Surfing on a stiffness gradient in skull morphogenesis

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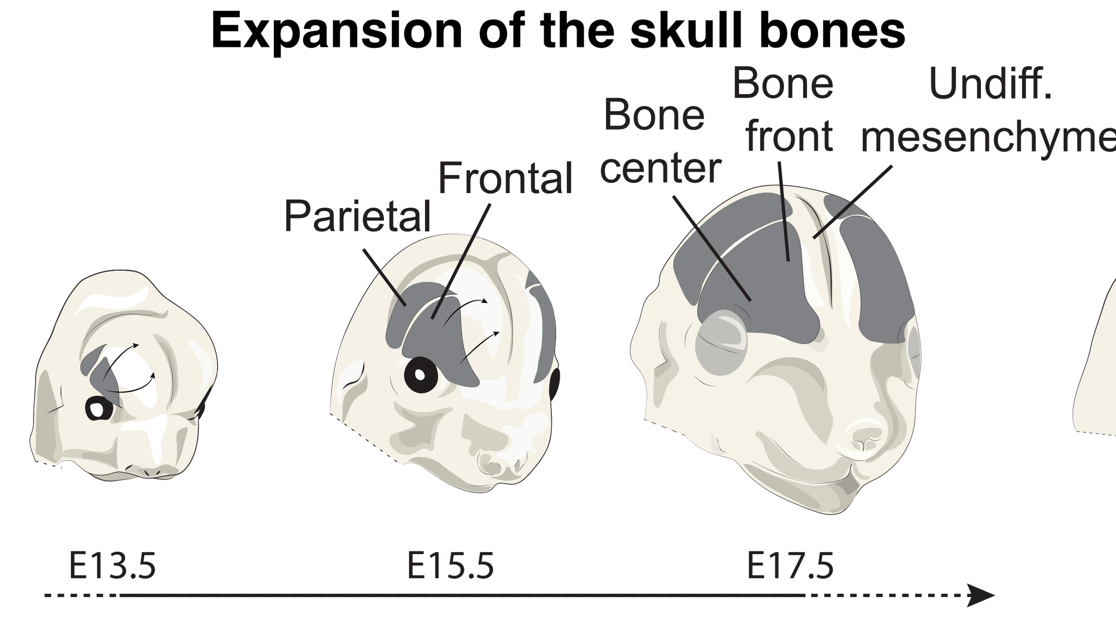
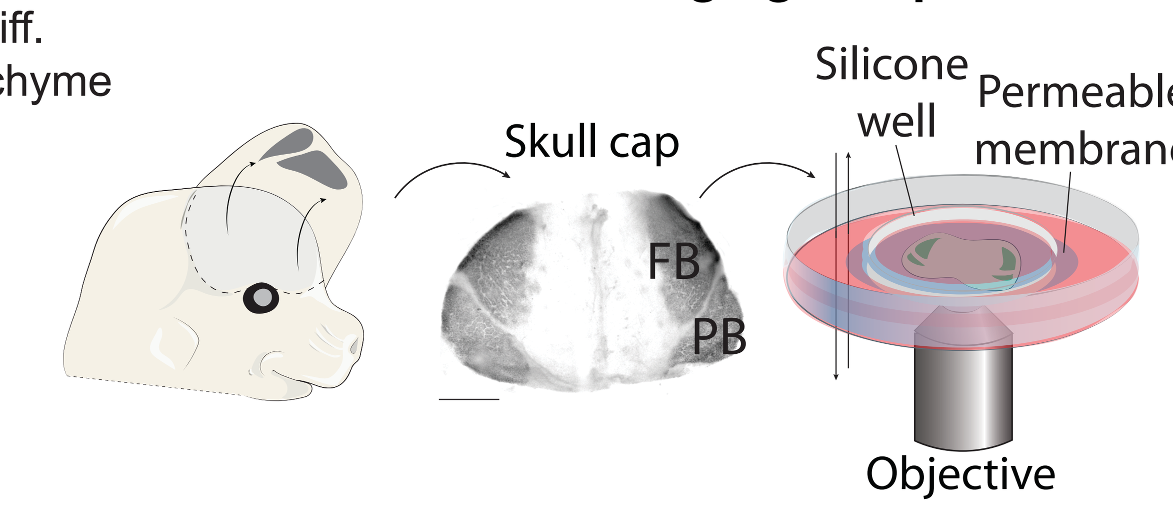
Introduction

During **skull development**, a thin sheet of osteoblasts grows anisotropically from the sides towards the top of the head. How different **cellular behaviours** processes such as proliferation, differentiation and motion collectively drive this expansion remains unclear. Here, we combined **quantitative live imaging**, **atomic force microscopy** and **biophysical modelling** to dissect the different processes driving expansion of a **mesenchymal tissue** in a heterogeneous extracellular environment characterised by a **stiffness gradient**.

