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A Literature-Based Dynamic Loop System Modeling the Piezo1-TRPV4 Interaction as a Potential Mechanism of Osteoarthritis Pathogenesis

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Abstract

Background/Objectives: Osteoarthritis (OA) is an age-related degenerative joint disease whose pathogenic mechanisms remain poorly understood. Experimental evidence implicates dysregulated mechanotransduction mediated by Piezo1 and TRPV4 channels, but how their interaction with inflammation may drive pathogenic state transitions remains unknown. Here, we aimed to study whether a Piezo1–TRPV4 network can intrinsically produce distinct stable physiological and pathological regimes. **Methods:** Based on literature data, we developed a nonlinear dynamical model describing closed-loop interactions involving Piezo1, TRPV4, and inflammation. The system was translated into a set of ordinary differential equations and studied using stability and bifurcation analysis. **Results:** Computational analysis revealed bistability, allowing the system to shift from a physiological to a pathogenic regime in response to specific stimuli. Critical bifurcation parameters were linked to Piezo1 and inflammation, suggesting that the bidirectional interaction between these two components represents a key node for interventions aimed at preventing or reversing transitions from non-pathogenic to pathogenic states. **Conclusions:** Our results suggest that OA pathogenesis may emerge from the intrinsic nonlinear dynamics of Piezo1/TRPV4/inflammation interactions. Bifurcation analysis indicates the sensitivity of TRPV4 to the inhibitory effect of Piezo1 as a key target for preventing or reversing pathogenic state transitions. Further investigations in preclinical and clinical settings are warranted to validate the model.

Keywords: aging; bifurcation analysis; closed-loop interactions; systems biology; inflammation; menopause; nonlinear dynamic systems; Piezo1 inhibitors; therapeutic targets



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1. Introduction

Osteoarthritis (OA) is a chronic, degenerative joint disease characterized by progressive degradation of articular cartilage, remodeling of subchondral bone, synovial inflammation, and changes in periarticular tissues [1]. Although OA can affect virtually any synovial joint, it most commonly involves weight-bearing joints such as the knees and hips, as well as the spine and hands, and less frequently the ankles and temporomandibular joints [2]. Typical symptoms include joint pain, stiffness, crepitus, swelling or effusion, and in advanced cases mechanical symptoms such as locking and instability [3].

Epidemiologically, OA is among the most prevalent musculoskeletal disorders worldwide, affecting more than 10% of people over the age of 60 [4]. Risk factors include increasing

age, female sex, obesity or excessive mechanical loading, joint injury or repetitive joint stress, muscle weakness, anatomical alignment abnormalities, and genetic predisposition [5].

Currently, there is no cure for OA, and management is aimed at symptom relief, preservation of joint function, and delay of disease progression. Therapeutic strategies combine nonpharmacologic measures with analgesics and anti-inflammatory drugs, as well as surgical interventions in advanced disease [6]. In parallel, ongoing research explores disease-modifying strategies targeting molecular signaling pathways, cartilage repair and regeneration, and modulation of joint mechanobiology [7].

The absence of satisfactory cures for OA is largely attributable to the limited understanding of its pathogenic mechanisms. Modern reviews emphasize that inflammatory, metabolic and post-traumatic processes, together with aging and obesity, shape divergent OA phenotypes rather than a single pathogenic pathway [8]. Mechanisms implicated in OA progression involve cellular senescence of joint cells, ferroptosis [9], obesity-related metabolic inflammation, dysregulated lipid/glucose metabolism, and gut microbiota–joint interactions [10]. Taken together, OA pathogenesis is considered a network problem, in which mechanical, inflammatory, metabolic, and aging-related processes interact, thus explaining the clinical heterogeneity of the disease and suggesting multimodal therapeutic strategies [8].

The complexity of OA represents a major limitation, as it hinders the development of coherent and manageable models capable of describing the interactions and dynamic processes underlying disease onset. Nevertheless, within the extensive body of data on OA mechanisms, certain unifying principles can be discerned. At the tissue and cellular level, chondrocyte dysfunction appears to be central: chondrocytes show altered differentiation, increased production of matrix-degrading enzymes such as MMPs (matrix metalloproteinases) and ADAMTS (A Disintegrin And Metalloproteinase with Thrombospondin Motifs), impaired matrix repair, and susceptibility to apoptosis or other regulated cell-death programs. These changes destabilize cartilage extracellular matrix, expose subchondral bone, induce low-grade synovial inflammation (production of pro-inflammatory cytokines such as IL-1 β , IL-6, TNF- α), and amplify catabolism and pain signaling, thereby leading to the complex of the disease symptoms [11]. More importantly, molecular data have allowed linking chondrocyte destabilization to biochemical degenerations triggered by abnormal mechanotransduction. Mechanosensitive ion channels such as Piezo1 and Transient Receptor Potential Vanilloid 4 (TRPV4) regulate calcium signaling, inflammatory responses, chondrocyte catabolism, and pro-senescence programs. Dysregulation of these channels under excessive or abnormal mechanical stress has been shown to promote cartilage breakdown and synovial pathology [12].

