

Article

A Simplified Equilibrium Framework for Investigating Calcium and Magnesium Relationships in Plasma

Fanel Dorel Scheaua 

SIM Department, Engineering and Agronomy Faculty of Braila, “Dunarea de Jos” University of Galati, 810017 Braila, Romania; fanel.scheaua@ugal.ro

Abstract

Calcium (Ca^{2+}) and magnesium (Mg^{2+}) are essential divalent cations whose homeostasis is essential for cardiovascular, muscular and metabolic function. Absolute or relative imbalances between Ca and Mg can lead to cardiovascular, metabolic and neurological pathologies. Ionized calcium (Ca^{2+}) is a biologically active fraction of plasma calcium that is tightly regulated by protein binding, phosphate complexation, magnesium modulation and acid–base status. Ionized calcium plays a central role in multiple physiological processes and is strongly influenced by plasma pH, phosphate concentration and magnesium levels. However, the combined effects of these parameters are difficult to evaluate intuitively because of their nonlinear interactions. In this study, a numerical simulation framework was used to explore how simultaneous variations in pH, phosphate and magnesium may influence ionized calcium under typical physiological plasma conditions as a phenomenological framework linking ionic equilibrium with viscosity-dependent flow parameters under well-mixed plasma conditions. The simulations reveal phenomenological changes in which concurrent increases in pH and phosphate or reductions in magnesium produce disproportionately large decreases in ionized calcium. Within the physiological ranges examined, the results also indicate a region of relative stability for ionized calcium corresponding to Ca/Mg ratios close to 3, while this value should be interpreted as an emergent feature of the modeled parameter space rather than a universal physiological constant. These findings illustrate the importance of considering multiple electrolyte interactions simultaneously when evaluating calcium homeostasis and may provide a conceptual framework for further experimental investigation.

Keywords: ionic equilibrium; calcium; magnesium; plasma; zero-dimensional model; parametric analysis; sensitivity analysis; phenomenological modeling



Academic Editor: Philip J. Atherton

Received: 25 May 2026

Revised: 3 July 2026

Accepted: 3 July 2026

Published: 7 July 2026

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1. Introduction

Calcium homeostasis is a cornerstone of physiological stability, with ionized calcium representing the biologically active fraction that directly participates in neuromuscular excitability, coagulation and intracellular signaling. While total plasma calcium provides a bulk measurement, it does not account for dynamic partitioning between ionized, protein-bound and complexed forms. This partitioning is influenced by extracellular pH, which modulates protein binding, and by phosphate, which forms soluble complexes with calcium and magnesium and regulates calcium mobilization via parathyroid hormone. Furthermore, blood flow conditions and plasma viscosity-dependent flow behavior introduce additional spatial and temporal heterogeneity, with equilibrium and ionic balance processes influencing the local availability of ions.

Despite these complexities, understanding this partitioning is crucial for recognizing functional hypocalcemia, where ionized calcium is reduced despite normal total calcium [1–13].

A multivariate numerical modeling approach was employed to systematically explore these interactions, visualize three-dimensional response surfaces and assess their implications in the context of the fluid equilibrium state within the circulatory system.

Calcium (Ca) and magnesium (Mg) are essential divalent cations with interconnected roles in human physiology. Calcium is primarily involved in neuromuscular excitability, cardiac contractility, blood coagulation and bone mineralization, whereas Mg serves as a cofactor in enzymatic reactions, glucose metabolism, neuromuscular relaxation and oxidative stress regulation [14–21].

Both cations are transported in the bloodstream, as a non-Newtonian fluid whose viscosity and flow characteristics vary with shear rate, hematocrit and electrolyte composition. The interactions of Ca and Mg with erythrocytes, platelets and plasma proteins influence blood viscosity, shear stress and microvascular perfusion, establishing a sensitivity link between electrolyte balance and circulatory dynamics [6,22–32].

A multivariate numerical model was developed integrating chemical equilibrium with physiologically relevant parameter ranges to examine the interactions governing ionized calcium. Numerical results were generated for Ca^{2+} versus pH and phosphate; magnesium versus pH and phosphate; and the Ca–Mg interaction space. The simulation results show that simultaneous elevations of pH and phosphate, or reductions in magnesium, produce disproportionate decreases in ionized calcium.

Incorporating principles of viscosity-dependent flow behavior in plasma underscores the importance of flow phenomena, diffusion and effective mixing conditions in shaping local ion concentrations, while the proposed model provides a predictive framework for interpreting discrepancies between total and ionized calcium.

The viscosity relationship is a simplified phenomenological expression used for exploratory purposes and restricted to parameter ranges that ensure physically meaningful values.

Ionized calcium represents the fraction of plasma calcium that is determined by the balance between multiple interacting components, including protein binding, complexation with low-molecular-weight anions, and the influence of extracellular pH and magnesium levels. This partitioning defines a phenomenological system in which several variables simultaneously influence the resulting equilibrium state.

In this context, pH modulates binding interactions, while phosphate contributes to the formation of soluble complexes with calcium.

Magnesium introduces an additional degree of co-variation through its interaction with the system variables. These dependencies form a multivariate structure characterized by nonlinear relationships between the governing parameters.

Despite the individual roles of these variables being well defined, their combined effects are not easily inferred due to the presence of nonlinear co-variation. In particular, simultaneous variations in multiple parameters may produce responses that differ significantly from those obtained by considering each variable independently.

To address this, a multivariate numerical modeling approach was employed to evaluate the sensitivity analysis equilibrium relationships between pH, phosphate concentration and magnesium levels within a well-mixed system. The model is based on algebraic equations describing equilibrium conditions between ionic species, allowing direct computation of steady-state solutions.

The numerical framework was used to systematically explore the parameter space defined by these variables. Simulations were performed over structured ranges of pH,

phosphate concentration, and magnesium levels, and the resulting equilibrium states are represented as three-dimensional response surfaces.

This approach enables the identification of regions of sensitivity, where small changes in one or more parameters produce large variations in the calculated equilibrium state, as well as regions of relative stability. In addition, the framework captures the effects of combined disturbances, revealing nonlinear interaction patterns that cannot be reduced to independent contributions.

