The IRIS Project: The long-term impact of low dose radiation on living systems

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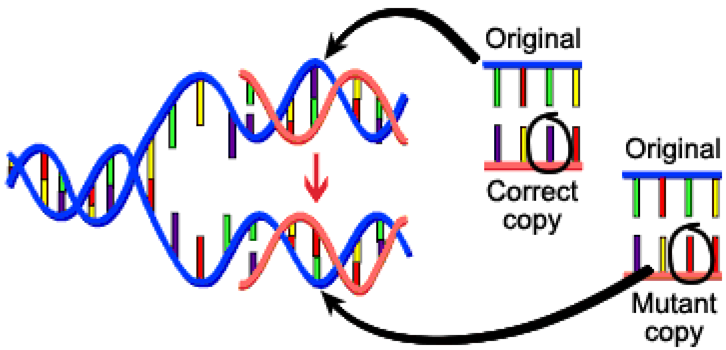
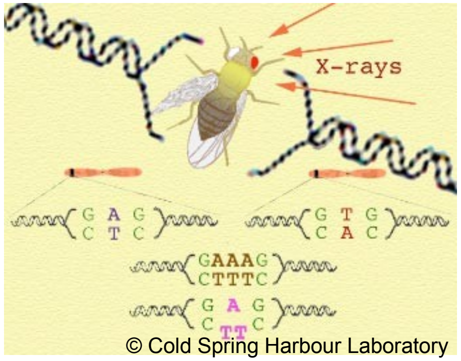
Motivation

Mutations are the fundamental ingredient that drives evolution.

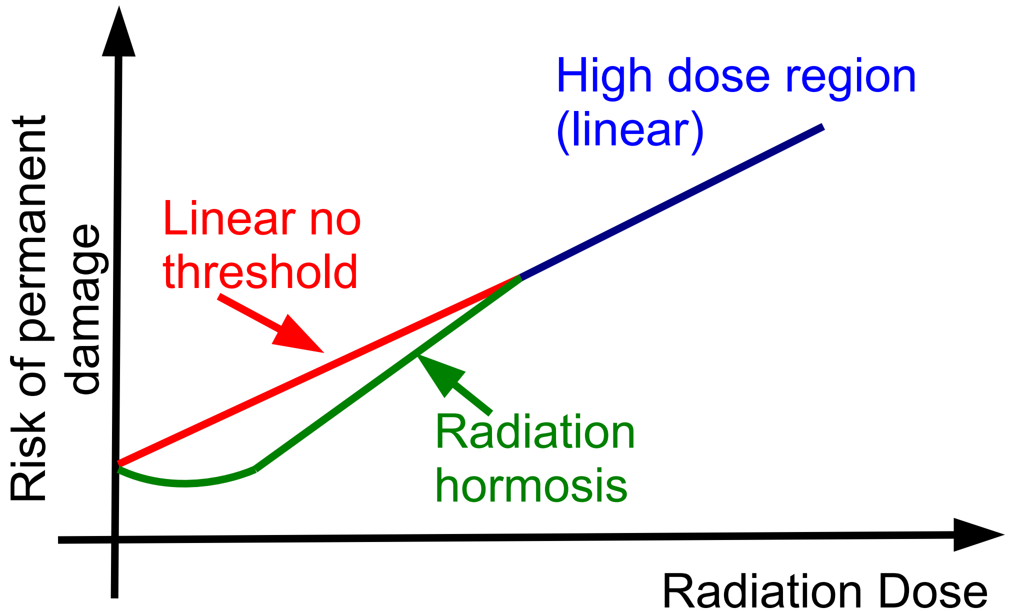




What role does radiation have to play in evolution compared to transcription and bio-chemistry.

Motivation

How does natural radiation impact life?



Role in the oxidation reponse?

Triggering unlikely mutations?

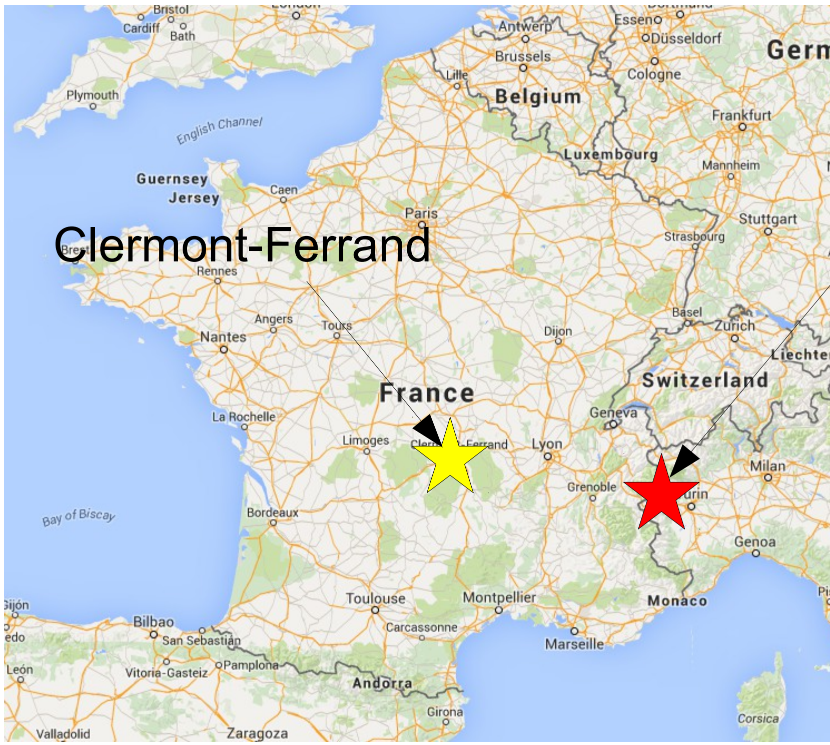
Are radiation environments correlated with evolution events?

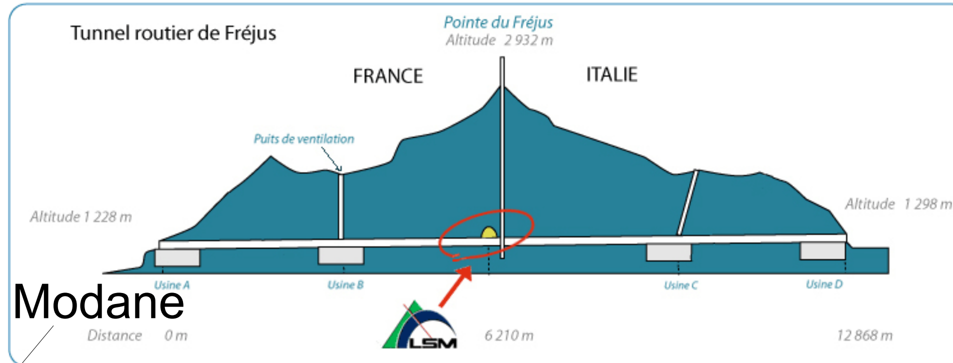
Summary

- Biology in the LSM.
- What is a Long Term Evolution Experiment?
- The radiation background for Biology
- LTEE results from Clermont-Ferrand
- Simulating DNA damage with low background

Biology at the LSM

The *Laboratoire Souterrain de Modane*



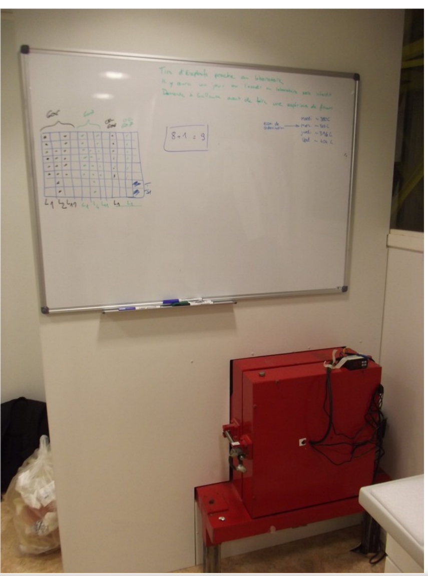


The lab at a glance:

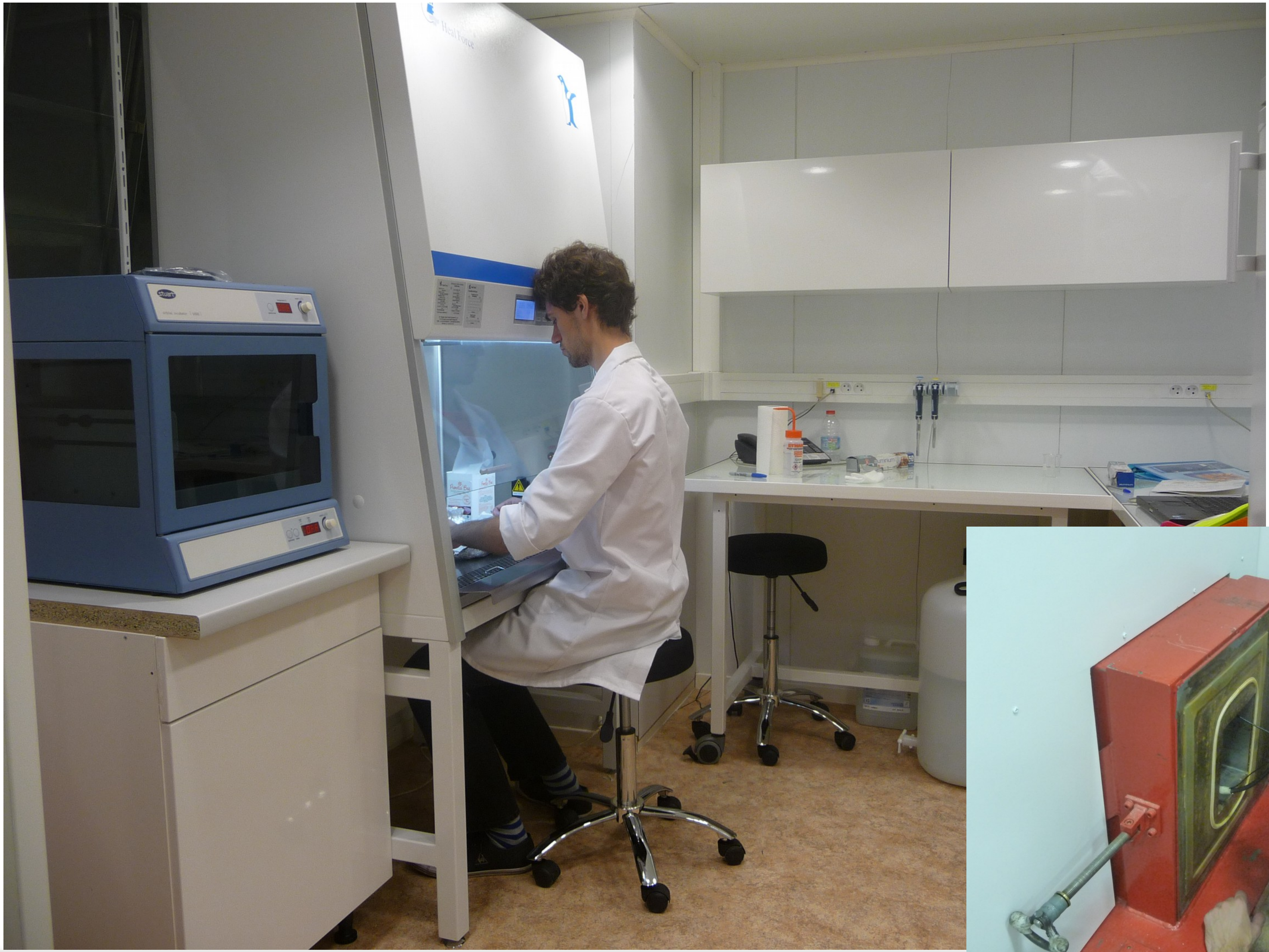
- Inside the Fréjus Tunnel, bordering Italy and France
- Under 1700m of rock (4800m water equivalent)
- Volume of 3500 m^3
- Low radon level (15 Bq m^{-3})
- Home to:
  - 17 germanium detectors
  - EDELWEISS (dark matter)
  - SEDINE (dark matter)
  - SUPER-NEMO (neutrino-less double beta)

