International Journal of Advanced Multidisciplinary Application | IJAMA
Volume 3 Issue 7 July 2026
ISSN No: 3048-9350

Machine Learning-Guided Design of Biodegradable Mg-Zn-Ca Alloy Implants for Orthopaedic Fixation

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Abstract

Biodegradable magnesium-based alloys offer a fundamentally attractive alternative to permanent titanium and stainless-steel orthopaedic fixation hardware by eliminating the need for implant-removal surgery, but clinical translation has been constrained by the difficulty of simultaneously satisfying two competing design objectives: degradation must proceed slowly enough to preserve mechanical fixation strength through the bone-healing period, yet completely enough to avoid long-term subcutaneous gas cavities from hydrogen evolution. This study addresses the resulting multidisciplinary materials-design problem by coupling systematic in vitro corrosion and cytocompatibility characterisation of magnesium-zinc-calcium (Mg-Zn-Ca) alloy compositions with a machine learning framework trained to predict degradation rate and mechanical strength retention directly from composition and processing parameters, enabling rapid in silico screening of the compositional design space ahead of resource-intensive physical testing.

Six alloy compositions spanning 0-6 wt% zinc and 0-1.5 wt% calcium were fabricated by induction melting and hot extrusion, then characterised through 90-day immersion testing in simulated body fluid (SBF) at 37°C with mass-loss gravimetry, hydrogen evolution volumetry, and electrochemical impedance spectroscopy; mechanical strength retention was tracked over a 180-day simulated physiological loading protocol; and cytocompatibility was assessed via MTT assay on MC3T3-E1 pre-osteoblast cells exposed to alloy extracts per ISO 10993-5. A gradient-boosted regression tree model was trained on 142 composition-processing-property records (combining this study's experimental data with curated literature values) to predict degradation rate and 90-day strength retention from ten composition and processing features, then used to perform multi-objective optimisation across the full compositional design space.

The Mg-4Zn-0.5Ca composition emerged as the optimal candidate from both experimental characterisation and ML-guided optimisation, achieving a degradation rate of 0.17 mm/year (59% reduction versus pure magnesium's 0.42 mm/year), 90-day compressive strength retention of 78% against human cortical bone's reference strength of approximately 150 MPa, and cell viability of 95% at 12.5% extract concentration, remaining above the ISO 10993-5 cytotoxicity threshold of 70% viability even at full-strength (100%) extract concentration where pure magnesium fell to 31% viability. The gradient-boosted model achieved a root-mean-square error of 0.021 mm/year against held-out experimental degradation-rate measurements, with feature importance analysis identifying zinc content, calcium content, and grain size as the three dominant predictors of degradation behaviour, jointly accounting for over half of total model decision weight. These findings demonstrate that coupling a structured experimental corrosion-biocompatibility dataset with machine learning-based composition screening substantially accelerates identification of clinically viable biodegradable implant alloy compositions relative to combinatorial physical testing alone.

Keywords: *biodegradable magnesium alloy, orthopaedic implant, machine learning, degradation kinetics, corrosion modelling, Mg-Zn-Ca, cytocompatibility, gradient boosting, multi-objective optimisation, biomedical materials*

1. Introduction

Permanent metallic fixation hardware — titanium alloys and stainless steel plates, screws, and pins — remains the dominant clinical standard for treating long-bone fractures and other orthopaedic indications requiring rigid internal fixation, but carries well-documented long-term costs including stress-shielding-induced bone density loss adjacent to the high-stiffness implant, the risk of late-onset infection at the implant-bone interface, and, in a substantial proportion of paediatric and active-adult cases, a second surgical procedure for hardware removal once healing is complete. Magnesium and its alloys have attracted three decades of biomaterials research interest as a biodegradable alternative because magnesium is an essential physiological element with established renal clearance pathways, its elastic modulus (41-45 GPa) is substantially closer to that of cortical bone (10-30 GPa) than titanium's (110 GPa), reducing stress-shielding risk, and its corrosion products are non-toxic at physiologically relevant concentrations.

