Computer modeling of radiation effects

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1. Introduction

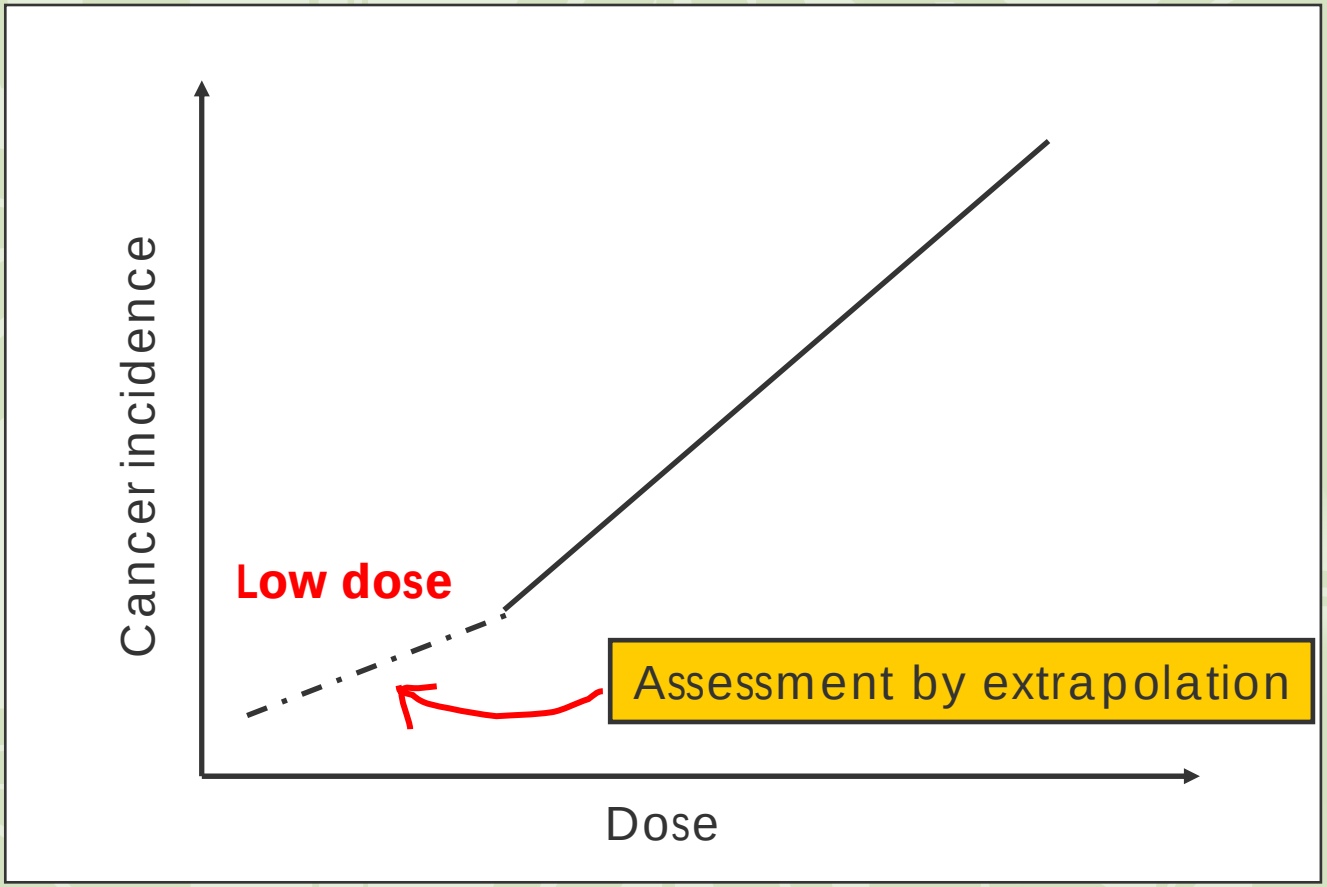
- Radiation Effects ?
  - Deterministic effect
    -- organ/tissue damage (or death)
  - Late time (stochastic) effect
    -- radiation induced cancer

High Dose effect

At low dose region, quantitative risk estimation are not so easily obtained.

- Low dose radiation risk
  - risk = probability of cancer incidence

Dose-Response



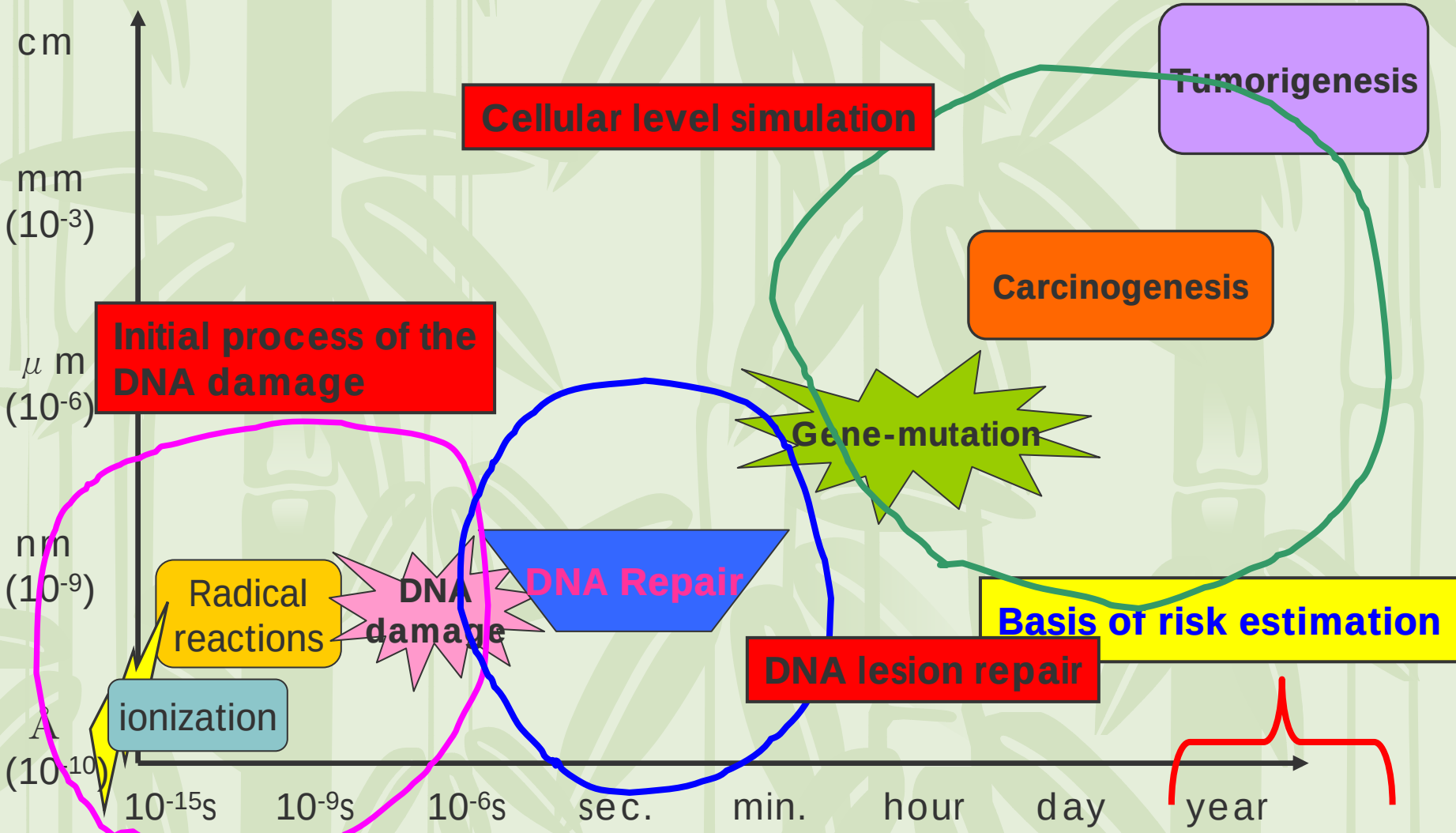
Risk estimation at low dose radiation needs further study based on the Biological mechanisms.

