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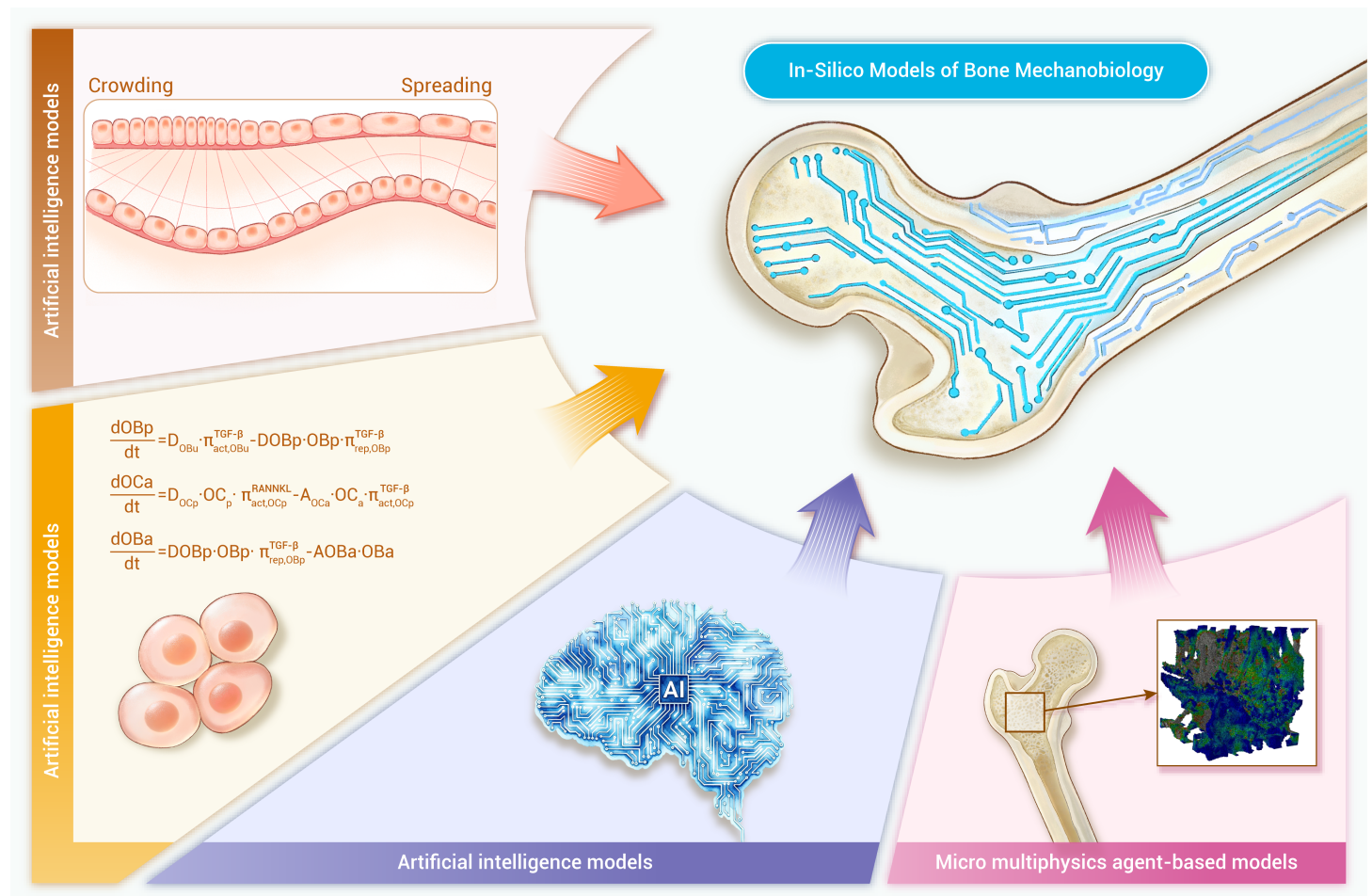
Joudi Altaieb,^{1,*} Ulrich Hansen,² Richard Abel,³ and Ian Mudway¹

*Correspondence: joudi.altaleb22@imperial.ac.uk

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GRAPHICAL ABSTRACT



PUBLIC SUMMARY

- In-silico models of bone are crucial for understanding the behaviour of bone under certain conditions.
- There are five types of in-silico models: bone cell population, bone tissue dynamics, FE, AI, and micro MPA models.
- Micro MPA models can include bone mediators, cells, as well as a response to 3D stress.

The evolution of *in-silico* physiological models of bone remodelling: From cell population models to micro-MPA approaches

Joudi Altaieb,^{1,*} Ulrich Hansen,² Richard Abel,³ and Ian Mudway¹

¹MRC Centre for Environment and Health, School of Public Health, Faculty of Medicine, Imperial College London, London W2 1PG, United Kingdom

²Department of Mechanical Engineering, Faculty of Engineering, Imperial College London, London W2 1PG, United Kingdom

³Department of Surgery & Cancer, Faculty of Medicine, Imperial College London, London W2 1PG, United Kingdom

*Correspondence: joudi.altaieb22@imperial.ac.uk

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Bone remodelling is a mechanically regulated, multiscale process that maintains skeletal integrity and is disrupted in common metabolic bone diseases. Experiments, however, cannot easily resolve the coupled cellular, biochemical, and mechanical feedback that drive long-term outcomes. In this Review, we examine five *in-silico* modelling classes used to study bone remodelling: bone cell population dynamics models, bone tissue dynamics models, finite element models, AI models, and three-dimensional micro-multiphysics agent-based models. We compare these approaches through biological fidelity, computational tractability, and translational readiness. FEM excels at macro-scale mechanics but depends on explicit material laws. Cell population models remain dominant for long-horizon and pharmacological simulations because they are interpretable and efficient, although their non-spatial structure limits prediction of microarchitecture. Tissue dynamics models capture curvature-controlled growth efficiently but often rely on simplified mechanobiology. Micro-multiphysics agent-based models provide the strongest link between cell behaviour, mechanics, and microarchitecture, but face major challenges in parameter identifiability, scalable computation, and validation. AI models can bypass explicit material laws and accelerate other methods through surrogate modelling, but risk non-physical predictions without appropriate constraints. We conclude that the field's next step is to develop integrated, testable workflows that improve calibration and validation while making assumptions explicit. In this context, AI is best viewed as an enabling tool for surrogate modelling, inverse problems, and data-assimilation workflows, rather than as a replacement for mechanistic understanding.

INTRODUCTION

Bones are not static structures; they are living tissues that continually adapt and renew themselves throughout our lives. This process, known as bone remodelling, is driven by the coordinated actions of specialized cells responding to physical forces, hormones, and signals from their environment.¹ Understanding how these cellular and molecular interactions shape bone health and disease is a major scientific challenge.

In recent years, computer-based *in-silico* models have become powerful tools for studying these complex systems. This Review traces the development of bone-remodelling models from early mathematical descriptions of cell populations through tissue-based models, finite element methods,^{2,3} AI and other data-driven approaches, and advanced agent-based multiphysics simulations.⁴⁻⁶ Our aim is to make these approaches accessible to a broad audience while showing how they clarify bone biology, expose current gaps, and guide future research and therapy.

Despite decades of experimental and computational work, four questions still shape the field: how much biological and mechanical detail is needed for clinically relevant prediction, which methods can simulate long-term multiscale remodelling, what evidence supports translation to clinical use, and where AI fits as a surrogate or complementary tool. This Review addresses these questions by comparing five *in-silico* modelling approaches.

These approaches are bone cell population dynamics models, tissue dynamics models, finite element models, three-dimensional micro-multiphysics agent-based models, and AI or other data-driven models. Together, they span interpretable long-horizon simulation, spatial tissue adaptation, mechanical stress analysis, high-fidelity cell-level modelling, and computa-

tional acceleration.

We compare these approaches through biological fidelity, computational tractability, and translational readiness. This framework clarifies where methods complement one another, for example when FEM provides mechanical fields for agent-based models or AI serves as a fast surrogate. Throughout, we treat AI as an enabling tool rather than a replacement for mechanistic understanding. We begin with cell population models, which provide the most established quantitative description of osteoblast, osteoclast, and osteocyte dynamics. Although later tissue- and organ-scale methods add spatial detail, these models remain a foundation for multiscale descriptions of bone remodelling.

Figure 1 shows key relevant physiological models in the literature, covering the papers deemed significant to the development of a realistic model of bone mechanobiology. For example, Kameo et al.'s paper relies heavily on Scheiner et al. which is based on Pivonka et al. and Lemaire et al.²⁻⁵ Moreover, Pastrama et al., Martinez-Reina et al. all use the Pivonka et al. or their own applications.^{4,6-10} Likewise, Boaretti et al., Kendall et al., and Tourolle et al. all use the original Duncan Tourolle's PhD thesis, model for their own applications.¹¹⁻¹⁴

Classification principles

We distinguish the five modelling categories by three features: the state variables they use, whether space and microarchitecture are represented explicitly, and how mechanical and biochemical signals are coupled. On this basis, cell population models are compartment-averaged and non-spatial; tissue dynamics models are spatially explicit but simplified; FEM resolves continuum mechanics without direct cell biology; micro-multiphysics agent-based models represent individual cells and local physics; and AI or data-driven models mainly serve as surrogates, inverse tools, or pattern recognisers.

BONE CELL POPULATION DYNAMICS MODELS

Bone remodelling is the mechanism of bone replacement that maintains its load bearing capacity in response to numerous factors such as mechanical stress, hormonal changes, growth, microcracks that appear in bone, or mineral homeostasis.¹⁵⁻¹⁹ Remodelling involves basic multicellular units including osteoclasts, osteoblasts, and osteocytes.^{15,20} Osteocytes are mechanically sensitive cells that respond to changes in their local environment to trigger bone remodelling.²¹ Osteoblasts are bone forming cells and osteoclasts are bone resorbing cells.

Bone remodelling begins by the initiation of bone resorption by osteoclasts in response to the secretion of RANKL by osteoblastic cells.^{22,23} RANKL is a protein expressed by osteoblasts that binds to its receptor, RANK, on osteoclasts, promoting osteoclast formation. This interaction is controlled by OPG, another protein released by osteoblasts. OPG acts as a decoy by binding to RANKL, blocking its interaction with RANK and preventing osteoclast formation. This system is called the RANK-RANKL-OPG pathway.^{24,25} Imbalances in the RANKL/OPG ratio play a key role in many bone diseases.²⁶⁻³⁰

Bone cell population models are the earliest type of mathematical models of bone remodelling. Such models have been able to simulate how bone cells change over time, providing insights into bone remodelling. However, these models have their own challenges related to their failure to fully capture the complex microarchitecture of bone which is crucial for assessing bone quality.

