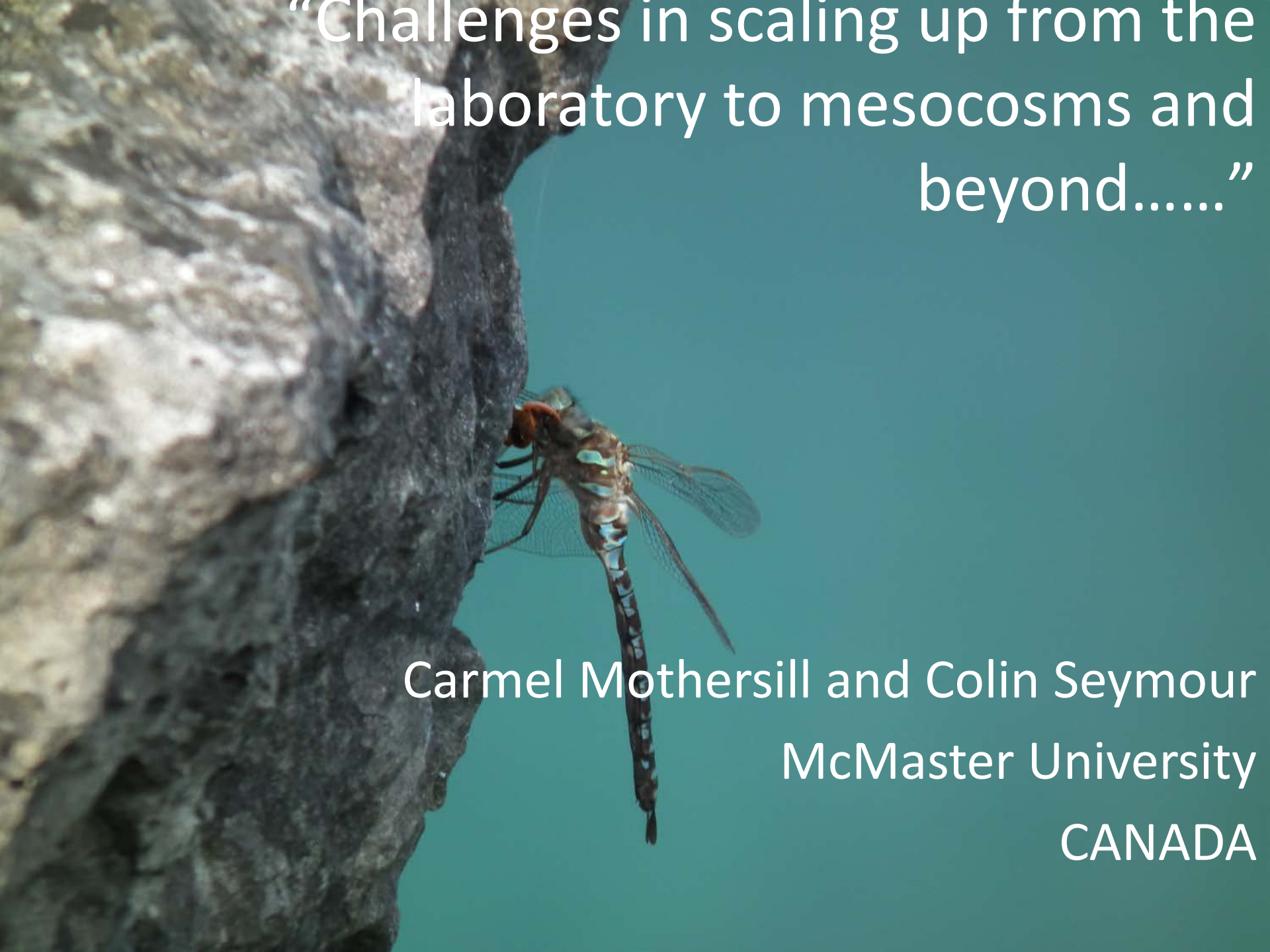


"Challenges in scaling up from the laboratory to mesocosms and beyond……"

