19th November 2021

Workshop

BioDynaMo

# Agent-based modelling of radiation-induced lung fibrosis

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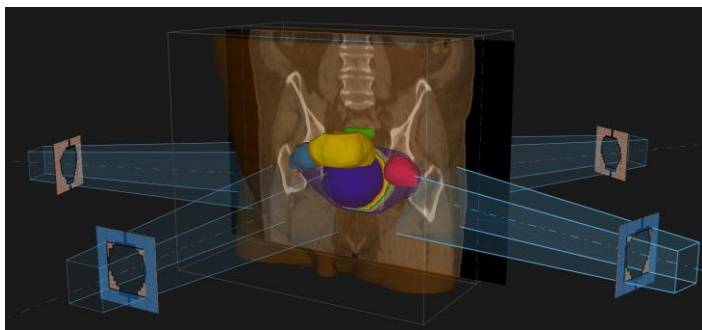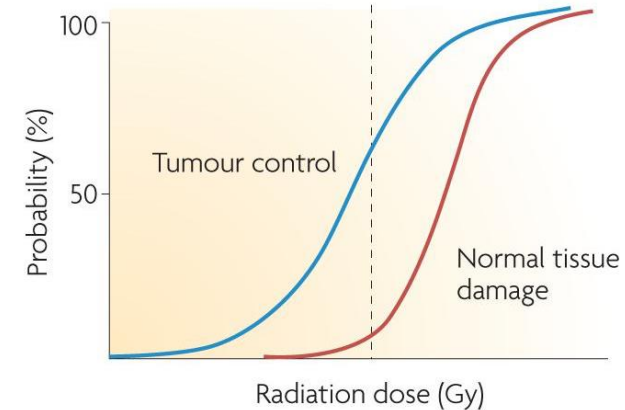
Involves the use of **ionizing radiation** (such as photon beams, ions, charged and uncharged particles) as a tool **to sterilize cancers**

**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?
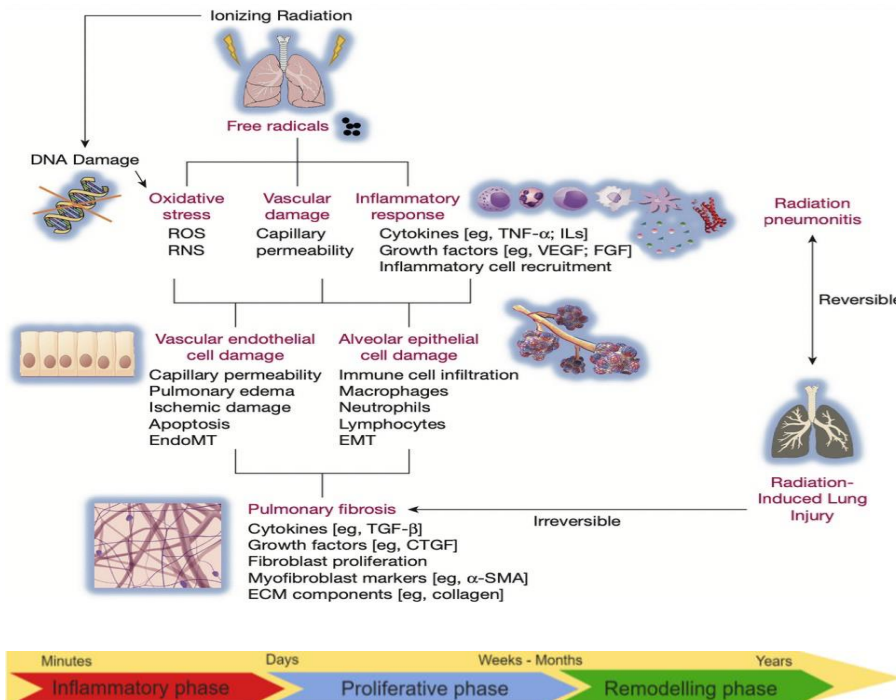


Figure from RECENT ADVANCES IN CHEST MEDICINE | VOLUME 156, ISSUE 1, P150-162, JULY 01, 2019

## Why?



➢ 

➢ ...ng

➢ 

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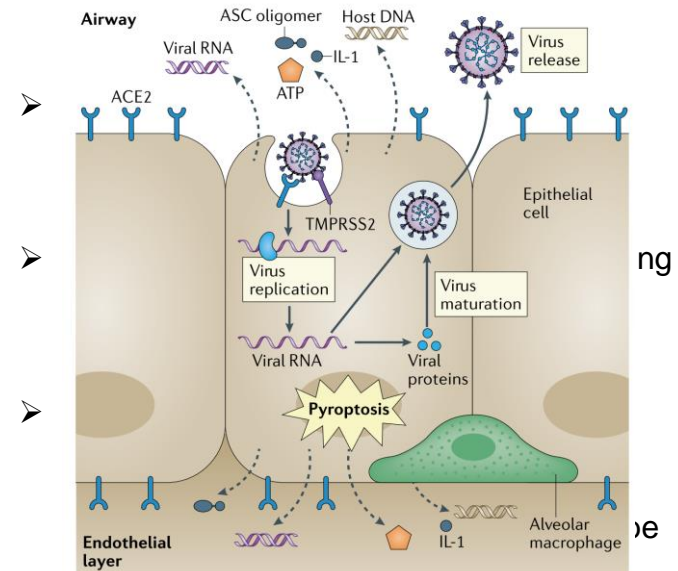
➢ a RILI model could be tailored to a COVID-19 (coronavirus SARS-CoV-2) disease progression model*.

