

19th November 2021

Workshop

BioDynaMo

Agent-based modelling of radiation-induced lung fibrosis

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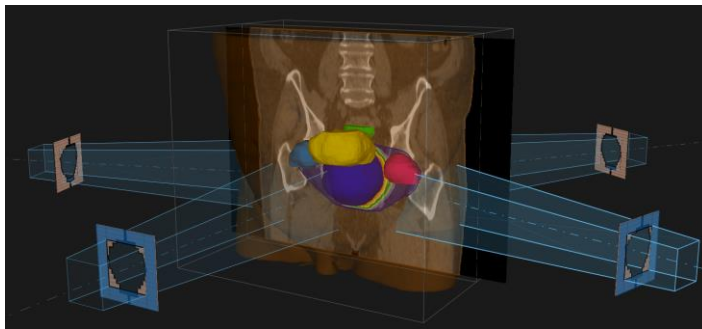
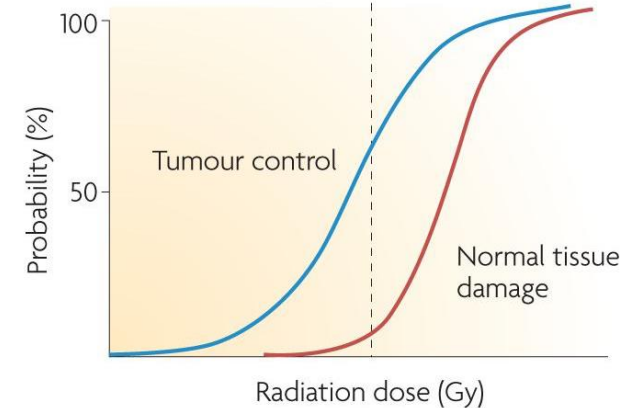


BioDynaMo
BIOLOGY DYNAMICS MODELLER

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)

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

What?

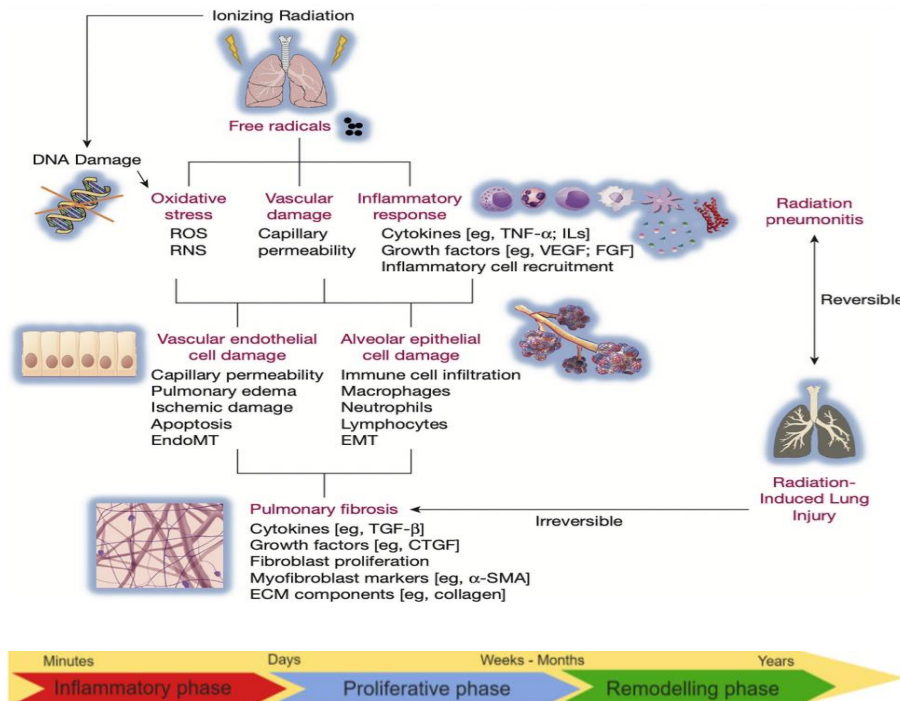
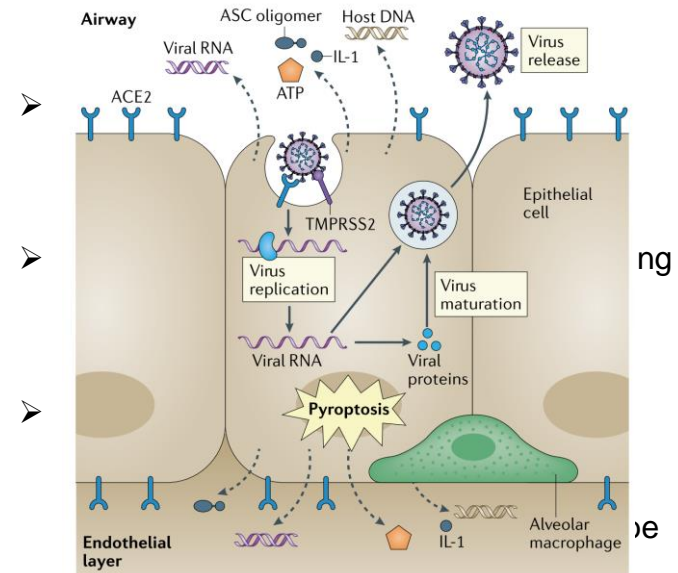


Figure from RECENT ADVANCES IN CHEST MEDICINE | VOLUME 156, ISSUE 1, P150-162, JULY 01, 2019

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**



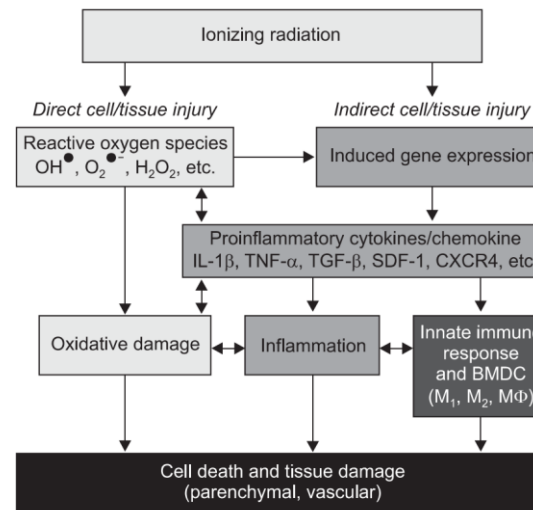
Math/Comp models can provide valuable insights useful for **tuning the RT parameters**