The objective of the present study is therefore to analyze the structure of the phenomenological equilibrium relationships defined by the model and to characterize the response patterns that emerge from their interaction across the explored parameter space.

The study does not establish a mechanistic coupling between ionic composition and blood rheology, but instead explores a simplified parametric relationship in order to assess potential sensitivities.

2. Results and Discussion

The numerical simulations reveal a complex, nonlinear regulation of ionized calcium by extracellular pH and phosphate, even when total calcium and albumin are held constant as an assumption for equilibrium partitioning effects.

The diagrams presented in Figures 1–3 reveal regions where minor deviations in pH, phosphate, or magnesium can result in disproportionately large changes in ionized calcium, emphasizing the limitations of relying solely on total calcium measurements for clinical assessment.

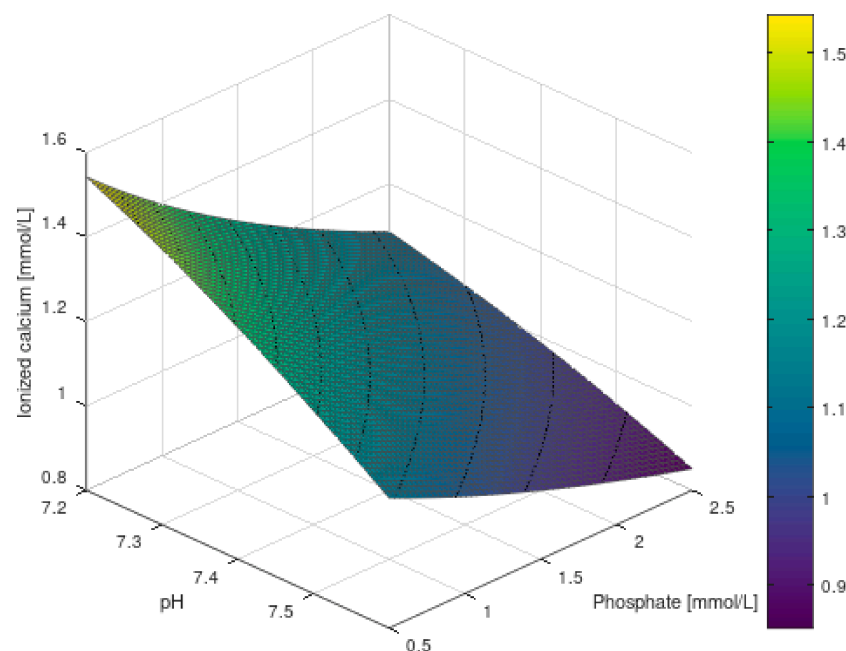


Figure 1. Parametric surface of ionized calcium as a function of pH and phosphate concentration, computed from the equilibrium model over a discretized parameter space.

The nonlinear topology observed suggests that compensatory mechanisms, including hormonal regulation via parathyroid hormone, that may be insufficient in combined alkalemic, hyperphosphatemic, or hypomagnesaemia states, predisposing to functional hypocalcemia.

The sensitivity to multiple variables, revealed by the steep gradients and curved topology of the response surfaces, provides a quantitative explanation for the variability in ionized calcium observed under seemingly normal total calcium conditions.

The numerical results can establish a framework for predictive modeling of electrolyte disturbances.

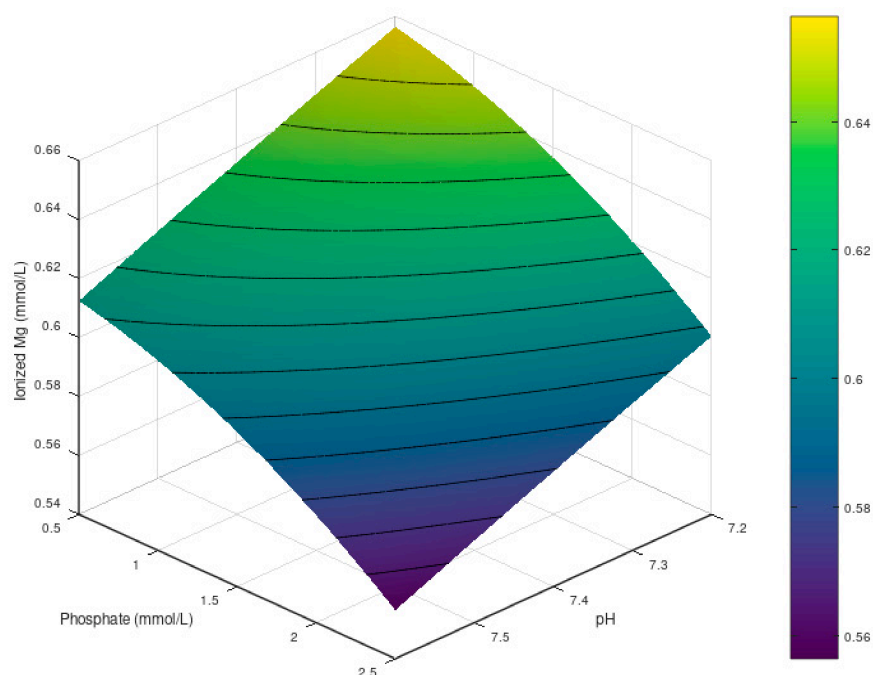


Figure 2. Three-dimensional surface of ionized magnesium as a function of extracellular pH and phosphate.

