Symposium on science @ PAUL
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Ultra-low radioactivity, a new frontier for biology ?

Vincent Breton

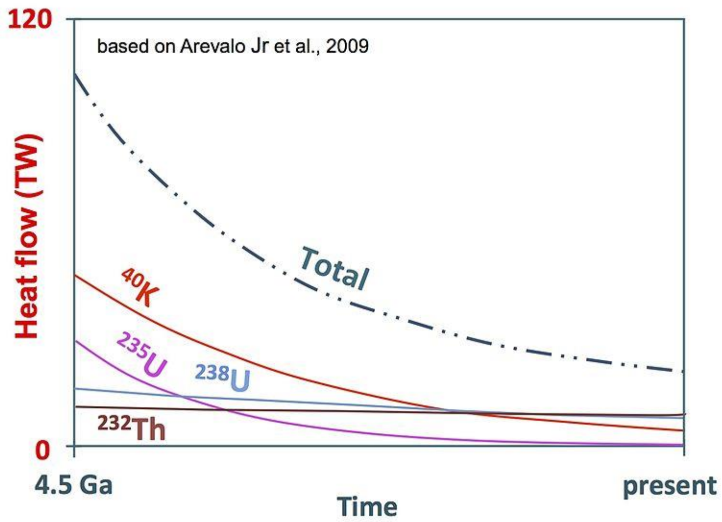
Credit: M. Belli, D. Biron, D. Dauvergne, N. Lampe, P. Morziano, G. Warot

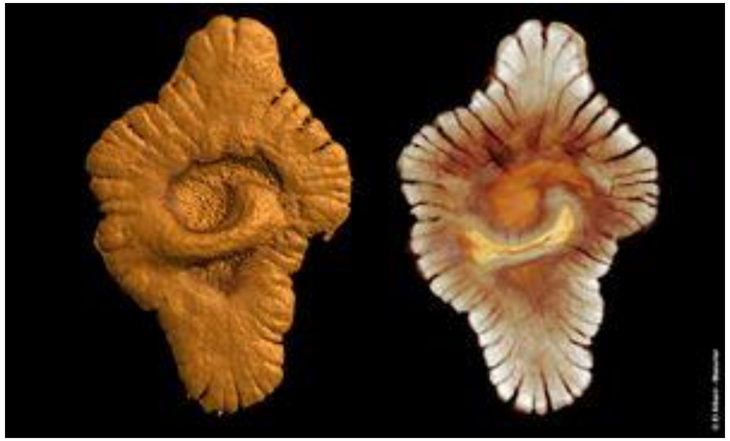
CNRS IN2P3 Les deux infinis

LPC Particules pLasmas Univers applicationS – Laboratoire de Physique de Clermont

UCA Université Clermont Auvergne

Everywhere there is life on earth, there is radioactivity





El Albani et al, nature 2010

- Radioactivity is at the heart of every living organism
  - ^{40}K: isotopic fraction = 0,1167 % , half life = 1,248 Billion years

- How long ago did the first multicellular organisms appear: 600 millions or 2,1 Billion years?
  - Fossils discovered 30 km away from natural nuclear reactors (Oklo, Gabon)

