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25^{èmes} JOURNÉES JEUNES CHERCHEURS EN CANCÉROLOGIE

Multiscale modelling of sarcoma and bone tissue synergy and interactions

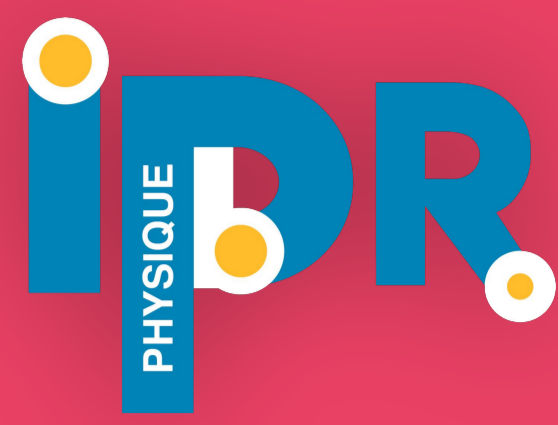
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F. Rédini, S. Battaglia & J. Amiaud



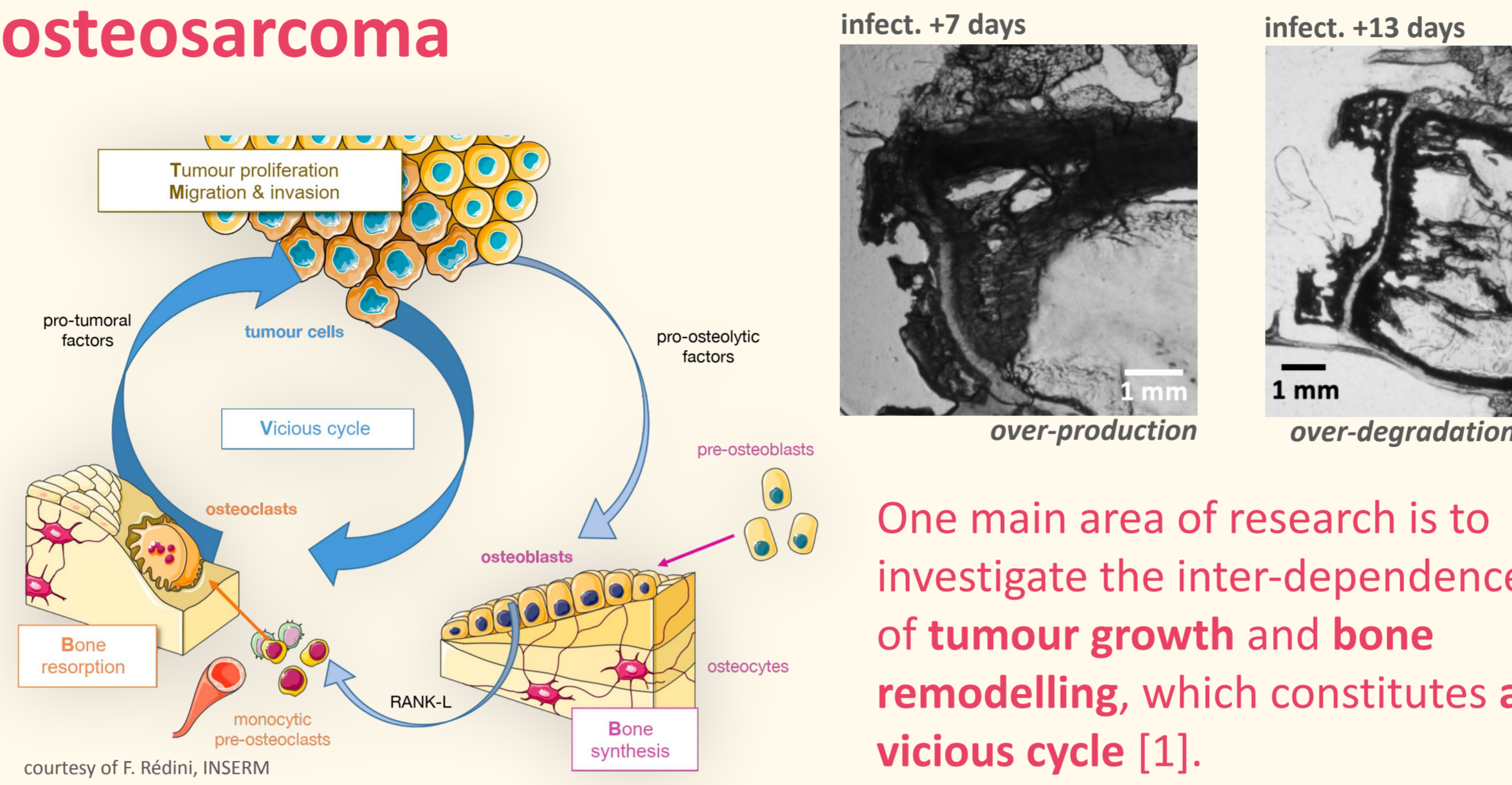