Biology at the LSM

Biology at the LSM



Biology at the LSM

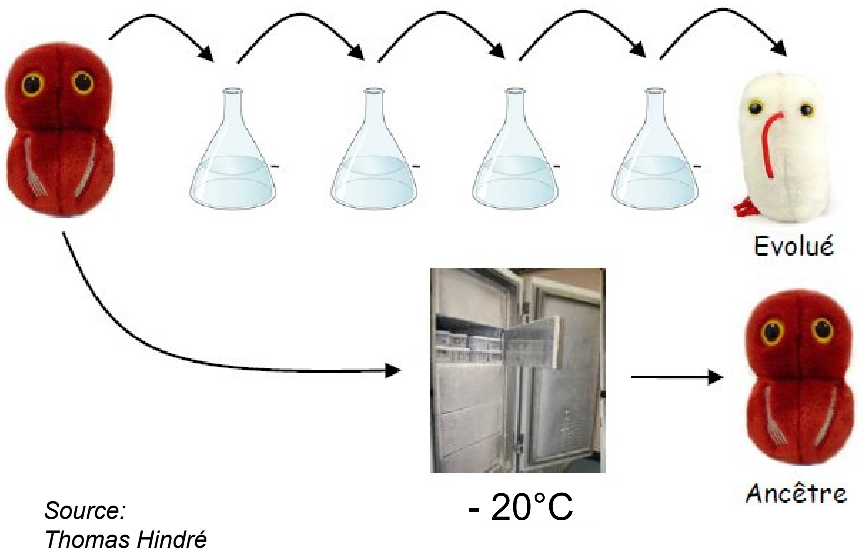


Pôle Physique Environnement Santé

Experimental Background

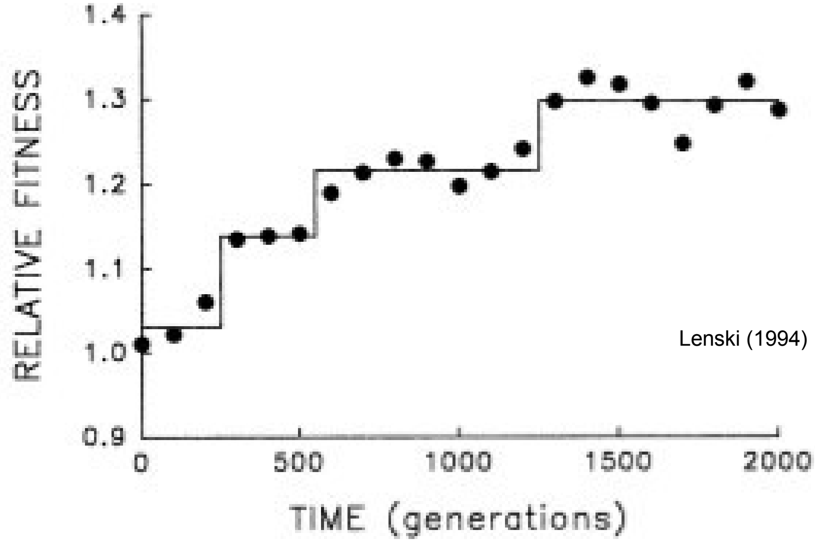
Experimental Background

- The Lenski et al.(1991) Long Term Evolution Experiment is able to identify when beneficial mutations become dominant in a population.



Experimental Background

- Step-like changes in the bacterial behaviour can be noticed following this method.
- These come from a single mutation coming to dominate the entire population.
- They provide a measure of the beneficial mutation rate.

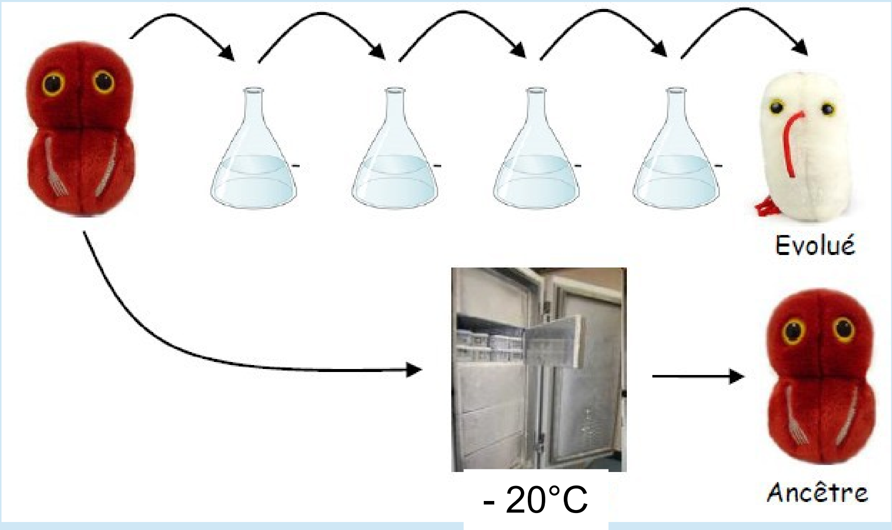


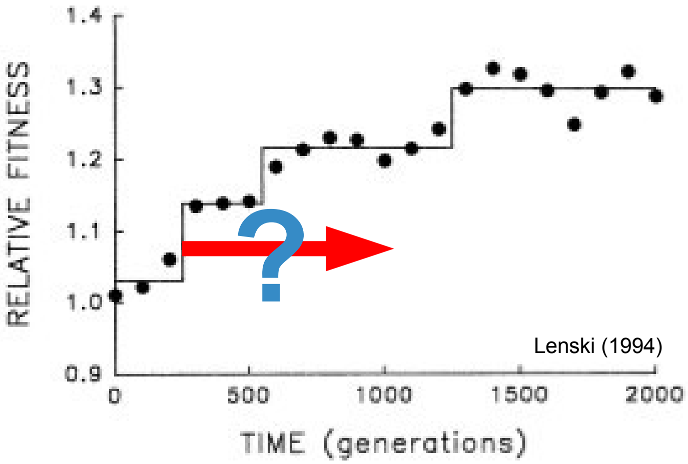
Lenski (1994)

Experimental Background

- Underground, radiation's role in DNA mutation and cell oxidation can be greatly reduced.
- How does this change the evolutionary behaviour?

Radiation protected environment





Our Experiment

- Run Long Term Evolution Experiment in multiple radiation environments
  - 500 generations to begin

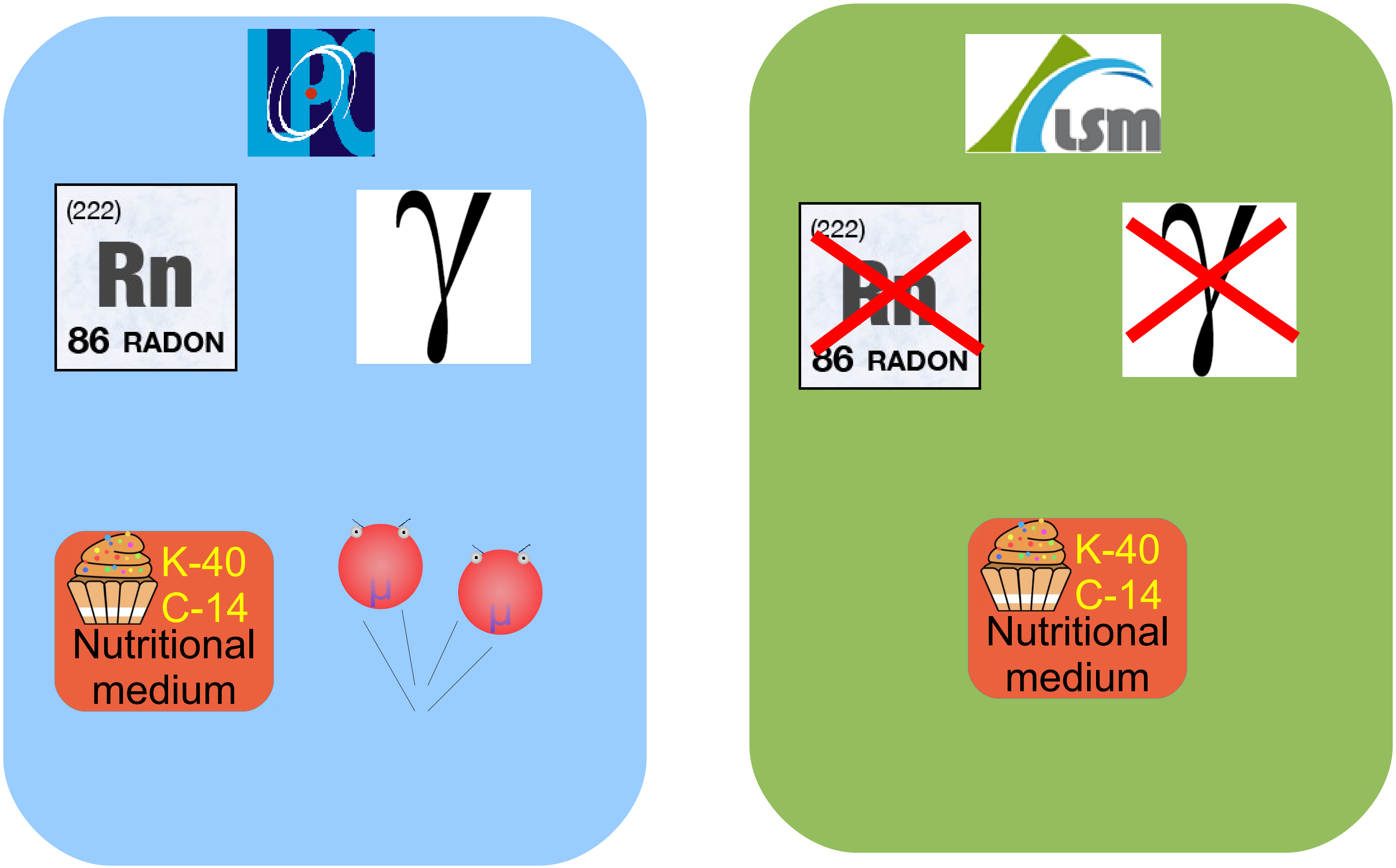
- Our radiation environments:

Active
Reduced Background
Ambient Background

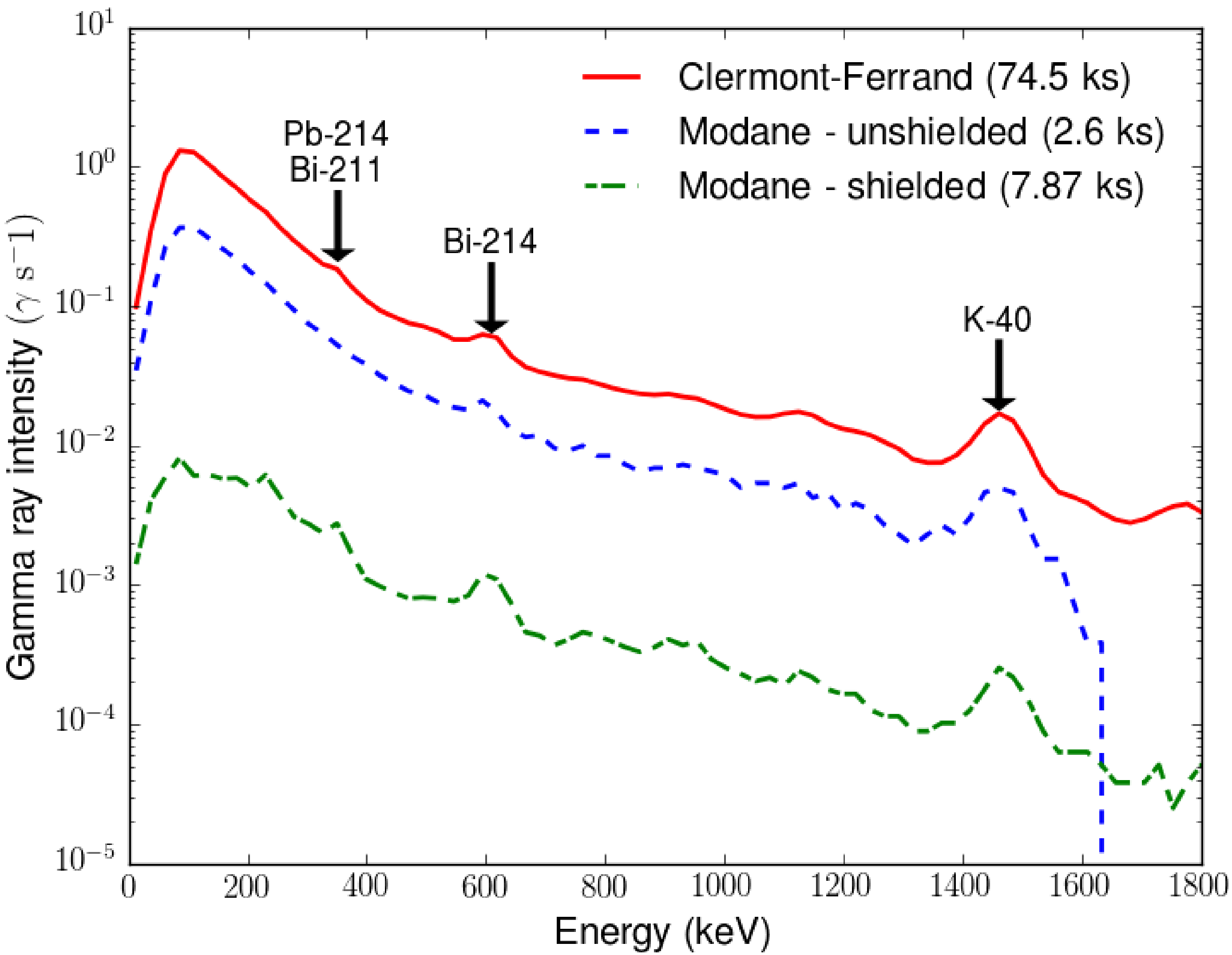
Planned
Controlled Source

Radiation background studies

Relevant Sources



Gamma Background



NaI measurements

The macro: dosages

Source	Measurement Method	LPC Clermont (nGy/day)	Modane (nGy/day)	Modane (shielded) (nGy/day)
γ background	Dosimeter measurement (rate varied by 10%)	2400	480	15
Muon flux	From theory	460	0	0
Potassium-40 (γ)	Simulations based on concentration	0.4	0.4	0.4
Potassium-40 (β)	Simulations based on concentration	74.4	74.4	74.4
Carbon-14 (β)	Simulations based on concentration	0.02	0.02	0.02
Total		2935	555	90

