19th November 2021

Workshop

BioDynaMo

Agent-based modelling of radiation-induced lung fibrosis

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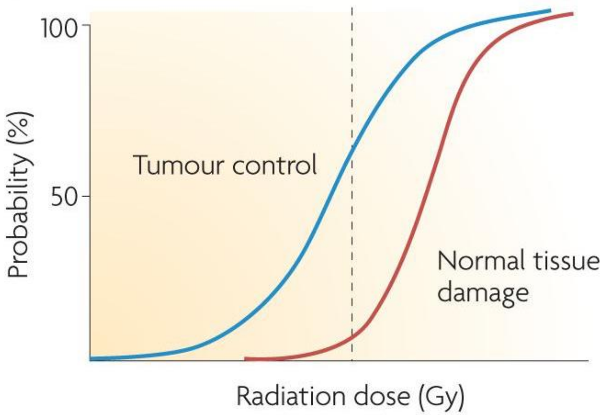
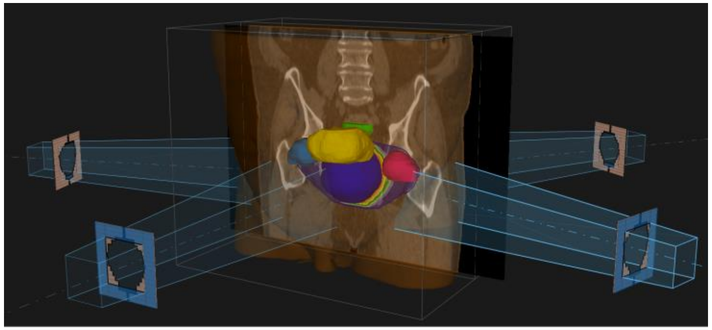
Introduction: *Radiotherapy & NT toxicity*

Involves the use of **ionizing radiation** (such as photon beams, ions, charged and uncharged particles) as a tool **to sterilize cancers**





BUT

Normal tissue (i.e. nontumoral) **toxicity limits the lethal doses to be delivered to the tumors** (irradiated volume and/or radiation dose)

Figures from https://gray.mgh.harvard.edu/attachments/article/166/Treatment%20Planning%201.pdf and Nat Rev Cancer. 2009 Feb; 9(2): 134–142

Introduction: *Radiation-Induced Lung Injury (RILI)*

What?

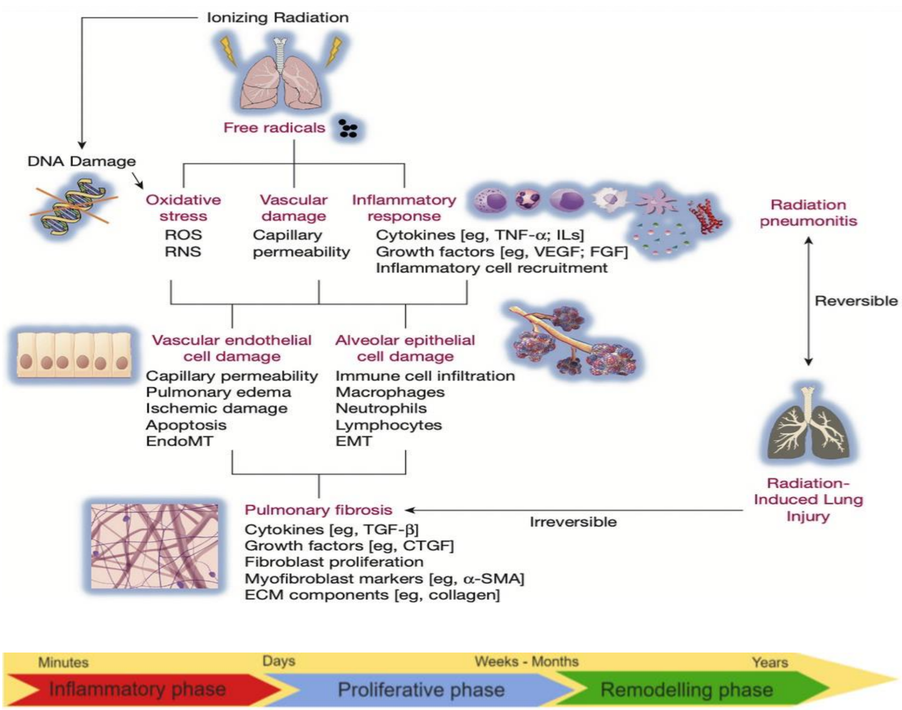
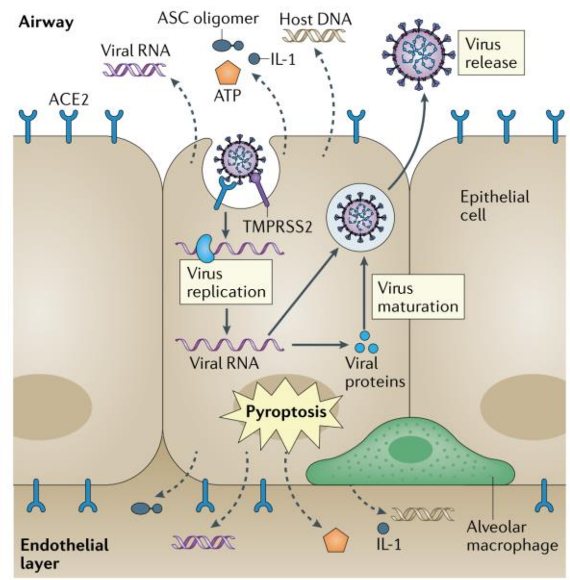


Figure from RECENT ADVANCES IN CHEST MEDICINE | VOLUME 156, ISSUE 1, P150-162, JULY 01, 2019

Why?



- a RILI model could be tailored to a COVID-19 (coronavirus SARS-CoV-2) disease progression model*.