Expansion of the skull bones

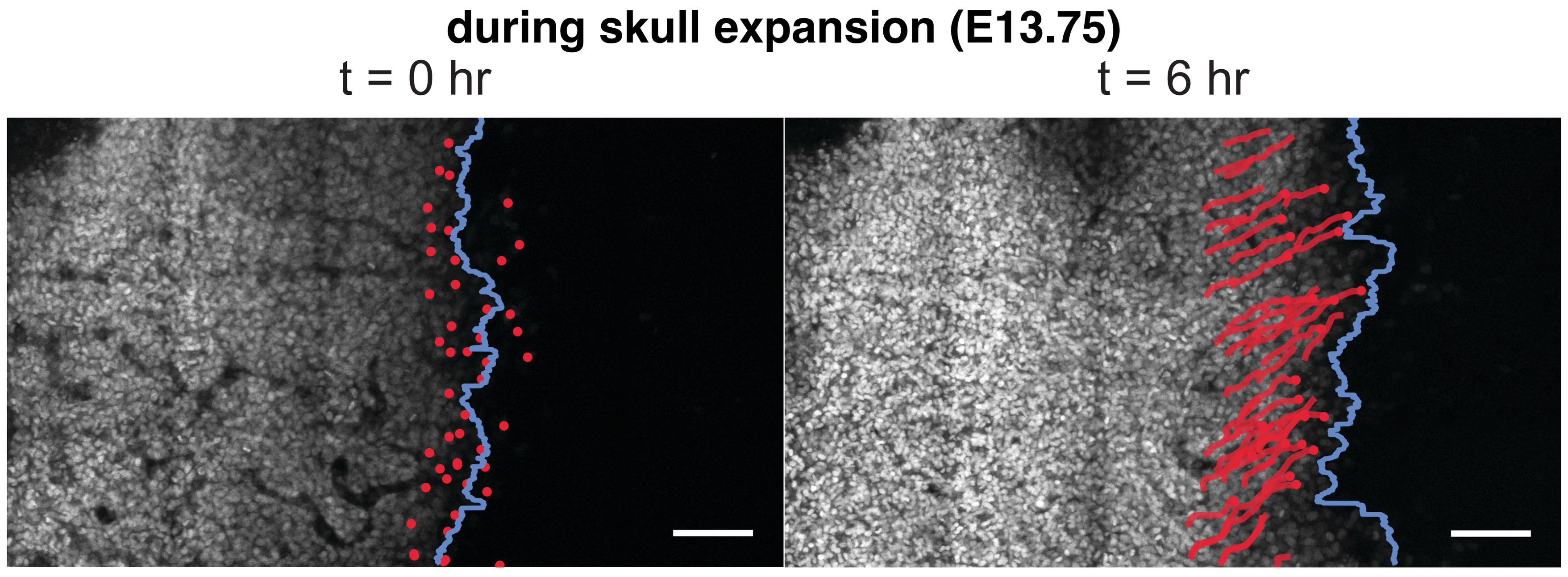


Ex vivo **live imaging setup**

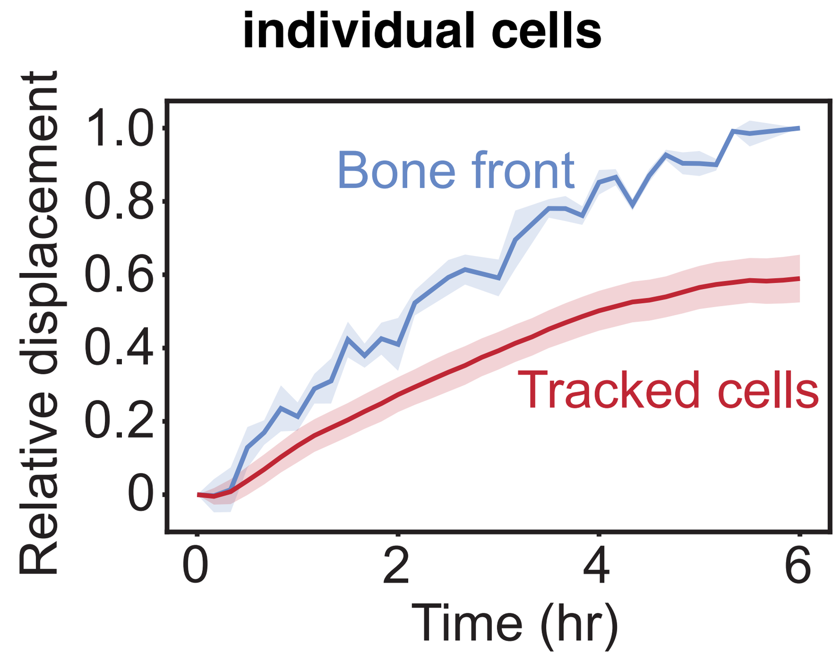


