Principles and Methods In animal genetics

Integrating genetics

PRIAM- September 2019

Thomas Heams
thomas.heams@agroparistech.fr
What is Animal Breeding?

Animal Breeding is a branch of animal science that addresses the evaluation (using best linear unbiased prediction and other methods) of the genetic value (estimated breeding value, EBV) of domestic livestock.

Animal Breeding is the selective mating of animals to increase the possibility of obtaining desired traits in the offspring.

The science of Animal Breeding is defined as the application of the principles of Genetics and Biometry to improve the efficiency of production in farm animals.

Animal breeders select and breed animals using their knowledge of genetics and animal science to produce offspring with desired traits and characteristics, such as chickens that lay more eggs, pigs that produce leaner meat, and sheep with more desirable wool.
First, there was domestication

An animal species is considered domesticated when it has had its behavior, life cycle, and/or physiology systematically altered by human control for many generations.

- Started 15000 years ago with dog (earlier attempts may have existed)
- Then: sheep, pig, goat, cow, cat, chicken etc.
- In Africa too: donkey, guinea fowl

Modern Taurine Cattle Descended from Small Number of Near-Eastern Founders

Domestication, semi-domestication...

Several purposes: production, work force, pets ...

Impacted human evolution too!

Paved the way for artificial selection

Kikkuli's treatise - 1350 BC
First text on domestication (horses)

and more coming?

sugar glider
(Petaurus breviceps)
Modern foundations of artificial selection

**Robert Bakewell** (1725-1795)

- He was the first to separate males from females with the intention of controlling which traits were passed on to subsequent generations.

- He also pioneered **close breeding strategies to fix desirable characteristics in his flock** and ensure they were passed on to subsequent generations.

- Traveled a lot

- Very influential all around Europe e.g. in Brno, Moravia...

Bloodlines survive today as the *English Leicester*
An interesting theory....

Charles Darwin
(1809 - 1882)
An interesting theory....

Charles Darwin
(1809 - 1882)

1837, page 36....

+ Alfred R. Wallace

1859

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Gregor Mendel (1822-1884)

Bezeichnet $A$ das eine der beiden konstanten Merkmale, z. B. das dominierende, $a$ das recessive, und $Aa$ die Hybridform, in welcher beide vereinigt sind, so ergibt der Ausdruck:

$$A + 2Aa + a$$
1900 Re discovery of the Mendel laws

De Vries, Correns, von Tschermak

1903 : American Breeders Association

First issue of The American Breeders Magazine - 1910
In France:

Genetics is introduced in 1907 by Schribsaux lectures (Institut National Agronomique)
1936: Felicien Boeuf is the first professor in Genetics in France (In. Nat. Agron.)

University is reluctant: first Department of Genetics in 1946 (only!) supported by physicists rather than biologists

Even in l'Institut National Agronomique:
-Agronomists and Geneticists teach mendelian laws
-Botanists and Zoologists teach a neo-lamarckian kind of heredity ...

Mid 1950s: Introduction in France of (animal) quantitative genetics by Jacques Poly at l'Institut national agronomique

Jacques Poly is the founder of the Department of Genetics at l'INRA

1960: Quantitative Genetics lectures in La Sorbonne
1965: Certificate of Quantitative and applied genetics Faculty of Sciences, Paris
Gene effects on character

1 - polygenes
2 - QTL
3 – Major / causal gene

Polygenic character
mixt determinism
monogenic character
Ronald Fisher  
1890-1962  

Trained as a statistician, becomes a quantitative geneticist  
Founder of Population Genetics  

In 1918, he demonstrates that inheritance of continuous traits is consistent with Mendelian principles  

He developed ideas on sexual selection, mimicry, on the evolution of dominance, and heterozygote advantage.  
He showed that the probability of a mutation increasing the fitness of an organism decreases proportionately with the magnitude of the mutation.  
He also proved that larger populations carry more variation so that they have a larger chance of survival.  
He was first to use diffusion equations to study the distribution of gene frequencies among populations, and pioneered the estimation of genetic linkage and gene frequencies by maximum likelihood.
Thomas Morgan
Genetic recombination and the first genetic maps

Morgan, with Sturtevant, Muller & Bridges:

- A theory for genetic recombination and crossing over (observed since 1909 by F.A. Janssen)
- Shows the linear organization of genes on chromosomes
- Estimate approx 3000 genes/chromosome (not that bad)

The Mechanism of Mendelian Heredity (1915-1923) with Sturtevant, Muller & Bridges
A Critique of the Theory of Evolution, (1916)
Physical and Genetic Maps

Cytological  | Physical  | Genetic

Mb (Megabases)  | Centimorgan

Gene A  | 10
Gene B  | 20
Gene C  | 30
Gene D  | 40
Gene E  | 50

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JBS Haldane (1892-1964)

A Mathematical Theory of Natural and Artificial Selection (1924 - 1934)
It treated many major cases for the first time, showing the direction and rates of changes of gene frequencies.

The Causes of Evolution (1932)
Investigates the interaction of natural selection with mutation and with migration

Sewall Wright (1889 – 1988)
A founder of Population Genetics, with animal science background.
• Investigated the inbreeding that had occurred in the artificial selection of leading breeds (Cattle – USA).
• He pioneered methods for computing the distribution of gene frequencies among populations as a result of the interaction of natural selection, mutation, migration and genetic drift.
• Developed the shifting balance theory by describing the relationship between genotype or phenotype and fitness as fitness surfaces or fitness landscapes.
Jay Lush (1896 - 1982)
The father of modern, scientific, Animal Breeding

Lush advocated breeding based on (quantitative) statistics and genetic information, not upon subjective appearance of the animal.

A famous scientist and teacher, with students from all around the world (32 countries), he tackled all aspects of animal breeding: heritability, selection response, use of collaterals, selection index, breeding systems and inbreeding...

2 important papers (among many others!)
Family merit and individual merit as bases for selection, 1947
The impact of genetics on animal breeding, 1951

His major theoretical achievement : introduction of the « Breeder’s equation »
Selection response = Heritability x Selection differential
JayLush wrote his classical book *Animal Breeding Plans* in 1937, after 16 years of teaching to college students. The last edition (1945) was printed 11 times and translated in several languages.

Over 22,000 copies were sold!