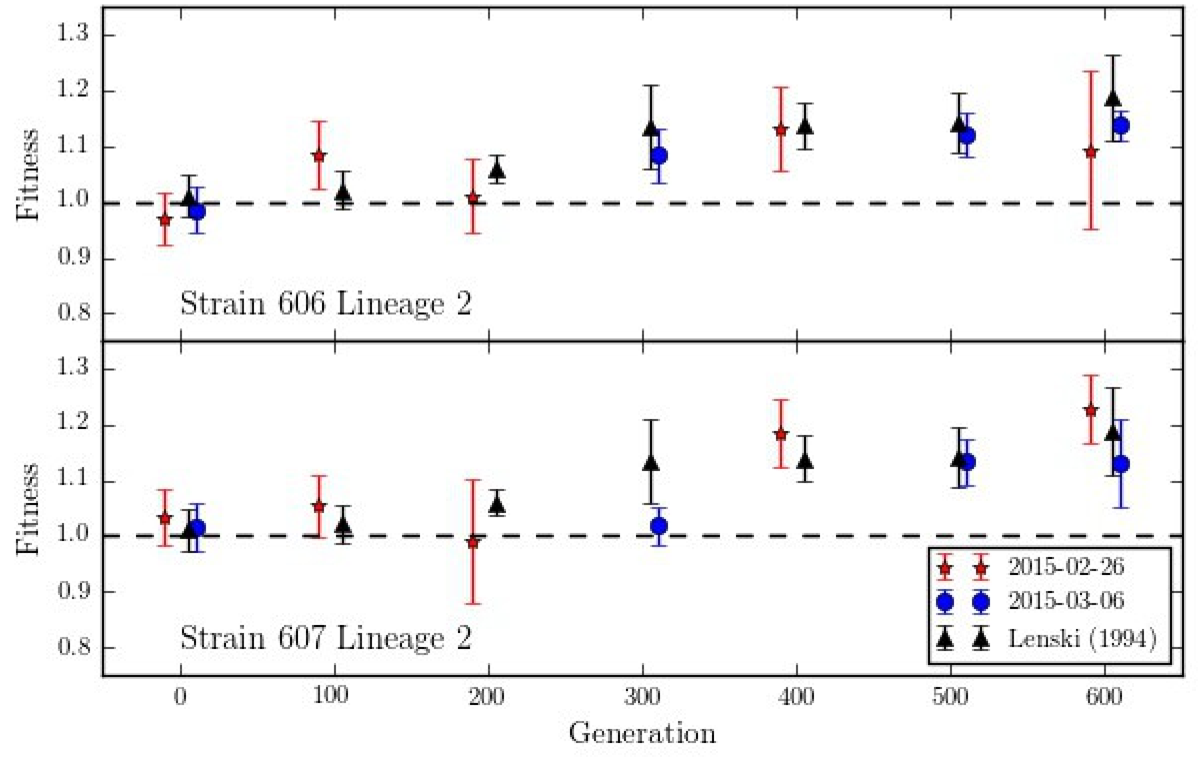
Using measured dosages, the background is reduced by a factor of 32

Pôle Physique Environnement Santé

Biological Results

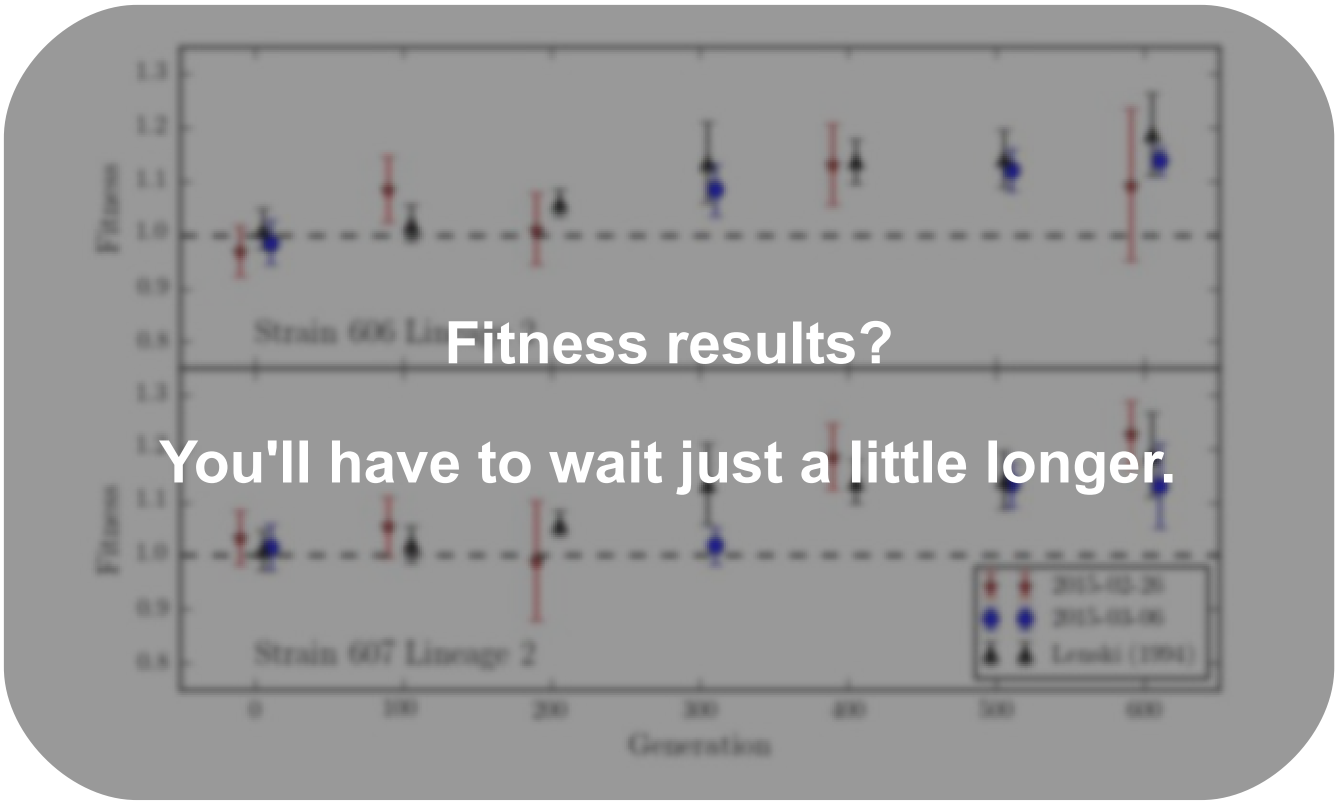
Clermont-Ferrand

- Contamination-free growth to 500 generations
- Experimental protocols fully developped
- Observation of adaptation, as expected occurring near 300 genera…



Modane

- Contamination-free growth to 405 generations
- Development of protocols to measure fitness

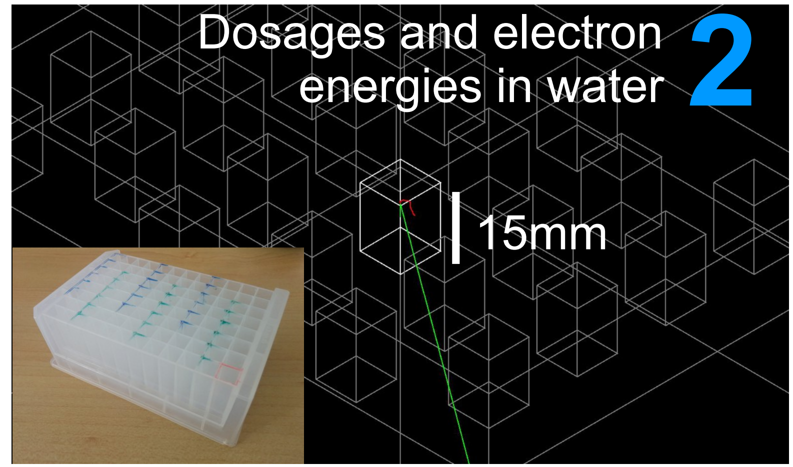


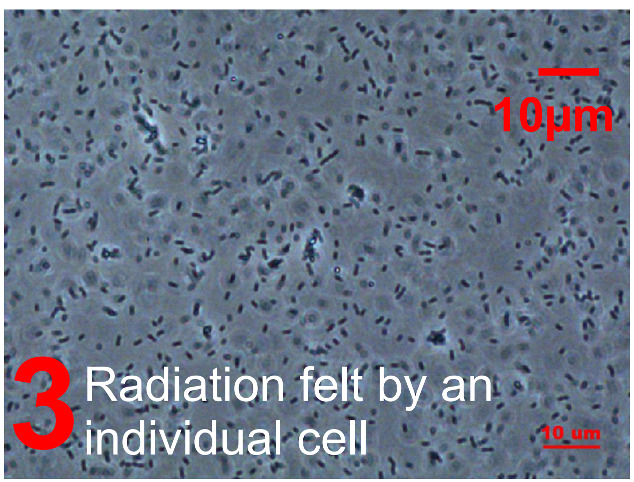
Simulating DNA damage in low background environments

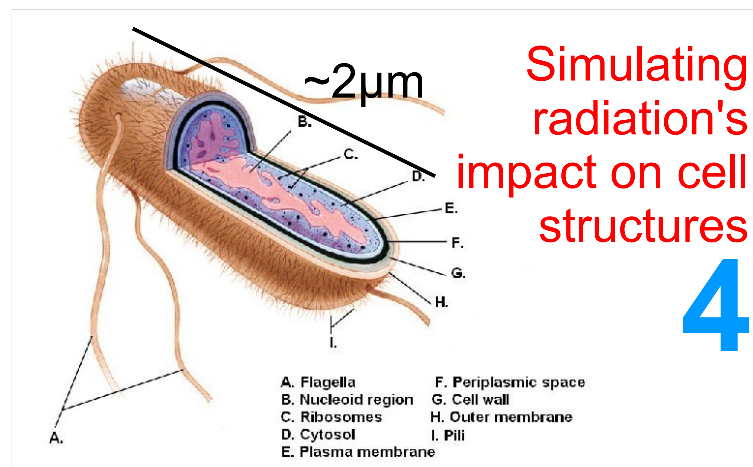
Why Simulation?