LKB model (*Mohan*)

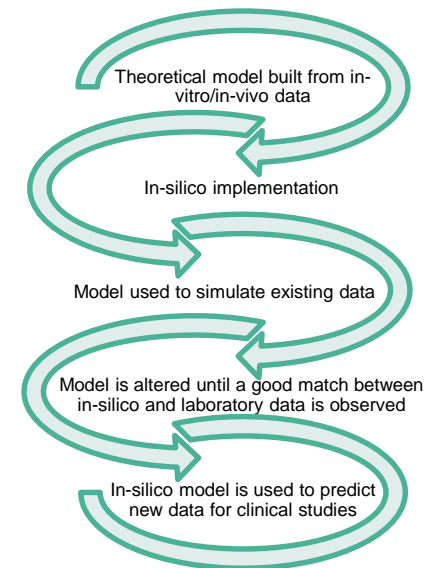
$$\text{NTCP}(d_{\text{eud}}|d_{50}, m) = \frac{1}{\sqrt{2\pi}} \int_{-\infty}^{(d_{\text{eud}} - d_{50}) / (m d_{50})} \exp\left(-\frac{x^2}{2}\right) dx$$

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

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

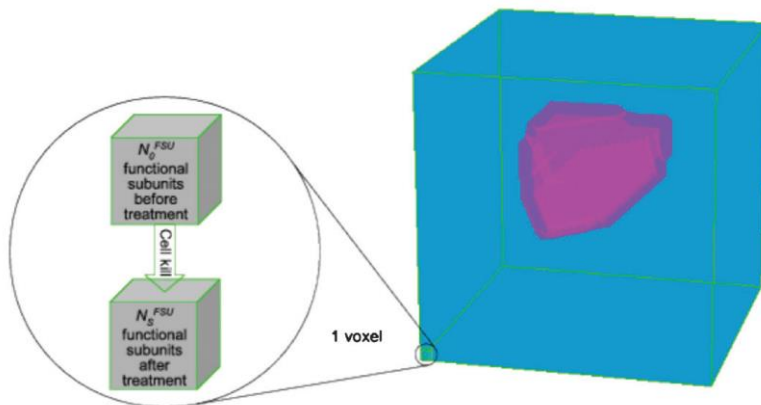


Much more complex!



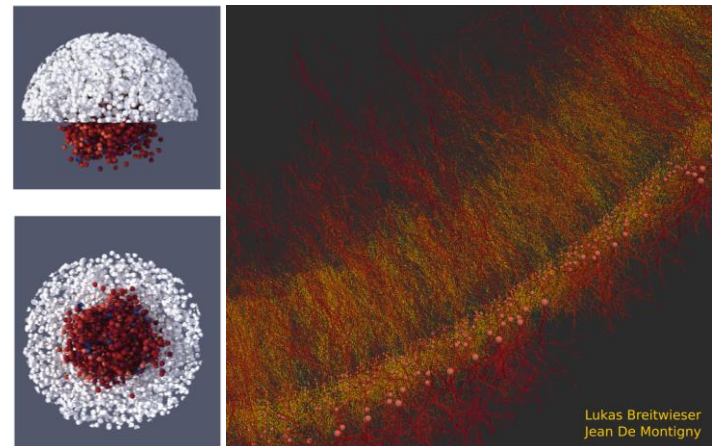
Introduction: *Proposed approach*

Example of current mechanistic approach



Lack of inflammation-induced tissue damage modelling

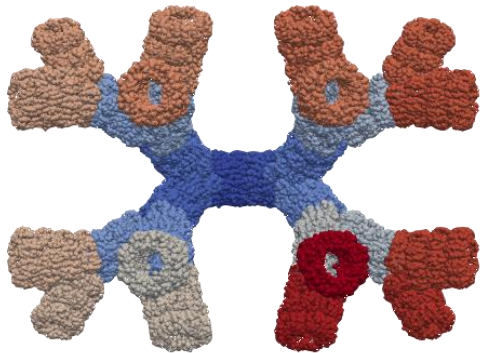
Proposed agent-based approach



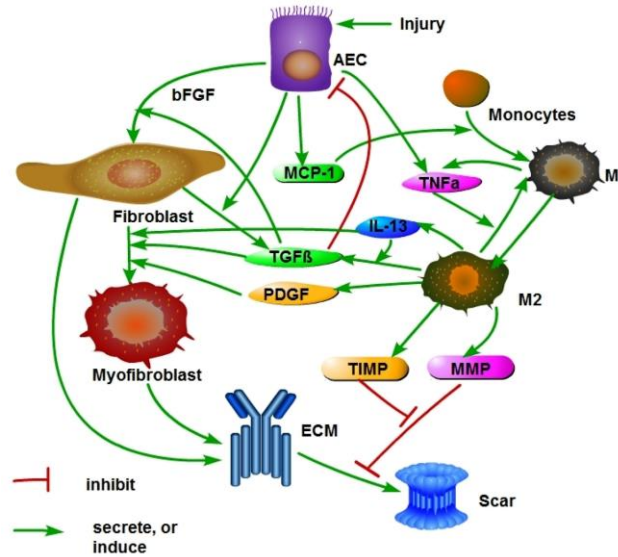
- Agent-based modelling
- User-defined agent behaviours (i.e. no centralization)
- Extensible platform (C++)
- Simulate biological dynamics
- Mechanical interactions between agents
- Substances diffusion

Introduction: *Proposed approach*

Agents and simulation space



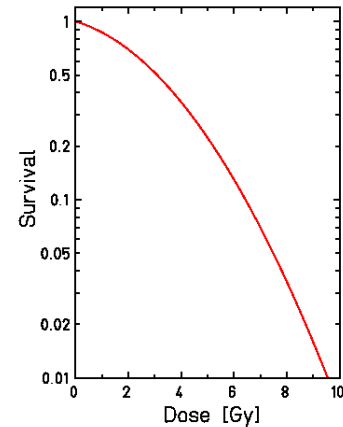
Behaviours



IPF ~ RILI (known onset causes)