Temporal, non-spatial early bone cell population dynamic models segment

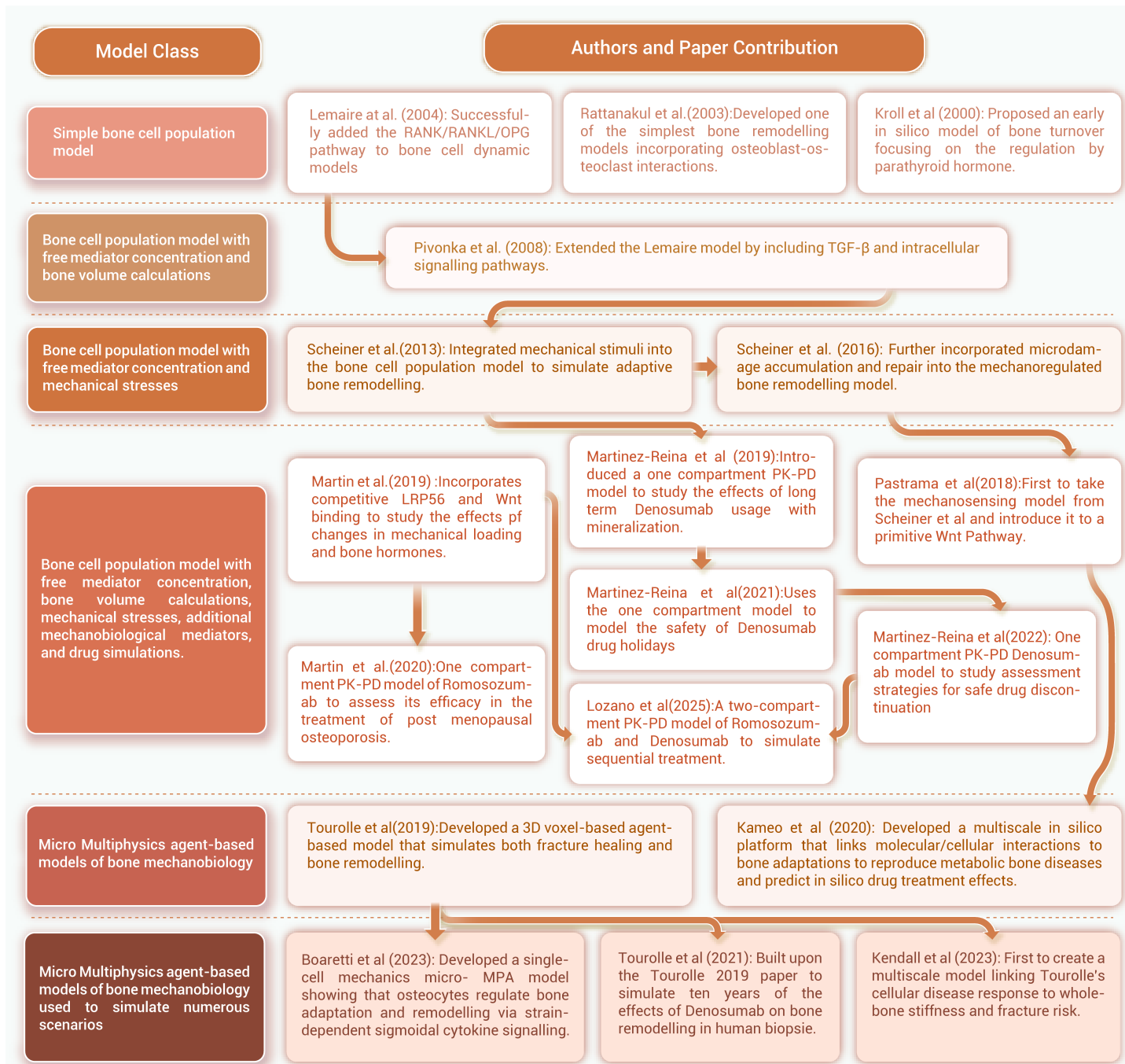


Figure 1. Evolutionary hierarchy of physiological bone remodelling models Models are arranged from simplest (top) to most complex (bottom) based on biological detail, number of state variables, and mechanistic coupling. Solid arrows indicate direct evolutionary lineage (a later model explicitly building upon an earlier one). Dashed arrows indicate conceptual influence without direct mathematical inheritance. The earliest models, Lemaire et al. (2004), Rattanakul et al. (2003), and Kroll et al. (2000), describe basic osteoblast-osteoclast population dynamics.^{4,5,53,54} Pivonka et al. (2008) extends Lemaire et al. by introducing RANKL/RANK/OPG signalling. From this, two main branches emerge: Scheiner et al. (2013) and Scheiner et al. (2016), both evolving from Pivonka et al. (2008).^{3,31} The Scheiner 2013 branch leads to Martin et al. (2019) and Martinez-Reina et al. (2019), with further descendants including Lozano et al. (2025) (from Martin et al., 2019) and Martinez-Reina et al. (2022) (from Martinez-Reina et al., 2021, itself from Martinez-Reina et al., 2019).^{7,8,10,33,35} The Scheiner 2016 branch leads to Pastrama et al. (2018) and subsequently to Kameo et al. (2020) (also influenced by Scheiner et al., 2013).⁶² An independent lineage from Tourolle et al. (2019) gives rise to Boaretti et al. (2023), Tourolle et al. (2021), and Kendall et al. (2023).^{2,13,11,12} This visual hierarchy clarifies how increasing biological fidelity and mechanical coupling accumulate along each evolutionary path.

bone into representative volume elements (RVE). A representative volume element is simply a modelling framework used to analyse bone where the interactions between cellular activity and biochemical signalling is simulated.^{3,10,31-35} Within these elements, the model tracks the concentration of each cytokine and the population of the variable cells. The activities of cell resorption, formation, proliferation, differentiation, and apoptosis within the RVE are determined based on the concentrations of cytokines, utilizing Hill coefficients (a parameter used to quantify the ligand protein binding) to regulate repression and activation.^{4,21}

Simple cell population dynamics models

Early cell population dynamics models simply constitute three first order differential equations which dictate the population dynamics of osteoblasts, osteoclasts, and pre-osteoblasts. This is because the proportions of preosteoclasts and active osteoblasts control osteoclastic resorptive activity and osteoclasts in turn control osteoblasts.^{4,5} Despite this simplification, those models show good correlations between model simulations and experimental data. They explain the interactions between bone cells and some crucial chemical pathways that are responsible for bone remodelling.

Such early models consider four cell types within the osteoblast lineage,

with two as state variables, and three cell types within the osteoclast lineage with one as a state variable.^{4,5} The non-state variable cells are treated as a constant within the model. This means that osteoblasts in this model change in value with time. Osteoblasts come from mesenchymal stem cells that can turn into various cell types, including bone, cartilage, and fat cells.³⁶ These stem cells are called uncommitted osteoblast progenitors (OBu). When they start specializing into bone cells, they become pre-osteoblasts (OBp), which are early-stage osteoblasts responsive to growth factors like Tumour Necrosis Factor-Beta TGF- β or hormones like PTH.³⁷ Osteoclasts release TGF- β during bone resorption. TGF- β inhibits the differentiation of responding osteoblasts which leads to a larger pool of pre-osteoblasts,^{16,38,39} and also induces osteoclast apoptosis.⁴⁰⁻⁴³ Osteoclasts come from blood stem cells, called uncommitted osteoclast progenitors (OCu), which develop into osteoclast precursors (OCp).^{22,40,44}

Cell interactions are depicted using the first-order differentials shown in Equations 1-3. Pre-osteoblasts mature into active osteoblasts. The model represents mediator effects on bone cells using activator and repressor functions. An activator function is a mathematical representation of how a biochemical signal positively regulates a cellular response. A repressor function is a representation of how a biochemical signal negatively regulates a cellular response.^{36,37} Eventually, osteoblasts either perish or transform into lining cells or osteocytes, which act as stress sensors.^{16,45} However, the movement from lining cells to osteoblasts is not accounted for in those models.

RANKL production promotes the differentiation of pre-osteoclasts into active osteoclasts and is included as an activator function.^{16,45,46} Parathyroid hormone (PTH) is included in the model through the RANK/RANKL/OPG pathway as it has multiple effects on bone cell proliferation, differentiation, and regulating calcium homeostasis.⁴⁷⁻⁴⁹ PTH receptors are expressed on the osteoblast surface.^{44,50} When PTH binds to those receptors, it increases the production of RANKL and inhibits the production of OPG by osteoblasts which increases the number of osteoclasts.^{44,46,51,52}

There are four early models of this simple cell population model; however, only one of them is comprehensive enough to describe in detail in this section, Lemaire et al. Kroll et al and Rattankul et al are two models which describe the effects of PTH administration on bone remodelling.^{5,53,54}

Another model by Komarova proposes the interactions among osteoblasts and osteoclasts but does not include the RANK/RANKL/OPG pathway which is crucial for describing osteoclast differentiation.⁵⁵

$$\frac{dR}{dt} = D_R \cdot \pi_C - \frac{D_B}{\pi_C} \cdot R \quad (1)$$

*Notes: R means concentration of pre-osteoblasts, D_R means differentiation rate of OB progenitors, D_B means factor of differentiation rate of responding osteoblasts, π_C means activator/repressor function related to TGF- β binding to its receptors on osteoblasts or osteoclasts.

$$\frac{dB}{dt} = \frac{D_B}{\pi_C} \cdot R - k_B \cdot B \quad (2)$$

*Notes: R means concentration of pre-osteoblasts, B means concentration of osteoblasts, D_B means factor of differentiation rate of responding osteoblasts, π_C means activator/repressor function related to TGF- β binding to its receptors on osteoblasts or osteoclasts.

$$\frac{dC}{dt} = D_C \cdot \pi_L - D_A \cdot \pi_C \cdot C \quad (3)$$

*Notes: π_C means activator/repressor function related to TGF- β binding to its receptors on osteoblasts or Osteoclasts, π_L means activator function related to RANKL binding to its receptor RANK expressed on OC precursor cells, D_A means rate of osteoclast apoptosis caused by TGF- β , k_B means rate of elimination of active osteoblasts, D_C means differentiation rate of OC precursors.

Cell dynamics with bone volume calculations and new mediator implementation

A significant development in cell population models was the inclusion of bone volume calculations which allowed data output by the models to be

compared to clinical data as well as the explicit modelling of the concentration of free mediators such as OPG, RANKL, TGF- β and PTH.⁴ Another crucial improvement was the expression of OPG and RANKL on both osteoblastic cells as well as the adjustment of activator/repressor functions to more clearly state what they influence.

Bone volume calculations were formulated to link cell numbers of changes to changes in bone volume over time,⁴ shown in Equation 4.

$$\frac{dBV}{dt} = k_{res} O\check{C}a + k_{form} \cdot O\check{B}a \quad (4)$$

*Notes: BV means total bone volume, k_{res} and k_{form} denote the relative bone resorption and formation rates, respectively, $O\check{C}a$ and $O\check{B}a$ represent the number of active osteoclasts and osteoblasts, respectively.

The expression of RANKL and OPG in different cell types within the maturing osteoblast cell lineage was also explored in this stage of cell population models.⁵⁶⁻⁶¹ Four extreme cases were tested. In case 1, RANKL was expressed on active osteoblasts (OBa) and OPG on precursor osteoblasts (OBp). In case 2, RANKL was expressed on OBp and OPG on OBa. In case 3, both RANKL and OPG were expressed on OBps. In case 4, both RANKL and OPG were expressed on osteoblasts. The effectiveness of the model structure was assessed by BV's sensitivity to its structure. Modelling RANKL to be expressed on OBp and OPG on OBa was found to be the most optimal as it was the most sensitive to parametric changes.⁴

Moreover, as the models developed, cell responses, such as differentiation, proliferation, and apoptosis, which are influenced by various receptor-ligand interactions, some stimulating, and others inhibiting and were often described using the "Hill function".⁴ The approach of modelling cell populations as differentials did not change as models evolved; however, repressor/activator functions started being stated and expressed more explicitly (See Supplemental Equations S1 – S3).

The modelling of the concentration of free OPG and RANKL is what allowed for the experimentation of the expression of the RANK/RANKL/OPG pathway on different osteoblast cells² (See Supplemental Equations S4 – S7).

Figure 2 is a visual schematic of most of the simple bone cell population models.² It includes two main types of cells: osteoblasts and osteoclasts, along with factors influencing their differentiation and elimination rates. The model also incorporates the RANK/RANKL/OPG pathway, where RANKL binds to RANK to encourage osteoclast precursor (OCp) differentiation. OPG binds to RANKL to inhibit OCp differentiation. PTH encourages RANKL to bind to RANK. TGF- β has an inhibitory effect on the differentiation of responding osteoblasts and encourages the differentiation of progenitors to responding osteoblasts as well as the apoptosis of osteoclasts.

Cell dynamics models with bone volume calculations and mechano-regulatory feedback

The next advancement in cell population models was the inclusion of mechano-regulatory feedback.^{3,31} Such models include an algorithm for estimating bone stiffness, bone strength, and poro-elastic properties of bone, based on the concept of multiscale continuum micromechanics as opposed to the use of the finite element (FE) method or molecular dynamics simulations.⁶²⁻⁶⁵ Multiscale continuum micromechanics is a computational technique linking behaviour of materials from the microscale to the macroscale. This model considers the hierarchical organisation of bone and is based on the volume fraction of the different bone constituents,⁶⁶ their mechanical properties, and their mechanical interactions.⁶⁷⁻⁶⁹

Current research suggests two ways that osteoblast precursors might react to mechanical stress: directly, through cell stretching caused by changes in the surrounding matrix, and indirectly, through chemical signals from osteocytes.⁷⁰⁻⁷⁵ Both methods are believed to control the growth of these precursor cells. In the first models which attempted to include mechanosensing into their biological algorithm, a general activator function of mechanical stress on osteoblast proliferation was used to simulate the effect of both methods. The maximum proliferation rate of precursor osteoblasts, P_{OBp} , was related to the activator function of extravascular bone matrix strains on OBp. The proliferation of OBp is promoted by strains in extravascular bone matrix. It has been found that low strain values reduce the proliferation rate by 25–50%.^{76,77}