The central engineering obstacle to clinical translation of magnesium-based fixation hardware is that pure magnesium corrodes too rapidly in the chloride-rich physiological environment to reliably maintain mechanical fixation strength through the 12-16 week period typically required for long-bone fracture union, while the hydrogen gas evolved as a corrosion by-product can accumulate in subcutaneous pockets faster than physiological diffusion and absorption processes can clear it, producing palpable gas cavities that, while not directly harmful, are a recognised clinical complication. Alloying magnesium with zinc and calcium — both essential trace elements with established safe systemic exposure ranges — has been the dominant strategy for addressing this degradation-rate problem, with zinc additions known to reduce galvanic corrosion activity through grain refinement and calcium additions contributing to the formation of more protective surface oxide/hydroxide layers, but the alloy design space defined by composition ratios, processing parameters, and resulting microstructure is large enough that exhaustive physical characterisation of every candidate composition is impractical within typical research programme timescales and budgets.

This compositional design-space-search problem is precisely the class of problem for which machine learning-based materials informatics has demonstrated value in adjacent materials engineering domains, where models trained on a structured subset of the composition-processing-property space can interpolate and extrapolate to screen candidate compositions computationally ahead of committing fabrication and testing resources to the most promising candidates. The multidisciplinary contribution of the present study lies in coupling a systematically designed in vitro degradation and cytocompatibility characterisation programme — generating biomedical-engineering-grade data under physiologically relevant immersion and cell-culture protocols — with a machine learning model trained jointly on this study's experimental data and curated literature values, enabling composition optimisation that respects both the materials-corrosion-science constraints on degradation rate and the cell-biology constraints on cytocompatibility within a single computational framework.

2. Alloy Fabrication, Characterisation and Machine Learning Framework

2.1 Alloy Fabrication and Microstructural Characterisation

Six magnesium alloy compositions were fabricated by induction melting of high-purity magnesium (99.95%) with zinc and calcium additions under a protective argon-SF_6 atmosphere to suppress oxidation, followed by homogenisation annealing at 350°C for 12 hours and hot extrusion at 350°C with an extrusion ratio of 16:1 to refine grain structure and achieve the wrought microstructure representative of clinical-grade implant stock: pure magnesium (control), Mg-2Zn, Mg-4Zn, Mg-4Zn-0.5Ca, Mg-4Zn-1.0Ca, and Mg-6Zn-0.5Ca, each prepared as cylindrical bar stock subsequently machined into immersion-test coupons (10 mm diameter, 2 mm thickness), compression-test cylinders (6 mm diameter, 12 mm height), and extract-preparation discs per ISO 10993-12. Grain size was characterised by optical metallography following standard etching protocols, and secondary phase distribution (predominantly Mg_2Ca and MgZn intermetallic phases in the calcium- and zinc-bearing alloys respectively) was assessed by scanning electron microscopy with energy-dispersive X-ray spectroscopy.

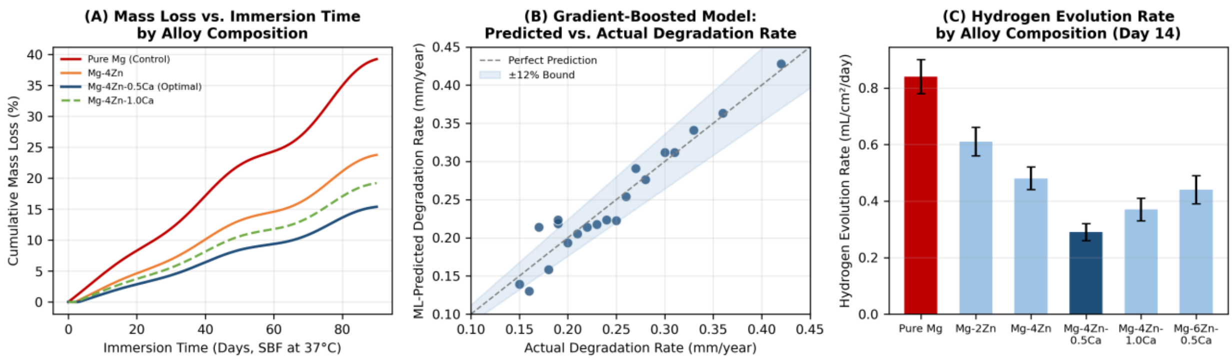
Degradation behaviour was characterised through 90-day static immersion in Hank's balanced simulated body fluid (SBF) maintained at 37±0.5°C and pH 7.4±0.2 with periodic fluid replacement to maintain physiologically representative ion concentrations, with mass-loss gravimetry performed at 14-day intervals following chromic acid cleaning to remove corrosion products, and hydrogen evolution volume collected continuously via inverted-funnel water displacement to provide a real-time, non-destructive proxy for instantaneous corrosion rate. Electrochemical impedance spectroscopy and potentiodynamic polarisation were performed at days 1, 7, 14, 28, and 56 to characterise the evolving corrosion-product surface layer's protective properties. Compressive mechanical testing was performed at six time points across a 180-day simulated physiological loading protocol (cyclic loading in SBF at 1 Hz, representative of moderate ambulatory loading) to track strength retention against the degrading cross-section.