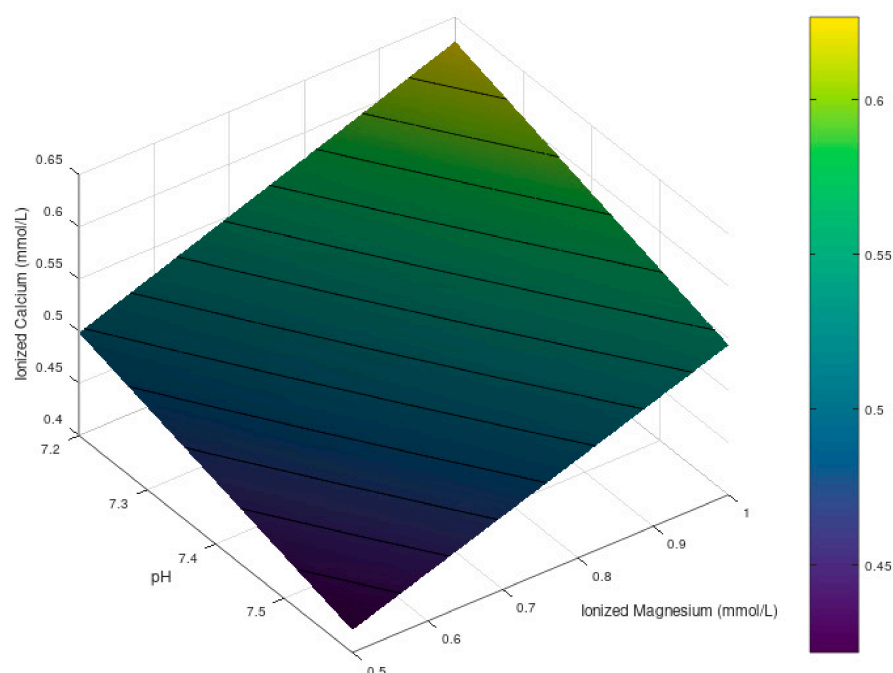


Figure 3. Three-dimensional Ca–Mg parametric dependence surface showing ionized calcium as a function of pH and magnesium (0.5–1.0 mmol/L).

The predicted reduction in ionized calcium with increasing pH is consistent with the well-established physiological increase in calcium binding to albumin during alkalosis, resulting in lower circulating free calcium concentrations despite unchanged total calcium. Similar observations have been reported in both physiological and clinical studies investigating calcium homeostasis [5–37].

The numerical simulations, as illustrated by the three-dimensional response surface in Figure 1, show a pronounced nonlinear dependence of ionized calcium concentration on the variations in extracellular pH and inorganic phosphate.

Even with total calcium assumptions and albumin held constant, progressive alkalization produces a systematic decline in the free calcium fraction, reflecting the enhanced affinity of plasma proteins for calcium as pH increases. This effect is clearly visible along the pH axis of the surface, where ionized calcium decreases smoothly and consistently with rising pH at low phosphate concentrations.

The simulations show that increasing phosphate concentration further decreases ionized calcium through chemical complexation, in agreement with previous studies describing the close physiological relationship between calcium and phosphate metabolism and their coordinated regulation [6,18–34].

As shown by the surface curvature in Figure 2, increasing phosphate concentration introduces an additional, independent mechanism of calcium sequestration through chemical complexation.

At lower phosphate levels, the pH-driven reduction in ionized calcium remains relatively moderate; however, at higher phosphate concentrations, the same pH shift results in a markedly steeper decline in free calcium.

Figure 3 illustrates how the applied modulation term influences the calculated response under combined parameter variation. The surface represents the response of the system under imposed combinations of calcium and magnesium values, rather than the solution of a coupled system.

The observed influence of magnesium is also consistent with previous physiological studies showing that magnesium modulates calcium homeostasis through interactions with parathyroid hormone secretion, calcium sensing, and intracellular calcium regulation [15,17,20,23,38].

The nonlinear topology of the response suggests that compensatory regulatory mechanisms may be insufficient in states combining alkalosis and phosphate excess, thereby predisposing to functional hypocalcemia.

New extensions from this method would include dynamic simulations of hormonal feedback, patient-specific parameterization and exploration of additional electrolytes or pathophysiological scenarios, providing a comprehensive platform for understanding and managing complex calcium disorders.

The results emphasize the need to consider acid–base balance and phosphate status explicitly when interpreting calcium measurements and provide a quantitative framework for understanding complex electrolyte disorders encountered in clinical and experimental settings.

The present work is based on a numerical simulation framework designed to explore the parametric dependence between pH, phosphate concentration, magnesium levels (Mg-related effects represented phenomenologically) and ionized calcium in plasma. While the model provides useful insights into nonlinear relationships between these variables, several limitations should be acknowledged.

First, the simulations were performed using simplified response term concentration ranges corresponding primarily to normal adult plasma conditions. Consequently, the quantitative results should be interpreted as representative of a reference scenario rather than universally applicable to all populations or pathological states.

Electrolyte ranges in pediatric patients, renal disease, or severe metabolic disturbances may significantly alter the parameter space.

Second, the model focuses on ionic equilibria and simplified chemical interactions and does not incorporate the full biochemical complexity of plasma, including protein binding dynamics, hormonal regulation of calcium metabolism, or intracellular buffering systems.

Third, although potential implications for blood rheology were mentioned, the present model does not explicitly simulate blood flow dynamics, coagulation pathways, erythrocyte deformability, or hematocrit-dependent viscosity and therefore any connection between ionic balance and rheological properties should be regarded as conceptual and exploratory rather than as a direct mechanistic prediction, while the viscosity relationship is a phenomenological expression used for exploratory purposes and restricted to parameter ranges ensuring physically meaningful values.

Although the present work represents a theoretical modeling study, the trends predicted by the simulations are consistent with several observations reported in the clinical literature. Hypocalcemia is a common finding in critically ill patients and is often associated with disturbances in acid–base balance and electrolyte composition [39].

Large cohort studies have also reported significant associations between ionized calcium levels and clinical severity in intensive care populations, with nonlinear relationships between ionized calcium concentration and patient outcomes [40].

The present model has not been quantitatively validated against experimental or clinical datasets. Rather than providing patient-specific predictions, the framework was developed to investigate physiologically plausible equilibrium behavior and to identify qualitative relationships between interacting variables.

Although the predicted trends are consistent with published experimental and clinical observations, quantitative validation through independent datasets, parameter calibration and prospective evaluation will be required before the model can be considered for predictive physiological or clinical applications.

The present model reproduces qualitatively similar behavior, showing that simultaneous variations in pH, phosphate and magnesium can produce disproportionate changes in ionized calcium. These findings therefore provide a sensitivity analysis interpretation that may help explain the electrolyte patterns observed in clinical settings.