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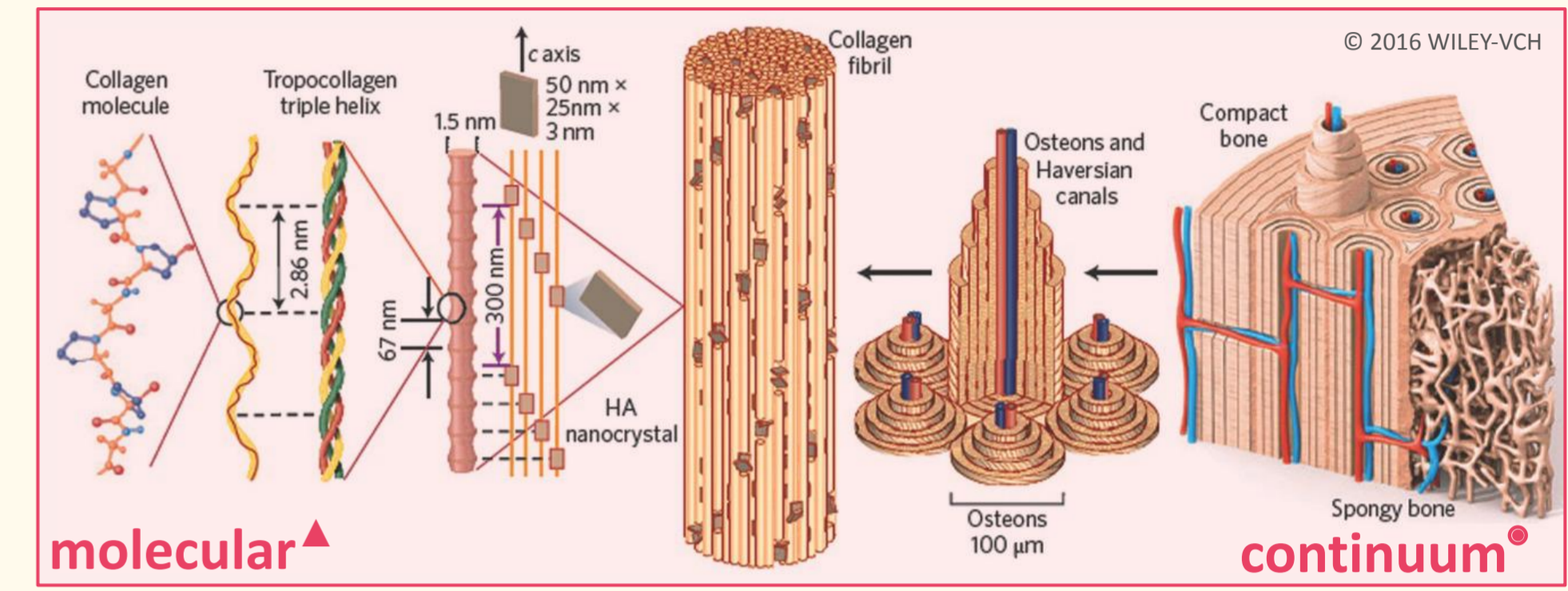
Understanding the morphology of osteosarcoma

Osteosarcoma, along with Ewing sarcoma, is one of the **most frequent malignant primary bone tumour**, the eighth most common malignancy of childhood. Osteosarcomas are aggressive tumours, rapidly invasive, which **signalling pathways are hardly understood**.