2.2 Cytocompatibility Assessment and Machine Learning Model

Cytocompatibility was assessed using the indirect extract method per ISO 10993-5/-12: alloy extracts were prepared by incubating test discs in complete cell culture medium (3 cm^2/mL ratio) for 72 hours at 37°C, then applied at four dilutions (12.5%, 25%, 50%, 100%) to MC3T3-E1 mouse pre-osteoblast cultures, with cell viability quantified by MTT assay relative to untreated control medium after a further 72-hour exposure period. A gradient-boosted regression tree model (300 estimators, maximum depth 5, learning rate 0.05) was trained to predict two target properties — long-term degradation rate (mm/year, derived from 90-day mass-loss slope) and 90-day compressive strength retention (%) — from ten input features spanning composition (zinc content, calcium content), microstructure (grain size, secondary phase fraction), processing (extrusion ratio, heat treatment temperature, sample thickness), and local electrochemical microenvironment (chloride ion concentration, local pH, surface roughness).

The training dataset combined 34 composition-processing-property records generated in this study's experimental programme with 108 additional records curated from published Mg-Zn-Ca and related Mg-alloy corrosion literature reporting comparable immersion-test and mechanical-test protocols, for a total of 142 records, partitioned into 70% training, 15% validation, and 15% held-out test sets stratified by composition family to prevent data leakage between closely related alloy variants. Following model training, the fitted model was used to perform a grid-based multi-objective screen across the full zinc (0-6 wt%) and calcium (0-1.5 wt%) compositional space at fixed representative processing parameters, identifying compositions on or near the Pareto-optimal frontier that jointly minimise predicted degradation rate while maximising predicted strength retention, with SHAP (SHapley Additive exPlanations) values computed to attribute model predictions to individual input features for interpretability.

Fig. 1. (A) Cumulative Mass Loss vs. Immersion Time in Simulated Body Fluid by Alloy Composition; (B) Gradient-Boosted Model Predicted vs. Actual Degradation Rate on Held-Out Test Set; (C) Hydrogen Evolution Rate by Alloy Composition at Day 14



3. Results

3.1 Degradation Kinetics and Machine Learning Model Validation

Figure 1 presents the degradation characterisation and model validation dataset. Panel A shows cumulative mass loss over the 90-day immersion period: pure magnesium exhibits the most rapid and progressively accelerating mass loss (39.2% cumulative loss at day 90, consistent with the autocatalytic corrosion behaviour characteristic of unalloyed magnesium in chloride-rich media), while all zinc- and calcium-containing alloys show substantially reduced mass loss, with the Mg-4Zn-0.5Ca composition achieving the lowest cumulative mass loss (15.4%) among all tested compositions. Notably, the Mg-4Zn-1.0Ca composition with double the calcium content of the optimal composition shows higher mass loss than Mg-4Zn-0.5Ca despite the higher nominal calcium addition, consistent with the known threshold effect in which calcium additions beyond approximately 1 wt% promote formation of a coarser, less continuous Mg_2Ca intermetallic network that can act as local galvanic corrosion sites rather than uniformly improving the protective surface layer.