*See *Rios et al.*, RADIATION RESEARCH 195, 1–24 (2021) and Tay MZ, Poh CM, Rénia L, MacAry PA, Ng LFP, Nat Rev Immunol. 2020 Jun;20(6):363-374

Introduction: *Normal tissue toxicity models*

As yet there are **no mechanistic models of normal tissue toxicities**

Phenomenological models rely on input data of tolerance doses for organs at risk which are **derived from clinical experience**

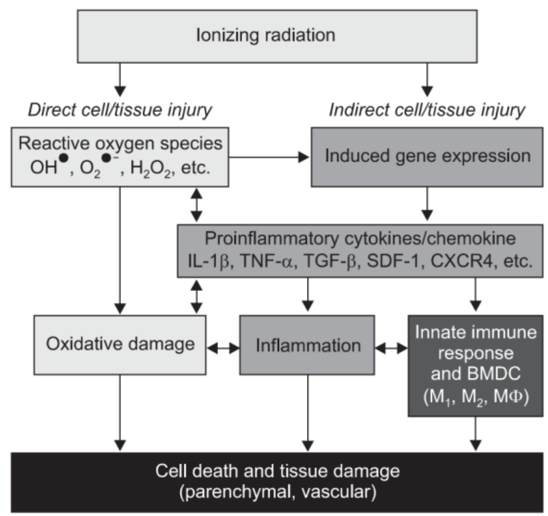
Math/Comp models can provide valuable insights useful for **tuning the RT parameters**

LKB model (*Mohan*)

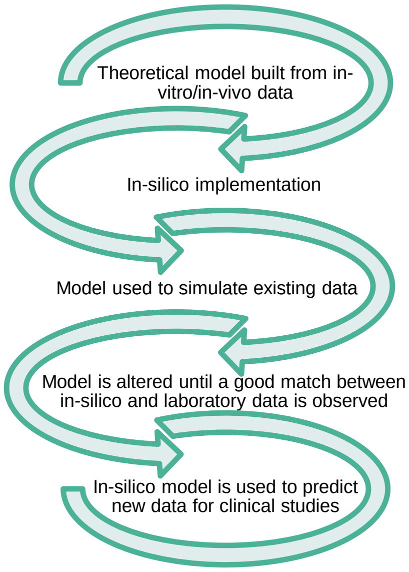
$$\mathrm{NTCP}(d_{eud}|d_{50},m)=\frac{1}{\sqrt{2\pi}}\int_{-\infty}^{(d_{eud}-d_{50})/(md_{50})}\exp\left(-\frac{x^2}{2}\right)\mathrm{d}x$$

$$d_{eud}(\{d_i\};n)=\left(\sum_{i=i}^{N}v_i d_i^{1/n}\right)^n$$

- d_{eud} = equivalent uniform dose
- N = voxel number
- {di} = set of doses to all voxels
- d_i = dose to the ith voxel
- v_i = partial volume of the ith voxel
- n = volume effect parameter
- d_{50} = equivalent uniform dose corresponding to 50% complication probability
- m = ramp parameter



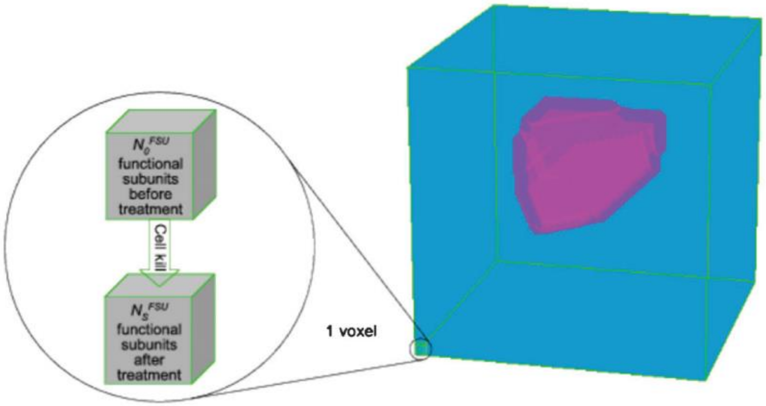
Much more complex!



Figures from Radiat Oncol J. 2014 Sep; 32(3): 103–115

Introduction: *Proposed approach*

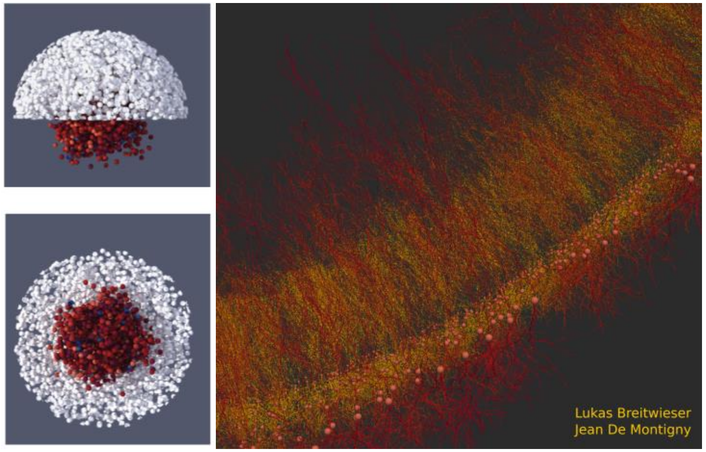
Example of current mechanistic approach



Lack of inflammation-induced tissue damage modelling

Proposed agent-based approach

BioDynaMo
Biology Dynamics Modeller

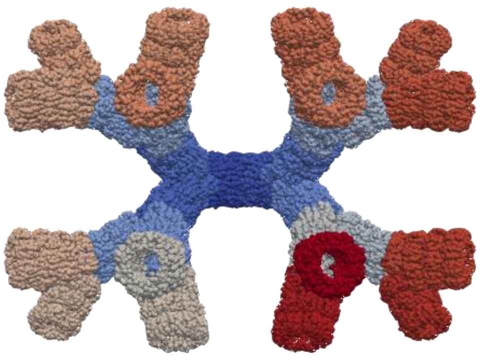


- Agent-based modelling
- User-defined agent behaviours (i.e. no centralization)
- Extensible platform (C++)
- Simulate biological dynamics
- Mechanical interactions between agents
- Substances diffusion