Carmel Mothersill and Colin Seymour

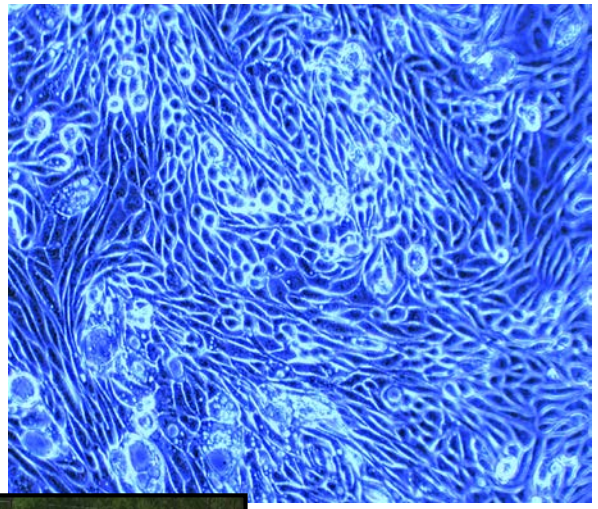
McMaster University

CANADA

Outline

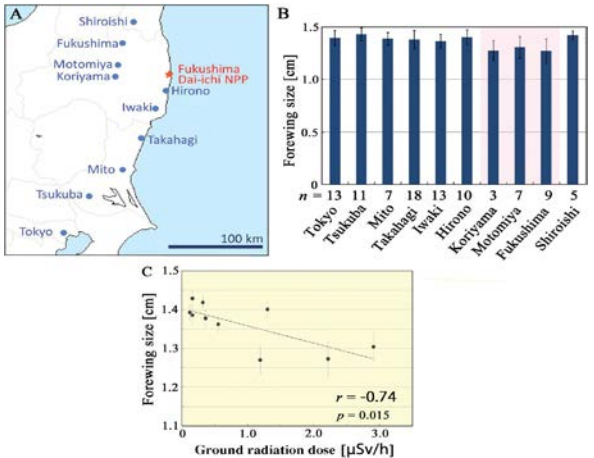
- Address question I was given!
- Link to bystander/Non-targeted effects
- Outline challenges/opportunities for ecosystem approach using bystander biomarkers