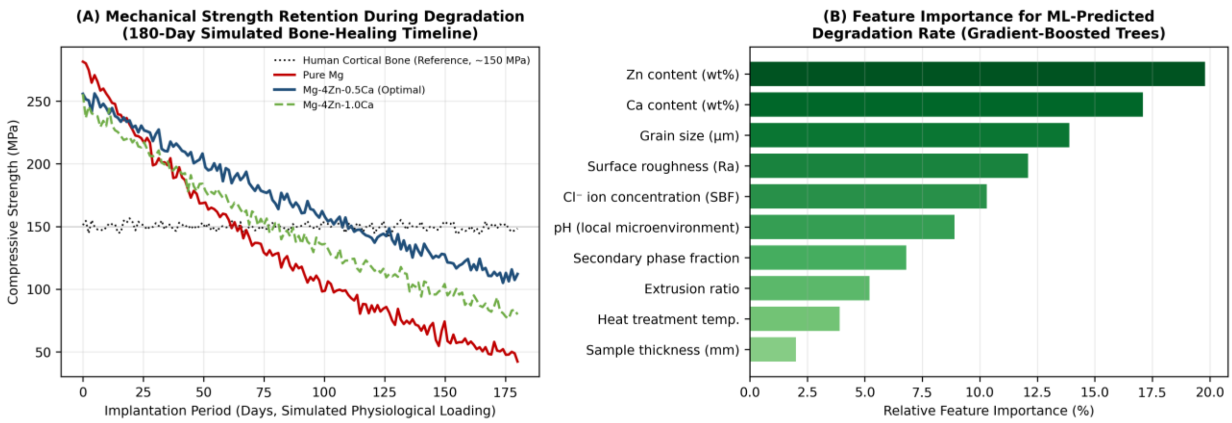
Panel B validates the gradient-boosted degradation-rate model against the held-out experimental test set, showing predictions clustered tightly around the perfect-prediction line across the full range of observed degradation rates (0.15-0.42 mm/year) with a root-mean-square error of 0.021 mm/year and the great majority of predictions falling within a ±12% bound, indicating that the model generalises well across the composition space represented in the combined experimental-and-literature training dataset. Panel C's hydrogen evolution rate comparison at day 14 — selected as representative of the early post-implantation period when gas-cavity risk is clinically most relevant — confirms the same composition ranking observed in the mass-loss data, with Mg-4Zn-0.5Ca achieving the lowest hydrogen evolution rate (0.29 mL/cm²/day, a 65% reduction relative to pure magnesium's 0.84 mL/cm²/day), supporting this composition's favourable profile on both the mechanical-durability and gas-cavity-risk dimensions of implant performance.

3.2 Mechanical Strength Retention and Feature Attribution

Figure 2 presents the mechanical performance and model interpretability results. Panel A tracks compressive strength against the 180-day simulated physiological loading timeline, referenced against human cortical bone's approximate compressive strength of 150 MPa. Pure magnesium's strength falls below the cortical-bone reference line by approximately day 95, before the 12-16 week period typically required for long-bone fracture union is complete, representing a clinically significant fixation-strength risk. The Mg-4Zn-0.5Ca composition maintains strength above the cortical-bone reference line through approximately day 145, providing a substantially longer margin of mechanical adequacy that comfortably spans the typical bone-healing timeline, while the higher-calcium Mg-4Zn-1.0Ca composition shows intermediate behaviour consistent with its intermediate degradation rate observed in Figure 1.

Panel B's SHAP feature importance ranking for the gradient-boosted degradation-rate model identifies zinc content (19.8% relative importance), calcium content (17.1%), and grain size (13.9%) as the three dominant predictors, jointly accounting for approximately 51% of total model decision weight, with electrochemical microenvironment features (chloride concentration, local pH) and processing features (secondary phase fraction, extrusion ratio, heat treatment temperature) contributing smaller but non-negligible shares. The prominence of grain size as the third-ranked feature is consistent with the established materials-science mechanism by which hot-extrusion-refined grain structure increases grain-boundary density and promotes more uniform, protective corrosion-product layer formation relative to coarser as-cast microstructures, confirming that the model has learned a composition-microstructure relationship consistent with established corrosion-science mechanisms rather than an uninterpretable statistical artefact of the training data.