What is “low dose”?

- Experimental viewpoint
  - < 100mSv
  - Limit of the observation of radiation effects.
- Average annual effective dose of radiation workers = ~15mSv
- Various suggestions: 10mSv – 100mSv

The definition of low dose is physically and operationally ambiguous, only some effect-based guidelines have been suggested.

Scale of the++


cm
mm
(10-3)
μm
(10-6)
nm
(10-9)
Å
(10-10)
10-15s
10-9s
10-6s
sec.
min.
hour
day
year
Cellular level simulation
Tumorigenesis
Carcinogenesis
Initial process of the DNA damage
Gene-mutation
Radical reactions
DNA damage
DNA Repair
Basis of risk estimation
DNA lesion repair
ionization

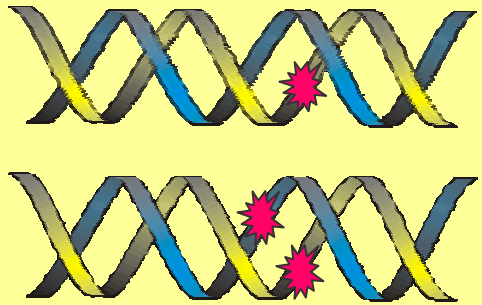
Check point #1

1

2. Initial process of radiation induced DNA Damage

Radiation to the cell nucleus causes damage to DNA

Biologically important damage



Single Strand Break (SSB)

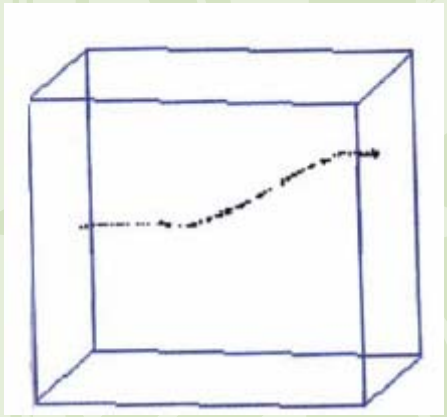
Double Strand Break (DSB)

Question:

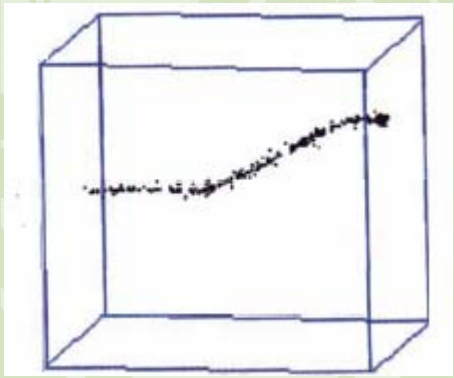
What kind of radiation with what type of track generate how much damages ?

To clarify the relations between track structure and DNA strand breaks.