This study presents a hypothesis-generating framework designed to model OA pathogenesis and provide possible insights for the development of potential therapeutic strategies. We followed the principles of conceptual systems biology and a general hypothesis proposed by one of us, which posits that all changes occurring in living systems result from transitions among different equilibrium states governed by loop-arranged, nonlinear dynamical systems [13]. Since the onset of a disease clearly represents a transition in the functional state of the organism, we started from the hypothesis that, at the basis of OA pathogenesis, there must exist a dynamical system admitting multistability, most likely with a closed-loop structure. The idea of describing pathological conditions using nonlinear models has permeated several studies [14]. However, to the best of our knowledge, it has generally been applied on a case-by-case basis. Conversely, we used it as a putative general theory, consistent with our interpretation of life as a phenomenon governed by nonlinear dynamics with simple attractors, generating regular and predictable patterns [15].

We therefore attempted to construct a multistable model of OA pathogenesis by extracting mechanistic data from the scientific literature. The TRPV4/Piezo1 system, previously

validated in both *in vitro* and *in vivo* preclinical investigations [12,16], provided a suitable framework for building a dynamical model with the features described above. This theoretical system exhibited transitions from mono- to bistability, enabling the identification of critical bifurcation parameters potentially relevant to OA pathogenesis, which might represent ideal targets for therapeutic intervention.

2. Materials and Methods

2.1. Literature Survey and Inclusion Criteria

To inform the conceptual framework and mathematical modeling presented in this study, we conducted a targeted literature survey using PubMed (<https://pubmed.ncbi.nlm.nih.gov>). Reference inclusion criteria focused on the most updated papers addressing the following: (1) general information on the clinical and biological features of OA; (2) mechanistic processes of the disease in human or animal models that could be integrated into a network of interacting elements, convertible into a dynamical loop system; and following the identification of a TRPV4/Piezo1 loop in chondrocytes, (3) studies addressing the modulatory roles of sex hormones and cortisol, as well as (4) the potential therapeutic effects of Piezo1 inhibitors.

Relevant articles published up to October 2025 were identified using combinations of keywords in the following Boolean operators:

“osteoarthritis”[Title] AND “year in review”[Title], 74 results;
 “osteoarthritis”[Title] AND “molecular”[Title] AND “mechanisms”[Title], 68 results;
 (“Piezo1”[Title/Abstract] OR “TRPV4”[Title/Abstract]) AND “osteoarthritis”[Title/Abstract], 71 results;
 (“estrogen*”[Title] OR “progesterone”[Title]) AND “osteoarthritis”[Title], 86 results;
 (“estrogen*”[All Fields] OR “progesterone”[All Fields]) AND (“TRPV4”[Title] OR “Piezo1”[Title]), 10 results;
 “cortisol”[Title] AND “osteoarthritis”[Title], 7 results;
 “Piezo1”[Title] AND “inhibitors”[Title], 3 results;
 “salvianolic”[All Fields] AND “osteoarthritis”[Title], 9 results;
 “artemisinin” [Title] AND “osteoarthritis”, 8 results;
 “GsMTx4”[Title] AND “osteoarthritis”[Title], 1 result.

Moreover, some papers on loop-arranged nonlinear dynamics in biological systems, including some of our own, were cited to support the mathematical and stability analyses underlying the proposed theoretical framework.

Information gathered from the literature search was then used to construct a dynamical system with interacting feedback loops for computational analysis, as summarized in the flowchart in Figure 1.

2.2. Mathematical Model

The loop-based interaction system reconstructed from literature data was translated into a set of nonlinear ordinary differential equations (ODEs). These equations described the nodes of the loop (variables) and the interactions among them (functions). The mathematical modeling and computations were performed in MATLAB R2025b (MathWorks, Natick, MA, USA). Interaction functions were implemented and numerically solved using the ode45 solver, while additional routines were employed to perform parameter scans and generate phase portraits and bifurcation plots.

The loop system representing the theoretical pathogenesis model comprises three biological elements: Piezo1, TRPV4, and inflammation. When these terms are mentioned in the text as components of the model, they are written in *Italics*; when they refer to the actual biological entities, they are written in Roman. In the ODEs, the variables corresponding to

these elements are denoted as X_1 , X_2 , and X_3 , for improved equation readability, standing for *Piezo1*, *TRPV4*, and *inflammation*, respectively.

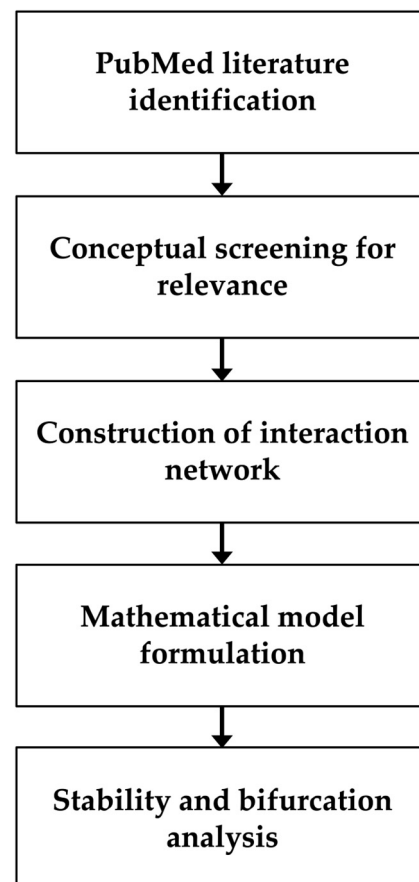


Figure 1. Overview of the literature selection process and data analysis. The flowchart summarizes the literature screening and illustrates how the selected studies were integrated to construct the biological interaction network and the corresponding dynamical model proposed in this study.