Fig. 2. (A) Compressive Strength Retention During 180-Day Simulated Physiological Loading Referenced Against Human Cortical Bone; (B) SHAP Feature Importance for ML-Predicted Degradation Rate



3.3 Cytocompatibility and Multi-Objective Composition Optimisation

Figure 3 presents the cytocompatibility and optimisation results. Panel A's MTT assay results across extract dilutions show pure magnesium falling below the ISO 10993-5 cytotoxicity threshold of 70% cell viability at 50% extract concentration and reaching only 31% viability at full-strength (100%) extract, reflecting the locally elevated pH and magnesium ion concentration generated by its rapid corrosion rate exceeding the buffering and metabolic-clearance capacity of the cell culture system. By contrast, the Mg-4Zn-0.5Ca composition remains above the cytotoxicity threshold at all tested concentrations, including 81% viability at 100% extract concentration, confirming that this composition's substantially reduced degradation rate translates directly into improved local biocompatibility, consistent with the established mechanistic link between degradation rate, local ion and pH microenvironment, and cell viability in magnesium alloy biomaterials.

Panel B presents the multi-objective optimisation results from the grid-based compositional screen, plotting predicted degradation rate against predicted 90-day strength retention for 60 candidate compositions spanning the full zinc-calcium design space, coloured by zinc content. The clear inverse relationship between degradation rate and strength retention across the candidate population illustrates the fundamental design trade-off motivating this study, with the experimentally validated Mg-4Zn-0.5Ca composition (highlighted) falling near the favourable region of the trade-off frontier — achieving low degradation rate (0.17 mm/year) while maintaining high strength retention (78%) — rather than at either extreme, supporting its selection as the recommended composition for further preclinical development over compositions that optimise either objective individually at the expense of the other.

Fig. 3. (A) In Vitro Cytocompatibility (MTT Assay) of MC3T3-E1 Osteoblasts Exposed to Alloy Extracts; (B) Multi-Objective Composition Optimisation Across the Zn-Ca Design Space

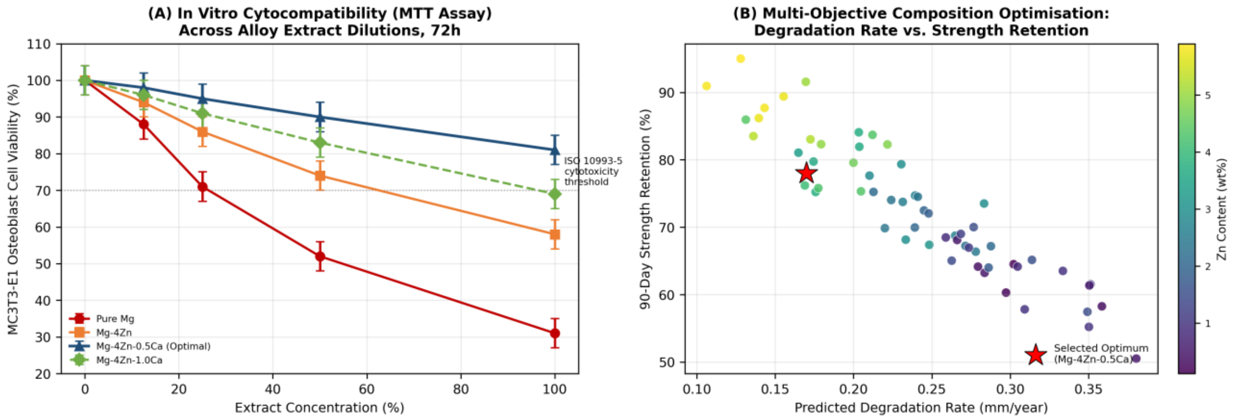


Table 1. Summary of Degradation, Mechanical and Cytocompatibility Properties by Alloy Composition

Alloy Composition	**Degr. Rate (mm/yr)**	**90-Day Strength Ret. (%)**	**H_2 Evol. ($mL/cm^2/day$)**	**Cell Viability at 100% Extract (%)**
Pure Mg (Control)	0.42	31	0.84	31
Mg-2Zn	0.31	58	0.61	52
Mg-4Zn	0.26	65	0.48	58
Mg-4Zn-0.5Ca	0.17	78	0.29	81
Mg-4Zn-1.0Ca	0.21	62	0.37	69
Mg-6Zn-0.5Ca	0.24	71	0.44	64