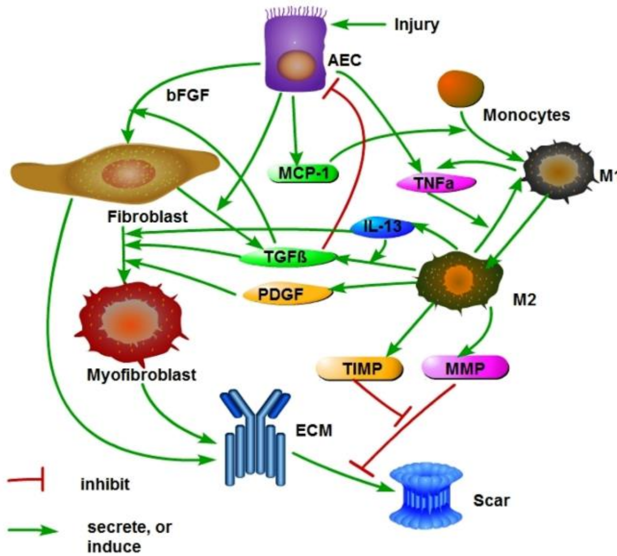
Figures from Rutkowska et al., The British Journal of Radiology, 85 (2012), e1242–e1248 and https://biodynamo.org

Introduction: *Proposed approach*

Agents and simulation space



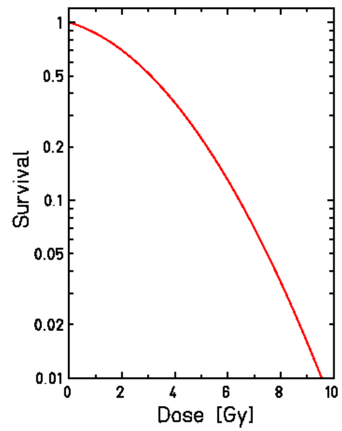
Behaviours



IPF ~ RILI (known onset causes)

Mathematical model (differential equations) → ***Agent-based model (agents behaviours)***

Damage



Dose → Survival → AECII activation

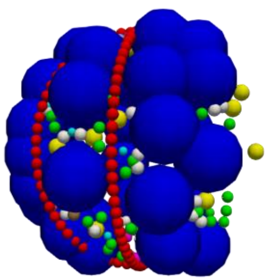
BioDynaMo
Biology Dynamics Modeller

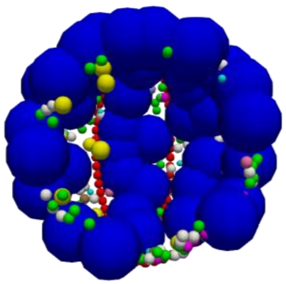
Input data

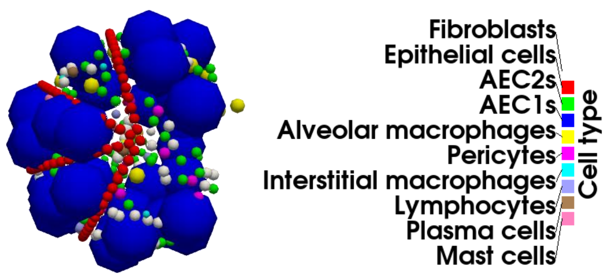
Figure from Hao W, Marsh C, Friedman A (2015), PLOS ONE 10(9)

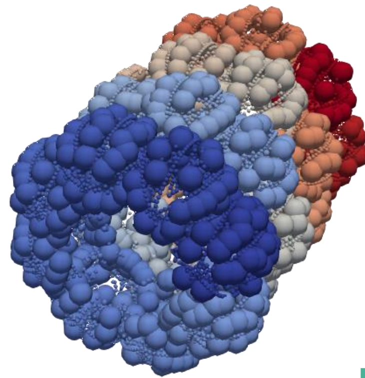
Methods: *Geometrical framework 1*

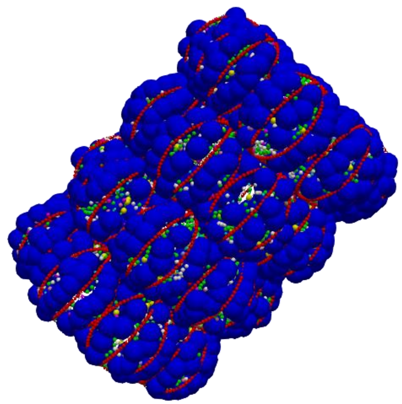
- Hollow ¾ Sphere, ~ 200um diameter
- ~ 480’000’000 in human lungs
- More than 10 different cell types
- ~ 300 cells per alveolus in the model