3. Results

3.1. Construction of the Pathogenic Loop System

As mentioned above, our goal was to describe the transition of cartilage from physiological to pathological functioning as a shift between different equilibrium points in a dynamical system. To this end, we sought to identify a feedback loop capable of generating multistable nonlinear dynamics. Among the cellular and molecular studies on OA pathogenesis, the most suitable candidates appeared to be a network of interactions between chondrocytes and their environment, involving *Piezo1*, *TRPV4*, and key inflammatory cytokines.

The calcium-permeable, non-selective cation channel *TRPV4* is a mechanosensitive and osmosensitive ion channel that is expressed in chondrocytes and plays key roles in regulating extracellular matrix (ECM) synthesis and inflammation [4]. *TRPV4* contributes to the pathogenesis of OA, exerting multifaceted effects on cartilage integrity, chondrocyte survival, and disease progression. *TRPV4*-deficient mice develop spontaneous OA at an earlier age, showing severe cartilage fibrillation, proteoglycan loss, and associated bone alterations. Chondrocytes lacking *TRPV4* also lose osmotically induced Ca^{2+} signaling, highlighting the channel's essential role in mediating mechanical and osmotic stress responses in cartilage [16]. Acting as a mechanotransducer, *TRPV4* links dynamic mechanical loading to matrix-building and anti-catabolic gene expression in chondrocytes. Pharmacological stimulation of *TRPV4* (e.g., with the agonist GSK1016790A) enhances ECM biosynthesis

and mechanical properties even in the absence of loading [17]. Conversely, loss of TRPV4 is associated with joint arthropathy and OA-like changes [17].

Beyond TRPV4 homeostatic function in cartilage, its upregulation under excessive mechanical stress causes abnormal Ca^{2+} influx in chondrocytes, leading to apoptotic cell death. In vivo OA models have shown that TRPV4 hyperactivation disrupts mechanotransduction and cartilage maintenance [18], promotes chondrocyte pyroptosis (a form of inflammatory cell death), induces mitochondrial dysfunction, and drives cartilage degradation. Conversely, the inhibition or blockade of the channel reverses these deleterious effects [19–21]. In summary, under physiological mechanical loading TRPV4 activation leads to moderate Ca^{2+} influx, which promotes cartilage homeostasis, supports anabolic signaling pathways, and stimulates extracellular matrix synthesis (collagen II, aggrecan). Excessive mechanical stress or chronic overload leads to hyperactivation of TRPV4 triggering catabolic signaling, including activation of MMPs and pro-inflammatory cytokines (IL-1 β , TNF α). In addition, aged or senescent chondrocytes exhibit altered Ca^{2+} handling and signaling, which may favor catabolic over anabolic responses, tipping the balance toward OA progression [22].

Piezo1 is another mechanosensitive, non-selective cation channel expressed in chondrocytes. It opens in response to mechanical stimuli such as stretch, compression, or shear stress, generating intracellular Ca^{2+} transients that trigger diverse signaling cascades [23]. A growing body of research has identified the channel as a key mechanosensor in cartilage and joint tissues, where its aberrant activation contributes to chondrocyte dysfunction, cartilage degradation, and joint degeneration [24]. In rat OA models, Piezo1 upregulation leads to catabolism vs. anabolism imbalance, characterized by reduced production of collagen II and aggrecan, mitochondrial disruption, reactive oxygen species increase, and chondrocyte apoptosis [23,25]. Mechanical stress-driven Piezo1 activation also accelerates chondrocyte senescence, marked by increased expression of the indicators p16 and p21 [26]. In chondrocytes exposed to IL-1 α , a key inflammatory mediator in OA, Piezo1 expression and function are increased, leading to detrimental mechanosensitivity and biomechanical injury [27]. Consistent with these data, Piezo1 has been recognized as a central mediator of OA onset and progression [28].

Specifically, Piezo1 functions as a dual mechanical and inflammatory sensor in articular chondrocytes, establishing a loop that amplifies catabolic and inflammatory processes in OA. Mechanical overstimulation of Piezo1 activates signaling pathways such as NF- κ B and MAPK, leading to the transcription and release of pro-inflammatory cytokines, including IL-1 β , IL-6, and TNF α [29]. These cytokines, in turn, upregulate Piezo1 expression and sensitize its mechanotransduction, further enhancing Ca^{2+} signaling and chondrocyte damage under mechanical stress [27]. This reciprocal regulation contributes to chronic inflammation, matrix degradation, and cartilage degeneration in OA.