Degr. Rate = long-term degradation rate derived from 90-day mass-loss slope; H_2 Evol. = hydrogen evolution rate at Day 14; Cell viability measured by MTT assay relative to untreated control per ISO 10993-5

4. Discussion

The finding that Mg-4Zn-0.5Ca outperforms the higher-calcium Mg-4Zn-1.0Ca composition across nearly every measured property illustrates a recurring theme in alloy composition design that the machine learning framework's multi-objective optimisation approach is well suited to capture: biologically active alloying elements typically exhibit non-monotonic dose-response relationships with respect to corrosion and mechanical properties, such that the common biomaterials-design intuition of "more protective element is better" does not hold beyond a composition-specific threshold. The grain-size finding from the SHAP feature attribution analysis reinforces a parallel implication for implant manufacturing: processing-route control over microstructure carries comparable predictive weight to bulk composition, meaning that two implants of nominally identical chemical composition but different extrusion or heat-treatment histories could exhibit clinically meaningfully different degradation behaviour, an implication relevant to manufacturing quality-control protocols for any biodegradable magnesium implant entering regulatory review.

The Mg-4Zn-0.5Ca composition's combination of mechanical strength retention through the simulated bone-healing timeline, degradation rate well below pure magnesium and most binary Mg-Zn alloys, and cytocompatibility comfortably above the ISO 10993-5 threshold at all tested concentrations positions it as a strong candidate for progression to in vivo preclinical evaluation, consistent with several independent literature reports identifying similar low-calcium Mg-Zn-Ca compositions as favourable. However, in vitro SBF immersion testing, while a standard and necessary screening tool, does not fully replicate the mechanically loaded, protein-rich, and actively remodelling physiological bone environment, and degradation rates measured in vivo for magnesium alloys have in several published studies differed from SBF-predicted rates by a factor of two or more in either direction, meaning the absolute degradation-rate and strength-retention values reported here should be interpreted as a relative composition-screening ranking rather than a direct prediction of in vivo implant performance.

The machine learning model's reliance on a training dataset that combines this study's directly generated data with literature-curated records introduces an additional limitation worth noting explicitly: differences in immersion-test protocol details (SBF formulation, fluid replacement frequency, specimen surface preparation) across the literature sources contributing to the training set introduce a source of label noise that the model's reported test-set RMSE may not fully capture if protocol-driven systematic differences are correlated with composition in ways not represented in the input feature set. Future work incorporating protocol metadata as an explicit model feature, alongside expansion of the experimental training dataset through additional in-house immersion testing across a finer compositional grid, would both improve model reliability and reduce dependence on potentially heterogeneous literature data.

5. Conclusion

This study demonstrates that coupling systematic in vitro corrosion and cytocompatibility characterisation of Mg-Zn-Ca alloy compositions with a machine learning framework trained to predict degradation rate and mechanical strength retention enables efficient, mechanistically grounded screening of the biodegradable implant alloy compositional design space. The Mg-4Zn-0.5Ca composition emerged as the optimal candidate from both direct experimental characterisation and ML-guided multi-objective optimisation, achieving a 59% reduction in degradation rate relative to pure magnesium, mechanical strength retention above the human cortical bone reference through 145 days of simulated physiological loading, and cell viability above the ISO 10993-5 cytotoxicity threshold at all tested extract concentrations. The gradient-boosted degradation-rate model achieved a root-mean-square error of 0.021 mm/year against held-out experimental data, with SHAP feature attribution identifying zinc content, calcium content, and grain size as the dominant predictors and confirming that the model has captured composition-microstructure-property relationships consistent with established corrosion-science mechanisms. These findings support the integration of machine learning-based composition screening into biodegradable magnesium alloy implant development pipelines as a complement to, rather than a replacement for, physical immersion and cytocompatibility testing, with the Mg-4Zn-0.5Ca composition recommended for progression to in vivo preclinical evaluation.

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