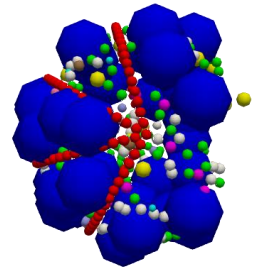
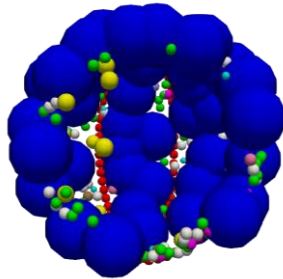
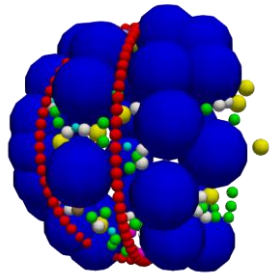
Mathematical model (differential equations) → Agent-based model (agents behaviours)

Damage

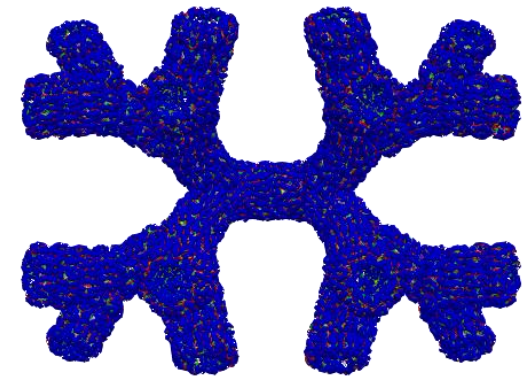
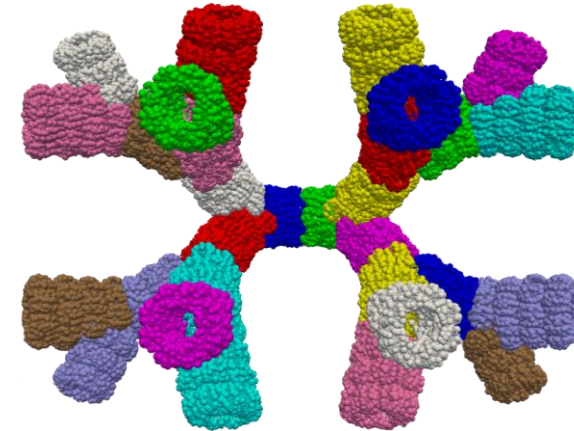
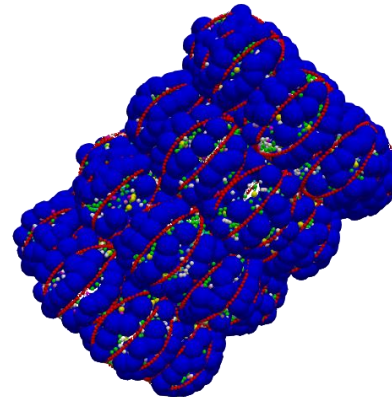
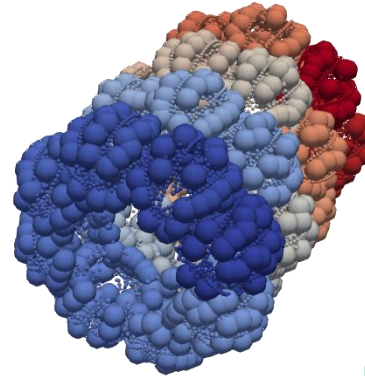


Methods: Geometrical framework 1

- Hollow $\frac{3}{4}$ Sphere, ~ 200um diameter
- ~ 480'000'000 in human lungs
- More than 10 different cell types
- ~ 300 cells per alveolus in the model



Fibroblasts
 Epithelial cells
 AEC2s
 AEC1s
 Alveolar macrophages
 Pericytes
 Interstitial macrophages
 Lymphocytes
 Plasma cells
 Mast cells
 Cell type

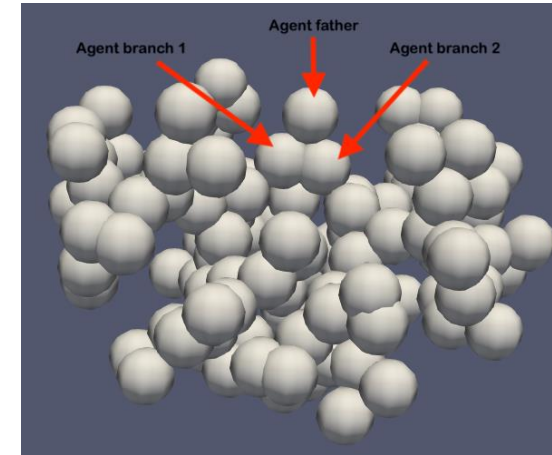
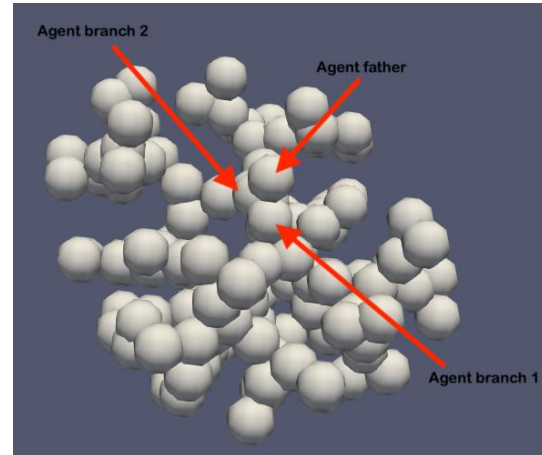
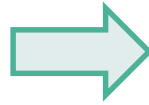
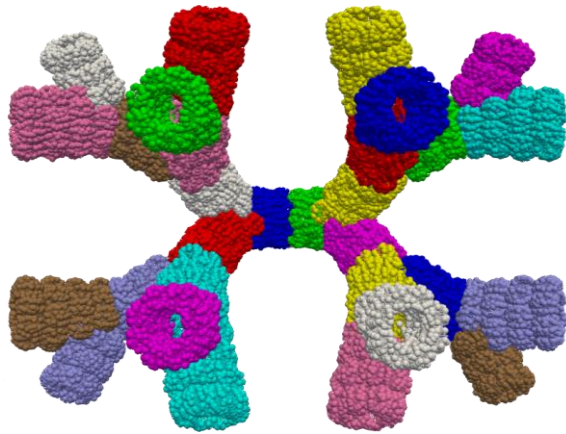