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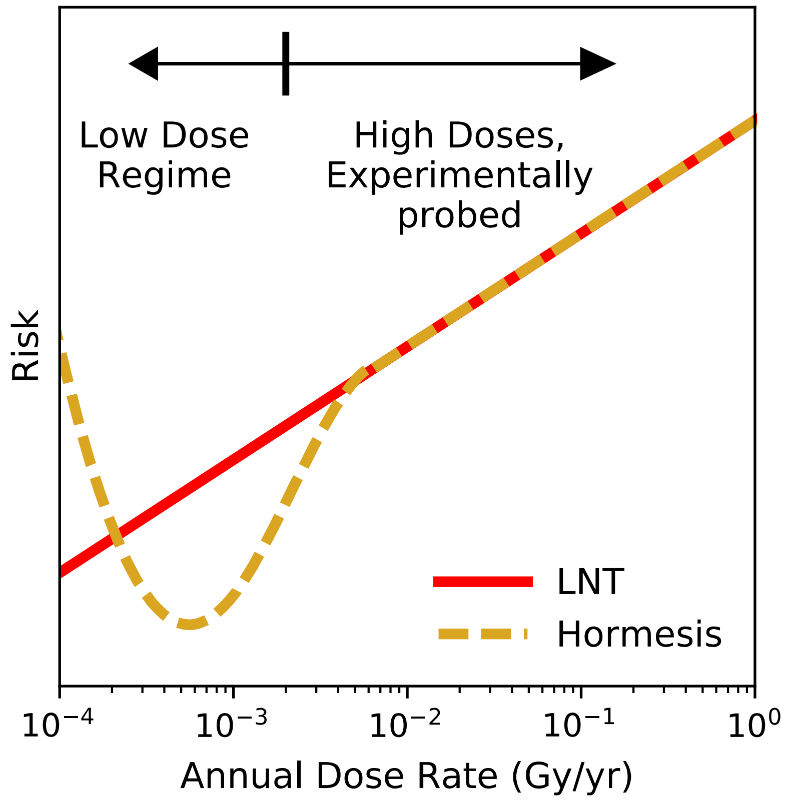
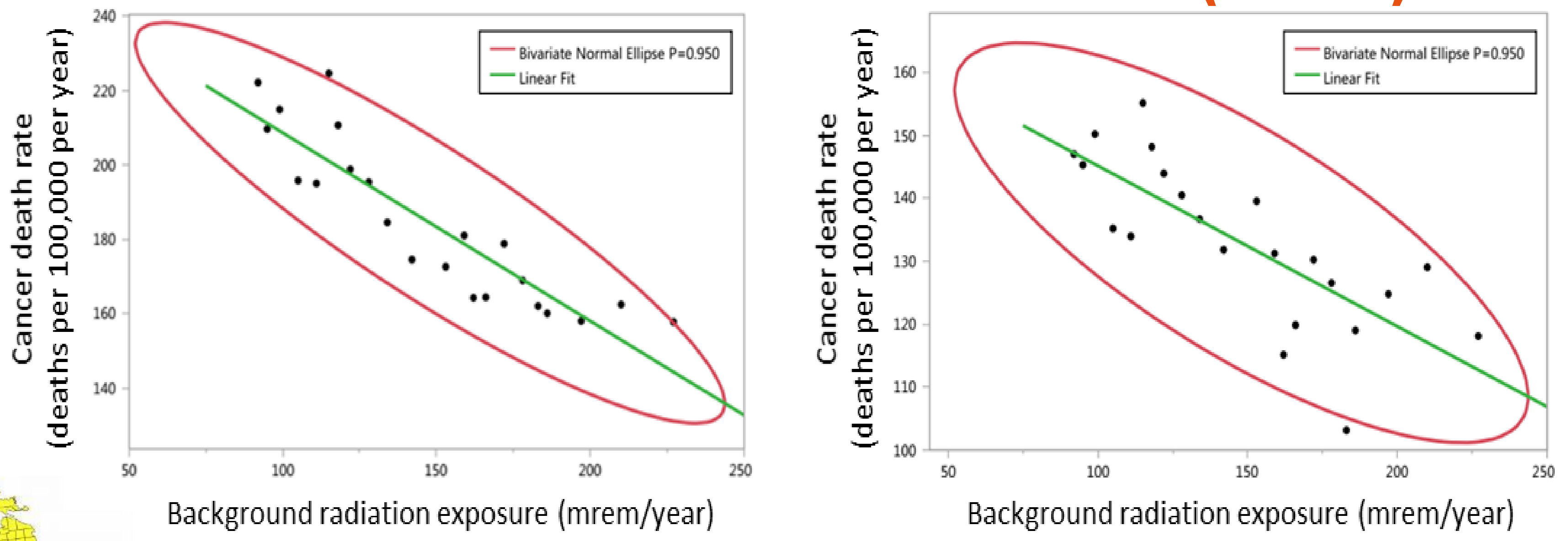
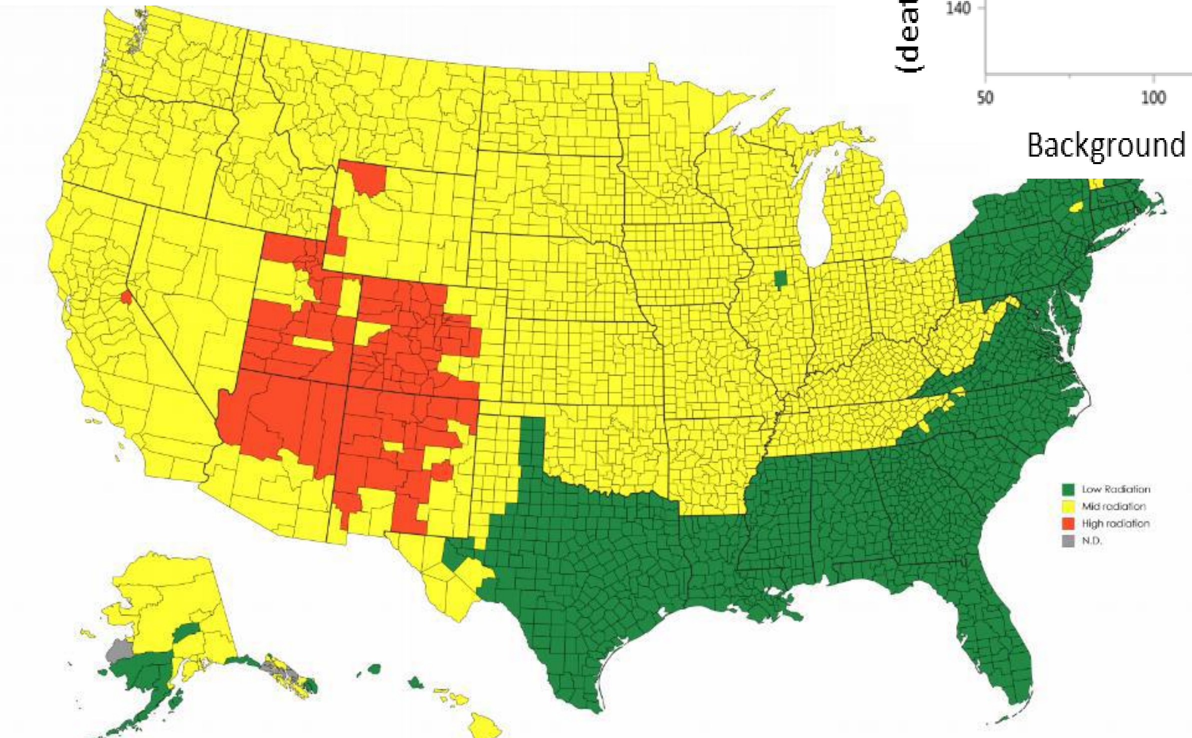
Radiation risk in humans