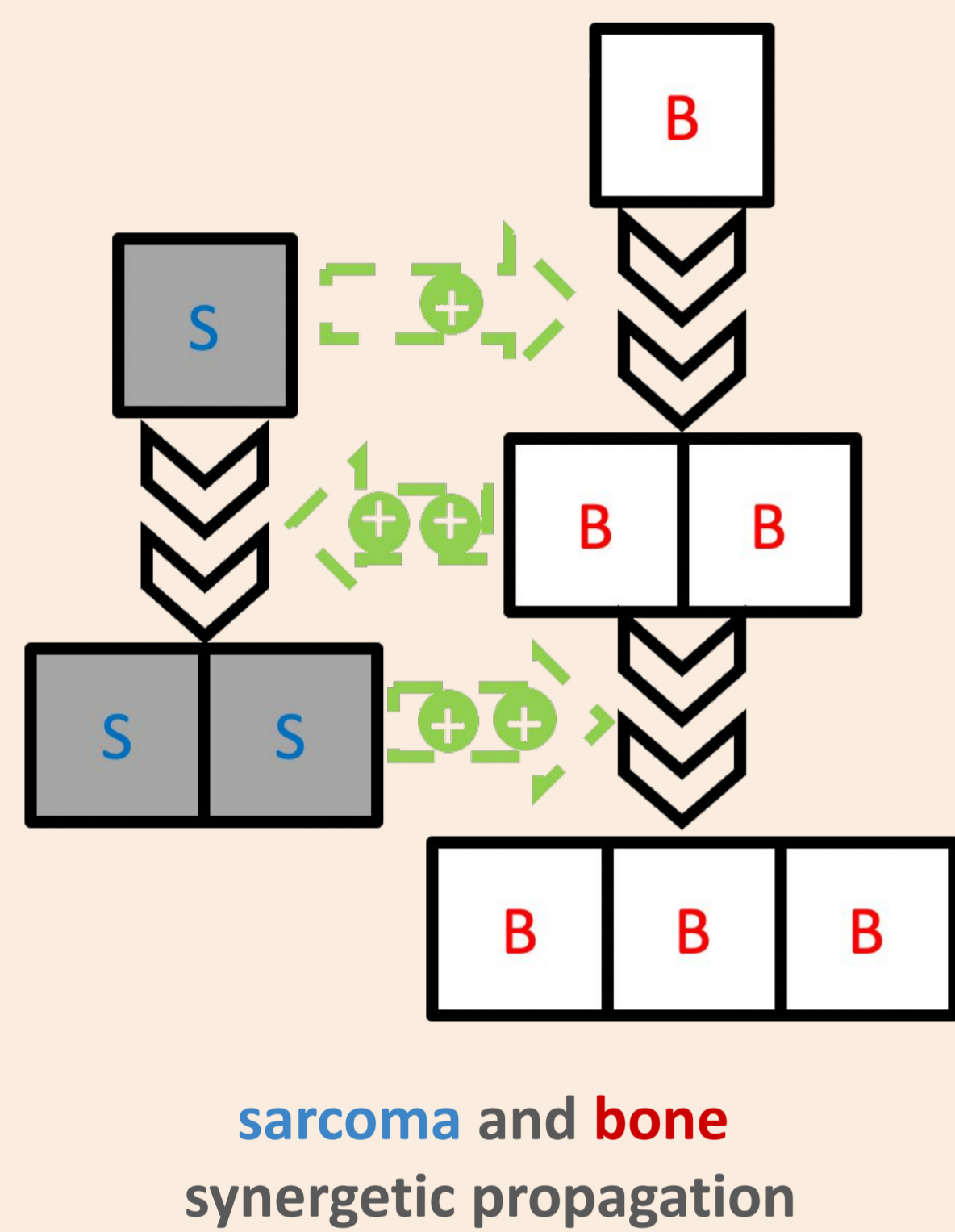
One main area of research is to investigate the inter-dependence of **tumour growth and bone remodelling**, which constitutes a vicious cycle [1].

The design of treatment or diagnosis requires to clarify the **physical mechanisms** associated with tumour initiation and **growth at multiple scales**.



Continuum^o modelling of osteosarcomas' growth

On the **microscale**, we simulate bone tissue remodelling and morphology in pathological conditions associated with osteosarcoma using a 3D continuum model based on Cellular Automata (CA).