The key role of Piezo1 in OA has been confirmed by *in vitro* and *in vivo* studies, showing that its downregulation alleviates inflammation and slows OA progression. Pharmacological blockade of Piezo1 with the peptide inhibitor GsMTx4 or genetic ablation reduces mechanically induced chondrocyte death and apoptosis, as well as matrix breakdown in *ex-vivo* cartilage and *in vivo* OA models [12]. Mechanistically, Piezo1 blockade interrupts several pathogenic pathways implicated in OA, including Ca^{2+} overload in mechanically stressed chondrocytes, activation of downstream calcineurin/NFAT and NF- κ B inflammatory signaling, mitochondrial dysfunction and oxidative stress, and production of pro-inflammatory cytokines and matrix-degrading enzymes [30]. In sum, preclinical evidence strongly supports the idea that Piezo1 inhibition (pharmacologic or genetic) reduces inflammation and slows OA-like pathology in cells and animal models.

Genetic studies support the therapeutic potential of Piezo1 targeting but also reveal its complexity. Chondrocyte-specific deletion of mechanosensitive channels can protect

against some OA features (pain, synovitis, cartilage degeneration) in some models, yet other data indicate that the role of Piezo1 is context-dependent and that combined modulation of Piezo1 and related channels, such as Piezo2 and TRPV4, may determine net outcomes. Thus, while Piezo1 inhibition shows clear chondroprotective and anti-inflammatory effects in multiple preclinical systems, the channel also plays physiological roles in cartilage development and homeostasis that require cautious translational development [31].

Interest in TRPV4 and Piezo1 in OA stems from their ability to interact, revealing additional dynamics that influence cartilage health and disease progression. Studies have shown that activation of these channels with specific agonists, such as Yoda1 for Piezo1 and GSK1016790A for TRPV4, increases intracellular Ca^{2+} levels in chondrocytes. Interestingly, when these agonists are applied sequentially, the activation of either channel can inhibit the response of the other, suggesting mutual inhibition between Piezo1 and TRPV4. In the context of OA, this crosstalk appears altered, possibly affecting the chondrocyte ability to respond appropriately to mechanical stimuli, leading to pathological changes in the joint [32]. The altered interaction between Piezo1 and TRPV4 in OA further suggests that these channels play significant roles in disease progression. A shift in their crosstalk may influence inflammatory responses, extracellular matrix remodeling, and chondrocyte apoptosis, all of which are thought to be key factors in OA pathogenesis.

In summary, under physiological loading, TRPV4 predominates, supporting protective, homeostatic responses. However, during excessive or chronic mechanical loading and inflammatory priming, TRPV4 can become hyperactivated, shifting to a pro-inflammatory mode that promotes cytokine release and disrupts matrix homeostasis. When strong mechanical forces and an inflammatory milieu persist, Piezo1 becomes increasingly engaged and sensitized, and its downstream signaling becomes destructive and self-sustaining through positive feedback with inflammatory cytokines. Thus, TRPV4 may contribute to an initial wave of dysfunction upon hyperactivation, whereas Piezo1 assumes a central, sustaining role in disease progression under intense mechanical stress [33].

Based on the above evidence, we developed a system composed of interacting elements representing a biomolecular interaction network that may drive OA pathogenesis. The interacting elements are designated as *Piezo1*, *TRPV4*, and a third element referred to as *inflammation*, representing the main OA-related inflammatory cytokines. A more detailed specification of this latter element is not provided, as the specific interactions of individual cytokines with the mechanoreceptors have not yet been fully elucidated. The system includes various feedback loops, i.e., closed-chain interactions, capable of generating nonlinear dynamics and transitions between distinct functional regimes. The element *Piezo1* activates *inflammation*, i.e., the rate of cytokine release, and inhibits *TRPV4*, while *inflammation*, in turn, activates *Piezo1*. *TRPV4* inhibits *Piezo1* and exerts an activating effect on *inflammation*, although this effect tends to diminish as *Piezo1* activity increases (Figure 2).

3.2. Mathematical Modeling of the Loop System and Dynamics

Starting from the theoretical model of OA pathogenesis described above, we developed a mathematical representation as a nonlinear dynamical system and analyzed its behavior computationally. The system consists of three ordinary differential equations (ODEs) describing the dynamics of three variables corresponding to the components of the model, namely X_1 for *Piezo1*, X_2 for *TRPV4*, and X_3 for *inflammation*. In the ODEs, the interactions among variables, that is, the effects of each variable on the others, were modeled nonlinearly using increasing Hill functions for activation and decreasing Hill functions for inhibition. These functions provide a compact phenomenological description of cooperative or threshold-like responses that emerge from underlying molecular or network mechanisms. They allow the model to capture ultrasensitive interactions using a small

number of parameters, which is particularly important when the detailed biochemical reaction scheme is unknown or when the modeled variables represent aggregated populations rather than single molecular species. Operationally, a wide range of data demonstrates that these functions accurately fit or approximate biological input–output relationships [34–36]. Moreover, to represent the combined effects of two variables on a third one, we used additive or multiplicative combinations of Hill functions, as previously reported [37–39]. For each variable, self-limiting terms were also included to reflect a well-known property of biological systems, whereby the growth of a factor imposes limits on its further growth [40].