Alveoli

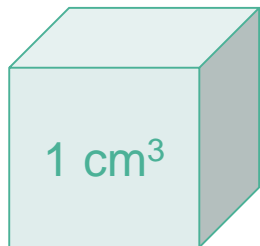
Alveolar Ducts

5-generations Acini

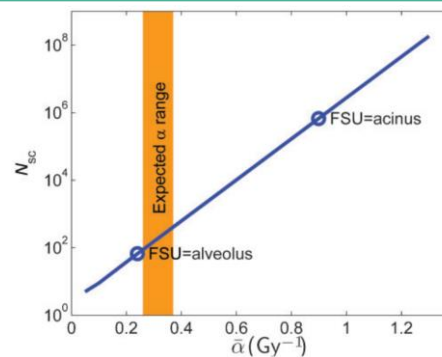
Methods: Geometrical framework 2



Bigger portion of the lungs



Functional subunits

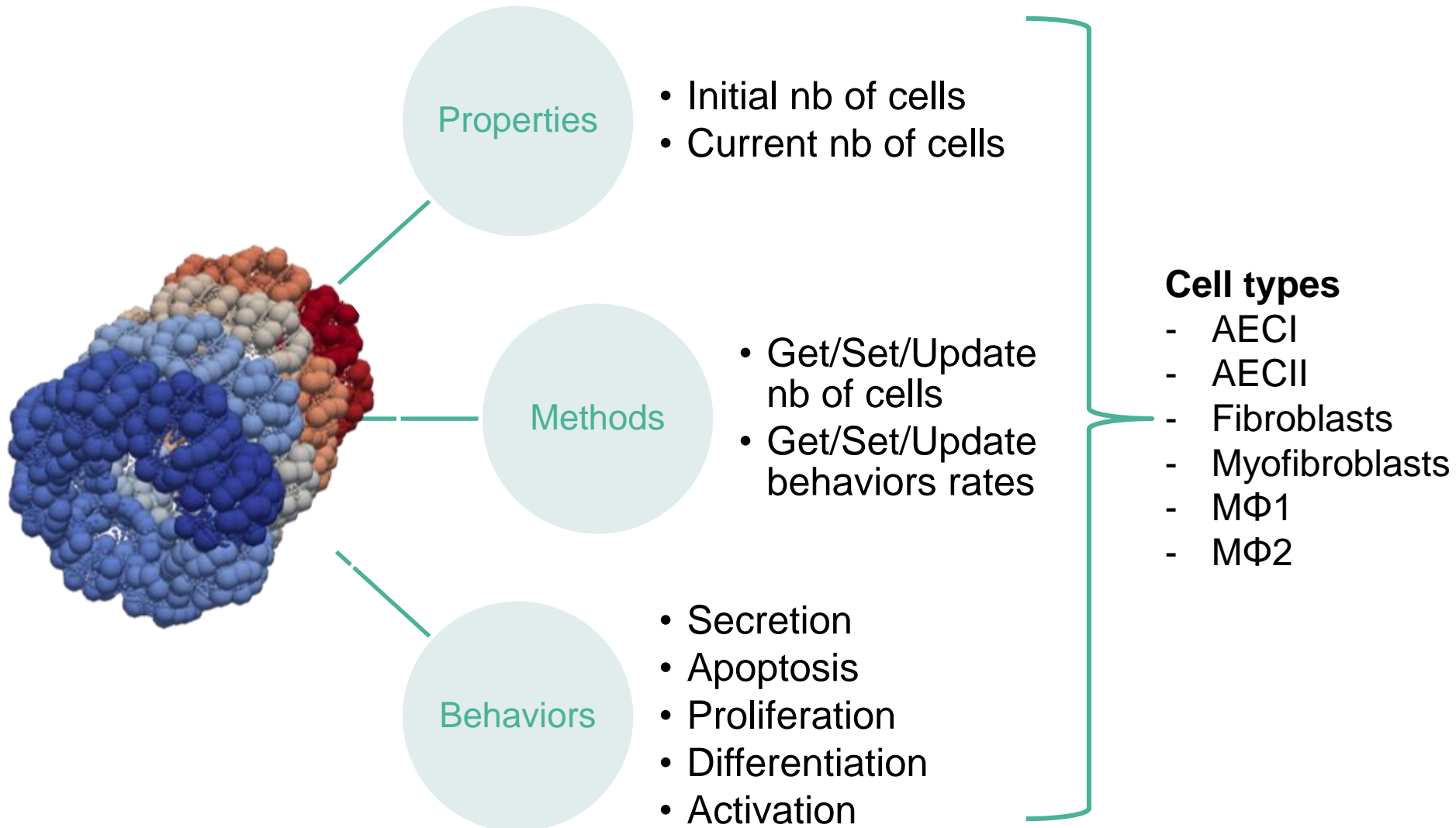


Multiple interacting substances

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

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