*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

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**
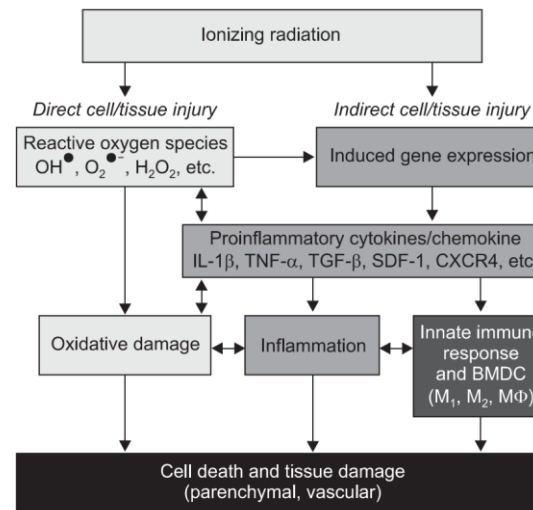
Math/Comp models can provide valuable insights useful for **tuning the RT parameters**
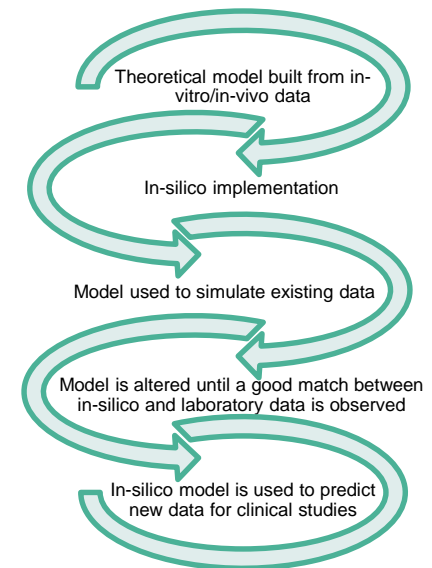
## LKB model (*Mohan*)

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

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

- $d_{eud}$ = 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
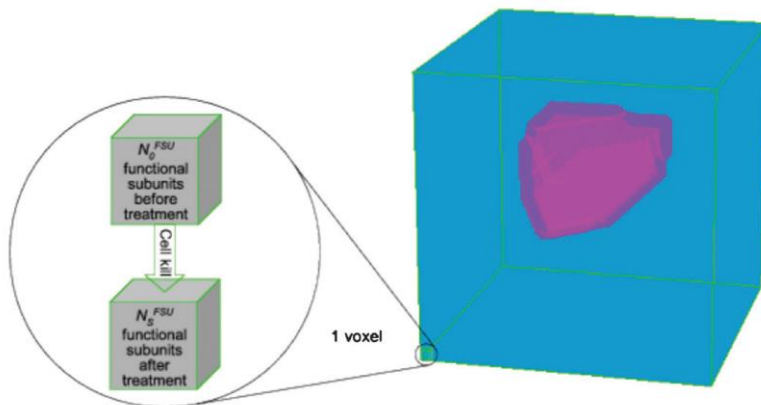- $m$ = ramp parameter



Ionizing radiation

*Direct cell/tissue injury* — *Indirect cell/tissue injury*

Reactive oxygen species OH•, O$_2$•⁻, H$_2$O$_2$, etc. → Induced gene expression

Proinflammatory cytokines/chemokine IL-1β, TNF-α, TGF-β, SDF-1, CXCR4, etc.

Oxidative damage — Inflammation — Innate immune response and BMDC (M$_1$, M$_2$, MΦ)

Cell death and tissue damage (parenchymal, vascular)

## Much more complex!



Theoretical model built from in-vitro/in-vivo data

In-silico implementation

Model used to simulate existing data

Model is altered until a good match between in-silico and laboratory data is observed

In-silico model is used to predict new data for clinical studies

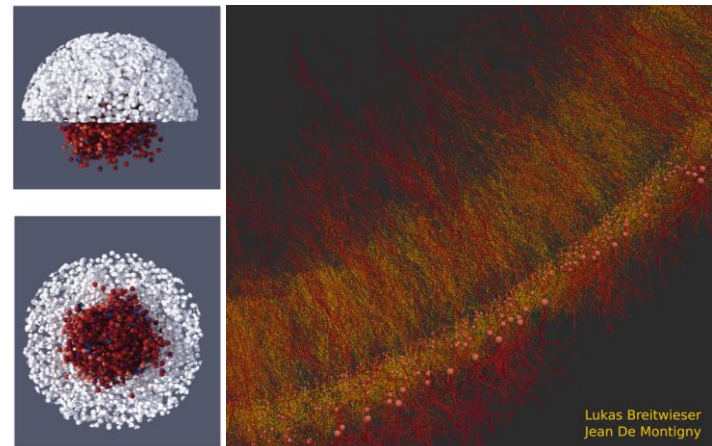Figures from Radiat Oncol J. 2014 Sep; 32(3): 103–115

# Introduction: *Proposed approach*

## Example of current mechanistic approach

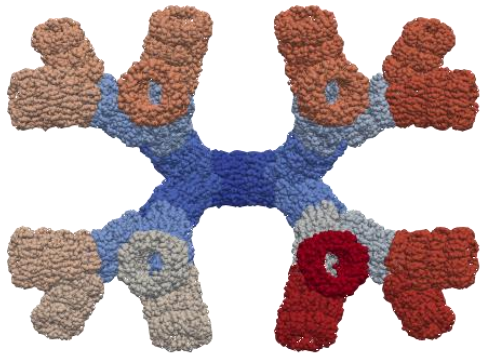**Lack of inflammation-induced tissue damage modelling**
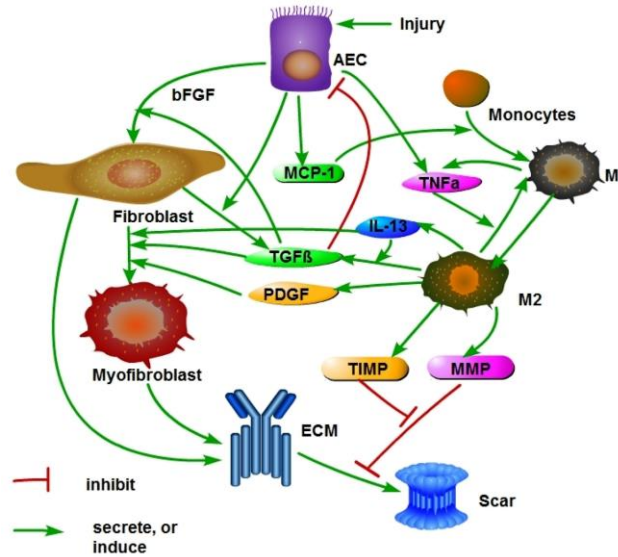
## Proposed agent-based approach