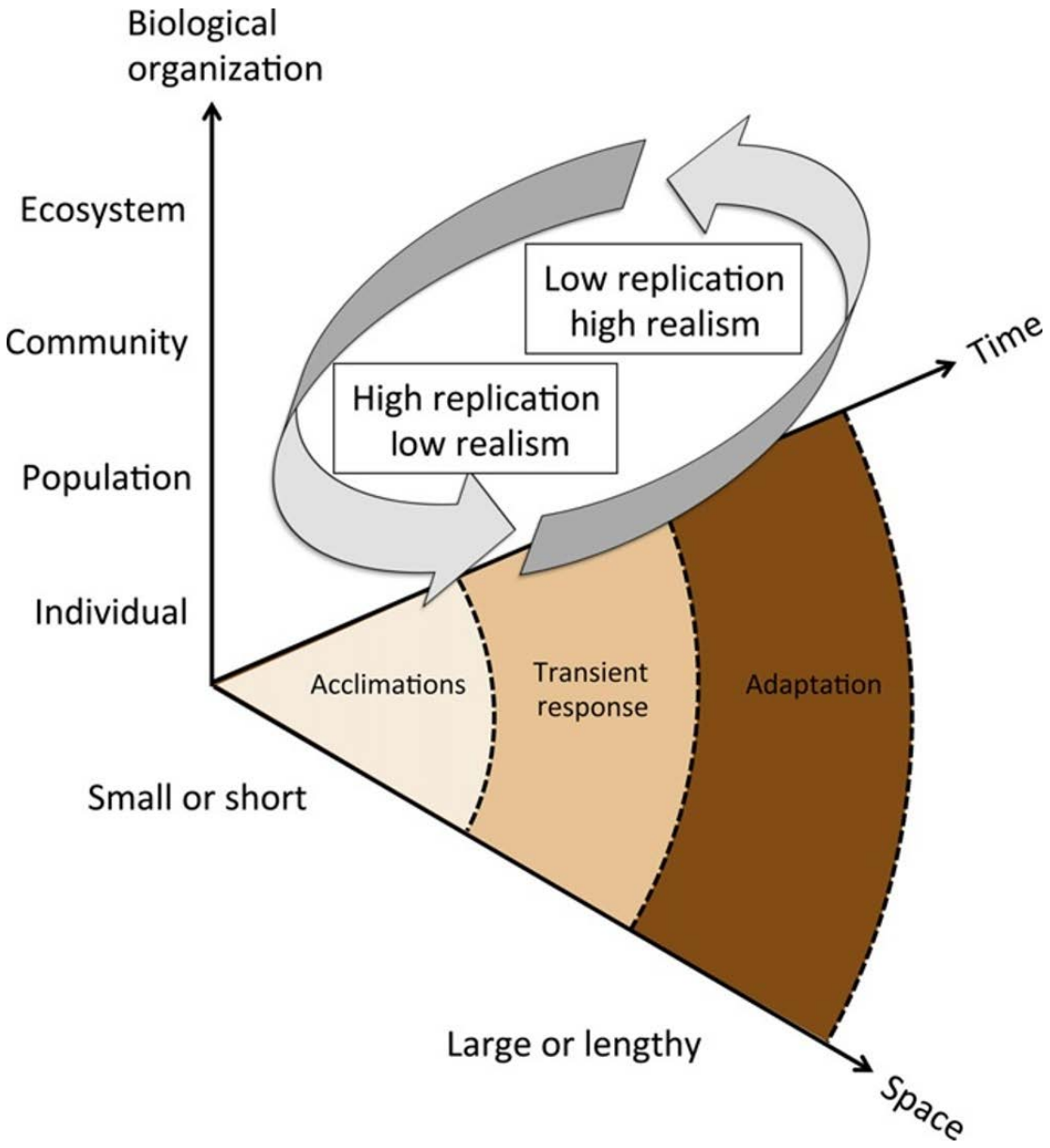
Going from



via

To



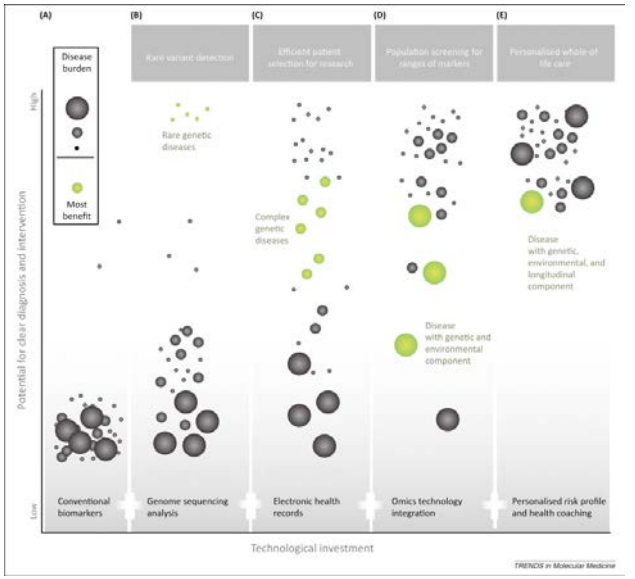

Biological organization
Ecosystem
Community
Population
Individual
Low replication high realism
High replication low realism
Time
Acclimations
Transient response
Adaptation
Small or short
Large or lengthy
Space