Methods: *Behaviours*



Goals

Short-term: Reproduce laboratory data

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

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

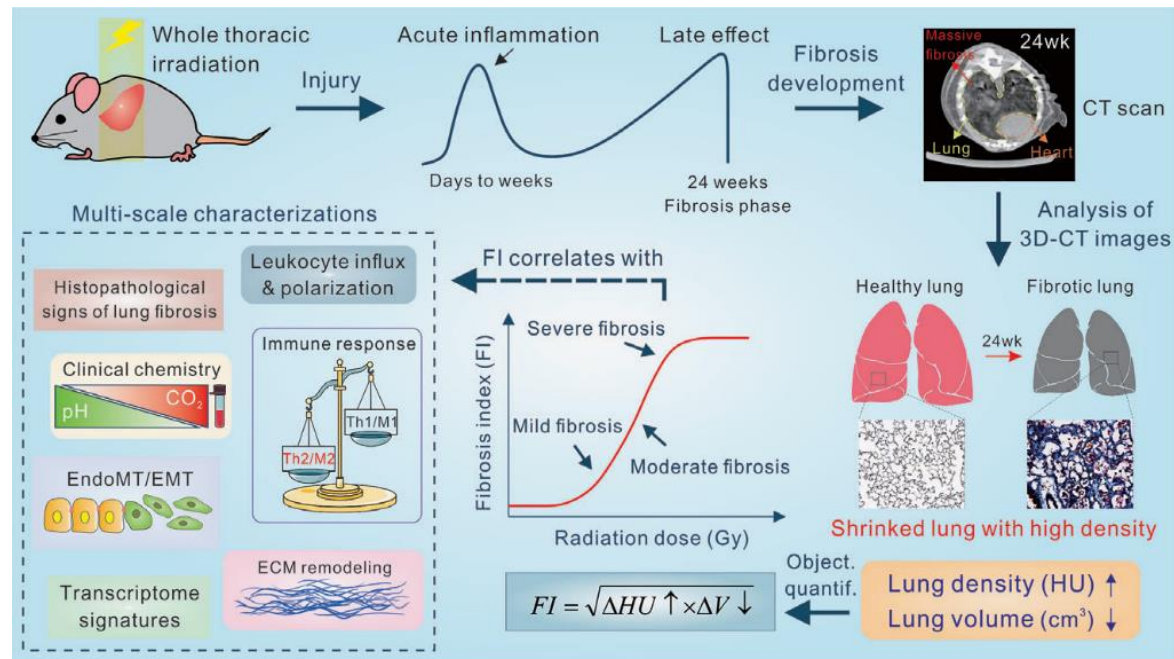
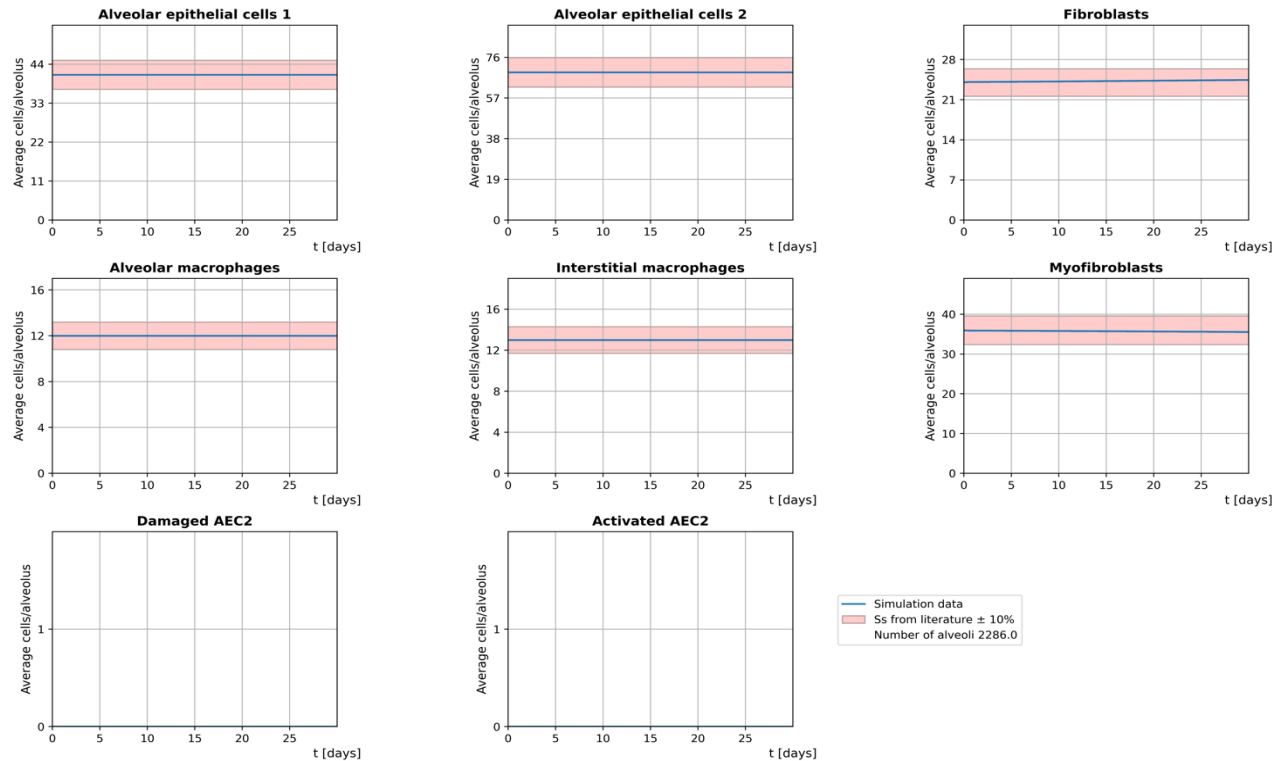


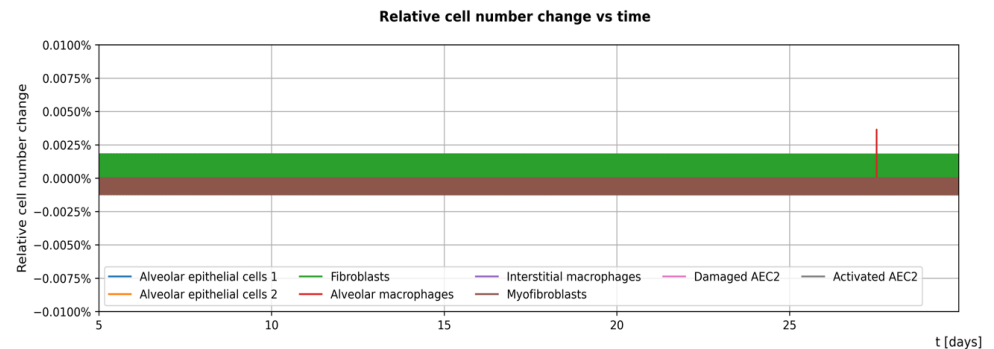
Figure from Zhou et al. (2019), International Journal of Cancer 144(12)