- ➢ 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

## Agents and simulation space

## Behaviours

## Damage



**IPF ~ RILI** (known onset causes)

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

Dose → Survival → AECII activation

**Input data**

Figure from Hao W, Marsh C, Friedman A (2015), PLOS ONE 10(9)
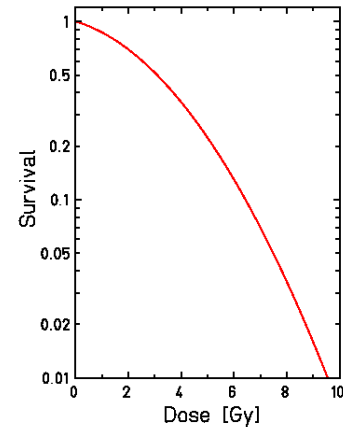
# Methods: *Geometrical framework 1*

➢ Hollow ¾ Sphere, ~ 200um diameter
➢ ~ 480'000'000 in human lungs
➢ More than 10 different cell types
➢ ~ 300 cells per alveolus in the model
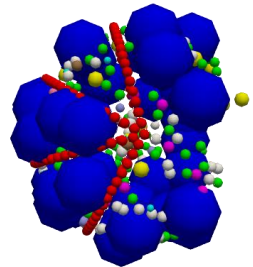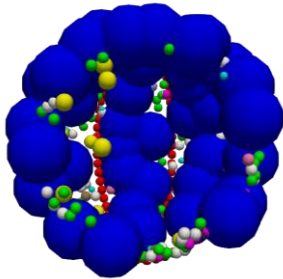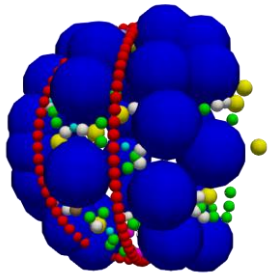
**Fibroblasts**
**Epithelial cells**
**AEC2s**
**AEC1s**
**Alveolar macrophages**
**Pericytes**
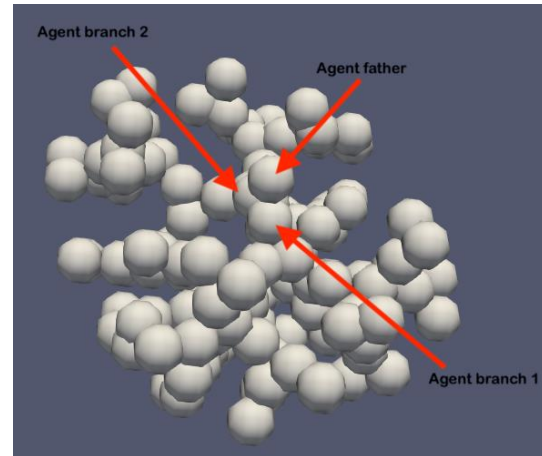**Interstitial macrophages**
**Lymphocytes**
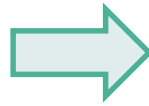**Plasma cells**
**Mast cells**
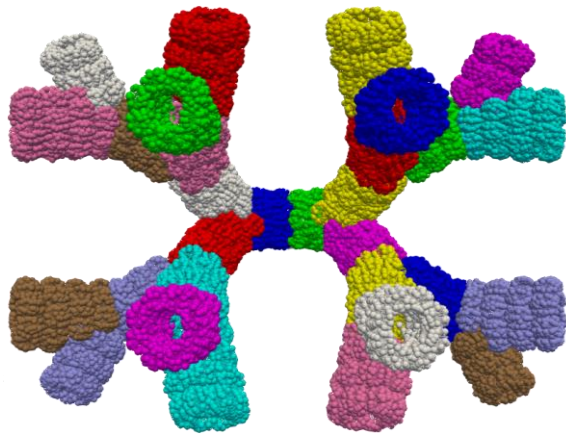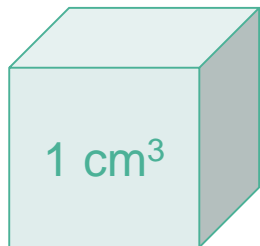
Cell type
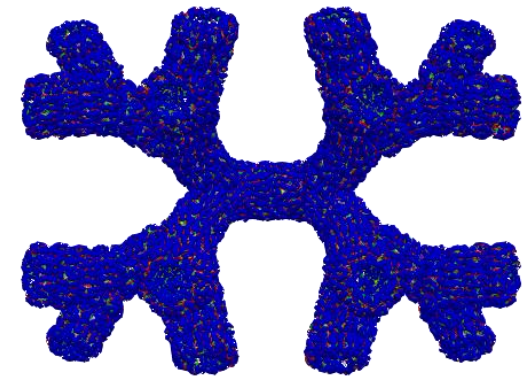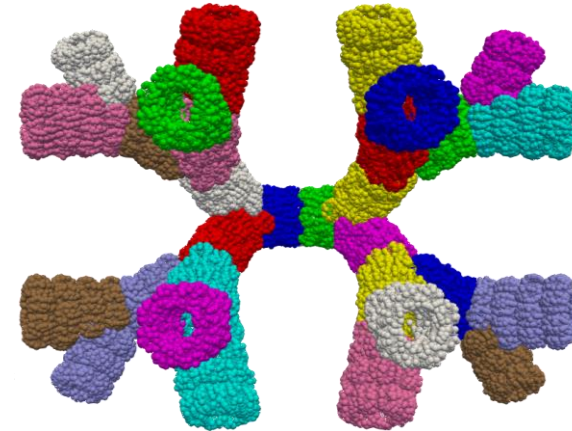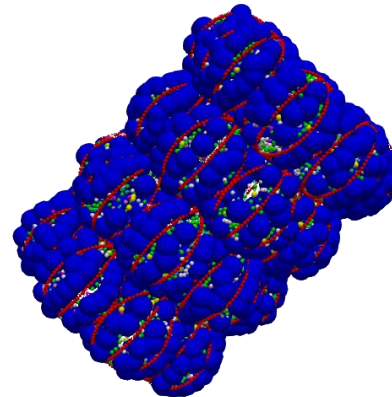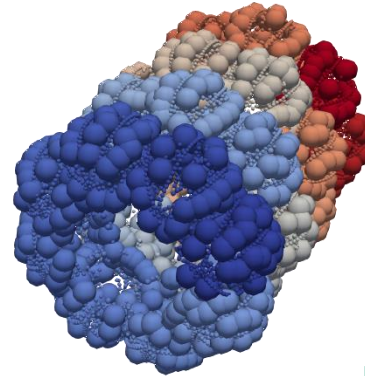
**Alveoli**

