

19<sup>th</sup> November 2021

Workshop

BioDynaMo

# Agent-based modelling of radiation-induced lung fibrosis

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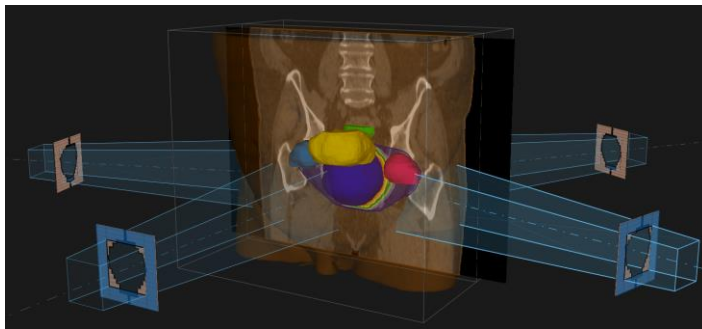
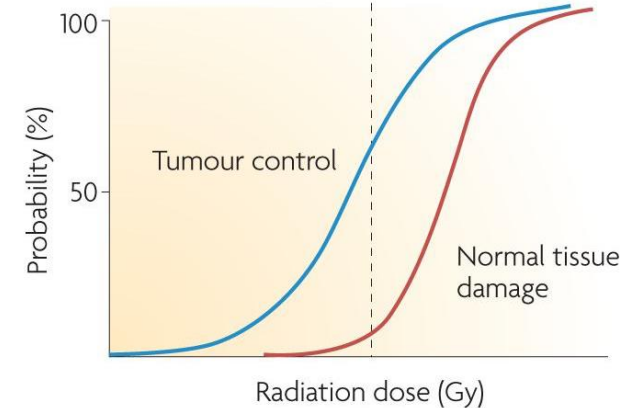


**BioDynaMo**  
BIOLOGY DYNAMICS MODELLER

# 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?

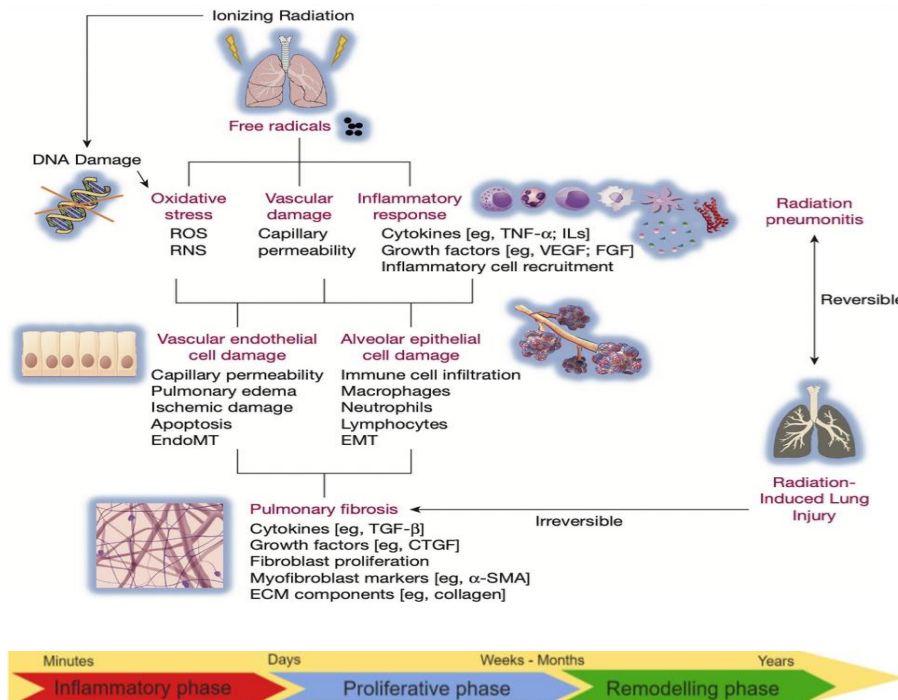
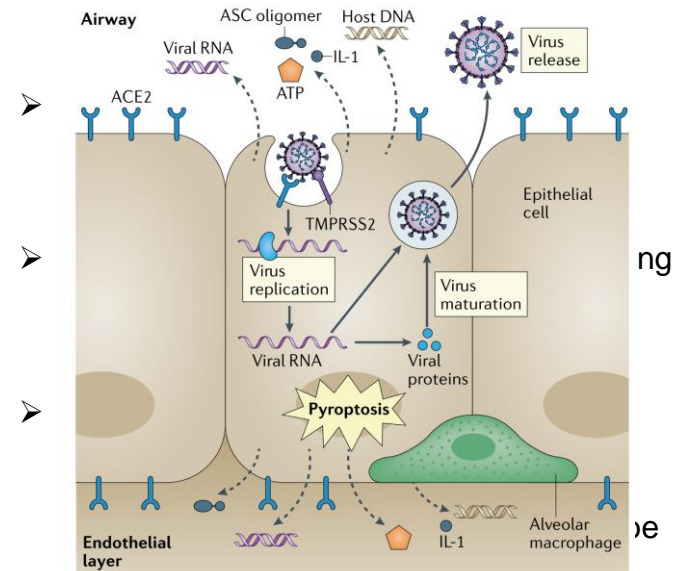


Figure from RECENT ADVANCES IN CHEST MEDICINE | VOLUME 156, ISSUE 1, P150-162, JULY 01, 2019

## 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**



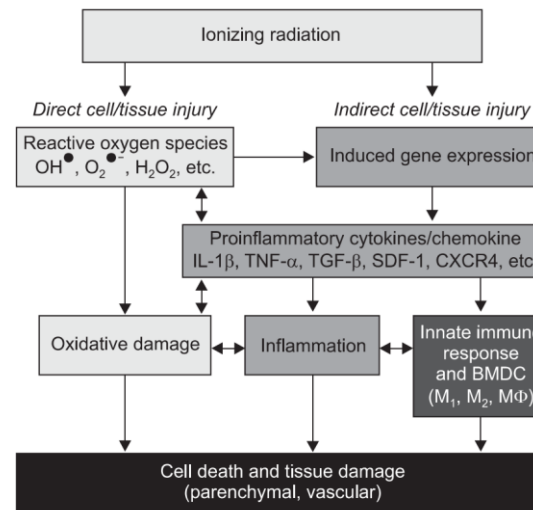
Math/Comp models can provide valuable insights useful for **tuning the RT parameters**

