

# Bioinformatic approaches to regulatory genomics and epigenomics

376-1347-00L | week 02

Pierre-Luc Germain

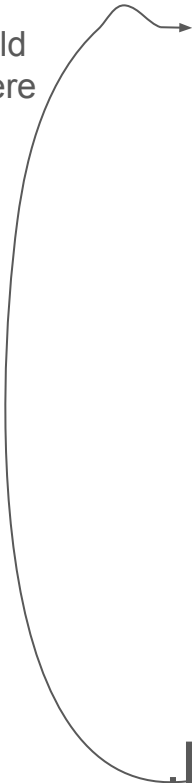
# Plan for today

- Debriefing on the assignments
- The notion of gene
- Genome builds and transcriptome assemblies
- Practical:
  - *AnnotationHub* and *EnsDb* objects
  - *GenomicRanges* and their manipulations

# Debriefing on the assignment

- Many are registered to the course but didn't give me their github username (nor have forked the repo)
- 2 students forked the repo but did not upload an assignment

Should  
be here



week01	added slides for week 1	last week
week02	initiated folders	last week
week03	initiated folders	last week
week04	initiated folders	last week
week05	initiated folders	last week
week06	initiated folders	last week
week07	initiated folders	last week
week08	initiated folders	last week
week09	initiated folders	last week
week10	initiated folders	last week
week11	initiated folders	last week
week12	initiated folders	last week
week13	initiated folders	last week
Assignment1.Rmd	Add files via upload	yesterday
Assignment1.html	Add files via upload	yesterday
LICENSE	initial commit	2 weeks ago
README.md	initial commit	2 weeks ago
Troubleshooting_FAQs.md	initial commit	2 weeks ago

```
---  
title: "assignment.Rmd"  
author:   
output: html_document  
date: "2025-02-27"  
---
```

This is a code chunk:

```
``{r}
```


```
---
```

```
BiocManager::install(c("GenomicRanges", "rtracklayer", "EnrichedHeatmap", "AnnotationHub",  
                        "ensemblldb", "edgeR", "esATAC", "sechm", "motifmatchr", "rGREAT",  
                        "bsseq", "DMRcate", "data.table", "InteractionSet", "limma",  
                        "universalmotif", "MotifDb", "TFBSTools", "Biostrings", "PWMErich",  
                        "Rsubread", "Rfastp"))  
  
BiocManager::install(c("Bioconductor/BiocFileCache", "chromVAR"))  
BiocManager::install("ETHZ-INS/epiwraps")  
  
---  
  
library(epiwraps)  
sessionInfo()  
---
```

A very brief history of genetics & genomics

... or why nobody knows how many genes we have

# A very brief history of genetics & genomics

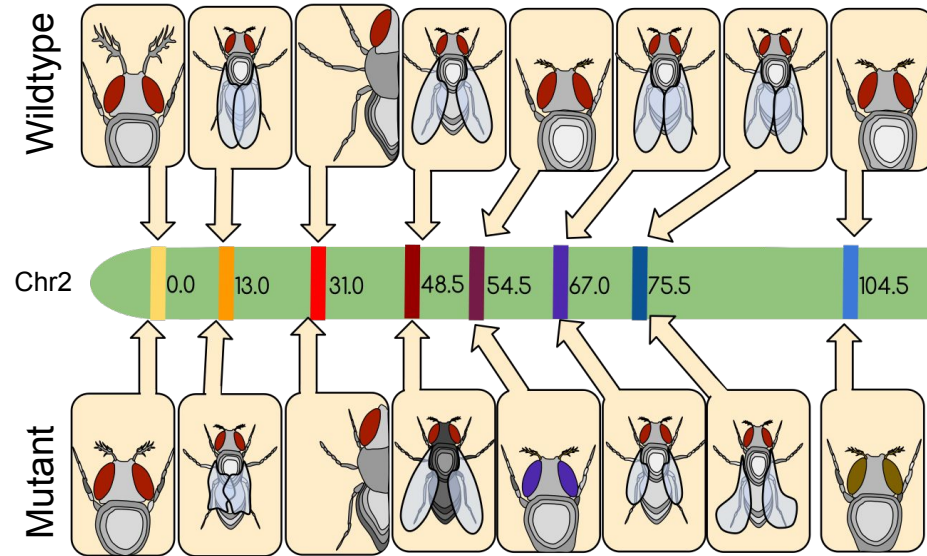
- 
- 1900 - Rediscovery of Mendel's work (1860s)
  - 1903 - Chromosomes are hereditary units
  - 1913 - Chromosomes are linear arrays of genes
  - 1941 - Beadle & Tatum:
    - the one-gene-one-enzyme hypothesis
  - 1944 - DNA is the genetic material
  - 1951 - First protein sequences
  - 1953 - DNA is a double helix
  - 1961 - Jacob and Monod:
    - the *lac* operon
  - 1977 - DNA sequencing
  - 1977 - Eukaryotic genes are spliced
  - 1995 - First bacterial genomes sequenced
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  - 2001 - Draft of the human genome
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Classical  
genetics:

A “gene” is a unit of  
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(Morgan's *Drosophila* genetic map, adapted from  
Twaanders17, CC BY-SA 4.0, via Wikimedia Commons)



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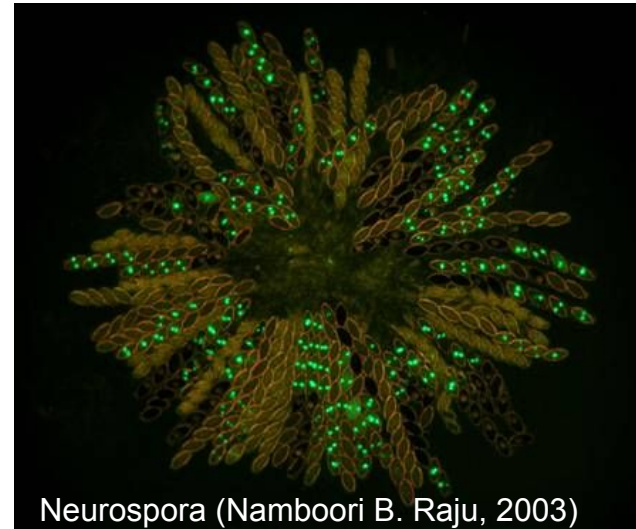
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Neurospora (Namboori B. Raju, 2003)

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- "structural" genes encode for proteins
- "regulatory" genes → regulate the structural genes

REVIEW ARTICLE

# Genetic Regulatory Mechanisms in the Synthesis of Proteins †

FRANÇOIS JACOB AND JACQUES MONOD

*Services de Génétique Microbienne et de Biochimie Cellulaire,  
Institut Pasteur, Paris*

*(Received 28 December 1960)*

The synthesis of enzymes in bacteria follows a double genetic control. The so-called structural genes determine the molecular organization of the proteins. Other, functionally specialized, genetic determinants, called regulator and operator genes, control the rate of protein synthesis through the intermediacy of cytoplasmic components or repressors. The repressors can be either inactivated (induction) or activated (repression) by certain specific metabolites. This system of regulation appears to operate directly at the level of the synthesis by the gene of a short-lived intermediate, or messenger, which becomes associated with the ribosomes where protein synthesis takes place.

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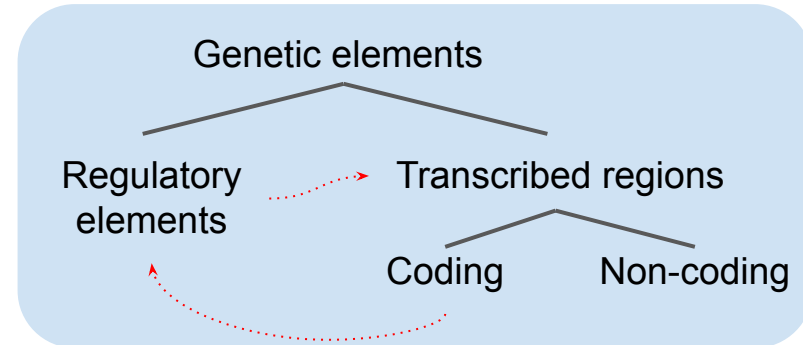
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## **Ignoble Nano-lectures:**

- A 24sec technical summary
- A 7-words summary everyone can understand

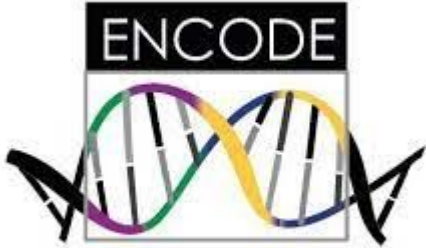
# So what's a gene today?