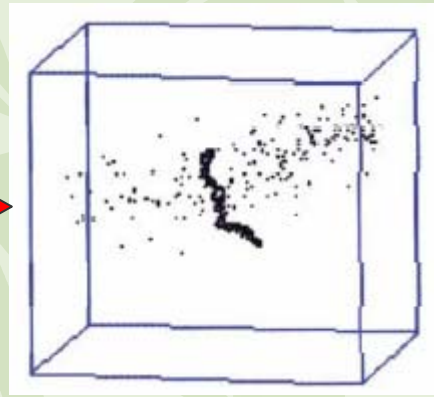
Simulation method



Track structure

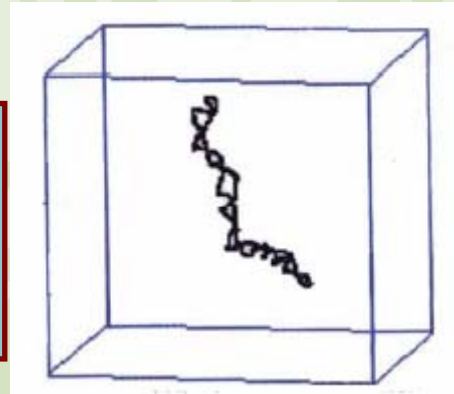


Radical production



Radical diffusion

1. Track structure calculation
2. Radical production
3. DNA modeling
4. Calculating DNA and radical reactions

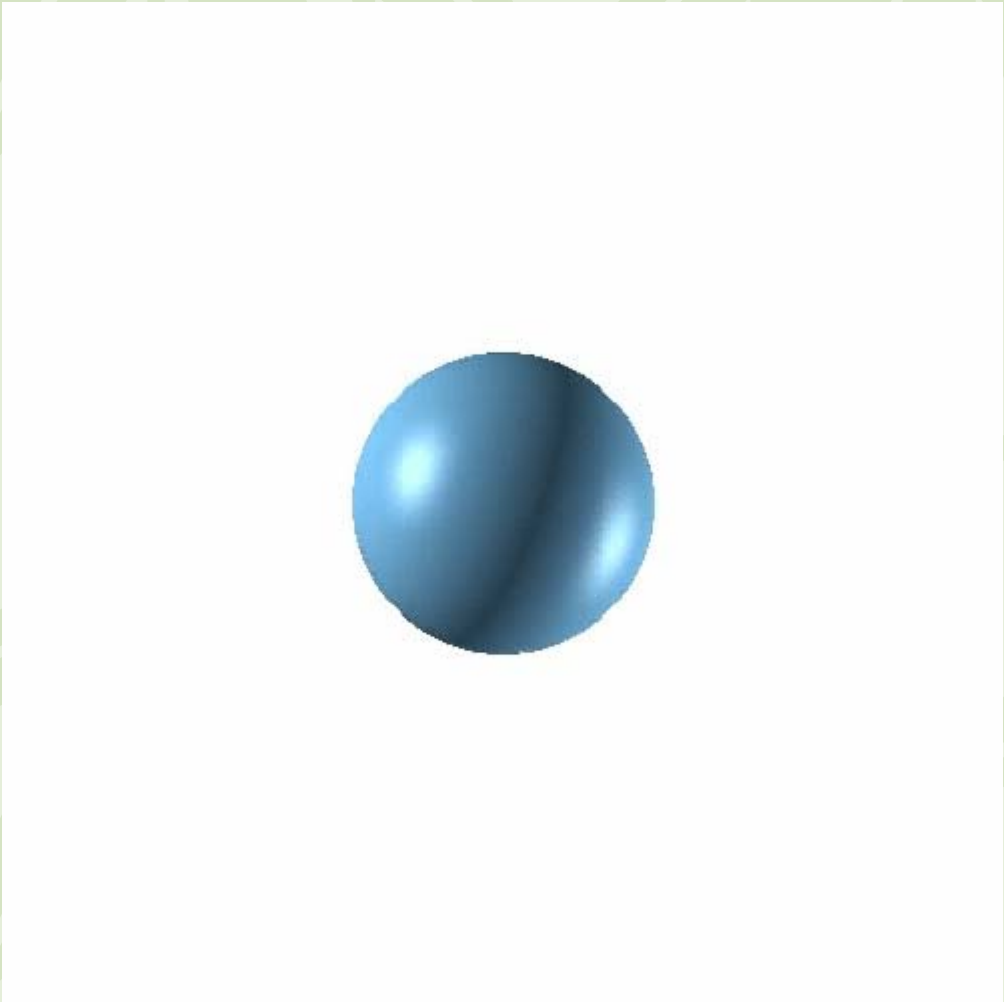


Target DNA modeling

Track structure: spatial distribution of energy deposition of ionizing radiation

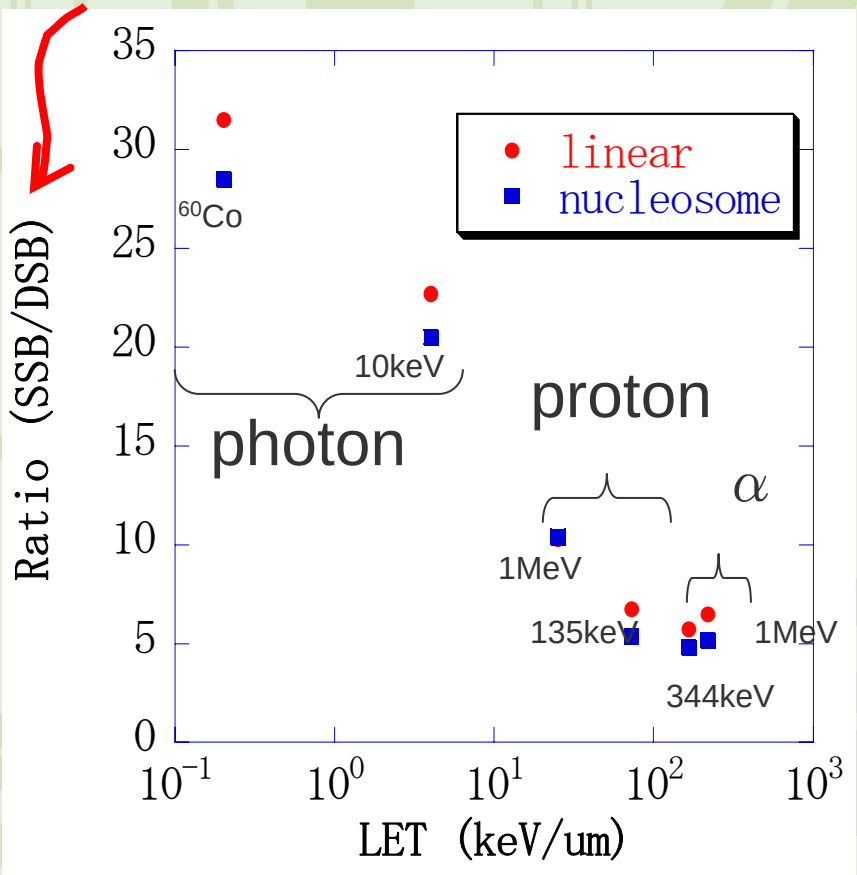
Simulation example

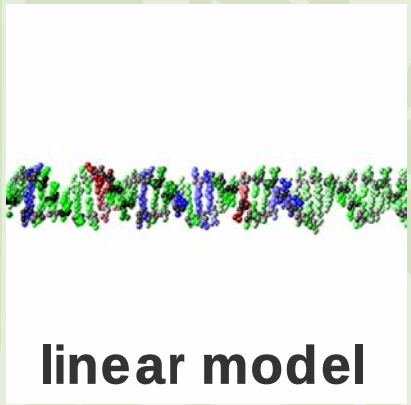
DNA damage induction simulation
(proton + solenoid DNA)



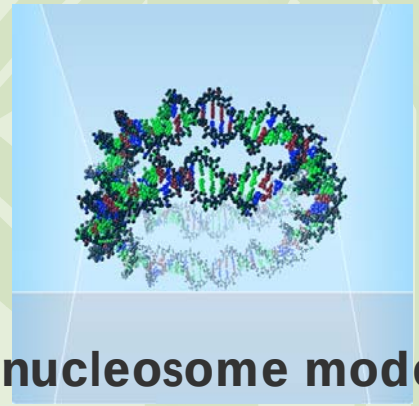
Result [SSB/DSB ratio]

Indicator of complexity of DNA damage





linear model



nucleosome model

LET [Linear Energy Transfer] - energy deposition by the charged particle per unit path length