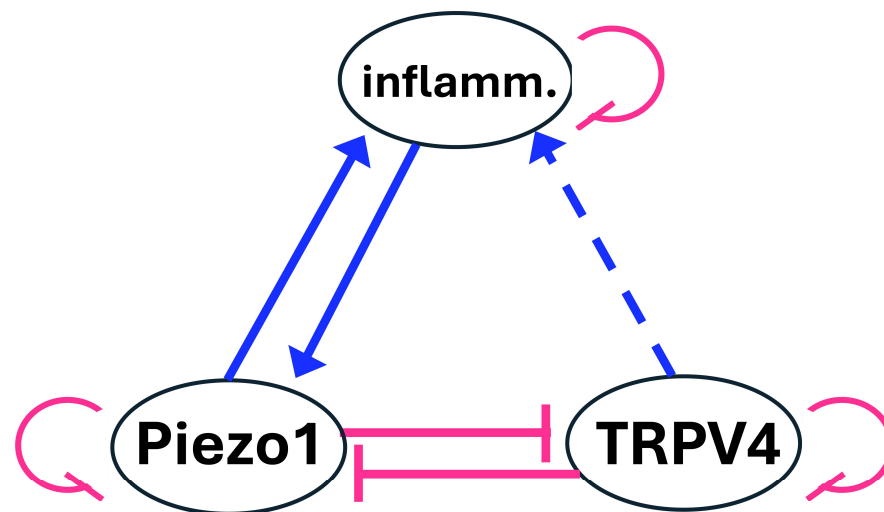


Figure 2. Diagram illustrating the OA pathogenesis model, consisting of three elements that interact with each other through a series of closed loops. *Piezo1* stimulates *inflammation* (blue line) and inhibits *TRPV4* (pink line). *Inflammation*, in turn, activates *Piezo1* (blue line). *TRPV4* inhibits *Piezo1* (pink line) and stimulates *inflammation*, although this latter effect tends to disappear as *Piezo1* activity increases (blue dashed line). The curved pink lines indicate the limiting effect exerted by each element on itself.

The system of ODEs was constructed as follows. The combined effects of *inflammation* (activation) and *TRPV4* (inhibition) on *Piezo1* were represented by the time variation of variable X_1 , defined as the product of an increasing Hill function depending on X_3 and a decreasing Hill function depending on X_2 , plus a negative self-limiting term depending on X_1 (Equation (1)). The effect of *Piezo1* (inhibition) on *TRPV4* was represented by the time variation of variable X_2 , defined as a decreasing Hill function depending on X_1 , plus a negative self-limiting term depending on X_2 (Equation (2)). Finally, the combined effects of *Piezo1* (activation) and *TRPV4* (biphasic activation) on *inflammation* were represented by the time variation of variable X_3 , defined as the sum of an increasing Hill function depending on X_1 , a biphasic Hill function depending on X_2 and modulated by X_1 , and a negative self-limiting term depending on X_3 (Equation (3)).

$$dX_1/dt = H_{X_3 \rightarrow X_1} \cdot (1 - H_{X_2 \rightarrow X_1}) - p_1 X_1 \quad (1)$$

$$dX_2/dt = (1 - H_{X_1 \rightarrow X_2}) - p_2 X_2 \quad (2)$$

$$dX_3/dt = H_{X_1 \rightarrow X_3} + H_{biphasic_X_2 X_3} - p_3 X_3 \quad (3)$$

In these equations, the terms $p_i X_i$ represent the negative feedback exerted by each variable on itself, where the parameter p_i denotes the strength of the self-limiting effect.

The functions $H_{X_i \rightarrow X_j}$ describe the effect of the i_{th} variable on the j_{th} variable, and are modeled by increasing Hill functions having the form:

$$H_{X_i \rightarrow X_j}^{increasing} = \frac{X_i^{h_{X_i X_j}}}{e_{X_i X_j}^{h_{X_i X_j}} + X_i^{h_{X_i X_j}}} \quad (4)$$

or by decreasing Hill functions, expressed as:

$$H_{X_i \rightarrow X_j}^{decreasing} = \left(1 - H_{X_i \rightarrow X_j}^{increasing}\right). \quad (5)$$

In these functions, the indices i and j vary between 1 and 3, with the exclusion of the diagonal cases for which $i = j$, and in addition the X3X2 case, which is not present in the model, and the X2X3 case, represented by a biphasic function reported below. The parameters $e_{X_i X_j}$ represent the response threshold, i.e., the value at which the response reaches half of its maximum, while $h_{X_i X_j}$ are the Hill coefficients, which determine the steepness of the Hill curve and thus the ultrasensitive nature of the response.