- Models for radiation risk in humans have existed for decades
  - Origin: Nuclear disasters, high radiation exposure (UNSCEAR, 2008)
- However there is still debate about what happens at low dose
- At very low (approaching natural) doses, there is debate about whether these models:
  - remain linear,
  - or even display hormesis



Negative correlation between cancer risk and background radiation in the United States (2021)



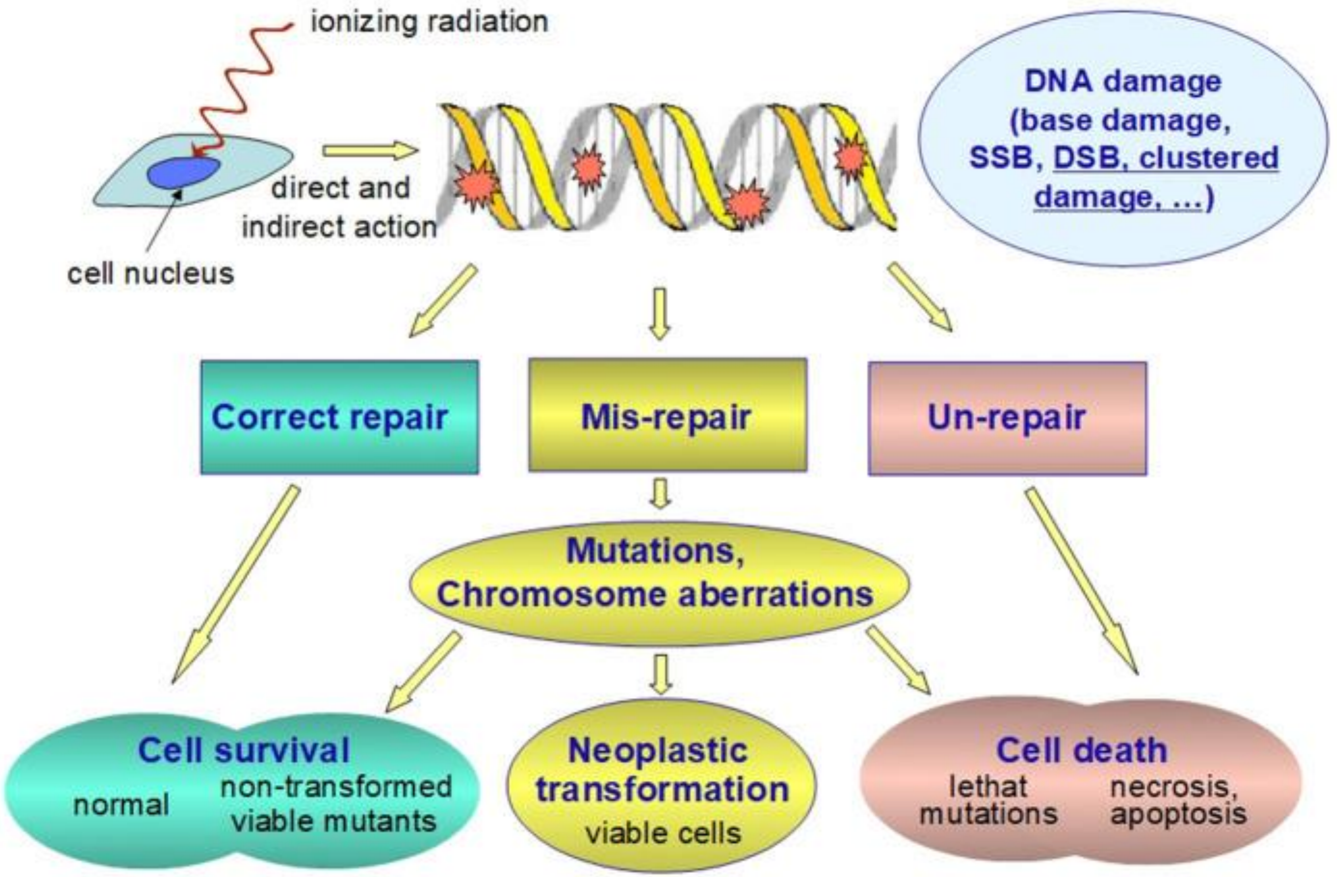


1 mrem = 0,01 mSievert

David, E., Wolfson, M. & Fraifeld, V.E. Background radiation impacts human longevity and cancer mortality: reconsidering the linear no-threshold paradigm. *Biogerontology* **22,** 189–195 (2021). https://doi.org/10.1007/s10522-020-09909-4

Conventional paradigm of radiobiology

- The DNA damage in directly exposed cells is the main event for biological effects
- DNA damage occurs during or very shortly after irradiation of the nuclei in targeted cells