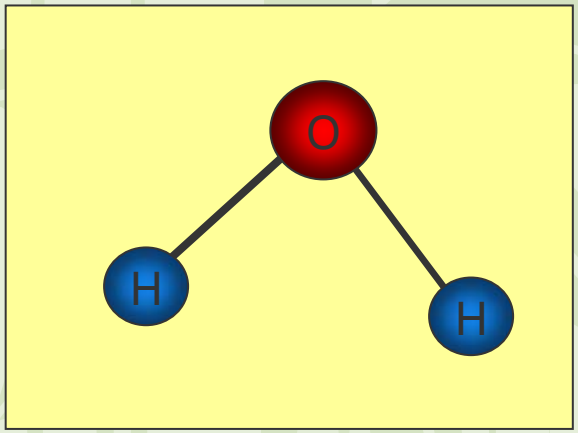
DSB yield increasing with LET up to 100 keV/μm

Check point #2

2

3. Molecular dynamical study of the DNA lesion repair

Molecular Dynamics simulation



$$F_i = -\frac{\partial V(\mathbf{r}_i)}{\partial \mathbf{r}_i} = m_i \frac{\partial^2 \mathbf{r}_i(t)}{\partial t^2}$$

$\mathbf{r}_i$ Position of each atoms (i)

m_i mass

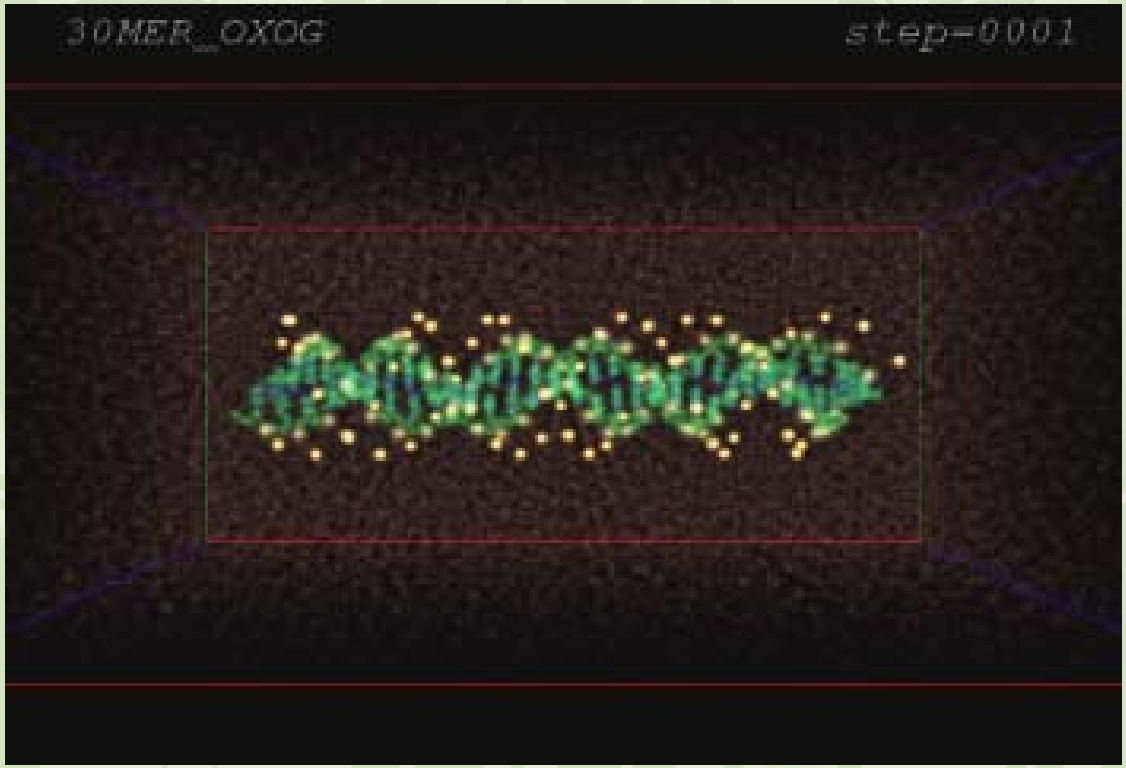
F_i Force acting on atom i

$V(\mathbf{r}_i)$ Potential energy of the system

$(\mathbf{r}_i(0), \dot{\mathbf{r}}_i(0))$ Initial condition (configuration)

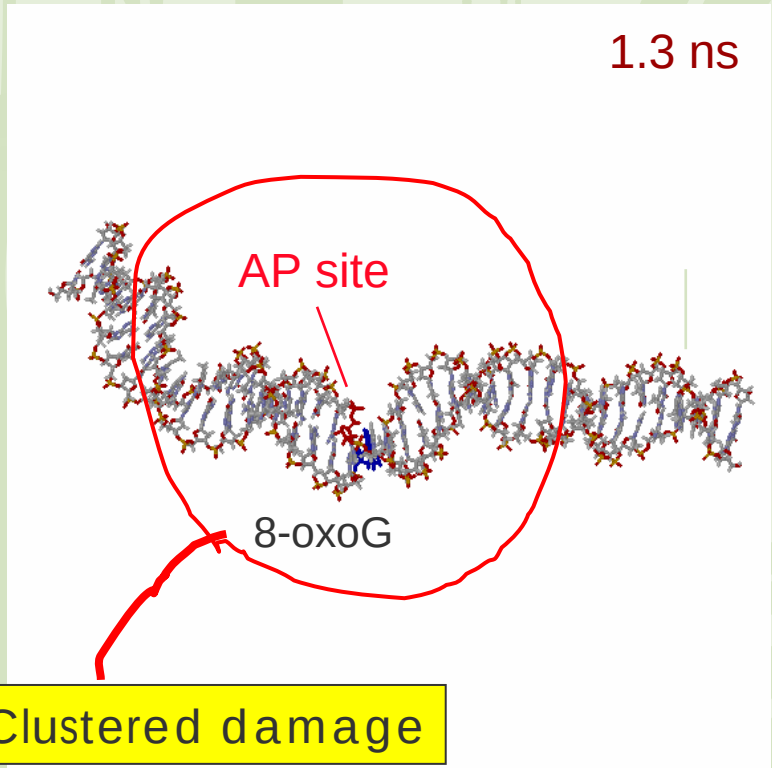
To clarify a dependency between damaged DNA structural change and capability of the DNA repair.