In Equation (3), the biphasic Hill function, indicated as $H_{biphasic_X2X3}$ (Equation (6)), was modeled by the product of an increasing Hill function representing the activation exerted by X2 on X3 (H_{X2_high} ; Equation (7)), and a decreasing Hill function representing the damping effect of X1 on X2 ($1 - H_{X1_low}$), where H_{X1_low} is defined by Equation (8):

$$H_{biphasic_X2X3} = H_{X2_high} \cdot (1 - H_{X1_low}) \quad (6)$$

$$H_{X2_high} = \frac{X2^{h_{X2X3_high}}}{e_{X2X3_high}^{h_{X2X3_high}} + X2^{h_{X2X3_high}}} \quad (7)$$

$$H_{X1_low} = \frac{X1^{h_{X2X3_low}}}{e_{X2X3_low}^{h_{X2X3_low}} + X1^{h_{X2X3_low}}} \quad (8)$$

It should also be noted that our model represents a subset of biological elements tightly interconnected on a common timescale. For this reason, we adopted an arbitrary time scale and set all time constants to the same value ($\tau = 1$), which is not explicitly written in the ODEs because it appears as a multiplicative factor of the dX_i/dt terms.

For computational purposes, numerical values and variable ranges had to be defined. Precise kinetic parameters for the considered biochemical interactions are not available. Therefore, parameters were assigned within biologically plausible ranges commonly used in models of receptor dynamics, signaling pathways, phosphorylation cascades, gene regulation, and inflammatory processes. Hill coefficients were varied within the range $1 \leq h \leq 5$, spanning behaviors from near-linear responses (no cooperativity) to moderately strong ultrasensitivity, as reported in experimental and modeling studies of signaling cascades and multisite phosphorylation systems [41–43].

Threshold levels e (half-maximal response levels) were selected within the dynamic range of the normalized variables. In the absence of quantitative concentration data, state variables were rescaled to the interval $[0, 1]$, and threshold values were chosen around the mid-range of activity in the $0.1 \leq e \leq 0.9$ interval, in order to represent physiologically plausible operating regimes [41,43].

In many ODE models, decay or inactivation terms are explicitly written as first-order loss terms ($-pX$) where the rate constant p is treated as a dimensionless or order-one parameter after non-dimensionalization. This practice is widespread because models are often non-dimensionalized and normalized to focus on system dynamics rather than specific units, thus making typical decay parameters on the order of 1 [44]. We therefore

chose self-limitation values ranging from $p = 1$, for balanced decay in nondimensional form, up to $p = 3$ for faster turnover conditions.

Given the above parameter ranges, the limitations arising from uncertainty in parameter values were overcome by adopting a systematic bifurcation analysis. One- and two-parameter continuations were performed to identify regions of monostability or multistability. This approach allowed us to identify parameters that most strongly influence the system's qualitative behavior, determine the conditions under which transitions between mono- and bistable regimes occur, and evaluate the robustness of the system's dynamics with respect to variations in Hill coefficients, threshold values, and self-limitation parameters. The goal of this analysis was not to fit specific experimental time series, but rather to characterize the repertoire of dynamical regimes compatible with biologically plausible parameter values and transitions associated with multistability.

In preliminary computational analyses of the system's dynamics, conducted in MATLAB, we verified that the system exhibits bistability for specific parameter values. Therefore, as a starting point for the subsequent bifurcation analysis, we manually adjusted all parameter values to obtain a bistable behavior, with the phase space approximately equally divided between the basins of attraction of the two stable equilibrium points (Figure 3, Table 1). One stable equilibrium occurs at mid-to-high X_2 (*TRPV4*), and low X_1 (*Piezo1*) and X_3 (*inflammation*) levels (representing a healthy condition). Another stable equilibrium occurs at low X_2 , and high X_1 and X_3 levels (representing a pathogenic condition). Blue trajectories converge toward the healthy equilibrium, whereas red trajectories converge toward the pathogenic one.

Table 1. Values and ranges of the ODE parameters used in the bifurcation analyses of the dynamic system.

Parameter		Fixed Value	Bifurcation Range
Self-limiting coefficients	p_1	1	1–3
	p_2	2	1–3
	p_3	1	1–3
Threshold levels	$e_{X_1X_3}$	0.4	0.1–0.9
	$e_{X_3X_1}$	0.4	0.1–0.9
	$e_{X_1X_2}$	0.2	0.1–0.9
	$e_{X_2X_1}$	0.2	0.1–0.9
	$e_{X_2X_3_low}$	0.2	0.1–0.9
	$e_{X_2X_3_high}$	0.8	0.1–0.9
Hill coefficients	$h_{X_1X_3}$	3	1–5
	$h_{X_3X_1}$	3	1–5
	$h_{X_1X_2}$	3	1–5
	$h_{X_2X_1}$	3	1–5
	$h_{X_2X_3_low}$	3	1–5
	$h_{X_2X_3_high}$	3	1–5

The phase portrait in Figure 3 illustrates that when the system is located at the equilibrium point representing a pathogenic condition (high *Piezo1* and *inflammation* levels), it can be driven away from this state by forcing it to cross the boundary of its basin of attraction. Acting directly on the ODE variables, the most direct route to reach and cross this boundary is a simultaneous reduction in *Piezo1* and *inflammation*, and an increase in *TRPV4*. Once the boundary is crossed, the system will spontaneously evolve toward and settle at the equilibrium point characterized by low *Piezo1* and *inflammation* levels (blue trajectories). However, this type of intervention does not alter the intrinsic system behavior, as the geometry of the basins of attraction remains unchanged. Consequently, the system can be forced back to the pathogenic region of the phase space by stimuli that increase *Piezo1* and *inflammation*. Conversely, nonlinear dynamics theory and its application to biological systems show that acting on ODE terms that serve as bifurcation parameters can profoundly remodel the shape and extent of the basins of attraction, enabling transitions from mono- to multistability and vice versa [45–47]. In our system, this allows the pathogenic region to

be reduced or even eliminated, by converting the system from a bistable to a monostable condition characterized by low *Piezo1* and *inflammation*.