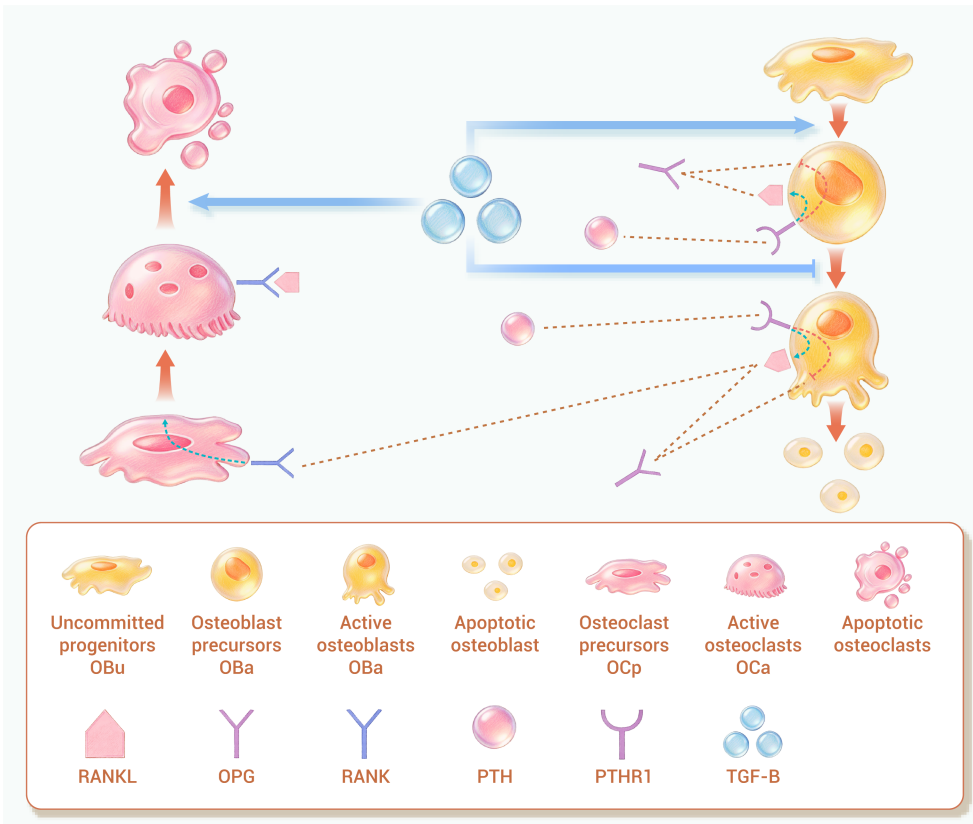


Figure 2. Visual representation of model depicting the interaction between bone cells It includes two main types of cells: osteoblasts and osteoclasts, along with factors influencing their differentiation and elimination rates. The model also incorporates the RANK–RANKL–OPG pathway, where RANKL binds to RANK to encourage OC precursor differentiation, while OPG binds to RANKL to inhibit OC precursor differentiation. TGF-β all have an inhibitory effect on the differentiation of responding OBs to active OBs yet simultaneously encourage the differentiation of progenitors to responding OBs as well as the apoptosis of osteoclasts. Double ended arrows indicate binding. Arrows with a plus sign indicate upregulation of a certain variable. Arrows with a dash at the end indicate an inhibitory effect. Adapted from Pivonka et al (2008).

*Notes: D_{OBu} means maximum differentiation rate of uncommitted osteoblast progenitor cells; OB_u means molar concentration of uncommitted osteoblast progenitor cells; $\pi_{act,OBu}^{TGF-\beta}$ means activator function of TGF-β on uncommitted osteoblasts; $POBu$ means maximum proliferation rate of precursor osteoblasts; OB_p means molar concentration of osteoblast precursor cells; $\pi_{act,OBp}^{mech}$ means activator function of extravascular bone matrix strains on osteoblast precursors as proliferation of osteoblast precursors is promoted by strains in extravascular bone matrix; D_{OBp} means maximum differentiation rate of

uncommitted osteoblast progenitor cells; $\pi_{rep,OBp}^{TGF-\beta}$ means repressor function of TGF-β on osteoblast precursors.

Other mechanobiological cell-population models extended this line of work in different directions. Bonfoh et al. coupled the Komarova formulation to strain energy density as the mechanical stimulus.⁹⁶ Rapisarda et al. added osteocyte-mediated remodelling pathways.^{97,98} Mertiya et al.⁹⁹ linked exercise loading to cortical bone remodelling, whereas Peyroteo et al.^{100,101} developed mechanobiological and meshless frameworks for load-driven remodelling. Ramtani et al.¹⁰² further extended the Komarova-based model to tumour-bone interactions.

Vemparala et al.¹⁰³ built on Rapisarda et al.^{97,98} by distinguishing active from inactive osteoblasts and osteoclasts and by adding bone-lining cells to the framework.

Cell population dynamics model with the inclusion of the Wnt pathway

The next development after the inclusion of mechanical stresses into the cell population models was the inclusion of the biochemical mechanistic pathway, which is directly influenced by the mechanical stresses, the Wnt pathway.

The first attempt at including this pathway was by including a parameter which quantifies how mechanical stimulation via the Wnt pathway is translated into increased pre-osteoblast proliferation in the mechanical activator function on pre-osteoblasts, the same activator function see in Equation 6.⁶ This is represented by the $\lambda_{WNT/SCLR}^{vas}$ term in the mechanical stress activator function on pre-osteoblasts, $\pi_{act,OBp}^{mech,vas}$. This model calculates mechanical stress using the pore pressure method described in the section above, hence the inclusion of the pore pressure terms in Equation 6.

$$\pi_{act,OBp}^{mech,vas} = \hat{\pi}_{act,OBp}^{mech,vas} [1 + \lambda_{OBp}^{vas} \left(\frac{p_{vas}^{peak} f}{p_{lac}^{peak} f} - 1 \right) + \lambda_{WNT/SCLR}^{vas} Ot \frac{1 - f_{vas}}{f_{vas}} \left(\frac{p_{lac}^{peak} f}{p_{vas}^{peak} f} - 1 \right)] \quad (6)$$

*Notes: $\hat{\pi}_{act,OBp}^{mech,vas}$ means the baseline value of $\pi_{act,OBp}^{mech,vas}$ means parameter which quantifies how mechanical stimulation is translated into increased pre-osteoblast proliferation; λ_{OBp}^{vas} means parameter which quantifies how mechanical stimulation via the Wnt pathway is translated into increased pre-osteoblast proliferation; $p_{lac}^{peak} f$, $p_{vas}^{peak} f$ mean vascular and lacunar pore pressure; O_t means extravascular osteocyte concentration; f_{vas} means

Such cell population dynamics models use continuum micromechanics to relate macroscopic strains to microscopic strains in the extravascular bone matrix. These microscopic strains influence cell behaviour through strain energy density (SED), a measure of mechanical strain and hydrostatic pressure and fluid flow in the bone matrix. SED is classically used in the field of mechanobiology.^{3,6,62-65,78-80} In bone biomechanics, SED is the mechanical energy absorbed by bone per unit volume due to applied strains.

Another method of incorporating physical stresses is as vascular and lacunar pore pressures where trapped fluid generates pore pressures through cyclical loading in bone. Those pressures influence macroscopic stresses and play a key role in cellular mechanobiology.⁸¹⁻⁹⁰ Such pressure calculations are functions of macroscopic stresses and second order Skempton tensors in papers like Scheiner et al and Pastrama et al.^{31,6} Skempton tensors are tensors which describe how a fluid filled porous material responds to mechanical loading by generating pore pressure.

Figure 3 shows how such cell population models of mechanobiology represent the bone material. Bone is treated as macroscopically homogeneous in this study while exhibiting microscopic heterogeneity. The RVE is defined as the smallest volume that captures the material's microstructure while remaining computationally efficient. In Figure 3, ℓ_{RVE} is the length of the RVE and d_{RVE} is the size of microscopic inhomogeneities in the bone. This study assumes that the overall constitutive behaviour of bone is anisotropic, meaning its mechanical properties depend on the loading direction due to the directional nature of the pore network and the inherent anisotropy of the bone matrix.^{67,91-95}

The concentration of OB_p cells is modelled using Equation 5.³ Red circles indicate terms added onto the OB_p ODE from the Pivonka et al model,⁴ described previously. Depending on the strain magnitude, the mechanical activator function on OB_p changes Supplemental Equations S8 – S12 represent the 3 scenarios modelled by Scheiner et al. for low straining,³ moderate, and high straining scenarios. Moreover, the RANKL dosage term and the as well as the maximum proliferation rate of precursor osteoblasts were also modified to incorporate SED's effects throughout the bone matrix (See Supplemental Equations S13 – S14).

$$\frac{dOB_p}{dt} = D_{OBu} OB_u \pi_{act,OBu}^{TGF-\beta} + P_{OBu} OB_p \pi_{act,OBp}^{mech} - DOB_p \cdot OB_p \cdot \pi_{rep,OBp}^{TGF-\beta} \quad (5)$$

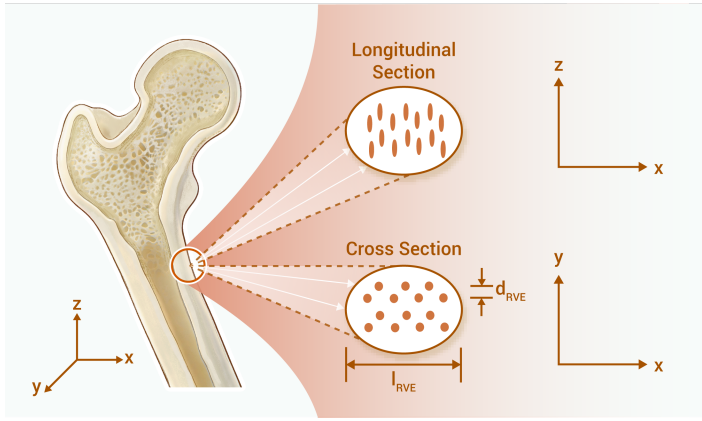


Figure 3. Visual representation of the representative volume element This micromechanical model treats cortical bone as a two-phase composite material, consisting of vascular pores and the extravascular bone matrix (the solid bone material). The analysis assumes a separation of scales, requiring that microstructural features are small enough relative to the overall bone dimensions to permit homogenization. Adapted from Scheiner et al (2013).

vascular porosity.

Osteocytes, the stress sensing cells, are embedded in the bone matrix and release sclerostin. Increased mechanical loading downregulates sclerostin production.^{72,104} When sclerostin binds to LRP5/6, it acts as an inhibitor of the Wnt protein, and the Wnt protein upregulates precursor osteoblast proliferation.^{76,77,105,106} Figure 4 illustrates the role of the Wnt pathway works in bone remodelling.

As these models evolved, more complex and realistic ways of modelling the Wnt pathway were introduced. Such models began including the concentration of free Sclerostin, competitive Sclerostin-LRP56 binding, Wnt-LRP56 binding, a repressor function of mechanical stress on sclerostin production, and an activator function of Wnt on pre-osteoblast production.^{32,33}

The first attempt at modelling the concentration of free sclerostin and its complexes made by binding to receptors, the expression of sclerostin was expressed using a second order polynomial equation (Equations 7 – 10).^{32,33} However, this makes the modelling of drugs that impact the Wnt pathway, like Romosozumab, more complex than necessary. This way of modelling Sclerostin was used to simulate Romosozumab in Martin et al.³² The quadratic equation approach creates a feedback loop where solving for sclerostin appears in both, the source and the sink terms, of the equations and makes for a stable sclerostin concentration in the model.

This model also included the positive effect that Wnt has on osteoblast proliferation and the repressive impact that strain energy density or mechanical stimulation of bone has on sclerostin production as repressor/activator functions (See Supplemental Equations S15 – S16).³²

$$[Sc] = \frac{-B + \sqrt{B^2 - 4AC}}{2A} \quad (7)$$

$$A = \tilde{D}_{Sc} + \frac{\beta_{Sc} [Ot] \pi_{rep,Sc}^{Wnt}}{[Sc]_{max}} \quad (8)$$

$$B = K_{d}^{Sc-LRP56} \left(\tilde{D}_{Sc} + \frac{\beta_{Sc} [Ot] \pi_{rep,Sc}^{Wnt}}{[Sc]_{max}} \right) \left(1 + \frac{[Wnt]}{K_{d}^{Wnt-LRP56}} \right) + \tilde{D}_{Sc-LRP56} [LRP56]_{tot} - P_{Sc,d} \beta_{Sc} [Ot] \pi_{rep,Sc}^{Wnt} \quad (9)$$

$$C = -P_{Sc,d} \beta_{Sc} [Ot] \pi_{rep,Sc}^{Wnt} \left(1 + \frac{[Wnt]}{K_{d}^{Wnt-LRP56}} \right) \quad (10)$$

*Notes: $K_{d}^{Sc-LRP56}$ The binding constant for sclerostin and LRP5/6, $K_{d}^{Wnt-LRP56}$ The binding constant for Wnt and LRP5/6, $\tilde{D}_{Sc-LRP56}$ The degradation rate of ScL-LRP56 complex, $[LRP56]_{tot}$ The total concentration of LRP5/6, $P_{Sc,d}$ External dosage term of sclerostin, β_{Sc} The production rate of sclerostin by osteocytes, $\tilde{D}_{Sc}$ Degradation rate of sclerostin, Ot Concentration of osteocytes, $\pi_{rep,Sc}^{Wnt}$ Repressor function of strain energy density, $[Sc]_{max}$ The maximum concentration of sclerostin allowed.