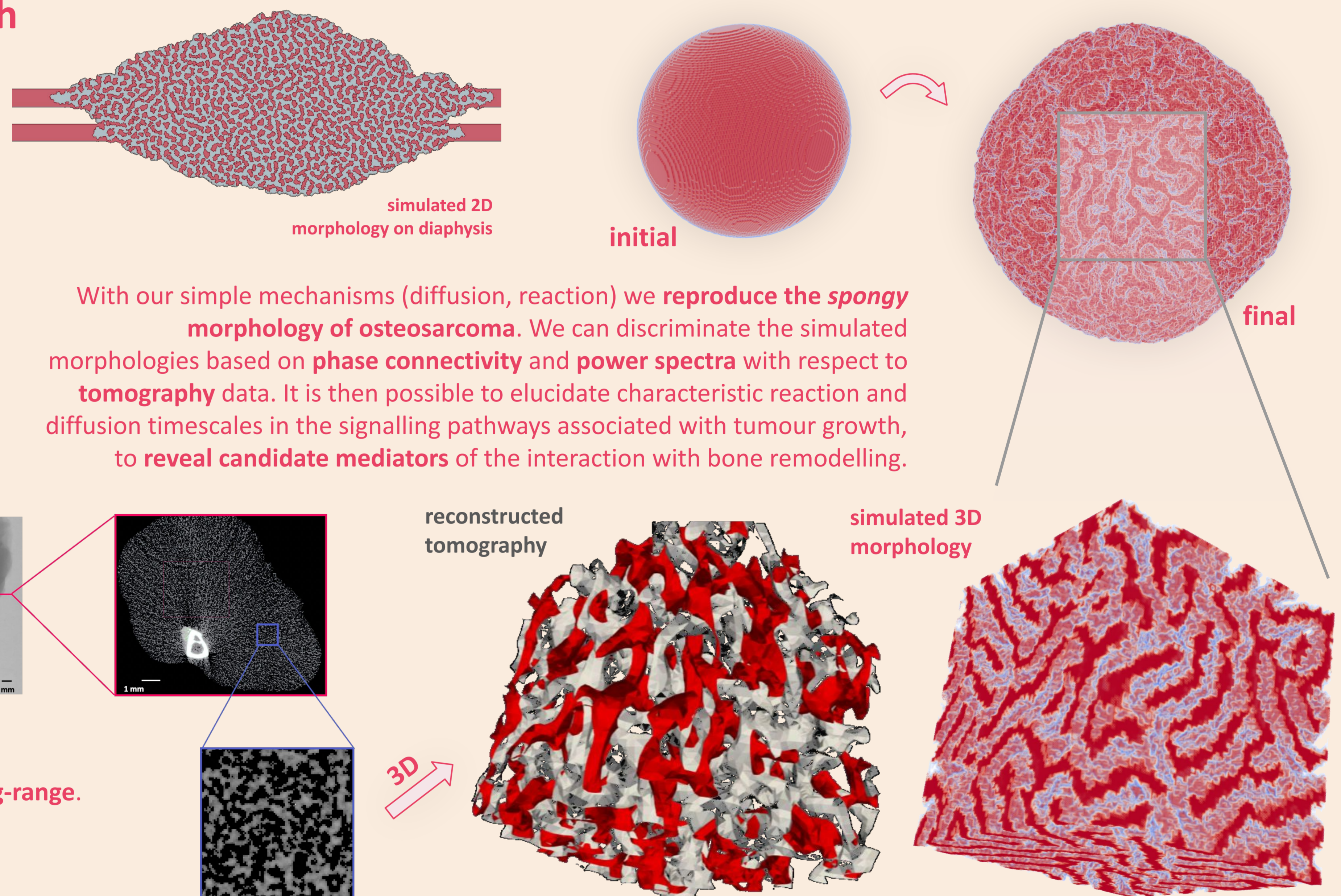


The model for osteosarcoma and bone **morphology growth** is formulated based **diffusion and reaction mechanisms**.

The model accounts for the following mechanisms:

- (i) **tumour phase concentration promotes bone synthesis;**
- (ii) **bone phase concentration promotes tumour synthesis;**
- (iii) **the one phase synthesis induce the other phase resorption;**
- (iv) **concentration influence is long-range.**