"The gene is a union of genomic sequences encoding a coherent set of potentially overlapping functional products"

(Gerstein et al., 2007)

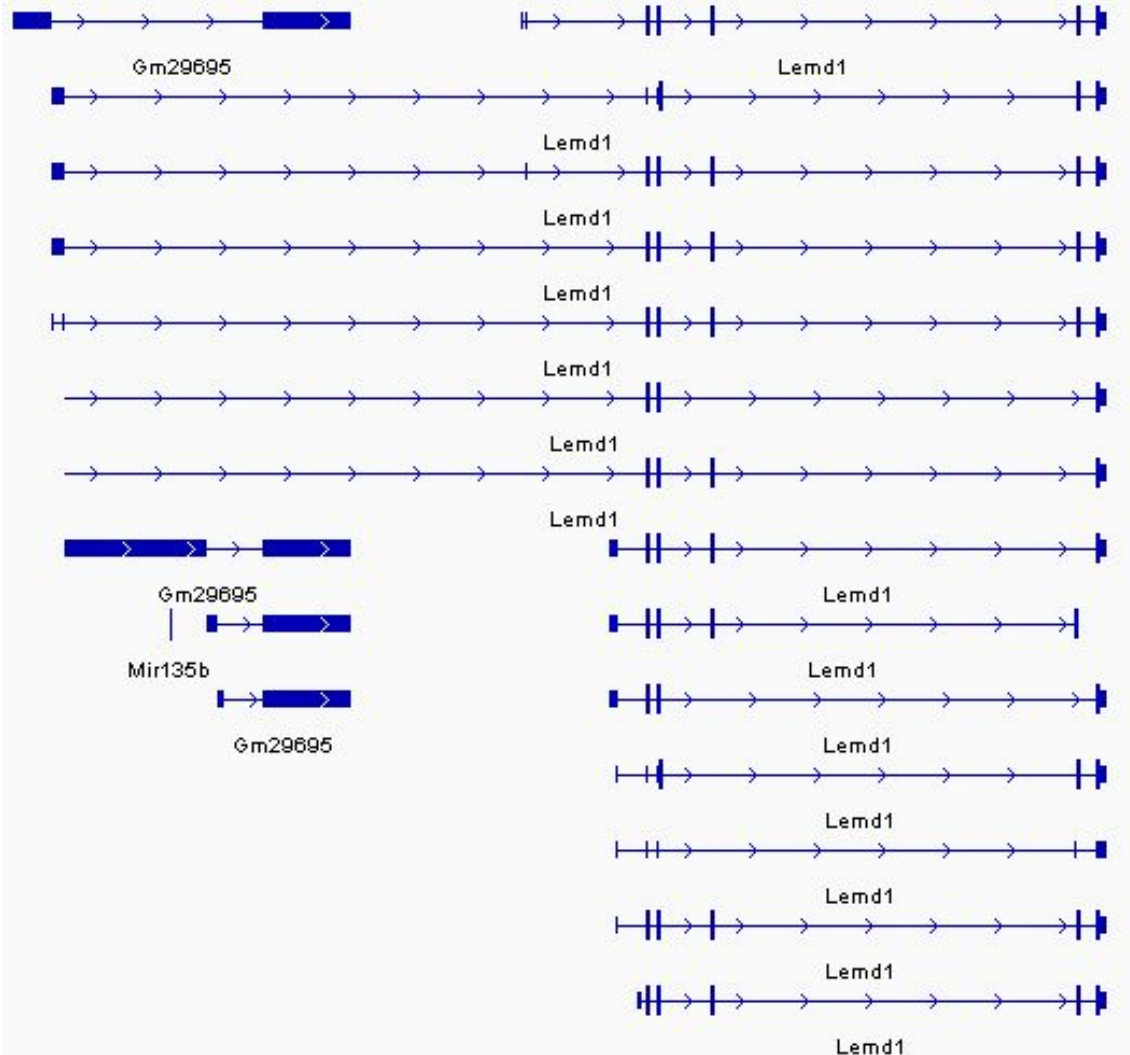
"On this view, genes represent a higher-order framework around which individual transcripts coalesce, creating a poly-functional entity that assumes different forms under different cellular states, guided by differential utilization of regulatory DNA."