- The potential for biological consequences can be expressed within one or two cell generations
- At low doses the biological effect is in direct proportion to the energy deposited in nuclear DNA (this is the rational basis for assuming a Linear No-Threshold (LNT) relationship between risk and dose)



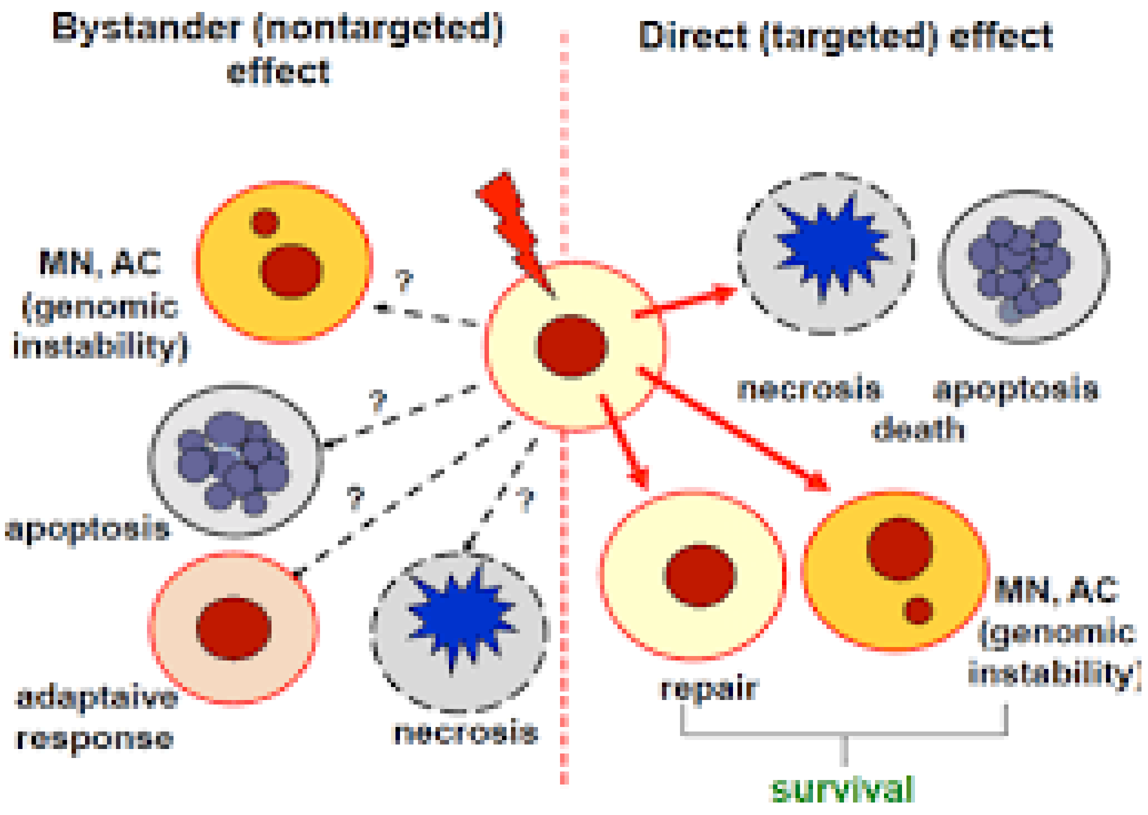
Goodhead D. New radiobiological, radiation risk and radiation protection paradigms. Mutat Res. (2010) 687:13–16. 10.1016/j.mrfmmm.2010.01.006

Belli M, Indovina L. The Response of Living Organisms to Low Radiation Environment and Its Implications in Radiation Protection. *Front Public Health*. 2020;8:601711. Published 2020 Dec 15. doi:10.3389/fpubh.2020.601711

Observation of radiobiological effects that do not follow the conventional paradigm

- Bystander effects: effects from hit cells to unhit ones -> Inter-signalling in cells