- His teaching and his book had an enormous impact on the development of Animal Breeding in Western countries after WWII
- An ebook version is available...
- Collaborators and followers
  - Lanoy Hazel
  Seminal papers (1942-1944) on selection indexes, multivariate selection, and integrative methods to maximize genetic gains.
  - Oscar Kempthorne
  *Introduction to Genetic Statistics* (1957)
Charles Henderson (1911-1989):

1950s: Introduced mixed model equations for BLUP, and variance components

*Applications of linear models in Animal Breeding* 1984

BLUP = Best Linear Unbiased Predictor = a statistical methodology for predicting genetic merits of animals

BLUP provides an effective way of ranking animals (or plants) given measurements on several traits of their own performance and on information of their relatives.
1953 (only!) – what DNA is ...

F. Crick & J. Watson

R. Franklin

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Douglas Falconer (1913-2004) :
concept of the genetic correlation for defining
« genotype by environment » interactions, heritability of threshold trait

Indebted to Alan Robertson works:
- interaction between selection and genetic drift
- long-term change potential of quantitative characters
- inbreeding due to selection

first published in 1960

Latest editions co-authored by Trudy Mackay

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Integrating Genetics
William « Bill » G. Hill
Born 1940

His contributions have included studies of
-how genetic variation is maintained in natural populations,
-how selection (both natural and artificial) changes the structure of genetic variation.
-how the effects of finite population size and mutation impact variability and selection responses, notably the role of mutation in maintaining continued responses to selection.

Pioneering work on linkage disequilibrium (LD) the non-random associations between genetic variants at different sites in the genome. LD is now an important tool for mapping and identifying genes involved in disease and other complex traits.

As a PhD student with Alan Robertson, he demonstrated how selection acting at a locus interferes with that happening simultaneously at linked loci: The Hill-Robertson effect.

Many important contributions to the application of genetics to animal improvement.
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Seminal contributions for the introduction of Bayesian / MCMC techniques and methods in animal genetics and breeding.

Daniel Gianola

Leif Andersson

Michel Georges

Theo Meuwissen

Jack Dekkers

Works on estimation of genetic parameters for traits of economic significance genetic evaluation methodology for international comparison of sires and design of breeding programs.

Mike Goddard

Cutting edge methods in genome biotechnologies for deciphering polygenic and monogenic traits

Introduction and development of Genomic Selection
Seminal contributions for the introduction of Bayesian / MCMC techniques and methods in animal genetics and breeding.

Daniel Gianola

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Michel Georges

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Works on estimation of genetic parameters for traits of economic significance, genetic evaluation methodology for international comparison of sires, and design of breeding programs.

Cutting edge methods in genome biotechnologies for deciphering polygenic and monogenic traits.

Introduction and development of Genomic Selection.

Ladies Wanted!
(pre)history of gene sequencing

1953 : DNA Structure by J. Watson and F. Crick.

1959 : first DNA molecule purified to homogeneity : Φ X174 genome by Sinsheimer


1965 : First sequencing of a nucleic acid : tRNA by Holley and coll.

1968-1971 : first sequencing of a DNA (12 bp!) by R. Wu and AD Kaiser

1970 : Discovery of restriction enzymes by Smith and coll.

1975 : « plus and minus method » by F. Sanger and Coulson

1977 : « chemical method » by A. Maxam and W. Gilbert


1978 : First complete sequence of phage Φ X (5kb)
Genetic Markers

A genetic marker is a gene or a polymorphic sequence of DNA easily detectable, on a known location on a chromosome. It can be used in cartography to map the genome, or to identify individuals or groups (e.g. species)

- polymorphic
- neutral
- co-dominant
- simple mendelian heredity
- present all along the genome
- No impact on sex differenciation
- Easily observable
- Cheap...
Sequencing yields interesting features on DNA

**Microsatellites**

Mammals: 1 microsatellite per 2-10 kb

faculty.vetmed.ucdavis.edu
Markers and genes leads to genetic maps
Single Nucleotid Polymorphism: SNP

Mammals: 1 SNP per kb → MARKERS!

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From genetic maps.....


Ex : Bovine genetic maps


1997, 10s markers

2009 10ks markers

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The Genome Sequence of Taurine Cattle: A Window to Ruminant Biology and Evolution

The Bovine Genome Sequencing and Analysis Consortium, Christine G. Elsk,1 Ross L. Tellam,2 Kim C. Worley3

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In animal genetics, gene maps with dense markers repartition:

- Allow genotyping and identification
  Identification is obtained by a combination of markers

- Allow association between markers and characters
  1. Crossing experiments between lines reveal location of zone(s) on DNA associated to a quantitative trait

  **These zones are the Quantitative Trait locus $i = \text{QTL}$**

  2. It may be then possible (time, money, data...) to find the actual causal gene(s)/mutation(s) in these QTL involved in the character.
     - by narrowing the QTL zone
     - by investigating on the genes already known to be present in the QTL

- Allow Markers Assisted Selection
  Animals can be selected on the basis of their genotype instead of their performance. Major time gain
Mauricio 2001
Genetics is a combination of approaches

**E.g. Double muscling phenotype:**

- Muscular hypertrophy
- Less intra-muscular fat
- Many problems in calving (systematic caesarean operations)

**Belgian Blue**

QTL Studies, genotyping → Candidate region on chromosome 2

- Further fine mapping
- Mice study (1997)

Identification of **myostatin**

Quantitative genetics → molecular tools → Comparative genomics

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Genomics : the institutional task force

2001 :
Academies Industries, producer groups, scientific societies
Alliance for Animal Genome Research.
Public fundings

Alliance + N.A.S : Workshop Exploring Horizons for Domestic Animal Genomics
-identify research goals
-find public and private fundings
http://www.nap.edu/catalog.php?record_id=10487#toc

Consensus : Sequencing cattle, chicken, swine, dog and cat + fish, honeybee
Animal model
food species
companion animal model
Appropriate scaling up of Bioinformatic ressources
Public Databases
Fundings from a variety of sources.

Interagencies Working Group on DAG : Specific goals to be achieved in 2003 to 2007 :
Sequencing of honeybee, chicken, canine, bovine, swine, and feline species.
Improvement of data management and accessibility, analysis softwares
Necessity of a concomitant investment in functional genomics

Identifying the Future Needs for Long-Term USDA Efforts in Agricultural Animal Genomics
Since 2002...

considerable progress in placing genome sequence and tools into the public domain
draft sequences of honey bee, chicken, dog genomes
bovine genome sequenced
sequencing of cat genome announced (Oct 2007 ) - Dog genome : ongoing
to reach these goals : leveraging of efforts in agricultural and biomedical research
unprecedented partnership between public and private structures

In 2004, sequencing goals within reach
further efforts remained to be done in bioinformatics and functional genomics

2005 The USDA Animal Genomics Workshop
Specific Structural genomics recommendaions
Sequence Swine genome (initiated 2006)
develop cDNA libraries for functional annotation of catfish, goat, horse, salmon, trout, and turkey.