## LKB model (*Mohan*)

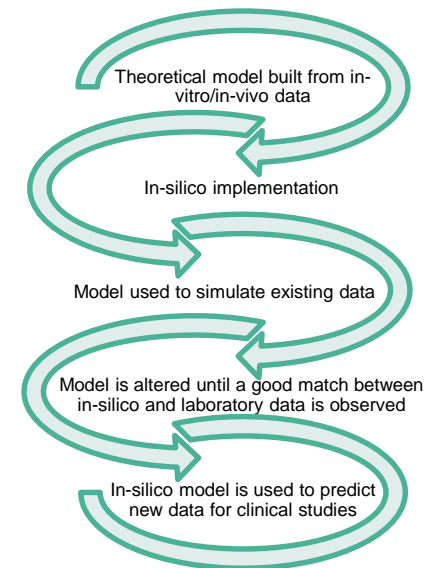
$$\text{NTCP}(d_{\text{eud}}|d_{50}, m) = \frac{1}{\sqrt{2\pi}} \int_{-\infty}^{(d_{\text{eud}}-d_{50})/(md_{50})} \exp\left(-\frac{x^2}{2}\right) dx$$

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

- $d_{\text{eud}}$  = 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

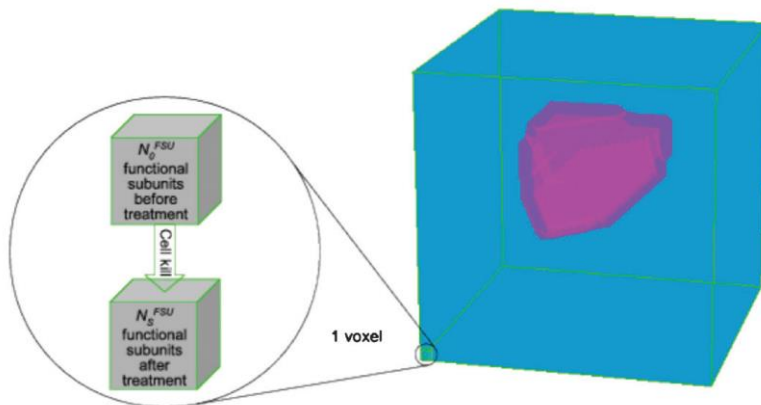


**Much more complex!**



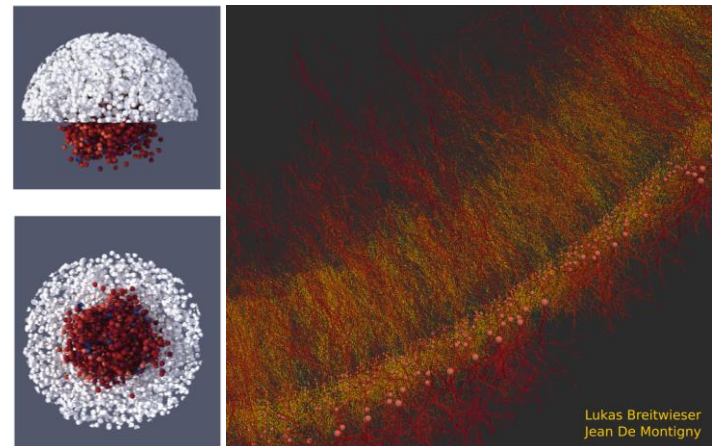
# Introduction: *Proposed approach*

## Example of current mechanistic approach



Lack of inflammation-induced tissue damage modelling

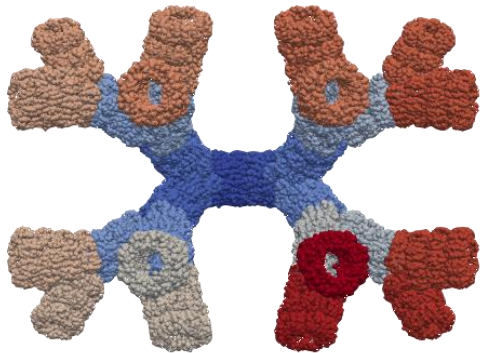
## Proposed agent-based approach



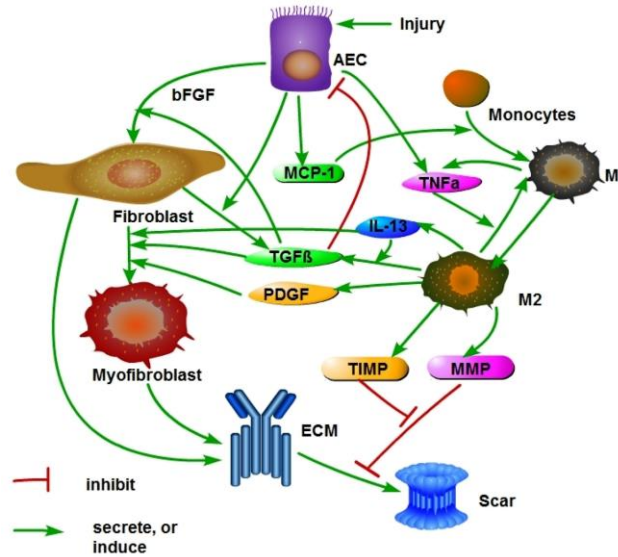
- Agent-based modelling
- User-defined agent behaviours (i.e. no centralization)
- Extensible platform (C++)
- Simulate biological dynamics
- Mechanical interactions between agents
- Substances diffusion