(Stamatoyannopoulos, 2012)



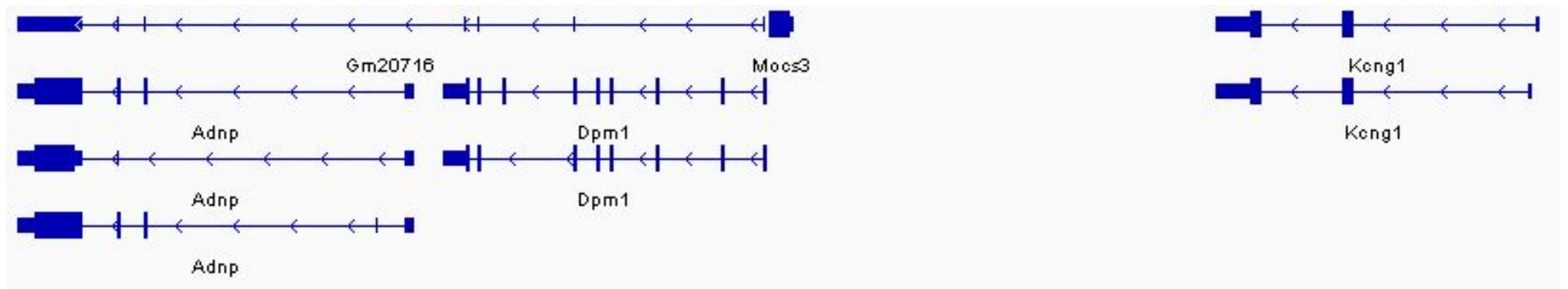


Transcripts tend to be grouped into genes depending on partially overlapping exonic sequences





But of course that's not a universal rule...



# Reference genomes and gene annotations

The **reference genome** refers to the **sequence** of the genome of a species.

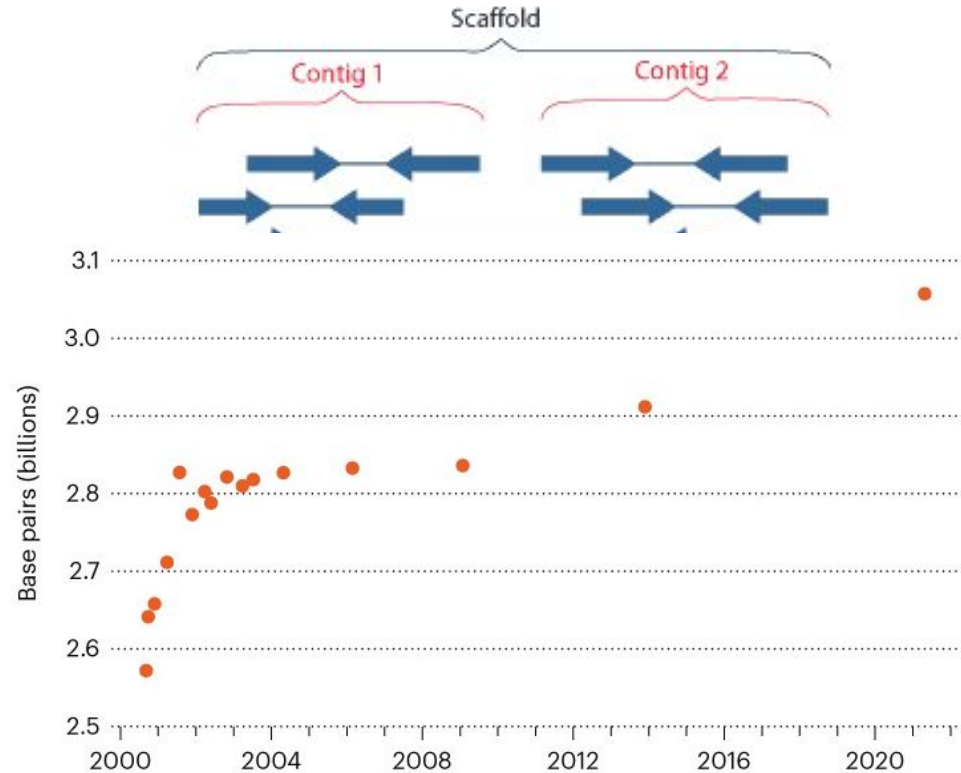
For mainstream organisms (e.g. human/mouse), there is one standardized genome (from the Genome Reference Consortium) which everyone uses, but different **build** versions of that genome, e.g.:

## Human:

- GRCh38/hg38 (released in 2013)
- GRCh37/hg19 (released in 2009)
- ...

## Mouse:

- GRCm39/mm39 (released in 2020)
- GRCm38/mm10 (released in 2011)
- GRCm37/mm9 (released in 2007)
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(Reardon, Nature News 2021)

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Within each genome build, there are also **patches**:

GRCh38.p13 (released in 2019)

GRCh38.p12 (released in 2017)

...

**Coordinates are stable *within* a build,  
but not *across* builds**

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**Annotations** refer to the catalogues of regulatory elements, genes and transcripts associated to a genome.

There are two main sources for gene annotations (aka “gene builds”) :

## Ensembl

- 104 (may 2021)
- 103 (nov 2020)
- 102 (april 2020)
- ...

example transcript:

ENST000012343.2  
ENST000012343.1  
ENST000012343.1

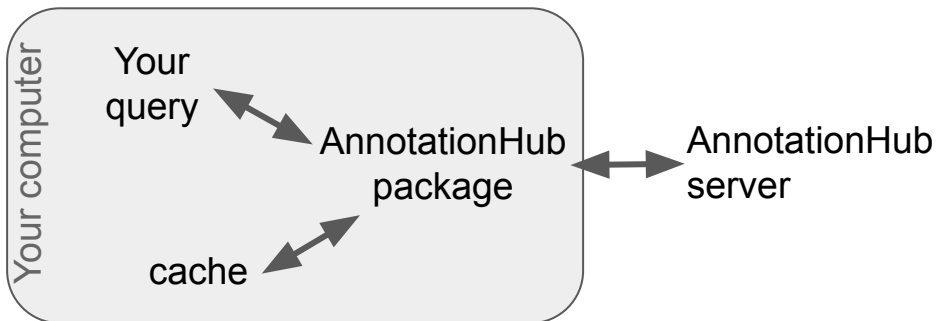


# Accessing ensembl annotations

- <http://ftp.ensembl.org/pub/>
- contains various types of data, most importantly:
  - **.fasta** files: sequences
    - (e.g. DNA or cDNA)
  - **.gtf/.gff** files: gene models
    - (i.e. exon coordinates and inclusion into transcripts)

- [AnnotationHub](#)

- Standardized access to a large variety of annotations



- including genomes, gene annotations (e.g. EnsDb objects) and more

## Further information

- See the documentation of the [ensemblDb](#) package for manipulating EnsDb objects
- See the documentation of the [GenomicRanges](#) package for manipulating GRanges objects (and their derivatives)

# Assignment for this week

- Using AnnotationHub, find and download the following annotations data:
  - The mouse (*Mus Musculus*) EnsDb object, version 102, genome build GRCm38
  - The mouse genome sequence ( `dna_sm` ) in TwoBit/2bit format for GRCm38
  - The drosophila melanogaster genome sequence ( `dna_sm` ) in TwoBit/2bit format for BDGP6
- Using the mouse EnsDb, find the following:
  - How many different *ensembl gene IDs* and *gene symbols* are there for protein-coding genes?
  - Plot the distribution of the (spliced) length of protein-coding transcripts
    - (tip: this will require you to extract exons of protein-coding transcripts from the database, and split them by transcript, before summing the width of the exons of each transcript)

Name your markdown file '`assignment.Rmd`', render it, and put it (along with the produced html) in the `week02` folder of your repository, and push!