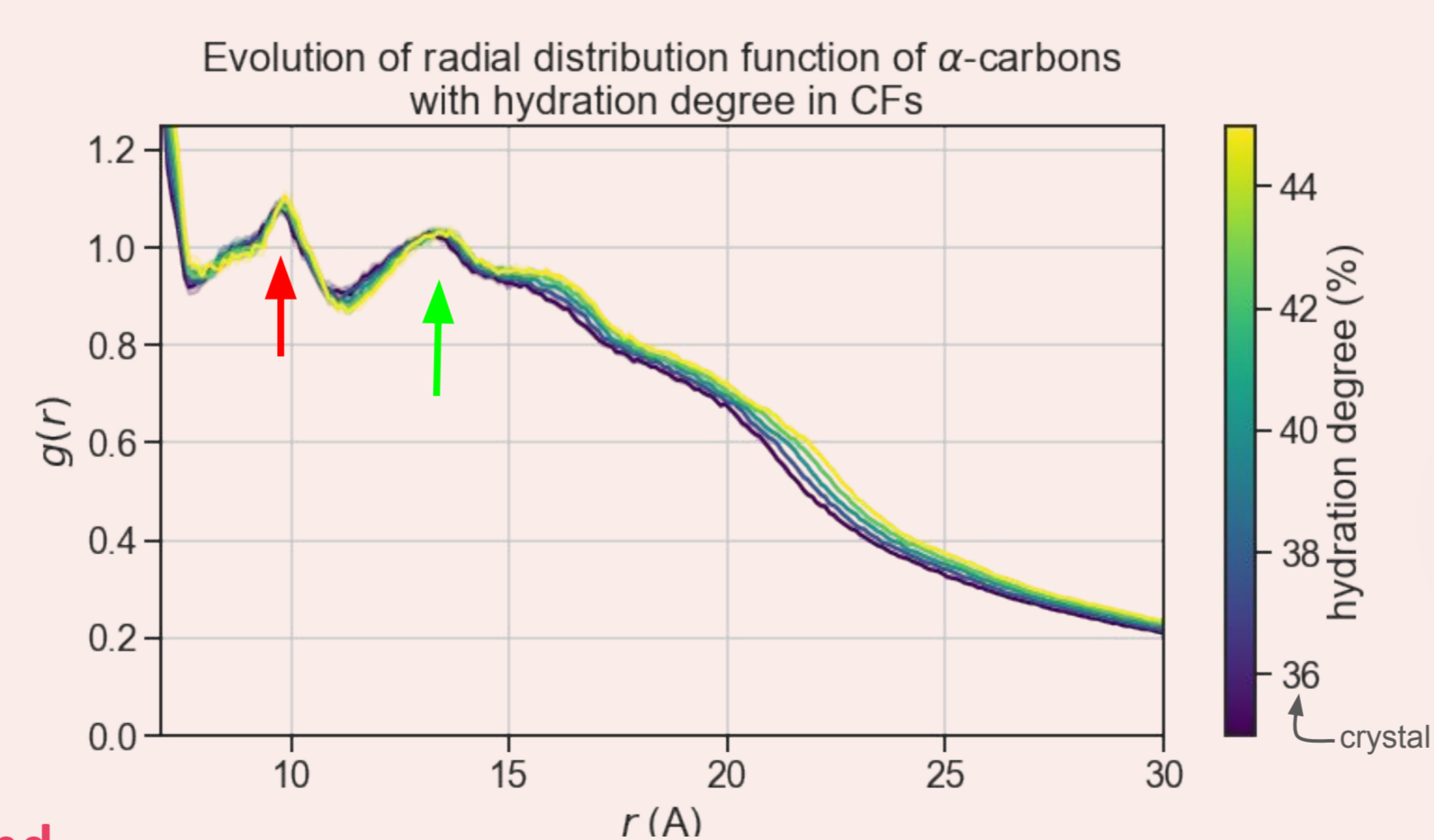
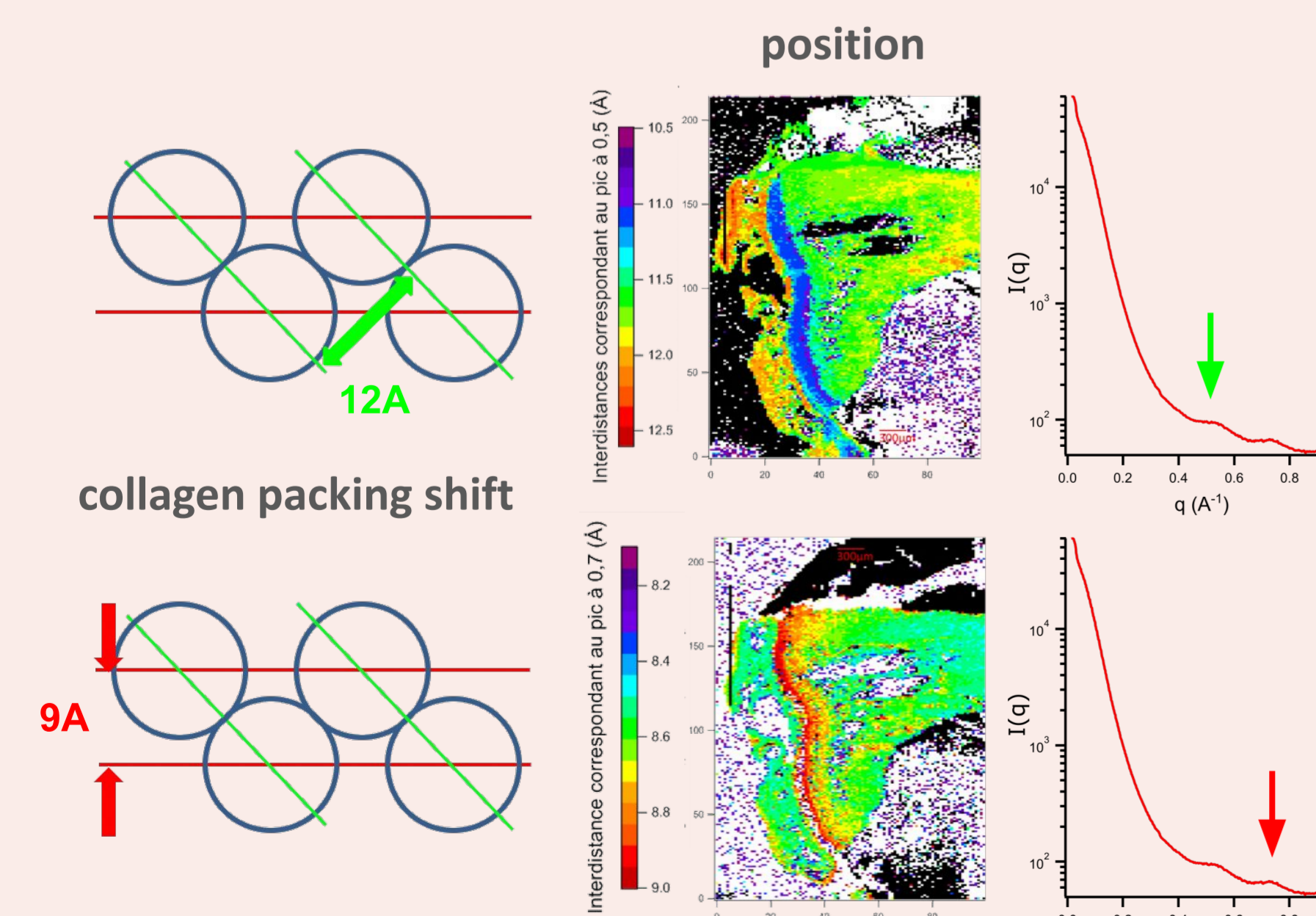
The three first mechanisms account for phase production and degradation (reaction), and the last mechanism accounts for signalling agents diffusion.