1 *Ex vivo* live imaging of skull bone expansion

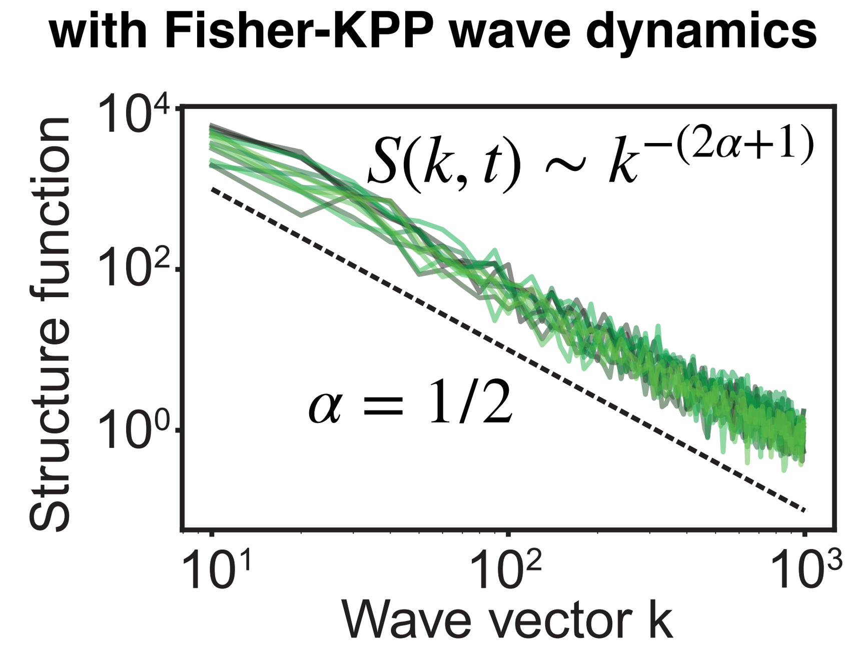
Tracking the bone front and individual osteoblast cells during skull expansion (E13.75)