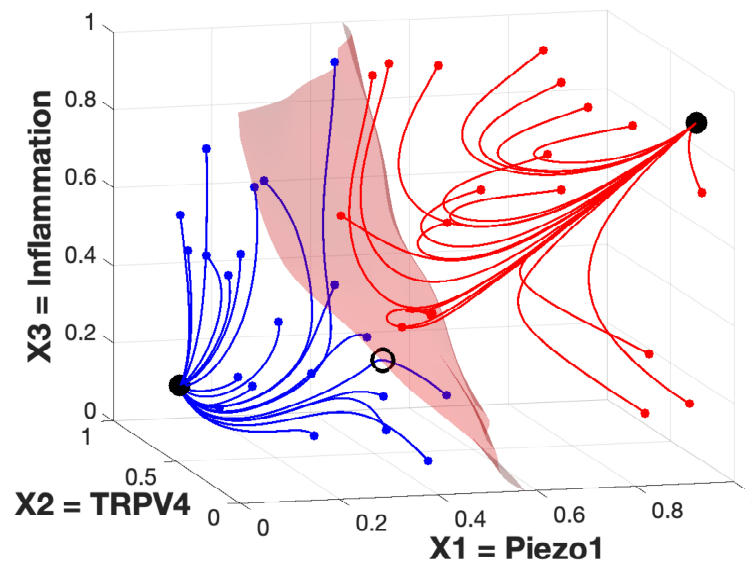


Figure 3. Phase portrait of the OA pathogenesis model showing the system's evolution over time through trajectories originating from different initial conditions. The system exhibits bistability for the ODE parameters set to the fixed values reported in Table 1. The colors of the trajectories indicate their corresponding equilibrium points. The small dots mark the initial conditions, the solid black circles represent stable equilibria, the open circle denotes the unstable equilibrium, and the pink surface marks the boundary between the basins of attraction of the two stable equilibria. The axis labels indicate the correspondence between the ODE variables and the putative biological factors involved in OA pathogenesis.

Therefore, we explored the possibility of abolishing the pathogenic behavior by converting the system from a bistable to a monostable regime, or by considerably reducing the basin of attraction of the pathogenic equilibrium point. To this end, we started from the ODE system described above (Figure 3) and performed a bifurcation analysis by varying each parameter individually. We varied each parameter within the biologically reasonable ranges reported above, while keeping the others at their fixed values (Table 1).

The bifurcation analysis aimed to identify the parameters capable of altering the system's behavior relative to the initial condition, driving it across bifurcation points as their values change. This approach reduces uncertainty due to the unknown actual values of parameters in the organism, as the parameter sweeping encompasses all biologically reasonable ranges. The analysis showed the occurrence of bifurcation points for the variation of two p parameters, namely p_1 and p_3 , and three e parameters, namely e_{X1X2} , e_{X1X3} , and e_{X3X1} (Figure 4). At bifurcation points, saddle-node transitions from bistable to monostable conditions occur. The bistable condition includes both the pathogenic and the healthy basins of attraction and their corresponding equilibrium points, whereas monostability admits only the healthy equilibrium. The p and e parameters that induce bifurcations always depend on either $X1$, representing the Piezo1 mechanoreceptor, or $X3$, representing inflammation. None of the e parameters associated with functions where $X2$ acts as the input variable, nor any h parameters, serve as bifurcation parameters in the system. In all cases, conversion from bistability to monostability depends on an increase in p_1 and p_3 , indicating that stronger self-limiting effects on the activation of Piezo1 and inflammation might hinder the insurgence of pathogenesis. The same transition is induced by increases of e_{X1X2} , e_{X1X3} , and e_{X3X1} , indicating that higher threshold values for the effects of Piezo1 on TRPV4 and inflammation, or of inflammation on Piezo1, also make pathogenesis more unlikely.