**Alveolar Ducts**

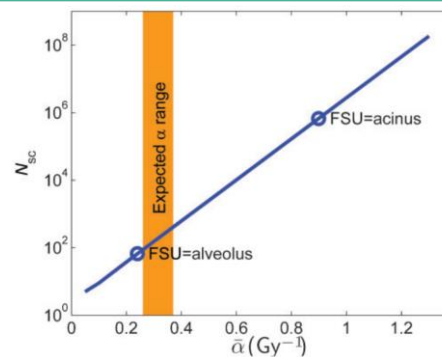**5-generations Acini**

# Methods: *Geometrical framework 2*
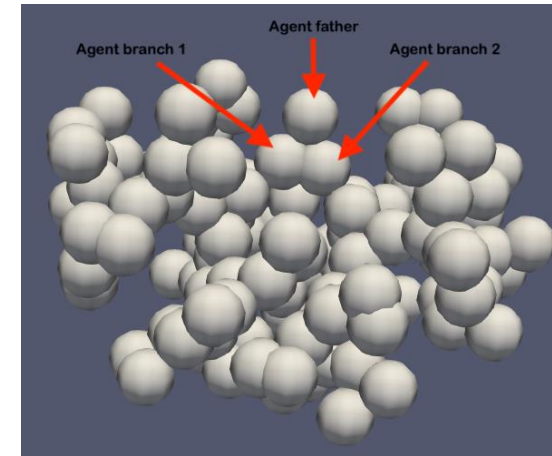






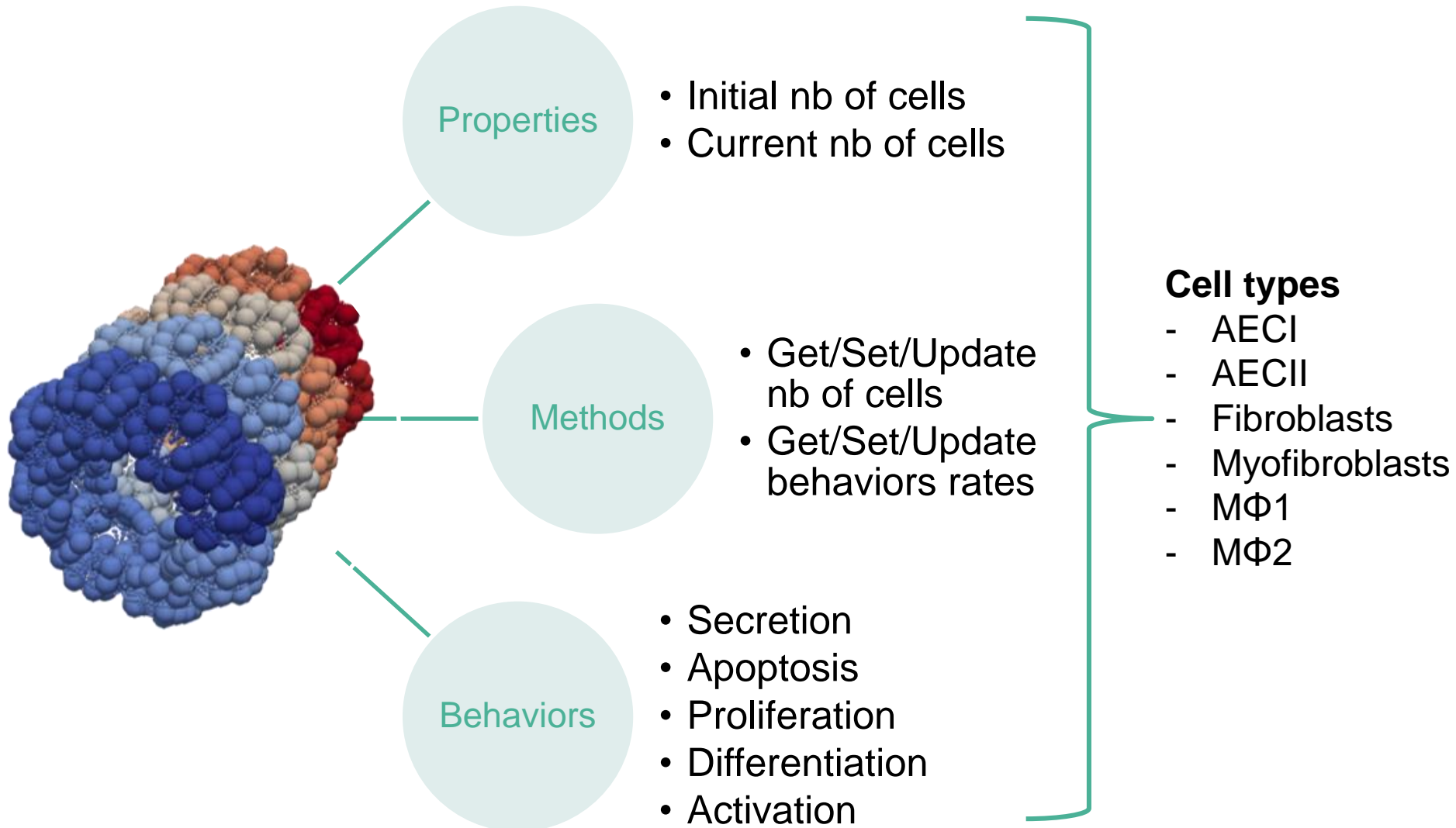Bigger portion of the lungs

Functional subunits

Multiple interacting substances

$1\ cm^3$



- TIMP
- ECM
- FGF2
- IL13
- PDGF

- TGFß
- TNF$\alpha$