Simulation example

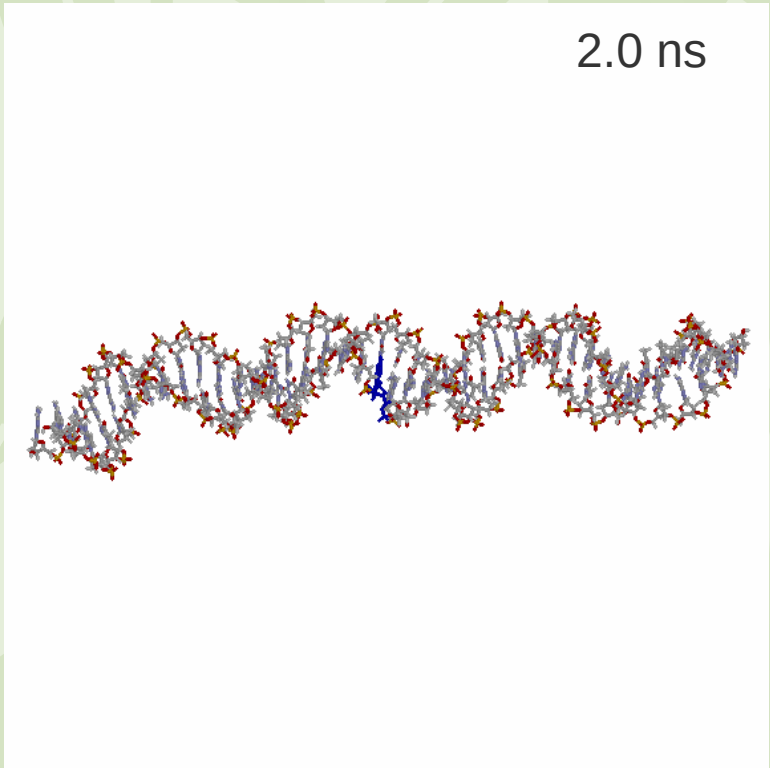


Shape change of damaged DNA

Damaged DNA: 8oxo-G + AP site



Native DNA (no damage)



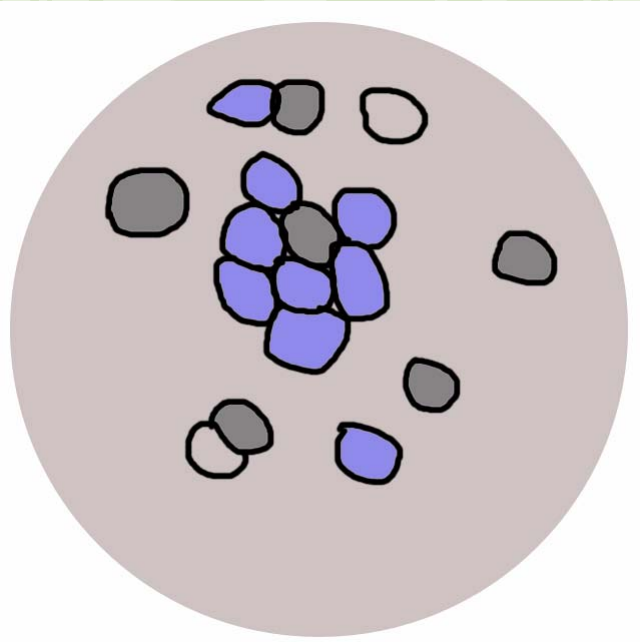
- **Damaged DNA shows bending movement at leisioned site**
- **Dynamic analysis of DNA structure is ongoing.**

Check point #3

3

3. Modeling and simulation of the cellular level tumorigenesis

The dynamics of the carcinogenesis is studied by the simulation of the cell group in the cell level.

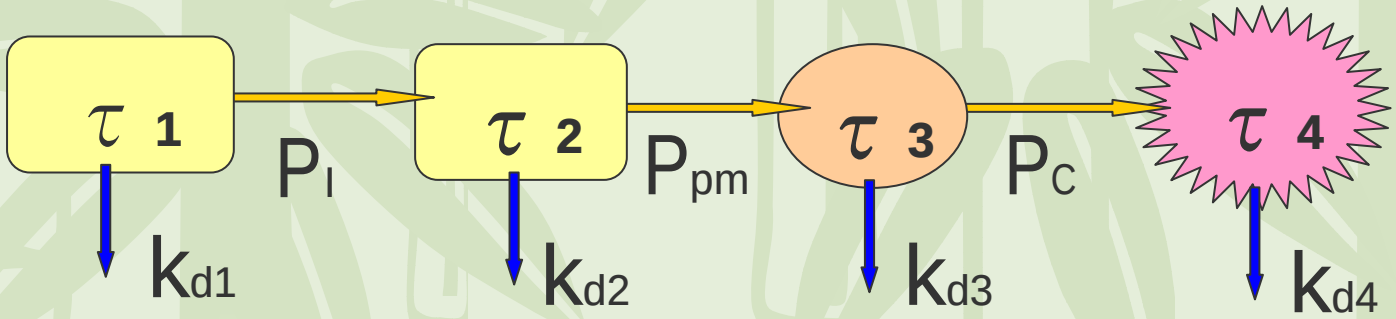


- Same configuration with Cell culture system
- Can study colony formation or tumorigenesis.
- Can introduce dynamical based group effect

- Easily comparable with the experiments.
- Molecular biologically based model.

Intracellular dynamics

Cell transformation



k_d : Prob. of cell death

P_I, P_{pm}, P_c : prob. of cell state change (genetic)

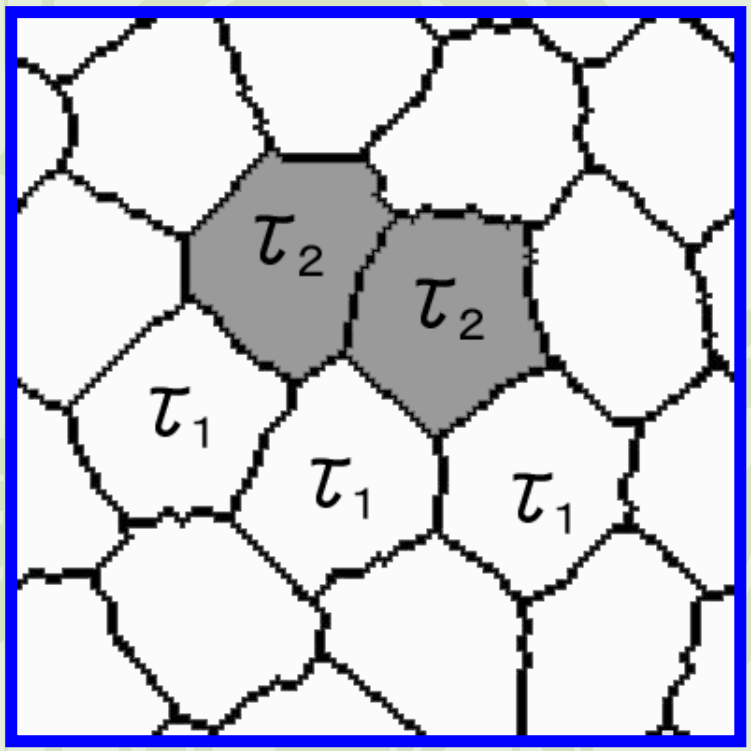
cell state τ : normal, initiation, promotion, cancer