However, the current framework does not include patient-specific physiological variability and therefore should be interpreted as a conceptual model rather than a predictive clinical tool. Its purpose is not direct clinical prediction but exploratory interpretation of electrolyte parametric dependence.

In the present formulation, low-molecular-weight complexation of calcium is represented primarily by phosphate. While phosphate is a major ligand for calcium under normal conditions, other anions may significantly contribute to calcium chelation in specific clinical contexts. In particular, citrate introduced during massive transfusion and elevated lactate levels in critically ill patients can substantially reduce ionized calcium concentrations. The current model does not explicitly include these additional ligands and their omission represents a limitation of the framework. Future extensions of the model could incorporate a generalized complexation term representing the cumulative effects of multiple clinically relevant anions.

Finally, the Ca/Mg ratio discussed in the manuscript should not be interpreted as a fixed physiological constant. Instead, it represents an emergent property of the modeled parameter space based on electrolyte concentrations.

Future work incorporating broader physiological ranges and more detailed biochemical and rheological models may further clarify these relationships.

The presented model is subject to several limitations that arise from its simplified mathematical formulation.

The system is represented as a zero-dimensional (0D), well-mixed compartment and is solved under steady-state conditions using algebraic equilibrium equations. As such, the model does not account for spatial heterogeneity, transport processes, or time-dependent dynamics. All relationships are evaluated as instantaneous equilibrium states and no temporal kinetics are resolved.

The assumption of a well-mixed plasma compartment neglects spatial concentration gradients arising from convection, diffusion, and local tissue exchange. Consequently, the present framework represents global equilibrium conditions rather than local intravascular microenvironments. This simplification was intentionally adopted to isolate equilibrium behavior and facilitate systematic sensitivity analysis. Extension toward one-, two-, or three-dimensional transport models incorporating convection–diffusion and fluid dynamics would enable investigation of spatial heterogeneity and represents an important direction for future studies.

The equilibrium equations for calcium and magnesium are evaluated independently within a shared parameter space. While the results are analyzed jointly, no intrinsic mathematical coupling exists between the two systems in the current formulation. Any interaction effects arise from the imposed functional parametric dependencies rather than from emergent coupling within the governing equations.

The modulation terms introduced in the model (e.g., functions dependent on magnesium concentration) are phenomenological in nature. These terms are intended to explore potential dependencies within the framework and do not represent mechanistically derived physiological processes.

The rheological component is not directly coupled to the equilibrium calculations.

The model does not solve fluid mechanics equations and does not incorporate feedback between viscosity and ion concentrations. Any reference to viscosity-related behavior should therefore be interpreted as a separate, exploratory extension rather than an integrated fluid–chemical model.

The relationship between the Ca/Mg ratio and viscosity is described using a simplified functional form that is not derived from experimental data. The formulation is restricted to parameter ranges that ensure physically meaningful values and is intended for qualitative exploration rather than quantitative prediction.

In human plasma, ionized calcium is strongly influenced by multiple low-molecular-weight anions, including bicarbonate, citrate, and lactate.

The model does not include these species and therefore, the partitioning between free and bound calcium is quantitatively incomplete. This simplification is particularly important in clinical contexts such as massive transfusion or critically ill patients, where citrate and bicarbonate concentrations vary and substantially alter calcium availability.

The present framework is deterministic and does not incorporate uncertainty quantification or probabilistic parameter estimation. Consequently, the reported response surfaces represent equilibrium solutions corresponding to specified parameter values rather than confidence intervals or prediction distributions.

Future work should incorporate uncertainty propagation, probabilistic sensitivity analysis and parameter estimation techniques to evaluate the robustness of model predictions under physiological variability.

Finally, the model assumes constant total calcium concentration, allowing isolation of equilibrium partitioning effects. In real systems, total calcium may vary due to additional processes not included in the present framework, such as exchange with external reservoirs or other regulatory mechanisms.

At its current stage, the proposed framework should be regarded as an exploratory computational model rather than a clinical decision support tool.

The absence of dynamic physiological regulation, patient-specific parameterization, spatial transport processes, comprehensive biochemical interactions, uncertainty quantification and external validation limits its predictive applicability in clinical practice.

Future validation of the proposed framework should combine computational simulations with controlled experimental measurements.

One possible approach would be plasma or serum samples with systematically varied pH, phosphate and magnesium concentrations while maintaining constant total calcium and albumin levels. Ionized calcium could then be measured using ion-selective electrodes or standard blood gas analyzers, and the experimental equilibrium values compared with the predicted response surfaces.

Additional validation could be achieved using retrospective clinical datasets containing simultaneous measurements of ionized calcium, pH, phosphate, magnesium and albumin, allowing assessment of the model's ability to reproduce observed physiological trends.

Future model development will require integration of these components together with calibration and validation against experimental and clinical datasets before individualized clinical prediction can be considered. The verification of the proposed model should involve comparison with real-world measurements obtained under controlled laboratory and clinical conditions.

Laboratory validation will be performed using plasma or serum samples in which pH, phosphate and magnesium concentrations are systematically varied, while ionized calcium is measured using ion-selective electrodes.

Complementary clinical verification will utilize retrospective or prospective datasets containing simultaneous measurements of ionized calcium, total calcium, albumin, phosphate, magnesium, and blood pH.

Quantitative comparison between measured values and simulated equilibrium states would enable calibration of model parameters and assessment of predictive accuracy.

3. Materials and Methods

The present study employed a deterministic numerical modeling framework to investigate the exploratory regulation of ionized calcium (Ca^{2+}) and magnesium (Mg^{2+}) in blood plasma as functions of pH, inorganic phosphate concentration and divalent cation interactions. The model integrates established chemical equilibrium relationships for calcium–protein binding and calcium–phosphate complexation with physiologically relevant parameter ranges reported in the literature.

The transport and mixing processes inherent to blood flow were incorporated conceptually through steady-state assumptions, allowing the system to be analyzed as a well-mixed compartment representative of circulating plasma.

The present model describes steady-state ionic equilibrium obtained from algebraic relationships between plasma components. The framework does not simulate time-dependent kinetic processes, such as calcium binding rates or hormonal feedback dynamics (e.g., parathyroid hormone secretion). Instead, it represents equilibrium states corresponding to specific combinations of physiological parameters.