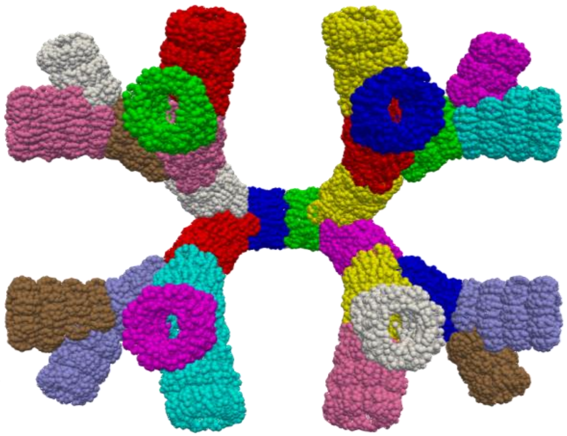


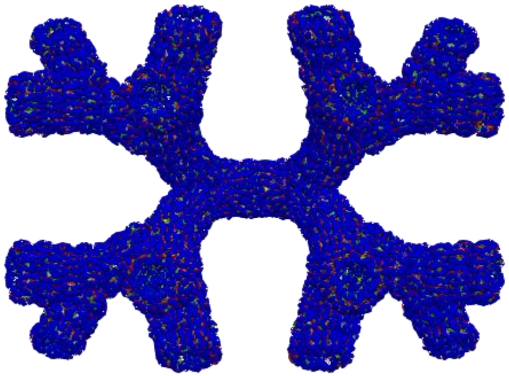










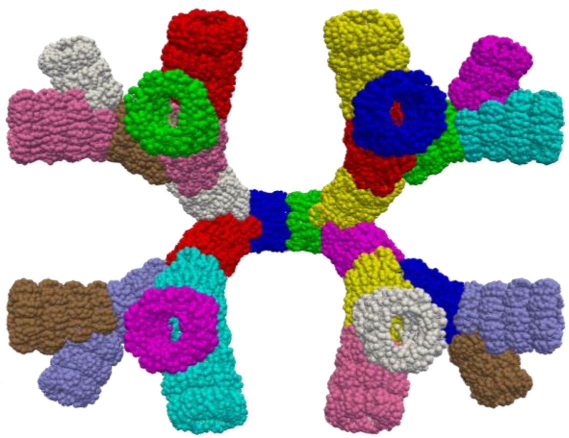


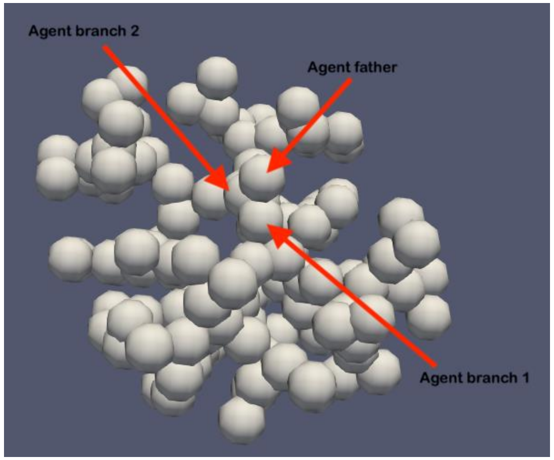
Alveoli

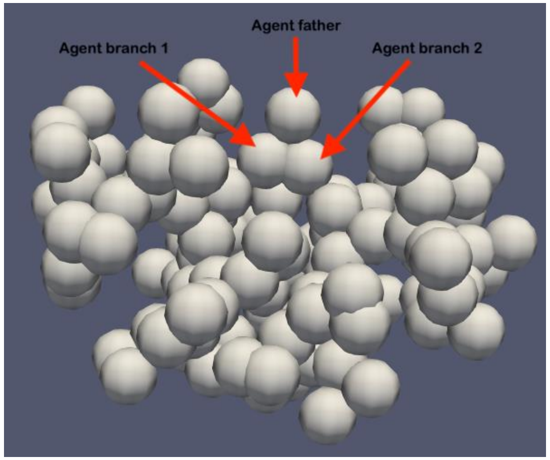
Alveolar Ducts

5-generations Acini

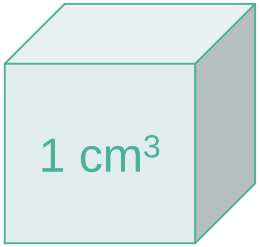
Methods: *Geometrical framework 2*



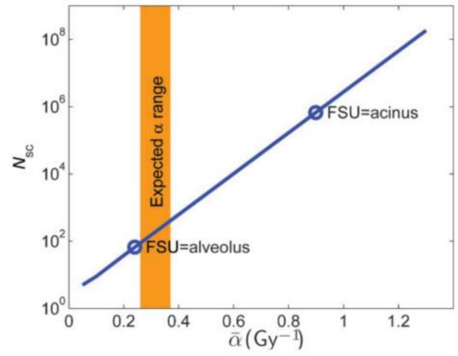




Bigger portion of the lungs



Functional subunits

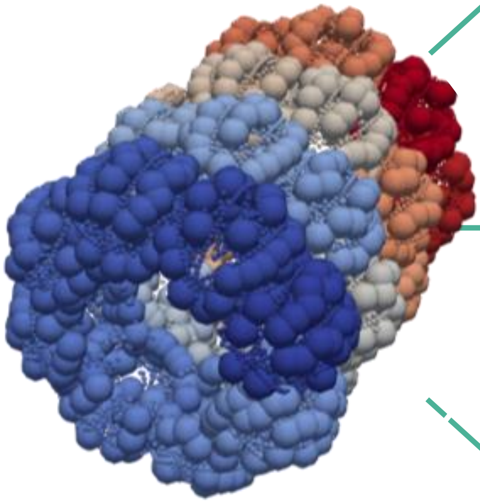


Multiple interacting substances

- TIMP
- ECM
- FGF2
- IL13
- PDGF
- TGFß
- TNFα
- MMP
- MCP1

Figure from Rutkowska et al., 2012, British Journal of Radiology

Methods: *Behaviours*



Properties

- Initial nb of cells
- Current nb of cells

Methods

- Get/Set/Update nb of cells
- Get/Set/Update behaviors rates

Behaviors

- Secretion
- Apoptosis
- Proliferation
- Differentiation
- Activation

Cell types

- AECI
- AECII
- Fibroblasts
- Myofibroblasts
- MΦ1
- MΦ2

Goals

Short-term: Reproduce laboratory data

$$\text{Fibrosis index (FI)} = \sqrt{\Delta\,\overline{\text{HU}\uparrow} \times \Delta\,\overline{\text{V}\downarrow}}$$

$$\text{FI(D)} = \frac{1}{2}\text{A}\left\{1 - \text{erf}\left(\sqrt{\pi}\gamma\left(1 - \frac{\text{D}}{\text{ED}_{50}}\right)\right)\right\}$$