Develop density of maps for all species
Develop standardized populations for each species
Seventh Research Framework Programme (FP7)

**Food, Agriculture and Fisheries, and Biotechnology**

**Knowledge Based Bio-Economy (KBBE)**

### Highlights
- Catalogue of all projects funded under the 'Food quality and safety' priority [available now]
- **FP7-KBBE-2007-2A** (second call) published
- Implementing 'Cooperation' theme 2 - Read the [introduction to the work programme]

### Objective

The primary aim of funding the 'Food, Agriculture and Fisheries, and Biotechnology' research theme under the Seventh Framework Programme (FP7) is to build a European Knowledge Based Bio-Economy (KBBE).

### What will be funded?

The EU Member States have earmarked more than **€ 1.9 billion** for funding this theme over the duration of FP7.

The 'Food, Agriculture and Fisheries, and Biotechnology' theme is built around three major activities:

- sustainable production and management of biological...
Toward personal genomics
Another polymorphism: Copy Number Variations

Copy number variation in the human genome
The Race for the $1000 Genome

Fast, cheap genetic analysis will soon become a reality, and the consequences—good and bad—will affect everybody.

MARCIS (2013), only thing getting you turnover is the fall. Yes genome sequence as estimated $30 000 per sequencing $300 mill.) Last placed a shaft of the new human g for $32 million. One company at $6 million, genome so 3000 did not. Yet still doing in once or they hope to do it $3000. "Aha, Sir," says Kevin Agemont, "GIAC And they say everyone wants back the era of the National Institute (NIHICU) is "People are more sickly says, it's technology that's their competition. A bit of stuff were on display, although no one cracked the $1 million mark. And it's real possibility, that's fine, but anything else they should be...

Free fall. As with computer technology, the plunging cost of DNA sequencing has opened new applications in science and medicine.
Personal Genomics

Population power. Extreme throughput. $1,000 human genome.

The HiSeq X Ten is a set of ten ultra-high-throughput sequencers, purpose-built for large-scale human whole-genome sequencing.

Others coming...
marker assisted selection, genomic selection

BEFORE

Parents Breeding

Bull's birth

Breeding

Daughters birth

Daughters first pregnancy

Daughters' daughter birth

First Lactation

Information

NOW

Parents Breeding

Bull's birth

DNA sample

Information
Inputs from **reproductive biotechnologies**

Artificial insemination  
Ovum pick-up + in vitro fertilization  
Sexed semen  
etc.

NB : species dependent

→ Huge impact on selection, diffusion

→ Challenge for diversity... and drawbacks

**Always remember** : Animal breeding and improvement is not only a matter of genetics. At the organism level : Reproduction, Physiology, etc. + farming practices, economy, sociology, politics, environmental sciences, ethics, and cultural differences !
The (post)genomic era

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A human gut microbial gene catalogue established by metagenomic sequencing

Junjie Qin¹*, Ruiqiang Li¹*, Jeroen Raes²,³, Manimozhiyan Arumugam⁴, Kristoffer Solvsten Burgdorf⁵, Chaysavanh Manichanh⁶, Trine Nielsen⁴, Nicolas Pons⁶, Florence Levenez⁶, Takuji Yamada², Daniel R. Mende², Junhua Li¹,⁷, Junming Xu¹, Shaochuan Li¹, Dongfang Li¹,⁸, Jianjun Cao¹, Bo Wang¹, Huiqing Liang¹, Huisong Zheng¹, Yinlong Xie¹,², Julien Tap³, Patricia Lepage⁴, Marcelo Bertalan⁹, Jean-Michel Batto⁶, Torben Hansen⁵, Denis Le Paslier¹⁰, Allan Linneberg¹¹, H. Bjørn Nielsen⁴, Eric Pelletier¹⁰, Pierre Renault⁴, Thomas Sicheritz-Ponten⁹, Keith Turner¹², Hongmei Zhu¹, Chang Yu¹, Shengting Li¹, Min Jian¹, Yan Zhou¹, Yingrui Li¹, Xiuxing Zhang¹, Songgang Li¹, Nan Qin¹, Huaming Yang¹, Jian Wang¹, Søren Brunak⁵, Joel Doré³, Francisco Guarner³, Karsten Kristiansen¹¹, Oluf Pedersen⁴,¹⁴, Julian Parkhill¹², Jean Weissenbach¹⁰, MetaHIT Consortium¹, Peer Bork², S. Dusko Ehrlich⁶ & Jun Wang¹,¹³
Molecular biological access to the chemistry of unknown soil microbes: a new frontier for natural products
Jo Handelsman¹, Michelle R Rondon¹, Sean F Brady², Jon Clardy² and Robert M Goodman¹

Cultured soil microorganisms have provided a rich source of natural-product chemistry. Because only a tiny fraction of soil microbes from soil are readily cultured, soil might be the greatest untapped resource for novel chemistry. The concept of cloning the metagenome to access the collective genomes and the biosynthetic machinery of soil microflora is explored here.

Addresses: ¹Department of Plant Pathology, University of Wisconsin–Madison, 1630 Linden Drive, Madison, WI 53706, USA. ²Department of Chemistry and Chemical Biology, Baker Laboratory, Cornell University, Ithaca, NY 14853, USA.

http://biomednet.com/elecref/10745521005R0245

Figure 1
Morphological diversity typical of microorganisms cultured from soil on a broad spectrum medium, tryptic soy agar.
Table 2. Currently catalogued and predicted total number of species on Earth and in the ocean.