- Allows us to test our theoretical understanding of the experiment, and of low background DNA damage
- Allows predictive estimates of how different radiation environments impact DNA
- Geant4 is a software platform that simulates the interactions of particles with matter
- Low energy electromagnetic simulations and biological effects can be simulated using models developed by the Geant4-DNA collaboration
- Geant4-DNA also permits the modelisation of chemistry

From the metre to the nanometre







A simulation workflow

Simulating cellular damage from an environment

The macroscopic scale:
Simulation of the experimental geometry in a radiation environment

Output/Input linked

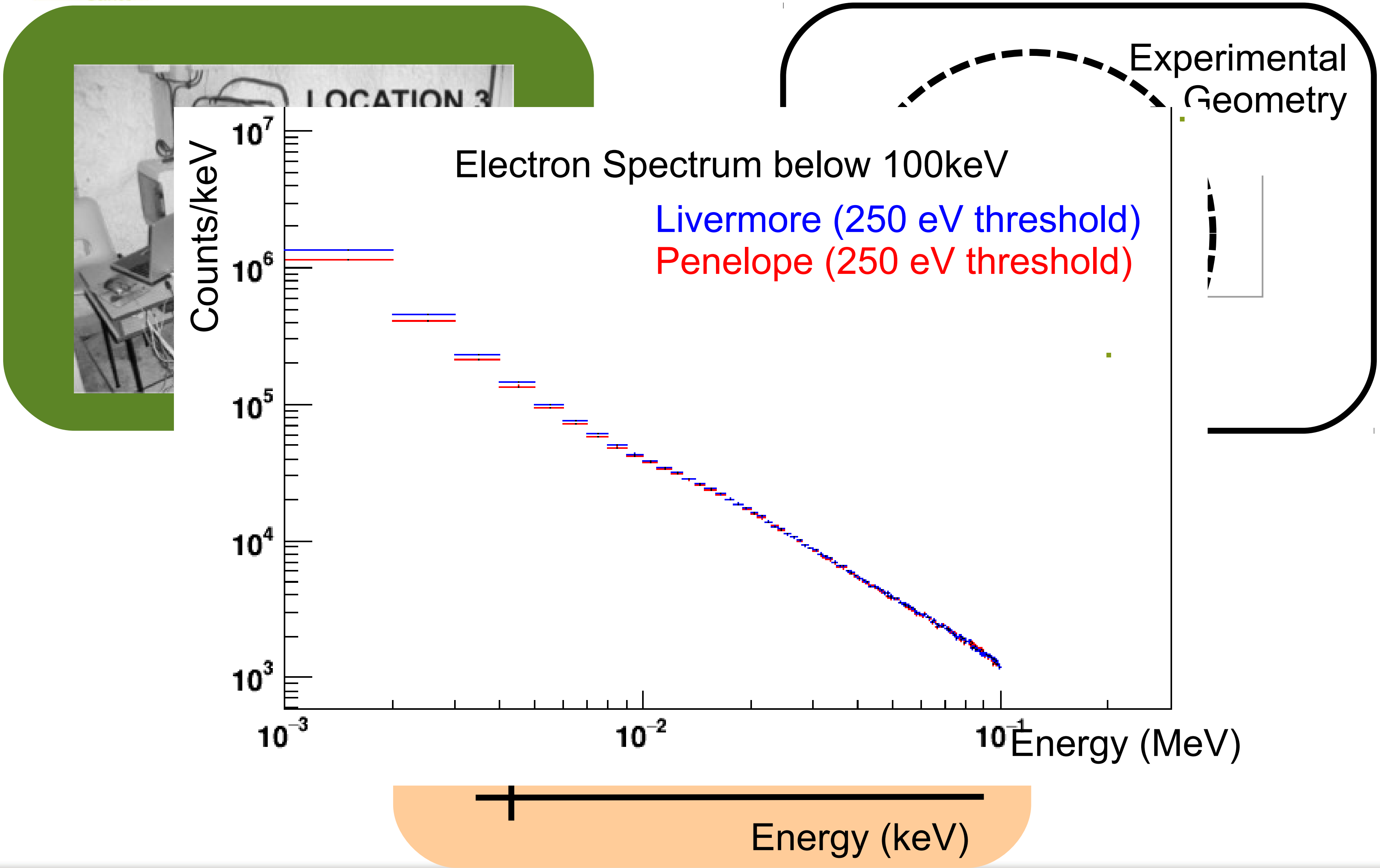
The microscopic scale:
Simulation of secondary particles created by environmental radiation and impact upon cells

Output/Input linked

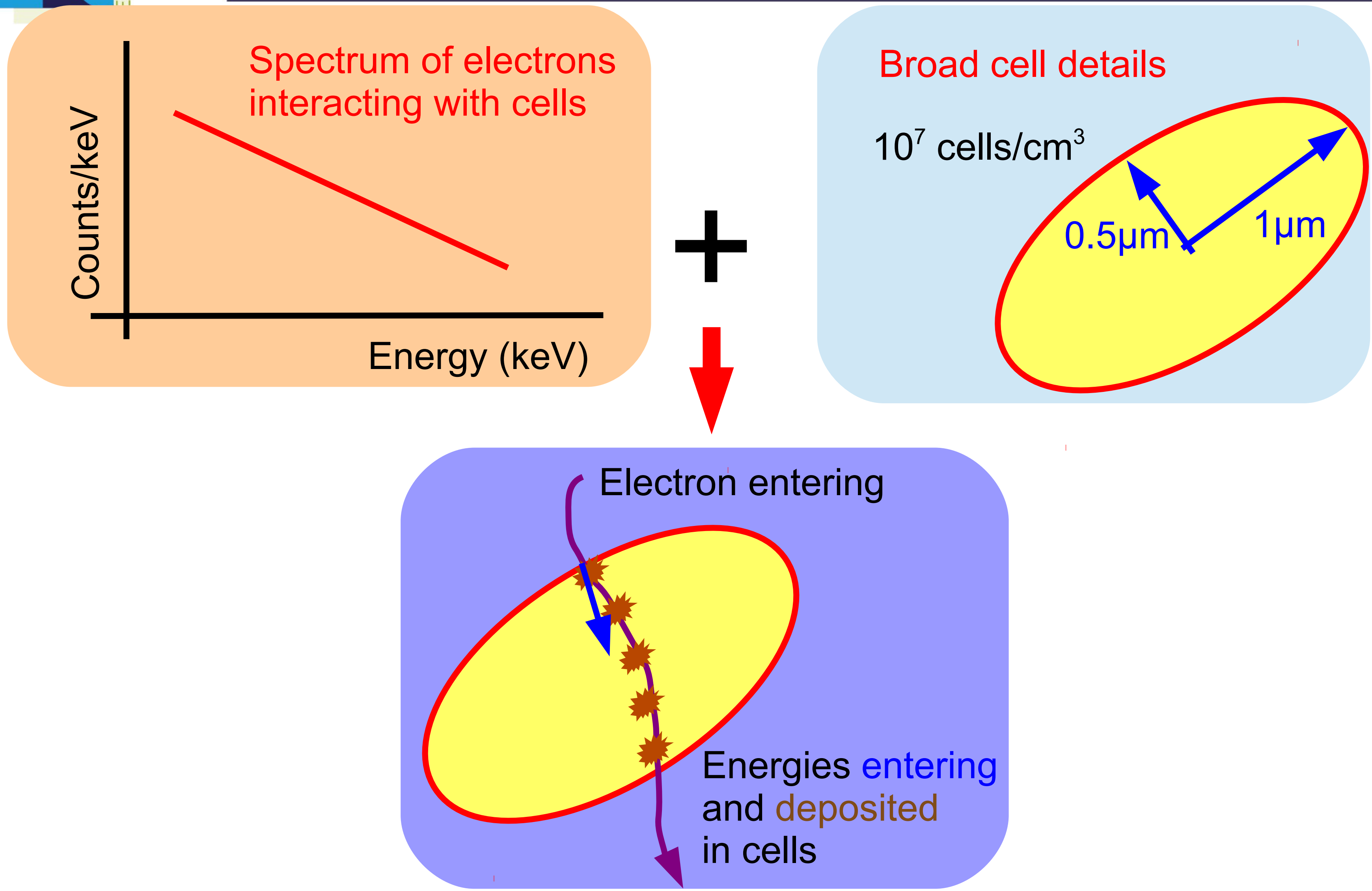
The cellular scale:
Direct and indirect damage within the cell
(Damage up to 1µs)

