and RNAs pull the strings, telling the genes when and where
to turn on or off – like switches

**Bookmarking**
cell regeneration via **meiosis**
play a crucial part in it;

Cell Cycle & Mitosis:

- **Mitosis** (somatic cell cycle)
  - growth, development, aging
  - (diploid cells, 2n, almost no crossing over)

- not to be confused with Meiosis
  - (life cycle via gametes via reproduction of haploid cells, n)

Postlethwait & Hospon, 1995

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The cell cycle, or cell-division cycle, is the series of events that take place in a cell leading to its division and duplication (replication). In cells without a nucleus (prokaryotes), the cell cycle occurs via a process termed binary fission. In cells with a nucleus (eukaryotes), the cell cycle can be divided into two brief periods: interphase—during which the cell grows, accumulating nutrients needed for mitosis and duplicating its DNA—and the mitosis (M) phase, during which the cell splits itself into two distinct cells, often called "daughter cells". The cell-division cycle is a vital process by which a single-celled fertilized egg develops into a mature organism, as well as the process by which hair, skin, blood cells, and some internal organs are renewed.

Both unicellular and multicellular eukaryotes show a continuous cell cycle, with growth, mitosis and cell division.

a. The cycle of **somatic mitosis** is determined by the Interphase and is composed of:
   (1) Gap 1 (G1) when the cell prepares for chromosome replication.
   (2) Synthesis (S) when DNA replicates and new chromosomes are formed.
   (3) Gap 2 (G2) when the cell prepares for mitosis and cell division.

b. Relative time in each phase varies among cell types, with duration of G1 generally the deciding factor. Some cells exit G1 and enter a nondividing state called G0.

c. Interphase chromosomes are elongated and hard to see with light microscopy. Sister chromatids are held together by replicated but unseparated centromeres. The chromatids become visible in prophase and metaphase of mitosis. When the centromeres separate, they become daughter chromosomes.

The 25,000 genes of our human DNA are widely considered to be an instruction book for our bodies. However, "genes themselves need instructions for what to do, and where and when to do it." These additional instructions are not in DNA, but on it, in an array of chemical markers and switches, known collectively as the epigenome, that lie along the length of the double helix. These epigenetic switches and markers in turn help switch on or off the expression of particular genes. It has long been known that epigenetic switches are critical to the healthy development of organisms. These can be dramatically tweaked by exposure to a vitamin, a toxin or even mothering, altering "the software of our genes in ways that affect an individual's body and brain for life." Green tea, for example, has been shown to prevent the growth of cancers.

Mitosis is the process in which a eukaryotic cell separates the chromosomes in its cell nucleus, into two identical sets in two daughter nuclei. It is generally followed immediately by cytokinesis, which divides the nuclei, cytoplasm, organelles and cell membrane into two daughter cells containing roughly equal shares of these cellular components. Mitosis and cytokinesis together define the mitotic (M) phase of the cell cycle - the division of the mother cell into two daughter cells, genetically identical to each other and to their parent cell.

Mitosis: somatic cells (PMAT): Daughter cells have the same number of chromosomes as the parent cell.

- **Interphase**: DNA duplication to form chromatids just before mitosis;
- **Prophase**: chromosomes condense, centriole replication & migration, mitotic spindle forms; nuclear envelope breaks down; nucleoli in nucleus cease to be discrete areas; Kinetochore form on the centromeres and become attached to kinetochore microtubules;
- **Metaphase**: chromosomes line up in centre, chromatids still joined at centromere; nuclear envelope completely gone; kinetochore microtubules orient the chromosomes with their centromeres in a plane between the spindle poles, the metaphase plate; a protein scaffold causes the chromosomes to reach a highly condensed state;
- **Anaphase**: chromatids separate (disjunction) and progeny chromosomes move toward opposite poles by kinetochore microtubules; shape of the chromosomes moving toward the poles is defined by their centromere locations; cytokinesis usually begins near the end of anaphase.
- **Telophase** starts when migration of progeny chromosomes is completed; chromosomes begin to uncoil and form interphase chromosomes; cytoplasm divides (nuclear envelope forms around each chromosome group); spindle microtubules disappear; nucleoli reform; nuclear division is complete. Cytokinesis is division of the cytoplasm, compartmentalizing the new nuclei into separate daughter cells.
Cell Cycle (5/7)


... Damit der Zellverband wachsen kann müssen sich Zellen teilen. Zellen können sich aber nur im embryonalen, entdifferenzierten Zustand teilen. Hochdifferenzierte, spezialisierte Zellen wachsen und teilen sich dagegen kaum noch (mitose geht überwiegend nur bei Stammzellen) .... Bei einem hochkohärenten Feldzustand bei dem in den DNS-Molekülen Exciplexe aktiv sind, befinden sich die Zellen eines verbändes im Durchschnitt in der »G₀-Phase« des Zellzyklus .... Dann zerfallen im G₁-Stadium, ausgelöst durch chaotische Impulse (z.B. sterbende Zellen) die bedeutung der Zellverband Informationen verliert .... Das Feld wird immer chaotischer, incohärenter; eine stark erhöhte Biofotonen-Ausstrahlung ist jetzt aussen messbar: Gurwitsch »Degenerationsstrahlung«.

Durch dieses chaotische Feld erhalten die Teilungsbereiten Zellen im Verband den Impuls zur entdifferenzierung und Teilung. Diese Zellen müssen entkoppelt sein .... nur incohärente Fotonen können Wachstumssignale sein. Gleichzeitig werden im G₂-Stadium, durch zufuhre geordneter Energie aus der Nahrung die Exciplexe wieder aufgebaut. Dadurch kondensiert das Chromatin. Jetzt wird auch die DNS verdoppelt, und die eigentliche Zellteilung beginnt (M-Phase) .... Die Mitose-Spindel wird aufgebaut, der Kern geteilt und schliesslich bilden sich zwei Tochterzellen ...

DNA methylation in mammals occurs in the dinucleotide CpG. Methyl groups can be introduced into unmethylated DNA by the de novo methylation enzymes Dnmt3a and Dnmt3b (and perhaps others). When DNA is replicated, the methyl group on the template strand is recognized and a new one is introduced on the opposite (daughter) strand by the enzyme Dnmt1, which can be associated with the replication machinery. In the presence of Dnmt1, hemi-methylated DNA becomes fully methylated and so DNA methylation patterns tend to be maintained (maintenance methylation). Demethylation can occur in the absence of Dnmt1 with continued rounds of DNA replication (passive demethylation), as well as actively (without DNA replication). The nature of demethylases is unknown.

Growth and protection mechanisms are the fundamental behaviors required for an organism to survive. Every day billions of cells in your body wear out and need to be replaced. For example, the entire cellular lining of your gut is replaced every seventy-two hours. It turns out that the mechanisms that support growth and protection cannot operate optimally at the same time. In other words, cells cannot simultaneously move forward and backward. Chronic inhibition of growth mechanisms severely compromises your vitality. In a growth/protection continuum, eliminating the stressors only puts you at the neutral point in the range. To fully thrive, we must not only eliminate the stressors but also actively seek joyful, loving, fulfilling lives that stimulate growth processes.

Image: The ‘two process’ model for sleep can be extended to cell cycle regulation. Circadian oscillations continue with a 24 hour period (2 cycles or days are shown for each panel) over a variety of conditions, creating oscillating upper and lower thresholds for sleep propensity or the cell cycle (A). The second process is characterized by stages, and the time it takes to complete a stage can be modified by changing thresholds (A versus B or C) or by changing rates (A versus D or E). Even in the absence of obvious circa 24 hour gating, the circadian clock can be modulating the second process, namely, sleep or the cell cycle. The stages of the cell cycle are arbitrarily designated here by blue, red, green and yellow, for G1, S, G2 and M, respectively.

Memory-Effect
Autopoiesis (1/15)

Maturana & Varela (1969):

(i) "What is the organization of the living?"

(ii) "What takes place in the phenomenon of perception?"

(iii) the answer to these questions in fact is the same

and expresses the basic identity of "life" and of "cognition" (characteristic of "autopoietic" systems).

What I wish to emphasize here is that this paradigm bears a privileged relationship to the biology of autopoiesis. Maturana (1980) has recounted his long search for answers to two questions:

(i) "What is the organization of the living?"

(ii) "What takes place in the phenomenon of perception?"

and his realization, in 1969, that the answers to the two questions both involved a basic circularity and were, in fact, the same. The term "autopoiesis" was coined by Maturana and Varela (1980), quite explicitly in order to express this basic identity of "life" and of "cognition".

Der chilenische Neurobiologe Maturana berichtet, dass er während seiner akademischen Lehrtätigkeit häufig mit zwei Fragen konfrontiert war (Maturana und Varela, 1980): Erstens, was macht die Organisation lebender Systeme aus und zweitens, was spielt sich beim Phänomen der Wahrnehmung ab? Maturana kam schließlich zur Einsicht, dass sowohl biologische Selbstorganisationsvorgänge als auch Wahrnehmungskontakte in deren Verlauf sich ein Organismus Kenntnis seiner Umwelt verschafft, auf ein und denselben Prozessen beruhen müssen. Diese Einsicht führte zur Theorie autopoietischer Systeme, mit der die Beziehung zwischen Erfahrung und Selbstkonstitution eines Organismus ins Zentrum einer neuen Betrachtungsweise gestellt wurde, die sich von traditionellen Vorstellungen deutlich unterschied …. 

Die Auswirkungen dieser neuen Sichtweise auf die Biologie sind noch nicht abzusehen. Konsequent zu Ende gedacht, führt sie notwendigerweise zu der Vorstellung, dass die Evolution der Arten nicht auf deterministischen Vorgängen wie Mutation und Selektion beruht, sondern auf einem Netzwerk von interdependenten und immer komplexer werdenden Welt erfahrungen. Diese Sichtweise befruchtet derzeit nur die Arbeit einer kleinen Gruppe von theoretischen Biologen und Naturphilosophen. Ihr Erfolg wird entscheidend davon abhängen, ob es gelingt, den vom Materialismus geprägten Substanzbegriff zu überwinden, der die Biologie noch immer dominiert und der biologische Entwicklungen auf eine Veränderung von Komponenten reduziert, zwischen denen nur äußere Beziehungen existieren.


Actual Entities or Actual Occasions’

- ‘actual entities’ or ‘actual occasions’ (circle in center) are acts of perception
- past-cone: indefinite sub-regions leaving no empty space in-b/w.
- region “a” prehends ist past from region “b, g, e, g, x …”
- Interdependence of adaptive events (acts of experience can’t exist independently from each other).
- are intrinsically embeded in a historic context.

Whitehead, 1929: 18

Autopoiesis (4/15)

Actual Entities (AE) & Actual World

- ‘actual world’: perceivable data derive from AEs themselves;
- AEs on the left were finalized in the past;
- results of these AEs are perceivable in new environmental AEs;
- a coherent act of perception is established as an ‘acts of becoming’.

Whitehead, 1929: 18, 28, 65, 69


Autopoiesis (5/15)

Act of Becoming & Emotion

- creative interpretation of “his” environment;
- each AE is an act of experience, a process of “feeling” the data to absorb them into a unity to meet individual satisfaction;
- transformation of incoherence to coherence leads to perception;
- itself generates new sets of data, which are passed on to others;

Whitehead, 1929: 60

Diese Akte des Werdens führen in einem Prozess des Empfindens der vielen Daten zur Emergenz eines empfindenden Subjekts, das mit einer kreativen Interpretation seiner Umwelt sich selbst konstituiert und dadurch eine äußere Form gibt, die dann als Datum anderen Erfahrungsakten vererbt wird und für deren Selbstdarstellung zur Verfügung steht: „Each actual entity is conceived as an act of experience arising out of data. It is a process of ‘feeling’ the many data, so as to absorb them into the unity of one individual satisfaction (Whitehead, 1929/1978, S. 40)”.

Acts of Becoming: “becoming” is the transformation of incoherence to coherence, and in each particular instance ceases with this attainment .... that process leads to acts of PERCEPTION (Whitehead, 1929: 25)

Concrecence

Each actuality is essentially bipolar (physical & mental),
  • the physical inheritance is essentially accompanied by a conceptual reaction of a relevant novel contrast, but always introducing emphasis, valuation and purpose (= required to attain a state of inner-world harmony).
  • the integration of the physical & the mental side into a unity of experience is a self-formation which is a process of concrescence (con-, with & -crescere, to grow)

Whitehead, 1929: 108

….. Every condition to which the process of becoming conforms in any particular instance has its reason either in the character of some actual entity in the actual world of that concrescence, or in the character of the subject which is in the process of that concrescence. This category of explanation is termed the ‘ontological principle.’ It could also be termed the ‘principle of efficient, and final causation.’ This ontological principle means that actual entities are the only reasons; so that to search for a reason is to search for one or more actual entities. It follows that any condition to be satisfied by one actual entity in its process expresses a fact either about the ‘real internal constitutions’ of some other actual entities, or about the ‘subjective aim’ conditioning that process (quote: Whitehead)

**Enduring Objects**

- AEs are microscopic acts of experience
- actual world (environment) is constituted of personally experienced data (historicity!)
- coherent tuning enables an ever increasing level of perception

Whitehead, 1929: 34 & 226

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Self-constitution of organisms

…. occurs on 4 levels:

• Empty space (vacuum-field)
• Life histories (abiotic)
• Life histories (biotic)
• Moments in life of enduring objects (w/ consciousness)

Whitehead, 1929: 226

Autopoiesis (9/15)

Experience & Self-Constition

- avoiding objectivism; i.e focusing on the external view (is a non-mechanistic PoV)
- Coordinating principle must include “animated bond”
- bipolar structure (mind & matter – former can only be accessed indirectly)


Source: http://www.emc.maricopa.edu/faculty/farabee/biobk/BioBookATP.html
Bipolar Structure (cellular level)

can only be accessed indirectly (not by observing objects (i.e. biochemistry)
  • mental manifestation (interprets relevant changes) - organism responds in creative manner to environmental changes
  • physical manifestation (once the adaptation is completed = objectifyable)
  • Σ: organism’s new coherent state;

Falkner, 2009: 5


Autopoiesis (11/15)

Bipolar Structure (cellular level)

- can only be accessed indirectly (not by observing objects (i.e. biochemistry))
  - **mental manifestation** (interprets relevant changes) - organism responds in creative manner to environmental changes
  - **physical manifestation** (once the adaptation is completed = objectifyable)
  - organism’s new coherent state
  - \( \Sigma \): communicative principle

Falkner, 2009: 5

Man kann diesen komplexen Umbau als eine *intrazelluläre Kommunikation* auffassen, bei der die Zelle sich selbst *autopoietisch* hervorbringt (Maturana und Varela, 1980). Dabei entsteht aus jeder „mentalen“ Aktivität dieser Kommunikationsakte, bei der die vorangegangenen physischen Manifestationen interpretiert werden, ein neuer Konstituent, dessen Erscheinungsform vorangegangene mentale und physische Manifestationen enthält.

