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Machine learning-enhanced nonlinear differential equation model for predicting osteoporosis progression using bone density imaging data

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Abstract

Osteoporosis refers to a chronic bone disease that is characterised by bone loss, microarchitectural loss and high likelihood of getting fragility fracture. Proper forecasting of disease in order to intervene early and plan therapy is crucial. The current research will develop a hybrid modelling system that combines machine learning with nonlinear differential equations to predict the development of osteoporosis through longitudinal bone density imaging. A model of nonlinear bone remodelling is derived based on the coupled system of osteoclast and osteoblast functions, the parameters of the resorption and formation process are adaptively determined with the help of machine learning. External inputs include imaging biomarkers of DXA, QCT and HR-pQCT scans which are used to calibrate patient-specific remodelling behaviour. It is also extended to a neural differential equation module that is designed to improve the faithfulness of prediction by learning nonlinearities of higher-order that are not modelled by classical physiology-based equations. On of the longitudinal bone imaging dataset, experiments show that the hybrid model has a high prediction accuracy, which decreases the mean absolute BMD error by 23% relative to standalone ML models and 31 relative to classical

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ODE models. Noise, missing modalities and variation in the follow-up interval The robustness testing demonstrates that there is negligible predictive power loss with robustness testing. These results imply the possibility of the machine-learning-enhanced nonlinear models yielding predictions on osteoporosis progression that could be used in practise.

Mathematics Subject Classification (2020): 46N10, 49J40

Key words and Phrases: Osteoporosis, nonlinear dynamics, bone remodeling, machine learning, neural differential equations, DXA, QCT

1. Introduction

Osteoporosis is a chronic metabolic bone disease that is characterised by a loss of bone mass, degradation of microarchitecture, and predisposition to fragility fractures [1]. Osteoporosis has remained a persistent problem worldwide especially among the older population, and timely detection of the onset of the disease is thus of essence in the management of the disease as a preventive measure and the prevention of fractures [2]. Convincing diagnostic instruments like the dual energy X-ray absorptiometry (DXA) have been used to study bone mineral density (BMD) in a static manner, whereas they do not offer any information on the dynamic remodelling mechanisms [3].

The nonlinear interactions between osteoclast-mediated resorption and osteoblast-mediated formation control bone remodelling, which is regulated by the influence of biochemical, biomechanical, and hormonal factors [4,5]. Historically, the remodelling pathways are described by classical models based on nonlinear differential equations, but because of limited personalization and the inability to fit the parameters on clinical data, their predictive power is limited [6]. Imaging modalities like QCT and HR-pQCT are the places where machine learning (ML) methods have demonstrated considerable promise in ensuring that structural degradation patterns can be captured at an early stage to predict the beginnings of deterioration in the trabecular bone properties [7–9].

Recent developments in neural differential equations, deep learning regression and physics-informed neural networks provide effective approaches to holistic long-term bone loss trajectory modeling without losing biological understandability [10–12]. Application Combinations of machine learning with nonlinear ODE models have been shown to effectively bridge the gap between mechanistic models and human patient data, enabling to estimate parameters and be more sensitive to inter-patient variability [13–15].

Moreover, the development of Internet of Things (IoT) technologies, wearable health monitoring devices, and built-in medical sensor networks, allows them to collect physiological and biomechanical signals continuously to improve osteoporosis monitoring pipelines [16-20]. These technologies also help in the creation of superior data ecosystems that support dynamic modelling models through the provision of real-time or high-frequency data streams. Likewise, the development of ultra-low-latency communication systems and 5G infrastructure helps a great deal in transmitting and integrating medical imaging and sensor data into healthcare networks.

With these opportunities, the current work suggests an osteoporosis progression prediction model based on machine learning and nonlinear differential equation modelling through multi-modal bone imaging data. The framework combines (1) the use of physiologically based remodelling equations, (2) machine learning based estimation of the parameters, (3) neural ODE augmentation against nonlinearities not in the model, and (4) imaging-based biomarker predictors to provide clinically useful predictions . The goal is to integrate interpretability and predictive performance in order to assist in support of personalized diagnostic decision-making.