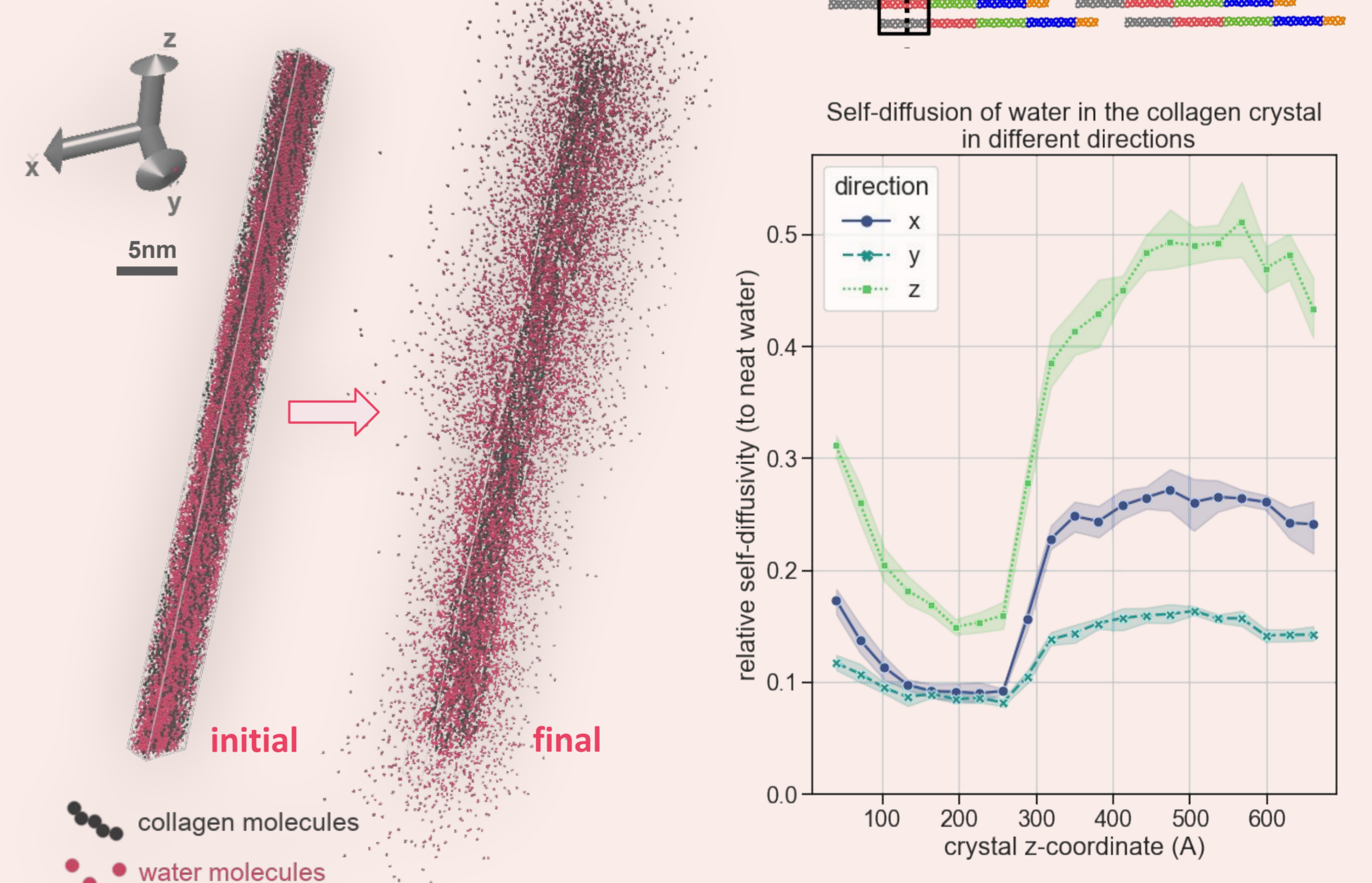
Molecular[^] modelling of pathological bone tissue self-assembly