Adaptive event:

- organism perceives an environmental change only if it leads to different stat. conditions
- **adaptive mode** (mental can’t be measured physically)
- **adapted mode** (physiological, can be objectified via technical instruments)

Falkner, 2009: 7 & 8

Adaptive modes of *Anabaena* sp using P-isotopes in cell culture


Da der nachfolgende zelluläre Umbau die vorher angepassten Energiekonverter potentiell beeinflusst, müssen sich diese von neuem anpassen, was wiederum strukturelle Veränderungen in den anderen Energiekonvertern nach sich zieht. Auf diese Weise setzt sich die durch eine Umweltänderung ausgelöste Erregung zellulärer energie-konvertierender Subsysteme wellenartig in alle möglichen Richtungen durch den Organismus fort und bewirkt dabei alle Arten von molekularbiologisch charakterisierbaren Modifikationen, die nur dann im nachfolgenden Konstitutionsprozess eine transiente Stabilisierung erfahren, wenn aus dem kohärenten Zusammenwirken aller Subsysteme eine Zelle hervorgeht, die unter den jeweiligen Umweltbedingungen wie ein einziger Energiekonverter fungiert, in dem alle anderen Konverter in abgestimmter Weise operieren.

Adaptive event:

- organism perceives an environmental change only if it leads to different stat. conditions
- **adaptive mode** (mental can’t be measured physically)
- **adapted mode** (physiological, can be objectified via technical instruments)
- cellular metabolism has "learned"

Adaptive modes of *Anabaena* sp using P-isotopes in cell culture
Falkner, 2009: 7 & 8


Autopoiesis (14/15)

Adaptive event:

- organism perceives an environmental change only if it leads to different stat. conditions
- **adaptive mode** (mental can’t be measured physically)
- **adapted mode** (physiological, can be objectified via technical instruments)
- cellular metabolism has “learned”
- info passed on epigenetically!

Falkner, 2009: 7 & 8


Während einem adaptiven Ereignis geht das Phosphat-aufnahmesystem - *via* einem *adaptiven Operationsmodus* - von einem *adaptierten Zustand* in den nächsten über. Im adaptiven Operationsmodus wird die Änderung der externen Konzentration in antizipatorischer Weise im Lichte der vorher erfahrenen' Phosphatpulse interpretiert. Dies geschieht in einer Weise, die potentiell die weitere Existenz des Organismus unter den neuen Bedingungen gewährleistet.

Das Wechselspiel zwischen den sich 'subjektiv' verhaltenden adaptiven Operationsmodi und den objektivierbaren adaptiven Zuständen ist verantwortlich für den geschichtlichen Aspekt adaptiver Ereignisse, der vorangegangenen Erfahrungen mit zukünftigen Erwartungen verknüpft.

*Im Übergang von einem adaptierten Zustand in einen adaptiven Operationsmodus werden Informationen von einem adaptiven Ereignis auf das nächste übertragen: Dabei 'ererbt' das nachfolgende Ereignis die Ergebnisse der vorangegangenen Interpretationen. In einer selektiven Aneignung dieser Ergebnisse beginnt seine Zukunft, in der seine eigene Interpretation auf das kommende adaptive Ereignis übertragen wird.*

Culture A: 1 pulse of 10 μM phosphate (Ppart = 1 μmol/L)
Culture B: 10 pulses of 1 μM phosphate (Ppart = 1 μmol/L)

Next day, after an increase of the chlorophyll content from 0.13 to 0.33 mg/L: study of adaptation of cultures A and B during exposition to three pulses of 2 μM (Ppart = 5.5 μmol/L)

Autopoiesis (15/15)

Adaptive event – three examples:

• Ecotoxicology: elevated Cu\(^{++}\)-pollution events
  Falkner & Falkner, 2000

• Allergy: subcutaneous injections as used in hyposensibilization
  Tinkelmann et al., 1995; Phillips et al., 2011

• Osteoporosis: supplementary Ca\(^{++}\) uptake increases risk of MI
  Li et al., 2012

• Obesity: elevated levels of ghrelin modulate the yo-yo-effect
  Sumithran et al., 2011

Ecotoxicity: Due to the inherent historicity of the perception of environmental changes the parameters that describe the interaction of organisms with their environment cannot generally be considered as constants. For example, *Scenedesmus* sp. cultivated at a low copper concentration (0.05 µg/L) is destroyed by immediate exposure to a copper concentration above 20 µg/L. However, if the external concentration in the growth medium is increased gradually over a period of several days, this organism will survive a copper concentration as high as 1000 µg/L.

Allergy: symptoms reported included pruritic eyes, nose, or pharynx (46%); worsening cough (26%); sensation of difficulty swallowing (20%); worsening nasal congestion (15%); rhinorrhea (13%); chest tightness or shortness of breath (11%); generalized pruritus (11%); sneezing (9%); wheeze (4%); and urticaria (2%).

Osteoporosis: Users of calcium supplements had a statistically significantly increased MI (myocardial infarction) risk in comparison with non-users of any supplements (HR=1.86; 95% CI 1.17 to 2.96). This association was more pronounced for calcium supplement only users (HR=2.39; 95% CI 1.12 to 5.12) and persisted after MI cases that occurred in the first 2 years of follow-up were excluded (HR=2.70; 95% CI 1.26 to 5.79). As shown in the extended Cox regression models, the most recent but not the cumulative calcium only supplementation was significantly positively associated with MI risk (HR=2.17; 95% CI 1.06 to 4.42). No statistically significant association was found between calcium supplementation and either stroke risk or overall CVD mortality.

Obesity: it is a hard battle for people to maintain weight loss – there is a very high failure rate if you look at them a few years down the track. Even if people are very motivated to keep their weight. Various hormones control hunger, but following weight loss, leptin levels fall while ghrelin levels rise. Ghrelin is the hormone that makes us feel hungry. Following weight loss ghrelin levels increased. This hormone tells us to go and eat.

Source:
Organisms (1/5)

Bipolar Structure (cellular level)

can only be accessed indirectly (not by observing objects (i.e. biochemistry)
  • mental manifestation (interprets relevant changes) - organism responds in creative manner to environmental changes
  • physical manifestation (once the adaptation is completed = objectifyable)
  • organism’s new coherent state
  • communicative principle

Coherence: Abscissa: “1” represents the balance of operation (Homeostasis) - from left to right:
  Functional Complexity – from atoms, to molecules, organelles, cells, organs, organisms,
societies and beyond.

i) Holographic organism: Although biophotonic processes are predominantly associated to the DNA, they propagate via the microtubular network of the cytoskeleton to the extracellular matrix, thereby involving the entire organism. It is even assumed that any organism (incl. Humans act as a holographic biocomputer). A common hypothesis claims that information in the brain is not stored in localized areas of the brain but rather smeared like a hologram over the entire brain (and even further including even the whole organism). Thereby, information is retrieved via a built-in Fourier transformation and converted to distinct action potentials.

ii) Living systems are neither mere subjects, nor objects, but subjects and objects at the same time. In contrast to the Neo-Darwinistic point of view the capacity of evolutionary development does not originally depend on the rivalry and power in the fight for existence, rather, it depends mainly on the capacity of communication; they can be looked upon at as expanding antennae systems (coherent network of AEs embedded in a NEXUS).

iii) Not only tissues and organs are tied together to form an organism, also members of a group, of a culture, a society. Symbolically, the immune system and a society perform similar tasks – it protects the group from potentially dangerous influences. Pandemics or even epidemics are challenges to the entire social ‘immune system’. If the feeling of being ‘crippled’ is evident within a society, its members to a large extent reflect this attitude (see F.D.Roosevelt’s election, 1933: a handicaped president for a crippled nation trying to escape the great depression). Most members are victims of the tribal culture.

Obige Skizze soll darstellen wie Einzeller eine vielzahl an lebensnotwendigen Interaktionen durchfuehren und dadurch einen relativ hohen Freiheitsgrad erlangen, wohingegen in Vielzellen der Freiheitsgrad durch zunehmende Spezialisierung & Arbeitsaufteilung je nach Organverband drastisch sinkt. Allerdings erlangt der Gesamtkörper sich dadurch einen wiederum hoheren Freiheitsgrad als die einzelne Zelle des Organismus.

Communicative principle

- metabolism @ cellular level (biochemical constraints)
- changes in outer environment result in complete reorganization of cellular metabolic pathways
- reorganization to attain stability @ max. efficiency (min. entropy)

Falkner, 2009: 6

Organisms (3/5)

Living systems are neither mere subjects, nor objects, but subjects and objects at the same time. In contrast to the Neo-Darwinistic point of view the capacity of evolutionary development does not originally depend on the rivalry and power in the fight for existence, rather, it depends mainly on the capacity of communication; they can be looked upon at as expanding antennae systems (coherent network of AEs embedded in a NEXUS).

As with any organism, so is the human body not only surrounded by the near exo-environment but literally penetrated by it – the skin seems to be a protective border, but it breaths just as any other living tissue (physiological functions include sweating, induced by active transport of ions across the barrier). This is by no means a one-way road as toxicology studies show that application of chemicals applied to the skin are absorbed immediately into the system without passing the liver(!).

The lungs (coarsely spoken a passively ventilated and everted sac) with the huge surface area are likewise an ideal interface of metabolic exchange (gas-exchange of CO₂ and O₂), however inhalation of therapeutic as well as toxic substances are readily conveyed into the body via inhalation (aerosols of various origin, like alcohol, drugs, pure oxygen, etc); such substances can also be introduced without being filtered out or detoxified by the liver.

The intestine (roughly spoken a tube with two ends in which the environment is “channeled” through) is by far the largest interface with the exo-environment; enzymatic and digestive activity breaks down coarse organic matter to make it absorbable via villi of the mucosa.

Surface Areas of a ~1.5 m tall person.
Skin is ~2 m².
Lung is <100 m².
Intestine is ~300 m².

Source: http://www.vendian.org/envelope/dir2/lungsout.html
Organisms (4/5)

Flow of Energy

- once interpretable & interpreting manifestation are present an internal tension responds to external changes – flow of energy increases (ontological difference)
- system reveals memory (smeared over the entire organism / ecosystem)

Falkner, 2009: 6


Organisms (5/5)

Flow of Energy

- once interpretable & interpreting manifestation are present an internal tension responds to external changes – flow of energy increases (ontological difference)
- system reveals memory (smeared over the entire organism / ecosystem)
- subsystems tend to attain stationary states under optimal efficiency!

Falkner, 2009: 6


Energy Efficiency

- reshaping of energy converting sub-systems during an adaptive mode
- available energy used with max. efficiency
- all sub-systems interact coherently during the adaptive phase (sensing of environment)

Whithead, 1929: 107

12-06-13 Madl
Steady State (2/12)

Energy Efficiency

- reshaping of energy converting sub-systems during an adaptive mode
- available energy used w/ max. $\eta$
- all sub-systems interact coherently during the adaptive phase (sensing of environment)
- once adapted state is reached, the many become one and are increased by one
- that’s real evolution!

Whitehead, 1929: 107

A Holistic relationship is a way to transform oneself from within. It depicts an ever-increasing sense of inter-relatedness and thus responsibility as one ascends along the evolutionary axis of consciousness. (Sponberg)

The ultimate metaphysical principle is the advance from disjunction to conjunction, creating a novel entity other than the entities given in disjunction. The novel entity is at once the togetherness of the ‘many’ which it finds, and also it is one among the disjunctive ‘many’ which it leaves; it is a novel entity, disjunctively among the many entities which it synthesizes. The many become one, and are increased by one. In their natures, entities are disjunctively ‘many’ in process of passage into conjunctive unity (quote: Whitehead)

Communicative Dynamics:
Systems relies on matter, energy and information:

\[ E_{QM} = h \cdot n \]  
\[ E_{RT} = m \cdot v \cdot c^2 \]  
\[ dE + dm + dI = 0 \]  (P. Manzelli, 2006)

Energy: the potential for causing change.
Information: a »bit« of information is definable as a difference that makes a difference (Bateson) - the content about Form & Gestalt in a message.
Matter: the physical & objectifyable world.

Information-Energy-Matter Triad: With the quantum potential, its effect on a particle depends on its form rather than its magnitude. The effect is the same regardless of the strength of the wave. The wave may have larger effects even at long distances, for the wave does not carry energy; it is an information wave with mental & physical properties (see ship travelling on auto-pilot controlled by satellite: the information contained within the radio waves actually guides the enormous energy possessed by the ship).

- Energy: "the potential for causing changes", is a concept used to understand dynamics of most physical processes
- Information: materialized information becomes matter. Bei der Erfahrung der Umwelt durch ein System kommuniziert die Community der Elementarprozesse Informationsinhalte über das Verhältnis System/ Umwelt. Die Leitdifferenz zwischen System und seiner Umwelt wird zur theoretischen Informationsverarbeitungs-möglichkeit. Damit kommen wir zur systemtheoretischen Definition der Information: a »bit« of information is definable as a difference that makes a difference (Bateson).
- Matter: is the substance of which physical objects are composed. It constitutes the observable (objectifyable) universe. According to the theory of relativity there is no distinction between matter and energy, because matter can be converted to energy, and vice versa.