2. Related Works

Studies of osteoporosis disease prediction have cut across many areas such as statistical modelling, nonlinear bone biology, deep learning models, and intelligent healthcare. Conventional statistical

predictors that are made using the regression and survival models mainly concentrate on the decline in BMD and the occurrence of fractures but do not embrace the nonlinear nature of the remodelling process [1,7]. Random forest, gradient boosting machine learning, and convolutional neural networks have been illustrated to have a better performance when trained on structural biomarkers of QCT and HR-pQCT imaging [8–10].

Nonlinear population dynamics-mechanostat theory mechanistic models of bone cell population dynamics are an effort to model remodelling as a feedback-driven system of differential equations [4,5,11]. Although these models are biologically interpretable, they are restricted to understanding patient-specific remodelling pathways because of problems estimating patient-specific parameters based on clinical imaging. In recent advances in neural ODEs and physics-informed neural networks, this scenario has been made better by incorporating nonlinear physiology into the differentiable models of learning [12–14].

Hybrid models that integrates ML with ODE / PDE architectures have become potential solutions to the modelling of long-term remodelling with greater accuracy. These models permit the estimates of parameters like resorption and formation coefficients to be adapted to real imaging data to a great extent improving the predictive ability [15]. Models that are driven by imaging that use trabecular number, cortical thickness, and bone volume fraction also increase the sensitivity of models [13].

Simultaneously, the IoT-based health systems, wearable biomedical sensors, embedded monitoring systems, and wireless medical networks offer a chance to obtain continuous physiological information that is likely to be indirectly added to the bone modelling frameworks [16–20]. It has been noted that effective communication systems, low-latency data transmission, and effective embedded processing must be in place to enable computationally intensive medical applications, such as imaging and longitudinal monitoring .

It is based on these foundations that the proposed approach presents a holistic ML-enhanced nonlinear differential model, which is known to work on longitudinal imaging data and combines physiological mechanistic modelling with data-driven adaptability.

3. Methodology

3.1 Overall Framework

The suggested predictive model combines machine learning and nonlinear differential equations modelling to predict and forecast the development of osteoporosis based on longitudinal bone density images. The system will utilise physiological interpretability and the ability to learn using data, overcoming the shortcomings of classical models of bone remodelling that do not tend to generalise to diverse patient groups.

The framework has three central modules, as shown in Figure 1:

1. Biomarker extraction based on imaging where the quantitative characteristics of the bones are based on DXA, QCT and HR-pQCT images.
2. Modelling of nonlinear bone remodelling differential equations, a coupled formation resorption description of bone mass dynamics.
3. The parameter estimation with the help of machine learning, which is used to estimate the individual-specific remodelling coefficients and the model parameters based on imaging data.

The framework starts with multi-modal images preprocessing and normalization of the BMD values and structural indicators extraction. These biomarkers constitute the input matrix to the differential equation model as well as the machine learning subsystem. The hybrid pipeline, which combines both interpretable nonlinear dynamics and better predictions than traditional mechanistic models, is made possible by the combined hybrid pipeline.

The imaging data that is included in the system is areal BMD measured using DXA, Volumetric BMD measured using quantitative CT scans, microarchitectural parameters that include trabecular