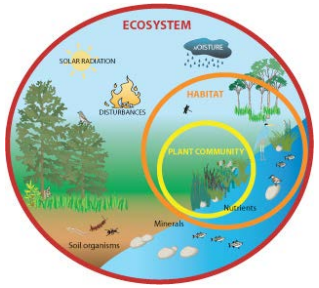
Fundamental Questions

- What is a mesocosm?
  - An attempt to simulate a more comprehensive but still closed environment
- What are the underlying assumptions?
  - That the main players have been identified
- What is the aim of lab experiments?
  - Attempt to provide mechanistic data and identify robust responses which can be extrapolated to more complex systems

My thoughts

- Two major types of challenge
  - Experimental
  - Conceptual
- However
  - Is scaling up really what we want to do?
  - Should we not rather accept the limitations/advantages of each approach and tailor our questions accordingly?



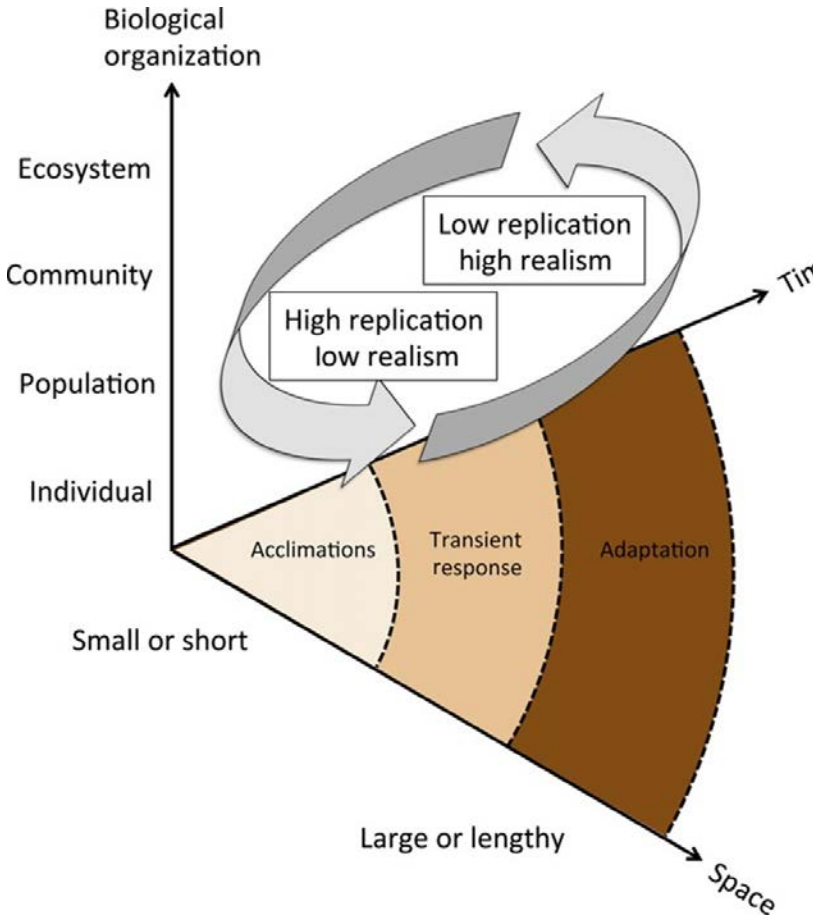


Advantages

- Lab: controlled, closed, can interrogate mechanisms, can manipulate physicochemical parameters of interest e.g. temperature, salinity
- Mesocosm: controlled, closed but allows limited ecosystem structure and controlled study of suspected players
- Field: open and difficult to control but real. Enables validation of suspected biomarkers in individuals from field

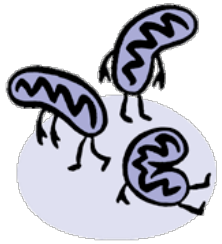
Towards an ecosystem approach

- Acclimation: homeostasis at population level
- Response: life and death of individuals but emergence of resistant population
- Adaptation: selection of fittest individuals leading to new phenotype/genotype