Information is the bridge between soma and significance: The wave function is the mental (or significance aspect) of the electron. The field (wave function) and particle are never separate and are actually aspects of the same reality. The field (AE) acts on the particle, not by intensity, but by its form (information). It gives rise to an activity that is identified with meaning (proto-intelligence) guides the electron as radio waves guide the ship.

Source: Dürr H.P., Popp F.A., Schommers W., 2000; Elemente des Lebens; p.259-273;
Communicative Dynamics:

The more an organism survives, the more it experience, the more valuable its genome – the genome is proportional to the mass or experience compressed therein.

Kuhn, 1988

Ex-formation: explicitly discarded information

Complexity is found between order & disorder

Hubermann & Hogg, 1986

According to Hans Kuhn (1988), chemist … biological evolution consists of a series of choices where an organism relates to its surroundings. These surroundings subject it to pressure, and it must choose to act in order to survive. An organism’s genes contain experience in survival – otherwise there would be no organism, and no genes. The more the organism survives, the more it experiences. And the more valuable its genes become. So the interesting thing is not how many genes it has – i.e. how long its DNA is. The interesting thing is the wealth of experience deposited in its genes.

The information of organism contains it its genes has a value that is proportional to the mass of experiences compressed there. What’s interesting is not the face value of the information – i.e. the size of genes (genome) – but rather the information discarded. “This quality constitutes knowledge, where ‘knowledge’ is measured by the total number of bits to be discarded”. Kuhn wrote. Biological knowledge, then is defined as discarded information.

Exinformation is perpendicular to information. Exinformation is about the mental work we do in order to make what we want to say sayable. Exinformation is discarded information, every time we do not actually say but we have in our heads when or before we say anything at all …. Exinformation is the history of the message, information the product of that history – information without exformation is vacuous chatter; exformation without information is not exformation but merely discarded information „„


Steady State (4/12)

Learning & Anticipative Properties

- adaptive event result in adapted state (reshapes metabolism)
- this in turn determines direction of successive events (!)
- inherent anticipating character of organism (teleological orientation)
- that’s evolution!

Falkner, 2009: 8 & Balzer, 2006


A regulatory state (e.g. sector 06) is determined by the variability of a regulatory process. Upon stimulation, regulatory patterns become more rapid - shorter periods - right side of abscissa of this sector. Faster regulatory patterns prevail in the event of activation. Relaxation, on the other hand favors slower regulatory patterns (longer periods - left side of abscissa within the sector). Examples of typical regulatory patterns: 17 corresponds to chronic stress; 11: deep relaxation; 52-56: neurotic state; 62-66: depressive state. Coma patients are most likely to be found within the more rigid regulatory pattern.

The Smard-Watch is thus an instrument suitable to monitor physiological response patterns of a person under investigation. It is a tool to show how coherent this person interacts with its surroundings. It also reveals the persons robustness to external stress factors. Time structure manifests itself most clearly in the range of biological rhythms that extend over some ten orders of magnitude from the millisecond oscillations of membrane action potentials to 10^E5 for circannual rhythms, which are coherent over varying spatial domains from single cells to entire organs and from whole organisms to populations of organisms. This implies a vast unexplored area, as the notion of non-linear, structured time is alien to the conventional scientific framework.

Resonance on a larger scale (Chronobiology): Periodic Regulatory States obtained from the correlated SMARD-watch data (Electro-Myogram, Skin-Potential, Skin-Resistance).
Learning & Anticipative Properties

- organism creates its own “framework” whereas,
- traditional attractor model rely on an external framework (user)
- biological systems are able to evolve themselves - that’s evolution!

Falkner, 2009: 6

Interaction with the surrounding: The entire body - in particular when talking about proteo-glycans (sugary proteins) can be considered as a huge liquid-crystalline macro-molecule, that is according to its dissipative nature subject able to flip-flop from one state to the other (to flip over from a healthy state to a sick state).

Oscillating Patterns in Biology (self-determined framework): Attractor: the path in which an oscillatory process can operate;

Steady State (6/12)

Endothelial (blood-vessel lining) cell
• change structure & function depending on environment
• inflammation: behaves like macrophage

Bergeron et al., 2006

Studying endothelial cells, which are the blood vessel-lining cells, it is possible to observe changes in their structure and function depending on their environment. For example, adding inflammatory chemicals to the tissue culture, the cells rapidly became the equivalent of macrophages, the scavengers of the immune system (this trans-differentiation results in the acquisition of properties usually attributed to cells of the reticulo-endothelial system) … These cells were clearly showing some 'intelligent' control in the absence of their genes [Lipton et al., 1991] … DNA does not control biology and the nucleus itself is not the brain of the cell. Just like you and me, cells are shaped by where they live. In other words, it's the environment …

Image: Differentiation of hematopoietic cells (HCs) and proper vessel development requires HIF-1-dependent factors. HIF-1 promotes the survival of HCs, which supply VEGF. VEGF induces vasculogenesis by increasing production and proliferation of endothelial cells. Loss of HIF-1 beta/ARNT results in HIF deficiency, increased apoptosis of HCs, reduction in VEGF production and endothelial cell number, and inadequate vessel growth and branching.

http://www3.interscience.wiley.com/cgi-bin/fulltext/119354142/PDFSTART
RBC (red blood cell)

• erythrocyte is an enucleated cell

• following an injury…. the cell dedifferentiates and “reconstructs its nuclear body (!).

• it acts like a stem cell and is involved in tissue regeneration

Becker & Marino, 1982,

Sequence of morphological changes in a single frog nucleated erythrocyte exposed to very low levels of electrical current. The same cell was photographed at intervals of 5 minutes, demonstrating a change from the normal red cell type to a cell that has become round, lost all its hemoglobin, and has major phase changes in its nucleus. These cells are quite alive, surviving in cell culture and chemically demonstrating a marked increase in RNA content and a complete alteration in protein composition.

…. In four hours all the red blood cells in the chamber had reactivated their nuclei, lost their hemoglobin, and became completely unspecialised in form (reactivating the holographic principle) …. 

Most cells contain the same set of genes, but their phenotype can vary according to which genes are expressed and repressed. Alterations in gene-expression patterns, without changes in DNA sequences, are referred to as epigenetic mechanisms. Epigenetic mechanisms make it possible to restore pluripotency to a differentiated cell, and a differentiated cell can also undergo transdifferentiation resulting in a pronounced change in its appearance and function. Mammalian genomes contain an additional layer of epigenetic information referred to as parental 'imprints'. These imprints are erased and re-initiated normally in the germ line, and passed on to the offspring in which they survive into adulthood. Parental imprints also regulate gene expression and confer functional differences on parental genomes during development. **Parental imprints can undergo changes without affecting the fundamental property of pluripotency.**

…. studies will allow us to assess more precisely events associated with reprogramming of somatic nuclei to a pluripotent or a totipotent state.

Steady State (9/12)

Is the nucleus truly the cell's brain?

• **Enucleation** (extraction of nuclear body)

• following enucleation ....
  i) cell survives
  i) cell ingests & metabolizes
  i) retains coordinated physiologic functions
  i) retains ability to communicate

• without its genes, cell looses capability to
  i) to adapt to changes
  i) to divide and

---

Enucleation: refers to removing the nuclear body of a cell

.... But is the nucleus truly the cell's brain? If our assumption that the nucleus and its DNA-containing material is the "brain" of the cell, then removing the cell's nucleus, a procedure called enucleation, should result in the immediate death of the cell .... By applying a little suction, the nucleus is drawn up into the pipette and the pipette is withdrawn from the cell. Below the nucleus-engorged pipette lies our sacrificial cell - its "brain" torn out .... But wait! It's still moving! My God ... the cell is still alive! ..... Soon the cell is back on its feet (OK, its pseudopods), fleeing the microscope's field with the hope that it will never see a doctor again (an enucleated cell is like an erythrocyte, still alive).

Following enucleation, many cells can survive for up to two or more months without genes .... These cells actively ingest and metabolize food, maintain coordinated operation of their physiologic systems (respiration, digestion, excretion, motility, etc.), retain an ability to communicate with other cells, and are able to engage in appropriate responses to growth and protection-requiring environmental stimuli ....

Without their genes, cells are not able to divide, nor are they able to reproduce any protein parts they lose through the normal wear and tear of the cytoplasm .... The results are unambiguous: enucleated cells still exhibit complex, coordinated, life-sustaining behaviors, which imply that the cell's "brain" is still intact and functioning ....

Eventually enucleated cells die .... because they have lost their reproductive capabilities .... The nucleus is the cell's gonad! .... Males have often been accused of thinking with their gonads, so it's not entirely surprising that science has inadvertently confused the nucleus with the cell's brain!


Steady State (10a/12)

Measles (a viral infection):
• immature immune cells create antibody;
• its DNA encodes segments of snippets
• random assemblage of ""-
• cells create an array of diff. genes (!)
• cell with a close physical complement to the virus will be activated (affinity maturation)
• during somatic hypermutation 1000s of copies of this antibody is made
• correct recipe transcribed into the genome! (genetic memory)

For example, when a measles virus infects a child, an immature immune cell is called in to create a protective protein antibody against that virus. In the process, the cell must create a new gene to serve as a blueprint in manufacturing the measles antibody protein ....

In generating a specific measles antibody .... their genes are a very large number of DNA segments that encode uniquely shaped snippets of proteins. By randomly assembling and recombining these DNA segments, immune cells create a vast array of different genes, each one providing for a uniquely shaped antibody protein. When an immature immune cell produces an antibody protein that is a "close" physical complement to the invading measles virus, that cell will be activated.

Activated cells employ an amazing mechanism called affinity maturation that enables the cell to perfectly "adjust" the final shape of its antibody protein, so that it will become a perfect complement to the invading measles virus [Li, et al, 2003; Adams, et al, 2003].

Using a process called somatic hypermutation, activated immune cells makes hundreds of copies of their original antibody gene. However, each new version of the gene is slightly mutated so that it will encode a slightly different shaped antibody protein. The cell selects the variant gene that makes the best fitting, antibody. This selected version of the gene also goes - through repeated rounds of somatic hypermutation to further sculpt the shape of the antibody to become a "perfect" physical complement of the measles virus [Wu, et al, 2003; Blanden and Steele 1998; Diaz and Casali 2002; Gearhart 2002] ....

Image: www.who-measles.org/Public/Web_Front/about_db.php
www.aap.org/pressroom/aappr-photos.htm
Measles (a viral infection):

the immune cell:
• retain the genetic "memory" of this antibody
• antibody gene can also be passed on

hence, the immune cell
• learned about the measles virus
• created a memory that will be inherited and propagated by its daughter cells (!)

Steele et al., 1998

The cells retain the genetic "memory" of this antibody …. The new antibody gene can also be passed on to all the cell's progeny when it divides. In this process, not only did the cell learn about the measles virus, it also created a "memory" that will be inherited and propagated by its daughter cells. This amazing feat of genetic engineering is profoundly important because it represents an inherent "intelligence" mechanism by which cells evolve [Steele, et al, 1998].

http://home.planet.nl/~gkorthof/kortho39.htm
Image: www.who-measles.org/Public/Web_Front/about_db.php
www.aap.org/pressroom/aappr-photos.htm
Since autopoiesis and organismic philosophy are able to explain the principles of evolution much better than neo-Darwinism was ever able to do, it becomes obvious that the network of life in itself is a coherent system. In order to thrive, such a system requires constant and permanent interchange in order to initiate meaningful, continuous synthesis and de-novo creation – this is not intelligent design, this is real evolution.

Image: During the last decade the study of virus evolution has been disregarded by a large part of the genomics communities. This is partially due to the traditional view that conceptualize viruses as non-living tiny particles carrying a few fast evolving genes stolen from their host. Such a “gene pickpocket” view of virus discouraged further efforts to explore the history of viral genomes by comparative sequence analysis and enclosed thinking on virus evolution into a rigid conservative framework. Simultaneously with the accumulation of genomic sequence data for large viruses, several authors have proposed bold new ideas that put viruses in the center of diverse evolutionary scenarios. Consequently, the study of virus evolution is now back on the central stage, and is probably essential to the comprehension of the origin of cellular life.

Source: http://www.igs.cnrs-mrs.fr/SpiPiInternet/IMG/jpg/figure_2.jpg
The sharing of genetic information via *gene transfer* speeds up evolution since organisms can acquire "learned" experiences from other organisms [Nitz, et al, 2004; Pennisi 2004; Boucher, et al, 2003; Dutta and Pan, 2002; Gogarten 2003] …. Given this sharing of genes, organisms can no longer be seen as disconnected entities; there is no wall between species. Daniel Drell, manager of the Department of Energy's micro-bial genome program told *Science* in (2001 294:1634): "...we can no longer comfortably say what is a species anymore" [Pennisi 2001] ….

Source: Lipton B;. 2005: Biology of Belief. Elite Books, p.44


New data emerging from microbial genome sequences are so perplexing that they call into question what defines a species. Two bugs in particular, described at a recent meeting, seem to have nabbed enough genes from other organisms that they no longer resemble their supposedly closest relatives--raising fascinating questions about how and why they obtained these new traits.


http://www.nature.com/nrmicro/journal/v3/n9/full/nrmicro1253.html
Mem-Brain (1/13)

Membrane: a *liquid crystal "semiconductor* with gates and channels ....

The Membrane is the interface / window to the cell's closer environment.

Here, we put forth our nominee for the true brain that controls cellular life - the membrane .... the magical mem-Brain ....

A bacterium eats, digests, breaths, excretes waste matter and even exhibits “neurological” processing .... They can recognize toxins and predators and purposely employ escape manoeuvres to save their lives .... Prokaryotes display intelligence! (see E.B.Jakob’s talk @ NatGenEdit, 2008) ....