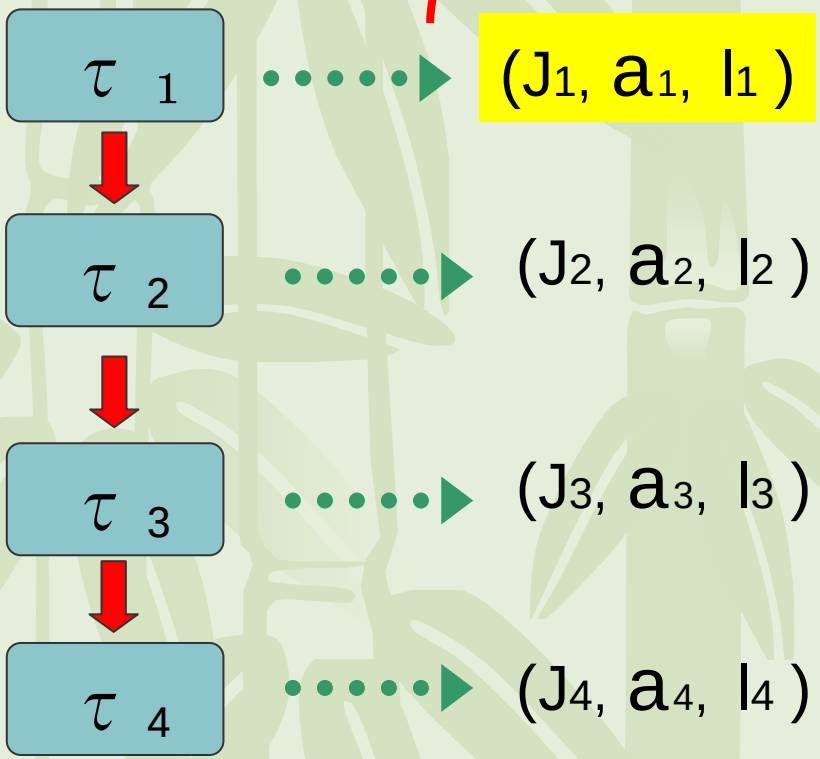
Cell division

If $a(s) > a_c$ then cell division occur

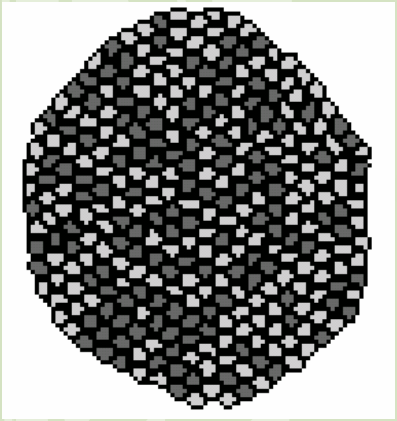
Details of the model

Intracellular state change affects the physical parameters (cell adhesion molecule, cell membrane)

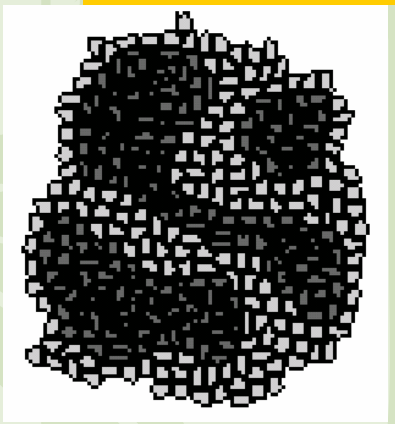




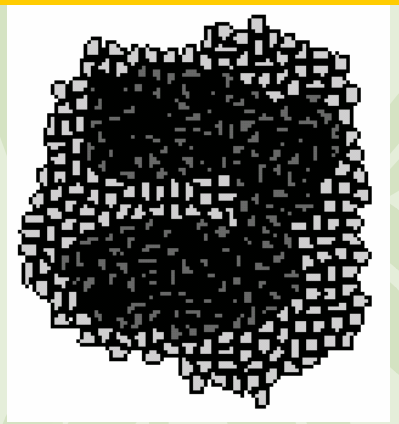
Spatial patterns (cell sorting)