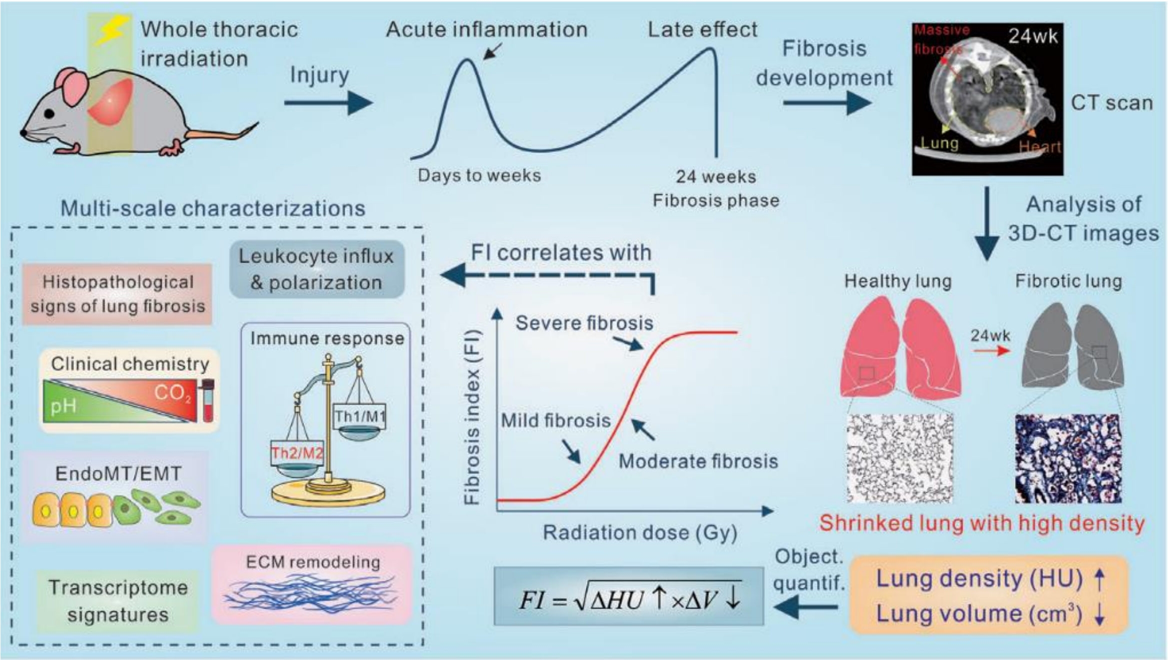
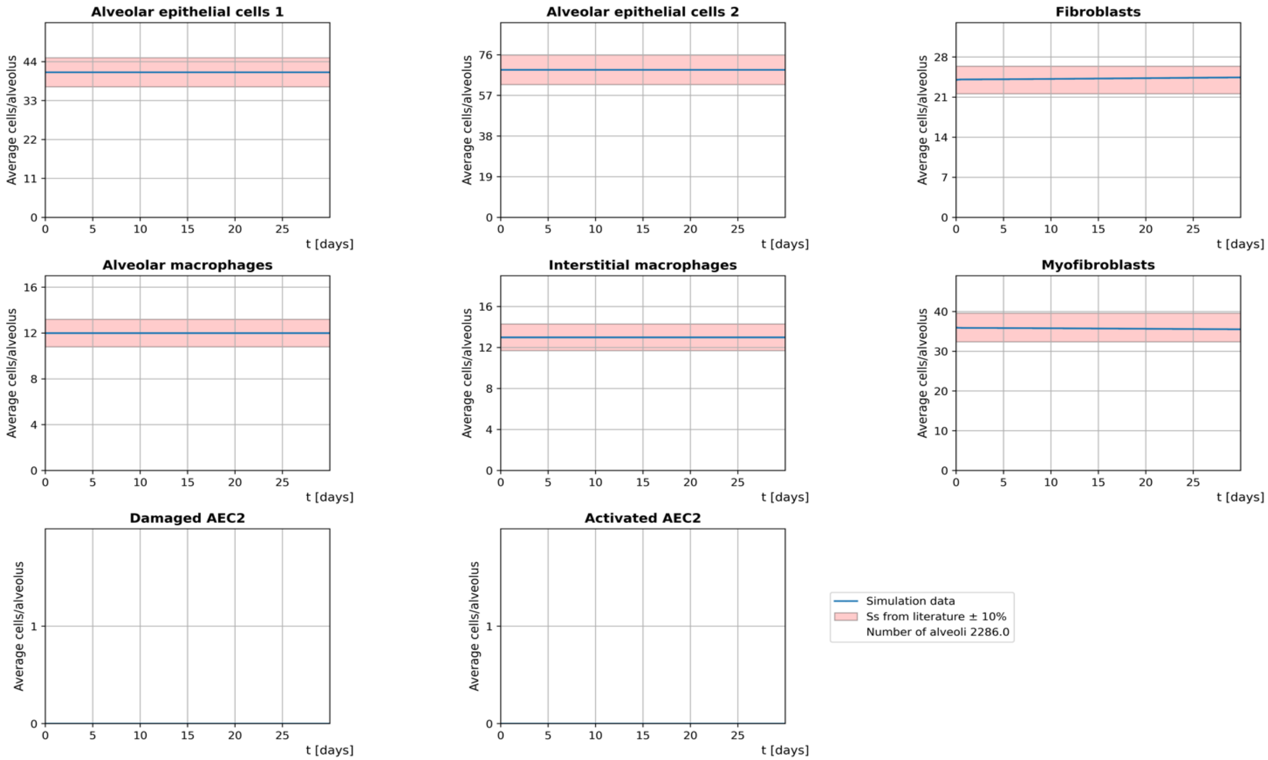
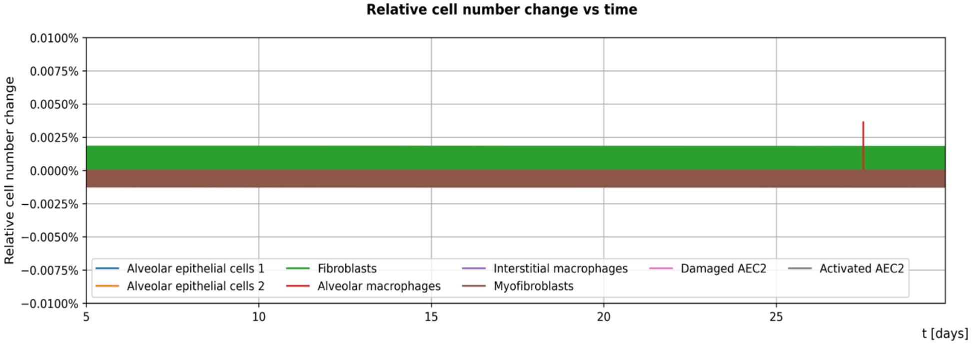