# Introduction: *Proposed approach*

Agents and simulation space



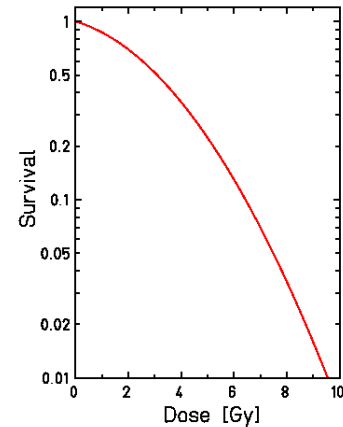
Behaviours



IPF ~ RILI (known onset causes)

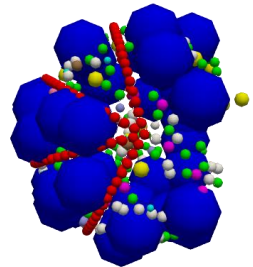
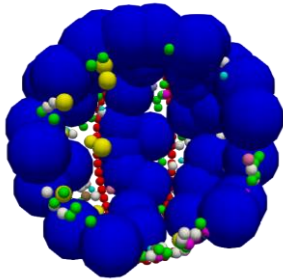
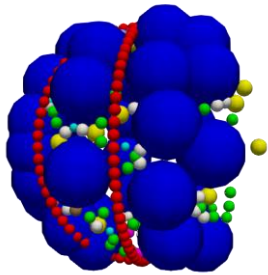
Mathematical model (differential equations) → Agent-based model (agents behaviours)

Damage

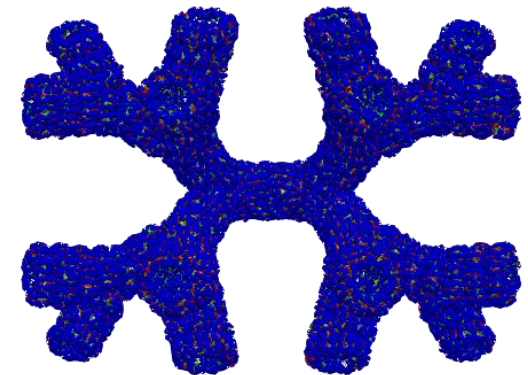
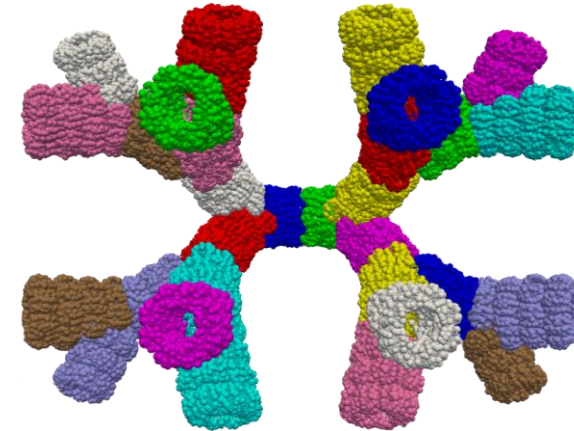
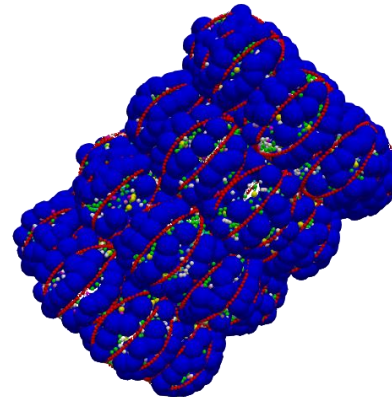
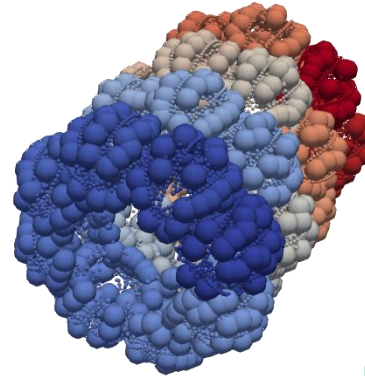


# Methods: Geometrical framework 1

- 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

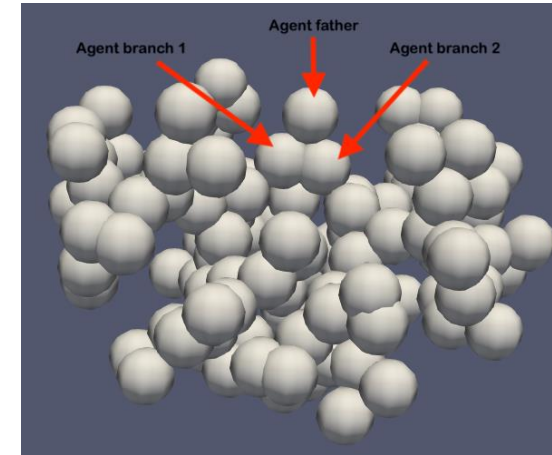
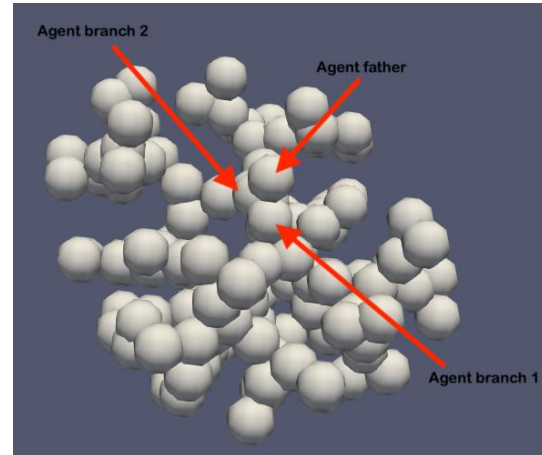
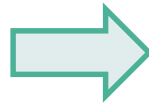
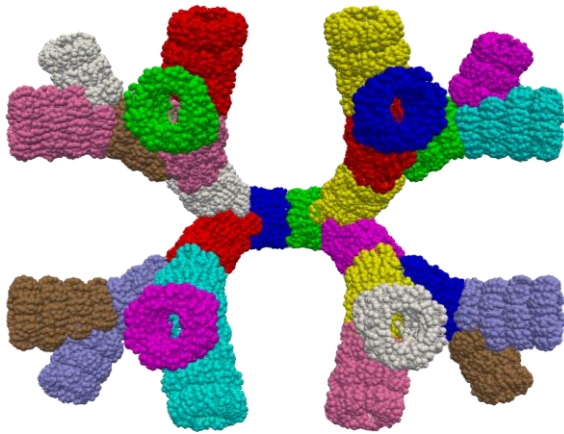