Repair:
Can be modelled afterwards to extend simulation beyond 1µs

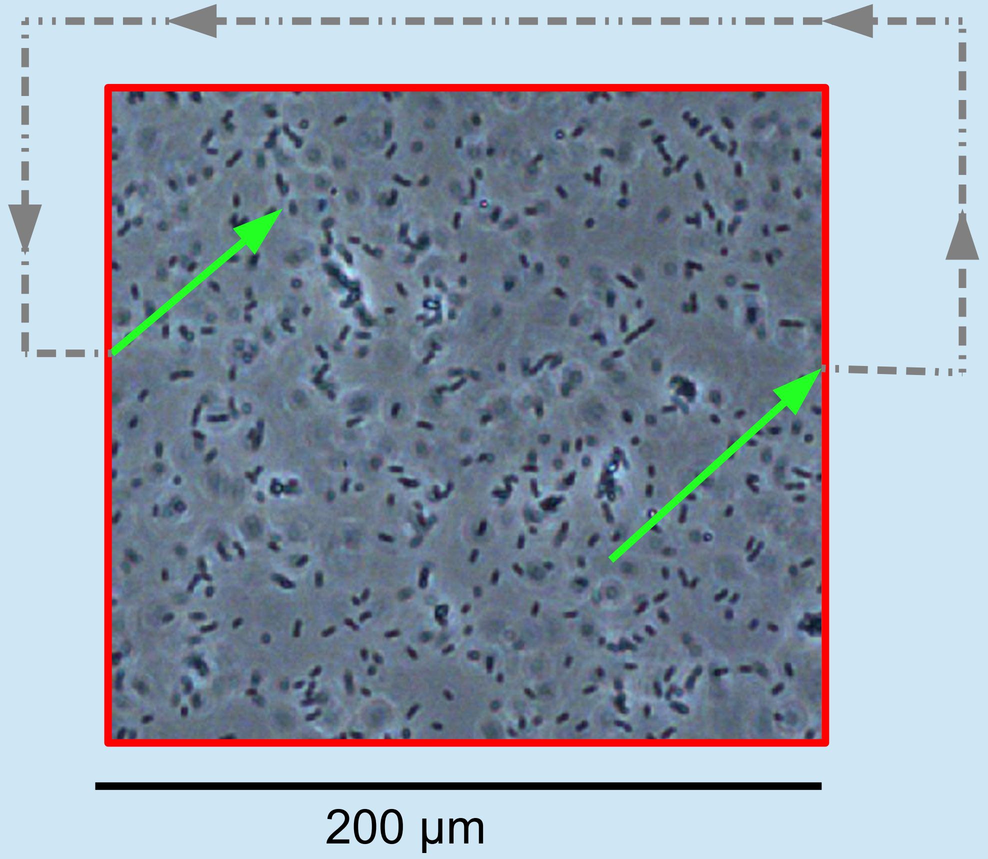
The macroscopic system



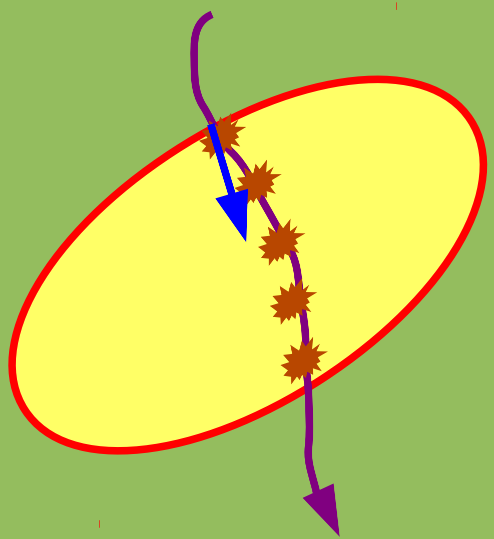
The microscopic system

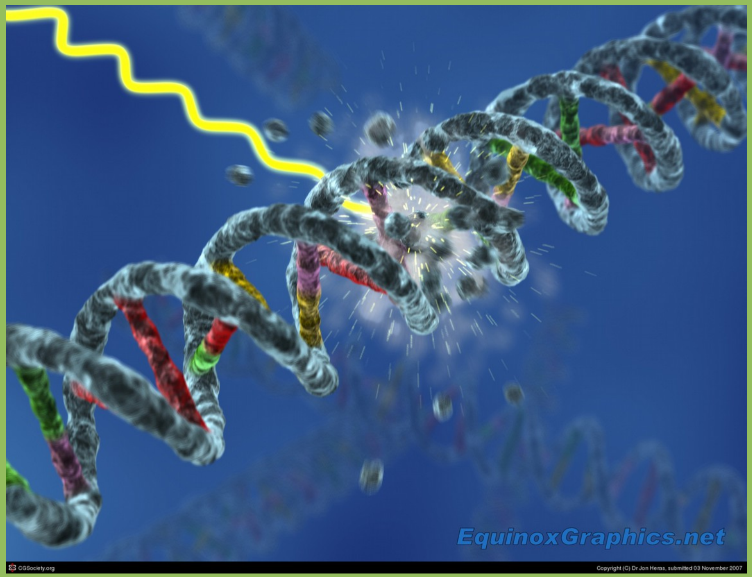


A periodic boundary to enable this



Measuring DNA damage



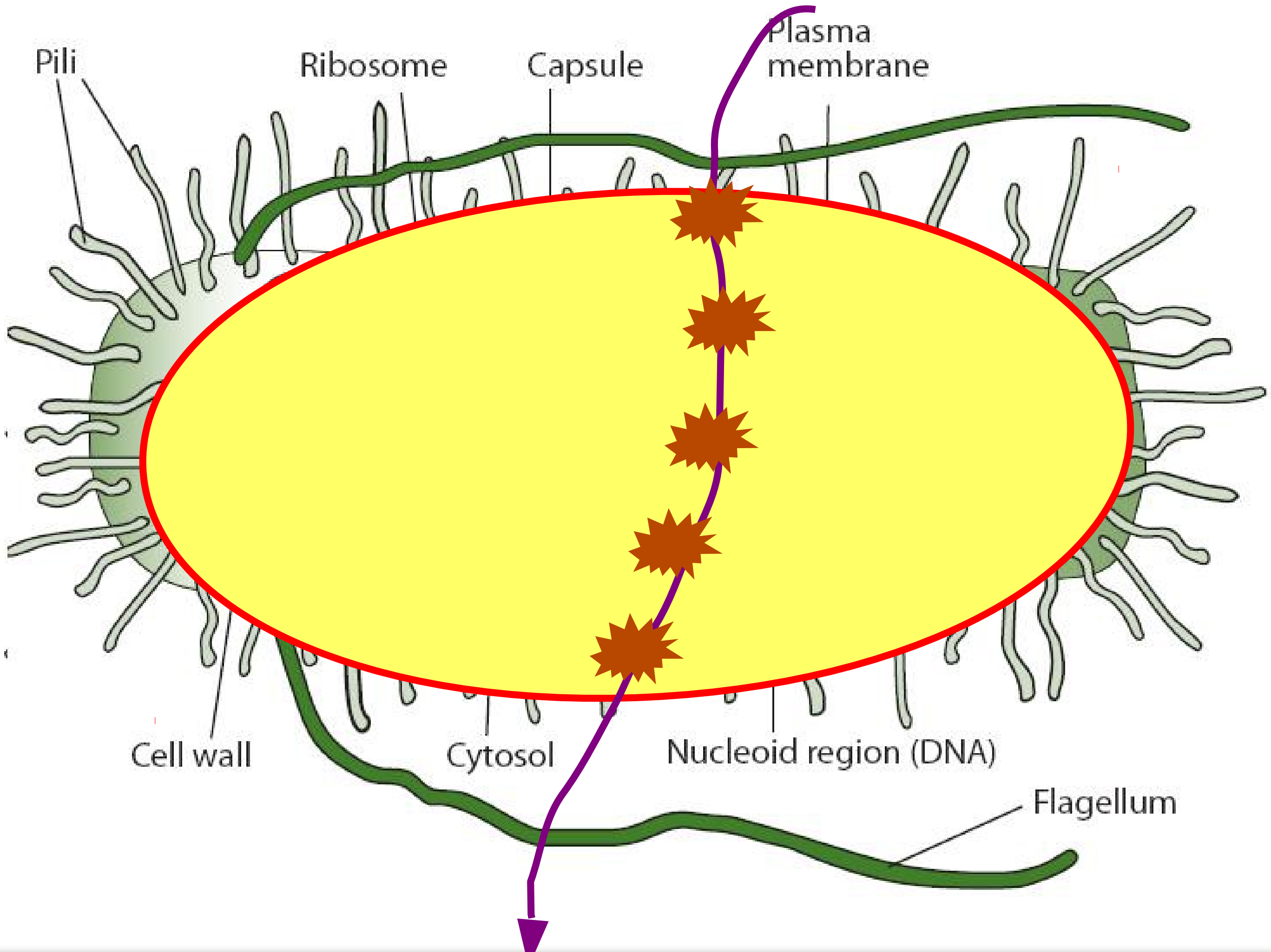


Damage to consider

Direct: Radiation breaks one or both DNA strands
Indirect: Radical oxygen species damage the DNA Strand

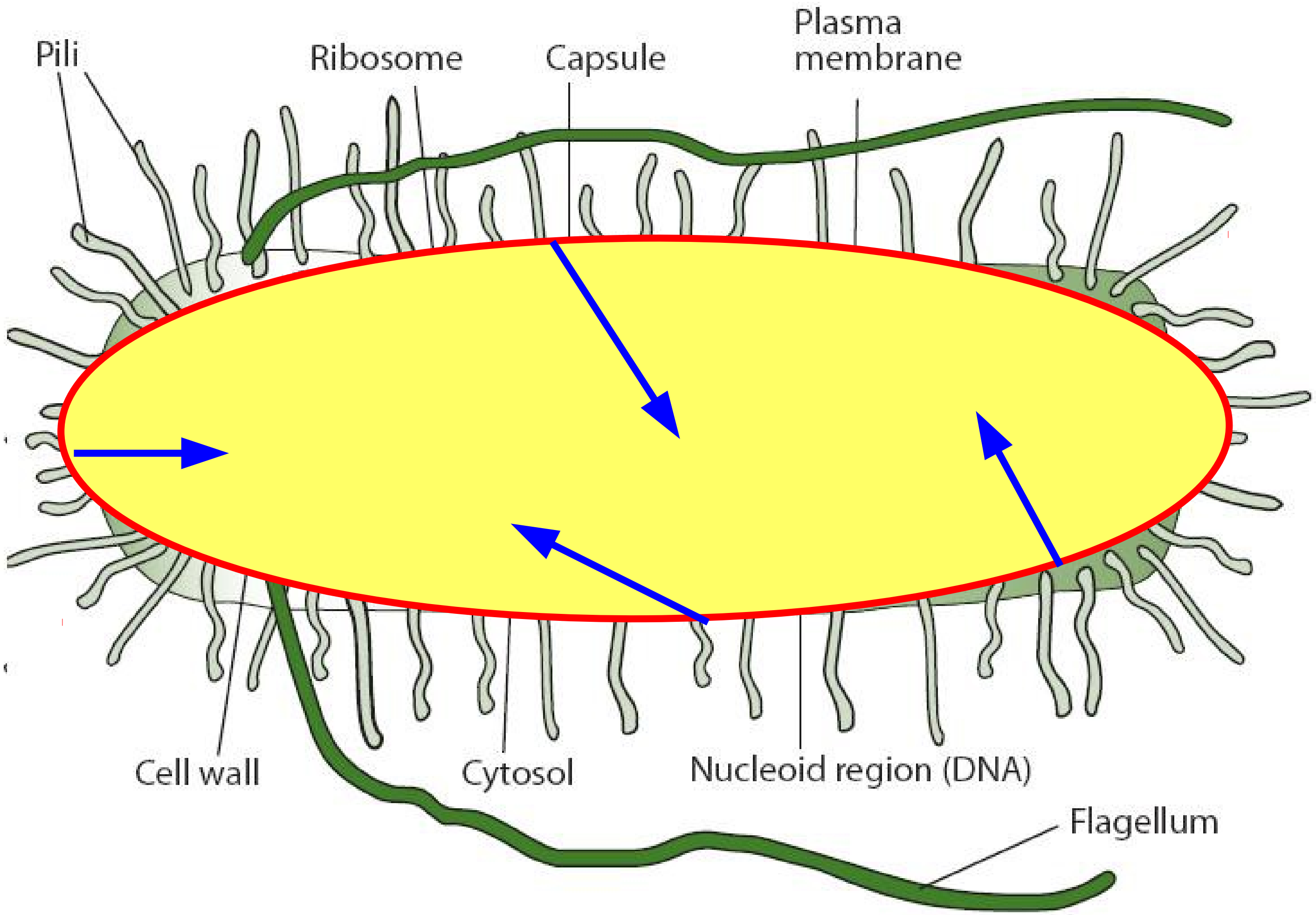
Measuring DNA damage

Method 1: Correlate energy deposits with position



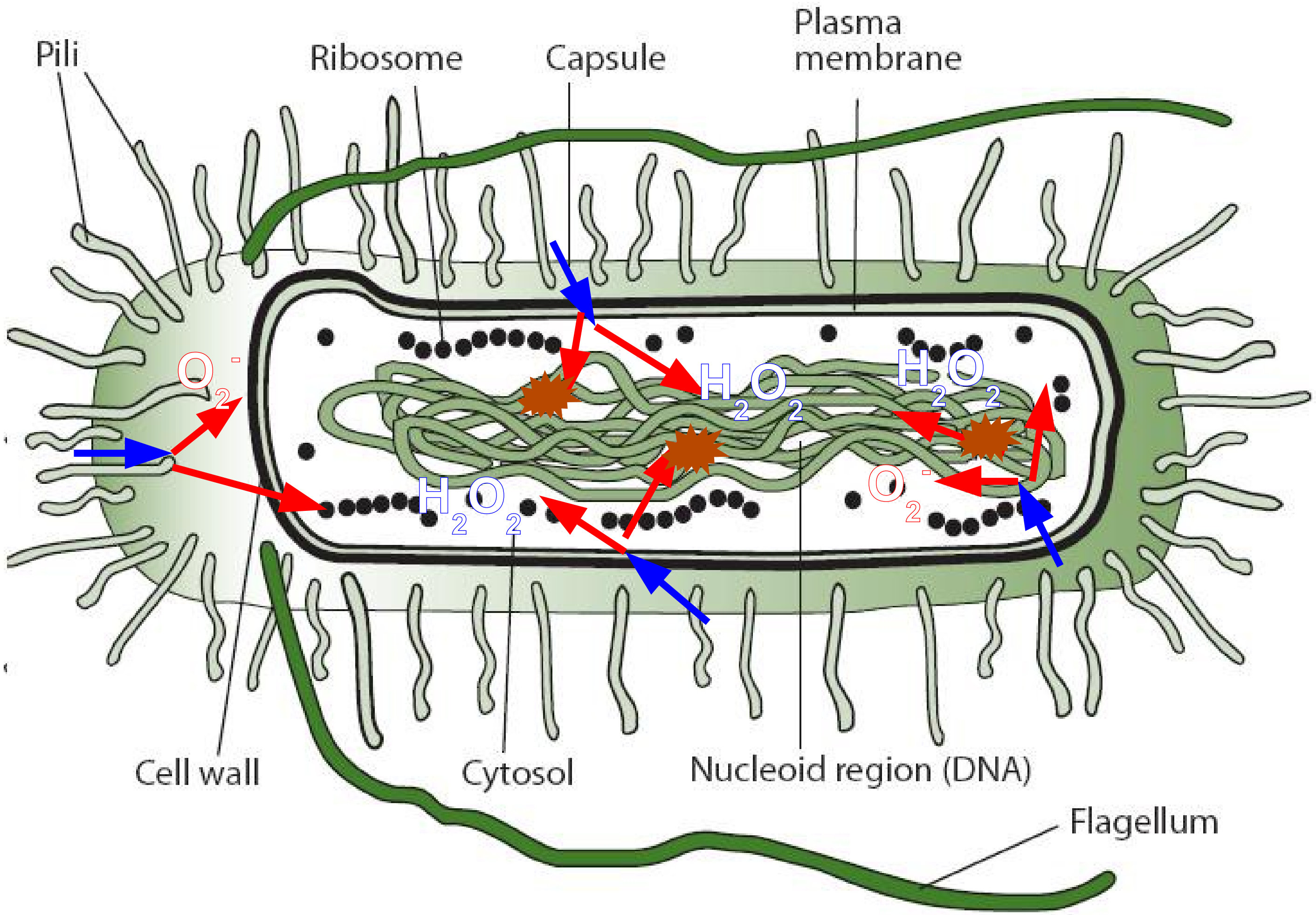
Measuring DNA damage

Method 2: Build a bacteria model, and simulate chemistry



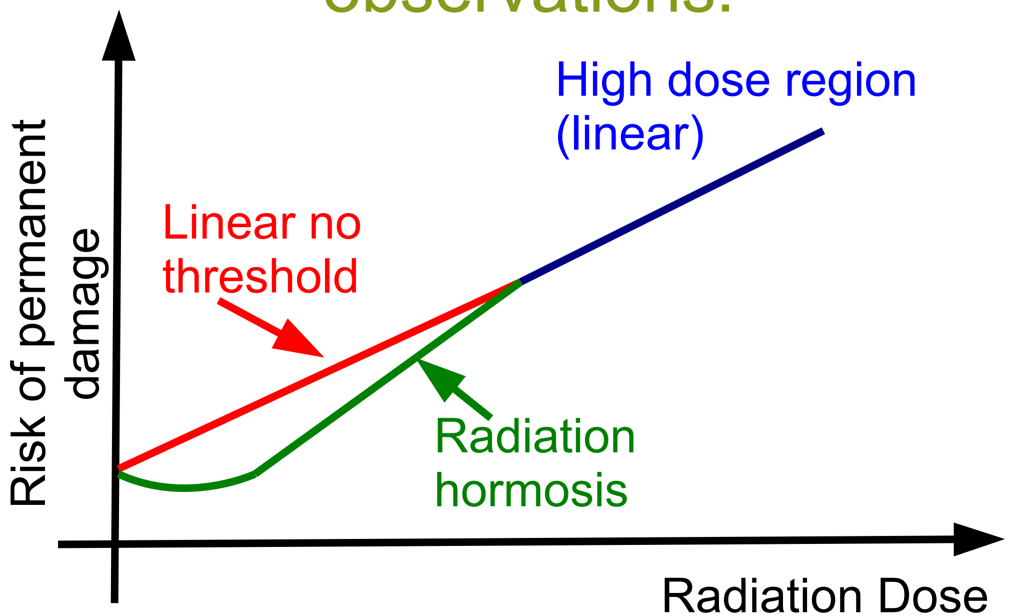
Measuring DNA damage

Method 2: Build a bacteria model, and simulate chemistry



Prospects: Simulation beyond the first μs

Simulating effects beyond the first μs, such as DNA repair allow us to probe the does-response curve at the low end, and build the theoretical support for LBE observations.