- 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

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

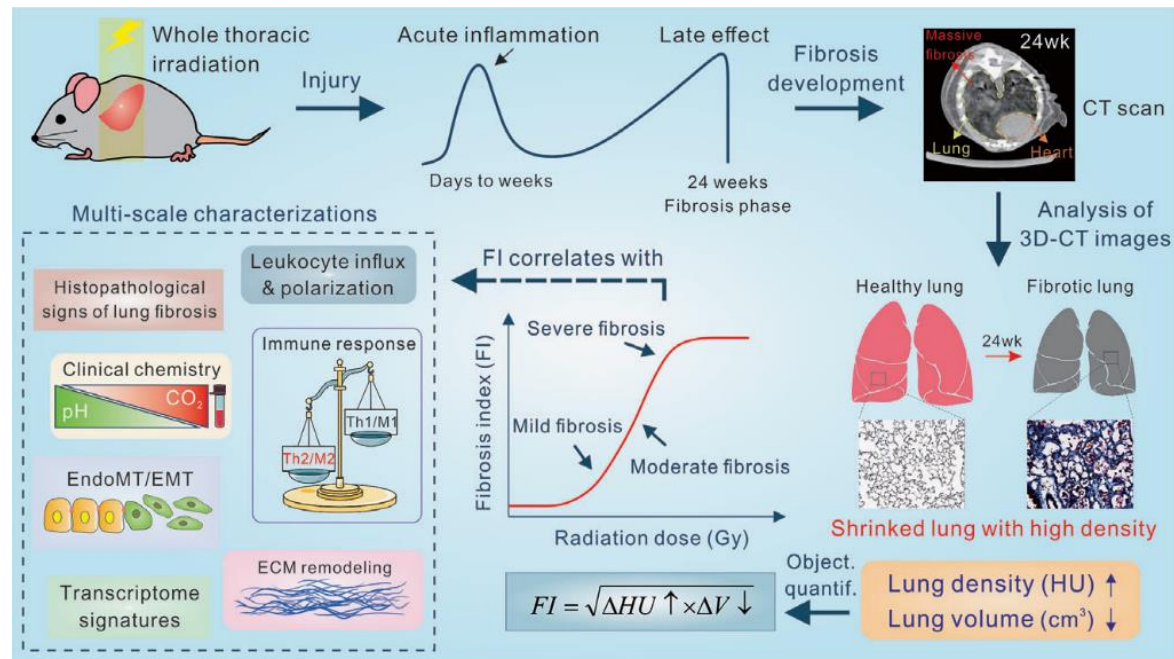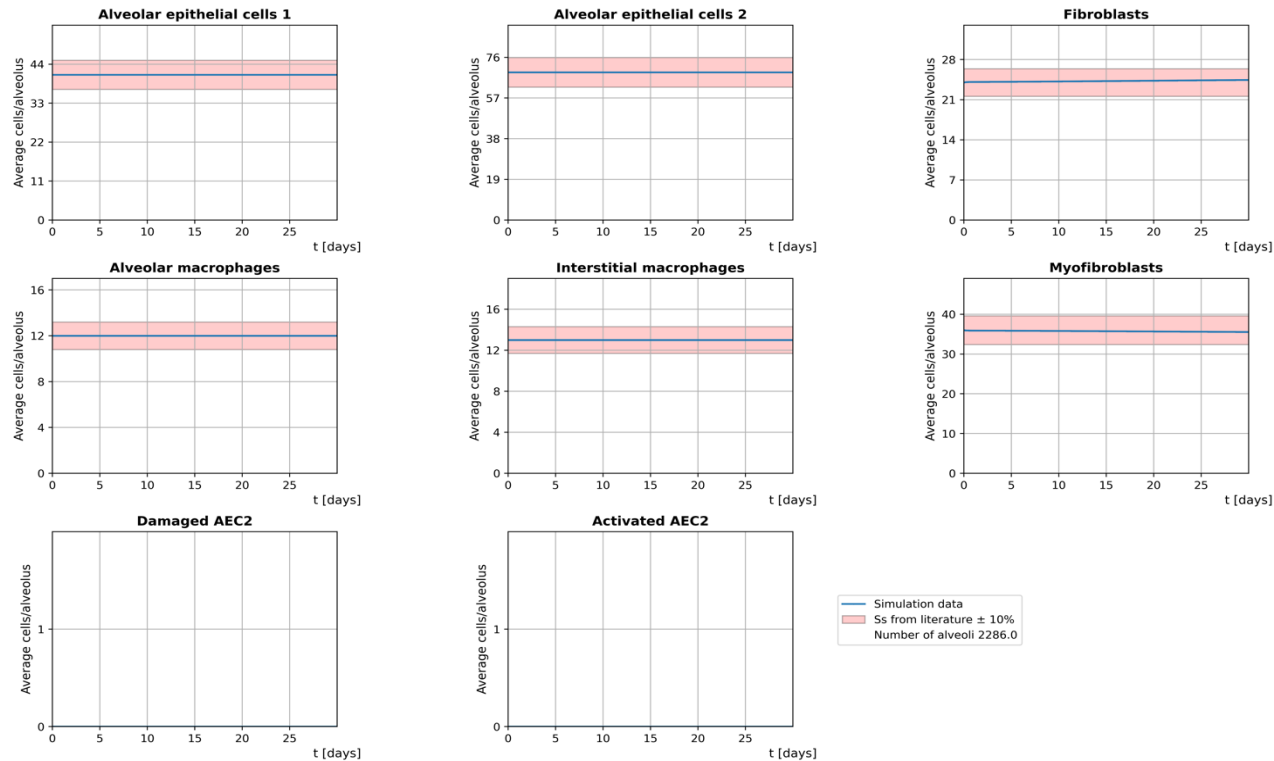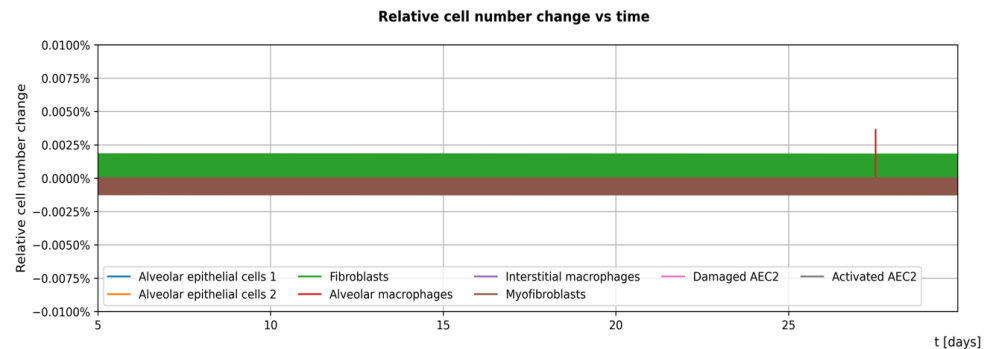$$FI(D) = \frac{1}{2}A\left\{1 - \text{erf}\left(\sqrt{\pi}\gamma\left(1 - \frac{D}{ED_{50}}\right)\right)\right\}$$