A simpler approach for modelling sclerostin was adopted as modelling shifted to including osteoporosis medications, like Denosumab and Romosozumab.³⁵ The concentration of free sclerostin began being modelled in a more standard and simple method (Equation 11), mirroring how free RANKL and OPG were modelled in Pivonka et al. 2008. In Equation 11,³⁵ it is much less computationally expensive to determine sclerostin. The old way of modelling sclerostin also included many more parameters which are realistically impossible to determine. Lately, the implementation of Sclerostin in Equation 11 more closely mimics RANKL implementation, making the implementation of Romosozumab and Denosumab more similar, maintaining drug implementation consistency in the model.

$$[Sc] = \frac{P_{Sc}}{\tilde{D}_{Sc} + \frac{\tilde{D}_{Sc-LRP56}}{K_{Sc-LRP56}} [Sc] + \frac{\tilde{D}_{Rmab-Sc}}{K_{Rmab-Sc}} [Rmab]_{BC}} \quad (11)$$

*Notes: $\tilde{D}_{Rmab-Sc}$ means the degradation rate of Romosozumab-sclerostin complex; $K_{Rmab-Sc}$ means the binding constant for Romosozumab and Sclerostin; $[Rmab]_{BC}$ means the concentration of Romosozumab in the bone compartment.

Pharmacokinetic Pharmacodynamic (PK-PD) modelling of osteoporosis drugs on bone

Pharmacokinetic modelling of drugs Pharmacokinetic modelling relates to how drugs are absorbed, distributed, and metabolized.^{7,9,10} The osteoporosis drugs that have been modelled in this way are Romosozumab and Denosumab.^{7-10,32,33,35} The models began with a single compartment and later evolved to two compartment PK-PD models.^{8-10,32,35} The drugs were assumed to be injected as a dose into the central compartment, CC (Equation 12). The absorption of the drug, $Dose_{D/R}$, is governed by a first order rate process, $k_{aD/R}$ from injection site into the central compartment.⁷⁻¹⁰ The elimination of the drug (Equation 13) from the central compartment is controlled by a linear first-order process, $k_{elD/R}$, and a Michaelis-Menten nonlinear saturation process, K_{MR} and $V_{maxD/R}$.

The concentration of the drug that enters the bone compartment BC (Equation 14) is governed by amount of the drug that is not excreted through urine, $\zeta_{D/R}$, multiplied by the amount of the drug eliminated from the central compartment with the natural degradation rate of the drug included as well as the competitive binding of the drug with RANKL if it is Denosumab and Sclerostin if it is Romosozumab.^{32,35}

$$\frac{d[Dmab/Rmab]_{CC}}{dt} = \frac{Dose_{D/R}}{V_{cD/R}/F_{D/R}} k_{aD/R} e^{-k_{aD/R}t} - Elim_{D/R} \quad (12)$$

*Notes: $[dmab/rmab]_{cc}$ means concentration of denosumab or romosozumab in the central compartment; $Dose_{D/R}$ means dose of denosumab $k_{aD/R}$ means first order rate of absorption constant; $Elim_{D/R}$ means denosumab elimination term; $V_{cD/R}/F_{D/R}$ means volume of the central compartment adjusted for bioavailability.

$$Elim_{D/R} = k_{elD/R} [Dmab/Rmab]_{CC} + \frac{V_{maxD/R}}{V_{cD/R}/F_{D/R}} \cdot \frac{[Dmab/Rmab]_{CC}}{K_{MR} + [Dmab/Rmab]_{CC}} \quad (13)$$

*Notes: $[Dmab/Rmab]_{cc}$ means concentration of denosumab or romosozumab in the central compartment; $V_{cD/R}/F_{D/R}$ means volume of the central compartment adjusted for bioavailability; $k_{elD/R}$ means first order rate of elimination constant; K_{MR} and $V_{maxD/R}$ mean michaelis-menten nonlinear saturation process constants.

$$[Dmab/Rmab]_{BC} = \frac{\zeta_{D/R} Elim_{D/R}}{\tilde{D}_{Dmab/Rmab_{BC}} + \frac{\tilde{D}_{Dmab-RANKL/Rmab-Sc}}{K_{Dmab-RANKL/Rmab-Sc}} [RANKL/Sc]} \quad (14)$$

*Notes: $\tilde{D}_{Dmab/Rmab_{BC}}$ means the degradation rate of denosumab/romosozumab out of the bone compartment; $\tilde{D}_{Dmab-RANKL/Rmab-Sc}$ means the degradation rate of the denosumab-rankl complex/romosozumab-scl complex; $K_{Dmab-RANKL/Rmab-Sc}$ means the binding rate constant of denosumab and rankl/romosozumab and sclerostin; $[Rankl/Ccl]$ means concentration of free rankl if the drug is denosumab and sclerostin if the drug is romosozumab; $\zeta_{D/R}$ means the amount of denosumab or romosozumab not excreted through urine.

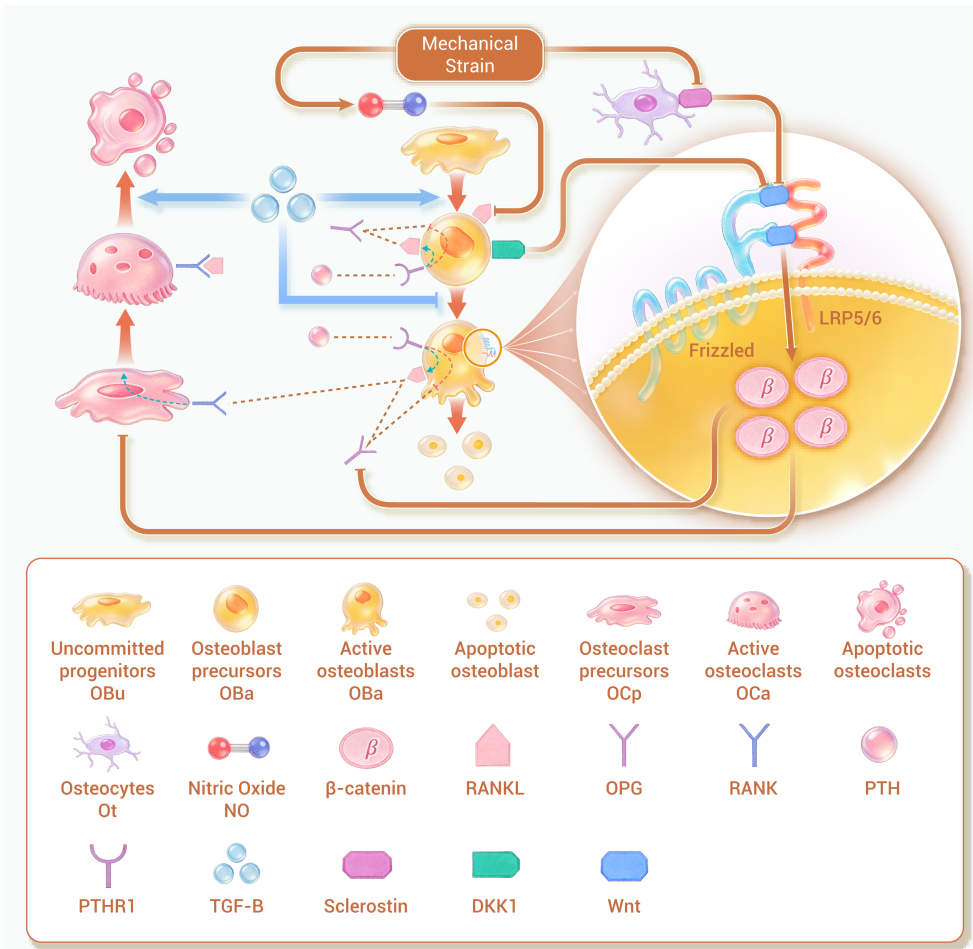


Figure 4. Schematic explaining how the Wnt pathway operates The figure includes 3 main cells: osteoblasts, osteoclasts, and osteocytes, along with factors influencing their differentiation and elimination rates. The model also incorporates the RANK–RANKL–OPG pathway, where RANKL binds to RANK to encourage osteoclast precursor differentiation, while OPG binds to RANKL to inhibit osteoclast precursor differentiation. TGF-B all have an inhibitory effect on the differentiation of responding osteoblasts as well as the apoptosis of osteoclasts. Wnt binds to Frizzled/LRP5/6 to increase the accumulation of β -catenin in the osteoblast. β -catenin increases the proliferation of osteoblast precursor, and increased the production of OPG. Sclerostin produced by osteocytes prevents Wnt from binding to Frizzled and LRP5/6. DKK produced by osteoblast precursors also has an inhibitory effect on Wnt binding to Frizzled/LRP5/6. Dashed lines indicate binding. Arrows indicate upregulation of a certain variable. Arrows with a dash at the end indicate an inhibitory effect.

ture and mechanical performance. This matters particularly in trabecular bone, where thickness, number, and connectivity govern strength. Because these architectural changes are omitted, cell population models cannot capture an important determinant of bone quality. Incorporating architecture would allow researchers to study how loading, hormones, or disease alter both cellular behaviour and the resulting bone structure, which is especially relevant in conditions such as osteoporosis. The Wnt pathway is also represented incompletely. Most models include sclerostin but

Pharmacodynamic modelling of denosumab Denosumab acts by binding to RANKL to prevent it from binding to RANK, so it is simulated by modelling the competitive binding of the concentration of Denosumab in the bone compartment to RANK within the concentration of the total RANKL concentration.^{10,35} The total concentration of RANKL being the concentration of all RANKL in the mode, bound and free. Equation 15 shows the concentration of the total amount of RANKL denoted by the concentration of free RANKL, RANKL bound to OPG, RANKL bound to RANK and lastly the RANKL bound to Denosumab in the bone compartment.^{10,35}

$$[RANKL]_{tot} = [RANKL] \cdot \left(1 + \frac{[OPG]}{K_{OPG-RANKL}} + \frac{[RANK]}{K_{RANK-RANKL}} + \frac{[Dmab]_{BC}}{K_{RANKL-Dmab}} \right) \quad (15)$$

*Notes: $[RANKL]_{tot}$ means the total concentration of RANKL (free and bound to its ligands); $[RANKL]$ means Concentration of free RANKL; $[OPG]$ means Concentration of free OPG; $[Dmab]_{BC}$ means Concentration of Denosumab in the bone compartment; $K_{OPG-RANKL}$ means Rate of OPG-RANKL binding; $K_{RANK-RANKL}$ means Rate of RANK-RANKL binding; $K_{RANKL-Dmab}$ means Rate of Denosumab-RANKL binding.

Pharmacodynamic modelling of romosozumab. Romosozumab binds to sclerostin to prevent it from binding to Wnt's receptors. This allows Wnt to bind to its receptors, continuing the β -catenin accumulation process described in the previous section. Romosozumab is modelled in the expression of free sclerostin concentration (Equation 13).^{32,35} Figure 5 is a schematic which visually explains the PK-PD modelling process for both, Denosumab and Romosozumab, and explains how the equations presented in this section fit in the model.

Limitations and identified gaps of cell population models

These models are valuable for analysing biochemical regulation of bone remodelling and for linking signalling pathways to net bone formation and resorption. Their main limitation is structural: they do not represent how spatial organisation and local cellular activity jointly determine bone architec-

omit DKK, even though both inhibitors contribute to remodelling dynamics.

Cell population models remained dominant because they are interpretable, relatively easy to parameterise, and well matched to long-term systemic and pharmacological questions. Their variables map directly onto experimental measurements such as turnover markers and cell counts, making them practical for drug and disease simulations even though they lack spatial detail. Cell population models predict changes in cell numbers, but not the evolving material properties or geometry of bone tissue. That limitation motivated tissue-level dynamics models, which replace discrete cell counts with continuous variables such as density or porosity and are often more efficient for macro-scale spatial simulations.

Cell population models reliably predict long-term trends in bone mass when calibrated against longitudinal DXA or biochemical marker data such as Martínez-Reina et al.⁷⁻¹⁰ However, their reliability degrades substantially when used to infer spatial bone loss patterns, as they lack any spatial representation of bone microarchitecture. A key conflicting finding in the literature concerns the nature of mechanical feedback. Furthermore, parameter settings vary significantly across research groups, prohibiting effective cross-comparisons of model predictions. Readers should therefore treat predictions of rapid bone loss with caution unless the mechanical rule has been specifically validated against time-lapse disuse data.

IN-SILICO BONE TISSUE DYNAMICS MODELS

Understanding how bone remodels and finding ways to influence this process requires a detailed knowledge of how osteoblasts deposit osteoid. The accompanying Figure 6 presents the chronological development of these models as reported in the literature.

Curvature's role in cell crowding and tissue shaping

Numerous mathematical models have been used to describe the growth and shaping of tissues in laboratory settings.¹⁰⁷⁻¹¹¹ These models propose that the speed of the tissue boundary or interface depends on its curvature.