<table>
<thead>
<tr>
<th>Species</th>
<th>Earth</th>
<th>Ocean</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Catalogued</td>
<td>Predicted</td>
</tr>
<tr>
<td>Eukaryotes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Animalia</td>
<td>953,434</td>
<td>7,770,000</td>
</tr>
<tr>
<td>Chromista</td>
<td>13,033</td>
<td>27,500</td>
</tr>
<tr>
<td>Fungi</td>
<td>43,271</td>
<td>611,000</td>
</tr>
<tr>
<td>Plantae</td>
<td>215,644</td>
<td>298,000</td>
</tr>
<tr>
<td>Protozoa</td>
<td>8,118</td>
<td>36,400</td>
</tr>
<tr>
<td>Total</td>
<td>1,233,500</td>
<td>8,740,000</td>
</tr>
<tr>
<td>Prokaryotes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Archaea</td>
<td>502</td>
<td>455</td>
</tr>
<tr>
<td>Bacteria</td>
<td>10,358</td>
<td>9,680</td>
</tr>
<tr>
<td>Total</td>
<td>10,860</td>
<td>10,100</td>
</tr>
<tr>
<td>Grand Total</td>
<td>1,244,360</td>
<td>8,750,000</td>
</tr>
</tbody>
</table>
Haeckel, 1866
Lateral gene transfer
*Escherichia coli*
A species ? A metagenome

The bacterial pan-genome: a new paradigm in microbiology

Alex Mira,¹ Ana B. Martín-Cuadrado,²° Giuseppe D’Auria,³° Francisco Rodríguez-Valera²

Pan-genome : 18000 genes
a typical *E. coli* : 4-5000 genes

6% of the genes (only!) present in all strains

Mira et al., 2010

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AgroParisTech
Bacterial Evolution

CARL R. WOESE

Department of Microbiology, University of Illinois, Urbana, Illinois 61801

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rRNAs, the Ultimate Molecular Chronometers

Why these are so good

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Welcome

The Barcode of Life Initiative (BOLI) began in 2003 with a proposal that we could tell species apart by using a very short gene sequence from a standardized position in the genome. Since that time, “DNA barcoding” has begun to emerge as a global standard for assigning biological specimens to the correct species. Research projects on insects, birds, fish, algae, and many other taxonomic groups are underway, and many more are being planned. Some are global research campaigns involving dozens to hundreds of contributors, and others are the work of a small team focusing on a small taxonomic group. All these barcoding projects share the goal of building an open-access database of reference barcodes that will improve our understanding of biodiversity and will allow non-taxonomists to identify species.

Identifying organisms can be difficult. Many species look so much alike that only a few experts can identify them. Even these experts can’t identify many juvenile forms or a specimen that has been damaged. This becomes critically important when it comes to identifying agricultural pests or invasive species at border.
Cytochrome c oxidase 1

Waugh 2007
5000 different virus species in 200 liters of sea water

65% never seen before sequences

Many micro-organisms and viruses can't be grown in culture
1 Gb of non redundant sequences
1800 estimated species
148 already know bacterial types
1,2 million unknown genes – 4000 unknown gene families
Les étudiants en biologie, petites mains de la génomique

Le Monde.fr

Metagenome Annotation Using a Distributed Grid of Undergraduate Students

Pascal Hingamp*, Céline Brochier, Emmanuel Talla, Daniel Gautheret, Denis Thieffry, Carl Herrmann

November 2008 | Volume 6 | Issue 11 | e296
Bioinformatics Training Through Metagenomic Sequence Annotation

- The Annotathon is featured in the November 2008 edition of PLoS Biology: Metagenome Annotation Using a Distributed Grid of Undergraduate Students
- Students, please take the time to read the Rule Book for details on bioinformatics work flow and evaluations of your annotations
- Bioinformatics teachers who wish to open a team are invited to read the Instructor Manual
- Other resources are in the About the Annotathon corner
## Marine Metagenomics: New Tools for the Study and Exploitation of Marine Microbial Metabolism

Jonathan Kennedy 1, Burkhardt Flemer 1, Stephen A. Jackson 1, David P. H. Lejon 1, John P. Morrissey 1,2, Fergal O’Gara 1,2,3 and Alan D. W. Dobson 1, 2, *  

Table 1. Marine enzymes discovered from Microbial and Metagenomic sources.

<table>
<thead>
<tr>
<th>Activity</th>
<th>Source</th>
<th>Habitat</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Esterase</td>
<td>Metagenome</td>
<td>Deep-sea sediment</td>
<td>[97]</td>
</tr>
<tr>
<td></td>
<td>Metagenome</td>
<td>Deep-sea basin</td>
<td>[72]</td>
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<td></td>
<td>Metagenome</td>
<td>Surface seawater</td>
<td>[69]</td>
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<tr>
<td></td>
<td>Metagenome</td>
<td>Arctic sediment</td>
<td>[98]</td>
</tr>
<tr>
<td></td>
<td>Vibrio sp.</td>
<td>Sea Hare Eggs</td>
<td>[99]</td>
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<tr>
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<td>Pseudomonas haloplankticus</td>
<td>Antarctic Seawater</td>
<td>[71]</td>
</tr>
<tr>
<td>Lipase</td>
<td>Metagenome</td>
<td>Tidal Flat</td>
<td>[74]</td>
</tr>
<tr>
<td></td>
<td>Metagenome</td>
<td>Deep Sea sediment</td>
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<td></td>
<td>Metagenome</td>
<td>Baltic Sea sediment</td>
<td>[67]</td>
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<td>Pseudomonas haloplankticus TAC125</td>
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<td>[72]</td>
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<tr>
<td></td>
<td>A. profundus strain IN2-3</td>
<td>Antarctic Seawater</td>
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<td>Sea saltern</td>
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<td>Pseudomonas sp. DY5</td>
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<td>T. teredinicola strain T7902T</td>
<td>Slipworm</td>
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<td>Marinobacter sp. MS1012</td>
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<td>Chitinase</td>
<td>Metagenome</td>
<td>Estuary</td>
<td>[80]</td>
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<td>A. profundus sp. TAD20</td>
<td>Antarctic ice</td>
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<td>R. marinus</td>
<td>Marine hot spring</td>
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<td>Amidase</td>
<td>Metagenome</td>
<td>Marine sediments / sludges</td>
<td>[192]</td>
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<td>A. profundus strain N13d</td>
<td>Deep sea sediment</td>
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<td>Metagenome</td>
<td>Deep sea hydrothermal vent</td>
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<td>Phytase</td>
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<td>Alkaline hydroxylase</td>
<td>Metagenome</td>
<td>Hydrocarbon seep</td>
<td>[82]</td>
</tr>
<tr>
<td></td>
<td>Metagenome</td>
<td>Deep sea sediment</td>
<td>[65]</td>
</tr>
<tr>
<td>Xylanase</td>
<td>Pseudomonas haloplankticus</td>
<td>Antarctic Seawater</td>
<td>[108]</td>
</tr>
</tbody>
</table>