- Adaptative response: induction, in cells pre-exposed to a low « priming » dose, of cellular radioresistance to subsequent larger doses -> epigenetic effects

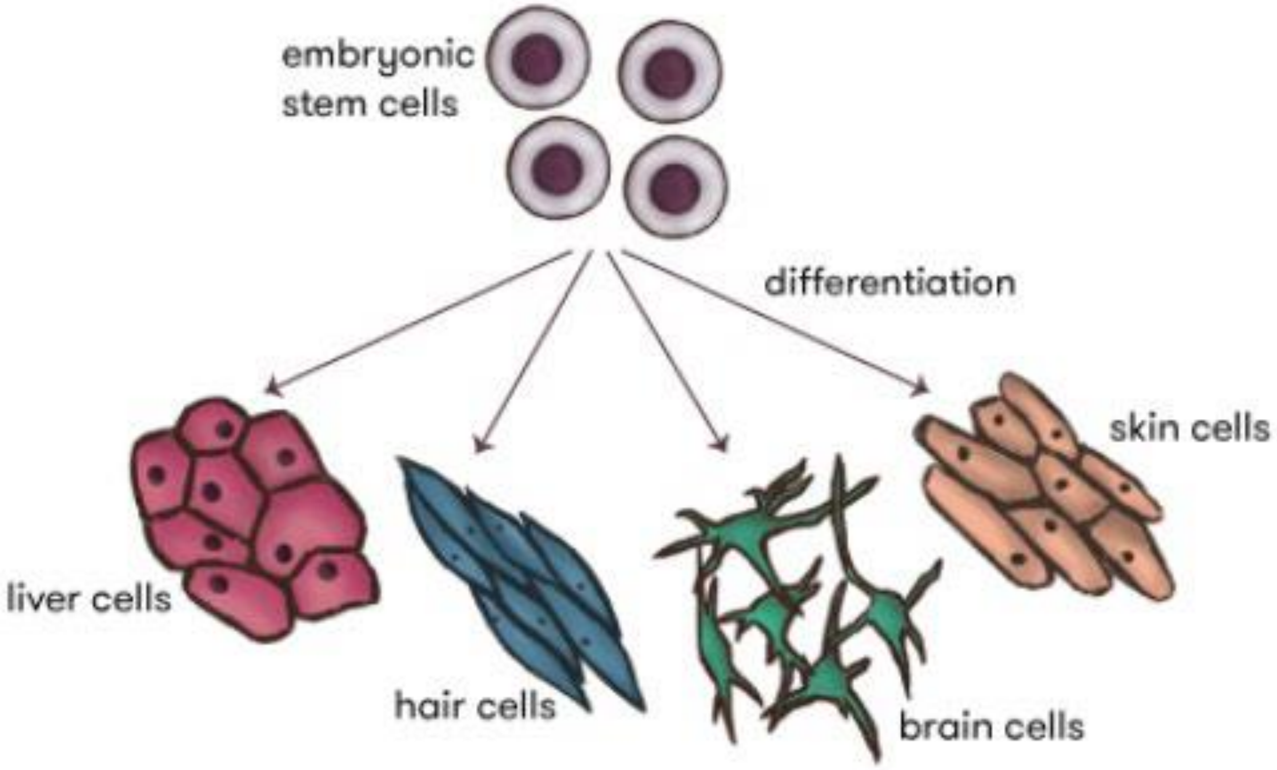


Credit: M. Widel

The role of epigenetics

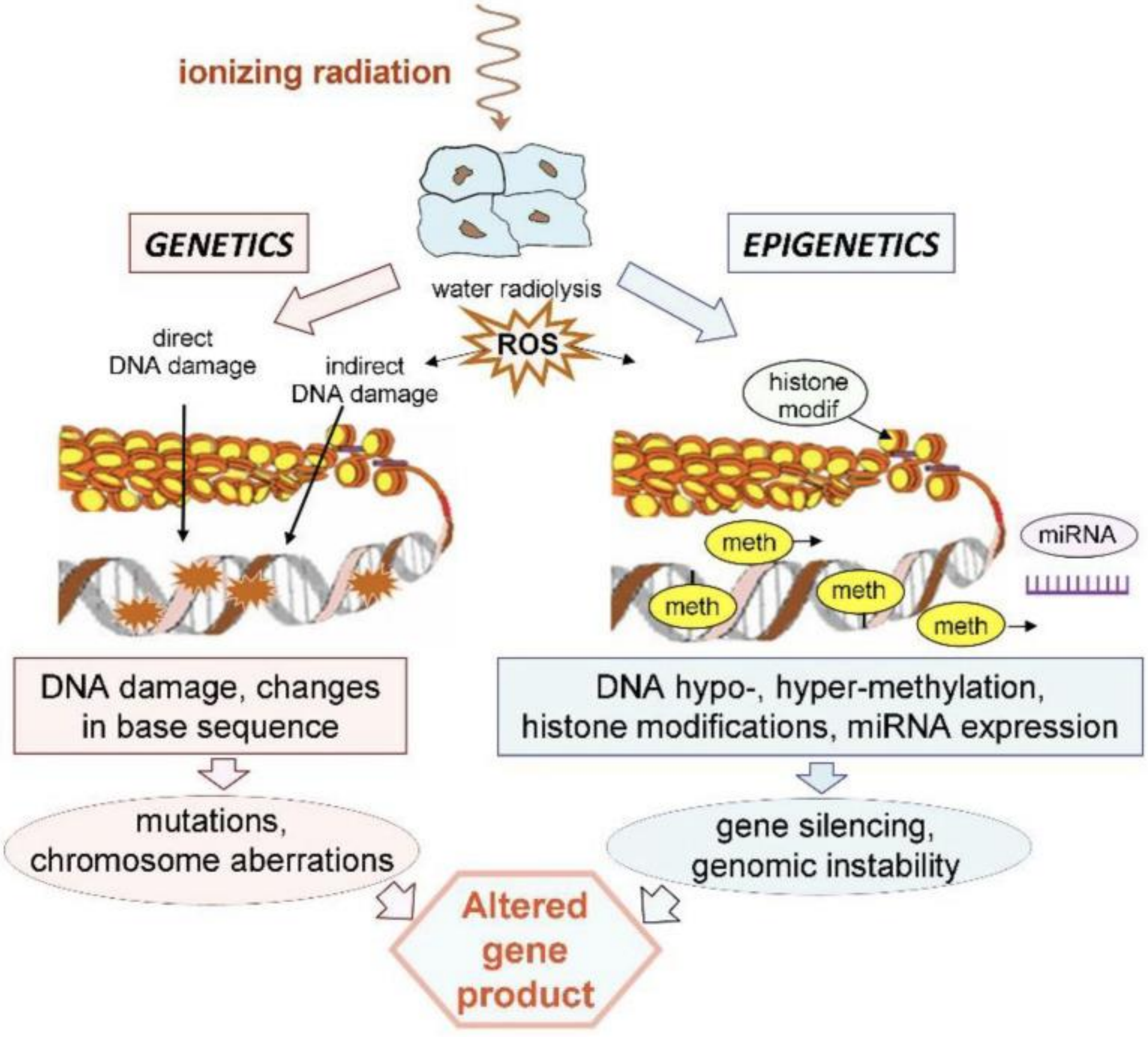
- Heritable changes in genes expression not related to changes in DNA sequence

- Epigenetic mechanisms regulate the gene expression in our body's cells to create all the different cell types of our body although they have the same genome.



How is epigenetics involved in radiation-induced effects? ?

- Epigenetic mechanisms are involved in adapting the gene expression programme of the cell to the stress situation, often when they are transient.



What happens to living organisms when natural background radiation is reduced ?

- Are organisms capable of sensing below-background levels of radiation?
- If they are, what are their response and sensing mechanisms ?
- Is this response different among prokaryotes/eukaryotes, unicellular/multicellular organisms?