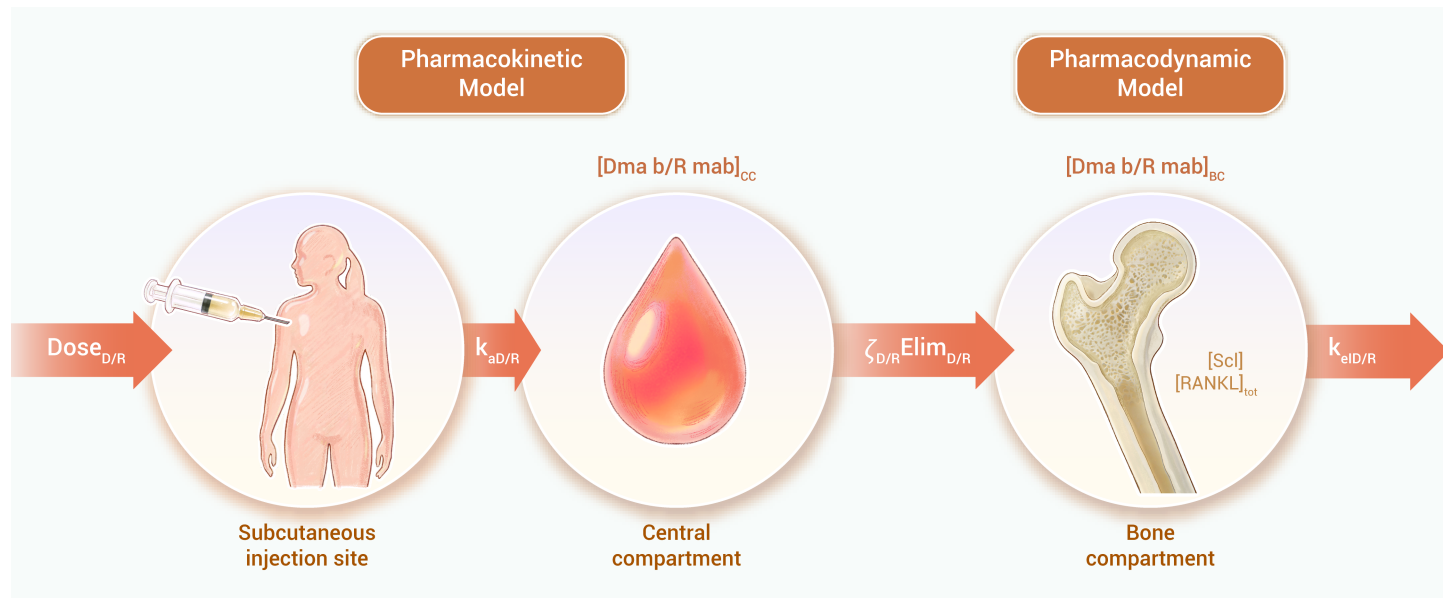


Figure 5. Schematic representation of how PK-PD modelling is implemented in cell population models The first 2 circles are the 1 compartment PK model. The third circle is the PD implementation in the bone compartment where the concentration of sclerostin and RANKL are modified by denosumab and Romosozumab.

So, regions with high mean curvature move or adjust faster, leading to a smoother shape. Those models compare surface tension in physics, where liquids minimize their surface area, with cell tension, where mechanical forces between cells act similarly, driving the tissue to smooth its shape. However, none of those models account for cell numbers which is crucial in physiological bone modelling.

Pascal Buenzli was one the first to include densities and numbers into models which predict tissue growth as well as differentiation of osteoblasts into osteocytes imbedded into the bone matrix in his 2011, 2014, 2015 and 2016 papers.¹¹²⁻¹¹⁵

The papers by Alias and Buenzli progressively advanced their mathematical model of curvature-controlled tissue growth.¹¹⁶⁻¹¹⁸ Alias & Buenzli investigates how the curvature of a tissue interface influences collective cell behaviour during tissue growth.¹¹⁸ The model highlights how tissue curvature influences cell behaviour. In convex regions, cells spread out, while in concave regions, they crowd together. This curvature effect is linked to tissue growth rates and is particularly relevant in processes like bone remodelling and wound healing (Figure 7).¹¹⁸⁻¹²⁰

This model demonstrates a hyperbolic curvature flow, where the normal acceleration of the interface depends on curvature, driven by geometric crowding or spreading of cells. Hyperbolic curvature flow here means that the speed and direction of a tissue's edge change dynamically based on how curved it is, with cell crowding or spreading driving this motion in a wave like, accelerated way. The study was limited to two-dimensional simulations using explicit parameterizations of the tissue interface, which restricted its application to simple geometries without topological changes. The explicit parametrization of the tissue interface means that the boundary of the growing bone tissue was directly defined by a set of predefined equations or geometric rules, rather than being inferred from the model. The focus was on establishing the mechanistic role of curvature in tissue growth, validated with analytical solutions for circular pores.

Pore geometry dictates bone formation

In 2018, Alias and Buenzli applied their model to osteoblast behaviour in bone tissue engineering, specifically examining how curvature and porosity influence cell activity.¹¹⁷ They attempted to understand how geometric factors such as curvature and porosity regulate osteoblast behaviour during bone pore infilling.¹²¹⁻¹²³ Alias and Buenzli develop a cell based mathematical model to simulate osteoblast behaviour during pore infilling.¹¹⁷ The model accounts for osteoblast bone formation, apoptosis rate, and movement along the bone surface, and osteocyte generation.

The authors created four models to test how curvature and porosity influence osteoblasts. In model 1, both osteoblast apoptosis and bone formation rely on curvature. In Model 2, bone formation relies on curvature and osteoblast apoptosis relies on porosity. In Model 3, bone formation relies on porosity and osteoblast apoptosis relies on curvature. In Model 4, both rates depend on porosity.

They found that Models 3 and 4 best matched experimental data because the bone formation rate depends on porosity. This suggests osteoblasts respond to pore wide mechanical or signalling cues rather than local curvature. While curvature influences cell crowding, porosity is the dominant factor for secretory behaviour. Irregular pores with sharp corners infilled faster due to higher cell crowding in concave regions.

Similar to their 2017 paper,¹¹⁸ the model remained constrained by the same 2D framework and explicit parameterizations, unable to simulate complex topological changes.

3D modelling enables complex shape changes

The Alias & Buenzli 2020 paper marked a significant advancement by introducing a level-set method to model tissue growth implicitly, enabling simulations in both two and three dimensions and accommodating topological changes such as fusion and fragmentation.¹¹⁶ The level-set method is a computational technique that treats shapes as contours in a 3D field to simulate biological growth in 3D.

The authors proposed a novel level-set method that couples two key components: a level-set function to implicitly track the evolving tissue interface and an additional Eulerian field representing the surface density of tissue synthesizing cells. A Eulerian field is a fixed grid based representation that tracks how cell density changes over time across the entire simulation space, without following individual cells. This coupling allows the model to simulate curvature driven growth where concave regions accelerate cell crowding and growth, while convex regions slow growth due to cell dispersion. The model generalises hyperbolic curvature flow by incorporating cell-based mechanics, enabling it to capture interface smoothing seen in biological systems.

Numerically, the method employs a hybrid approach combining level-set techniques with a cell-based particle method (CBPM) to efficiently track moving interfaces and cell densities. CBPM is a computational technique that tracks individual cells or clusters as discrete "particles" with properties like position, density, and activity, allowing precise modelling of cell-driven processes. The paper validated the model against analytical solutions and explicit parameterizations, demonstrating its accuracy in conserving cell numbers and handling complex geometries. Three numerical methods are

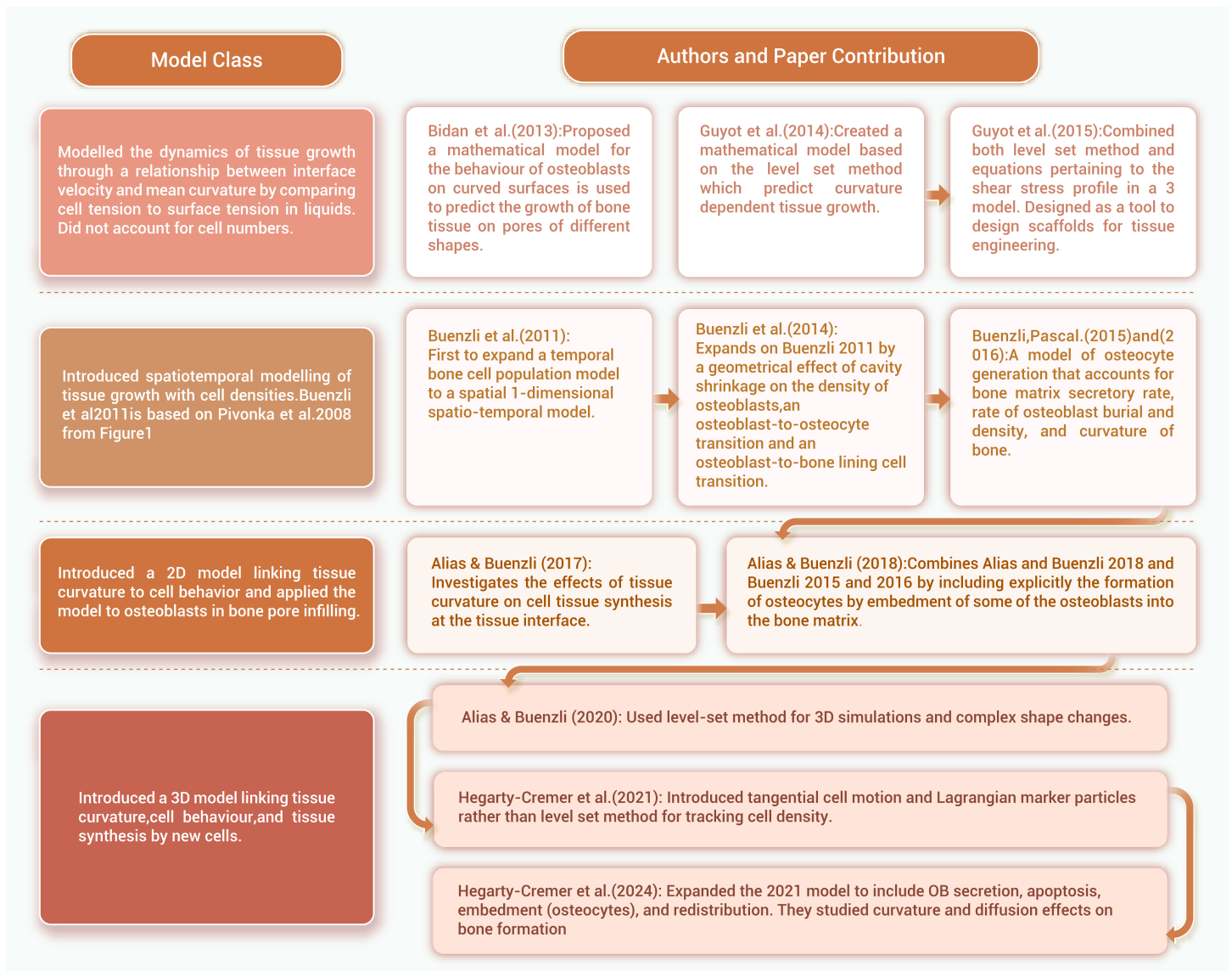


Figure 6. All relevant mathematical models of bone tissue growth in the literature and how they evolve from each other It begins with simple tissue growth models which modelled curvature-driven tissue growth, comparing it to surface tension in liquids and did not account for cell numbers, Buenzli et al (2014) and Buenzli et al (2015).^{115,114} Alias & Buenzli (2017) and (2018) both evolved from Buenzli et al. (2015).^{119,120,114} Hagarty-Cremer et al. (2024) evolved from Hagarty-Cremer et al. (2021) which evolved from Alias & Buenzli (2020) which evolved from Alias & Buenzli (2018).^{138,126,118,120} The column on the left describes the models and their evolution.¹⁰⁹⁻¹¹⁴

compared, with the third method, reinitializing both the level-set function and cell density field, showing superior performance in maintaining numerical conservation, especially in scenarios with sharp cusps or merging regions. In summary, the Alias & Buenzli 2017 paper established the foundational model in 2D, the Alias and Buelzi 2018 work applied it to biological data, and the Alias and Buelzi 2020 study generalized the framework to handle complex geometries and topological changes using level-set methods.¹¹⁶⁻¹¹⁸

Directed cell motion organizes bone structure

Hegarty-Cremer et al.,¹²⁴ presented a novel mathematical model that integrates curvature control and cell guidance mechanisms to study tissue growth and remodelling. The authors addressed a critical gap in understanding how tissue geometry and directed cell motion interact during biological processes like bone remodelling,^{125,117,126} wound healing,^{121,127} tumour growth and bio scaffold pore infilling.^{108,110,128-130} They introduced tangential cell motion, where cells move along the tissue surface. This allows the model to simulate anisotropic tissue properties, such as the alignment of collagen fibres in bone or the spiralling growth of shells. This is a significant advancement over previous models, which only considered normal growth directions.^{108,110,117,118}

The movement of the tissue interface is driven by new tissue formation

behind surface bound cells (Figure 8). As the tissue develops, local curvature influences interface stretching and cell density distribution convex regions cause cells to spread out while concave regions lead to cell crowding (Figure 8A). Additionally, directional tissue growth emerges from both this interface motion and lateral cell migration along the surface (Figure 8B).