Results: *Homeostasis*

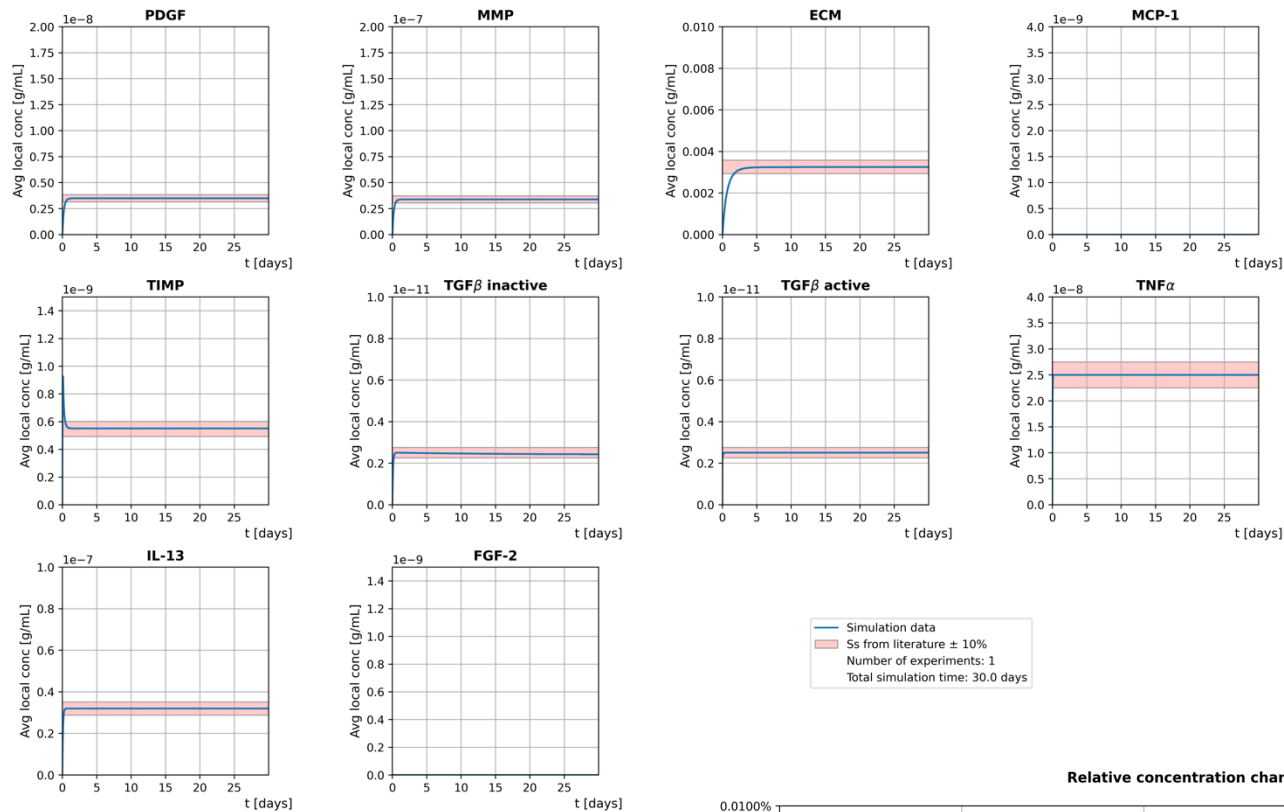


$$\Delta_m = \left(\frac{m(t+1) - m(t)}{m(t)} \right) * 100,$$

$m \in \{sub\ conc, cell\ \#\}$

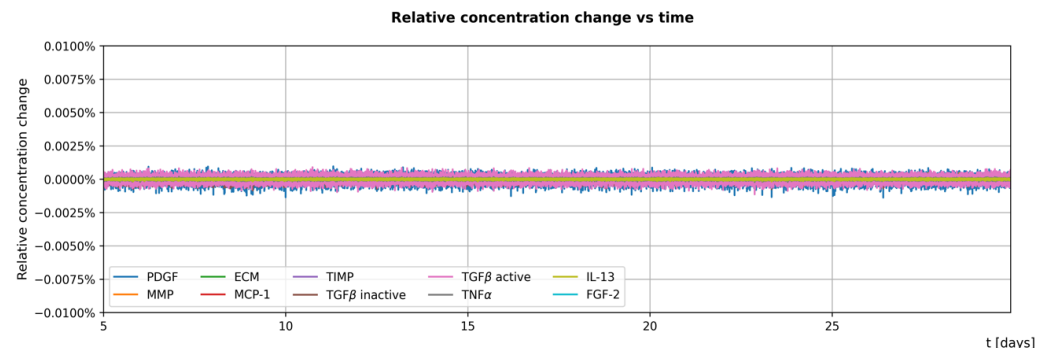


Results: Homeostasis