The present study does not analyze clinical patient datasets or experimental measurements. Instead, it employed a deterministic computational model in which all input variables were assigned physiological ranges reported in the published literature. These included plasma pH, albumin, phosphate, total calcium and magnesium concentrations. The governing equilibrium equations were solved numerically for multiple combinations of these parameters to generate response surfaces illustrating the predicted behavior of ionized calcium and magnesium under steady-state conditions. Therefore, the results should be interpreted as model-based simulations rather than direct clinical observations.

Numerical simulations were conducted to generate multidimensional responses, enabling visualization and quantitative assessment of nonlinear dependencies between variables under both physiological and perturbed conditions [23,33–37,40–49].

3.1. Fluid Models for Blood

When incorporating fluid models for blood, it is essential to recognize that blood acts as a fluid medium in which dissolved electrolytes are redistributed to equilibrium states and ionic balance processes mechanisms.

At the macroscopic scale relevant to circulating plasma, blood flow can be approximated as an incompressible, viscous fluid, allowing ion concentrations to be treated as spatially averaged fields transported by the velocity profile.

Under steady or quasi-steady conditions, this justifies the assumption of a well-mixed compartment in which chemical equilibrium for calcium, phosphate and magnesium are locally maintained.

From a phenomenological perspective, fluid flow influences the residence time of ions, the renewal of plasma at exchange surfaces, and the homogenization of concentration gradients generated by binding, complexation, or cellular uptake.

Although the present model does not explicitly resolve spatial gradients, acknowledging the underlying fluid transport processes provides a physical basis for co-variation biochemical equilibrium with systemic circulation. This approach allows ion regulation to be interpreted as an emergent property of both chemical interactions and blood flow-mediated equilibrium state.

Blood is fundamentally a non-Newtonian fluid, exhibiting shear-thinning behavior due to red blood cell aggregation and deformation. At high shear rates, such as in large arteries, its viscosity approaches a nearly constant value, allowing Newtonian approximations.

However, in low-shear conditions, such as those in microcirculation, non-Newtonian effects dominate and factors such as the calcium/magnesium ratio can further modulate apparent viscosity and flow resistance [38,50–53].

The power-law (Ostwald–de Waele) model represents shear-thinning behavior through a nonlinear relationship between shear stress and shear rate, offering a simple yet flexible approach for medium-sized vessels, although it does not account for yield stress and may overestimate viscosity at very low shear rates.

The Casson model incorporates a yield stress, representing the minimum stress required for blood to flow, and effectively describes the increased viscosity due to erythrocyte aggregation in microcirculation.

The Carreau–Yasuda model captures the full shear-thinning behavior of blood across a wide range of shear rates, transitioning smoothly from a high zero-shear viscosity to a lower asymptotic viscosity at high shear. It is widely used in numerical simulations of blood flow due to its flexibility and accuracy in representing rheological properties.

The Herschel–Bulkley model combines a yield stress with shear-thinning, describing the stress threshold needed to initiate flow and the nonlinear viscosity response, making it particularly suitable for microcirculatory or pathological conditions where erythrocyte aggregation is pronounced.

Figure 4 illustrates the parametric variation in apparent viscosity as a function of the Ca/Mg ratio using a phenomenological Carreau–Yasuda formulation. This representation is intended for exploratory purposes and does not constitute a validated rheological model.

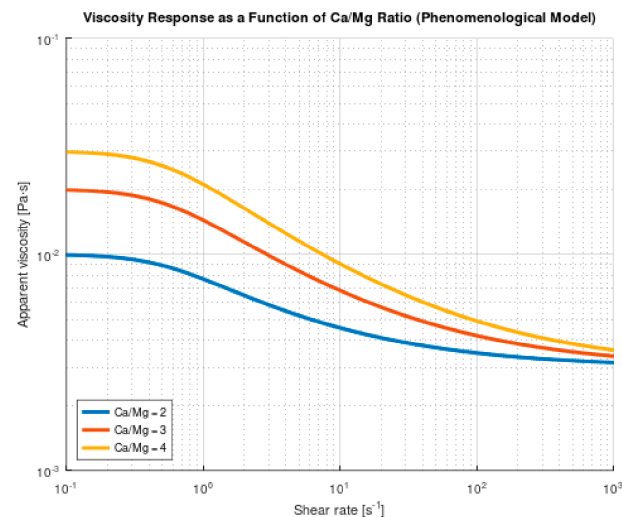


Figure 4. Parametric evaluation of viscosity variation as a function of the Ca/Mg ratio using a phenomenological Carreau–Yasuda formulation.

The zero-shear viscosity parametric assumption based on the Carreau–Yasuda model was expressed as a phenomenological function of the Ca/Mg ratio:

$$\eta_0 = \eta_r \left[1 + a \left(\frac{Ca}{Mg} - R_r \right) \right] \quad (1)$$

where

η_0 = zero-shear viscosity;

η_r = reference plasma viscosity;

Ca/Mg = ratio of calcium to magnesium concentrations;

R_r = reference physiological ratio;

a = phenomenological sensitivity parameter.

The resulting viscosity function was incorporated into the Carreau–Yasuda model:

$$\eta(\dot{\gamma}) = \eta + (\eta_0 - \eta) \left[1 + (\lambda \dot{\gamma})^a \right]^{\frac{n-1}{a}} \quad (2)$$

where $\dot{\gamma}$ is the shear rate and the remaining parameters correspond to the standard Carreau–Yasuda formulation.

Equation (1) is not derived from hemo-rheological theory and does not reflect established determinants of blood viscosity, introduced as a hypothetical linear perturbation to explore sensitivity to Ca/Mg variations.

Blood viscosity is primarily governed by hematocrit, erythrocyte deformability and plasma protein composition, while these dominant factors are not represented in the present formulation.

The viscosity assumption relation is considered a simplified phenomenological expression used for exploratory purposes, being restricted to parameter ranges and ensuring physically meaningful values.

In order to visualize the combined influence of the Ca/Mg ratio and shear rate on the response of the system, a three-dimensional response surface was generated using the equilibrium model described above.