Figure from Zhou et al. (2019), International Journal of Cancer 144(12)
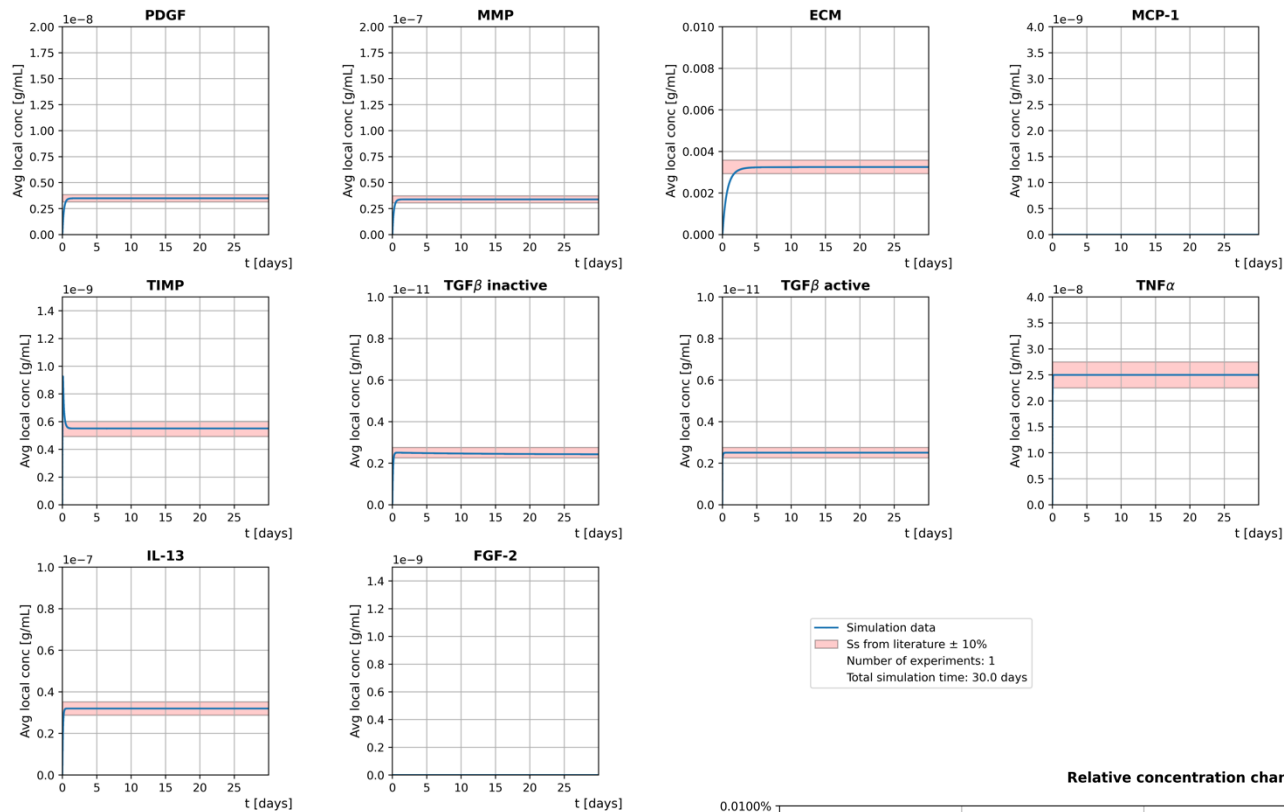
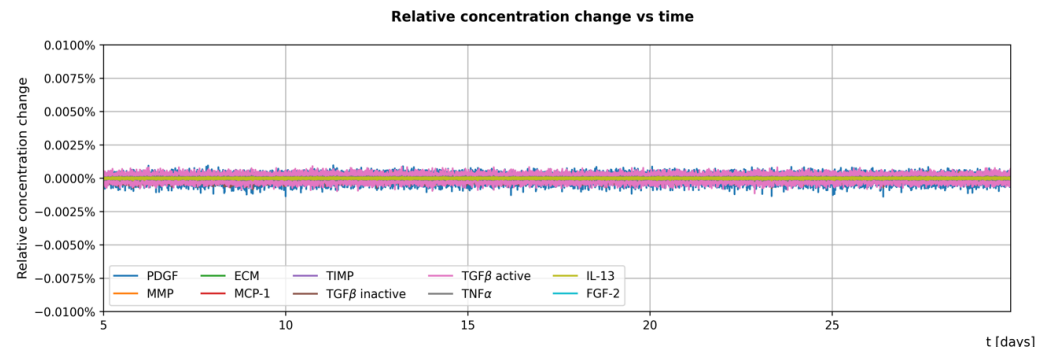$$\Delta_m = \left( \frac{m\,(t+1) - m\,(t)}{m\,(t)} \right) * 100,$$
$$m \in \{sub\,conc, cell\,\#\}$$