Figure from Zhou et al. (2019), International Journal of Cancer 144(12)

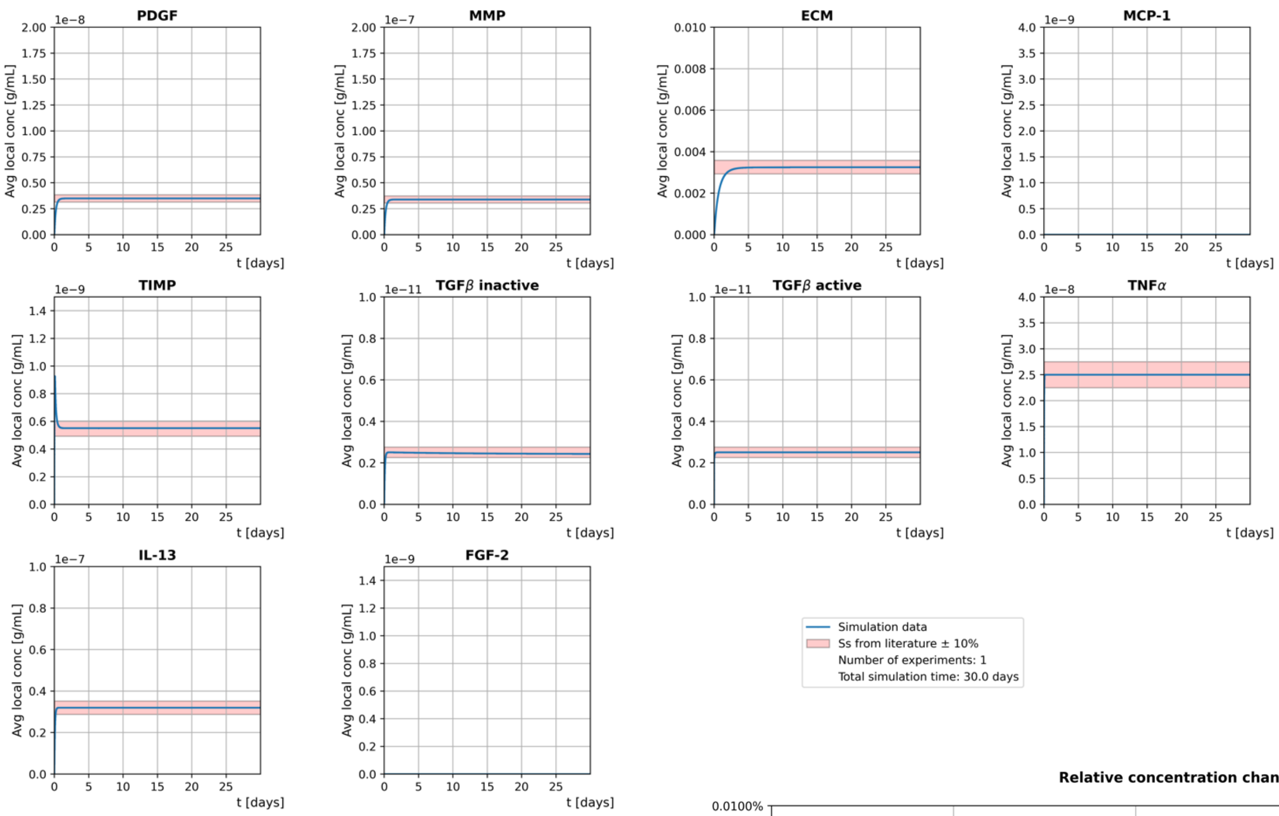
Results: *Homeostasis*



$$\Delta_m = \left(\frac{m\,(t+1) - m\,(t)}{m\,(t)}\right) * 100,$$
$$m \in \{sub\ conc, cell\ \#\}$$



Results: *Homeostasis*



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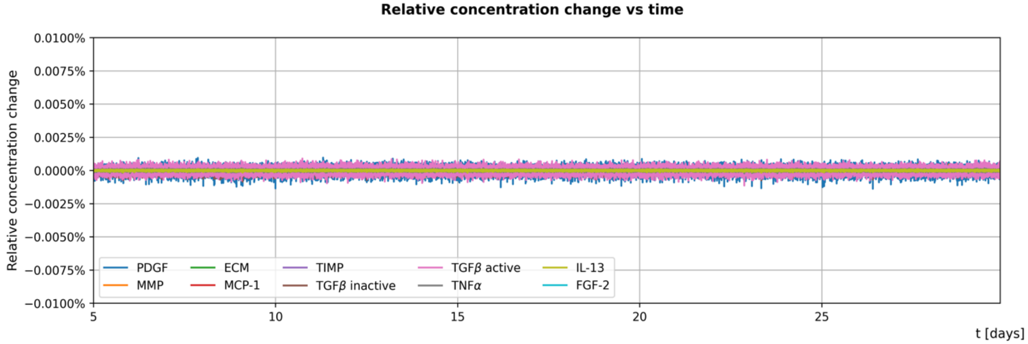