For this purpose, the governing algebraic equations were evaluated over a predefined parameter grid.

The numerical analysis results (Figure 5) show that at Ca/Mg ratios above the optimal value (~3), increased flow resistance and potential cardiovascular risk occur, highlighting

how variations in the Ca/Mg ratio may modulate viscosity across different shear rate regimes. The dashed line indicates the reference ratio ($R = 3$). Contours and mesh are included in order to highlight the variation across the parameter space. The representation is intended for exploratory purposes and does not constitute a validated physiological model.

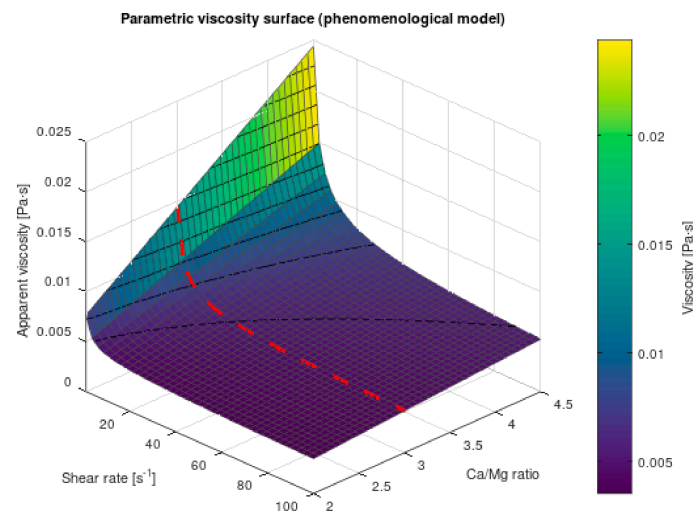


Figure 5. Parametric surface of apparent viscosity as a function of shear rate and Ca/Mg ratio based on a phenomenological formulation (dashed red line indicating the reference physiological ratio at ~ 3).

The mathematical response is illustrated for the assumed viscosity relation under varying Ca/Mg ratios, which should not be interpreted as a prediction of *in vivo* blood rheology.

Blood exhibits well-established non-Newtonian shear-thinning behavior, characterized by a progressive decrease in apparent viscosity with increasing shear rate as a consequence of erythrocyte deformation, orientation and reduced cell aggregation under flow conditions. This rheological behavior has been extensively documented experimentally and forms the basis of widely used constitutive models such as the Carreau and Carreau–Yasuda formulations, which are frequently employed in computational hemodynamics to describe blood viscosity over a broad range of shear rates [25,51–55].

In the present study, the viscosity surface is not intended to represent a validated constitutive law for blood but rather a phenomenological parametric framework designed to explore the possible influence of electrolyte-dependent variables on flow-related behavior. The inclusion of the Ca/Mg ratio should therefore be interpreted as an exploratory parameter motivated by the recognized physiological interactions between calcium and magnesium in vascular function, erythrocyte physiology and mineral homeostasis, rather than as evidence of a direct experimentally established causal relationship with blood viscosity [17,20,23,56–60].

Consequently, the proposed surface provides qualitative insight into potential parameter sensitivities and serves as a basis for future studies integrating experimentally validated rheological models with electrolyte regulation.

The rheological component is not dynamically coupled to the ionic equilibrium system, and no feedback between viscosity and transport or concentration fields is modeled.

The numerical model provides a quantitative framework linking ionic homeostasis with hemodynamic properties.

The model does not resolve time-dependent processes and represents all relationships within a steady-state framework.

The value of this framework lies in identifying whether simple parametric dependencies could motivate future experimental or mechanistic investigation.

3.2. Mechanisms of Ca/Mg Influence on Circulation and Metabolism

Calcium and magnesium influence physiological homeostasis through intertwined molecular, cellular and hemodynamic pathways. At the cellular level, Ca functions as a second messenger regulating muscle contraction, neurotransmitter release and enzymatic activity, whereas Mg acts as a natural Ca antagonist, stabilizing membrane potentials, inhibiting excessive Ca influx and modulating intracellular Ca release from the endoplasmic and sarcoplasmic reticulum. This interplay regulates neuromuscular excitability, cardiac rhythm and smooth muscle tone, with disruptions in Ca/Mg balance predisposing to arrhythmias, hypercontractility and vascular dysregulation. Mg also serves as a cofactor for over 300 enzymatic reactions, including those involved in ATP metabolism, glucose homeostasis and lipid metabolism, linking mineral status directly to systemic energy balance [54].

In the vascular system, Ca and Mg modulate endothelial function, vascular smooth muscle tone and platelet activity. Elevated Ca/Mg ratios favor Ca-mediated signaling that promotes vasoconstriction, platelet aggregation and thrombus formation, whereas Mg exerts vasodilatory and antithrombotic effects by reducing intracellular Ca in smooth muscle cells and platelets. These effects are amplified under conditions of altered blood rheology. Blood behaves as a shear-thinning, non-Newtonian fluid, meaning its apparent viscosity decreases with increasing shear rate, a property strongly influenced by red blood cell deformability, plasma protein composition and electrolyte concentrations. High Ca/Mg ratios enhance platelet activation and micro-vascular aggregation, which increases local resistance to flow, elevates shear stress and can impair tissue perfusion. Conversely, adequate Mg concentrations preserve erythrocyte flexibility, reduce platelet hyper-reactivity and maintain favorable shear profiles, thereby facilitating efficient microcirculatory flow and tissue oxygenation [55,56].

At the systemic level, Ca/Mg imbalance interacts with metabolic and inflammatory pathways. High Ca/Mg ratios are associated with insulin resistance, impaired glucose uptake and elevated oxidative stress, whereas balanced ratios enhance insulin signaling and antioxidant defenses [55].

Chronic imbalance may contribute to endothelial dysfunction, micro-vascular stiffening and hypertension, linking mineral homeostasis with macro-vascular complications.

Furthermore, Mg deficiency exacerbates inflammatory cytokine production, promoting vascular remodeling and increasing the likelihood of thrombosis, while elevated Ca promotes platelet-mediated clotting and disrupts laminar flow, highlighting the exploratory nature of electrolyte balance and hemo-dynamics [57,58].