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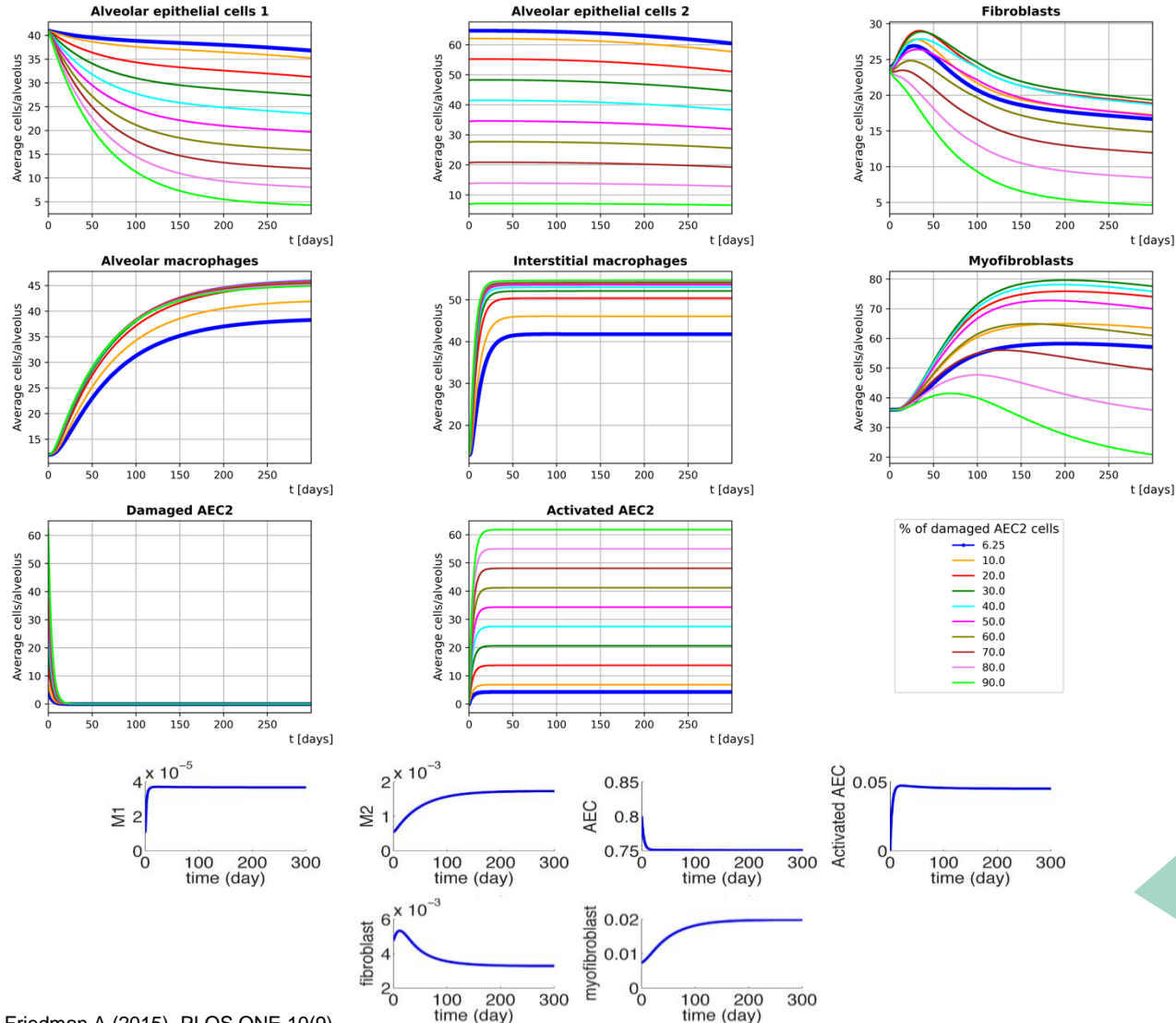$$m \in \{sub\ conc, cell\ \#\}$$

# Results: *Onset of Pulmonary Fibrosis*



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

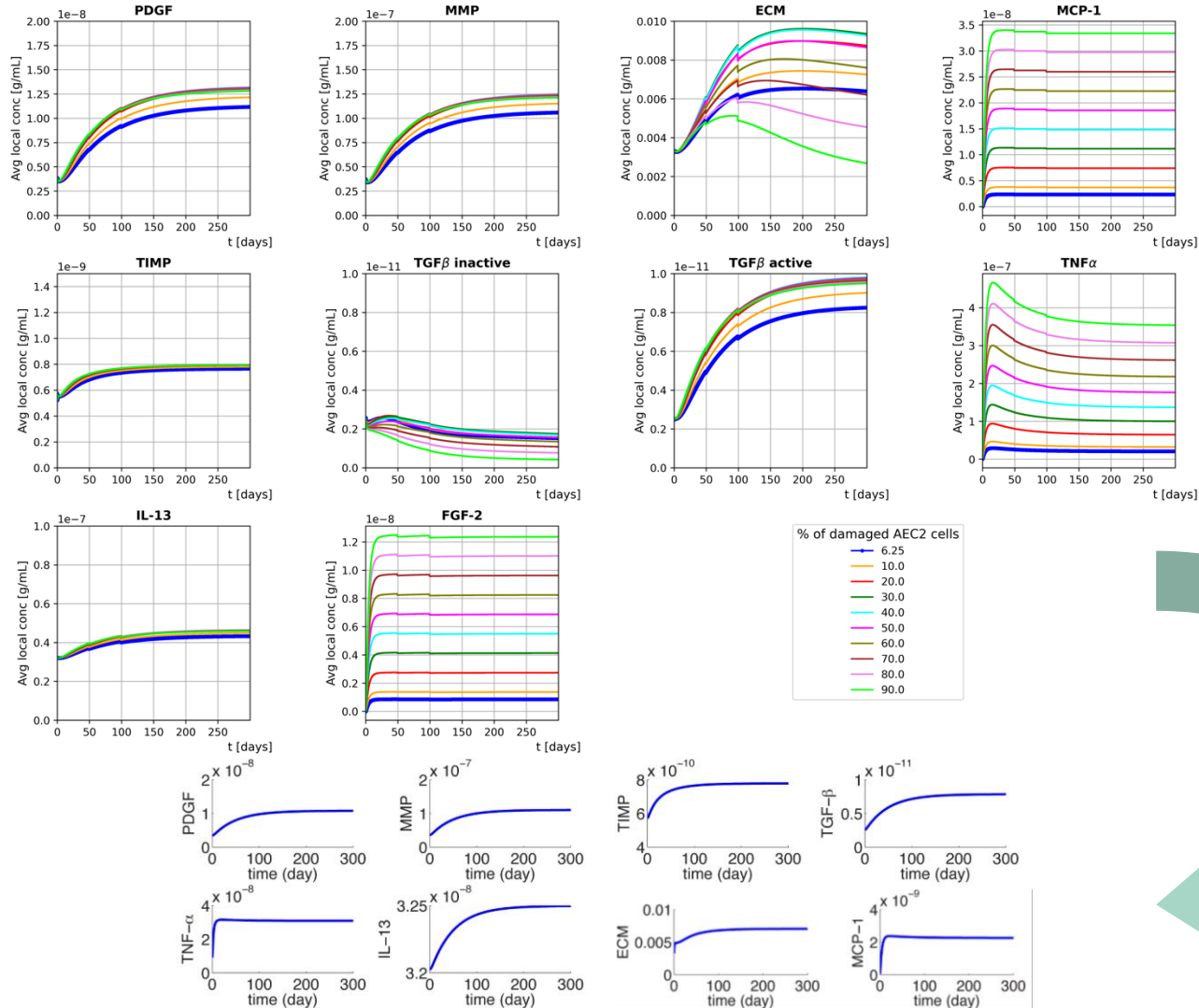Figure from Hao W, Marsh C, Friedman A (2015), PLOS ONE 10(9)