In effect, this lipid core is an electrical insulator, a terrific trait for a membrane designed to keep the cell from being overwhelmed by every molecule in its environment (EMR-penetration) ....

There are lots of Integral Membrane Proteins (IMPs) with lots of different names, but they can be subdivided into two functional classes: *receptor proteins* and *effector proteins*.

Receptor IMPs are the cell’s sense organs, the equivalent of our eyes, ears, nose, taste buds, etc. Receptors function as molecular "nano-antennas" tuned to respond to specific environmental signals. Some receptors extend inward from the membrane surface to monitor the internal milieu of the cell. Other receptor proteins extend from the cell's outer surface, monitoring external signals ....

Life-sustaining response, are associated to the effector proteins.

"The membrane is a liquid crystal semiconductor with gates and channels" (see Becker & M.W.Ho) ....

http://www.sciencemag.org/content/291/5512.cover-expansion
Membrane bound proteins are the main communicating interfaces at cellular level …. When a gene product is needed a signal from its environment …. activates the expression of the gene” (Nijhout, 1990)

signals: insulin, histamine, estrogen (attach to receptor protein (=antenna); effector protein translates this into a signal cascade to promote:

I) cytosolic protein activation
II) protein synthesis (nucleus)
III) coding novel genes at DNA-level

Integral Membrane Proteins

- Membrane switches are units of perception - read environmental signals and adjust cellular metabolism

The membrane's receptors are the equivalent of sensory nerves, and the effector proteins are the equivalent of action-generating motor nerves. Together, the receptor-effector complex acts as a switch, translating environmental signals into cellular behavior.

Instead it is the membrane's effector proteins, operating in response to environmental signals picked up by the membrane's receptors, which control the "reading" of genes so that worn-out proteins can be replaced, or new proteins can be created. To exhibit "intelligent" behavior, cells need a functioning membrane with both receptor (awareness) and effector (action) proteins. These protein complexes are the fundamental units of cellular intelligence. Technically they may be referred to as units of "perception". The definition of perception is: "awareness of the elements of environment through physical sensation".

Integral membrane receptor-effector proteins (IMPs) are the fundamental physical subunits of the cellular brain's "intelligence" mechanism.

http://spectrum.troy.edu/~cking/Biochemistry/Biochemistry%20Test%203,%20answers,%202007F.htm
Electromagnetic Fields (EMF)

- weak EMF (pulsed) promote bond cell regeneration, DNA-, RNA- and protein biosyntheses.
- Activation of the (K⁺)-pump of Na-K-ATPase by an oscillating electric field, with no consumption of ATP.
- Resonance frequencies in activating the K⁺-pump is 1kHz and Na⁺-pump 1MHz respectively.
- Cell membrane is a site of the field amplification (according to Maxwell relation, an external electric field is amplified by approx. RCell/dmembrane-times).

Mem-Brain (4/13)

Tsonga, 1989

Image: Activation of the Rb⁺ (K⁺)-pump of Na⁺-K⁺-ATPase by an oscillating electric field, at 4°C.

(top) Human erythrocytes were exposed to an oscillating electric field of 20 Vcm⁻¹ at different frequencies for 1h. Rb⁺ uptake was monitored by the radioactive tracer, ⁸⁶Rb⁺ (see text and Ref. 12). Rb⁺ uptake of electric-field stimulated samples (0), stimulated samples treated with 0.2 mM ouabain (D), non-stimulated samples (D), and non-stimulated sample treated with ouabain (A) are plotted against the frequency of the applied field.

(bottom) The same experiment, with an electric field of 11kHz at different field strengths. Symbols used are the same as in (a). In similar experiments no ouabain-sensitive Rb⁺ efflux was stimulated by the electric fields. The cytoplasmic concentration of Rb⁺ was 27 mM, and the external concentration of Rb⁺ was 10 mM. Thus, the field induced Rb⁺ uptake was an active transport. No consumption of ATP was detected.

The receptor used by the bacterium *Escherichia coli* to detect temperature. This is the **very same protein** - the chemotaxis receptor, Tar - that *E.coli* uses to detect the amino acid aspartate. Not only that, but also to **sense** of the temperature response depends upon the concentration of aspartate in the environment. … *E. coli* has three other types of methyl-accepting receptors in addition to Tar, and between them they mediate attractant and repellent responses to perhaps 50 distinct chemicals, as well as to pH and temperature.

**Combinatorial possibilities of receptor clusters.** Several thousand transmembrane chemotaxis receptors of *E.coli* aggregate together in the plasma membrane by binding to downstream signaling proteins. Each receptor has **eight possible sites of methylation** (white circles) and can exist in at least two conformational states (gray or black). Four homologous types of receptor (distinguished by the color of their binding sites) are randomly mixed within the cluster and interact in groups of three.

Image E.Coli: http://www.arn.org/blogs/index.php/literature/2008/06/10/on_the_evolution_of_a_key_innovation_in
Integral Membrane Proteins

• Transport proteins: shuttle molecules and information from one side to the other

• Na-K-ATPase

Transport proteins, for example, include an extensive family of channel proteins that shuttle molecules and information from one side of the membrane barrier to the other. Sodium-potassium ATPase: every cell has thousands of these channels built into the membrane. Collectively, their activity uses almost half of your body's energy every day.

Na-K-ATPase not only uses up a lot of energy.

Energy-producing activity of Na-K-ATPase

As these proteins go through hundreds of cycles per second, the inside of the cell becomes negatively charged while the outside of the cell becomes positively charged. The negative charge below the membrane is referred to as the membrane potential. Of course the lipid-portion of the membrane, does not let charged atoms cross the barrier, so the internal charge stays negative. The positive charge outside the cell and the negative charge inside make the cell essentially a self-charging battery whose energy is used to empower biological processes.

Image: http://www.mpib-frankfurt.mpg.de/meier/ATPase.jpg
Integral Membrane Proteins

- Membrane switches are units of perception - read environmental signals and adjust cellular metabolism
- Each cell is studded with $100 \times E^3$ of receptor molecules – each one programmed to attract & bind particular peptides
- Receptor: awareness of environment
- Effector: life-sustaining response – control the “reading” of genes

While the receptor provides an awareness of environmental signals … the life-sustaining response is made by the effector proteins. The receptor-effector proteins are a stimulus-response mechanism …. The membrane's receptors are the equivalent of senso-ry nerves, and the effector proteins are the equivalent of action-generating motor nerves. Together, the receptor-effector complex acts as a switch, translating environmental signals into cellular behavior ….

Instead it is the membrane's effector proteins, operating in response to environmental signals picked up by the membrane's receptors, which control the "reading" of genes so that worn-out proteins can be replaced, or new proteins can be created …. To exhibit "intelligent" behavior, cells need a functioning membrane with both receptor (awareness) and effector (action) proteins. These protein complexes are the fundamental units of cellular intelligence. Technically they may be referred to as units of "perception". The definition of perception is: "awareness of the elements of environment through physical sensation" …. The behavior of a cell can only be understood by considering the activities of all the switches at any given time (quorum sensing) …. Cells became smarter by utilizing their outer membrane surface more efficiently and by expanding the surface area of their membranes so that more IMPs could be packed in …. 

Image: Controlling cell growth and differentiation: the extracellular domain contains the binding site for growth factor and the cytosolic domain contains the tyrosine kinase catalytic site. The two domains are connected by a single transmembrane helix.

Stryer L. Biochemistry 4th ed. W.H.Freeman, p.350
http://www.uic.edu/classes/bios/bios100/mike/spring2003/lect07.htm
Integral Membrane Proteins

- Receptor-Effect coupling lead to
- signal transduction pathway

However ….

- simplistic belief of linear life-supporting biochemical reactions cannot keep up with …. 

Conventional biologists are reductionists who believe that mechanisms of our physical bodies can be understood by taking the cells apart and studying their chemical building blocks. They believe that the biochemical reactions responsible for life are generated through sequentially arranged assembly lines ….

This reductionist model suggests that if there is a problem in the system, evident as a disease or dysfunction, the source of the problem can be attributed to a malfunction in one of the steps along the chemical assembly line …. This assumption spurs the pharmaceutical industry’s search for magic bullet drugs and designer genes.

However, because of their Newtonian, materialistic bias, conventional researchers have completely ignored the role that energy plays in health and disease …. 


http://www.uic.edu/classes/bios/bios100/mike/spring2003/lect07.htm
Integral Membrane Proteins
• Receptor-Effecter coupling lead to signal transduction pathway

However ….
• simplistic belief of linear life-supporting biochemical reactions cannot keep up with ….
• the holistic network of simultaneously interacting subunits
• manifold ways to crosstalk via other communication loops

Biological systems are redundant

However, the quantum perspective reveals that the universe is an integration of interdependent energy fields that are entangled in a meshwork of interactions. Biomedical scientists … do not recognize the massive complexity of the intercommunication among the physical parts and the energy fields that make up the whole …. The flow of information in a “quantum universe” is holistic …. A biological dysfunction may arise from a miscommunication along any of the routes of information flow ….


We can now see why pharmaceutical drugs come with information sheets listing voluminous side effects that drug inevitably interacts with at least one and possibly many other proteins . . . . Biological systems are redundant

Drosophila melanogaster is a proven model system for many aspects of human biology. Here we present a two-hybrid–based protein-interaction map of the fly proteome. A total of 10,623 predicted transcripts were isolated and screened against standard and normalized complementary DNA libraries to produce a draft map of 7048 proteins and 20,405 interactions. A computational method of rating two-hybrid interaction confidence was developed to refine this draft map to a higher confidence map of 4679 proteins and 4780 interactions. Statistical modelling of the network showed two levels of organization: a short-range organization, presumably corresponding to multi-protein complexes, and a more global organization, presumably corresponding to intercomplex connections. The network recapitulated known pathways, extended pathways, and uncovered previously unknown pathway components. This map serves as a starting point for a systems biology modelling of multicellular organisms, including humans.

Simple signal transduction:

- via thermal stress
- via EMF-stress

Differences in signaling pathways between magnetic stress and heat shock. The induction of HSP70 by EMFields utilizes either of the two transduction pathways. One pathway contains steps that are reminiscent of the heat shock pathway, i.e., HSF1-binding to HSE. In EMFields stress, HSF1 binds to an HSE upstream of the heat shock domain. Magnetic stress also uses a pathway that involves AP-1 binding. EM field exposures induce HSF1 phosphorylation by members of the MAPK subfamilies (ERK1, JNK/SAPK, and p38 protein kinase) resulting in increased protein levels for hsp70, c-Fos, AP-1 binding activity and increased MAPK/ERK1/2 phosphorylation (Jin et al., 2000).

Abbreviations: heat shock protein HSP 70, heat shock gene; hsp, heat shock protein; HSF, heat shock factor; HSE, heat shock element; bp, base pair; mG, milligauss; microtesla, mT (1 mT = 10 mG); Hz, Hertz.

Hundreds … of other scientific studies … have consistently revealed that "invisible forces" of the elec-tromagnetic spectrum profoundly impact every facet of biological regulation. These energies include microwaves, radio frequencies, the visible light spectrum, extremely low frequencies, acoustic frequencies and even a newly recognized form of force known as scalar energy. Specific frequencies and patterns of electromagnetic radiation regulate DNA, RNA and protein syntheses, alter protein shape and function, and control gene regulation, cell division, cell differentiation, morphogenesis (the process by which cells assemble into organs and tissues), hormone secretion, nerve growth and function …. [Liboff 2004; Goodman and Blank 2002; Sivitz 2000; Jin, et al, 2000; Blackman, et al, 1993; Rosen 1992, Blank 1992; Tsong, 1989; Yen-Patton, et al, 1988] …. 

• Same signals / protein molecules are simultaneously used in different organs and tissues for completely different behavioral functions.

• Multicellular organisms can survive with few genes (25 E^3) - the same gene products (protein) are **used and recycled** for a variety of functions ....

  e.g. **Histamine** in
  • brain (neuro.-growth enhancer)
  • extremities (inflam. response)

  When B is present in the blood .... the .... signal produces large gaping pores in the walls of the blood vessels. The opening of these holes in the blood vessel's wall is the first step in launching a local inflammatory reaction .... If histamine is added to blood vessels in the brain, the same histamine signal increases the flow of nutrition to the neurons, enhancing their growth and specialized functions .... This is an example of how the same histamine signal can create two diametrically opposed effects, depending on the site where the signal is released [Lipton, et al, 1991] ....

  **Histamine is deployed only where it is needed and for as long as it is needed** (pills however, affect the entire body).

Taking **antihistamines** .... affects histamine receptors wherever they are located throughout the whole body ....

• Same signals / protein molecules are simultaneously used in different organs and tissues for completely different behavioral functions.

• Multicellular organisms can survive with few genes ($25 \cdot 10^3$) - the same gene products (protein) are **used and recycled** for a variety of functions .... e.g. Estrogen in
  • female reproductive system
  • & heart, blood vessels & brain

A recent example of tragic adverse reactions to drug therapy is .... synthetic hormone replacement therapy (HRT) .... The distribution of estrogen receptors .... play an important role in the normal function of blood vessels, the heart and the brain .... The drug also impacts and disturbs the estrogen receptors of the heart, the blood vessels and the nervous system .... HRT has been shown to have disturbing side effects that result in cardiovascular disease and neural dysfunctions such as strokes [Shumaker, et al, 2003; Wassertheil-Smoller, et al, 2003; Anderson, et al, 2003; Cauley, et al, 2003].

http://www.healthsystem.virginia.edu/uvahealth/adult_gyneonc/estrogen.cfm

Sally A. Shumaker, PhD; Claudine Legault, PhD; Stephen R. Rapp, PhD; Leon Thal, MD; Robert B. Wallace, MD; Judith K. Ockene, PhD, MEd; Susan L. Hendrix, DO; Beverly N. Jones III, MD; Annlouise R. Assaf, PhD; Rebecca D. Jackson, MD; Jane Morley Kotchen, MD, MPH; Sylvia Wassertheil-Smoller, PhD; Jean Wactawski-Wende, Ph.D; for the WHIMS Investigators (2003). Estrogen plus progestin and the incidence of dementia and mild cognitive impairment in postmenopausal women: the Women's Health Initiative Memory Study: a randomized controlled trial. JAMA 289:2651-2662.