The model is based on a partial differential equation (PDE) for cell density on a moving boundary. It accounts for cell proliferation, diffusion, and advection, while coupling these dynamics to the evolving tissue geometry. The equations are solved using a hybrid computational method called the cell-based particle method (CBPM),^{120,131,132} which efficiently tracks the moving interface and cell density.

The moving boundary is represented using Lagrangian marker particles, which move with the interface and track its position over time. Each marker particle is associated with a grid cell of an underlying Eulerian grid. The grid has a fixed cell length, Δx , which provides a structured framework for managing the particles. As the interface evolves, the marker particles may become unevenly distributed. To maintain quasi-uniform sampling of the interface, the particles are redistributed using the underlying grid. This ensures that the interface is accurately represented without gaps or clustering of particles. The paper claims that this method has a significant advantage over the level-set method because scalar quantities, such as cell density, can be directly

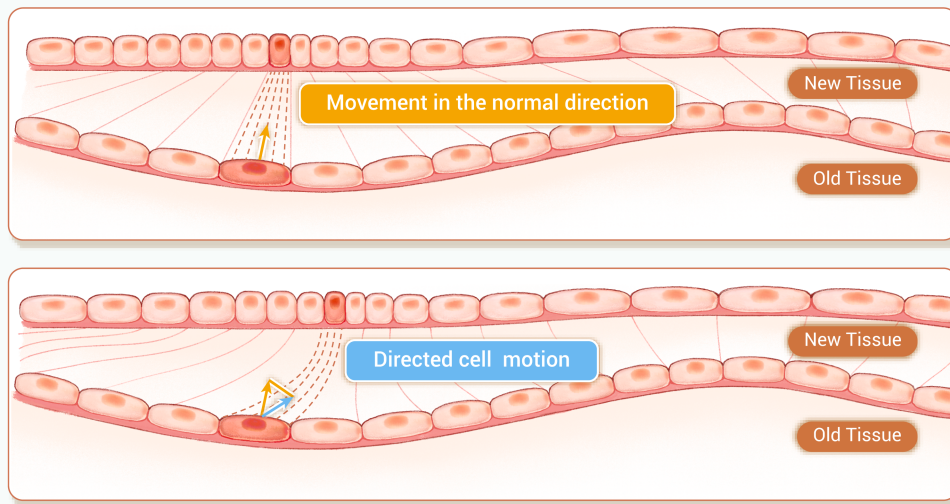


Figure 7. The influence of surface curvature on tissue growth mediated by surface-bound cells In regions with negative curvature ($\kappa < 0$) cell crowding is promoted resulting in faster tissue formation. Positive curvature ($\kappa > 0$) causes cell spreading, lowering cell density and slowing tissue formation.

models provide spatially explicit, high-fidelity solutions for stress and strain at the organ or tissue scale, but they do not inherently model adaptation or remodelling. Tissue-dynamics models require mechanical input to drive their update rules, yet they are not designed to compute detailed stress-strain fields. FEM can supply exactly that mechanical information, but it lacks any rule for how bone responds to those signals. Thus, each class answers a different question. FEM tells us where the mechanical stimulus is and tissue-dynamics

models tell how bone changes in response. associated with the marker particles. This is a significant advantage over methods like the level-set method, which require additional scalar fields, such as the level-set function in Alias & Buenzli,¹¹⁶ to represent quantities bound to the surface.^{116,133}

Alias and Buenzli simulated how osteoblasts fill circular pores in bone, demonstrating that tangential cell motion can explain the twisted plywood structure of collagen fibres in lamellar bone, matching experimental observations. The model also demonstrated that osteoclasts require directed motion to maintain stable resorption. Without such guidance, the resorption cavity would expand uncontrollably. The guidance mechanisms in the model are haptotaxis, where the cells move in response to a gradient of adhesion molecules on a substrate and chemotaxis where movement occurs along a chemical gradient.^{134,135}

Curvature and diffusion effects on bone formation

Hegarty-Cremer et al.,¹³⁶ presented a combined experimental and mathematical modelling study to investigate bone formation mechanisms during cortical bone remodelling, focusing on the asymmetry of osteon walls and how it evolves with age. The model was based on Hegarty-Cremer et al.¹²⁴ The authors developed a mathematical model to simulate bone formation in osteons. The model includes osteoblast behaviour, curvature effects, and diffusion. The osteoblast behaviour includes secretory activity, apoptosis, embedment as osteocytes, and redistribution along the bone surface. It also addresses crowding or spreading of osteoblasts due to changes in bone surface area during infilling.^{116,117}

Limitations and challenges of in-silico bone tissue dynamics models

The early Alias and Buenzli models were limited to two-dimensional simulations and a single continuous surface, so fusion and fragmentation could not be represented. The later level-set framework enabled complex three-dimensional geometries and topological change, but introduced numerical difficulties in preserving accurate cell counts, especially near sharp edges or merging interfaces.

Biologically, these models remain simplified. They omit most intercellular signalling and detailed responses to mechanical stimuli, and typically treat curvature as the main geometric driver while neglecting other physical influences such as strain patterns.

The Hegarty-Cremer et al.¹²⁴ model added cell guidance to curvature-driven growth, but still assumed simplified cell behaviour and did not incorporate biochemical feedback, broader microenvironmental effects, or clear molecular-to-tissue links. Tissue dynamics models occupy a useful middle ground. They capture spatial and topological change more realistically than cell population models yet remain much cheaper than micro-MPA approaches. Their main weakness is that mechanobiological coupling is usually phenomenological rather than explicitly grounded in cell or molecular behaviour.

Tissue-dynamics models capture net changes in bone geometry, they typically represent mechanics in a simplified or phenomenological way. FEM

models tell how bone changes in response.

FINITE ELEMENT METHOD MODELLING TECHNIQUES

Finite element methods (FEM) remain the main classical approach for bone mechanics and provide important context for later AI applications. Although they are not physiological remodelling models in the same sense as the other categories reviewed here, they are central for predicting where stress or strain concentrates and are widely used in cortical and cancellous bone analysis.

In cortical bone, FEM has been used to study collagen-mineral interfaces, representative volume elements, mineral heterogeneity, viscoelasticity, anisotropy, and electromechanical effects.¹³⁷⁻¹⁵⁴ These studies have improved mechanical insight, but they still rely on simplified geometry and usually omit biochemical signalling.

In trabecular bone, FEM has been used to analyse remodelling, anisotropy, damage, and implant loading.¹⁵⁴⁻¹⁵⁶ However, predictive fidelity remains limited by simplified architecture, weak treatment of marrow fluid interactions, and the absence of explicit mechanobiological signalling.

Other classical multiscale approaches, including quantum methods, molecular dynamics, continuum micromechanics, image-informed models, stochastic formulations, and optimisation-based models, have expanded mechanical understanding across scales.¹⁵⁷⁻¹⁷² Their main limitations are computational cost, short timescales, simplified assumptions, and limited biological realism.

Recent advances include hierarchical micromechanics for cortical bone and asymptotic expansion homogenization capturing elastic and plastic behaviours over large size ranges of bone (over six orders of magnitude); however, they were computationally intensive with over simplified stress assumptions. Image-informed models such as collagen alignment or osteon stiffness segmentation improve accuracy but still lack full mineralization representation.¹²⁸⁻¹³¹ Beyond deterministic approaches, some studies treat remodelling as a mixture of stochastic and directed events,^{131,133} while others frame it as an optimization process.^{79,134-136,173,174}

Limitations and challenges of finite element method models

FEM remains the gold standard for organ-scale bone mechanics because it directly solves solid mechanics on realistic geometries and produces outputs relevant to fracture risk and implant performance. Its strength is mechanical accuracy, not biological adaptation.

On its own, FEM cannot explain remodelling because it does not specify how cells sense and respond to mechanical cues. Remodelling applications therefore require an added mechanobiological rule and repeated solves on evolving geometries can become computationally expensive.

Overall, classical mechanics-based models are powerful but depend on explicit material laws, boundary conditions, and substantial computation for multiscale or nonlinear problems. Data-driven methods have emerged not as replacements, but as complementary tools that can bypass some constitutive assumptions and accelerate expensive simulations.

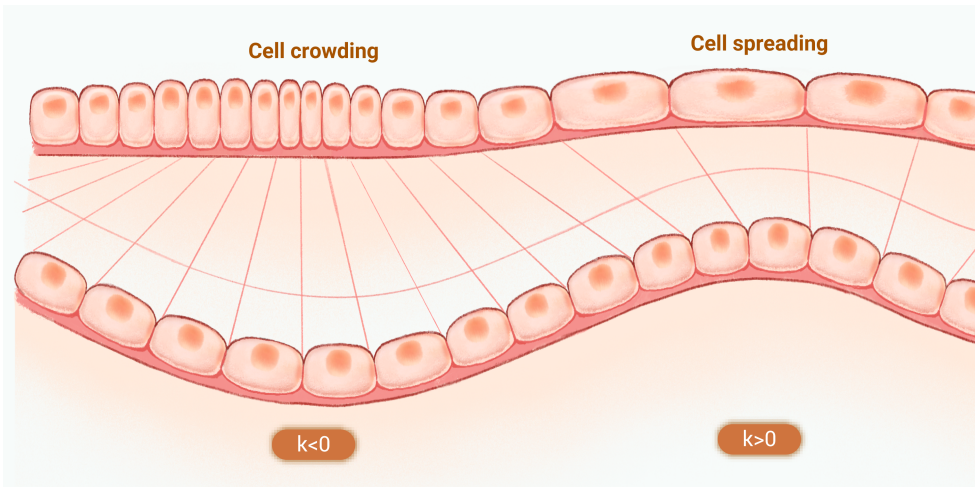


Figure 8. Curvature's effect on cell distribution and tissue development (A) Normal direction movement, highlighting how curvature alters cell density. Crowding in concave regions versus spreading in convex areas. (B) Combines curvature effects with guided cell motion, where lateral movement (orange lines) introduces structural anisotropy in the growing tissue.

performed on data from the same population or simulation, when tested on independent datasets, performance typically drops substantially.

At the micro-scale, first-principles agent-based models offer the mechanistic detail that purely data-driven methods lack. Rather than replacing AI, these models complement it: agent-based frameworks provide interpretable

biology, while AI can help parameterise or accelerate them.

MICRO MULTIPHYSICS AGENT BASED (MPA) MODELS OF BONE MECHANOBIOLOGY

These models are distinct because they show in detail how cells behave and how they interact with their environment. Building upon earlier bone cell population dynamics models, micro-MPA models of bone mechanobiology depict each cell as an independent entity that perceives and responds its local surroundings, including cytokine concentrations and mechanical signals. Thus cells influence their environment, leading to the emergence of the simulation of the microarchitecture of trabecular bone and how it responds to various external factors, including drugs.²¹

Among the existing models, only micro-MPA models possess the level of detail necessary to forecast how the complex interactions between cells and cytokines influence bone microarchitecture. Researchers such as Tourolle D,¹⁴ and Kameo et. al.,² have pioneered the development of micro-MPA models focused on OP and its treatments, including bisphosphonates and RANKL inhibitors.²¹

The Tourolle et al.¹³ model has been used to simulate ten years of the effects of Denosumab on bone remodelling in human biopsies, as well as an *in-silico* micro-multiphysics agent-based model of bone regeneration in a mouse femur defect model.¹² A Micro-Multiphysics agent-based model is a computational approach that combines cells with physics-based interactions to simulate how individual cell behaviours and microenvironments drive tissue scale processes like bone remodelling or in Tourolle's (2019) paper, fracture healing.¹⁴

Multiscale agent-based bone remodelling model

Kameo et al.'s biological approach draws heavily from the methodologies outlined in several previous studies.^{2,3,4} The authors developed an *in-silico* model predicated on the concept that mechanosensitive osteocytes within the bone matrix coordinate both bone resorption and formation through localized intercellular signalling.² This model disregards systemic hormonal fluctuations.