Experimental Challenges

- Controls and choice of species/experimental models
- Simulating the “real” environment
- Multiple stressors – may not all be identified or defined
- Difficulty of maintaining system long enough to do chronic exposures
- Isotope use and safety issues due to size of experiments
- Integrating dose over time when initial exposure may turn on long-term memory effects
- Extrapolating from measurements in individuals to system level effects



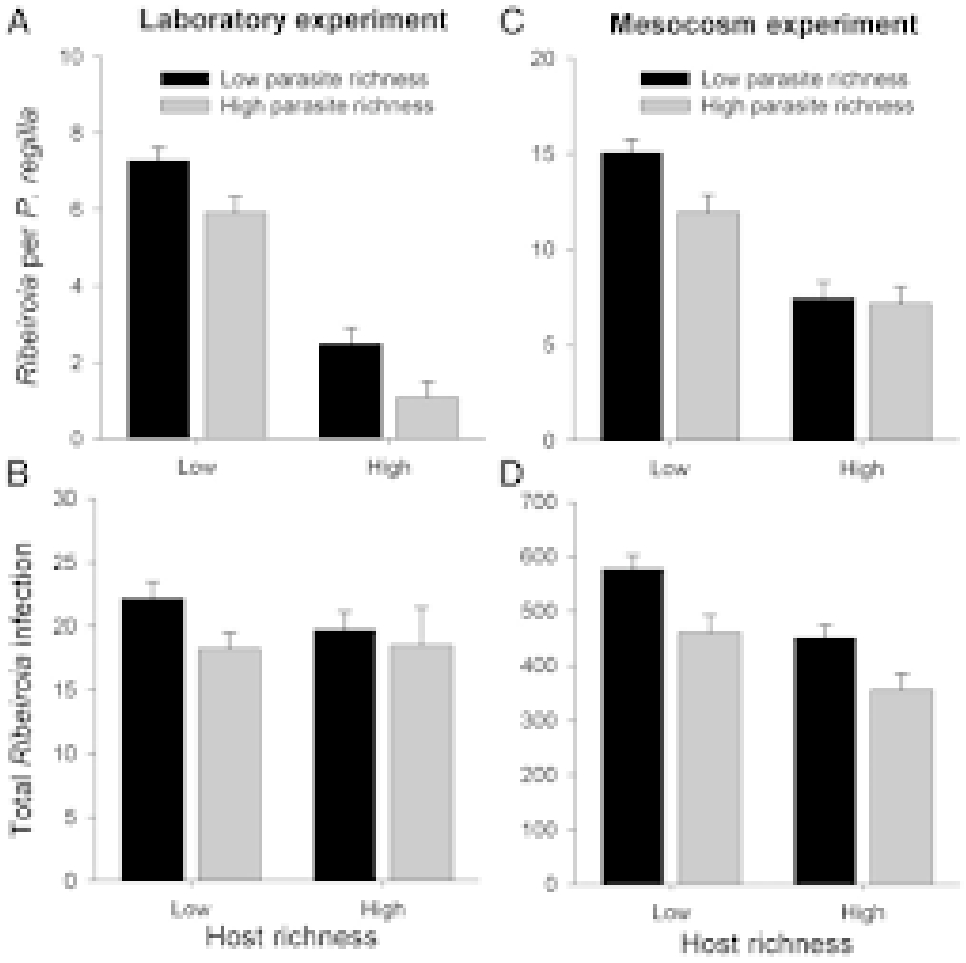
Conceptual Challenges

- Relevance of data from any closed system to the field which is an open system
- Problems of dose/dose rate conversions in the low dose range where dose does not necessarily drive response
- Interplay of low dose mechanisms such as adaptive response, bystander and genomic instability which saturate
- Complexity and emergent properties of systems
- Inter-animal and plant signalling

Validation of lab/mesocosm/field data

- Mechanistic understanding is key
- Validation of effects at several levels of organisation needed
- Not a problem for high doses but a problem for relevant low doses
- Realistic biomarkers of effect and impact needed in the low dose range
- Memory effects may need to be understood in the context of integrated dose

Sample of validation



Relevance of non-targeted effects (why I am here?)