These sensitivity analysis insights suggest that the Ca/Mg ratio is not only a biochemical marker but also a determinant of hemodynamic efficiency, influencing both macro and micro circulation through effects on blood viscosity, shear stress, endothelial transduction and platelet function.

Optimizing the Ca/Mg ratio could, therefore, have implications beyond traditional metabolic endpoints, potentially improving cardiovascular efficiency, reducing thrombotic risk and maintaining tissue perfusion, particularly in high-risk populations such as those with hypertension, diabetes, or cardiovascular disease [55–58].

3.3. Mathematical Model Framework

The use of equilibrium relationships is physiologically motivated by the rapid reversible exchange between ionized calcium, protein-bound calcium, and calcium complexed with low-molecular-weight anions in plasma. Compared with slower endocrine regulation mediated by parathyroid hormone, calcitriol, and calcitonin, these physicochemical processes occur sufficiently rapidly that they may be approximated as equilibrium

states under stable physiological conditions. Accordingly, the present model focuses on equilibrium partitioning of extracellular ions rather than on the dynamic regulation of whole-body mineral homeostasis.

A steady-state equilibrium model was developed to describe calcium (Ca^{2+}) and magnesium (Mg^{2+}) speciation in blood plasma. Total ion concentration was assumed to be distributed among three fractions: ionized (free), protein-bound and complexed with low-molecular-weight anions (primarily phosphate).

The main objective is to establish the equilibrium state of Ca^{2+} and Mg^{2+} in plasma, between the ionized (active) fraction, the albumin-bound fraction, the complexed fraction (phosphates, citrate) and how this equilibrium shifts when albumin, pH, phosphate concentration and magnesium level (via simplified response term) vary [44–49].

$$C_T = C_i + C_p + C_c \quad (3)$$

where C_T is total calcium, C_i is ionized calcium, C_p is protein-bound calcium and C_c is complexed calcium.

For simplicity, calcium complexation is modeled solely with inorganic phosphate, while this simplification ignores the substantial contribution of other low-molecular-weight anions such as bicarbonate, citrate and lactate. Therefore, absolute partitioning coefficients should not be interpreted as quantitatively accurate for clinical plasma.

The equilibrium relations contain the protein binding and anion complexation, which were modeled as reversible equilibrium reactions, first accounting for protein binding and then phosphate complexation:

$$C_i + [A] \rightleftharpoons C_p$$

$$k = \frac{[C_p]}{[C_i][A]} \quad (4)$$

$$C_i + \text{PO}_4^{3-} \rightleftharpoons C_c$$

$$k_p = \frac{[C_c]}{[C_i][\text{PO}_4]}$$

$$\text{Ca}^{2+} + \text{PO}_4 \rightleftharpoons \text{Ca} - \text{PO}_4$$

$$k_c = \frac{[\text{Ca} - \text{PO}_4]}{[\text{Ca}^{2+}][\text{PO}_4]} \quad (5)$$

$$C_p = k_p(\text{pH})C_iA$$

$$C_c = K_cC_i\text{PO}_4 \quad (6)$$

where

A —albumin concentration;

PO_4 —inorganic phosphate concentration;

k_p, k_c —equilibrium constants.

The above equation model provides a simplified estimation of ionized calcium assuming phosphate-only complexation.

Inorganic phosphate was selected as the representative low-molecular-weight ligand because it constitutes one of the major physiological determinants of calcium complexation and plays a central role in mineral homeostasis.

The inclusion of additional ligands such as bicarbonate, citrate and lactate would require a substantially expanded equilibrium system with additional binding constants and interaction terms. To preserve model transparency and facilitate systematic sensitivity analysis, the present framework was intentionally restricted to phosphate-mediated complexation.

Consequently, the model is intended to provide qualitative insight into equilibrium behavior rather than a complete quantitative description of plasma calcium speciation.

The pH dependence of calcium–protein binding was incorporated by allowing the binding constant to vary exponentially with pH, resulting in the following form:

$$k_p(pH) = k_p^0 \cdot 10^{\alpha(pH-7.4)} \quad (7)$$

with

k_p^0 —the reference binding constant at pH 7.4;

α —dimensionless sensitivity coefficient ($\alpha = 0.2 \div 0.25$).

The formulation introduces nonlinearity into the model, and substituting equilibrium expressions into the mass balance yields a nonlinear algebraic equation in C_i :

$$f(C_i) = C_T - C_i(1 + k_p(pH)A + k_cPO_4) = 0 \quad (8)$$

For magnesium:

$$M_T = M_i + M_p + M_c \quad (9)$$

where M_T is total magnesium, M_i is ionized magnesium, M_p is protein-bound magnesium and M_c is magnesium complexed with low-molecular-weight anions.

Magnesium binding and complexation were modeled analogously to calcium, with distinct equilibrium constants reflecting weaker protein affinity.

$$\begin{aligned} M_p &= k_{p,M}(pH)M_iA \\ M_c &= k_{c,M}M_iPO_4 \end{aligned} \quad (10)$$

where $k_{p,M} \ll k_{p,Ca}$, consistent with physiological binding data.

Protein binding of magnesium was assumed to exhibit weaker pH dependence than calcium:

$$k_{p,M}(pH) = k_{p,M}^0 \cdot 10^{\beta(pH-7.4)} \quad (11)$$

with $\beta < \alpha$, reflecting reduced electrostatic sensitivity.

Low magnesium concentrations suppress monotonic proxy function secretion and peripheral responsiveness, and this effect was incorporated using a phenomenological exploratory term modifying effective calcium mobilization:

$$\Phi(M_i) = \frac{M_i}{M_i + k_{Mg}} \quad (12)$$

with k_{Mg} as a half-maximal suppression constant, and $\Phi(M_i)$ as a phenomenological modulation term.

The functional form $\Phi(M_i)$ is a monotonic Michaelis–Menten-type expression introduced as a simplified proxy for magnesium-dependent modulation. It does not capture the well-established biphasic regulation of parathyroid hormone (PTH) by magnesium, including stimulation under mild hypomagnesemia and suppression under both severe hypomagnesemia and hypermagnesemia.