Central to this model is the assumption that osteocytes regulate bone remodelling to achieve a locally uniform stress and strain state, rather than focusing solely on their magnitude. This theory suggests that bone remodelling is influenced by spatial variations in stress and strain within bone tissue.^{133,165} This hypothesis is credible as it is supported by studies indicating that osteocytes respond to interstitial fluid flow, which is influenced by pressure gradients rather than absolute fluid pressure.²¹⁰ This means that interstitial fluid flows because of differences in pressure between areas, not because there's a certain amount of fluid in one spot in the matrix. The foundational FE model developed by Adachi et al.,¹³³ adheres to Wolff's law, positing that bone adapts its trabecular orientation to align with principal stress trajectories.^{211,212}

The mechanical signal, S_{occy} , is derived from osteocyte density, $\rho_{occy}(x)$,²¹³ and modified equivalent stress $\sigma_{occy}(x)$, as shown in Equation 16. However, the bone remodelling ultimately hinges on mechanical information S_i calcu-

DATA DRIVEN AND HYBRID MODELS

Artificial intelligence (AI), including machine learning and deep learning, offers a data-driven complement to classical bone modelling.¹⁷⁵⁻¹⁷⁷ In this field, such methods are mainly used for structure-property prediction, adaptation or regeneration problems, and inverse modelling.¹⁷⁸⁻¹⁸⁷ Their main appeal is speed, flexibility with noisy data, and reduced reliance on explicit constitutive laws.

For structure-property prediction, ANNs and CNNs have been used to infer mechanical response or trabecular arrangement from image or FE-derived data.¹⁸⁸⁻¹⁹⁷ These models can approximate equilibrium remodelling patterns efficiently, but their fidelity depends strongly on the quality and coverage of the training data.

For time-evolving remodelling, recurrent architectures are better suited because they can retain temporal information. Recent studies have proposed several recurrent or recurrent-fuzzy variants that improve efficiency or stability over standard feedforward models.¹⁹⁸⁻²⁰⁰

A major limitation of purely data-driven models is that they can lack physical context, require large datasets, and produce non-physical outputs.²⁰¹⁻²⁰³ This has motivated hybrid strategies that combine machine learning with established mechanical models.

A representative example is the FE-ANN hybrid framework, in which neural networks emulate expensive microscale FE calculations while preserving the broader mechanobiological workflow.^{180,204-208} These approaches can reduce computational cost substantially, but training can still be expensive and unstable.

Other hybrid examples include FEA-DVC approaches and nanoscale FEA-ANN models.^{179-183,209} Their common limitations are simplified anisotropy, limited generalisability, and weak feedback between damage, adaptation, and remodelling.

Limitations and identified gaps of data driven and hybrid models

AI and data-driven models are promising for pattern recognition, surrogate acceleration, and inverse problems, but they have not replaced mechanistic models in bone remodelling. Their main limitations are heavy data requirements, weak extrapolation outside the training distribution, and limited mechanistic interpretability. Physics-informed variants help but are harder to train. For this reason, AI is most valuable in hybrid workflows rather than as a standalone replacement.

AI models can achieve high accuracy within their training distribution for predicting material properties and biomechanical responses. However, reliability outside the training domain is poor and often unmeasured. A conflicting finding in the literature is whether physics-informed neural networks (PINNs) consistently outperform pure data-driven ANNs for bone mechanics. Some studies report that PINNs reduce prediction error substantially in sparse-data regimes, while others find that PINN performance is highly unstable, particularly when clinical supervision is limited. This conflict arises because PINN performance is highly sensitive to the weighting of PDE residuals versus data loss, and no standardised tuning protocol exists. For pure data-driven models, reliability is often overestimated because cross-validation is

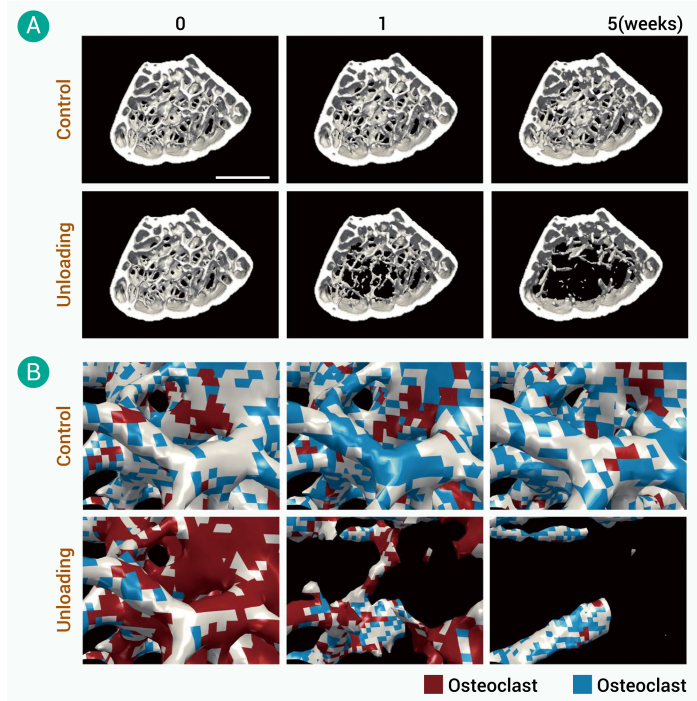


Figure 9. Figure depicting Kameo et al.'s 2020 model² This figure demonstrates the results of modelling osteoporosis and osteopetrosis. (A) Trabecular bone response to 5 weeks in control then reduced strain conditions (10% of control strain). (B) A close-up of the trabeculae in the control and unloading conditions over 5 weeks showing how the model assigns cells to the trabecular surface. Osteoclasts are red and osteoblasts are blue. Reproduced with permission from AAAS.

lated as the ratio of S_{ocy} to S_d , shown in Equation 17. S_d represents neighbouring mechanical states.

$$S_{ocy} = \rho_{ocy}(x) \cdot \sigma_{ocy}(x) \quad (16)$$

*Notes: $\rho_{ocy}(x)$ is the osteocyte density, $\sigma_{ocy}(x)$ is the modified equivalent stress.

$$S_i(x_{sf}) = S_{ocy}(x_{sf}) / S_d(x_{sf}) \quad (17)$$

*Notes: S_d is the neighbouring mechanical stress, S_{ocy} is the mechanical signal.

Osteocytes respond to mechanical stimuli by either activating or repressing osteoclast and osteoblast activities. Additionally, biochemical factors are incorporated via activator or repressor functions based on the Hill Function. The Hill function is a mathematical model that describes the relationship between the concentration of a substance and a biological response within a chemical environment.⁴

Intercellular signalling is formalized through equations, enabling the representation of molecular concentrations over time within the bone marrow. Notably, molecules such as Sclerostin, the RANKL/RANK/OPG pathway, and Semaphorin 3A (Sema3A) are integrated into the model based on signalling Equation 18. Sema3A is a protein which regulates bone remodelling by regulating osteoblastogenesis and osteoclastogenesis.²¹⁴ Sema3A works by binding to two receptors, neuropilin-1 (Nrp-1) and Plexin-A family, resulting in the formation of a functional Sema3A/Nrp-1/Plexin-A complex. Moreover, Sema3A has been linked by Wnt signalling by miR-196b-5p, a microRNA linked to cancers. miR-196b-5p has been found to inhibit Sema3A which inhibits Wnt.²¹⁵⁻²¹⁷

$$\frac{\delta \phi}{\delta t} = P_i - k_{deg} \phi_i + D_i \nabla^2 \phi_i - \sum_j R_{ij}(\phi_i, \phi_j) \quad (18)$$

*Notes: P_i means Production rate; k_{deg} means Degradation rate constant; D_i means Diffusion coefficient; R_{ij} means Reaction of molecule i with molecule j .

The model accounts for the likelihood of cell genesis and apoptosis in

osteoblasts and osteoclasts through activator and repressor functions, with the number density of stem cells for both cell lines held constant. Chemical signalling as well as a mechanical signalling in the model are function of the probability functions of the formation or apoptosis of the cells.

Kameo et al.² used their model to simulate numerous scenarios such as loading, unloading, drug treatments, and osteoporosis. Figure 9 below shows an *in-silico* simulation of osteoporosis compared with a controlled scenario. Figure 9 demonstrates how the model determines whether a surface is an osteoblast or an osteoclast and subsequently removes or adds and bone voxel to simulate resorption or formation.

Multiscale agent-based fracture healing model

Tourolle's (2019) model was used as a basis for many studies.¹¹⁻¹³ Tourolle's model is an *in-silico* model of mechanoregulated fracture healing using a combined micro-scale multiphysics and an agent-based approach and was validated with time-lapsed *in vivo* micro-CT measurements. The model included four levels: two fine lattice levels at 10.5 μm , a coarse lattice level at 42 μm , and a fourth level for intra-cellular updates of agent-based modelling. The direction in which Tourolle took the model represents the path forward for future research due to its complexities as well as the of the model's outcomes with *in vivo* mouse models.

The first fine lattice represented the cell space, where each cell occupied a single voxel, while the second fine lattice was used for chemical concentrations. A voxel is a representation of 3D space in a regular grid, the 3D version of a pixel. The coarse lattice calculated oxygen transport and consumption kinetics. When a voxel was more than 50% filled with osteoid, either no cell could enter if unoccupied, or if occupied, the cell became embedded and immobile. Reflective boundary conditions represented the callus boundaries, allowing information to enter and exit only through the vasculature cells, which acted as a source or sink for biomolecules and oxygen. Surface cells migrated randomly along the bone surface, and both cell proliferation and apoptosis were stochastic.

Vascular development was also probabilistic. Osteoclasts formed clusters requiring at least six cells in contact, with their movement biased along the RANKL gradient, while osteoblasts formed layers through random movement until joining a layer of three or more cells. Cell-substrate interactions were defined by a microscale mathematical framework, where bone and osteoid acted as substrates for the cells. The substrate domain is given in Equation 19. Cytokines diffuse throughout substrate domain as given Equation 20.

$$\Omega_{sub} = \{x \in R^3 : \text{substrate} > 0.5\} \quad (19)$$

*Notes: Ω_{sub} is the substrate domain, R means the set of all voxels within the region of interest.

$$\frac{\delta M}{\delta t} = D \nabla^2 M(x, t), t > 0, x \in \Omega \quad (20)$$

*Notes: D means Diffusivity; M means Cytokines; t means Time.

Cells within bone marrow, such as MSCs, HSCs, immune cells, and tip cells, moved randomly in a Moore neighbourhood, which is a 2D square lattice of nine cells in a 2D grid which allows cells to move randomly to any of these unoccupied neighbouring positions. These cells only moved to unoccupied voxels. Surface-attached cells like osteoblasts, osteoclasts, pre-osteoclasts, and lining cells had specific movement patterns based on their type. Osteoblasts had two movement modes: if not part of a layer, they moved randomly along the iso-surface of osteoid until they could form or join a layer. An iso surface is a 3D surface where a specific property has a constant value, acting like a line that guides cell movement. If part of a layer, they moved only if mechanically stimulated, the voxel beneath was filled with osteoid, and the voxel behind them was empty. Once within the osteoid iso-surface, osteoblasts were considered trapped and differentiated into pre-osteocytes.

Pre-osteoclast movement involved forming clusters with other Osteoclasts along the iso-surface of mineral > 0.5 . There was a 40% chance they followed the RANKL gradient, a 40% chance they moved randomly, and a 20% chance they stayed in place. Osteoclasts remained static until detachment from a surface voxel, moved like pre-osteoclasts. If unable to reattach, pre-osteoclasts and osteoclasts die.

Chemicals included in the model were RANKL, OPG, VEGF, sclerostin, TGF- β , RANKL-OPG, and oxygen. Mechanosensing by osteoblasts and osteocytes was included, with effective strain being linearly proportional to cell function activation. Binding kinetics were also incorporated into the model. The binding sites [B] on cells that bind with proteins [M] to produce a new compound [BM] are given in Equation 21. The reactions are discretised using ODEs characterised by Equation 22. For instance, the behaviour of RANKL is given by Equation 23.



*Notes: [B] are the binding sites and [M] are the proteins. [BM] is a new compound formed.

$$\frac{\delta[BM]}{\delta t} = K_a[M][B] - K_d[BM] \quad (22)$$

*Notes: [B] are the binding sites and [M] are the proteins. [BM] is a new compound formed, K_a means association constant; K_d means dissociation constant.

$$\frac{\delta[RANKL]}{\delta t} = K_a^{RANKL}[RANKL][OPG] - K_d^{RANKL}[RANKL \cdot OPG] \quad (23)$$

*Notes: K_a means association constant; K_d means dissociation constant; [RANKL] means RANKL concentration; [OPG] means OPG concentration.

In the Tourolle model, mineralization kinetics were also quantified and considered a passive process, shown in Equation 24. The amount of unbound osteoid represented the available sites for mineral formation, with the amount of available mineral in solute form considered constant. The maximum amount of mineral in a voxel was limited by the amount of osteoid within that voxel. In the proposed model, a mineralization rate of 0.125 per day was used.

$$\frac{d[\text{mineral}]}{dt} = k_{\text{mineralisation}} ([\text{osteoid}] - [\text{mineral}]) \cdot [\text{mineral}_{\text{solute}}] \quad (24)$$

*Notes: $k_{\text{mineralisation}}$ means the rate of mineralisation, ([osteoid]) is the concentration of osteoid, [mineral] is the concentration of mineral, [mineral_{solute}] is the concentration of mineral that is a solute.