Alveoli

Alveolar Ducts

5-generations Acini

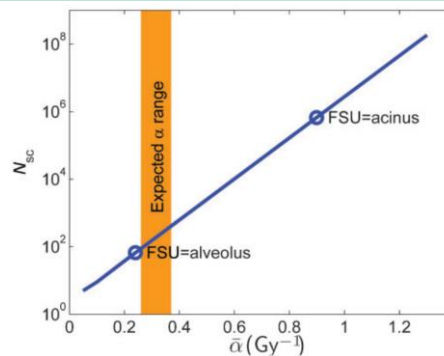
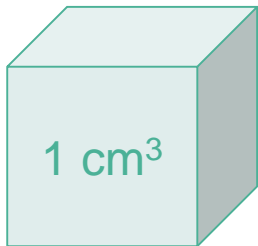
# Methods: Geometrical framework 2



Bigger portion of the lungs

Functional subunits

Multiple interacting substances

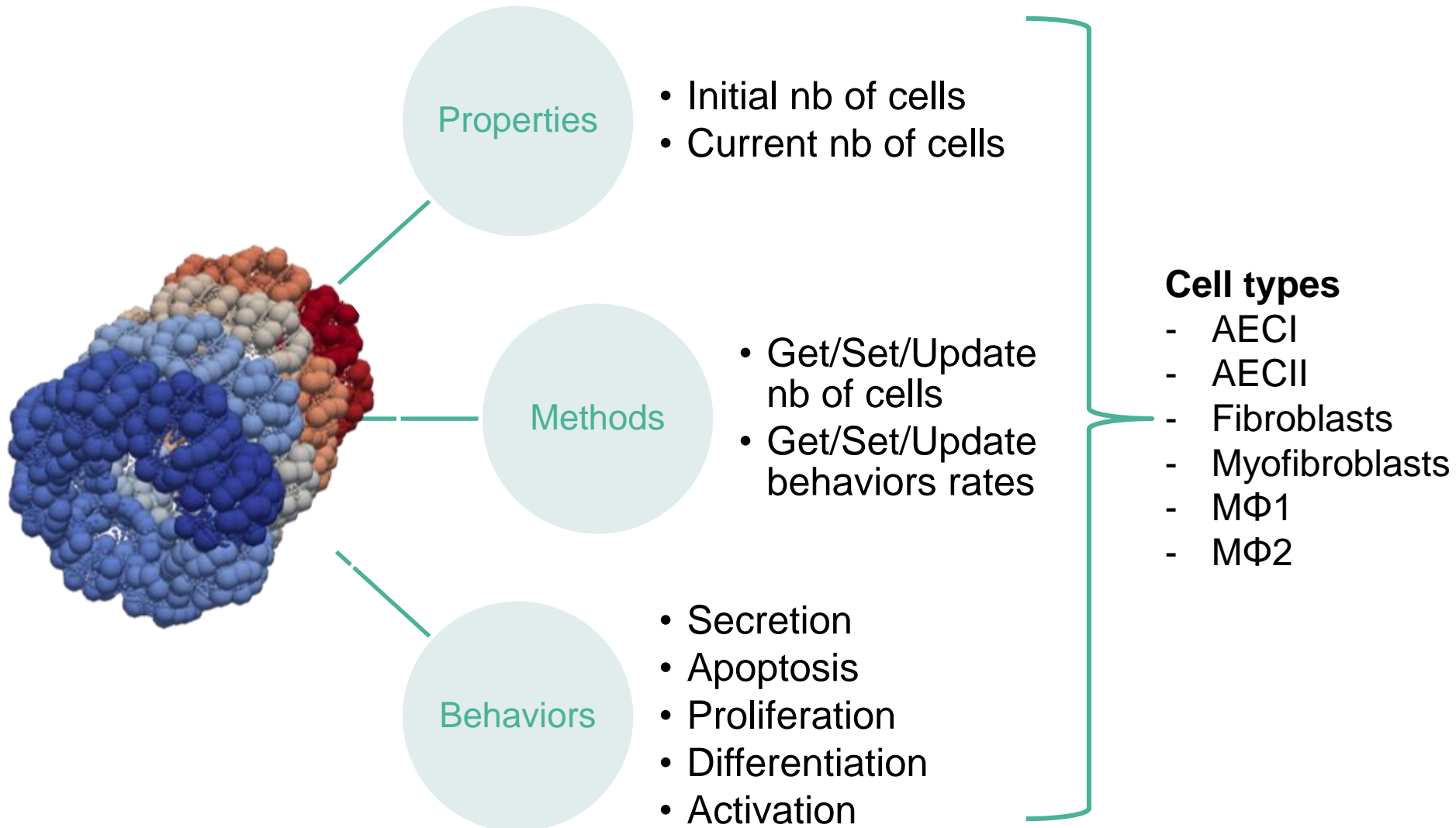


- TIMP
- ECM
- FGF2
- IL13
- PDGF
- TGFβ
- TNFα
- MMP
- MCP1

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