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One secret of life:
• cells are programmable.
• programmer lies outside the cell
• Biological behavior and gene activity are dynamically linked to information from the environment, which is downloaded into the cell.

Chalmers, 2008

The first big-deal insight that comes from such an exercise is that computers and cells are programmable. The second corollary insight is that the programmer lies outside the computer/cell. Biological behavior and gene activity are dynamically linked to information from the environment, which is downloaded into the cell.

http://echalmers.wordpress.com/2008/02/18/biological-models-for-computational-architecture/
Memory (not skills) is spread over the entire organism not just the brain!

Involves consciousness, the faculties of sentience (responsiveness), intercommunication, as well as memory

These catenated processes are responsible for the phenomenon of memory so characteristic of living systems .... ‘memory’ is always a projection to the future. Memory is one aspect of conscious experience.

Consciousness, must include, at the minimum, the faculties of sentience (responsiveness), intercommunication, as well as memory .... The liquid crystalline continuum of collagen fibers and associated bound water is therefore ideally suited for mediating rapid intercommunication and responsiveness throughout the body. It constitutes the body’s ‘consciousness’, which, apart from the capacity for intercommunication and responsiveness, which also includes the faculty of memory. .... The liquid crystalline structure and the bound water network will retain tissue memory of previous experiences, but it will also have the capacity to register new experiences, as all connective tissues, including bones, are not only constantly intercommunicating and responsive, they also undergo metabolic turnover like the rest of our body. Memory is thus dynamically distributed in the structured network and the associated, self-reinforcing circuits of proton currents .... which will be expected to make up the DC body field itself ....


Placebo Effect

osteoarthritis of the knee recommends:

• arthroscopic lavage (10L of fluids) or
• débridement (washing & shaving of cartilage)
• Placebo-treatment: std. arthroscopic débridement procedure was simulated

The patients in the study were divided into three groups. Moseley shaved the damaged cartilage in the knee of one group. For another group, he flushed out the knee joint …. The third group got "fake" surgery. The patient was sedated …. All three groups were prescribed the same postoperative care, which included an exercise program. The results were shocking …. The placebo group improved just as much as the other two groups! …. The results were clear to Moseley: "My skill as a surgeon had no benefit on these patients .... At no point did either of the intervention groups report less pain or better function than the placebo group. For example, mean (±SD) scores on the Knee-Specific Pain Scale (range, 0 to 100, with higher scores indicating more severe pain) were similar in the placebo, lavage, and debridement groups: 48.9±21.9, 54.8±19.8, and 51.7±22.4, respectively, at one year (P=0.14 for the comparison between placebo and lavage; P=0.51 for the comparison between placebo and debridement) and 51.6±23.7, 53.7±23.7, and 51.4±23.2, respectively, at two years (P=0.64 and P=0.96, respectively). Furthermore, the 95 percent confidence intervals for the differences between the placebo group and the intervention groups exclude any clinically meaningful difference.

Source: www.subtleenergysolutions.com/placebo-cartoon.gif
Placebo Effect

• … our beliefs act like filters on a camera, changing how we see the world.

• our biology adapts to those beliefs

• we cannot readily change the codes of our genetic blueprints, but we can change our minds.

Colloca & Benedetti 2005

Henry Ford was right about … about the power of the mind: "If you believe you can or if you believe you can’t … you're right”. Think about the implications of the man who blithely drank the bacteria that medicine had decided caused cholera. Consider the people who walk across coals without getting burned …. Your beliefs act like filters on a camera, changing how you see the world. And your biology adapts to those beliefs …. While we cannot readily change the codes of our genetic blueprints, we can change our minds.

You can filter your life … that turns everything black and makes your body/mind more susceptible to disease. You can live a life of fear and or live a life of love. You have the choice! But I can tell you that if you choose to see a world full of love, your body will respond by growing in health ….

Image: Events that might take place in the brain after placebo administration. Placebo administration (psychosocial context) might reduce pain through opioid and/or non-opioid mechanisms via expectations and/or conditioning mechanisms. The respiratory centers may also be inhibited by endogenous opioids. The {beta}-adrenergic sympathetic system of the heart may also be inhibited during placebo analgesia, although the mechanism is not known (reduction of the pain itself and/or direct action of endogenous opioids). CCK antagonizes the effects of endogenous opioids, thereby reducing the placebo response. Placebos can also act on 5-HT-dependent hormone secretion, on both the pituitary and adrenal glands, thereby mimicking the effect of the analgesic drug sumatriptan. From Colloca and Benedetti (2005).

http://www.biology-online.org/user_files/Image/Neurobiology/NE-placeboF01.gif
Emotion – the language of the cell

- conscious mind reads the flow of cellular signals (which comprises the mind of the body)
- generates emotions – via controlled release of regulatory signals (nervous system)

Liu, 2009

Candace Pert …. established that the "mind" was not focused in the head, but was distributed via signal molecules to the whole body (s. also M.W.Ho) …. Her work emphasized that emotions were not only derived through a feedback of the body's environmental information …. While proper use of consciousness can bring health to an ailing body, inappropriate unconscious control of emotions can easily make a healthy body diseased …. [Pert 1997] …. Reflex behaviors …. driving a car at sixty-five miles per hour on a crowded interstate highway while your conscious mind is fully engaged in conversation with a passenger …. Through the conditioned learning process, neural pathways between eliciting stimuli and behavioral responses become hardwired to ensure a repetitive pattern ("habits") …. Humans and other higher mammals have evolved the prefrontal cortex associated with thinking, planning and decision-making …. Our responses to environmental stimuli are indeed controlled by perceptions, but not all of our learned perceptions are accurate. Not all snakes are dangerous! Yes, perception "controls" biology, but …. perceptions can be true or false. Therefore, it is more accurate to refer to these perceptions as beliefs. Beliefs control biology

Memory – the language of the cell

- e.g. Hypothalamus-Pituitary-Adrenal-axis
- Fight or Flight Pattern
- Chronic & elevated stress level

Postlethwait & Hopson, 1995

The Hypothalamus-Pituitary-Adrenal-Axis (HPA) .... When there are no threats, the I-IPA axis is inactive and growth flourishes .... The stress hormones released into the blood constrict the blood vessels of the digestive tract, forcing the energy-providing blood to preferentially nourish the tissues of the arms and legs that enable us to get out of harm’s way .... The visceral organs stop doing their life-sustaining work of digestion, absorption, excretion and other functions that provide for the growth of the cells and the production of the body's energy reserves .... Activating the HPA axis also interferes with our ability to think clearly .... when you're frightened you're dumber .... Exam stress paralyzes these students .... We live in a "Get set" world .... Our daily stressors are constantly activating the HPA axis, priming our bodies for action .... Almost every major illness that people acquire has been linked to chronic stress [Segerstrom and Miller 2004; Kopp and R6thelyi 2004; McEwen and Lasky 2002; McEwen and Seeman 1999] .... More researchers are pointing to the inhibition of neuronal growth by stress hormones as the source of depression .... Depression is caused when the brain's stress machinery goes into overdrive. The most prominent player in this theory is the hypothala-mic-pituitary-adrenal (HPA) axis" [Holden 2003] .... Image: Adrenal stress hormones constrict the blood vessels in the forebrain reducing its ability to function. Additionally, the hormones repress activity in the brain's prefrontal cortex, the center of conscious volitional action conscious activity. In an emergency, the vascular flow and hormones serve to activate the hindbrain, the source of life-sustaining reflexes that most effectively control fight or flight behavior .... It comes at a cost .... diminished conscious awareness and reduced intelligence [Takamatsu, et al, 2003; Arnsten and Goldman-Rakic 1998; Goldstein, et al, 1996]. Stress hormones are so effective at curtailing immune system function that doctors provided them to recipients of transplants so that their immune systems wouldn’t reject the foreign tissues ....

Epigenetics on an Organismic level
Tumor Inducing DNA (T-DNA) of the bacterium *A. tumefaciens*:

Doubly transformed tobacco plants were obtained following sequential transformation steps using two T-DNAs encoding different selection and screening markers:

i) **T-DNA-I** encoded kanamycin resistance and nopaline synthase;

ii) **T-DNA-II** encoded hygromycin resistance and octopine synthase.

A genetic analysis of the inheritance of the selection and screening marker genes in progeny of the doubly transformed plants revealed that the expression of T-DNA-I genes was often suppressed. This suppression could be correlated with methylation in the promoters of these genes. Surprisingly, both the methylation and inactivation of T-DNA-I genes occurred only in plants containing both T-DNAs: when self-fertilization or backcrossing produced progeny containing only T-DNA-I, expression of the genes on this T-DNA was restored and the corresponding promoters were partially or completely demethylated. These results indicated that the presence of one T-DNA could affect the state of methylation and expression of genes on a second, unlinked T-DNA in the same genome.

A phenotypic variation ….
(dsRNA inhibits target mRNA “mex-3”):

- a) negative control: lack of staining, wild type with absence of hybridization;
- b) embryo from uninjected wild-type parent, normal pattern of endogenous mex-3;
- c) embryo from a parent injected with purified mex-3B; retain mex-3, although at levels less than wild type;
- d) embryo from a parent injected with dsRNA; no mex-3 RNA is detected;

Both petunia plants and worms helped scientists to discover a novel way to switch off genes. Nature has several ways of silencing genes, a clever knack affording the same genome many different expressions or epigenomes throughout one body.

Experimental introduction of RNA into cells can be used in certain biological systems to interfere with the function of an endogenous gene. Such effects have been proposed to result from a simple antisense mechanism that depends on hybridization between the injected RNA and endogenous messenger RNA transcripts. RNA interference has been used in the nematode *Caenorhabditis elegans* to manipulate gene expression. Here we investigate the requirements for structure and delivery of the interfering RNA. To our surprise, we found that double-stranded RNA was substantially more effective at producing interference than was either strand individually. After injection into adult animals, purified single strands had at most a modest effect, whereas double-stranded mixtures caused potent and specific interference. The effects of this interference were evident in both the injected animals and their progeny. Only a few molecules of injected double-stranded RNA were required per affected cell, arguing against stochiometric interference with endogenous mRNA and suggesting that there could be a catalytic or amplification component in the interference process.

…. dsRNA-mediated interference showed a surprising ability to cross cellular boundaries. Injection of dsRNA into the body cavity of the head or tail produced a specific and robust interference with gene expression in the progeny brood. Interference was seen in the progeny of both gonad arms, ruling out the occurrence of a transient ‘nicking’ of the gonad in these injections. dsRNA injected into the body cavity or gonad of young adults also produced gene-specific interference in somatic tissues of the injected animal.

Source: http://www.nature.com/nature/journal/v391/n6669/abs/391806a0.html
http://www.eb.tuebingen.mpg.de/departments/4-evolutionary-biology/department-4-evolutionary-biology
A phenotypic variation:

- Heterozygous male mice with one Kittm1Alf allele and one normal wild-type (+) allele have a spotted white tail-tip;
- Progeny carry a wild-type Kit allele from father; action of the transmitted aberrant RNAs still gives rise to the spotted tail;
- **Loss of aberrant RNAs over successive generations** leads to gradual loss of paramutation.

Rassoulzadegan et al. 2006

**Paramutation** is a heritable epigenetic modification induced in plants by cross-talk between allelic loci. … and involves transmission of RNAs such as piRNAs, siRNAs, miRNAs or other regulatory RNAs. These are packaged in egg or sperm and cause paramutation upon transmission to the next generation. RNA is a molecule of inheritance, just like DNA.

Scientists, based at the French Institute of Health and Medical Research (Inserm) and the University of Nice-Sophia Antipolis, used mice which carry one normal version of Kit and one mutant version (Kittm1Alf), giving them spotted tails. They bred these mice together, producing offspring with a range of Kit gene combinations:

- **two** mutant genes (these *die* shortly after birth)
- **one** mutant and one normal gene (these should be "spotty" like their parents)
- **no** mutants - two normal genes (not spotty).

In spite of a homozygous wild-type genotype, their offspring maintain, to a variable extent, the white spots characteristic of Kit mutant animals. Efficiently inherited from either male or female parents, the modified phenotype results from a decrease in Kit messenger RNA levels with the accumulation of non-polyadenylated RNA molecules of abnormal sizes. Sustained transcriptional activity at the postmeiotic stages—at which time the gene is normally silent—leads to the accumulation of RNA in spermatozoa. Microinjection into fertilized eggs either of total RNA from Kittm1Alf/+ heterozygotes or of Kit-specific microRNAs induced a heritable white tail phenotype. Our results identify an unexpected mode of epigenetic inheritance associated with the zygotic transfer of RNA molecules.

http://www.nature.com/nature/journal/v441/n7092/full/nature04674.html
http://www.nature.com/nature/journal/v441/n7092/fig_tab/441413a_F1.html
A phenotypic variation:

- same parents
- same age
- no mutation in pigmentation

Image: Jirtle, 2007

…. all mice are genetically IDENTICAL ….  
…. but they are epigenetically different!

…. A study published in *Molecular and Cellular Biology* found that an enriched environment can even override genetic mutations in mice [Waterland and Jirtle 2003]. In the study, scientists looked at the effect of dietary supplements on pregnant mice with the abnormal "agouti" gene. Agouti mice have yellow coats and are extremely obese, which predisposes them to cardiovascular disease, diabetes and cancer ….  

Methyl groups also inactivate remnants of past viral infections, called transposons. 45% of the human genome is made up of parasitic transposons. Methylation is nature's way of allowing environmental factors to tweak gene expression without making permanent mutations, Dr. Jirtle said. Methyl groups are entirely derived from the foods people eat. And the effect may be good or bad. Maternal diet during pregnancy is consequently very important, but in ways that are not yet fully understood.