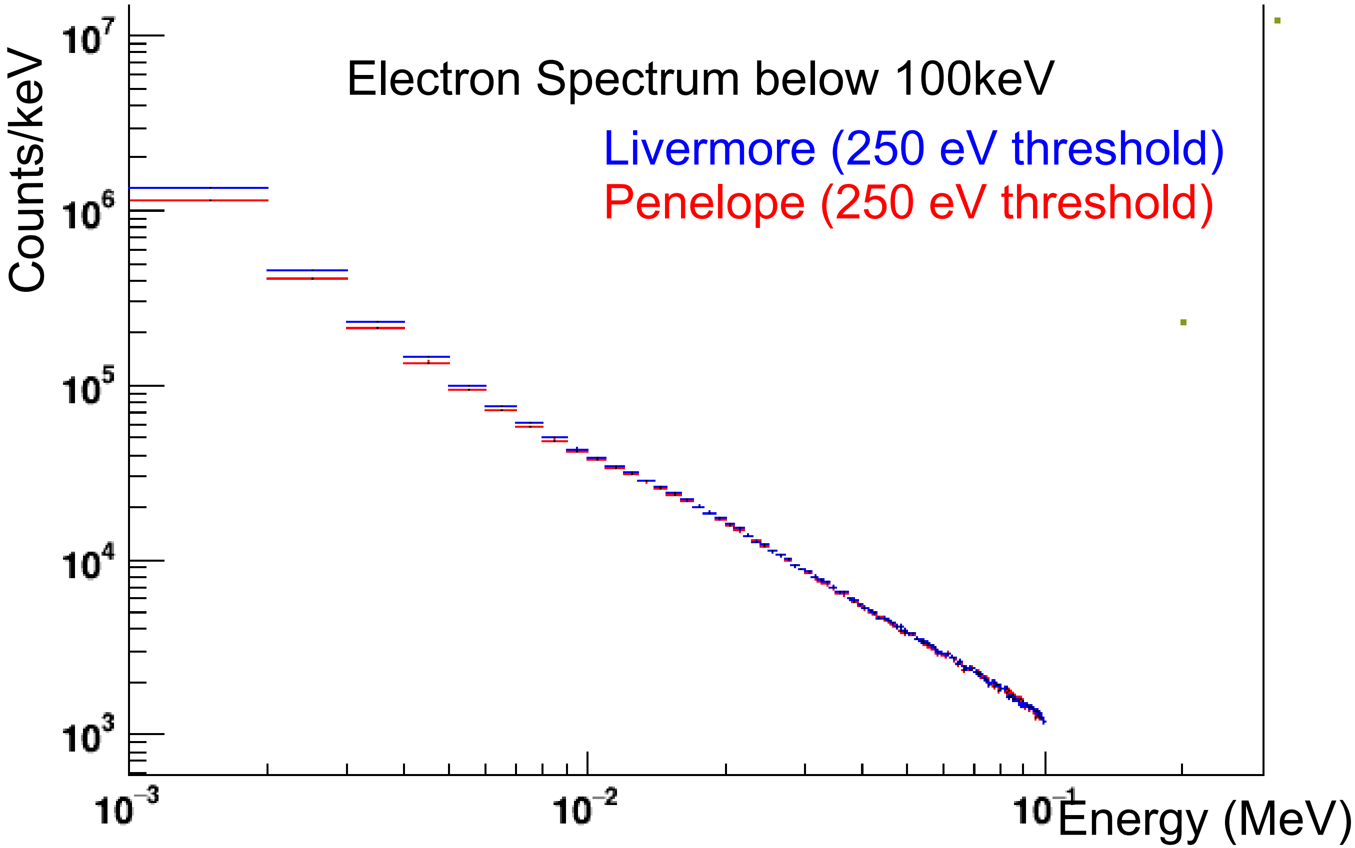


Conclusions

- We have set up a biological laboratory at Modane
- There, we are conducting Long Term Evolution Experiments to see how radiation affects evolutionary behaviour
- We are building a robust simulation workflow that will permit the simulation of DNA damage in low background environments


That's all Folks!

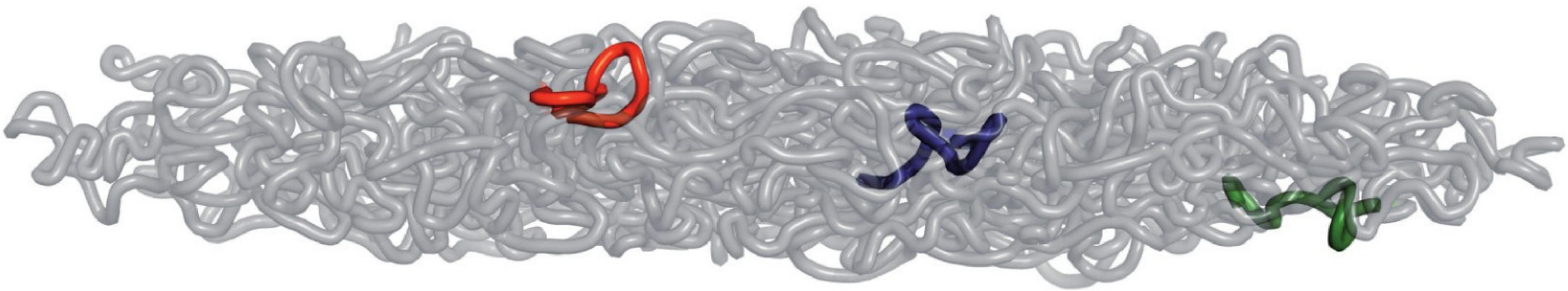
The macroscopic system - output



Bacterial DNA Organisation

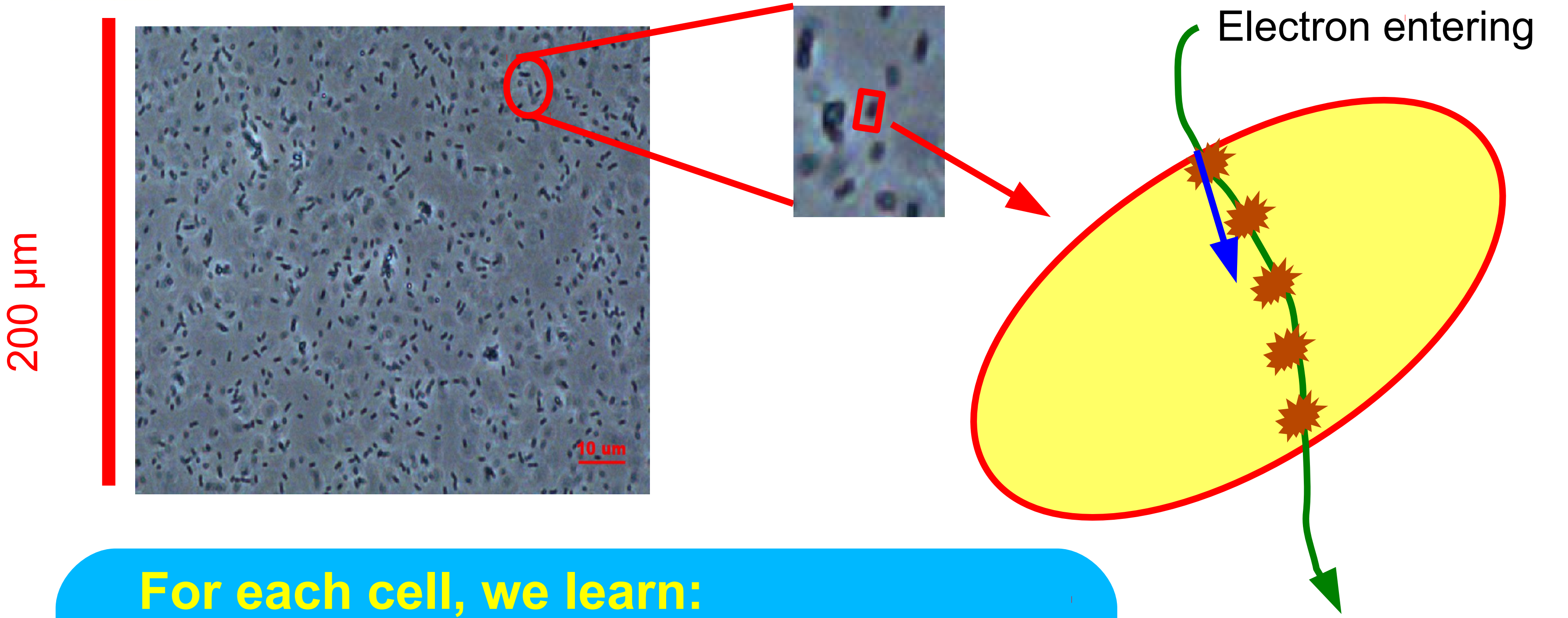
- Modelling the structure of DNA inside a bacterial nucleoid or an animal nucleus is a complex task

- Accuracy of the representation needs to be balanced with ease of modelling and desired outputs



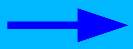
The organisation of the bacterial nucleoid from polymer models (Fritsche 2012), Genes that share the same transcription factor are clustered together.

What does this tell us?



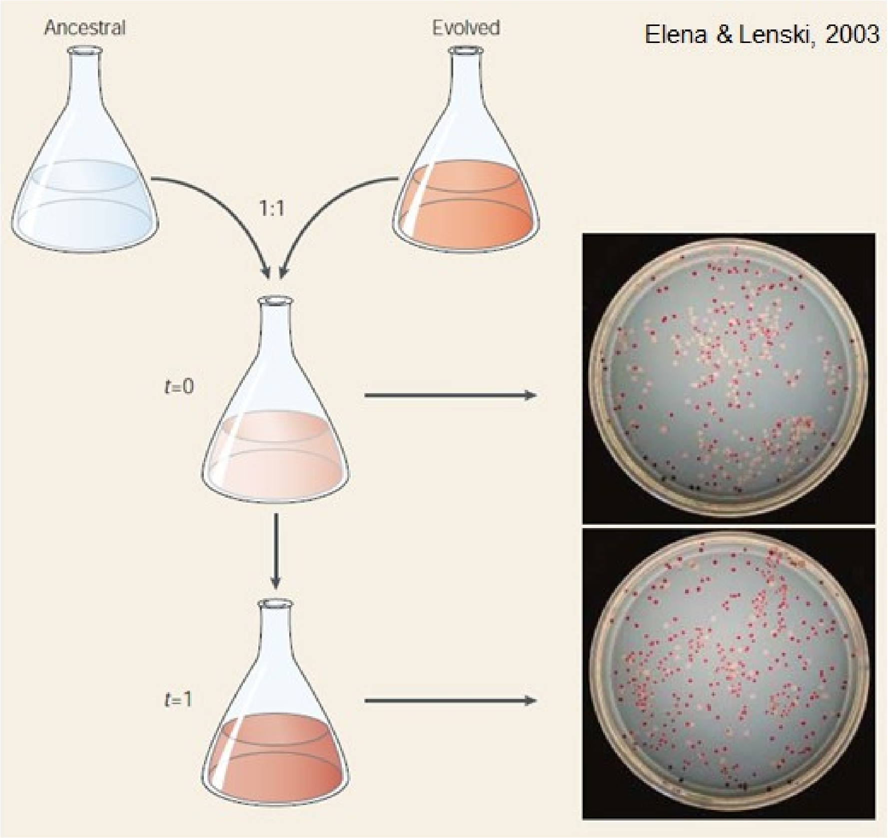
For each cell, we learn:

Position of energy depositions, and energy deposited



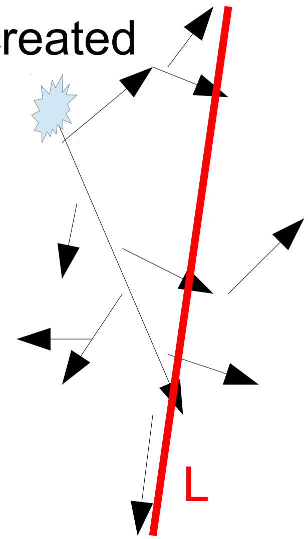
Energy, direction and position of entering electrons