# Methods: *Behaviours*



# Goals

## Short-term: Reproduce laboratory data

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

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

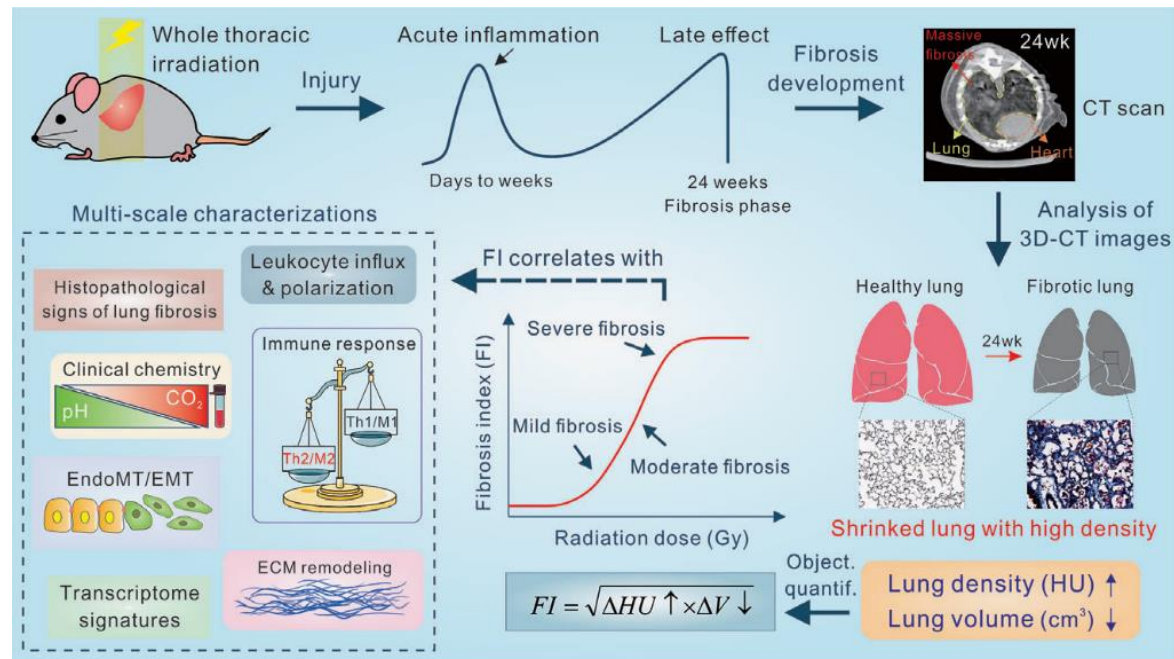
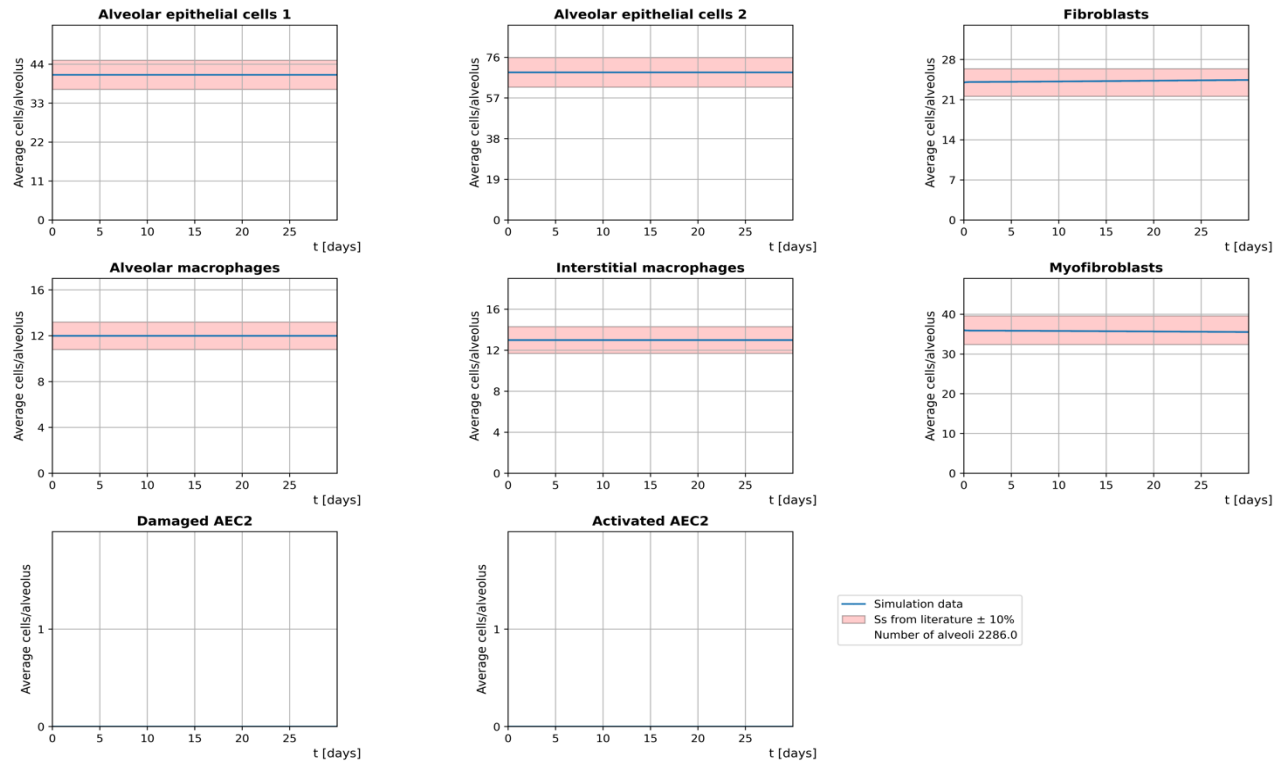


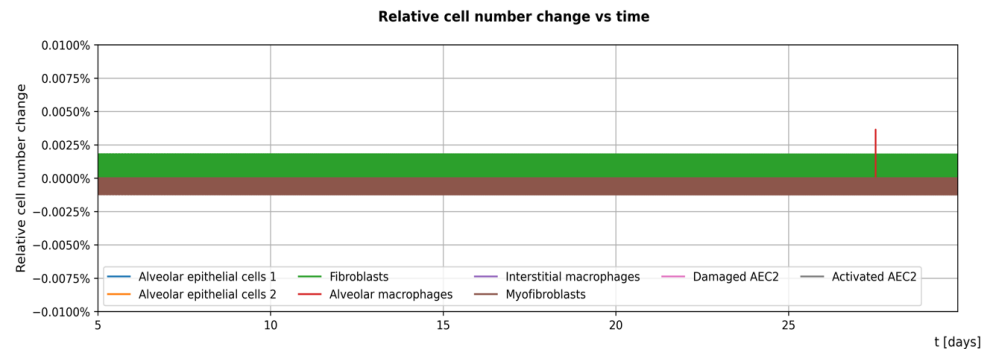
Figure from Zhou et al. (2019), International Journal of Cancer 144(12)