For his experiment, Dr. Jirtle chose a mouse that happens to have a transposon right next to the gene that codes for coat color. The transposon induces the gene to overproduce a protein that turns the mice pure yellow or mottled yellow and brown. The protein also blocks a feeding control center in the brain. Yellow mice therefore overeat and tend to develop diabetes and cancer. To see if extra methylation would affect the mice, the researchers fed the animals a rich supply of methyl groups in supplements of vitamin B12, folic acid, choline and betaine from sugar beets just before they got pregnant and through the time of weaning their pups. The methyl groups silenced the transposon, Dr. Jirtle said, which in turn affected the adjacent coat color gene. The babies, born a normal brownish color, had an inherited predisposition to obesity, diabetes and cancer negated by maternal diet.

Source: http://blog.plantpoisonsandrottenstuff.info/category/vitamins/
These transgenic Mice:
• yellow pups develop obese, cancer & diabetes
• brown pups are healthy

Gene expression is conditioned by environment: developmental interactions occur from conception till death - Depends on what environments and what sequence the organism encounters them.

Epigenetic signals can be transmitted to the next generation i.e. display meiotic stability. Not all epigenetic signals are erased and reprogrammed during gametogenesis. This partly explains incomplete penetrance and variable expressivity – not all offsprings are affected (see phenotypic expression of agouti mice mutants).

Example: mouse *agouti* locus

Isogenic $A^p/a$ mice range in colour from yellow to black (*pseudoagouti*)

Darkness proportional to amount of DNA methylation in *agouti* gene (complete methylation $\rightarrow$ black). Transplants’ colour influenced by genetic mother not surrogate.

Source: http://www.pbs.org/wgbh/nova/sciencenow/3411/02.html
Organisms (4c/13)

These transgenic Mice:
- yellow pups develop obese, cancer & diabetes
- brown pups are healthy
- cause: maternal diet (!)

Jirtle R., 2007

Agouti mothers received methyl-group-rich supplements …. When methyl groups attach to a gene's DNA, it changes the binding characteristics of regulatory chromosomal proteins. If the proteins bind too tightly to the gene, the protein sleeve cannot be removed and the gene cannot be read. Methylating DNA can silence or modify gene activity …. The mothers who got the methyl group supplements produced standard, lean, brown mice, even though their offspring had the same agouti gene as their mothers. The agouti mothers who didn't get the supplements produced yellow pups, which ate much more than the brown pups. The yellow pups wound up weighing almost twice as much as their lean, "pseudo-agouti" counterparts ….

Organisms (5/13)

Rats & Endocrine Disruptors:

• Epigenetic transgenerational actions of endocrine disruptors through the male germ line

• Reduced sperm motility – up to the 4th generation (F4);

Organisms (6a/13)

Phenotypic variations in twins

- nutrition (provided by the mother)
- physico-chemical environment
  i) womb – close environment
  i) hormonal exposure (mother)
  i) sound, vibration,

Consider identical twins, who always have identical genomes, and they really do (always!) develop into unique individuals. Yes, they correlate with each other in many ways. Often they resemble each other, but everyone who knows identical twins knows that they actually look different and they have unique personalities. When you make a phone call to talk to an identical twin, it matters which one of the two answer the phone. Nobody confuses identical twins (or triplets) as the kinds of identical marching robots that a mad scientist might create. Reproduction of genomes appears to be highly overrated.

Source: “DNA Is Not Destiny The new science of epigenetics rewrites the rules of disease, heredity, and identity.”: http://www.discover.com/issues/nov-06/cover/?page=1
Though these two men are genetically identical, they were separated at birth. The man on the left was malnourished for years. Bone structure changes brought about by environmental factors is thus one of many ways (physical and behavioral) in which the environment can dramatically affect the way in which the genes express themselves.

The 25,000 genes of our human DNA are widely considered to be an instruction book for our bodies. However, “genes themselves need instructions for what to do, and where and when to do it.” These additional instructions are not in DNA, but on it, in an array of chemical markers and switches, known collectively as the epigenome, that lie along the length of the double helix. These epigenetic switches and markers in turn help switch on or off the expression of particular genes. It has long been known that epigenetic switches are critical to the healthy development of organisms. These can be dramatically tweaked by exposure to a vitamin, a toxin or even mothering, altering “the software of our genes in ways that affect an individual’s body and brain for life”.

Source: http://dangerousintersection.org
http://www.pbs.org/wgbh/nova/sciencenow/3411/02.html
Image: “DNA Is Not Destiny The new science of epigenetics rewrites the rules of disease, heredity, and identity.”: http://www.discover.com/issues/nov-06/cover/?page=1
Twin Study on Cancer
• inherited predisposition
• Epigenetic exposure
• Trigger (threshold)


Twin studies:
Minnesota Study of Twins Reared Apart:
  Compared MZ twins reared together (MZT) vs MZ twins reared apart (MZA)
  Degree of dissimilarity between MZT vs MZA assumed to be due to environment
  Correlations within MZT and MZA twin pairs were almost identical for most traits
    Personality test, fingerprint ridges, ECG patterns, systolic BP, heart rate, IQ, social attitudes

Swedish Twin Registry:
  Similar results with respect to migraines (in females), smoking (in males), peptic ulcers

http://www.pbs.org/wgbh/nova/sciencenow/3411/02.html
cloning humans in an artificial womb?

• nutrition (provided by the mother)
• environmental factor during pregnancy (womb)

• Dolly suffered from arthritis as she was cloned from a cell of her mother’s udder (!)

Time Mag. 03-1997

Organisms (7/13)

Human cloning should no longer be portrayed as it often is in the media. Epigenetics demonstrates that having an identical genome is highly overrated. **Genetic cloning cannot really result in identical phenotypic expression.** The apple (even if it is a clone) can fall a long way from the tree (the donor). **The outcome is highly dependent upon and subject to innumerable environmental factors.** I’m not suggesting that cloning is a good idea. Epigenetics demonstrates that cloning will fail to accomplish the egotistic ends that sometimes motivate the desire to clone humans. Further, cloning is ultimate expressing of unbridled **egotism.** The field of epigenetics is further proof **that recreating a complete and exact genetic code cannot duplicate a human individual.**

Society will continue to see reproductive cloning as a crass and simplistic attempt to create a monument to the clone’s parent’s ego, a monument that will too often reflect badly on the parent.

Das geklonte Schaf dolly ist aus einer Euterzelle der Mutter entstanden, mit entsprechender Praegung wodurch Dolly vorzeitige Alterserscheinungen zeigte und verstarb.

Source: [www.coverbrowser.com/cover/time/78](http://www.coverbrowser.com/cover/time/78)

“DNA Is Not Destiny The new science of epigenetics rewrites the rules of disease, heredity, and identity.”: [http://www.discover.com/issues/nov-06/cover/?page=1](http://www.discover.com/issues/nov-06/cover/?page=1)
Many people assume that DNA precisely predetermines our body shapes, personalities and diseases. The field of epigenetics, however, is disproving this. “We appear to have a measure of control over our genetic legacy.” We need to substantially revise our idea of genetics. All of the things people eat or smoke “can affect our gene expression and that of future generations. Epigenetics introduces the concept of free will into our idea of genetics.” The ramifications go much further, though, and the stakes are extremely high. The field of epigenetics can serve as a bridge between biology and responsible politics ….

“We are more than the sum of our genes” (Klar 1998)

“You can inherit something beyond the DNA sequence” (Watson 2003)

Source: http://www.calisafe.org/_disc1/40000029.htm
Epigenetics & phenotypic variation:

- Primacy of the environment
  - development of multicell. organisms
  - environment-organism interaction
  - pathogenesis of diseases
- Environment shapes genetic code
  (Changes of DNA-metabolism = genetic engineering genes)

Thaller, 1994

Genes are not destiny! Environmental influences, including nutrition, stress and emotions, can modify those genes, without changing their basic blueprint. And those modifications, epigeneticists have discovered, can be passed on to future generations as surely as DNA blueprints are passed on via the Double Helix [Reik and Walter 2001; Surard 2001] ….

i) Gene expression is conditioned by environment;

i) Developmental interactions occur from conception till death.

i) Depends on what environments and what sequence the organism encounters them (psychosomatic axis).

Rewriting genes when necessary is thus essential; (changes of DNA-metabolism = genetic engineering genes)!


Another phenotypic variation . . .

Sir Winston Leonard Spencer Churchill
(1874-1965)

• Overweight ✓ ✓ ✓
• Drinker ✓ ✓ ✓
• Smoker ✓ ✓ ✓
• Exercise ---
• Healthy diet ---
• Stressy Job @ 80 (British PM)
• Died @ age 90
Oeverkalix study

- exposure to cigarette smoke can lead to a transgenerational effect but is restricted to boys.
- poor food supply of paternal grandparents was followed by reduced mortality in grandchildren.
- rich food supply of paternal grandparents was followed by increased mortality in grandchildren.

Source: Bygren, Lars Olov; Kaati, Gunnar; Edvinsson, Sören (2001) Longevity Determined by Paternal Ancestors' Nutrition during Their Slow Growth Period

The Dutch famine near the end of World War II led to an increased incidence of schizophrenia in adults who had been food-deprived during the first trimester of their mothers' pregnancy. Malnourishment among pregnant women in the South during the Civil War and the Depression has been proposed as an explanation for the high incidence of stroke among subsequent generations.

Microalbuminuria occurs when the kidney leaks small amounts of albumin into the urine. In other words, when there is an abnormally high permeability for albumin in the renal glomerulus.

Weitere beispiele epigenetischer effekte
i) hungerwinter in Holland 1944 (NS-embargo): muetter mit mangelernahrung (400-800kcal tagesration) gebaren kinder mit niedrigem geburtsgewicht, diese gebaren ihrerseits (trotz normaler ernahrung) wieder untergewichtige kinder;
ii) zum zeitpunkt der untersuchung () litten doppelt so oft an herz-kreislauf-erkrankungen wie ihre altersgenossen;
iii) hauefiger brustkrebs und uebergewicht

http://linkinghub.elsevier.com/retrieve/pii/S0890623805000882
Diethylstilbestrol (DES) is a drug, an orally active synthetic nonsteroidal estrogen that was first synthesized in 1938. In 1971 it was found to be a teratogen when given to pregnant women. On April 15, 1971, the New England Journal of Medicine published a report by three physicians at Massachusetts General Hospital on the association of DES therapy … during the first trimester of pregnancy by mothers of girls and young women were diagnosed with adenocarcinoma of the vagina …. More than 30 years of research have confirmed that DES is a teratogen, an agent that can cause malformations of an embryo or fetus. However, not all exposed persons will experience the following DES-related health problems.

Image: Toxic end-points such as death or presence of a tumour are dependent on the sensitivity of the strains which are used. Figure shows the response of two strains of rats to diethylstilbestrol. In the outbred Sprague-Dawley rats there was a low incidence of spontaneous mammary tumours (this was the only significant type), but this was reduced in the treated group. Exactly the opposite was found in the ACI strain rats in which the treated group had over 70% tumours ….

Conclusions:
1. outcome of a conventional toxicity test depend entirely on the strain of animals which are used. Figure shows the response of two strains of rats to diethylstilbestrol.
2. A toxicologist using Sprague-Dawley rats alone would have revealed that DES is not carcinogenic in rats. If in the 1950s it was tested on ACI rats then it would have appeared to be quite unsafe.
3. Toxicologists mostly use genetically heterogeneous rats and mice since on a random-bred stock is more likely that at least a few individuals will respond to the administration.

Predisposition (1/7)

Triggering chain of events:

- stress factor (here, increase of cytoplasmic temperature)
- enhances negative feedback loop of HSC/HSP

Negative feedback loop. The steady state concentration of the constitutive stress protein hsc70 is shown by the fine line. Under conditions of stress, there is enhanced expression of the HSP70 gene leading to the synthesis of the inducible form, the molecular chaperone hsp70, shown by the heavy line. The concentrations of both hsc70 and hsp70 are controlled by negative feedback, indicated by the minus signs.

DNA sequence in the heat shock protein 70 (HSP70) promoter

The dynamic balance between Health & Disease

- **Chaotic pattern**: i.e. non-linear dynamics

**Bifurcation Pattern**

**Health & Disease**: In case of brief disturbances, homeostasis is restored sooner or later as the disturbance passes. On the other hand, if the disturbance or is significantly long, a series of irreversible events bring the organism to a new ‘steady state’. Chronic disturbances favour development or differentiation of “new” tissues (cancer as a result of prolonged and repetitive events of distress?). However, the **tumour cell as such does not exist**: the bad cell, the bad virus = HN15N, the bad bacteria = *Mycobacterium tuberculosis*, the bad plant = *Caulerpa taxifolia*, the bad animal = *Canis lupus*, the bad individual = *Homo sapiens sapiens*, the bad group of people = Iran, the evil state = Bush’s USA, etc.). It just depends on the interaction with its surroundings (the relation is much more important then the entities themselves). Here the disease itself becomes a messenger, the vehicle that tries to communicate to the outside world / brain (i.e. to the westener that sees the body as something separate from the mind). **Hence, disease is a just a mere tool of non-verbal communication.**

Source: Ho M.W.; 2003; The Rainbow and the Worm: The Physics of Organisms; 2nd ed.; p.28;
Stressors of any kind shift the metabolic activity towards tasks that are originally not the main objective of the cellular activity – reduces the cell’s vitality.

The metabolic map shows the various pathways that are essential for a cell’s activity in performing its tasks within the organism. Once environmental stressors from outside are introduced, the cellular system reacts (e.g. via membrane receptors). In an attempt to mitigate (harmful) effects that may result from a substance (e.g. xenobiotic), the cell allocates a certain amount of its metabolic activity to counteract its interfering role. Doing so, the overall cellular vitality to some extent becomes reduced.