Physiologically, the relationship between magnesium and PTH secretion is biphasic, since mild-to-moderate hypomagnesemia stimulates PTH release, while severe hypomagnesemia leads to a paradoxical suppression.

In addition, hypermagnesemia suppresses PTH via activation of the calcium-sensing receptor. These nonlinear dynamics are not represented in the present formulation.

Substituting equilibrium relations into mass balances yields two equations:

$$\begin{aligned} C_T &= C_i[1 + k_{p,Ca}(pH)A + k_{c,Ca}PO_4] \\ M_T &= M_i[1 + k_{p,Mg}(pH)A + k_{c,Mg}PO_4] \end{aligned} \quad (13)$$

The steady-state algebraic system (Equation(13)) consists of two independent equations for calcium and magnesium, while no intrinsic coupling is present in the governing equations.

Baseline response term conditions were defined using literature-derived plasma concentrations. Systematic parameter perturbations were applied to pH, albumin and phosphate levels to reproduce clinically relevant scenarios.

3.4. Numerical Analysis Solution

The resulting nonlinear system was numerically solved and parameter sweeps were conducted for pH (7.20–7.60), albumin concentration (2.0–4.5 g/dL) and phosphate concentration (0.8–2.5 mmol/L).

The primary outcome measures included ionized calcium and magnesium concentrations, along with percentage deviation from baseline concentration.

The algorithm was verified for robustness by varying initial conditions and applying continuation methods until the system exhibited a unique steady-state solution across simplified response term parameter ranges.

The numerical model was constructed to simulate the equilibrium distribution of ionized calcium (Ca^{2+}) in plasma as a function of pH, phosphate (PO_4^{3-}) and magnesium (Mg^{2+}). Total calcium and albumin concentrations were held constant to isolate the effects of chemical equilibrium, while this assumption was adopted to isolate equilibrium partitioning effects.

The present model represents a zero-dimensional (0D) well-mixed plasma compartment in which ionic equilibria are evaluated using algebraic relationships.

The framework does not explicitly solve the Navier–Stokes equations or simulate spatial flow fields.

Instead, the shear rate parameter is treated as an externally specified simple response term variable representing typical microvascular flow conditions.

The rheological component does not influence the equilibrium calculation but is evaluated separately based on the computed Ca/Mg ratio.

The space parameter was explored using structured parameter sweeps over physiologically relevant ranges of pH, phosphate, albumin, and magnesium concentrations. For each parameter combination, the nonlinear equilibrium equations were solved numerically and the resulting equilibrium states were used to construct three-dimensional response surfaces.

The present study evaluated sensitivity qualitatively by examining changes in the topology and gradients of these response surfaces. No formal variance-based or global sensitivity analysis was performed.

The well-mixed steady-state assumption implies that the calculated solutions represent equilibrium states corresponding to specified physiological conditions rather than the dynamic evolution of plasma ion concentrations. Therefore, the model does not capture transient changes caused by blood flow, tissue exchange, endocrine feedback, or rapid metabolic disturbances. Instead, it identifies the equilibrium sensitivity of ionized calcium to simultaneous variations in pH, phosphate, and magnesium.

Consequently, the predicted response surfaces should be interpreted as equilibrium reference maps that may guide future development of dynamic transport and kinetic models.

4. Conclusions

This research study provides a comprehensive, exploratory analysis of ionized calcium regulation under the combined influence of extracellular pH, phosphate and phenomono-

logical magnesium, employing a multivariate numerical modeling approach grounded in chemical equilibrium principles.

This study did not establish mechanistic coupling between ionic composition and blood rheology but instead explored a simplified parametric relationship to assess potential sensitivities.

The numerical simulations generated three-dimensional response surfaces that revealed the nonlinear, phenomenological parametric dependence governing ionized calcium availability.

The surfaces highlight regions of heightened sensitivity, where minor perturbations in one or more variables produce disproportionately large changes in biologically active calcium, elucidating mechanisms underlying functional hypocalcemia that cannot be inferred from total calcium alone.

By integrating pH, phosphate, magnesium and flow-related transport phenomena, the study identified key phenomenological drivers, critical regions of sensitivity and actionable insights for clinical evaluation, bridging the gap between theoretical chemistry, physiology and practical management of calcium-related disorders.

The simulations demonstrated that the system exhibits pronounced nonlinear behavior, with simultaneous variations in multiple parameters producing disproportionate changes in the calculated equilibrium state.

In particular, combined increases in pH and phosphate concentration, as well as reductions in magnesium levels, were associated with significant decreases in ionized calcium across the explored parameter space.

The analysis further revealed the presence of distinct regions characterized by differing sensitivities to parameter variation.

In certain regions, small perturbations produced large shifts in the equilibrium state, whereas in others the system displayed relative stability.

These findings highlight the importance of considering multivariate parametric dependence rather than isolated parameter effects.

From a methodological perspective, the use of structured parameter space exploration and response surface representation provides a systematic approach for analyzing complex equilibrium systems.

This framework allows the identification of parametric dependence effects and nonlinear response patterns that are not accessible through single-variable analysis.

Although the present model is limited to steady-state solutions derived from algebraic equilibrium equations and does not include time-dependent kinetics or spatial transport processes, it establishes a basis for further extensions.

Overall, although the present framework is intentionally simplified and phenomenological, and the qualitative behavior predicted by the simulations is consistent with previously reported physiological and clinical evidence, supporting the biological plausibility of the proposed equilibrium model.

Future developments may incorporate additional variables, generalized interaction terms, or coupling with transport models to increase the descriptive scope of the framework.

In this context, the proposed approach may serve as a computational tool for exploring parameter dependencies and for supporting the interpretation of systems governed by exploratory equilibrium relationships.

Funding: This research received no external funding.

Institutional Review Board Statement: This study was conducted using retrospective, fully anonymized data with no direct patient contact or identifiable information. Therefore, ethical approval was not required in accordance with institutional and national guidelines.

Informed Consent Statement: Patient consent was waived due to the retrospective nature of the study.

Data Availability Statement: The data that support the findings of this study are available from the corresponding author upon reasonable request.

Conflicts of Interest: The author declare no conflicts of interest.

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