- Bystander effects enable effects at the individual level to be processed at the level of the community or ecosystem
- Genomic instability enables effects occurring in one generation to be transmitted to succeeding generations
- Inter and intra species signaling documented

Non-targeted effects, memory effects and integrated dose

- NTE and ME refer to persistence of (usually) damage in distant progeny so that even if the radiation was acute, the progeny continue to show higher than control levels of mutations and chromosome damage
- Question is how to distinguish this effect from de novo damage attributed to current very low chronic doses in e.g. Chernobyl or Fukushima
- Do we need to integrate the dose from Day 1? Or using lab data can we estimate what the NTE burden is?
- Issue is where effects are currently occurring at doses below established benchmark values (e.g. some M+M data)

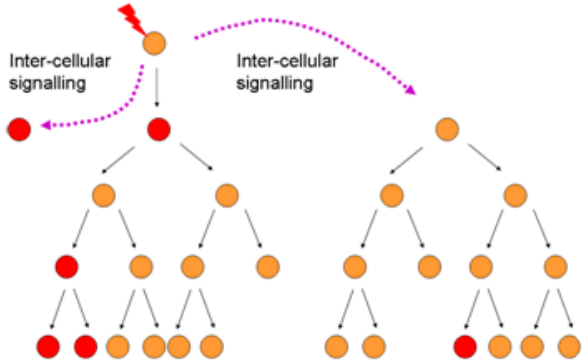
'Non-targeted' radiation effects

Bystander effects

Effects in neighbouring cells

Genomic Instability

Effects in unirradiated descendant cells

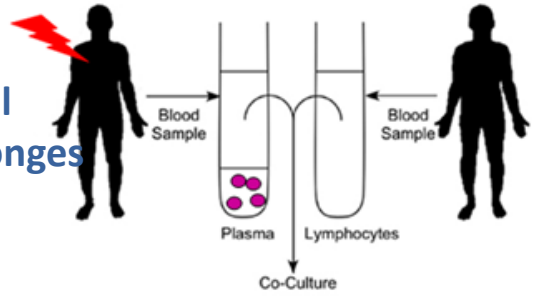


Abscopal effects

Effects in neighbouring tissues

Clastogenic factors

Ex vivo effects in cultured cells



Inter-animal signaling

Effects in neighbouring animals (fish, mice, rats, tadpoles). Inferential

Effects in tunicata, crustacea and sponges

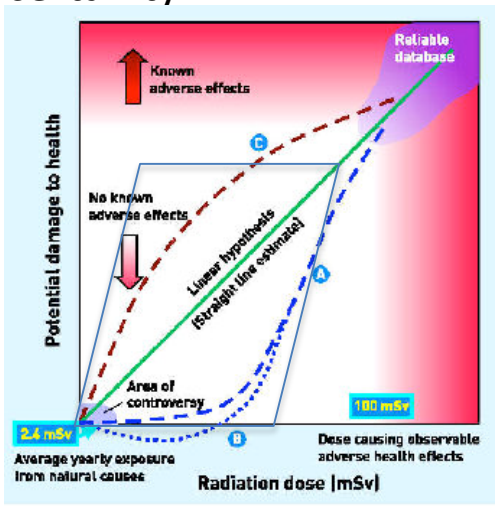
Inflammatory Processes may provide mechanistic link