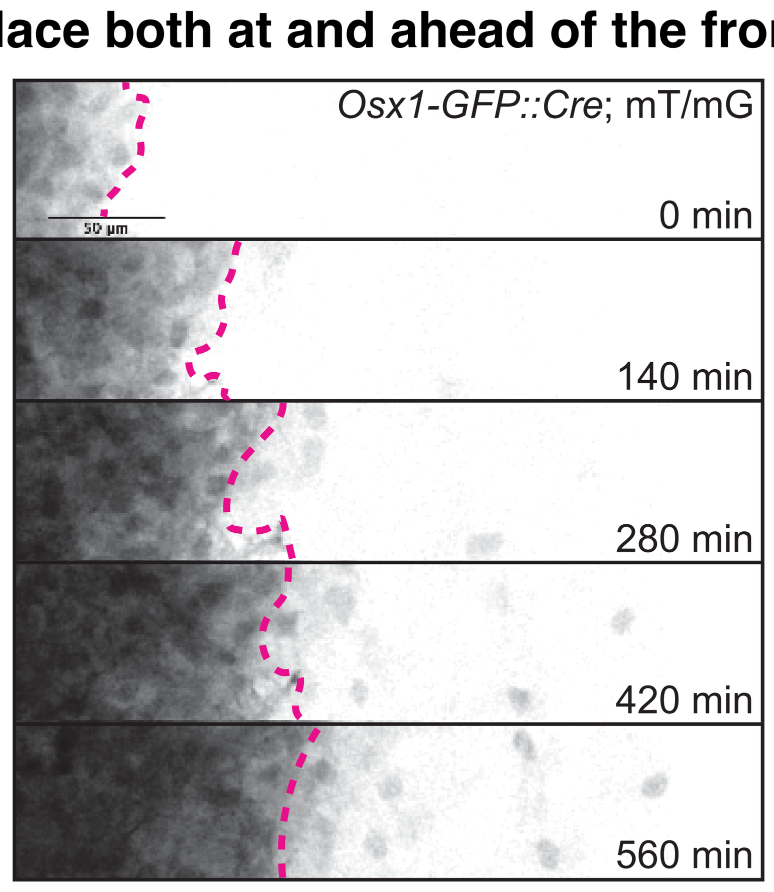
Bone front expands faster than individual cells



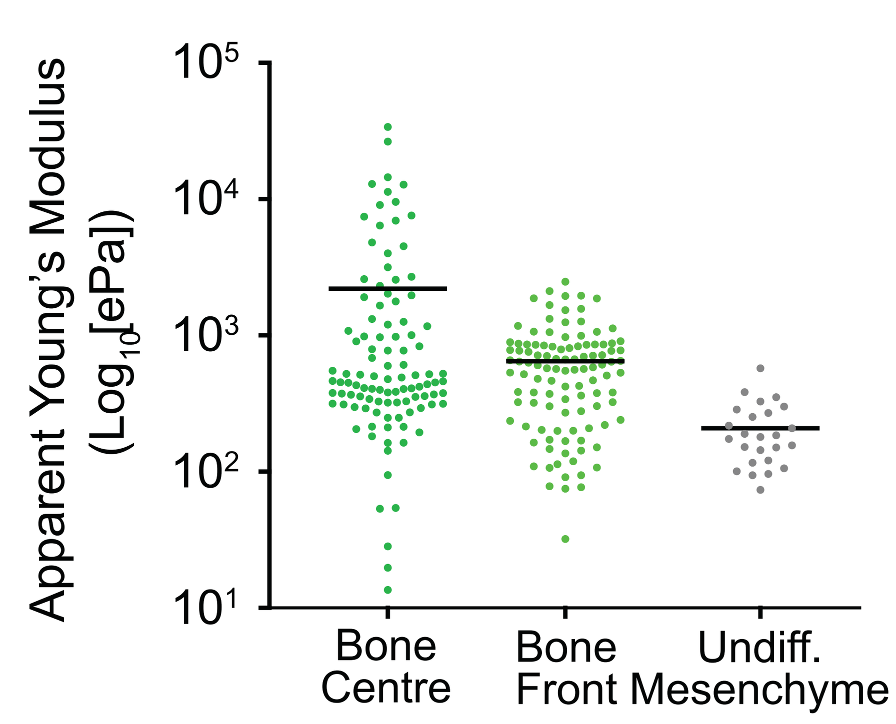
Front roughness is consistent with Fisher-KPP wave dynamics