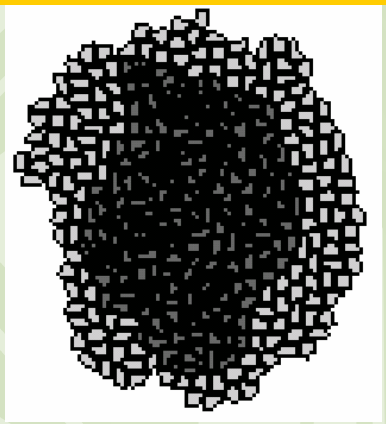
Initial



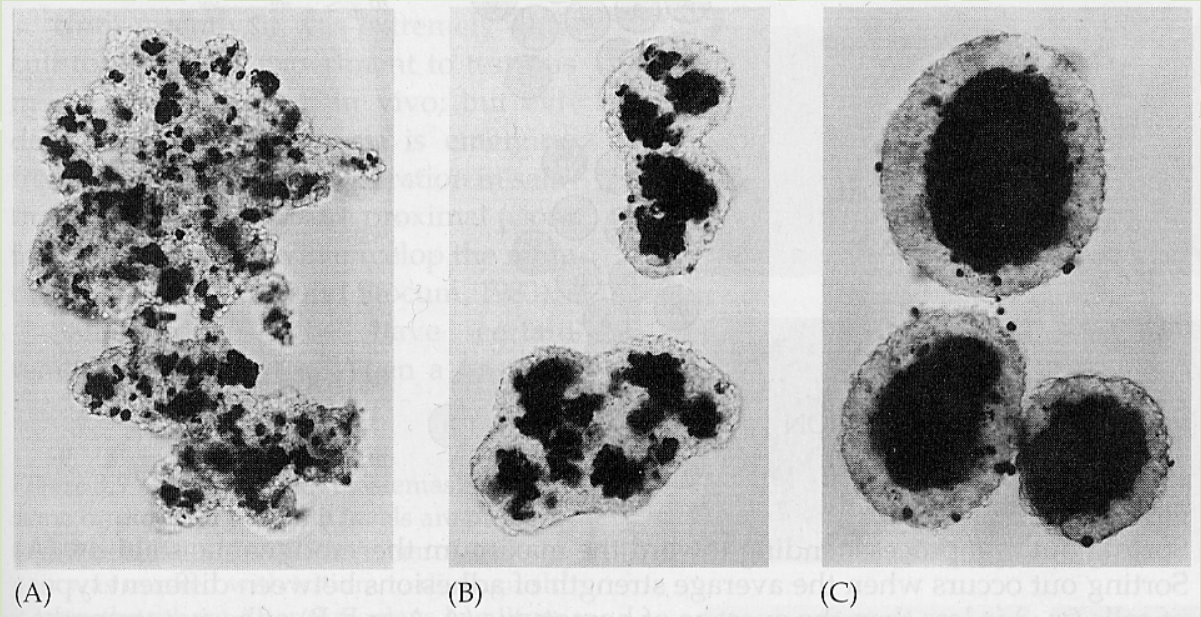
500steps



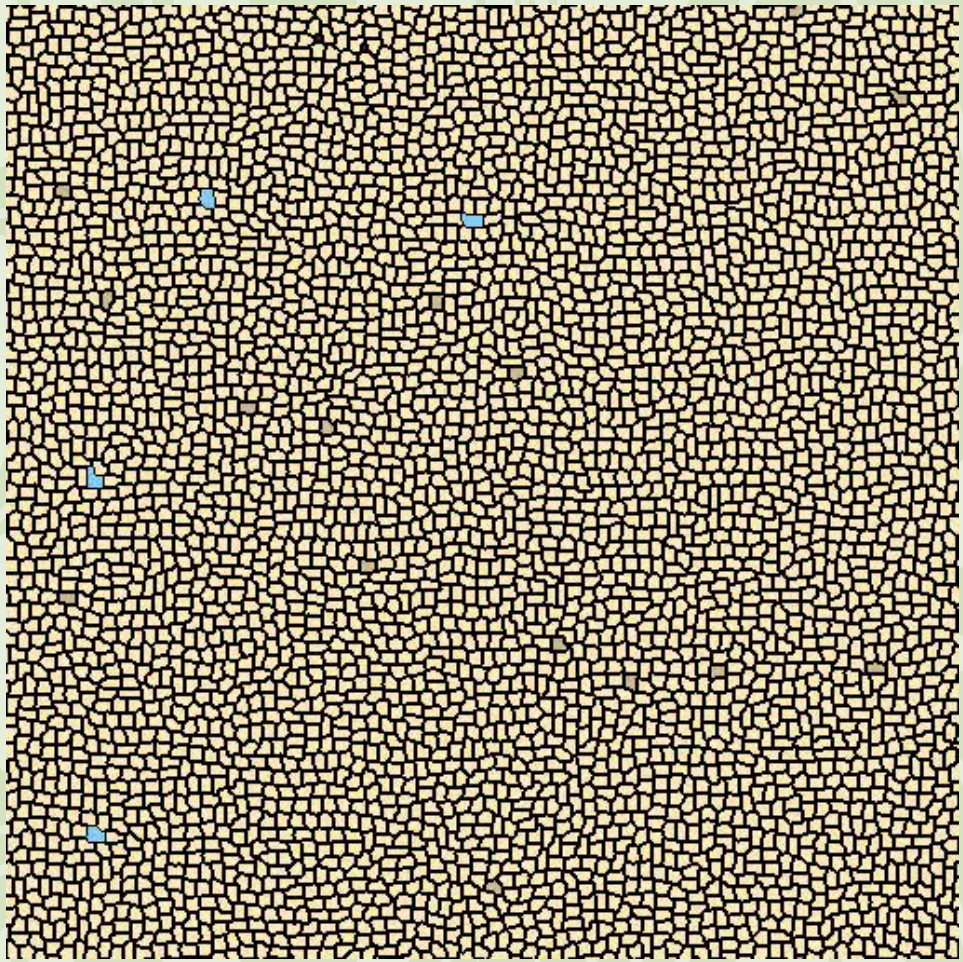
3000steps



8000steps

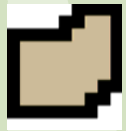


Simulation example



Medium

Normal cell τ_1



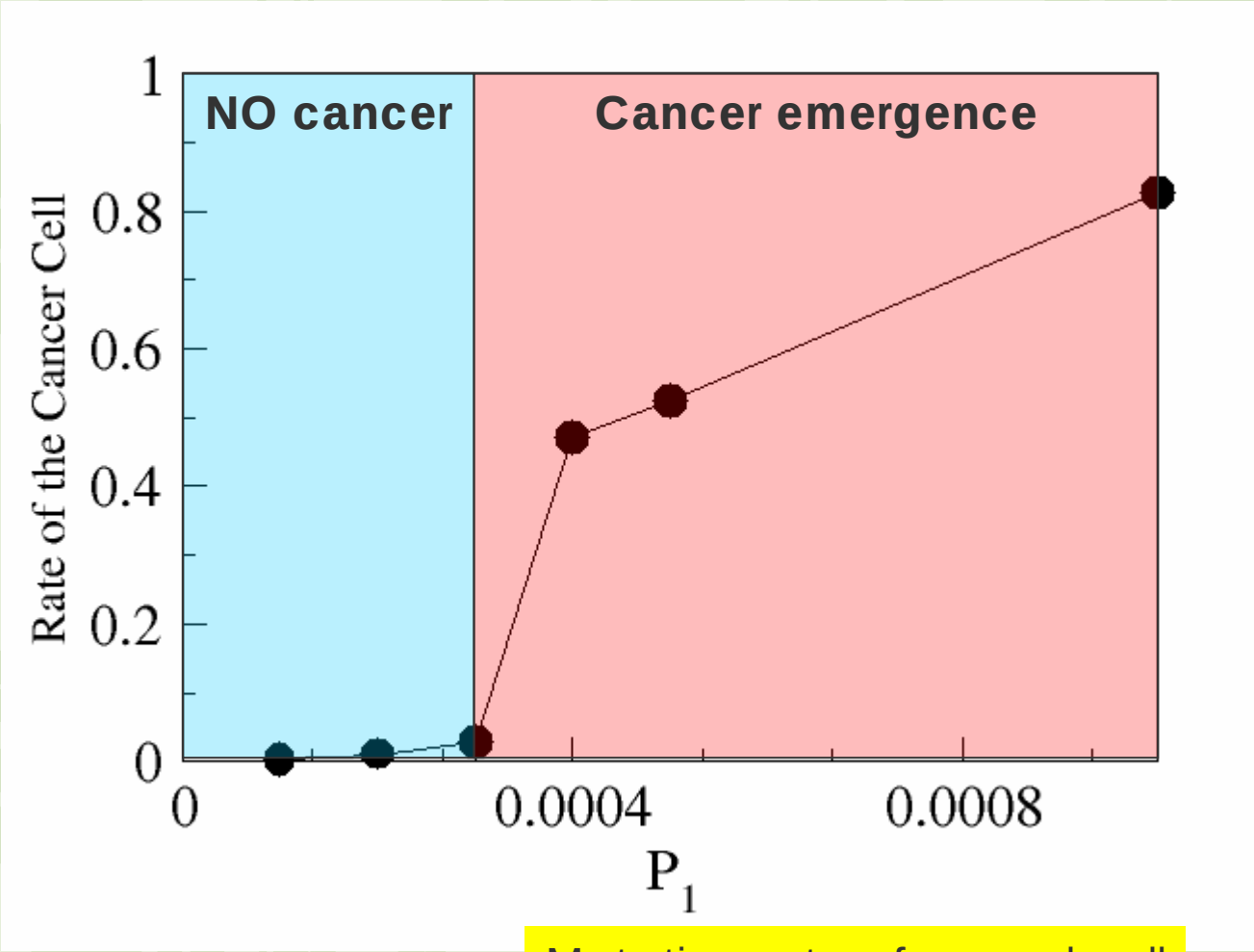
Initiated cell τ_2

Progressed cell τ_3

Cancer cell τ_4

Large mutation rates are used for the time limitation.

Mutation rate vs. Cancer cell production



Mutation rate of normal cell

Conclusion

- Our ongoing study about initial to cellular level biological radiation effects using computer modeling and simulations is showed.
- LET dependency of the DNA damage complexity is studied.