Figure 2. Examples of positive lipase (A) and protease activities (B) from a *Himicola simulans* metagenomic library.
### Table 5. Bioinformatics tools/databases in metagenomics

<table>
<thead>
<tr>
<th>Name</th>
<th>Information</th>
</tr>
</thead>
<tbody>
<tr>
<td>AMPHORA (<a href="http://bobcat.genomecenter.ucdavis.edu/AMPHORA">http://bobcat.genomecenter.ucdavis.edu/AMPHORA</a>)</td>
<td>Phylogenetic analysis of single gene or whole genomes</td>
</tr>
<tr>
<td>ARB (<a href="http://www.arb-home.de">http://www.arb-home.de</a>)</td>
<td>Interacting software tools for sequence database (RNA/DNA/amino acids) maintenance and analysis</td>
</tr>
<tr>
<td>GenBank (<a href="http://www.ncbi.nlm.nih.gov/Genbank">http://www.ncbi.nlm.nih.gov/Genbank</a>)</td>
<td>i) Redundant archival database ii) Represents several alternate views of proteins, names and other information</td>
</tr>
<tr>
<td>GOLD (<a href="http://www.genomesonline.org">http://www.genomesonline.org</a>)</td>
<td>Metadata information related to genome and metagenome projects worldwide</td>
</tr>
<tr>
<td>MEGAN (<a href="http://www-ab.informatik.uni-tuebingen.de/software/megan">http://www-ab.informatik.uni-tuebingen.de/software/megan</a>)</td>
<td>Analysis (geographical and statistical) of several data sets</td>
</tr>
<tr>
<td>MEGX.net (<a href="http://www.megx.net">http://www.megx.net</a>)</td>
<td>Database tools for analysis of Marine Metagenomics</td>
</tr>
<tr>
<td>RAST (<a href="http://metagenomics.nmpdr.org">http://metagenomics.nmpdr.org</a>)</td>
<td>Automatic phylogenetic and functional analysis of genome</td>
</tr>
<tr>
<td>SILVA (<a href="http://www.arb-silva.de">http://www.arb-silva.de</a>)</td>
<td>i) Comprehensive rRNA database of bacteria, archaea, eukaryotes. ii) ‘Parc’ datasets of small and large subunit rRNA sequences</td>
</tr>
<tr>
<td>SINA (<a href="http://www.arb-silva.de/aligner">http://www.arb-silva.de/aligner</a>)</td>
<td>Sequence alignment based on curated SEED alignment</td>
</tr>
<tr>
<td>UniFrac (<a href="http://bmfz.colorado.edu/unifrac/index.jsp">http://bmfz.colorado.edu/unifrac/index.jsp</a>)</td>
<td>Comparison of microbial communities using phylogenetic information</td>
</tr>
<tr>
<td>XploReSeq (<a href="http://vent.colorado.edu/phloware">http://vent.colorado.edu/phloware</a>)</td>
<td>Compilation, management and phylogenetic analysis of DNA sequences</td>
</tr>
</tbody>
</table>

Many databases...

Singh et al., 2010

September 2019 Integrating Genetics
Fields of interest for metagenomics

Marine biology
Extreme environments
Rumen / gut
Virology
Soil biology
....

Langer et al. 2006
Extreme environments

Very high temperatures
Japan, South Africa, Norway, USA

Very cold temperatures
Canada, Germany, Antarctica

Saline environments

High Pressures environment

And combination of these...

Lewin et al., 2012
Figure 1. Phylogenetic composition of a battery of environmental communities. Results are the average of a total of 700 Mbp. As can be seen, the composition differs significantly among geographically and niche-specific environments.

Vieites et al., 2008
Fig. 2. Composition of the prokaryotic protein diversity in different environmental samples. Results are the average of a total of 700 Mbp. Note that the major representatives are those related to hypothetical protein.

Vieites et al., 2008
Exploring the viral world through metagenomics
Karyna Rosario and Mya Breitbart

2011:
50% of viral sequence from metagenomics Are unknown
810 MB of data not previously in GenBank
=70% of data produced by viral metagenomics
« Everything is everywhere ? »

Virus distribution : ubiquitous or local ?

A vast majority of viruses is found 'everywhere' with local variations.

Some viruses strains are conserved in warm areas (both locally and globally).

Some viral sequences are conserved in very distant saline zones.

But

In soil metagenomics, there seems to be more isolation and more phylogenetic overlap.
On distingue assez clairement les communautés virales d'eau douce v/s eau de mer.

Viral communities from sea water v/s fresh water can be distinguished.
Insights into novel antimicrobial compounds and antibiotic resistance genes from soil metagenomes

Alinne P. de Castro¹, Gabriel da R. Fernandes² and Octávio L. Franco¹,² *

¹ Programa de Pós-Graduação em Biociência, Universidade Católica Dom Bosco, Laboratório Inova, Campo Grande, Brazil
² Programa de Pós-Graduação em Ciências Genômicas e Biologia, Centro de Análises Protonômicas e Bioquímicas, Universidade Católica de Brasília, Brasília, Brazil

FIGURE 1 | Schematic depiction of the typical screening for novel antimicrobial compounds and antibiotic resistance genes from the soil environment through metagenomics. After collecting soil samples, the metagenomic DNA is extracted and sequenced from a microbial community in its natural habitat, bypassing microbial isolation and traditional cultivation methods, generating several million reads. Once coding sequences have been obtained, their corresponding antimicrobial compounds can be sought through conserved domain search or novel gene discovery in the reference functional databases by in silico analysis. Complementary methods reconstruct the identification of the molecules of interest. Large-scale production of the target molecule is then carried out for various biotechnological applications including agribusiness and human health.
FIGURE 2 | Prototypes of different antibiotics isolated from soil environments using metagenomic technology.

de Castro et al, 2014
The human microbiome: at the interface of health and disease

Ilseung Cho¹,² and Martin J. Blaser¹,²,³,⁴

September 2019

Integrating Genetics
Effect of maternal exposures
- Environment
- Antiseptic
- Antibiotics
- Diet
- Other hosts
- Epigenetics

Oral (pre-mastication of food)
Mammary, through breastfeeding (selection)
Cutaneous (contact with skin)
Vaginal (passage through birth canal)