Experimental Background

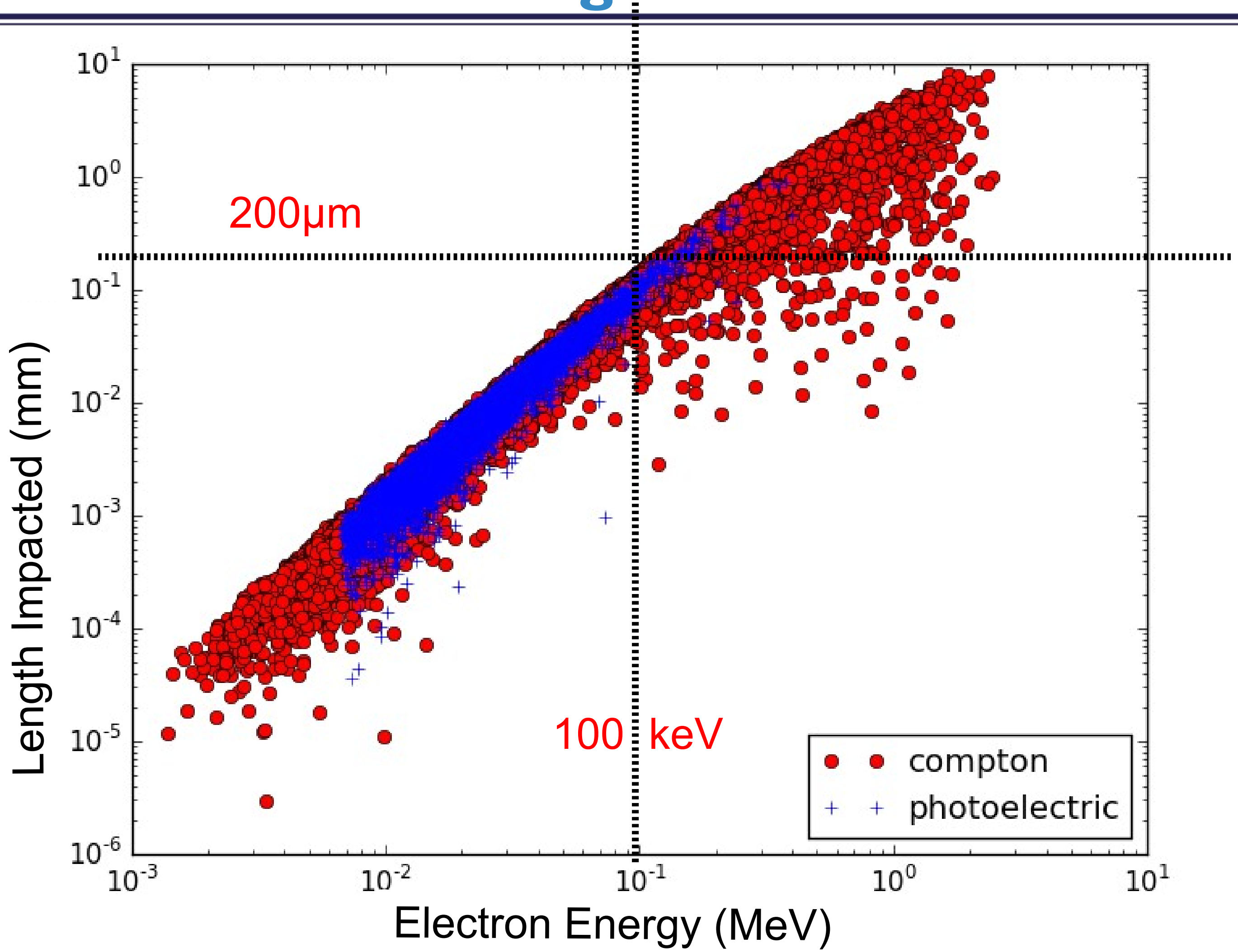


- Lenski, and us, measure bacterial fitness to measure the adaptation of the strain to its environment.
- An evolved strain is placed in competition with its ancestor, and the difference in their respective growths indicates the relative fitness

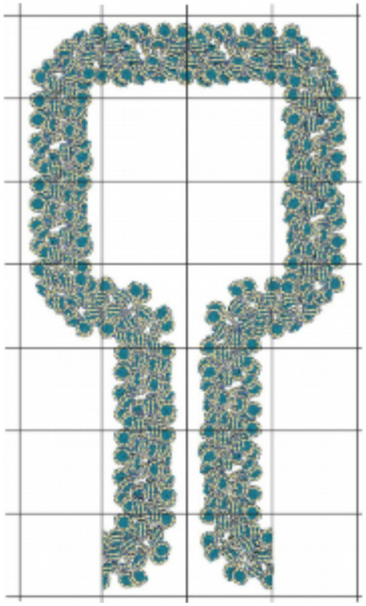
Results: Electron energies in the well



The length impacted measures the longest possible length scale impacted in each event



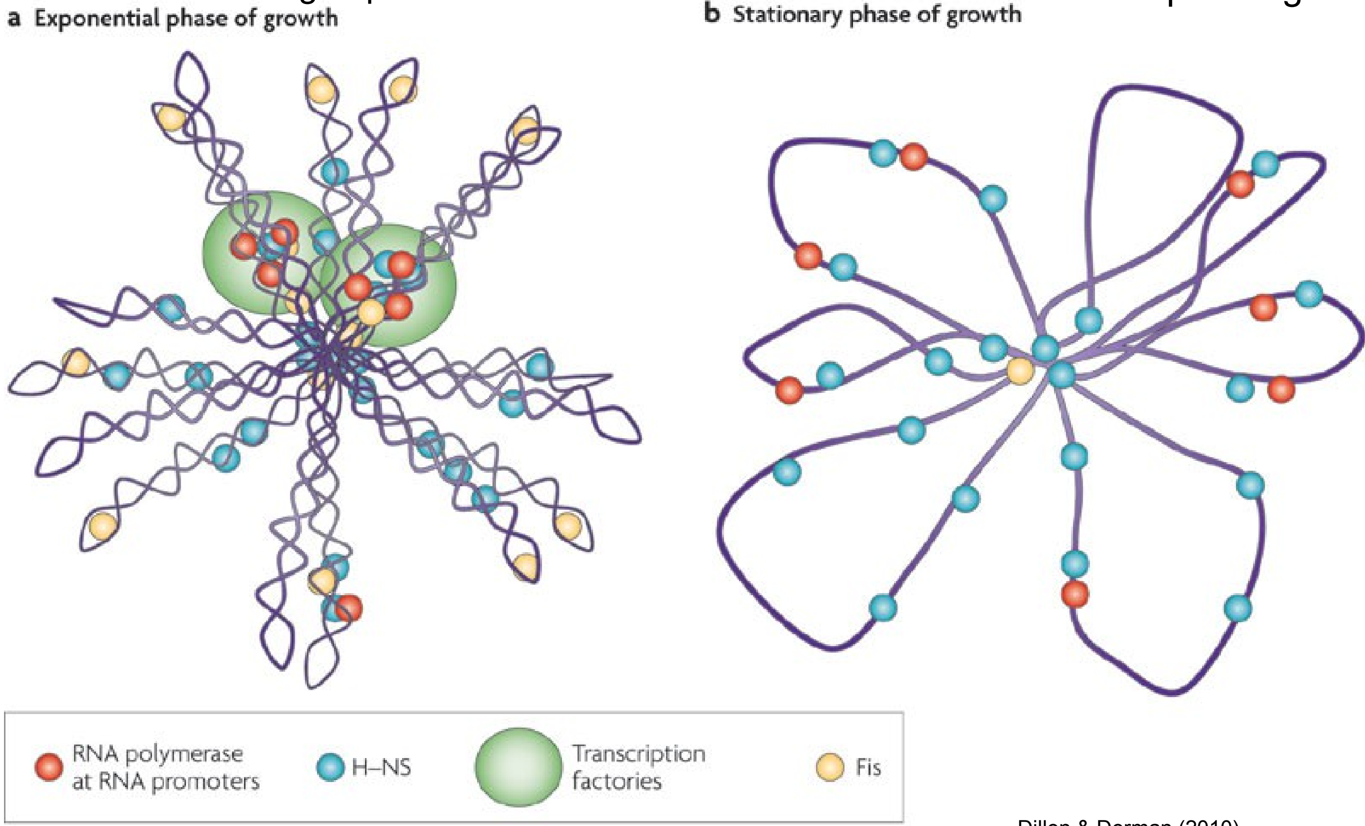
The individual cell – Bacterial DNA



Eukaryotic DNA model (Friedland et al., 2011)

Bacterial DNA being duplicated

DNA when bacteria is not replicating

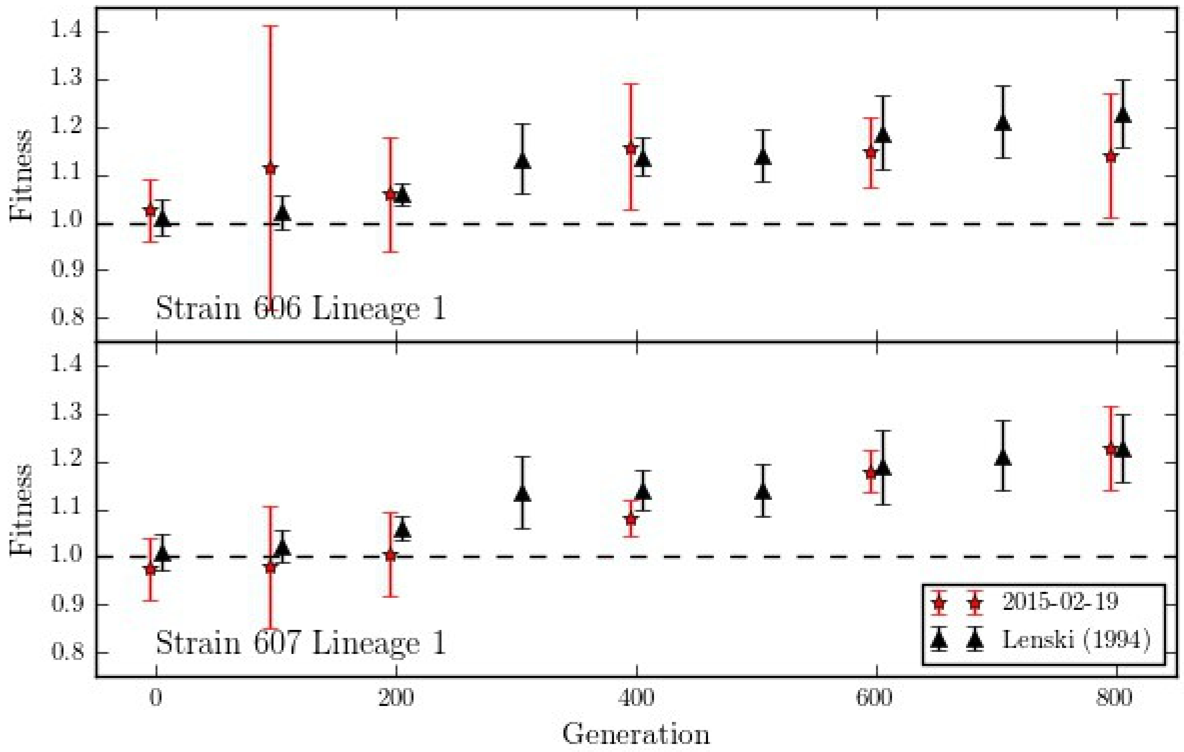


Dillon & Dorman (2010)