- Relationship between structural change of damaged DNA and its repair is studied.
- Cellular level dynamics of the carcinogenesis is modeled and parameter (mutation rates) dependency is examined.

Thanks!

JAEA

Dr. Ritsuko Watanabe : Simulation of DNA damage induction
Dr. Miroslav Pinak : Simulation of DNA repair
Dr. Julaj Kotulic Bunta : Simulation of Ku70/80 binding
Dr. Mariko Higuchi : Simulation of multiple lesioned DNA

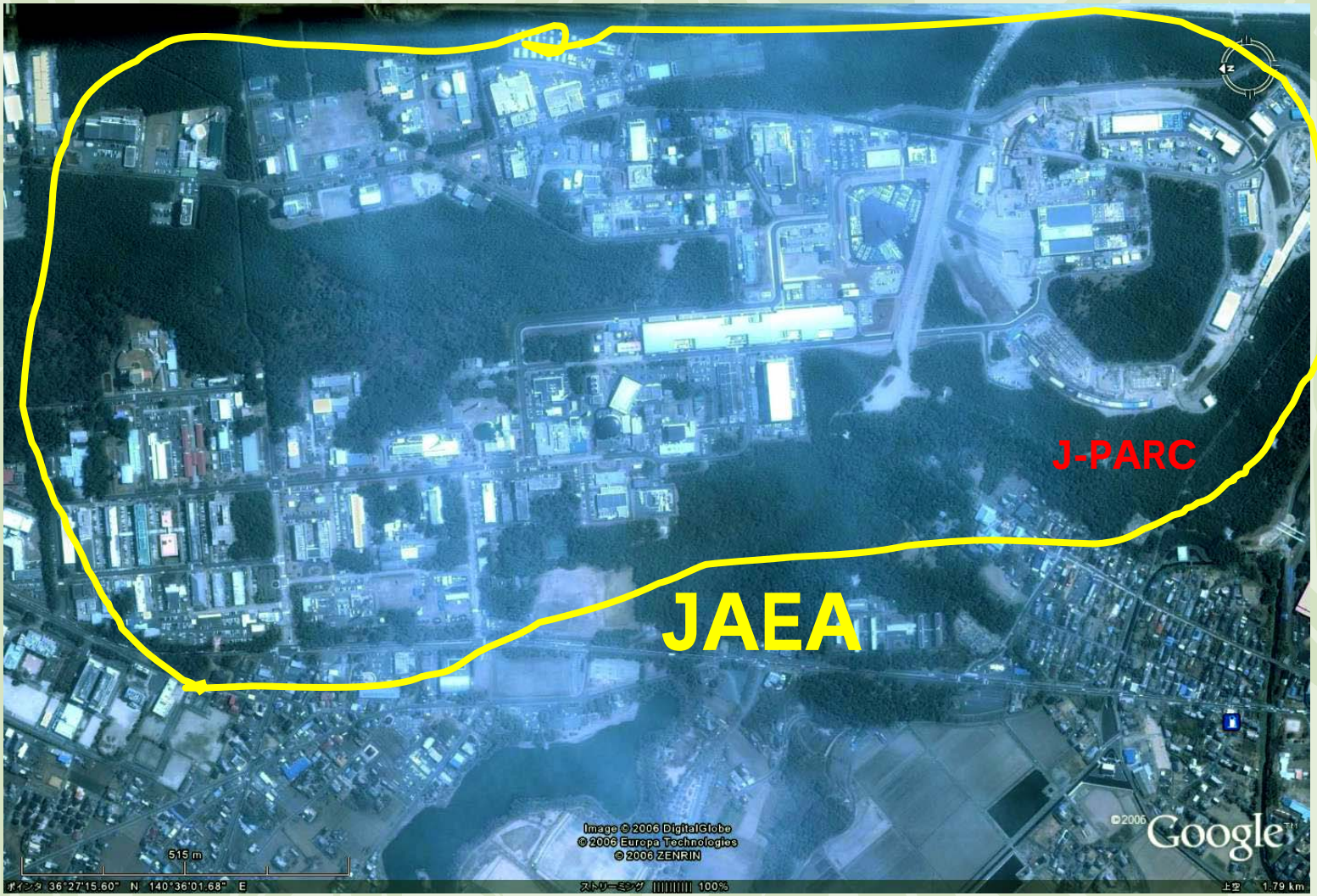
NIID

Dr. Hideaki Maekawa : DNA damage induction experiment
Dr. Hirofumi Fujimoto : DNA repair simulation

NIRS

Dr. Manabu Koike : DNA repair experiment

JAEA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515 m
1.79 km

Divider