Dental amalgam
Bottle feeding
Early-life antibiotics
Caesarean section
Early/extensive bathing

Cho & Blaser, 2012
### Table 1 | Examples of associations of human conditions with particular microbiota characteristics

<table>
<thead>
<tr>
<th>Disease</th>
<th>Relevant finding</th>
<th>Refs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Psoriasis</td>
<td>Increased ratio of Firmicutes to Actinobacteria</td>
<td>88</td>
</tr>
<tr>
<td>Reflux oesophagitis</td>
<td>Oesophageal microbiota dominated by gram-negative anaerobes; gastric microbiota with low or absent <em>Helicobacter pylori</em></td>
<td>75,133</td>
</tr>
<tr>
<td>Obesity</td>
<td>Reduced ratio of Bacteroidetes to Firmicutes</td>
<td>17,31</td>
</tr>
<tr>
<td>Childhood-onset asthma</td>
<td>Absent gastric <em>H. pylori</em> (especially the cytotoxin-associated gene A (cagA) genotype)</td>
<td>96,134</td>
</tr>
<tr>
<td>Inflammatory bowel disease (colitis)</td>
<td>Larger populations of Enterobacteriaceae</td>
<td>113</td>
</tr>
<tr>
<td>Functional bowel diseases</td>
<td>Larger populations of <em>Veillonella</em> and <em>Lactobacillus</em></td>
<td>135</td>
</tr>
<tr>
<td>Colorectal carcinoma</td>
<td>Larger populations of <em>Fusobacterium spp.</em></td>
<td>101,102</td>
</tr>
<tr>
<td>Cardiovascular disease</td>
<td>Gut-microbiota-dependent metabolism of phosphatidylcholine</td>
<td>136</td>
</tr>
</tbody>
</table>

Cho & Blaser, 2012
Metagenomic Discovery of Biomass-Degrading Genes and Genomes from Cow Rumen


Hydrolytic activity detected
No hydrolytic activity detected

<table>
<thead>
<tr>
<th>Genome Bin</th>
<th>Genome Size (Mb)</th>
<th>Phylogenetic Order</th>
<th>Estimated Completeness</th>
</tr>
</thead>
<tbody>
<tr>
<td>AFa</td>
<td>2.87</td>
<td>Spirochaetales</td>
<td>92.88%</td>
</tr>
<tr>
<td>AMa</td>
<td>2.21</td>
<td>Spirochaetales</td>
<td>91.23%</td>
</tr>
<tr>
<td>Alfa</td>
<td>2.53</td>
<td>Clostridiales</td>
<td>90.10%</td>
</tr>
<tr>
<td>AGa</td>
<td>3.08</td>
<td>Bacteroidales</td>
<td>89.77%</td>
</tr>
<tr>
<td>AN</td>
<td>2.02</td>
<td>Clostridiales</td>
<td>78.30%</td>
</tr>
<tr>
<td>AJa</td>
<td>2.24</td>
<td>Bacteroidales</td>
<td>75.96%</td>
</tr>
<tr>
<td>AG2a</td>
<td>2.07</td>
<td>Bacteroidales</td>
<td>75.96%</td>
</tr>
<tr>
<td>AWa</td>
<td>2.02</td>
<td>Clostridiales</td>
<td>75.77%</td>
</tr>
<tr>
<td>AH</td>
<td>2.52</td>
<td>Bacteroidales</td>
<td>75.45%</td>
</tr>
<tr>
<td>AQ</td>
<td>1.91</td>
<td>Bacteroidales</td>
<td>71.56%</td>
</tr>
<tr>
<td>A51a</td>
<td>1.75</td>
<td>Clostridiales</td>
<td>70.99%</td>
</tr>
<tr>
<td>APb</td>
<td>2.41</td>
<td>Clostridiales</td>
<td>64.85%</td>
</tr>
<tr>
<td>BOa</td>
<td>1.67</td>
<td>Clostridiales</td>
<td>64.16%</td>
</tr>
<tr>
<td>ADa</td>
<td>2.99</td>
<td>Myxococcales</td>
<td>62.13%</td>
</tr>
<tr>
<td>ATa</td>
<td>1.87</td>
<td>Clostridiales</td>
<td>60.41%</td>
</tr>
</tbody>
</table>

Genome Bin APb
55 Scaffolds
2.41 Mb
Insect gut microbiome – An unexploited reserve for biotechnological application

Muthukalingan Krishnan¹, Chinnapandi Bharathiraja¹, Jeyaraj Pandiarajan¹, Vimalanathan Arun Prasanna¹, Jeyaprakash Rajendhram², Paramasamy Gunasekaran²

Figure 1. Image of the morphology and different regions of the insect gut.
Table 1
List of enzymes/genes from the insect gut microbiome by functional screening.

<table>
<thead>
<tr>
<th>Insect gut source</th>
<th>Enzyme/Gene</th>
<th>Potential applications</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reticulitermes flavipes</td>
<td>RIBGlc−1 beta− glucosidase</td>
<td>Lignocellulose digestion</td>
<td>Mattiacci et al. (1995)</td>
</tr>
<tr>
<td>Rotschildia lebaue (Lepidoptera)</td>
<td>Xylanase</td>
<td>Xylan degradation</td>
<td>Brennan et al. (2004)</td>
</tr>
<tr>
<td>Termites (Nasutitermitidae)</td>
<td>Endo−1,4−β-xylanase</td>
<td>Xylane degradation</td>
<td>Brennan et al. (2004)</td>
</tr>
<tr>
<td>Nasutitermes ephratae</td>
<td>Glycosyl hydrolase</td>
<td>Lignocellulose digestion</td>
<td>Warnecke et al. (2007)</td>
</tr>
<tr>
<td>Termites (Nasutitermes takasagoensis)</td>
<td>Bacterial glycosidase genes</td>
<td>Polysaccharide degradation</td>
<td>Chaffron et al. (2007)</td>
</tr>
<tr>
<td>Reticulitermes flavipes</td>
<td>esterase</td>
<td>Hemicellulose solubilization</td>
<td>Marsha et al. (2009)</td>
</tr>
<tr>
<td>Gypsy moth (Lymantria dispar)</td>
<td>Quorum−sensing compound</td>
<td>Communication within the microbial communities</td>
<td>Tartar et al. (2009)</td>
</tr>
<tr>
<td>Termites (Reticulitermes flavipes)</td>
<td>Beta−glucosyl ceramidase</td>
<td>Cellulose</td>
<td>Tartar et al. (2009)</td>
</tr>
<tr>
<td>Termites (Reticulitermes flavipes)</td>
<td>Trehalase</td>
<td>Trehalose</td>
<td>Tartar et al. (2009)</td>
</tr>
<tr>
<td>Termites (Reticulitermes flavipes)</td>
<td>Alpha−mannosidase</td>
<td>Mannose</td>
<td>Tartar et al. (2009)</td>
</tr>
<tr>
<td>Termites (Reticulitermes flavipes)</td>
<td>Endo−beta−N−acetylglucosaminidase</td>
<td>Oligosaccharides</td>
<td>Tartar et al. (2009)</td>
</tr>
<tr>
<td>Limnoria quadripunctata</td>
<td>glycosyl hydrolase genes</td>
<td>Lignocellulose digestion</td>
<td>Andrew et al. (2010)</td>
</tr>
<tr>
<td>Coptotermes formosanus</td>
<td>β−glucosidase</td>
<td>Cellulose degradation</td>
<td>Zhang et al. (2010)</td>
</tr>
</tbody>
</table>