Results: *Onset of Pulmonary Fibrosis*

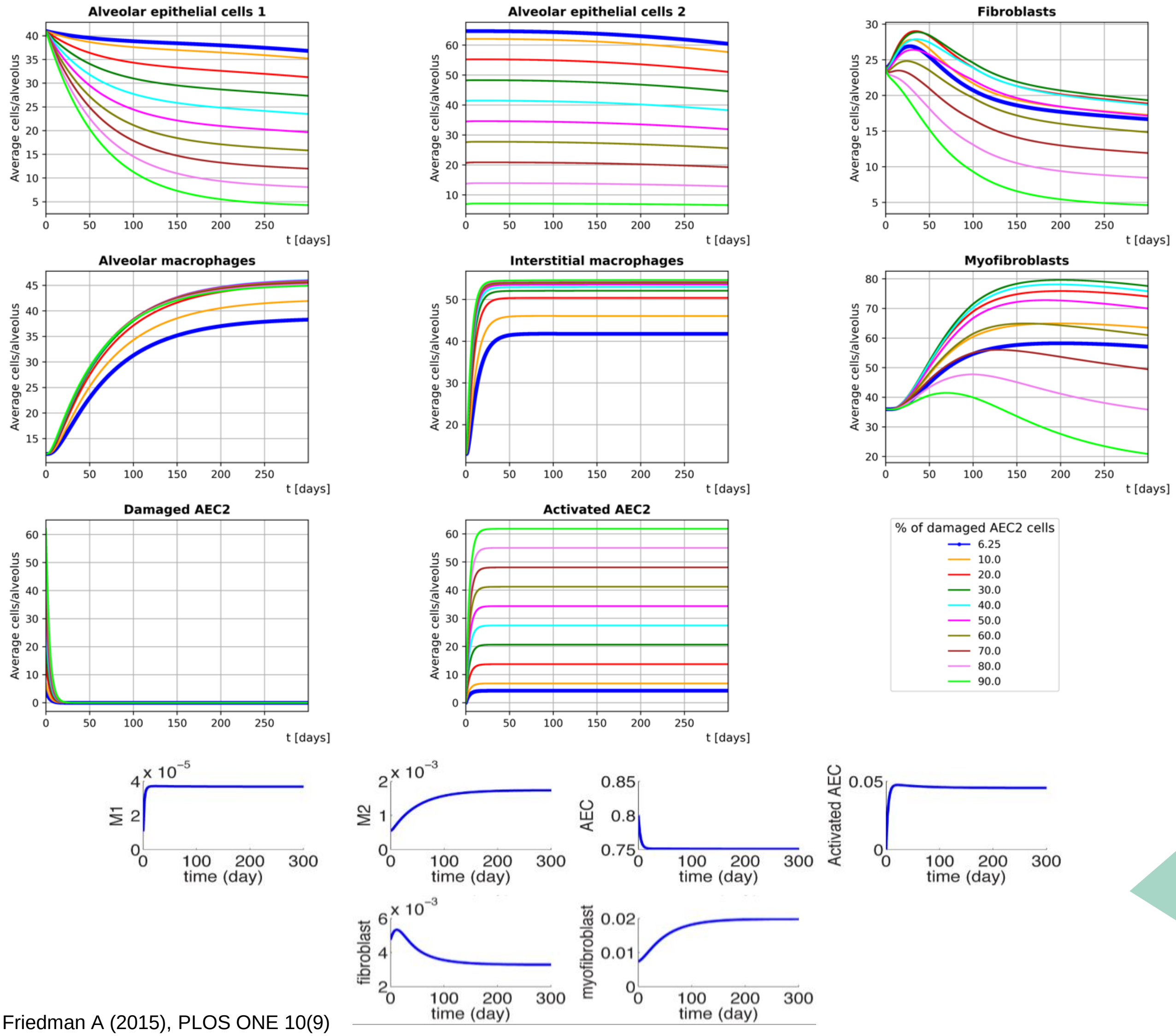


Figure from Hao W, Marsh C, Friedman A (2015), PLOS ONE 10(9)

Results: *Onset of Pulmonary Fibrosis*

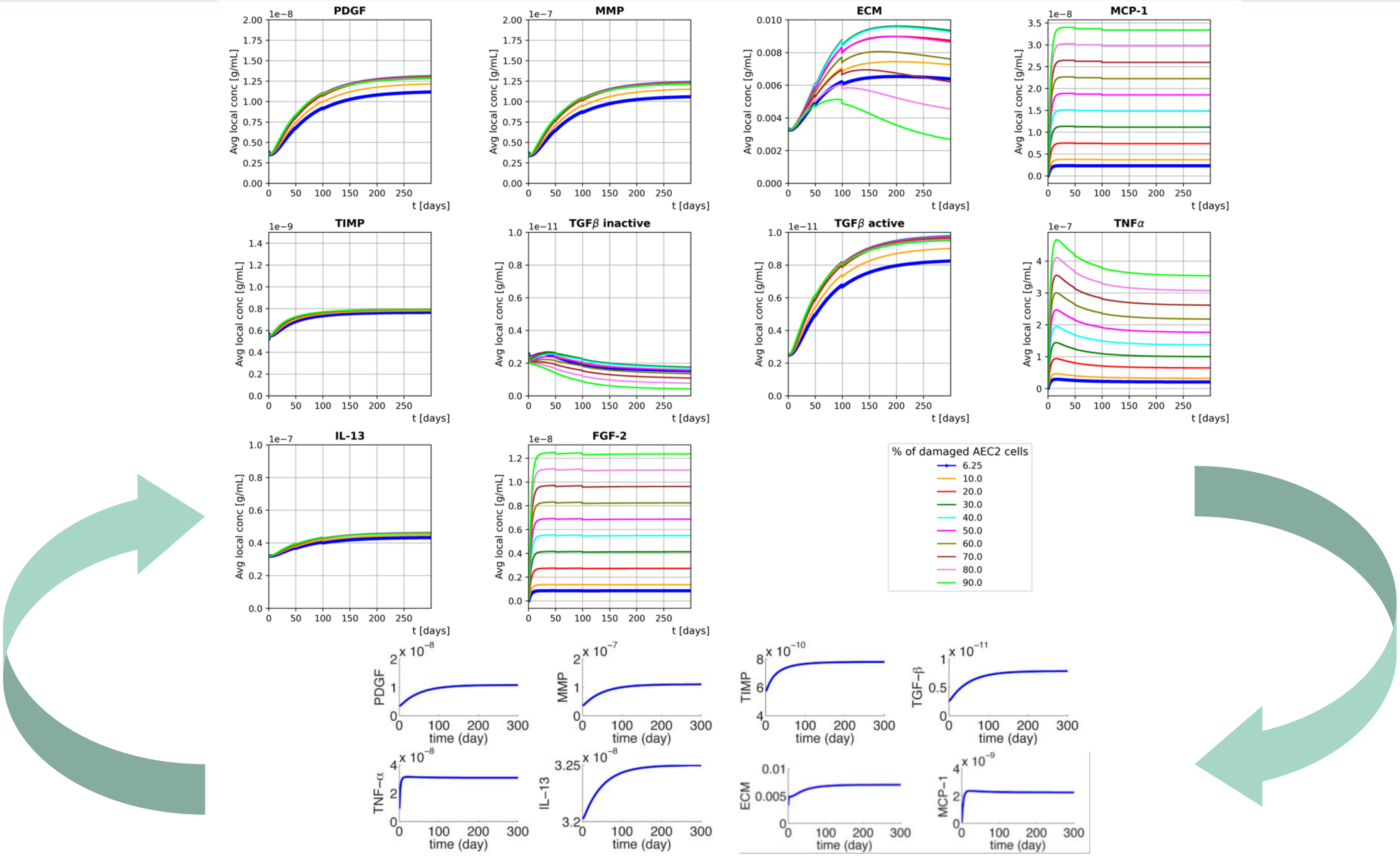
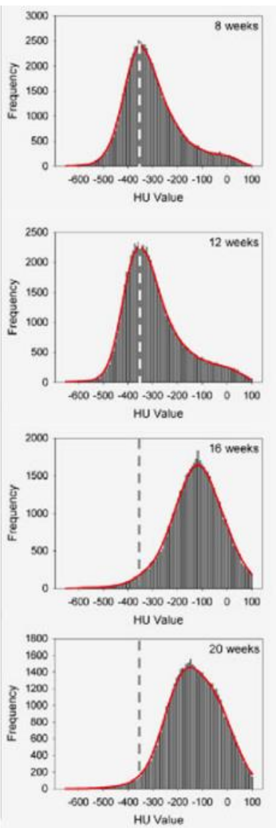
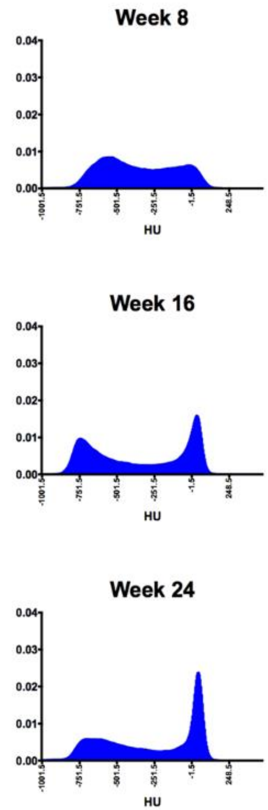