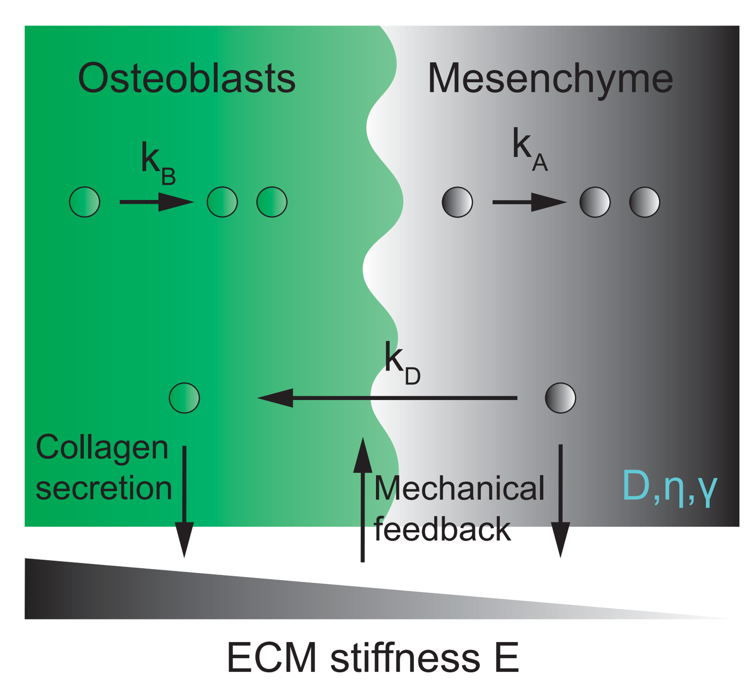
Differentiation into osteoblasts takes place both at and ahead of the front



AFM measurements show stiffness gradient along the direction of bone growth



2 Biophysical model for bone expansion



$$E[\phi] = (E_A + (E_B - E_A)\phi)$$

Differentiation

$$k_D = k_D(E)$$

Cell number balance — ρ: Total cell density

$$\partial_t \rho + \nabla\cdot(\rho \mathbf{v}) = \left(k_A(1-\phi) + k_B\phi\right)\rho$$

Advection — Cell division/death

Differentiation dynamics — ϕ: Fraction of osteoblasts

$$\partial_t \phi + \mathbf{v}\cdot\nabla\phi = D\frac{1}{\rho}\nabla\cdot(\rho\nabla\phi) + \left(k_B - k_A\right)\phi(1-\phi) + k_D(1-\phi)$$

Advection — Diffusion — Proliferation gradient — Differentiation

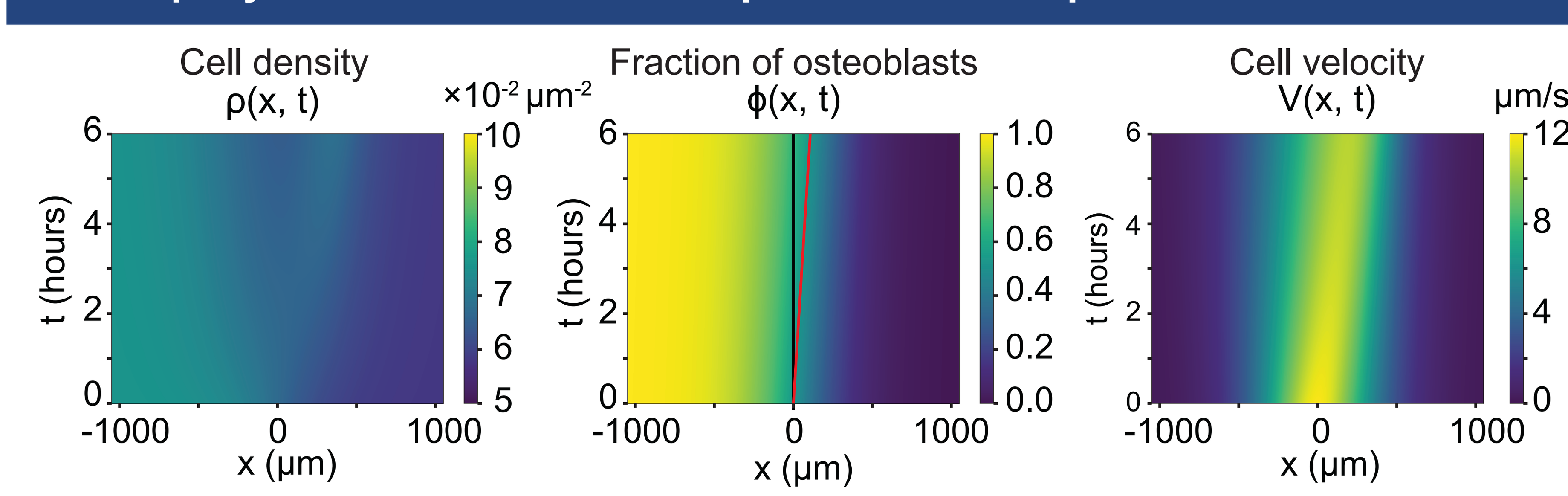
Force balance — v: Advection velocity

$$\nabla\cdot\sigma = \gamma\mathbf{v} \qquad \sigma = -P\mathbf{I} + 2\tilde{\eta}\tilde{\mathbf{v}} + \xi(\nabla\cdot\mathbf{v})\mathbf{I}$$