Deep Underground Laboratories (DULs)
are unique places where it is possible to investigate
the effects of reduced natural background radiation

Experimental method

- Set up parallel experiments under different radiation environments

Underground laboratory:
- Cosmic rays (charged) << 1nGy/hr^{-1}
- Cosmic rays (neutrons) << 1nGy/hr^{-1}
- Gamma background : 10 -100 nGy/hr^{-1} -> << 1nGy/hr^{-1} using shielding
- Radon: 10-100 Bq/m^3 -> 100 mBq/m^3

Reference laboratory (above ground):
- Cosmic rays (charged): tens of nGy/hr^{-1}
- Cosmic rays (neutrons): A few nGy/hr^{-1}
- Gamma background : tens - hundreds nSv/h
- Radon: 10-100 Bq/m^3

Same temperature
Same humidity
Same atmospheric pressure
Same culture medium

Focus on Long Term Evolution Experiments

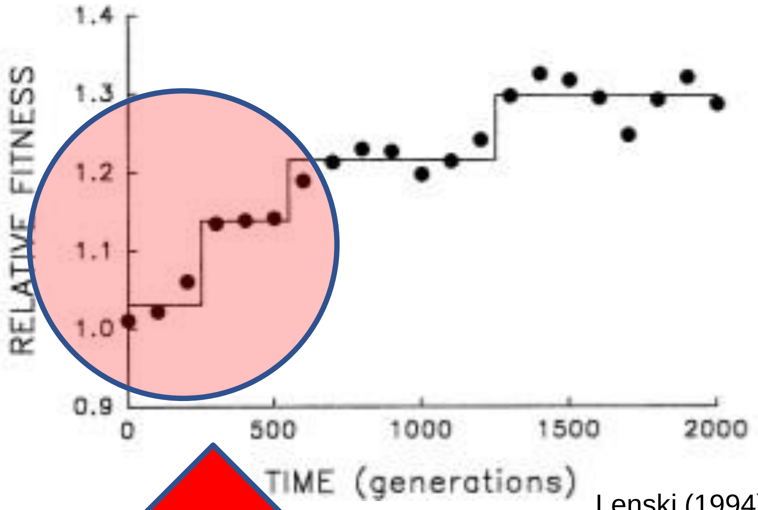
- Question: is natural radioactivity playing a role on the evolution of microorganisms ?
- Method: **compare** the evolution of bacterial strains in Underground and Reference laboratories
- First attempt : 2014-2017@LSM
  - 1000 generations
  - E. Coli strain from Lensky Experiment