We want to explain **early-stage interactions** between primary bone tumours and bone tissue remodelling at the **nanoscale**. We recently correlated **tumour development with rapid changes** in the structure of **Collagen Fibrils (CFs)** in bone tissue. However, not only self-organisation but also **structural packing of CFs is poorly elucidated**.

In order to clarify interactions between bone cancer cells and bone tissue remodelling, we designed a nanoscale **molecular models of CFs** based on X-ray crystallography data [2] and an artificial hydration process, and we simulated **hydration up to 50%** in water content of the crystallography structure.



water diffusion in the microfibril crystal



We apply the molecular models of microfibril crystals to **understand how rearrangements in CFs could occur**. Molecular dynamics simulations capture the evolution of the **tropocollagen inter-distances** with the degree of hydration or other thermodynamic variables. We then can elucidate the origin of **structural reorganisation associated with sarcomas' growth**.

Simulations of the hydration of the collagen microfibril crystal reveal **highly anisotropic water dynamics**. We found high water diffusion along the main axis of the tropocollagen molecules, but also in one orthogonal direction. Anisotropy indicate preferential directions for the transport of mineral phase precursors. Our results correlate with the specific platelet morphology of hydroxyapatite crystals within CFs.

References

- [1] Corre, I., et al. The osteosarcoma microenvironment: a complex but targetable ecosystem. *Cells* (2020), 9 (4).
- [2] Orgel, J. P., et al. Microfibrillar structure of type I collagen in situ. *Proc. Natl. Acad. Sci.* (2006) 103 (24).

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