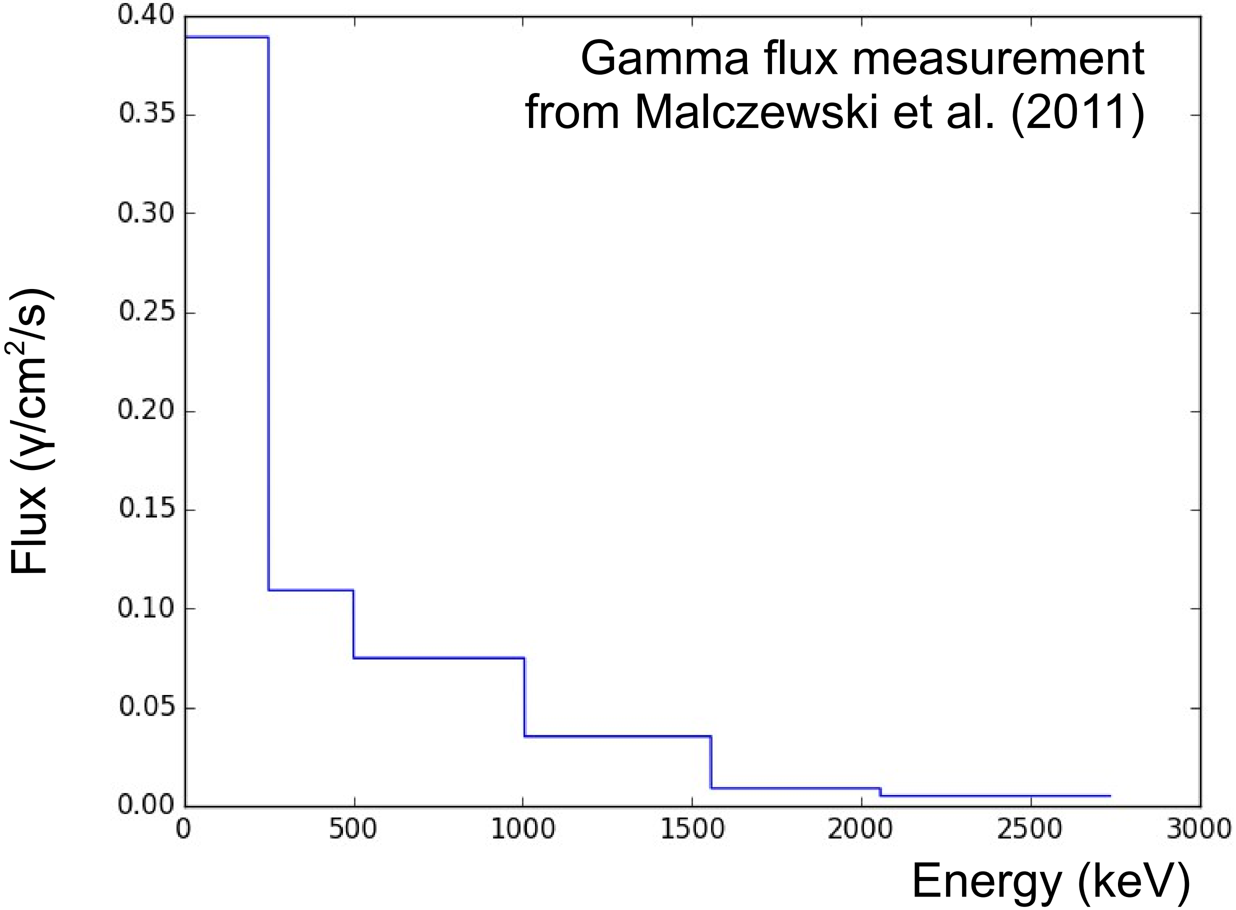
Nature Reviews | Microbiology

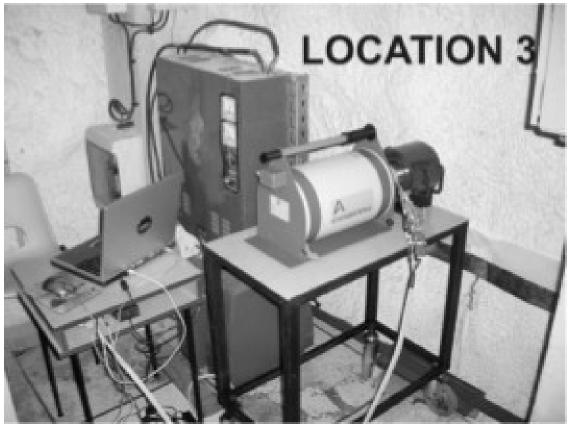
Bacterial DNA has a significantly different secondary and tertiary structure to eukaryotic DNA

Fitness measurements at CF

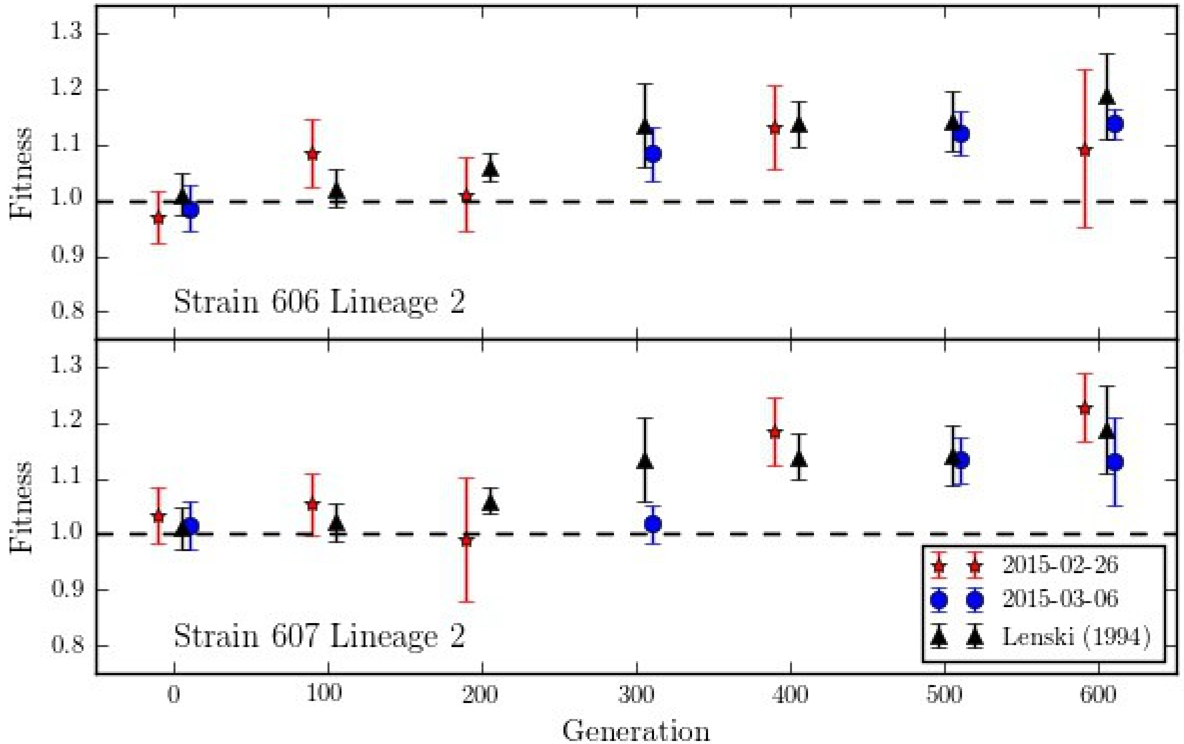


Measurements of radiation in the environment

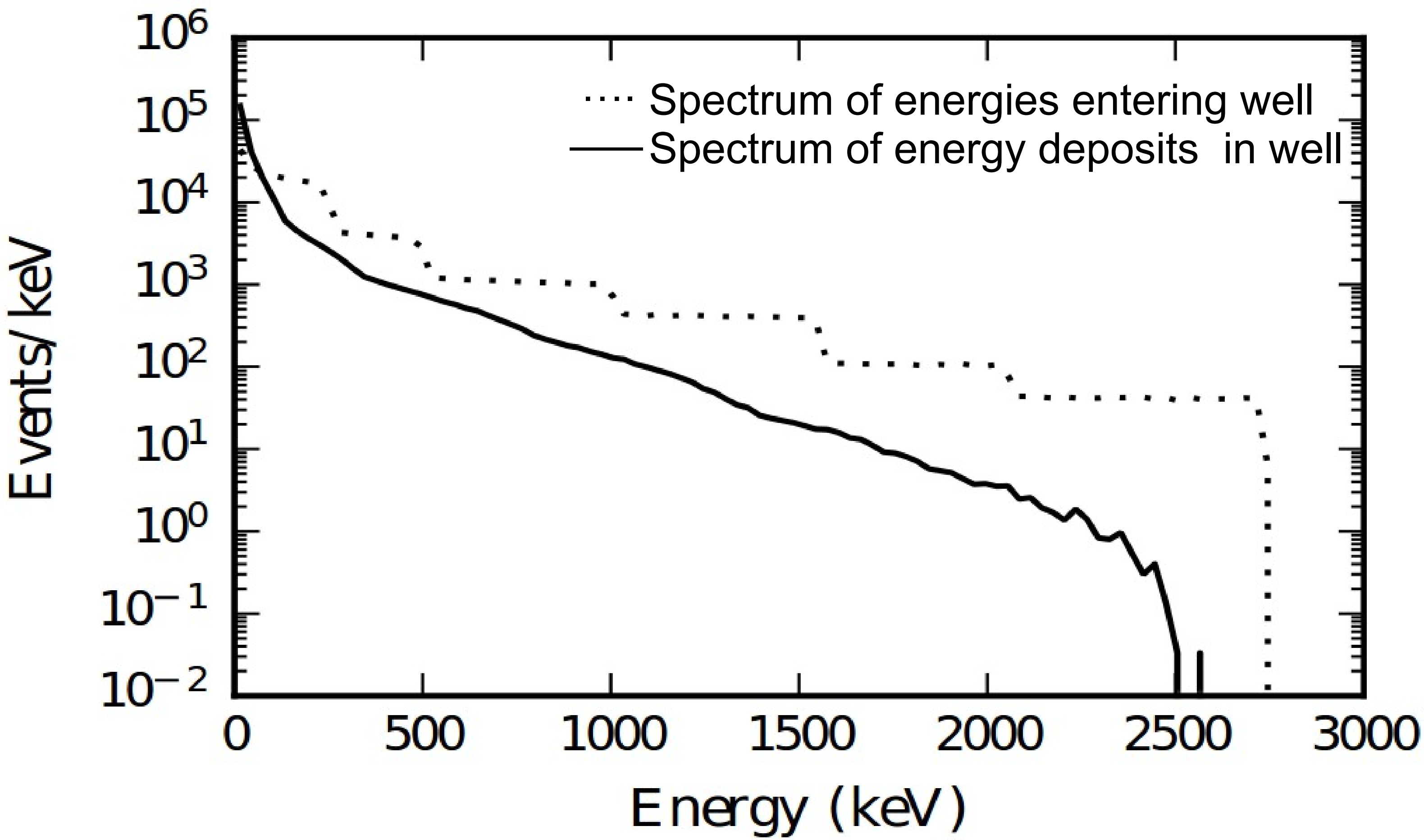




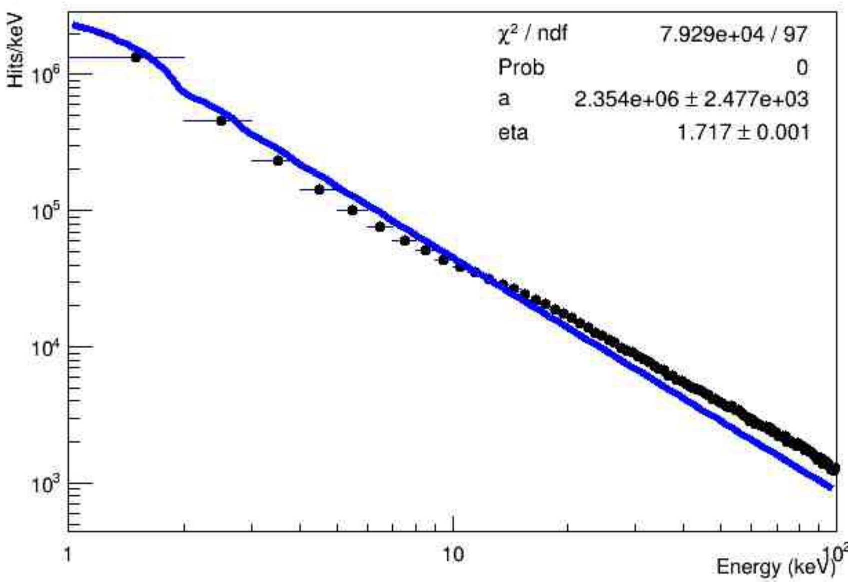
Fitness measurements at CF



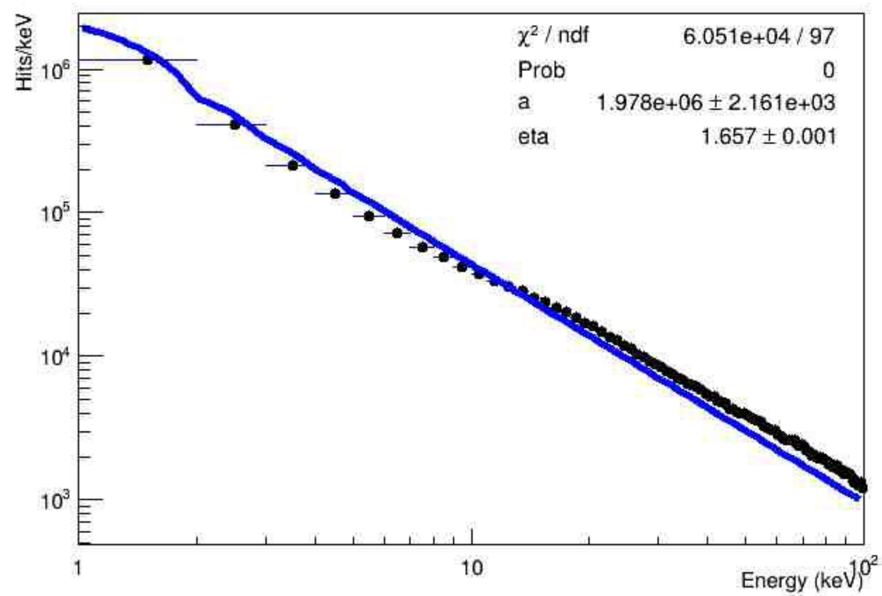
Energy deposit spectrum in well



A power law below 100keV



Livermore



Penelope

From the environment to the cell

- We have now knowledge of the secondary electrons in the cell.
- Typical bacteria:
  - ~10^8 bacteria cm^{-3}
- For us, 4000 bacteria in a cube with side length $200 \mu m^3$
- Putting 10^8 bacteria into memory is a bad idea, better to use a repeating boundary condition

Simulation Geometry

Particles leaving are transported by the periodic boundary