Lampe N. et al, Understanding low radiation background biology through controlled evolution experiments. *Evol Appl*. (2017) 10:658–66. doi: 10.1111/eva.12491

N. Lampe et al, Scientific Reports (2019)9:14891

The Lensky Evolution Experiment

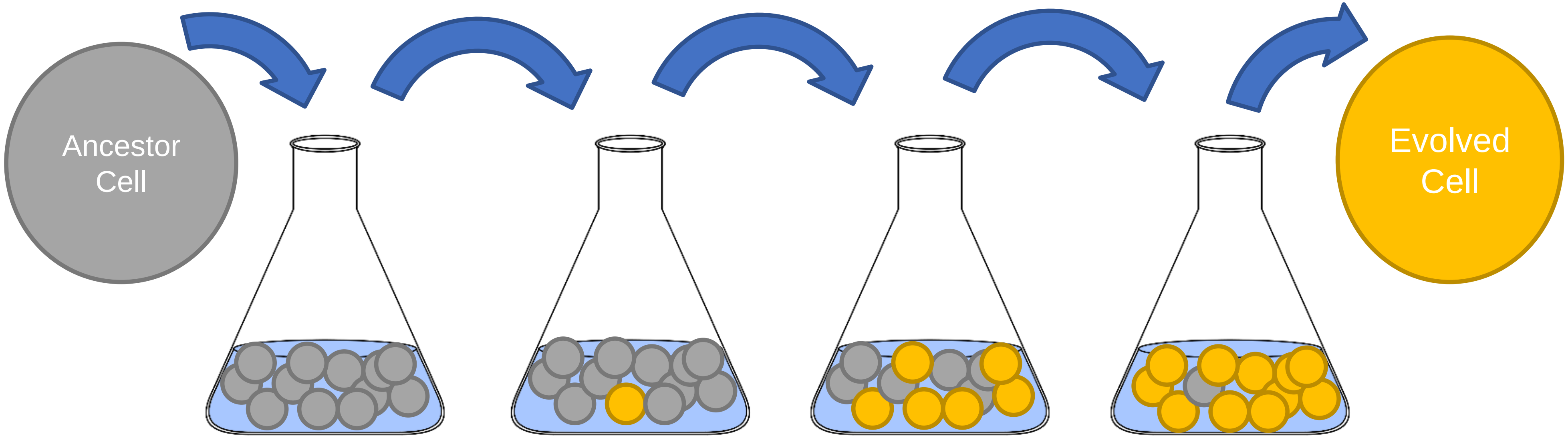
- A wealth of data exists from the Lenski Evolution Experiment on *E. coli*.
    - 60,000 generations grown over 25 years
    - Well-known likely mutations
- Early mutations are known to cause fitness changes
- We have replicated this experiment in two radiation environments.
- The aim was to see if the fitness trajectory was different in the absence of radiation.

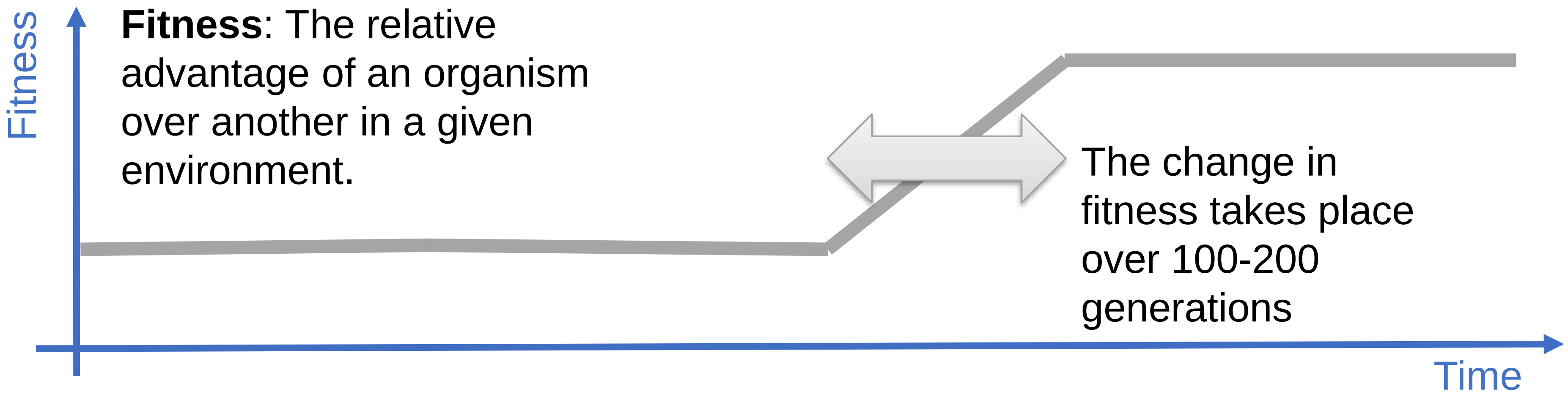


Lenski (1994)