# Results: *Homeostasis*

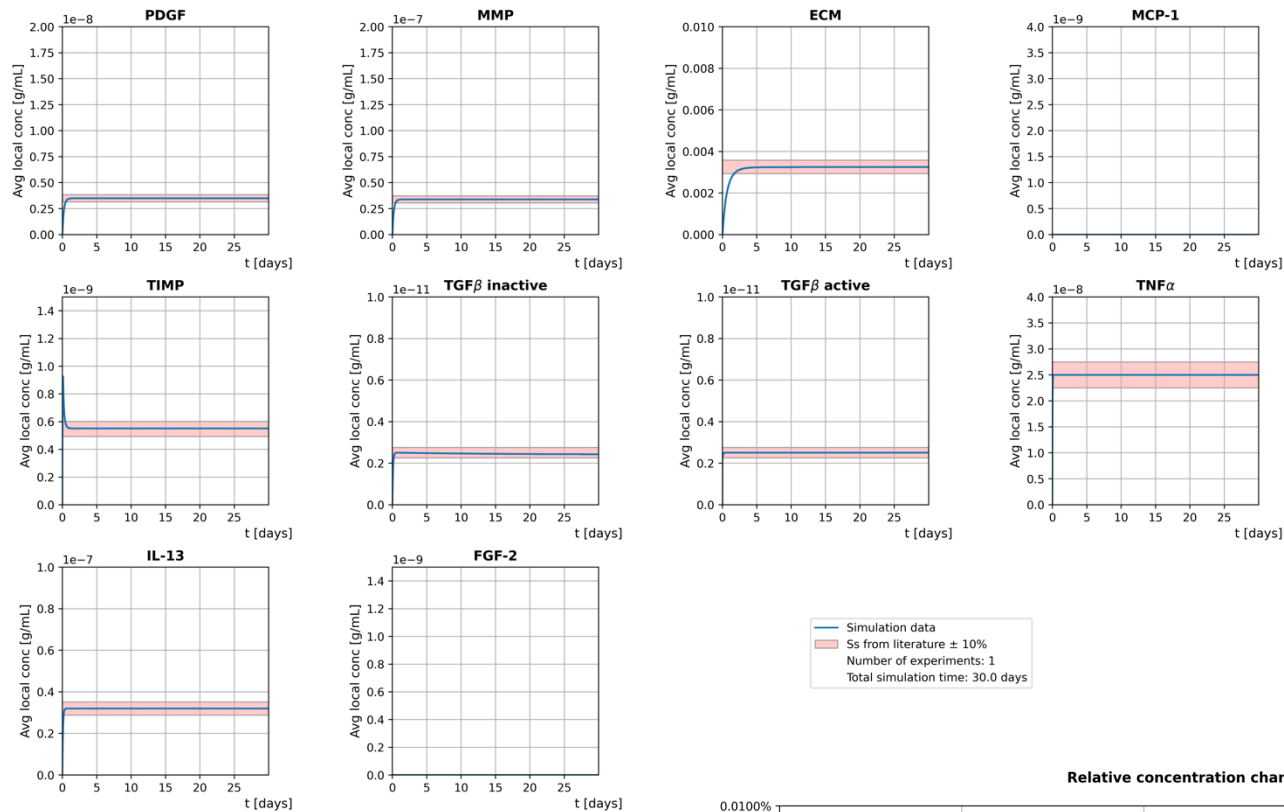


$$\Delta_m = \left( \frac{m(t+1) - m(t)}{m(t)} \right) * 100,$$

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

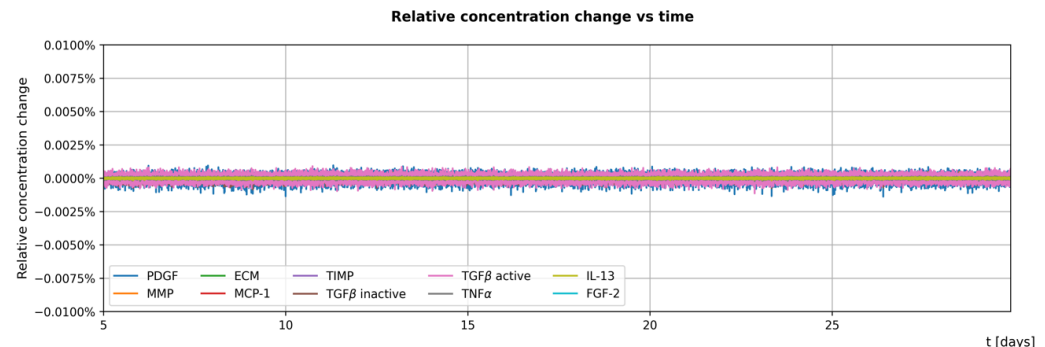


# Results: Homeostasis



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

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



# Results: Onset of Pulmonary Fibrosis

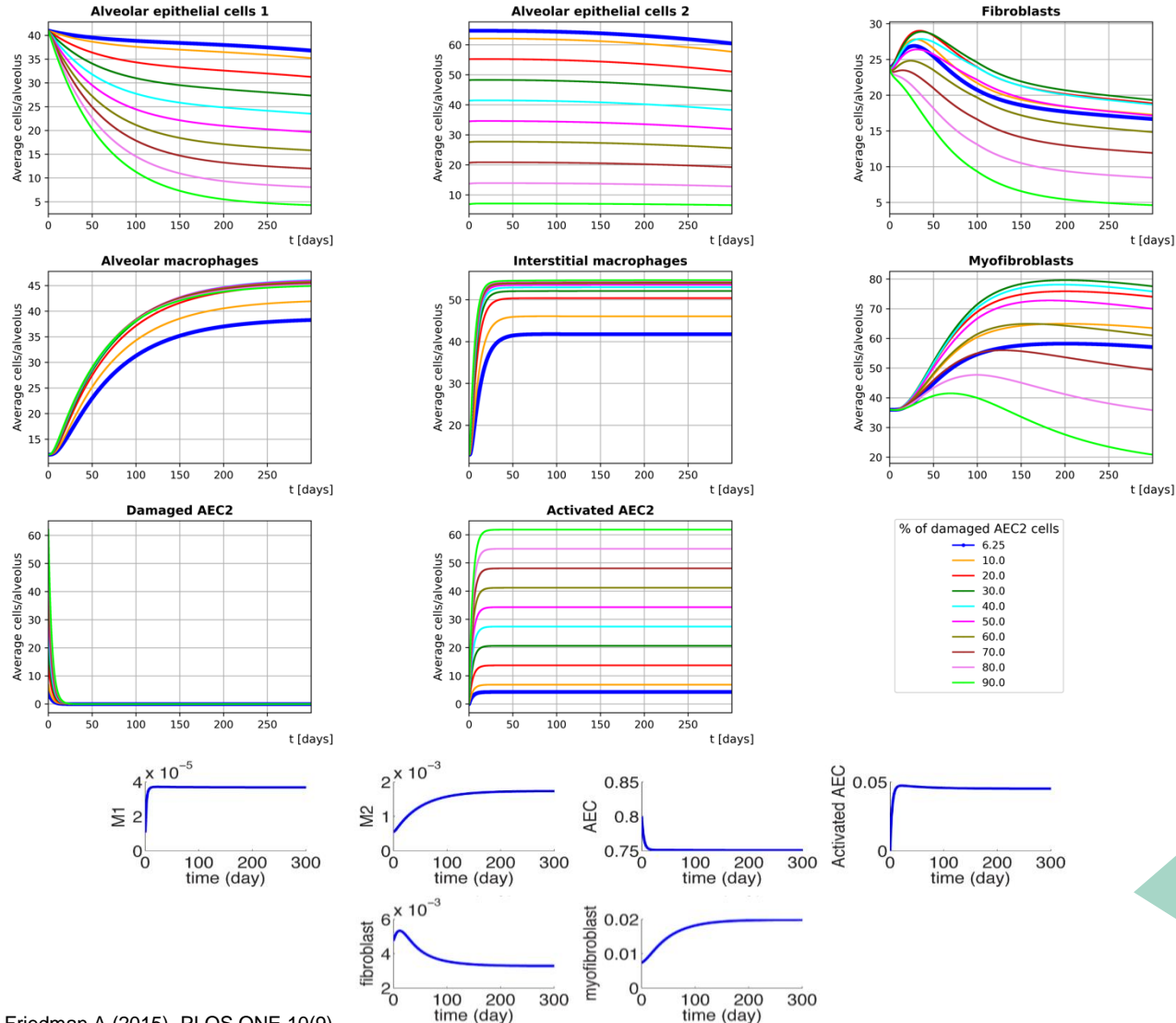


Figure from Hao W, Marsh C, Friedman A (2015), PLOS ONE 10(9)