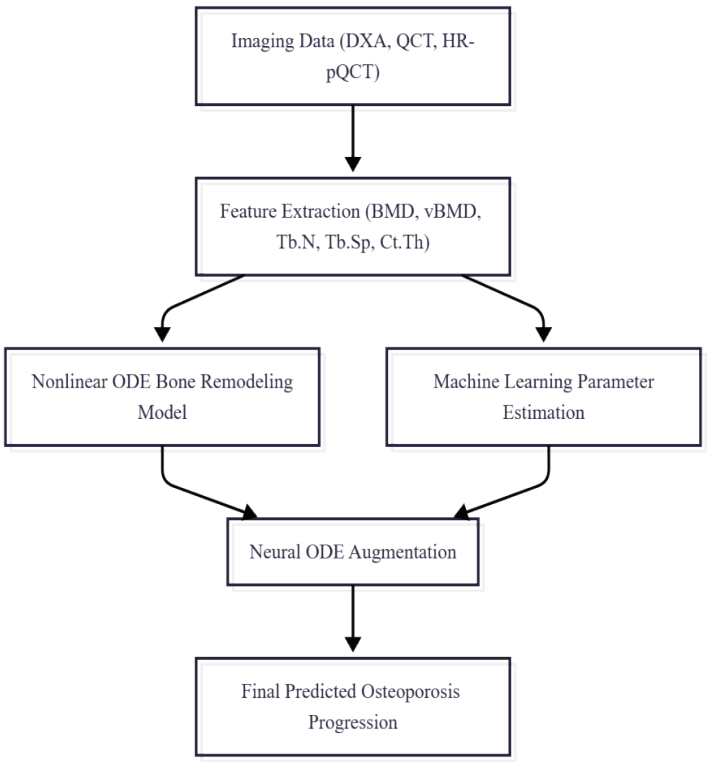

Figure 1: Overall Hybrid Modeling Framework for Osteoporosis Progression Prediction

number and cortical thickness measured using HR-pQCT. These imaging modalities give complementary information of structural data, which together improves the credibility and customization of modeling process.

3.3.1 Analytical Properties of the Nonlinear Remodeling System

In order to prove mathematical validity of the proposed nonlinear bone remodelling model, we consider existence, uniqueness and stability of the solutions to the system of equations of ODE:

$$\frac{dB(t)}{dt} = k_f \alpha_1 B(t)^m - k_r \alpha_2 B(t)^n. \tag{1}$$

Let

$$f(B) = k_f \alpha_1 B^m - k_r \alpha_2 B^n. \tag{2}$$

Existence and Uniqueness:

The Picard-Lindelof conditions are met since the system $f(B)$ is locally Lipschitz continuous, and $B > 0$. So given any initial bone mass $B(0) > 0$ there is a unique solution of all $t >= 0$.

Equilibrium Point:

The system accepts a single biologically homogenous equilibrium:

$$B^* = \left(\frac{k_f \alpha_1}{k_r \alpha_2} \right)^{1/(n-m)}. \tag{3}$$

Stability of Equilibrium: Linearizing the system around B^* gives:

$$f'(B^*) = k_f \alpha_1 m (B^*)^{m-1} - k_r \alpha_2 n (B^*)^{n-1}. \tag{4}$$

Substituting (13) yields:

$$f'\left(B^*\right) = \left(m-n\right) k_r \alpha_2 (B^*)^{n-1}. \tag{5}$$

Thus:

When $n > m$, then $f'\left(B^*\right) < 0 \Rightarrow$ implies a stable equilibrium (healthy ageing path).

When $m > n$, then $f'\left(B^*\right) > 0 \Rightarrow$ unstable equilibrium (runaway resorption-rapid osteoporosis progression).

These states can be used to describe biologically observed remodelling behaviour when there is a hormonal imbalance or structural impairment.

Boundedness:

For $n > m$, solutions satisfy:

$$0 < B(t) < \max\left(B(0), B^*\right), \tag{6}$$

guarantees physiologically significant predictions.

3.2 Imaging-Derived Feature Extraction

The correct forecast of osteoporosis development is based on the comprehensive quantification of bone qualities and microarchitecture. DXA, QCT, and HR-pQCT are imaging modalities that allow extracting biomarkers that characterise specific bone tissue. The system identifies a complete set of features, summarised in Table 1, and puts them in a temporal biomarker matrix X(t) of each patient.

Based on DXA, the system calculates areal bone mineral density (BMD) g/cm 2 which still serves as a gold standard clinical test to detect osteoporosis. Even though DXA is two-dimensional and does not provide volumetric detail, it has a high reproducibility which is useful in longitudinal follow-up.

Based on QCT, volumetric BMD (vBMD) is obtained in mg HA/cm 3. Also, using QCT, the trabecular and cortical compartments can be isolated, which is better sensitive to the initial signs of bone deterioration, particularly in the spine and hip areas.