$$\Delta_m = \left(\frac{m(t+1) - m(t)}{m(t)} \right) * 100,$$

$$m \in \{sub\ conc, cell\ \#\}$$



Results: Onset of Pulmonary Fibrosis

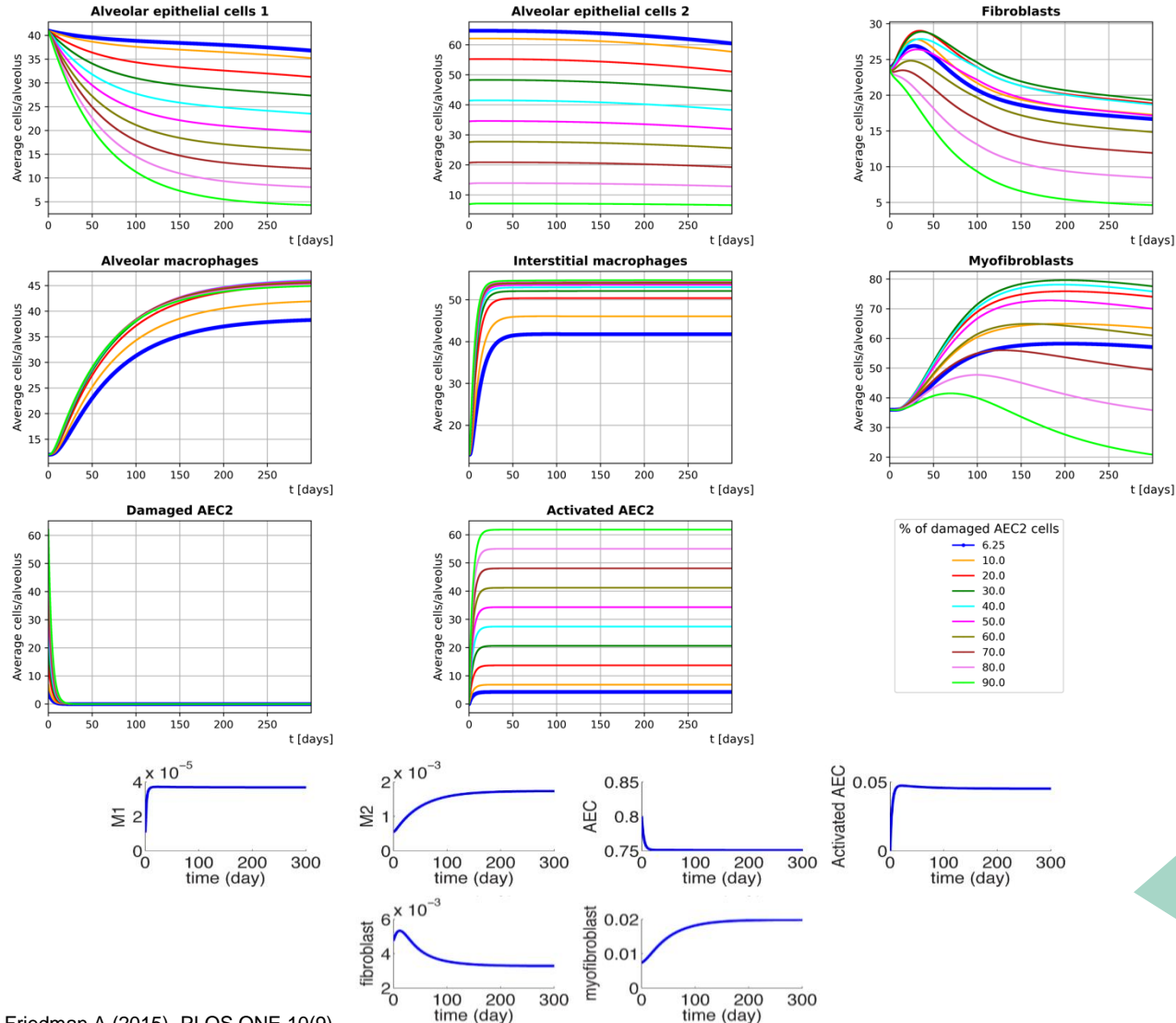


Figure from Hao W, Marsh C, Friedman A (2015), PLOS ONE 10(9)