# Results: Onset of Pulmonary Fibrosis

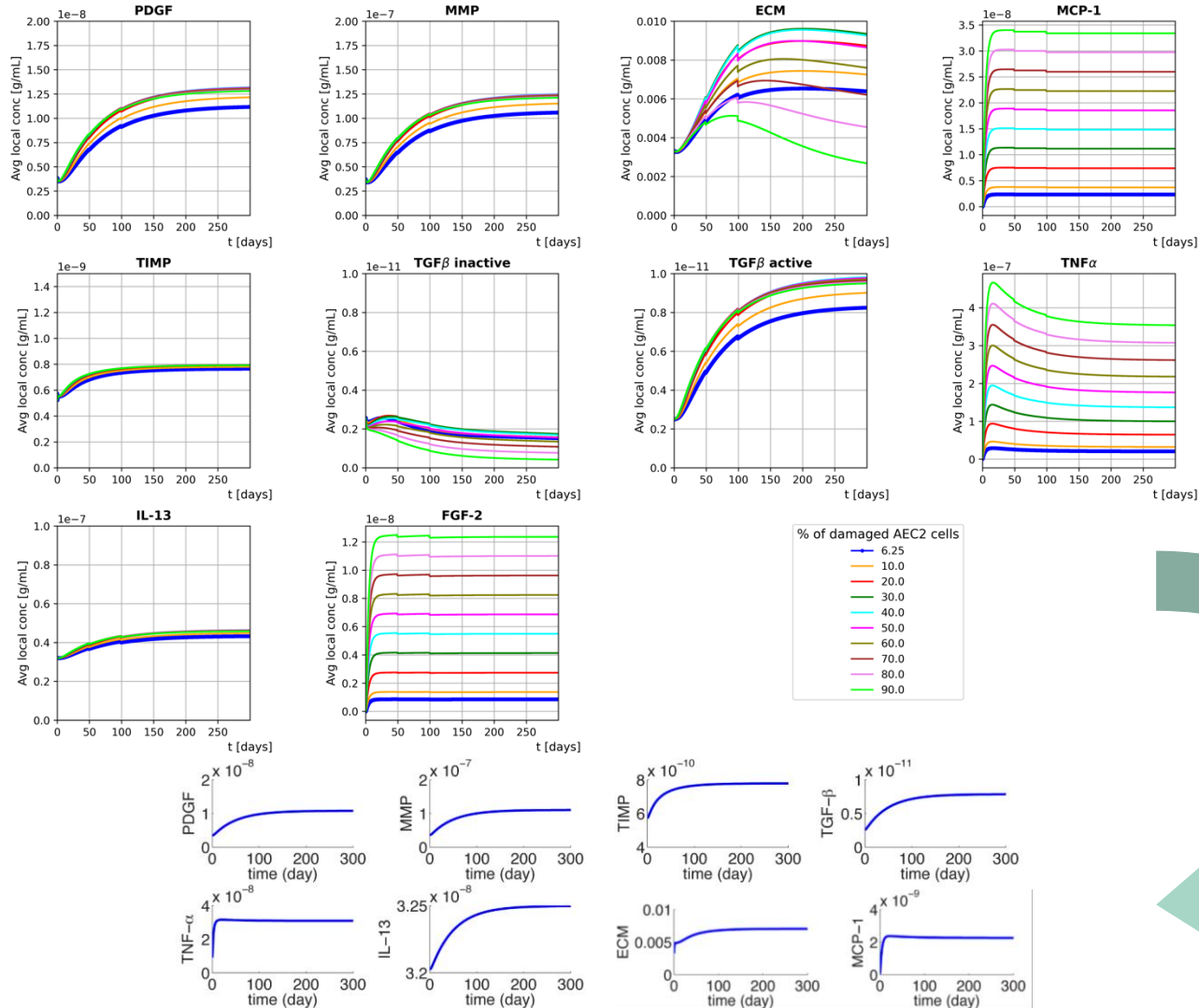


Figure from Hao W, Marsh C, Friedman A (2015), PLOS ONE 10(9)

# Current state: *Simulating the onset of RILI*

## Laboratory data

## Simulation results (week 43)