The mechanical signal was calculated using the FE method with the solver ParOSol.²¹⁸ Mineral concentration was scaled linearly from a range of [0,1] to a BMD range of [0,800] mg HA/cm³. This BMD was converted to stiffness. Effective strain was calculated for each voxel, and the conversion of effective strain to a mechanical signal was performed using Gaussian dilation. Gaussian dilation is a mathematical operation that smooths and spreads out localized strain values across neighbouring voxels using a Gaussian (bell-curve) weighting function to simulate how mechanical signals diffuse through bone tissue. Soft tissue and hard tissue were treated independently i.e. marrow and bone.

Limitations and identified gaps of the micro MPA models

Micro-MPA models offer high biological and mechanical fidelity, but their translation is limited by validation, parameter identifiability, and computational cost. They require rare high-resolution longitudinal data for calibration, often involve many poorly constrained parameters, and remain expensive to run repeatedly for uncertainty analysis. As a result, they are currently most useful as research tools and proof-of-concept platforms rather than routine translational models.

There are numerous limitations of the Kameo model. Firstly, the model did not validate the microarchitecture of trabecular bone using specific methods for analysing bone structure, which is a critical aspect of bone health and strength. Trabecular microarchitecture validation involves comparing a model's simulated trabecular bone structure against high-resolution imaging data (like micro-CT scans), or experimental measurements to ensure it accurately replicates real bone's porous network. Accurate representation and validation of trabecular microarchitecture are essential for understanding how bone responds to various stimuli and for predicting fracture risks accurately.

Additionally, the model simplified the complex cell biology of bone remodelling. Osteocytes, which are the most abundant cells in bone, play a crucial

role in bone homeostasis. In response to mechanical stimuli, osteocytes can either activate or repress the activities of Osteoclasts and osteoblasts through intricate signalling pathways. These pathways involve numerous molecules and interactions and simplifying them can lead to an incomplete or inaccurate understanding of bone remodelling dynamics. Furthermore, hormonal signalling, which is essential in bone metabolism, was not reflected in the model. Pathways such as the Wnt signalling pathway, which plays a significant role in bone formation and remodelling, were also not fully incorporated, limiting the model's ability to simulate these critical regulatory mechanisms. Moreover, sex hormones are also not incorporated in any of the models, and they can be crucial in accurately representing bone remodelling.²¹⁹

The Tourolle model also has several limitations. The use of *in-vivo* micro-computed tomography, while providing detailed images of hard callus formation, did not offer insights into the development of cartilaginous soft callus. This limitation is significant because the soft callus stage is crucial in the bone healing process. MRI would have been a more suitable imaging modality as it allows for the visualization of both osteoid formation and its subsequent conversion into mineralized bone, providing a more comprehensive understanding of the bone healing process.

Moreover, the model's use of a homogeneous Poisson's ratio failed to reflect the realistic mechanical environment of bone. A homogeneous Poisson's ratio means the model assumed bone tissue deforms uniformly. The FE solver, ParOSol, cannot handle meshes with a heterogeneous Poisson's ratio, which limits the model's accuracy in simulating bone's mechanical behaviour. A heterogeneous Poisson's ratio is more representative of the actual mechanical environment in bone, where regions may exhibit varying mechanical properties.

The reliance on a linear FE solver was another limitation. Bone, especially soft tissue, behaves as a poro-elastic material, meaning it has both fluid and solid characteristics. A linear solver does not adequately capture this behaviour, but the absence of scalable non-linear or poro-elastic micro-FE solvers necessitated its use. This limitation means that the model could not accurately simulate the complex mechanical interactions within the bone tissue.

Further, the model simplified the biological processes involved in bone remodelling. For instance, Osteoclasts, which are naturally multi-nucleated cells, were modelled as clusters of individual cells. Similarly, osteoblast "layers" were represented as clusters of touching osteoblasts without considering the geometric constraints that typically govern their organization and function in real bone tissue.

Notably, these models fail to account for curvature- and porosity-dependent growth mechanisms, which fundamentally regulate cellular patterning through crowding and spreading phenomena and directional growth components,^{124,136} particularly the distinction between normal and tangential tissue deposition. The omission of tangential growth dynamics represents a significant limitation, as Hegarty-Cremer's 2021 work established its essential role in determining final bone architecture.¹²⁴

Taken together, these modelling families face different but complementary limitations. This makes integration, rather than replacement, the clearest route forward for improving calibration, validation, and predictive utility.

CHALLENGES AND PROSPECTS

Across modelling classes, the main barriers to progress are shared: limited validation, weak parameter identifiability, incomplete uncertainty quantification, and the difficulty of coupling mechanics and biology in a tractable, data-supported way. Addressing these issues will be essential for reproducibility and translation.

Field-wide bottlenecks beyond individual model families. Beyond the limitations specific to each modelling family, four cross-cutting bottlenecks slow the entire field. Those limitations are reproducibility, standardisation, open data, and clinical translation barriers. The majority of published bone remodelling models are not accompanied by publicly available code or complete parameter sets. Independent re-implementation is often impossible, and reported results cannot be verified. No community-agreed bench-

Table 1. Comparative model-selection framework for physiological bone remodelling models The table maps each modelling category to its best-suited research questions, typical outputs, spatio-temporal scale, computational cost, minimum data required for calibration and validation, validation level, key validity/accuracy boundaries, principal limitations, and representative disease or application areas. It is intended to help readers identify which model class is most appropriate for a given biological question, scale, dataset, and computational constraint.

Modelling Category	Best Suited Research Questions	Typical Outputs	Minimal Data for Calibration/Validation	Key Validity / Accuracy Boundaries	Validation Level	Principal Limitations	Representative Disease/Application Areas	Computational Cost	Typical spatio-temporal scales
Classic Finite Element Method	How do loads or implants affect local stress/strain and bone strength?	Stress/strain fields or displacement.	Bone geometry, material properties, boundary conditions, real life validation data	Linear elasticity valid for small strains, non-linear models needed for overload, mesh-dependent	Against strain gauges or DVC.	Requires explicit material law, costly for multiscale or time-evolving, no direct cell biology	Osteoporotic fracture risk, implant design, fracture healing.	Hours to Days	Organ to tissue (mm–cm), static or quasi-static (second to minutes)
Cell Population Dynamics	How do systemic/local factors change cell numbers and bone mass over years?	Time courses of osteoblast/osteoclast populations, bone density, protein dynamics	Cell kinetic parameters/dose response data.	Valid for bulk bone mass trends, not spatial	Quantitative error against DXA or markers.	No microarchitecture limited mechanobiological coupling, parameters often non-identifiable	Osteoporosis, age-related bone loss, drug development.	Minutes/Hours	Cell/RVE. Months to decades
Tissue Dynamics	How does bone shape adapt to changing loads? How do curvature-driven processes evolve?	Changes in bone surface.	Tissue parameters, local curvature and mechanical stimuli	Valid for curvature-controlled remodelling, assumes constant tissue material properties	Qualitative pattern matching (trabecular bone).	Simplified signalling and mechanotransduction, often 2D or simplified 3D, limited cellular detail	Osteoporosis, ageing remodelling, disuse.	Hours	Tissue scale (100 μ m–cm). Weeks to months.
Micro-Multiphysics Agent Based	How do cell behaviours, biochemical transport, and mechanical cues interact to produce tissue-scale patterns?	Spatiotemporal maps of cell positions, bone deposition/resorption, local strains	High-resolution imaging (time-lapse), mechanical data, transport coefficients	Valid at microscopic scale (100s μ m) for short-to-medium times	Qualitative agreement with in vitro or ex vivo imaging.	High computational cost, parameter identifiability, uncertainty quantification	Fracture healing (callus formation), bone regeneration (scaffolds), early osteoporotic changes.	Hours to Days	Tissue Scale. Days to Weeks.
Data Driven Models	Can we bypass explicit material laws to accelerate simulations?	Predicted density, stress, strain, or trabecular arrangement.	Large training datasets, boundary data, high-fidelity simulation outputs	Valid only within training distribution unless physics-constrained.	High within training distribution, out-of-distribution validation often poor, uncertainty estimates rarely reported.	Black-box risk, non-physical outputs without constraint, data hungry, training cost.	Osteoporosis (trabecular pattern prediction), implant optimisation (surrogate assisted), fracture healing.	Hours to Days for training and minutes for inference.	Depends on the training data.

mark problems exist for bone remodelling (unlike FE analysis of implants where standardised test cases are routine). Different groups use incompatible input formats, output metrics, and validation protocols, making direct comparison of model performance impossible. Longitudinal, multi-scale datasets that couple imaging (micro-CT), mechanical loading histories, and cellular or molecular readouts are extremely scarce, especially for human bone. Without such data, models cannot be rigorously calibrated or validated outside a narrow range of conditions. Lastly, pathways for in silico bone remodelling models are undefined. Most models lack prospective clinical validation, and integration with standard clinical data (DXA, CT, biochemical

markers) has not been demonstrated. Clinicians and regulators therefore have no evidence-based framework for trusting model predictions for individual patients. Addressing these bottlenecks will require initiatives such as shared code repositories, benchmark challenges, open datasets, and regulatory science partnerships rather than isolated technical advances.

Near-term prospects and emerging directions. Progress is most likely to come from hybrid workflows that combine efficient systemic models with spatially explicit local modules where needed. Shared benchmarks, clearer reporting standards, and prospective validation against longitudinal imaging would also improve comparability across studies.

Roles and boundaries of AI in bone remodelling modelling. AI is most useful here for surrogate modelling, inverse problems, segmentation, and data assimilation. Its value depends on integration with mechanistic models, transparent reporting, and rigorous validation. To avoid misleading presentation, we explicitly distinguish where AI models are appropriate as supporting tools and where they are not. AI (including ANNs, CNNs, RNNs, PINNs, and hybrid FE-ANN surrogates) is suitable for surrogate acceleration, inverse problem, and pattern recognition. AI is not suitable, at this time, for discovering causal biological, extrapolating far outside the training data distribution, or replacing biological or clinical validation. The most powerful and reliable use of AI in this field is currently in hybrid workflows where a mechanistic model provides physical structure, and AI accelerates or informs specific sub-tasks. Researchers should avoid presenting AI as a stand-alone replacement for mechanistic understanding, and manuscripts should explicitly state which of these roles the AI component fulfils.

Overall, the field is moving toward models that are not only more detailed, but also more testable, with explicit assumptions, quantified uncertainty, and clearer links to longitudinal data. In summary, bone modelling now consists of complementary approaches rather than a single dominant framework. The most useful advances will likely come from principled combinations of mechanical, biological, and data-driven methods.

Model selection summary

Table 1 summarises the main trade-offs across modelling categories, including the questions they suit best, their typical outputs, their data requirements, and their main limitations. The aim is not to prescribe a single best model, but to make model choice more explicit and question driven.

CONCLUSION

Bone remodelling models have progressed from systemic frameworks centred on cell population dynamics to spatially explicit micro-MPA models. Foundational work by Lemaire and Pivonka established a quantitative basis for biochemical regulation, particularly the RANK/RANKL/OPG axis, but these early frameworks were largely non-spatial and therefore could not capture architectural heterogeneity or local mechanical-biological coupling.

Micro-MPA models marked a major shift by integrating biochemical signalling with mechanical stimuli and by treating bone cells as autonomous agents that respond to local microenvironments. These models offer deeper insight into how physics and biology jointly shape bone morphology, but they also expose major technical challenges, especially in reproducing trabecular microarchitecture and heterogeneous tissue mechanics.

Even so, many current models still underrepresent the poroelastic nature of bone and simplify key biological pathways such as Wnt signalling and systemic hormonal feedback. These omissions become especially visible in pharmacological applications, where clinically observed effects, such as the waning efficacy of romosozumab after 12 months, remain difficult to reproduce mechanistically.

Returning to the four questions posed in the introduction, no single modelling class is sufficient across all scales and applications. FEM remains strongest for macro-scale mechanics, cell population models for interpretable long-horizon and pharmacological simulations, tissue dynamics models for spatial geometry change, and micro-MPA models for high-fidelity coupling of cells, mechanics, and microarchitecture. AI and other data-driven methods can accelerate these approaches and support inverse problems, but their value depends on careful integration with mechanistic models and rigorous validation. The field's next step is therefore not complexity alone, but integrated and testable workflows that make assumptions explicit and improve calibration and validation.

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AUTHOR CONTRIBUTIONS

Conceptualisation: Ian Mudway, Joudi Altaieb. Investigation: Joudi Altaieb. Funding Acquisition: Ian Mudway. Supervision: Richard Abel, Ian Mudway, Ulrich Hansen. Writing Original Draft: Joudi Altaieb. Writing, Review and Editing: Joudi Altaieb, Richard Abel, Ian Mudway, Ulrich Hansen. All authors contributed to the manuscript and approved the final version.

DECLARATION OF INTERESTS

The authors declare no competing interests.

DATA AND CODE AVAILABILITY

No new data were created or analysed in this study.

SUPPLEMENTAL INFORMATION

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