Results: Onset of Pulmonary Fibrosis

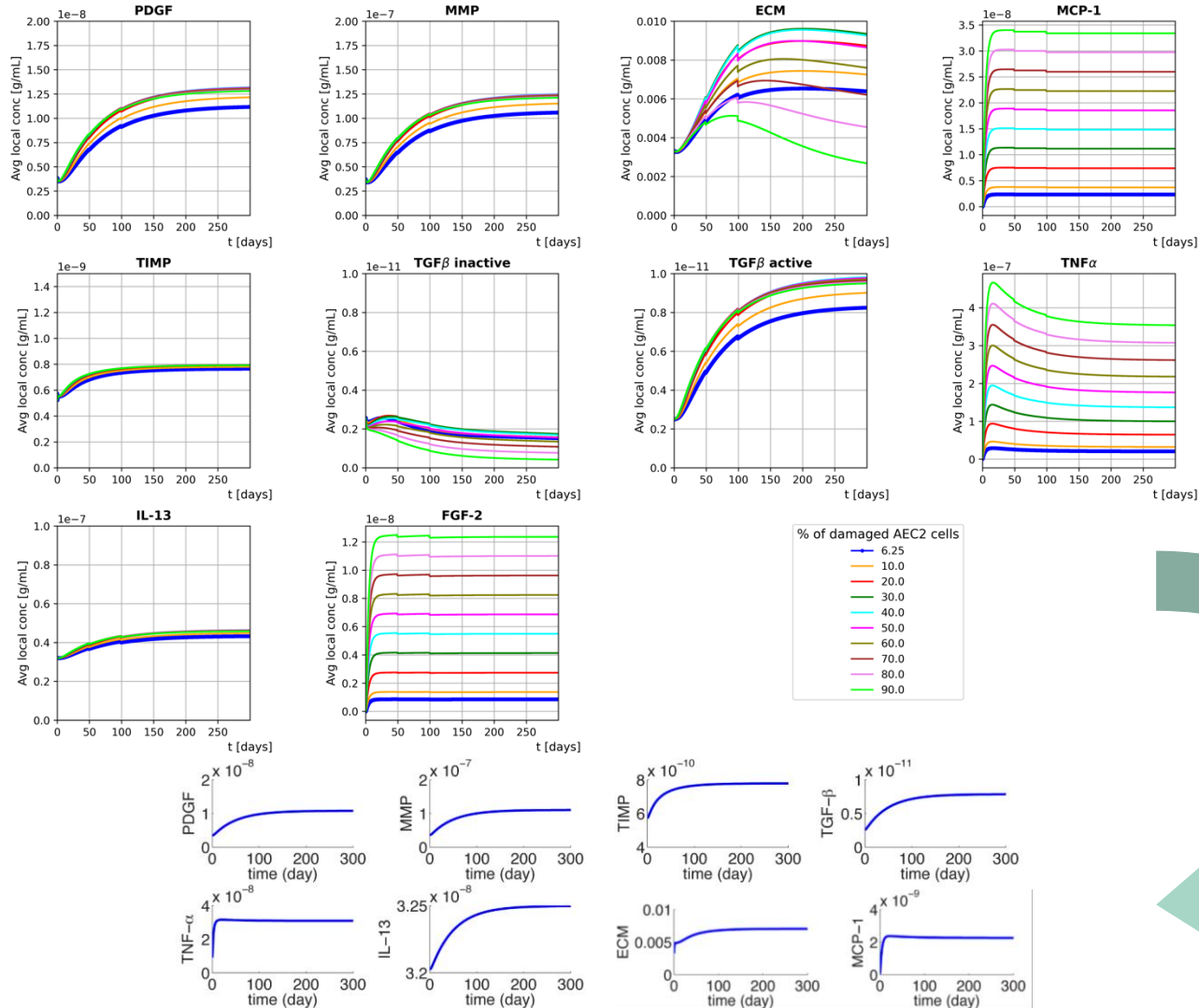


Figure from Hao W, Marsh C, Friedman A (2015), PLOS ONE 10(9)

Current state: *Simulating the onset of RILI*

Laboratory data

Simulation results (week 43)

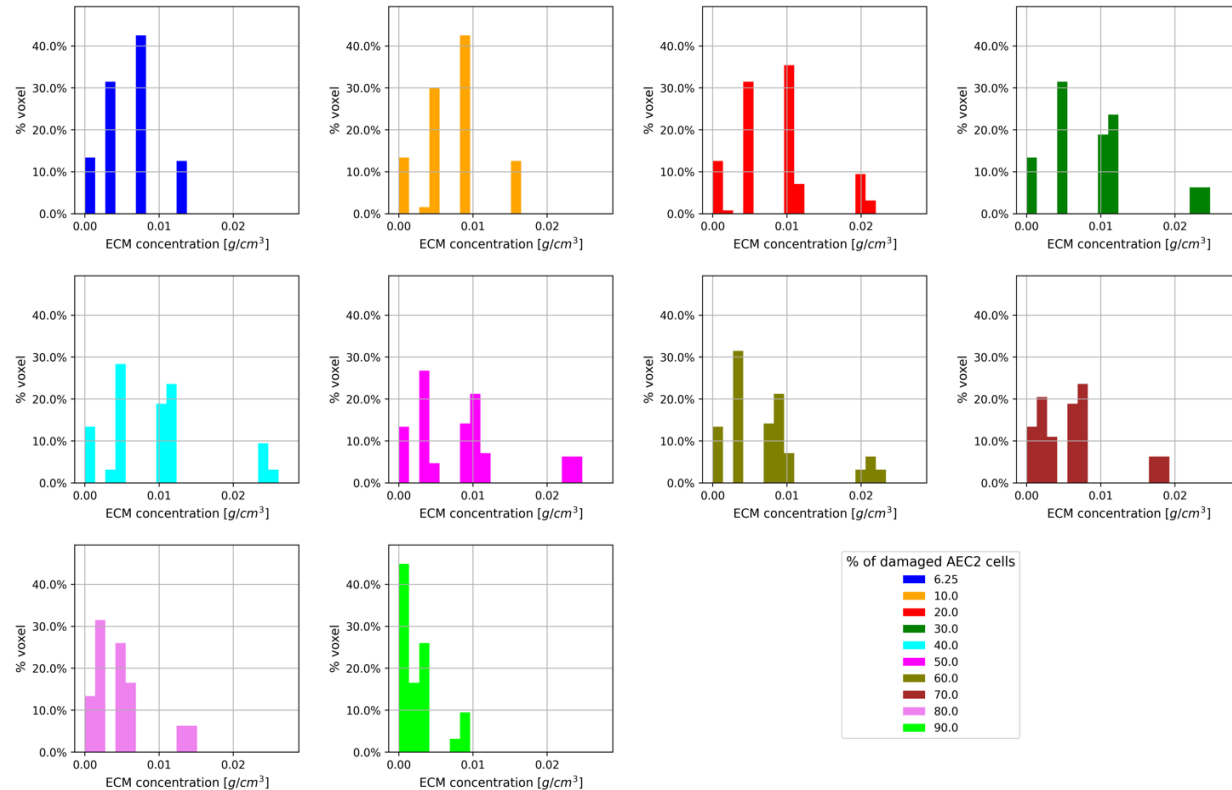
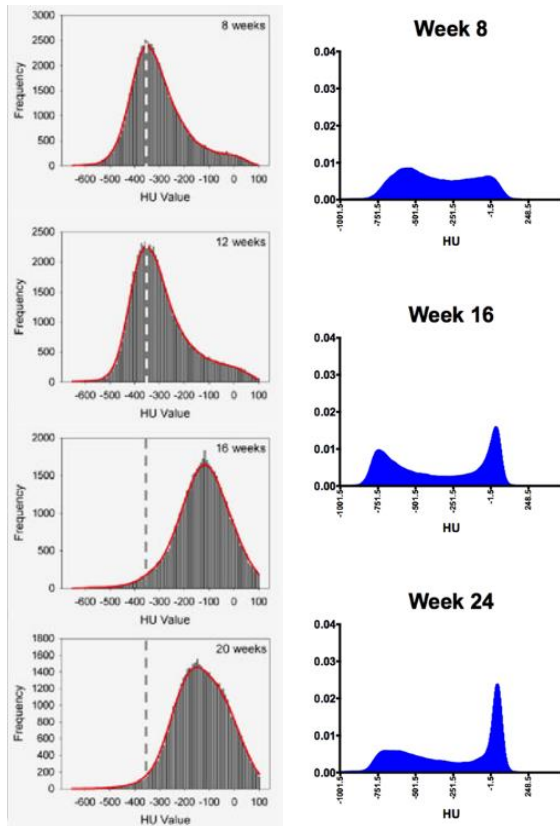


Figure from Zhou et al. (2019), International Journal of Cancer 144(12) and Perez et al. (2017), Scientific Reports 7(1)

Thank you for your attention!

Questions?