## Laboratory data
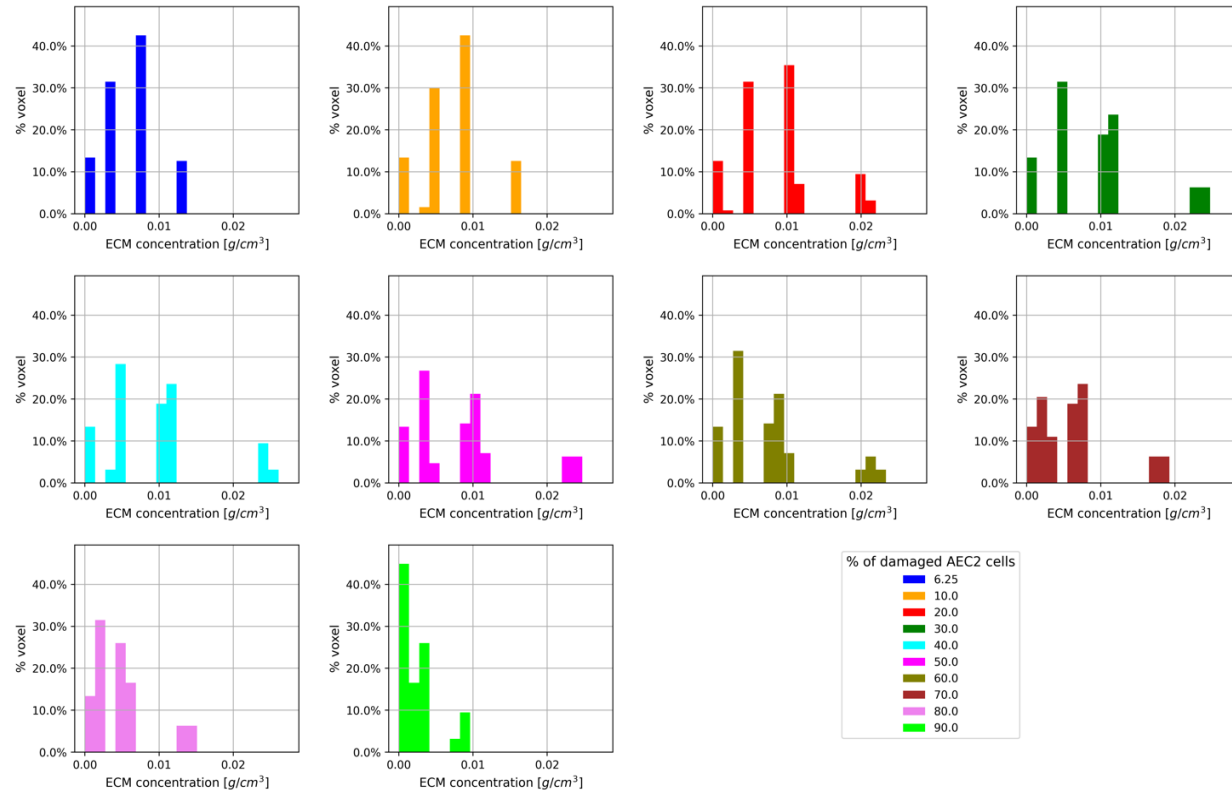

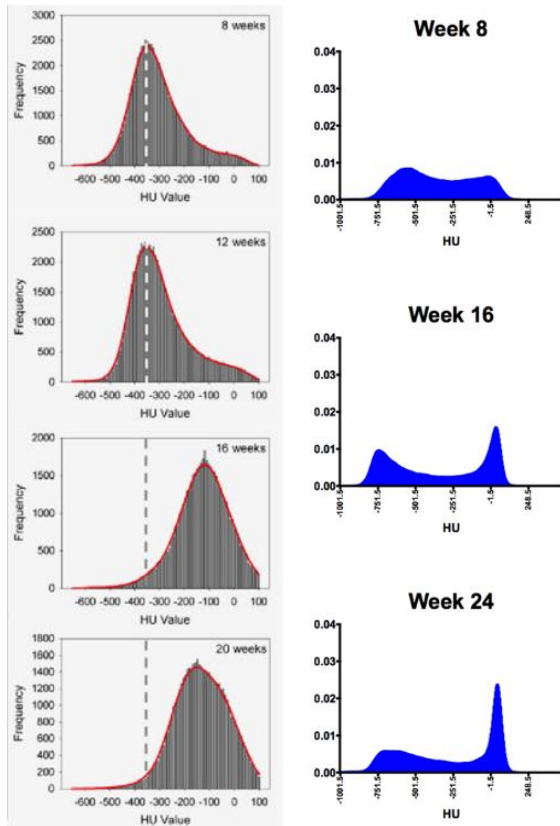
## Simulation results (week 43)



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?