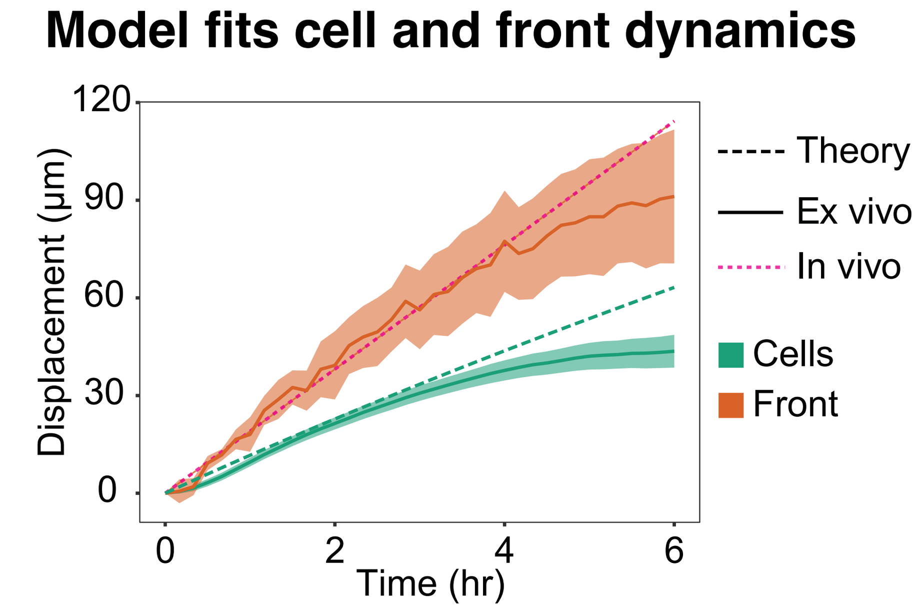
Friction — Constitutive equation for a viscous fluid

Fisher-KPP wave dynamics implies $\left.\frac{dk_D}{dE}\right|_{E=E_A} > 0$, to first order $k_D(E) = \alpha(E[\phi] - E_A)$.

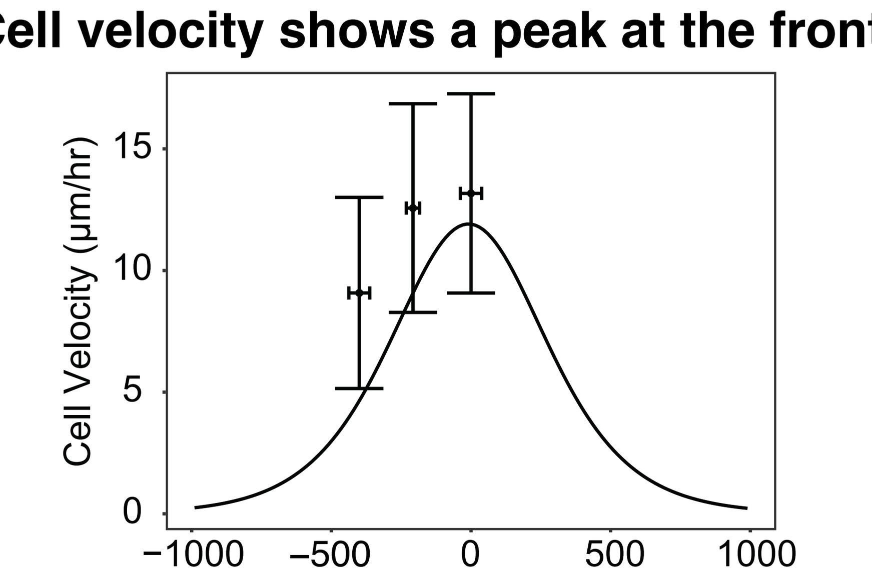
3 Biophysical model recapitulates experimental results