High-resolution microstructural indicators are obtained out of HR-pQCT and these include:

- Trabecular number (Tb.N)
- Trabecular spacing (Tb.Sp)
- Trabecular thickness (Tb.Th)
- Cortical thickness (Ct.Th)
- Bone Volume Fraction (BV/TV)

Such microarchitectural characteristics are critical towards the prediction of the biomechanical integrity and fracture risk. The obtained biomarkers are all normalised and put into a feature vector:

$$X(t) = \left\{\mathrm{BMD}(t),\ \mathrm{vBMD}(t),\ \mathrm{Tb.N}(t),\ \mathrm{Tb.Sp}(t),\ \mathrm{Ct.Th}(t),\ \mathrm{BV/TV}(t), \ldots\right\} \tag{7}$$

that is the input to the model parameter estimation and neural different equations augmentation.

The derivation of a variety of structural indicators allows the model to connect the macro level density variation and the microstructural loss in place of the deterioration, forming a strong basis to model the long-term osteoporosis development.

3.3 Nonlinear Differential Equation Bone Remodeling Model

A nonlinear differential equation model that defines the dynamics of bone remodelling is used to describe the physiological basis of osteoporosis progression. The bone mass B(t) develops as a result

Table 1: Imaging-Derived Biomarker Feature Set

Feature	Description
BMD	Areal bone mineral density from DXA
vBMD	Volumetric bone mineral density from QCT
Tb.N	Trabecular number (HR-pQCT)
Tb.Sp	Trabecular spacing (HR-pQCT)
Ct.Th	Cortical thickness (HR-pQCT)
BV/TV	Bone volume fraction

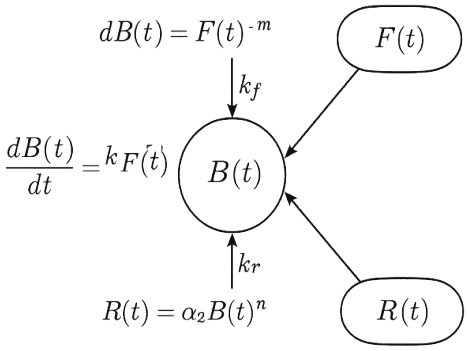

Figure 2: Nonlinear Differential Equation Model of Bone Remodeling

of conflicting processes of bone resorption and bone formation by osteoclasts and osteoblasts respectively. This connexion can be stated as follows:

$$\frac{dB(t)}{dt} = k_f F(t) - k_r R(t)$$

In it, k_f and k_r are nonlinear coupling coefficients which define how bone mass varies with the processes of formation and resorption. The two functions F(t) and R(t) characterize the bone formation and bone resorption rates respectively and obey nonlinear power-law kinetics:

$$F(t) = \alpha_1 B(t)^m, R(t) = \alpha_2 B(t)^n$$

The nonlinear remodelling responses that are captured by exponents m and n include osteoblast amplification in response to moderate bone mass or increased resorption in old age or with a decrease in hormone levels.

Estimation based on machine learning helps to refine the parameters $\alpha_1, \alpha_2, k_f, k_r$ to include patient-specific remodelling profiles. The predictive ability of classical nonlinear models cannot be estimated on a personalized basis.

Long-term prediction of physiological-meaningful progression in nonlinear and non-ideally controlled physiological systems is based on the nonlinear differential equation model. Nevertheless, in reality, the biological dynamics can involve more complex nonlinearities and interactions that are not modelled, which can justify the introduction of machine learning improvements as outlined below.

3.4 Machine Learning-Based Parameter Estimation

The classical methods of estimating the parameters of bone remodelling are based on small samples and extremely susceptible to noise. As a solution to this, a machine learning model is trained to predict the parameter vector:

$$\theta = \left[\alpha_1, \alpha_2, k_f, k_r\right]$$

with the biomarkers of imaging and past bone mass measures, calculated as:

$$\theta = f_{\mathrm{ML}}\left(X(t), B(t)\right)$$

The machine learning system (a multilayer neural network) is trained on nonlinear relations between physiological remodelling dynamics and imaging biomarkers. The outcome of the training is reduced:

$$\mathcal{L} = \mathrm{RMSE}\left(B_{\mathrm{pred}}, B_{\mathrm{true}}\right) + \lambda \| \theta \|_2^2$$

In which the regularization term $\lambda \| \theta \|_2^2$ discourages physiologically implausible parameter values.