Focus on first 500 generations

Experimental evolution





Fitness: The relative advantage of an organism over another in a given environment.

The change in fitness takes place over 100-200 generations

Absorbed Dose during Evolution Experiment at LPC and LSM

Source	Method	LPC Clermont (nGy hr^{-1})	LSM (nGy hr^{-1})	LSM (shielded) (nGy hr^{-1})
γ background	Dosimeter (simulations support this value)	150	20	<1
Cosmic rays (charged)	UNSCEAR	31	<<1	<<1
Cosmic rays (neutrons)	Simulation	4.4	<<1	<<1
^{40}K (γ)	Simulation	0.13	0.13	0.13
^{40}K (β)	Simulation	26	26	26
^{14}C (β)	Simulation	<<1	<<1	<<1
	Total	212	46	26

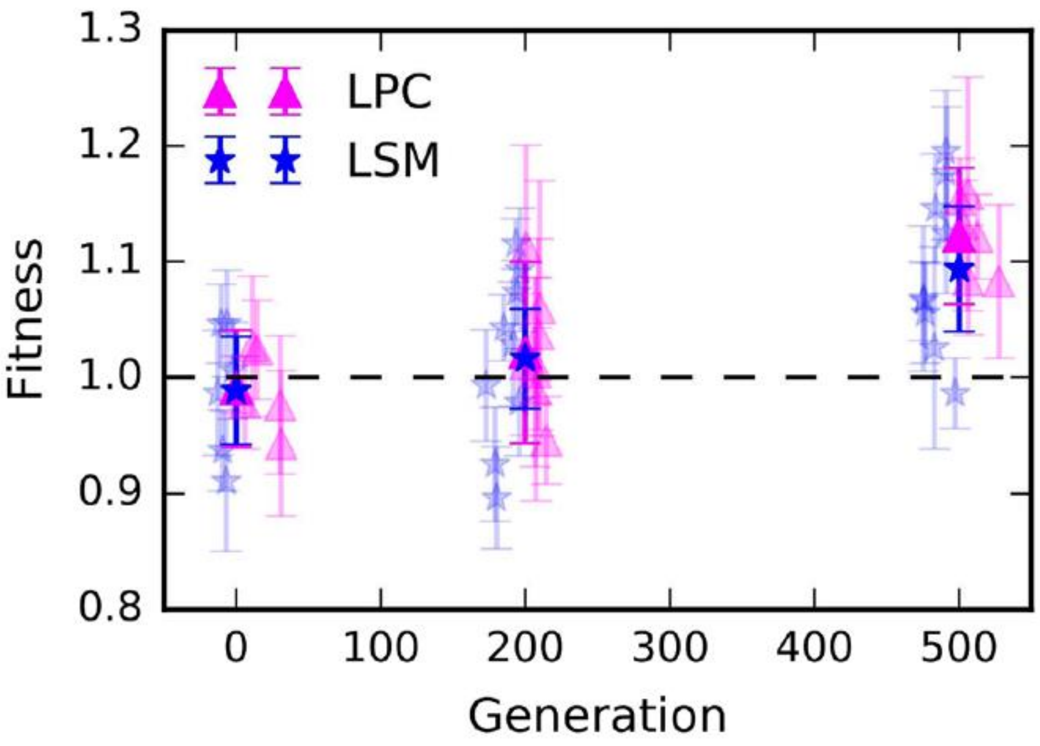
99% of the residual radiation comes from E. coli nutritive medium

Dose reductions for biology experiments in underground laboratories are limited by ^{40}K in the nutritive medium

Lampe et al. (2016), EPJ Web of Conferences

Experimental Evolution Experiment

- No impact of low radiation background observed on E. coli first evolution step



N. Lampe et al, Scientific Reports (2019)9:14891

Next steps for Deep Underground Evolutionary Biology

- Pursue long term experiments on *in vitro* models
  - Only first 1000 generations of E. coli evolution studied so far @LSM
- Cultivate underground microorganisms adapted to large radioactivity
  - Microalgae growing in radioactive mineral springs (> 100µGy/h)
- Increase the signal by increasing radiation suppression
  - Beyond a factor 10 in radiation reduction: the ^{40}K frontier for E. coli culture