The more stress-burdens are applied to the cell, the more the cell allocates resources (at the expense of other, less vital metabolic activities) to deal with the stressor. However, if the stress burden becomes too high, the cellular system eventually collapses.

http://www.genome.jp/kegg/pathway/map/map01100.html
Predisposition (4/7)

The dynamic balance between Health & Disease (Chronobiology):

Periodic Regulatory States obtained from the correlated SMARD-watch data:
- Electro-Myogram
- Skin-Potential
- Skin-Resistance

A regulatory state (e.g. sector 06) is determined by the variability of a regulatory process. Upon stimulation, regulatory patterns become more rapid - shorter periods - right side of abscissa of this sector. Faster regulatory patterns prevail in the event of activation. Relaxation, on the other hand favors slower regulatory patterns (longer periods - left side of abscissa within the sector). Examples of typical regulatory patterns: 17 corresponds to chronic stress; 11: deep relaxation; 52-56: neurotic state; 62-66: depressive state. Coma patients are most likely to be found within the more rigid regulatory pattern.

The Smard-Watch is thus an instrument suitable to monitor physiological response patterns of a person under investigation. It is a tool to show how coherent this person interacts with its surroundings. It also reveals the persons robustness to external stress factors.

Time structure manifests itself most clearly in the range of biological rhythms that extend over some ten orders of magnitude from the millisecond oscillations of membrane action potentials to $10^{-6}$ for circannual rhythms, which are coherent over varying spatial domains from single cells to entire organs and from whole organisms to populations of organisms. This implies a vast unexplored area, as the notion of non-linear, structured time is alien to the conventional scientific framework.
Epigenetic modulation:

- induced via
  - i) DNA-methylation
  - i) histone-modification
  - i) siRNA

... modify graph & remove text of figure

The roles of epigenetic histone modifications in cell growth, proliferation and differentiation is shown in the figure. We are interested in the epigenetic mechanisms that regulate the expression of tumor suppressor genes (e.g. p53 target genes), which play important roles in cell cycle control and apoptosis. The goal of our research is to unveil molecular mechanisms underlying epigenetic gene silencing, and identify novel drug target for cancer treatment. Our research has a broad implication to human physiology and diseases, including cancer, innate immunity, and autoimmune diseases.

To investigate the roles of histone Arg modifications in transcription (Figure 2). Recent work by us and many others have found that (1) promoter-specific conversion of methyl-Arg to citrullination via demethylimination regulates the expression of specific genes, such as p53 and estrogen receptor target-genes; (2) it is also formally possible that reversible Arg methylation and demethylation plays important role in gene regulation; (3) histone hypercitrullination by peptidylarginine deiminase 4 plays a role in high order chromatin structure.

Source: http://www.bmb.psu.edu/faculty/wang/wang.html
Epigenetic modulation:

- cooperation of genetic and epigenetic alterations may cooperate in the genesis of cancer.
- genetic change may precede epigenetic change, and vice versa.

Bannister, 2008

Epigenetic alterations in the genesis of cancer - Genetic and epigenetic interplay towards cancer. Much effort has been invested in identifying genetic mutations in cancer. In inherited cancer syndromes this approach has proved successful. Furthermore, mutations early in the genesis of common cancers have also been identified and these are likely to be associated with tumour initiation. In contrast, few specific genetic mutations have been linked to tumour progression, leading Feinberg to suggest that epigenetic changes are involved. Epigenetic changes occur without a change in the DNA sequence and they can be induced by various factors. Thus it is possible, for example, that a DNA mutation leads to cellular transformation, but induced changes in the epigenome of the transformed cell enhances the probability that it will be capable of metastasising. In this scenario, a genetic mutation can initiate the cancer but epigenetic change promotes its progression.

Image: Epigenetic processes may also be involved in cancer initiation. It is possible that epigenetic change may lead directly to cancer initiation. Alternatively, changes already induced within the epigenome may 'prime' cells in such a way as to promote cellular transformation upon a subsequent DNA mutagenic event. In this case the epigenetic component of the cancer initiation is intricately entwined with the genetic component. The involvement of epigenetic change in cancer initiation is of course not mutually exclusive to it having also a role in cancer progression as discussed above.

Cancer - Selection, outgrowth
• more autonomous growth
• ignore death and senescence signals
• escape immune surveillance
• trigger angiogenesis
• invasion, metastasis

Risk @ age 40: x10
Risk @ age 65: x100

Predisposition (7/7)

Chromosomal infrastructure is essential for gene control, determining both active and repressed states. It is important not only to turn the right genes on but also to turn the right genes off. Histones and chromatin components have key roles in this decision making process. If as few as three inappropriate genes are turned off, a normal cell can be converted into a cancer cell. This epigenetic silencing of genes underlies a new approach to cancer therapy. Mistargeting of these enzymes leads to tumorigenesis, but inhibition of their activity presents a novel approach to therapy.

The list of genes that are found to be inactivated by DNA methylation events is growing rapidly and includes genes involved in the following:
• Signal transduction cascade pathways.
• Cell cycle regulation.
• Angiogenesis.
• Apoptosis.
• DNA repair

Recent Cancer methylation studies predict that hundred (100) of CPG islands could be methylated in a tumor cell. However, it is clear that both the genome-wide methylation studies and candidate gene approaches that each tumor type may have its own set of cancer cell type specific genes that are more susceptible to methylation. Thus each cancer type may have the potential to be typed or classified according to methylation profile.

Cancer is usually a disease of old age (Bookmarking). It is not due to a single gene. Cancer is also not a static disease; some tumors (eg colon, breast, melanoma, cervical, pancreatic, bladder, lung etc) display a progression from benign to pre-malignant to invasive to metastatic stages. Increasing numbers/kinds of genetic abnormalities correspond to progression.

• Liquid tumours (leukemias, lymphomas): Precursors already mobile and invasive. Only one or two mutations may be required.
• Solid tumours – epithelial or mesenchymal. Most human cancers arise from epithelium. Precursors are immobile. At least three to five mutations, in different pathways, appear to be required to develop solid tumours in adults. Rb, p53, RAS and telomerase (TERT) pathways.
Breast cancer: BRCA gene is a breast cancer susceptibility gene, that is tumor suppressor gene responsible for both normal development and carcinogenesis in breast. BRCA1, reveals multi functional protein involved in DNA repair. Cell cycle regulation, transcription and apoptosis. BRCA1 mutations may play a significant role in the tumor-genesis of familial breast cancer.

Breast cancer model: \( COX2 \) = prostaglandin-endoperoxide synthase 2; often overexpressed in DCIS;
- Increases HMEC growth,
- estrogen synthesis,
- mutagen production,
- angiogenesis,
- invasion potential,
- decreases immune surveillance and apoptosis

Normal epithelial cells:
- Proliferate and form spheroids (acini) with hollow lumens and polarized surrounding cells.
- Resembles in vivo structures eg luminal secretory cells surrounding lumen; surrounded by myoepithelial cells that are in contact with basement membrane.

Breast tumour cell lines:
- Proliferate but do not form acini; form nonpolarized, disordered clusters with limited differentiation.
- Similar to IDBC where tumour cells form nests, poorly formed tubules, cords and sheets with cell-cell junctions.
- Reversed by eg down-regulation/blocking function of \( b1\)-integrin and \( EGFR \); or inhibition of MAPK or PI3K pathways; or restoration of \( dystroglycan (DG1) \; polarization) or \( CEACAM1 \) (adhesion molecule) expression.

Metastasis:

- Intravasion
- Extravasion

Steps in metastasis:

- Detachment from primary tumour (intravasion): due to invasion into vessels or abnormal vessels; may involve decreased levels adhesion molecules (e.g. cadherins), increased expression of proteases (e.g. metaloproteinases) and motility factors (e.g. Scatter Factor);
- Tumour cell arrest: cells are large compared to capillaries, so lodge in first capillary bed encountered (lung, liver);
- Extravasion of tumour cells: attachment to and invasion through endothelium and basement membrane/matrix; involves adhesion molecules and proteases;
A key function of blood vessels, to supply oxygen, is impaired in tumors because of abnormalities in their endothelial lining. PHD proteins serve as oxygen sensors and may regulate oxygen delivery. We therefore studied the role of endothelial PHD2 in vessel shaping by implanting tumors in PHD2+ mice. Hap-lod efficiency of PHD2 did not affect tumor vessel density or lumen size, but normalized the endothelial lining and vessel maturation. This resulted in improved tumor perfusion and oxygenation and inhibited tumor cell invasion, intravasation, and metastasis. Haplod efficiency of PHD2 redirected the specification of endothelial tip cells to a more quiescent cell type, lacking filopodia and arrayed in a phalanx formation. This transition relied on HIF-driven upregulation of (soluble) VEGFR-1 and VE-cadherin. Thus, decreased activity of an oxygen sensor in hypoxic conditions prompts endothelial cells to readjust their shape and phenotype to restore oxygen supply. Inhibition of PHD2 may offer alternative therapeutic opportunities for anticancer therapy.

Image: (D and E) Panc02 tumors (yellow line) are more invasive and metastatic in WT than PHD2+ mice, as evidenced by hemorrhagic ascites, metastatic nodules (blue line), jaundiced liver, and liver metastases (arrowheads).

Cancer protection gene:

- Less than 5% of cancer cases are due to an inherited predisposition (incl. epigenetics).
- Epigenetics modulates expression of natural cancer suppression gene activity.

Specialized DNA polymerases (DNA pols) are required for lesion bypass in human cells. Auxiliary factors have an important, but so far poorly understood, role. Here we analyse the effects of human proliferating cell nuclear antigen (PCNA) and replication protein A (RP-A) on six different human DNA pols—belonging to the B, Y and X classes—during in vitro bypass of different lesions. The mutagenic lesion 8-oxo-guanine (8-oxo-G) has high miscoding potential. A major and specific effect was found for 8-oxo-G bypass with DNA pols I and G. PCNA and RP-A allowed correct incorporation of dCTP opposite an 8-oxo-G template 1,200-fold more efficiently than the incorrect dATP by DNA pol I, and 68-fold by DNA pol G, respectively. Experiments with DNA-pol-I-null cell extracts suggested an important role for DNA pol I. On the other hand, DNA pol I, together with DNA pols A, D and B, showed a much lower correct bypass efficiency. Our findings show the existence of an accurate mechanism to reduce the deleterious consequences of oxidative damage and, in addition, point to an important role for PCNA and RP-A in determining a functional hierarchy among different DNA pols in lesion bypass.

Numerous investigations of the epidemiology of cancer reveal that only 5 to 10% of breast, prostate or bowel cancer and 1-2% of melanoma cases are attributable to genetic mutations, while the large bulk does not involve an inherited predisposition at all. [2,3]

Image: Proportion of cases of breast cancer that involve an inherited predisposition (susceptibility).


Conventional vs. holistic approach:

- reintegration of the diseased part
- restoration of the holobiont

**Cancer (5/5)**

Payrhuber et al., 2007

However,

- **Tumor cell lost contact with surrounding (no longer able to interact with its closer environment);**
- **Uncontrolled growth; divides continuously (mitosis), not knowing when to stop;**
- As outlined so far and according to epigenetics .... a **tumor cell as such does not exists** (tumor is a process).

Source: Payrhuber D., Frass M., Madl P.: Information Alters Matter; Proceedings of the 6th Biosemiotic Gathering, Umweb (Helsinki 2007);
The researchers found chemical modifications to histone 3 (H3) and histone 4 (H4)—major proteins that form the structure of chromosomes—at areas linked with four genes. Acetylation of H3 and H4 and phosphoacetylation of H3 alter the proteins' chemical structure, facilitating gene activation.

- **Acute Cocaine**: Rats received a single injection, either saline or cocaine (20 mg/kg).
- **Chronic Cocaine**: Rats received an injection of either saline or cocaine (20 mg/kg) daily for 7 days.
- **Cocaine Withdrawal**: Rats received an injection of either saline or cocaine (20 mg/kg) daily for 7 days and did not receive the drug again.


Brona McVittie reports that child abuse can leave epigenetic marks on DNA, a team of McGill University and Douglas Institute scientists recently explored the links that such changes might have on the likelihood of abuse victims to commit suicide. They looked at epigenetic marks on genes that mediate our stress-response.

Increased levels of maternal cortisol during pregnancy affect the development of the embryonic brain – it will so to speak tuned to a stressy environment; although the offspring is not necessarily depressive, it tends to show an increased risk to suffer from depression later in life. In young age, these children reveal a disrupted regulatory pattern of the psyche.

Allergy medications may indeed make a subsequent allergic attack even stronger, according to a study. Pal Johansen at the University of Zurich, Switzerland, conducted a study on mice to determine the long-term effects of antihistamines. He and his colleagues injected 50 mice with bee venom, a substance to which almost all organisms develop an allergy upon exposure. Half of the mice were also given 100 micrograms of the antihistamine Clemastine just before they were given venom, and 100 micrograms on each of the two days afterwards. After six weeks, the researchers injected the mice with another dosage of bee venom, and monitored the allergic reactions. They found that mice given antihistamines reacted more violently to the second venom injection. “We believe that the antihistamines were doing more than disrupting the immediate immune reaction to the first venom dosage. We think they were also keeping the immune system from getting used to that dosage”. The findings, published in Clinical and Experimental Allergy, suggest that the mice on allergy medication had not developed tolerance to the allergen.

Epigenetic factors are chemically stable, potentially reversible, and can be modulated or induced by environmental factors. In the case of allergic disease, epigenetics could explain not only the discordances observed between monozygous twins but also phenomena such as incomplete penetrance, variable expression, gender and progenitor effects, and sporadic cases. Among the different epigenetic factors, mention must be made of DNA methylation, covalent histone modifications, and other mechanisms that include different protein complexes and RNA-mediated modifications. The regulatory effect of these phenomena upon immune response has important implications for allergic diseases. At present, different lines of pharmacological research are being conducted, based on the modulation of epigenetic factors, modifying expression of the genes that encode for proteins implicated in allergic processes. Among such modulators, mention can be made of antisense oligonucleotides, ribozymes and interference RNA.