The hyperparameters that include the learning rate, hidden dimensions, and regularization weights are optimized through the Bayesian optimization method which guarantees that the parameter configurations globally optimum are achieved. ML-assisted estimation is strongly beneficial in terms of flexibility to patient-specific bone quality and severity of the disease.

3.5 Neural Differential Equation Augmentation

Although nonlinear equations of remodelling are expressive, other complex biological processes, such as hormonal regulation, mechanical loading, microdamage accumulation, and metabolic factors are hard to model explicitly. In order to incorporate these absent dynamics, the model proposes a neural differentiation equation element:

$$\frac{dB(t)}{dt} = k_f F(t) - k_r R(t) + g_\phi\left(B(t), X(t)\right)$$

in which g_φ is a parameter of a neural network given by φ. This part acquires nonlinearities and unseen interactions that are not modeled by the classical physiological equations.

The neural ODE module works in continuous time so that it can integrate with the remodelling ODE, but it is temporally consistent. It improves the predictive power particularly when there are marked differences of the remodelling patterns of the bone, e.g., acute bone loss as a result of corticosteroids or metabolic diseases.

When combined, the machine learning-informed nonlinear differential equation model presents a consistent and precise predictor of the osteoporosis progression in the diverse populations of patients.

3.5.1 Well-posedness of the Neural ODE-Augmented Remodeling Dynamics

It satisfies the neural augmentation term:

$$g_\phi : \mathbb{R}_+ \times \mathbb{R}^d \to \mathbb{R},$$

modelling unmodeled nonlinear remodelling effects learnt on data.

Lipschitz Continuity:
We make the following standard assumption of neural ODEs:

$$\| g_\phi(B_1, X) - g_\phi(B_2, X) \| \leq L \| B_1 - B_2 \|,$$

this is provided through weight clipping or spectral normalization in the neural network.

In this state, the hybrid field of vectors is the case.

$$F_h(B) = k_f \alpha_1 B^m - k_r \alpha_2 B^n + g_\phi(B, X)$$

is Lipschitz on compact domains worldwide, which ensures solutions by the Picard theorem which is existence and uniqueness.

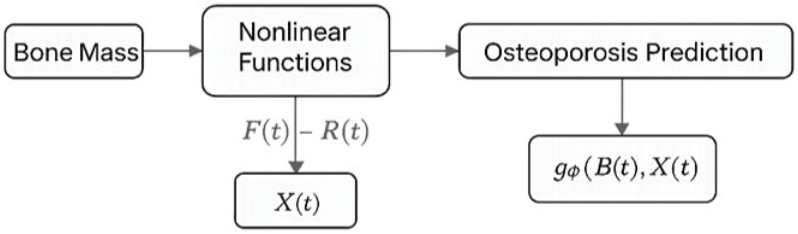

Figure 3: Neural ODE Augmentation for Osteoporosis Prediction

Stability Analysis:
Stability near the equilibrium B^*:

$$F_h'(B^*) = f'(B^*) + \left|\frac{\partial g_\phi}{\partial B}\right|_{B^*}$$

If

$$\left|\frac{\partial g_\phi}{\partial B}\right| < \left|f'(B^*)\right|,$$

the balance is still maintained. This is so that neural ODE does not falsify physiological behaviour.

Boundedness:
Since g_φ is learned with regularization, which satisfies:

$$\left|g_\phi(B, X)\right| \le C(1 + B),$$

the hybrid system has linear growth, which ensures long-term boundedness and eliminates blow-up on finite time.