Model fits cell and front dynamics

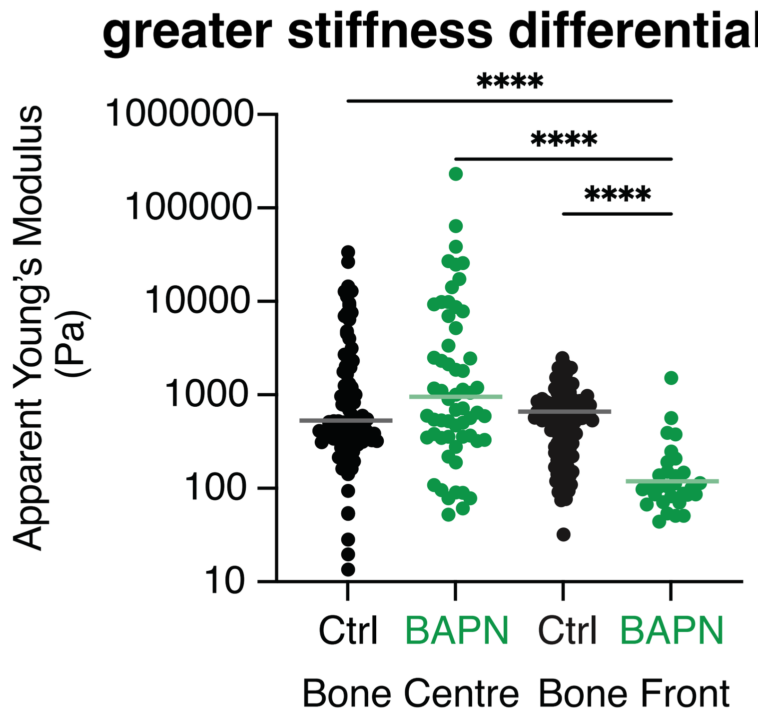


Cell velocity shows a peak at the front

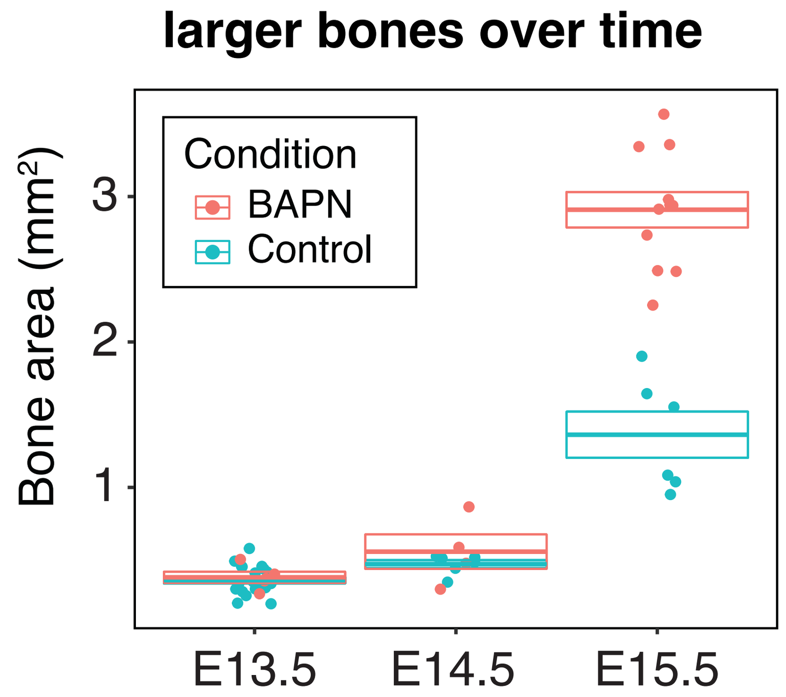


4 BAPN increases stiffness gradient and enlarges bone

BAPN-treated samples have greater stiffness differential



BAPN-treated samples samples grow larger bones over time



Conclusion

- Skull development reveals biophysical mechanisms controlling **mesenchymal morphogenesis**.
- **Mechanical feedback** orchestrates cell differentiation *and* cell motion.
- **Mathematical modelling** reveals simplicity that underscores robustness of morphogenesis.

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