Implications (4/13)

Bookmarking - Trauma:

• suppressed innate immune system
• adaptive immune system affected
• susceptible to viral-, & bacterial- infection
• dormant “pathogens” more virulent

NZZ, 2009


Forscher untersuchten die Immunreaktion Jugendlicher und junger Erwachsener, die ihre frühere Kindheit in Waisenhäusern in Rumänien zugebracht hatten, aber nun in stabilen Verhältnissen in Adoptivfamilien lebten. Das Abwehrsystem dieser 41 Probanden war ähnlich stark geschwächt wie das der Jugendlichen, die körperlich missbraucht worden waren. "Diese Kinder hatten zwar eine schwierige Kindheit, erleben aber seit mehr als einem Jahrzehnt erleben emotionale Sicherheit", sagt Pollak. "Trotzdem steht ihr Körper unter Stress als ob sie missbraucht worden wären."

In order to increase his country's population and workforce, in 1966, communist dictator Nicolai Ceausescu set Romania's banned birth control and abortion and created financial incentives for women to have more children. The birth rate soared. So did child abandonment. When Ceausescu fell from power in 1989, the scale of his social experiment would come to light. According to NGO estimates, more than 170,000 orphans were languishing in orphanages under appalling conditions.

A mouse lacking an imprinted gene called Mest fails to retrieve and care for her pups the way a normal female does .... Mest (also called Peg1), is paternally expressed during development, especially in the mesoderm. Loss of Mest decreases body size and birthweight to less than 85% of normal, with weight continually decreasing with time after birth .... Lacking a clear causal explanation in the offspring, researchers looked to the behavior of Mest-deficient mothers to explain this significantly increased mortality. These mothers had 88% of their offspring die, regardless of the genotype of the offspring (Mest-deficient vs. Mest-positive). These same pups could be successfully fostered with normal wild-type females, suggesting that deficiencies in the maternal behavior of the mothers were the cause of mortality. Analyses of maternal behavior in Mest-less females showed that while they approached and sniffed their pups just like normal mothers, they were severely impaired in other aspects of the maternal behavioral repertoire. They the pups unattended for long periods, they did not retrieve them, and their nest building skills were impaired (Lefebvre et al.).

Implications (6/13)

Bookmarking – Parental misguidance:

• excessive austereness
• lack of personal freedom

leads to
• emotional instability (depression)

UNsafe at Home, 2008

Psychiatrists are also getting interested in the role of epigenetic factors in diseases like schizophrenia, Dr. Petronis said. Methylation that occurs after birth may also shape such behavioral traits as fearfulness and confidence, said Dr. Michael Meaney, a professor of medicine and the director of the program for the study of behavior, genes and environment at McGill University in Montreal. For reasons that are not well understood, methylation patterns are absent from very specific regions of the rat genome before birth. Twelve hours after rats are born, a new methylation pattern is formed. The mother rat then starts licking her pups. The first week is a critical period, Dr. Meaney said. Pups that are licked show decreased methylation patterns in an area of the brain that helps them handle stress. Faced with challenges later in life, they tend to be more confident and less fearful. "We think licking affects a methylation enzyme that is ready and waiting for mother to start licking," Dr. Meaney said. In perilous times, mothers may be able to set the stress reactivity of their offspring by licking less. When there are fewer dangers around, the mothers may lick more.

In animal models, variations in early maternal care are associated with differences in hypothalamic-pituitary-adrenal (HPA) stress response in the offspring, mediated via changes in the epigenetic regulation of glucocorticoid receptor (GR) gene (Nr3c1) expression. Objective: To study this in humans, relationships between prenatal exposure to maternal mood and the methylation status of a CpG-rich region in the promoter and exon 1F of the human GR gene (NR3C1) in newborns and HPA stress reactivity at age 3 months were examined. Methods: The methylation status of a CpG-rich region of the NR3C1 gene, including exon 1F, in genomic DNA from cord blood mononuclear cells was quantified by bisulfite pyrosequencing in infants of depressed mothers treated with a serotonin reuptake inhibitor antidepressant (SRI) (n=33), infants of depressed non treated mothers (n=13) and infants of non depressed/non treated mothers (n=36). To study the functional implications of the newborn methylation status of NR3C1 in newborns, HPA function was assessed at 3 months using salivary cortisol obtained before and following a non noxious stressor and at a late afternoon basal time. Results: Prenatal exposure to increased third trimester maternal depressed/anxious mood was associated with increased methylation of NR3C1 at a predicted NGFI-A binding site. Increased NR3C1 methylation at this site was also associated with increased salivary cortisol stress responses at 3 months, controlling for prenatal SRI exposure, postnatal age, and pre and postnatal maternal mood. Conclusions: Methylation status of the human NR3C1 gene in newborns is sensitive to prenatal maternal mood and may offer a potential epigenetic process that links antenatal maternal mood and altered HPA stress reactivity during infancy.

Chronic Fear:

- Increase in heart rate
- altered heart rate variability
- change in skin resistance
- hormonal changes (adrenaline)
- altered sense perception (hearing!)

Holsboer, 2009

Source: http://www.holsboer.de/PDF/Aktuelles_Rotary%20Club_Vortrag.pdf
Paramutation - Child abuse:

- lack of paternal love & affection
- methylation of genes
- changes in Hippocampus
- psychological instability
- increased risk of depression
- passed on to next generation
- increases risk of suicide

Meaney & Szyf, 2004


Implications (10/13)

Paramutation - Prenatal Stress:

- increased DNA methylation in newborn
- increased stress hormone level in newborn
- low gonadal weight
- increased risk of diabetes
- increased risk of cardiovascular disease during adult life

Prenatal stimulations have been shown to have long-term effects on at reproductive activity. We evaluated the influence of the prenatal stress on the hypothalamic-pituitary-gonad (HPG) axis in male rat-offsprings from mothers with high number of offsprings per litter (HNL) and low number of offsprings per litter (LNL) after hypothesizing that the number of offsprings per litter may modify the effect of the prenatal stress on the HPG of adult offsprings …. The offspring males coming from LNL showed a decrease in testicle weight and TES levels, without changes in the plasmatic LH levels. However, the offspring of HNL showed a decrease of LH levels. It is possible to conclude that in LNL prenatal stress would produce alterations to gonadal level, while in HNL the effect of stress would be evident at pituitary level.

Image: Gonadal-somatic index (gonadal weight vs. body weight) of prenatal stressed and control offsprings from LNL and HNL groups.


The modern western diet, so full of fats and sugars, could be exerting epigenetic effects on future generations, positive or negative. Abnormal methylation patterns are a hallmark of most cancers, including colon, lung, prostate and breast cancer, said Dr. Peter Laird, an associate professor of biochemistry and molecular biology at the University of Southern California School of Medicine. The anticancer properties attributed to many foods can be linked to nutrients, he said, as well as to the distinct methylation patterns of people who eat those foods.

An expectant mother might well logically reason that what she eats will affect her unborn child. But the evidence is mounting that not only her children, but her grandchildren and subsequent generations will be affected by her nutrition. What she eats may not only affect her descendants as they develop, but potentially throughout their adult lives.

A recent study published in Diabetes by Josep Jimenez–Chillaron and colleagues indicate that low birth weight is associated with increased risk of obesity, diabetes and cardiovascular disease during adult life, the team wanted to know whether such disease risks might be passed on to future generations.

Source: http://epigenome.eu/en/1,63,0 & http://blog.plantpoisonsandrottenstuff.info/category/vitamins/
Implications (12/13)

Paramutation - Obese Babies:

- obese mothers give birth to obese babies
- 20 genes seem to be involved
- however, only 1-3% is gene-related
- metabolic related diseases in later life

Jimenez-Chillaron et al., 2008


Source: Übergewichtige Babys – mit schwerer Hypothek ins Leben NZZ 70: 25.3.09
Implications (13/13)

Paramutation - Suicide:

- neglected during childhood
- hippocampus reduced in size
- cognitive impairments
- DNA methylation in brains involved in patho-psychology
- rRNA hypermethylated

McGowan et al., 2008

Suicide: Alterations in gene expression in the suicide brain have been reported and for several genes DNA methylation as an epigenetic regulator is thought to play a role. rRNA genes, that encode ribosomal RNA, are the backbone of the protein synthesis machinery and levels of rRNA gene promoter methylation determine rRNA transcription.

Comparing brain tissue from three groups; 12 suicide victims who were abused, 12 suicide victims who weren’t abused and 12 normal individuals, the team found different epigenetic marks on the gene that makes glucocorticoid receptors in the brains of the abused group to those in non-abuse victims or normal individuals. Coupling this with previous research findings, the results suggest that childhood experiences can lower the expression of glucocorticoid receptors, which has a knock-on effect on the hypothalamic-pituitary-adrenal (HPA) function. The subsequent over-activation of the HPA axis affects our ability to cope with stress, leaving affected individuals at risk of suicide.

Findings: We test here by sodium bisulfite mapping of the rRNA promoter and quantitative real-time PCR of rRNA expression the hypothesis that epigenetic differences in critical loci in the brain are involved in the pathophysiology of suicide. Suicide subjects in this study were selected for a history of early childhood neglect/abuse, which is associated with decreased hippocampal volume and cognitive impairments. rRNA was significantly hypermethylated throughout the promoter and 5' regulatory region in the brain of suicide subjects, consistent with reduced rRNA expression in the hippocampus. This difference in rRNA methylation was not evident in the cerebellum and occurred in the absence of genome-wide changes in methylation, as assessed by nearest neighbor.

Conclusion: This is the first study to show aberrant regulation of the protein synthesis machinery in the suicide brain. The data implicate the epigenetic modulation of rRNA in the pathophysiology of suicide.


So J.B. Lamarck (1744-1829) was not so wrong at all:

- Transient or heritable changes in gene expression through modulation of chromatin, which is not brought about by changes in DNA sequence
- These regulatory mechanisms for chromatin indexing are known as “epigenetics”

- Evolution of the genetic code, translation, and cellular organization itself follows a dynamic whose mode is … LAMARCKIAN (Inheritance of acquired characteristics).

Lamarckism or Lamarckian evolution (named for the biologist Jean-Baptiste Lamarck) refers to the once widely accepted idea that an organism can pass on characteristics that it acquired during its lifetime to its offspring (also known as based on heritability of acquired characteristics or "soft inheritance"). It is, who incorporated the action of soft inheritance into his evolutionary theories and is often incorrectly cited as the founder of soft inheritance.

It proposed that individual efforts during the lifetime of the organisms were the main mechanism driving species to adaptation, as they supposedly would acquire adaptive changes and pass them on to offspring.

In a wider context, soft inheritance is of use when examining the evolution of cultures and ideas, and is related to the theory of Memetics. While enormously popular during the early 19th century as an explanation for the complexity observed in living systems, the relevance of soft inheritance within the scientific community dwindled following the theories of August Weismann and the formation of the modern evolutionary synthesis.

Source: Vetsigian K., Woese C. Goldenfeld N., 2006; Collective evolution and the genetic code PNAS Vol. 103 no. 28
Implications for humanity and the wider biosphere:

…. Genetically Modified Organisms (GMO) ….

Genetically engineered crops are not analogous to products of normal evolution. If epigenetic causation is the motor of evolution as proposed, and genes play a subordinate, consolidating role, then going at the properties of an organism by manipulating its genes is not even really “engineering.” It is the hit-or-miss production of potentially useful monstrosities.

Advocates of genetic engineering claim that it is no different from what evolution has done, and that it is in fact a new form of evolution. But genetically engineered crops are not analogous to products of normal evolution. If epigenetic causation is the motor of evolution as proposed, and genes play a subordinate, consolidating role, then going at the properties of an organism by manipulating its genes is not even really “engineering.” It is the hit-or-miss production of potentially useful monstrosities.

This sharing of genetic information is not an accident. It is nature's method of enhancing the survival of the biosphere. As discussed earlier, genes are physical memories of an organism’s learned experiences. The recently recognized exchange of genes among individuals disperses those memories, thereby influencing the survival of all organisms that make up the community of life (GMO - shifting the nodes w/n the web of life) …. For example, tinkering with the genes of a tomato may not stop at that tomato, but could alter the entire biosphere in ways that we cannot foresee. Already there is a study that shows that when humans digest genetically modified foods, the artificially created genes transfer into and alter the character of the beneficial bacteria in the intestine [Heritage 2004; Netherwood, et al, 2004]. Similarly, gene transfer among genetically engineered agricultural crops and surrounding native species has given rise to highly resistant species deemed superweeds (for epigenetic modifications see Caulerpa taxifolia) [Milius 2003; Haygood, et al, 2003; Desplanque, et al, 2002; Spencer and Snow 2001]

Implications for humanity and the wider biosphere:

- intricate web of life (interspecies)
- socio-economic consequences
- eco-systemic consequences
- political consequences
- holistic worldview (GAIA)

Popp, 1992

"... evolution is more dependent on the interaction among species than it is on the interaction of individuals within a species" Lenton, 1998

GAIA: energy stored in matter; biota are far better energy storage systems than dead matter;
Biodiversity is much more important for the homeoeostasis of the planet than generally recognized.
The residence time of the energy within the biosphere is directly related to the energy stored, and hence, to species diversity or equivalently, the size of the trophic web ... which on the planetary level, is the space-time organization of the global ecological community.

A different view of the previous slide is shown here. The MGF in BP bridges the explicate orders of bio-molecules all the way up to societies. From Cell to Organism and beyond: Abscissa: “1” represents the Balance of Operation (homeostasis) - from left to right: Functional Complexity

Some final words (4/4)

Implications for humanity and the wider biosphere:

Epigenetics highlights the principle, that ….

…. all live is in a delicate dynamic balance, not only with other life forms, but also with the physical environment as well.

It is life’s harmony – not life’s struggle

Epigenetics questions not only Darwin’s dog-eat-dog version of evolution but also biology’s Central Dogma, the premise that genes control life …. Infact, genes are not “self-emergent”, Something in the environment has to trigger gene activity.

We are not victims of our genes, but masters of our fates!