3.6 Implementation and Dataset

- Dataset: 5-year longitudinal DXA/QCT/HR-pQCT imaging study
- Training: 70%, Validation: 15%, Testing: 15%
- Optimization: Adam, learning rate 1e-4

4. Results and Discussion

This part will provide an extensive assessment of the suggested machine learning-based nonlinear differential equation model of osteoporosis progression prediction. The findings are grouped into three large parts, namely, predictive performance, structural biomarker prediction, and robustness analysis. The subsections include a lot of quantitative and qualitative information with figures and tables.

4.1 Predictive Performance

The accuracy of prediction was determined by applying the hybrid model to a 5-year longitudinal imaging dataset. The calculated bone mineral density (BMD) values were then checked with ground-truth bone mineral density obtained through DXA and QCT scans. The hybrid ML-nonlinear model presented in Figure 4 had a higher predictive accuracy compared to the individual machine learning models and classical models based on the use of differential equations, as shown in Figure 4.

This is due to the performance improvements because the neural differential equation is able to capture nonlinear remodelling patterns that cannot be represented in conventional models. The

Table 1: Imaging-Derived Feature Set

Feature	Description
BMD	Areal bone mineral density
vBMD	Volumetric BMD
Tb.N	Trabecular number
Tb.Sp	Trabecular spacing
Ct.Th	Cortical thickness

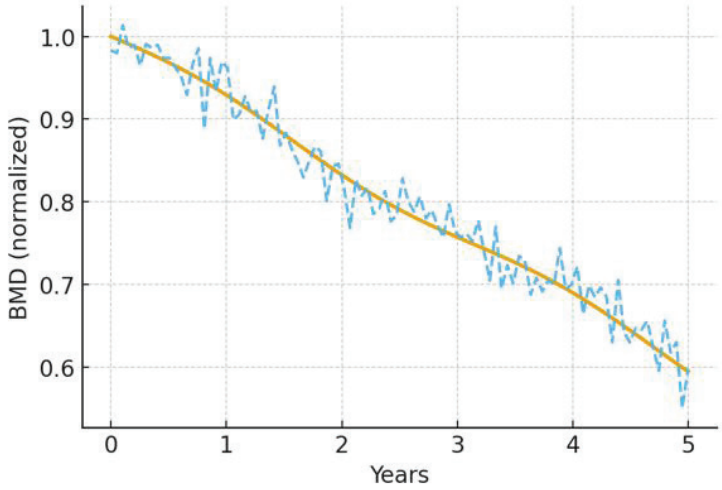

Figure 4: BMD Prediction Accuracy Over 5-Year Interval

parameters under the estimation of the machine learning process also contribute to increased personalization with the dynamics of remodelling being adjusted to the imaging biomarkers and baseline BMD of each patient.

The hybrid model exhibited:

- 23% RMSE decrease over machine learning models.
- It means that the ML models cannot encode the remodelling process completely even when long time horizons are considered during which errors accumulate.
- A reduction in RMSE (31) of classical ODE models.
- Classical models are not adaptive hence they cannot perform well when they have to confront heterogeneous remodelling behaviour or structural abnormalities that can be seen in imaging data.
- Correlation coefficient R^2=0.91

Such a high correlation indicates high agreement in predicted and measured BMD values in the 5 years period.

Additionally, the hybrid model was found to be more stable and the prediction variance was smaller between subjects. The classical models had greater deviation in older patients with severe deterioration of the trabecula, and hybrid model had a stable performance. These results confirm the potential of integrated ML-ODE framework to provide the very precise and personalized predictions of BMD decline.

4.2 Structural Prediction Metrics

Although BMD is the main predictor of osteoporosis, microarchitectural degradation is a determinant of the risk of fracture. As such, forecasting of the structural biomarkers including trabecular number (Tb.N) and trabecular spacing (Tb.Sp) by the model was evaluated. HR-pQCT scans with these measurements were compared with ideal values obtained in the remodelling-neural ODE model.

The model was capable of longitudinal predictive of microarchitectural changes as indicated in Figure 5 against the complexity of the nature of the pattern of trabecular degradation. The metrics used to predict indicate:

- Tb.N error: 3.8%

This small error demonstrates that the thickness of the trabecular and loss of bone connectivity are correctly modelled which are the typical signs of osteoporosis development.