Cellulose hydrolysis (termites)
Vitramin production
Nitrogen fixation and phenol metabolisme (terpenes)
Antibiotics resistance
Use of metagenomics to understand the genetic basis of malnutrition

Tahmeed Ahmed, Rashidul Haque, Abul Mansur Shamsir Ahmed, William A Petri Jr, and Alejandro Cravioto

Nutrition Reviews® Vol. 67(Suppl. 2):S201–S206

Figure 1 Interaction of human genetic polymorphisms, enteric infections, and gut microbiome in malnutrition.
The intestinal microbiota affect central levels of brain-derived neurotropic factor and behavior in mice.

Human Genetics Shape the Gut Microbiome

SUMMARY

Host genetics and the gut microbiome can both influence metabolic phenotypes. However, whether host genetic variation shapes the gut microbiome and interacts with it to affect host phenotype is unclear. Here, we compared microbiotas across >1,000 fecal samples obtained from the TwinsUK population, including 416 twin pairs. We identified many microbial taxa whose abundances were influenced by host genetics. The most heritable taxon, the family Christensenellaceae, formed a co-occurrence network with other heritable Bacteria and with methanogenic Archaea. Furthermore, Christensenellaceae and its partners were enriched in individuals with low body mass index (BMI). An obese-associated microbiome was amended with Christensenella minuta, a cultured member of the Christensenellaceae, and transplanted to germ-free mice. C. minuta amendment reduced weight gain and altered the microbiome of recipient mice. Our findings indicate that host genetics influence the composition of the human gut microbiome and can do so in ways that impact host metabolism.
Box 1 | Ten areas of microbiome inquiry that should be pursued

- Understanding microbiome characteristics in relation to families: which features are inherited and which are not?*
- Understanding secular trends in microbiome composition: which taxonomic groups have been lost or gained?‡
- For diseases that have changed markedly in incidence in recent decades, do changes in the microbiome have a role? Notable examples include childhood-onset asthma, food allergies, type 1 diabetes, obesity, inflammatory bowel disease and autism.*
- Do particular signatures of the metagenome predict risks for specific human cancers and other diseases that are associated with ageing? Can these signatures be pursued to better understand oncogenesis? (Work on *Helicobacter pylori* provides a clear example of this.)*
- How do antibiotics perturb the microbiome, both in the short-term and long-term? Does the route of administration matter?*
- How does the microbiome affect the pharmacology of medications? Can we ‘micro-type’ people to improve pharmacokinetics and/or reduce toxicity? Can we manipulate the microbiome to improve pharmacokinetic stability?**
- Can we harness knowledge of microbiomes to improve diagnostics for disease status and susceptibility?*
- Can we harness the close mechanistic interactions between the microbiome and the host to provide hints for the development of new drugs?‡
- Specifically, can we harness the microbiome to develop new narrow-spectrum antibiotics?‡
- Can we use knowledge of the microbiota to develop true probiotics (and prebiotics)?**

*Areas currently under investigation. ‡Proposed areas for investigation.

Cho & Blaser, 2012
### Biotechnology and metagenomics

<table>
<thead>
<tr>
<th>Functional genes/enzymes identified</th>
<th>Industrial application</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Decarboxylase</td>
<td>• Biosynthesis of coenzyme A</td>
<td>[136]</td>
</tr>
<tr>
<td></td>
<td>• Can be used for the development of new antibacterial agents</td>
<td></td>
</tr>
<tr>
<td>Dehydratase</td>
<td>• Biosynthesis of bulk chemicals, e.g., 1,3-propanediol, 1,3-propanediol</td>
<td>[114]</td>
</tr>
<tr>
<td>Lipases/esterases</td>
<td>• Active in organic solvents</td>
<td>[125, 137–141]</td>
</tr>
<tr>
<td></td>
<td>• Display exquisite chemo-, regio-, and stereoselectivities</td>
<td></td>
</tr>
<tr>
<td>Nitriases</td>
<td>• Hydrolytic conversion of organonitriles to corresponding carboxylic acids</td>
<td>[142]</td>
</tr>
<tr>
<td></td>
<td>• Commercial production of (R)-mandelic acid from mandelonitrile</td>
<td></td>
</tr>
<tr>
<td>Proteases</td>
<td>• Bio-detergents (Savinase and Alcalase)</td>
<td>[143]</td>
</tr>
<tr>
<td>Vitamin/biotin biosynthesis</td>
<td>• Production of vitamin C biotin synthesis</td>
<td>[40]</td>
</tr>
<tr>
<td>Alcohol oxidoreductases, dl-keto-d-gluconic acid reductases, 4-hydroxybutyrate dehydrogenases</td>
<td>• Synthesis of carbyl compounds, hydroxy acids, and amino acids</td>
<td>[41, 104]</td>
</tr>
<tr>
<td></td>
<td>• Chiral alcohols</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Preparation of deuterium- or tritium-labeled compounds</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Production of dihydroxyacetone for enzymatic analysis of serum lipids</td>
<td></td>
</tr>
<tr>
<td>α-Amylases</td>
<td>• Detergents to dissolve starches from fabrics</td>
<td>[42, 76, 126, 144]</td>
</tr>
<tr>
<td></td>
<td>• Bread making to break down complex sugars</td>
<td></td>
</tr>
<tr>
<td>α-1,4-Glucan branching enzymes</td>
<td>• Used in starch industries</td>
<td>[42, 126]</td>
</tr>
<tr>
<td>β-Agarases</td>
<td>• Breakdown of agarose</td>
<td>[42]</td>
</tr>
<tr>
<td>Chitinases</td>
<td>• Protection against fungal pathogens</td>
<td>[145]</td>
</tr>
<tr>
<td></td>
<td>• Potential insecticides</td>
<td></td>
</tr>
<tr>
<td>Cellulases</td>
<td>• Food, brewing, wine, animal feed, textile industry</td>
<td>[19]</td>
</tr>
<tr>
<td></td>
<td>• Pulp and paper industry</td>
<td></td>
</tr>
<tr>
<td>Pectinase</td>
<td>• Pectin degradation</td>
<td>[42]</td>
</tr>
<tr>
<td>Alkane hydroxylase</td>
<td>• Oxidation reaction</td>
<td>[146]</td>
</tr>
<tr>
<td></td>
<td>• Oil degradation</td>
<td></td>
</tr>
</tbody>
</table>
Biotechnology and metagenomics