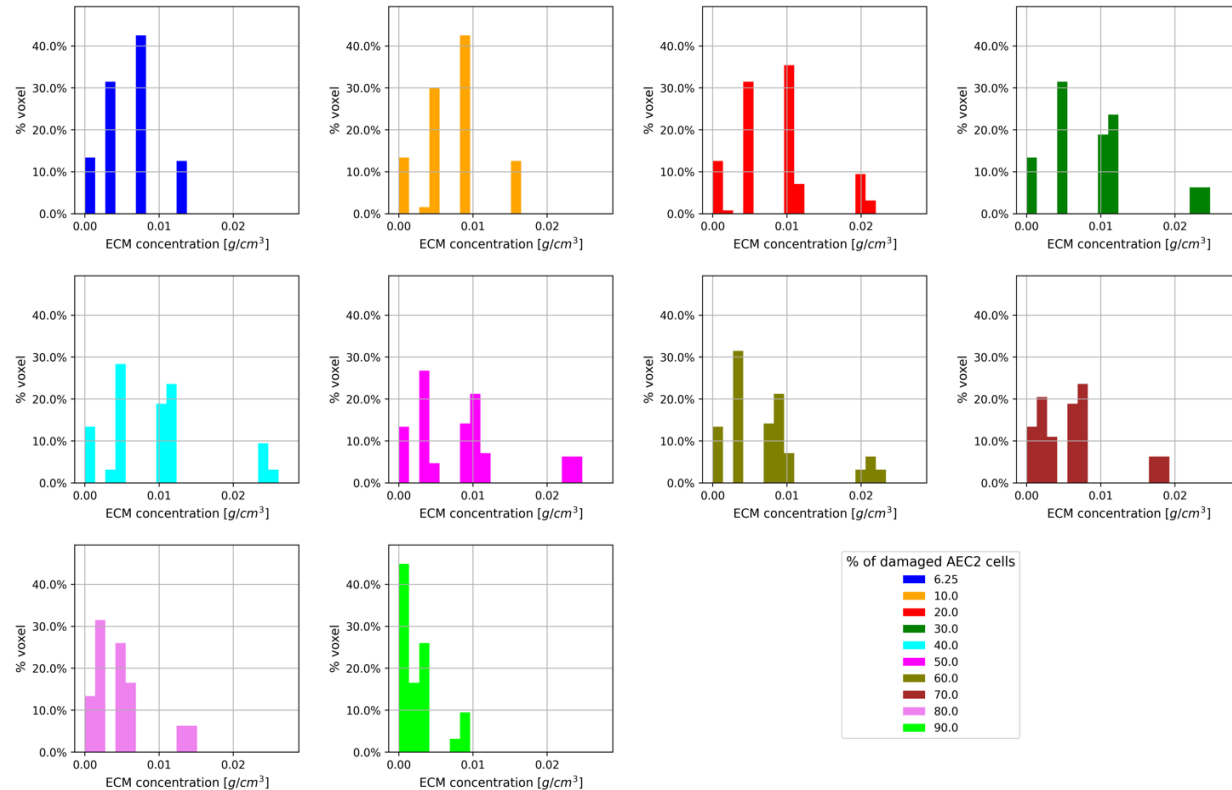
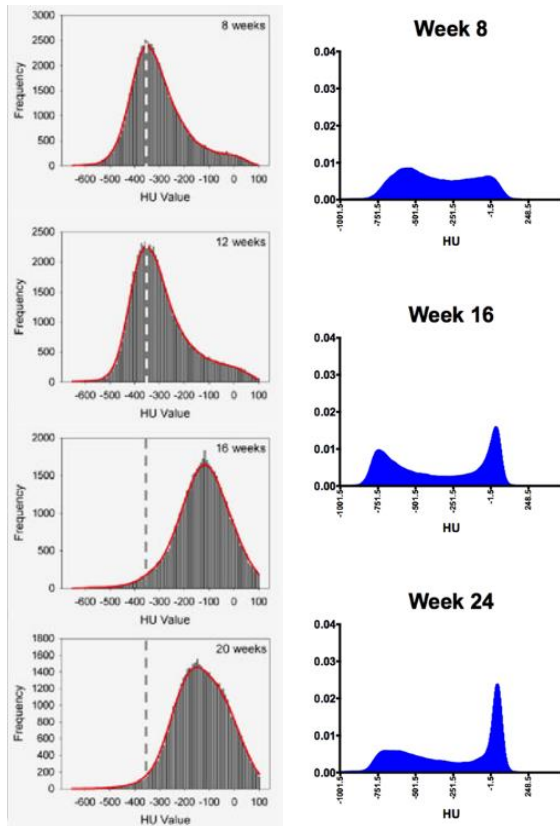


Figure from Zhou et al. (2019), International Journal of Cancer 144(12) and Perez et al. (2017), Scientific Reports 7(1)

# Thank you for your attention!

Questions?