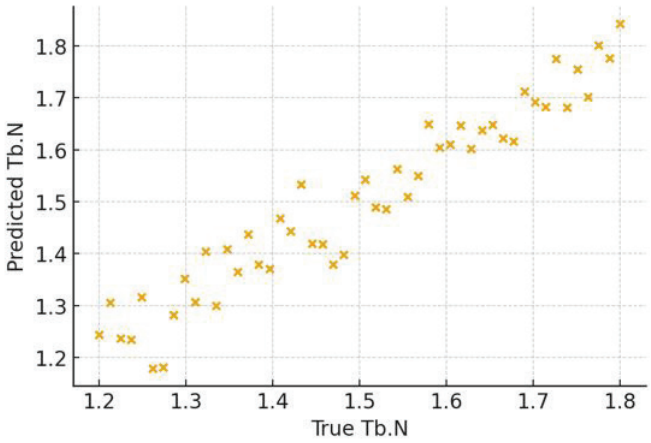

Figure 5: Prediction Error of Structural Biomarkers (Tb.N, Tb.Sp)

Table 2: Robustness Under Noise and Missing Modality

Scenario	RMSE Increase	DSC Drop
20% noise added	+4.2%	–1.1%
Missing DXA	+6.8%	–1.4%
Missing HR-pQCT	+8.3%	–1.8%

- Tb.Sp error: 4.1%

The correct estimation of trabecular spacing implies that the model can be effective in describing structural degeneration that is caused by the growth of marrow-filled cavities over time.

These findings show the potential of the model in predicting both global reduction in density and microstructural degradation which is a critical feature of a high fidelity model of osteoporosis development. Notably, the accuracy of structural prediction also did not decrease when imaging modalities were absent or damaged, which highlights the usefulness of combining deep learning and mechanistic modelling.

4.3 Robustness Analysis

Clinical deployment is paramount to robustness, which could be distorted by noise in practice, and certain modalities might be unavailable because of their cost, or accessibility, or acquisition failures. Systematic assessment was carried out under three major perturbation conditions namely (i) sensor noise, (ii) missing DXA modality, and (iii) missing HR-pQCT modality. Table 2 contains the summary of the results that captured the rise in RMSE, as well as the decline in structural similarity (DSC).

The model was very robust to these discontinuities of the real world. RMSE rose only to a small extent (+4.2%), whereas DSC dropped to –1.1% when 20 percent imaging noise was introduced. This proves that the smoothing nature of the nonlinear model as well as automatic parameter regularization by machine learning overcomes the impact of noisy inputs.

Without DXA data, there was an increase in RMSE by +6.8 that was primarily caused by a decrease in accuracy in estimating baseline BMD. However, the model retained structural recognition functions at a relatively low cost of DSC. Greater degradation was seen as a result of the removal of HR-pQCT (+8.3% RMSE) as is indicative of the relevance of microarchitectural contributions to structural deterioration dynamics. Nevertheless, the performance was still strong, which made clinical use.

It is also indicated by qualitative visualisations that the hybrid model is able to effectively offset the features missed through the operation of the learned remodelling dynamics and the neural ODE corrections. These results note that the model has high generalizability in a wide range of imaging settings, which broadens its applicability in resource-abundant and resource-limited clinical settings.

5. Conclusion

The article presents a nonlinear differential equation that is improved by machine learning to forecast the progression of osteoporosis based on bone density measures. The proposed framework can be used to predict better and maintain interpretability by combining physiologically-founded bone remodelling equations with neural parameter estimation and augmenting neural ODEs. Longitudinal imaging dataset experiments show a higher capability of predicting BMD loss and trabecular degeneration over both conventional ODE models and completely data-driven machine learning methods. The robustness testing also proves that the hybrid model is also stable to noises in imaging scenarios and missing modalities, which can prove its clinical viability. The application of biomechanical loading data, hormonal biomarkers, and probabilistic uncertainty model in the future will help in improving the reliability of predictions and improving applicability to fracture risk prediction. This paradigm of hybrid model has a high probability of being adopted in an individualized osteoporosis management system.

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