Figure from Hao W, Marsh C, Friedman A (2015), PLOS ONE 10(9)

Current state: *Simulating the onset of RILI*

Laboratory data





Simulation results (week 43)

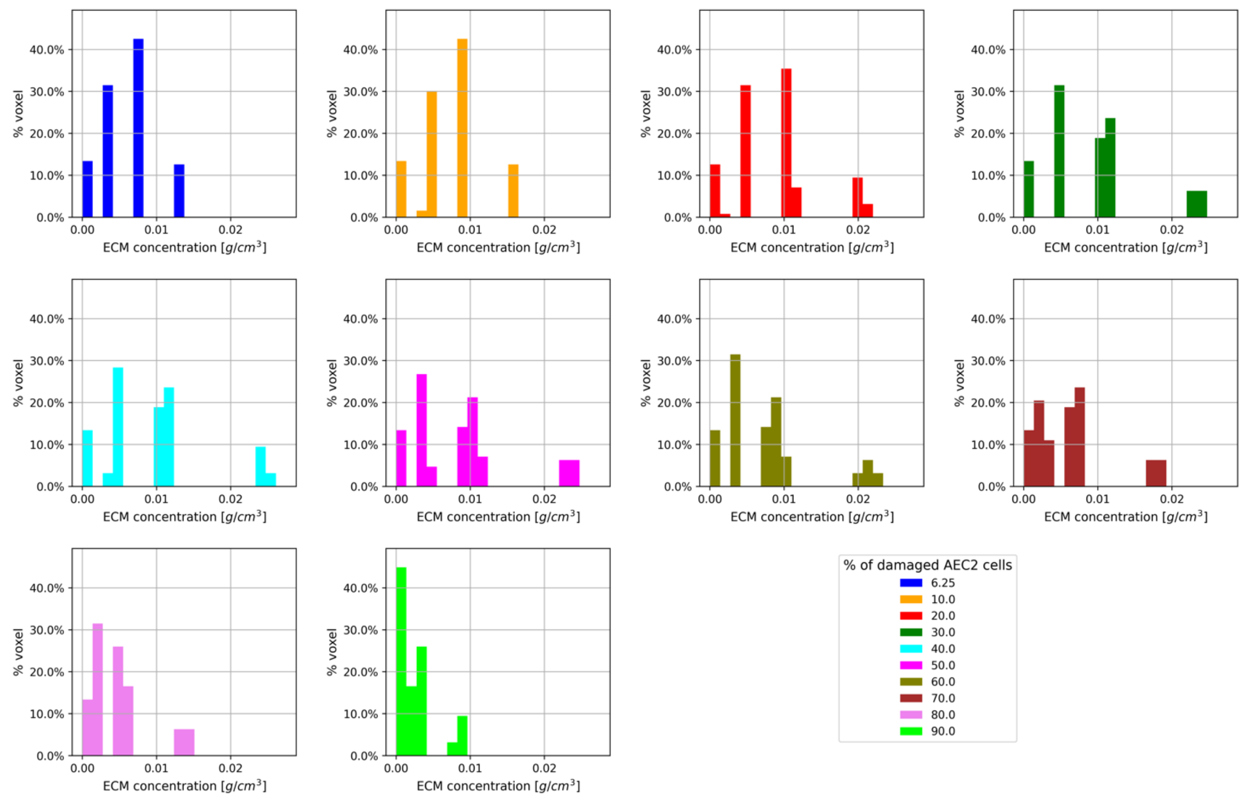


Figure from Zhou et al. (2019), International Journal of Cancer 144(12) and Perez et al. (2017), Scientific Reports 7(1)

Thank you for your attention!

Questions?