Drugs (including antibiotics)

<table>
<thead>
<tr>
<th>Drug</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acyltyrosines</td>
<td>[147, 149]</td>
</tr>
<tr>
<td>Indirubin</td>
<td>[99]</td>
</tr>
<tr>
<td><em>Mycobacterium</em>-inhibiting antibiotic, terragine</td>
<td>[102]</td>
</tr>
<tr>
<td>Polyketide synthase enzymes</td>
<td>[125, 150–153]</td>
</tr>
<tr>
<td>Turbomycin A and turbomycin B</td>
<td>[17]</td>
</tr>
<tr>
<td>Violacein</td>
<td>[42]</td>
</tr>
</tbody>
</table>

*Et aussi : Thermostable enzymes - extreme temperatures and conditions*

*Singh et al., 2010*
Other areas in fundamental metagenomics

Paleogenomics

biogeochemical cycles

Métazoans as ecosystems

Metatranscriptomics, metaproteomics
A perspective: Metatranscriptomics as a tool for the discovery of novel biocatalysts

Falk Warnecke\textsuperscript{a,\,*}, Matthias Hess\textsuperscript{b,\,1}

Review

Application of metatranscriptomics to soil environments

Lilia C. Carvalhais\textsuperscript{a,\,1}, Paul G. Dennis\textsuperscript{b,\,c,\,1}, Gene W. Tyson\textsuperscript{b,\,c}, Peer M. Schenk\textsuperscript{a,\,*}

\textsuperscript{a} School of Agriculture and Food Sciences, The University of Queensland, Brisbane, QLD 4072, Australia
\textsuperscript{b} Australian Centre for Genomics, The University of Queensland, Brisbane, QLD 4072, Australia
\textsuperscript{c} Advanced Water Management Centre, The University of Queensland, Brisbane, QLD 4072, Australia
(Waddington 1957)
EPIGENETICS

Functional modifications without modification on DNA Sequence

Chemical modifications
DNA Methylation
Methylation and acetylation of histones

Topology modifications
DNA Methylation

Figure 1. Maintenance methylation at CpG sites in mammalian DNA. The current view of DNA methylation in mammals involves de novo methylation in germ cells of the previous generation and in the early embryo, followed by maintenance methylation during development. Hemimethylated sites are thought to be the target for DNA methyltransferases of the DNA methyltransferase-1 (Dnmt1) family. As discussed in the text, this model is probably oversimplified to some degree.

DNA Replication and Human Disease © 2006 Cold Spring Harbor Laboratory Press, Chapter 7, Figure 1.

http://www.bio.miami.edu
Where to find DNA methylation?

Jeltsch, 2010
Genetic imprinting: differential allelic methylation

Kacem & Feil, 2009
Epigenetics: a new challenge in the post-genomic era of livestock

Oscar González-Recio*

Methylation impact on

-Nutrition
-Animal Health
-Reproduction

For animal as food, animal as model
‘Lamarckian’ mechanisms in darwinian evolution

Eva Jablonka
Marion J. Lamb
Eytan Avital

1998
Noyau interphasique de Poulet (G. gallus)
Chromatin and epigenetic modifications during early mammalian development

Karlla Mason\textsuperscript{a,b,1}, Zichuan Liu\textsuperscript{a,b,1}, Tiphaine Aguirre-Lavin\textsuperscript{a,b}, Nathalie Beaujean\textsuperscript{a,b,*}
Integrating genetics with environment

Landscape genomics

Integration of geographic data and genomic data

What genetic determinism in spatial repartition of animals (wild domestic)

http://www-leca.ujf-grenoble.fr/membres/taberlet.htm
Robot Cow Moos and Gives Milk

Hidden Motors Give Exhibit for World's Fair the Movements of a Living Animal

in the cow operates cams and levers to produce the various lifelike movements is illustrated by our artist's drawing. The different-shaped cams vary the speed of the movements of the tail, jaws, head, ears, and eyes to make them more realistic. Forming the support of the head is a flat flexible bronze spring that bends from side to side as the head moves. The sides of the mechanical cow move in and out in regular rhythm to simulate breathing.

A glass milking machine milks the cow, real milk coming from a tank in the udder. Spectators see it drawn through transparent tubes into the glass container. But they do not see a small centrifugal pump, in the pedestal upon which the animal stands, which pumps it back again. The cow cost $3,000.

An Electric cow that chews a cud, breathes, moves its head, winks its eyes, moos, and gives real milk will form one of the exhibits at the World's Fair next summer.

This robot animal has just been completed at the New York City workshop of Maurice and Daniel, specialists in creating mechanical beasts that range from prehistoric dinosaurs to modern poodles. It is an exact reproduction of a Holstein milk cow, the hide which covers the papier-mâché body being that of the real animal. This particular Holstein was chosen as a model because it had a large black spot on one side. In the reproduction, this spot forms a door that can be removed if anything goes wrong with the mechanism inside.

How a single silent electric motor with-

Popular Science, may 1933
INTEGRATIVE BIOLOGY

From DNA to function
and associated 'omics'

Time scales
Space
Money
Society?

From molecules to ecosystems

Transformation

Description
Knowledge

Ethics
Thanks!

Any questions?