Long-term effects on innate immune response function may occur

Disregarding NTE is essential if you need to apply LNT

BUT

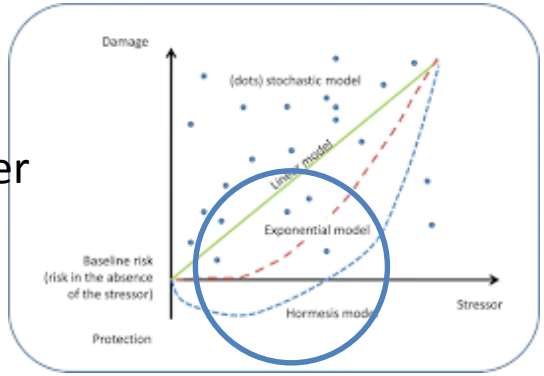
How can you disregard something which dominates the low dose region of the dose response curve and saturates in the milligray range??? It isn't even always "bad" implying uncertainty



"arena of opportunity" where all cooperate and all outcomes are Possible?

OR

"Circle of doom" Where the risks Are MUCH greater And we are all Going to die (or mutate)?



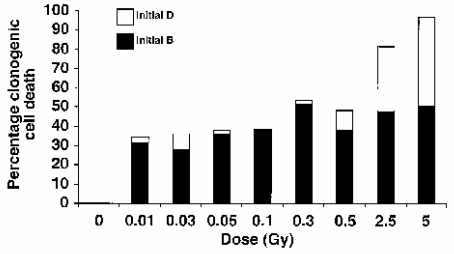


FIG. 1. Clonogenic cell death measured in human keratinocytes. The total bar represents the total death detected after exposure of cells to the radiation dose. The death measured after exposure to ICM (B) is repre-

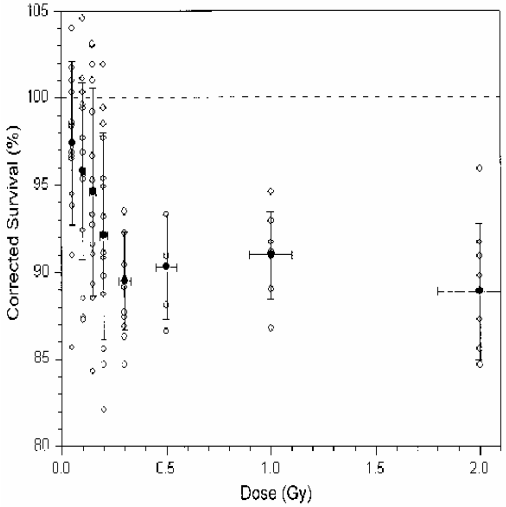
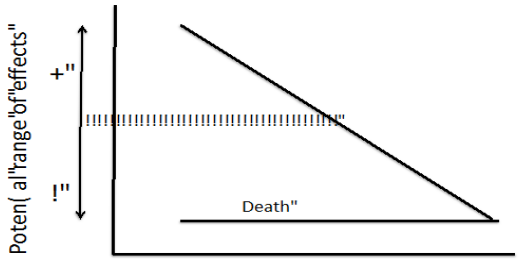


FIG. 1. Survival of a population of V79 cells after the irradiation of a single cell with focused C_K X rays. The data are reported as a function of the nuclear dose delivered to a preselected cell. (V) Measurements from individual experimental dishes (corrected for the control plating efficiency); (v) averages in each dose group. *X* errors are 10% of the delivered dose; *Y* errors are 6 1 standard deviation of the means.



If NTE dominate at low doses
and are like a stress response – then dose as energy deposited in a target does not drive the dose response

BUT
WHAT DOES???

MODULATORS
in
"The Zone"

Lifestyle
Existing stress
Immune status
Genetic background
Dose

Genetics?

Environment?

Lifestyle?

WHATEVER!

It is not the dose so all other factors must be relevant

Conclusions

- Lab, ‘cosm and field approaches all have their uses and can answer different questions
- Using all three approaches can help validate biomarker relevance
- Biomarker approach essential in low dose range and if trying to use ecosystem approach because of relevance of NTE (transmission across generations or to other members of the community)