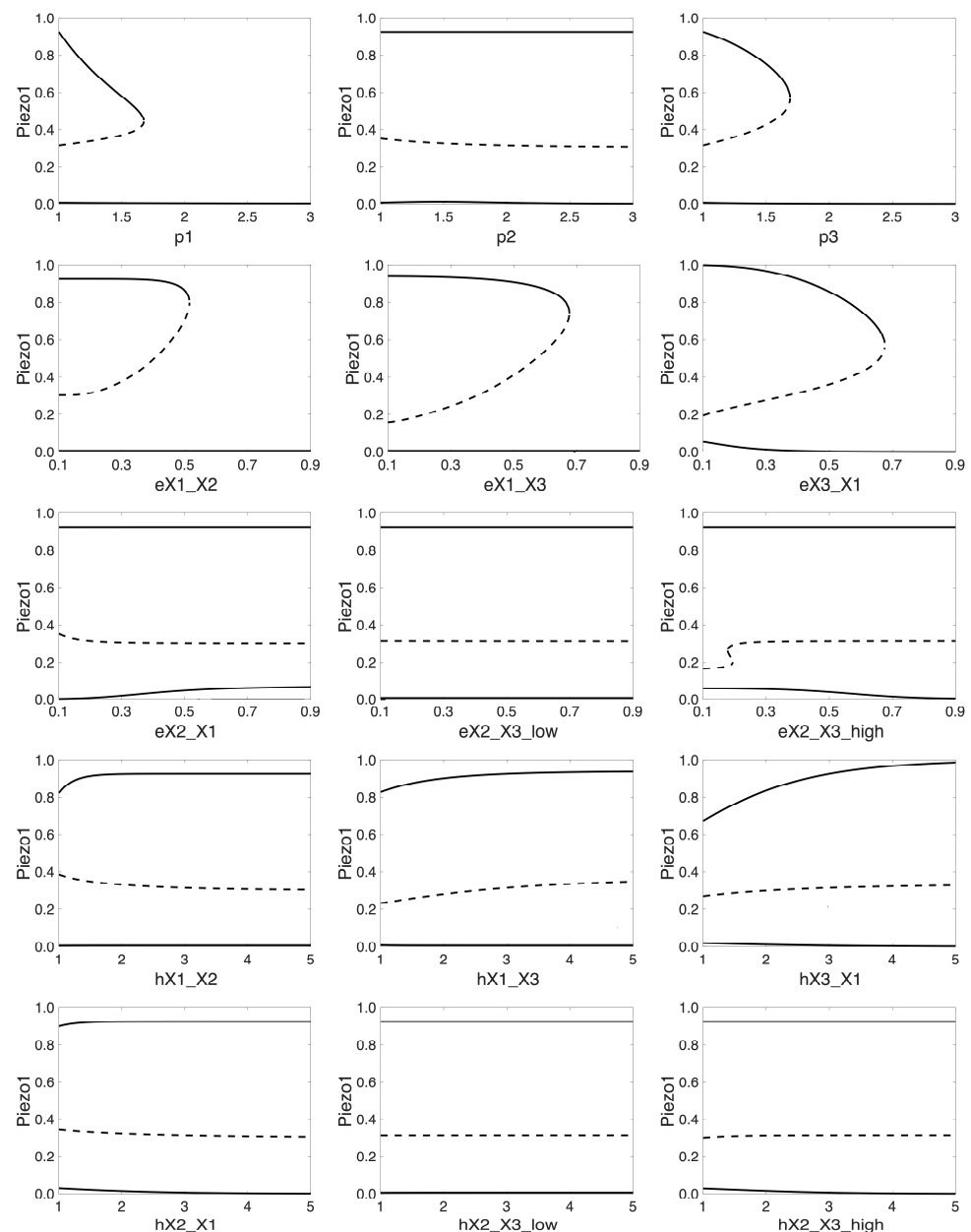


Figure 4. Bifurcation diagrams obtained by varying each parameter individually, starting from the bistable ODE system with the settings reported in Table 1. The plots illustrate how the equilibrium value of the X1 variable (*Piezo1*) changes as each parameter is varied. In some cases, transitions from bistability to monostability occur at saddle-node bifurcation points. Only plots for X1 are shown, as the plots of the other variables display the same bifurcation points. Solid lines = stable equilibria; dashed lines = unstable equilibria.

Thereafter, we conducted a two-parameter bifurcation analysis using the five parameters that exhibited bifurcation points in the previous one-parameter analysis, namely p_1 , p_3 , e_{X1X2} , e_{X1X3} , and e_{X3X1} . The initial parameter set corresponded to the bistable regime shown above (Table 1, Figure 3). Each parameter pair generated regions of monostability and bistability. In each plot, a single monostable region and a single bistable region are present, separated by a bifurcation line (Figure 5).

The overall dataset demonstrates that the patterns identified in the two-parameter bifurcation analyses are consistent with those obtained in the corresponding one-parameter analyses. The bifurcation topology elicited by each sweeping parameter can be modulated, though not fundamentally altered, by its interaction with other sweeping parameters.

Moreover, the parameter domain associated with bistability is broader for the threshold parameters e_i and their combinations than for the self-limiting terms p_i . Likewise, bistability extends over a wider parameter range for interactions involving *Piezo1* and *inflammation*, or their combinations, than for interactions involving *TRPV4* (Figure 5). However, the most relevant finding from these analyses was that the two-parameter bifurcation diagrams involving e_{X1X2} , except for the $e_{X1X2}/p1$ diagram, showed approximately rectangular bistable regions. This suggests that e_{X1X2} acts, to some extent, independently of the other parameters in determining the bifurcation thresholds (Figure 5).

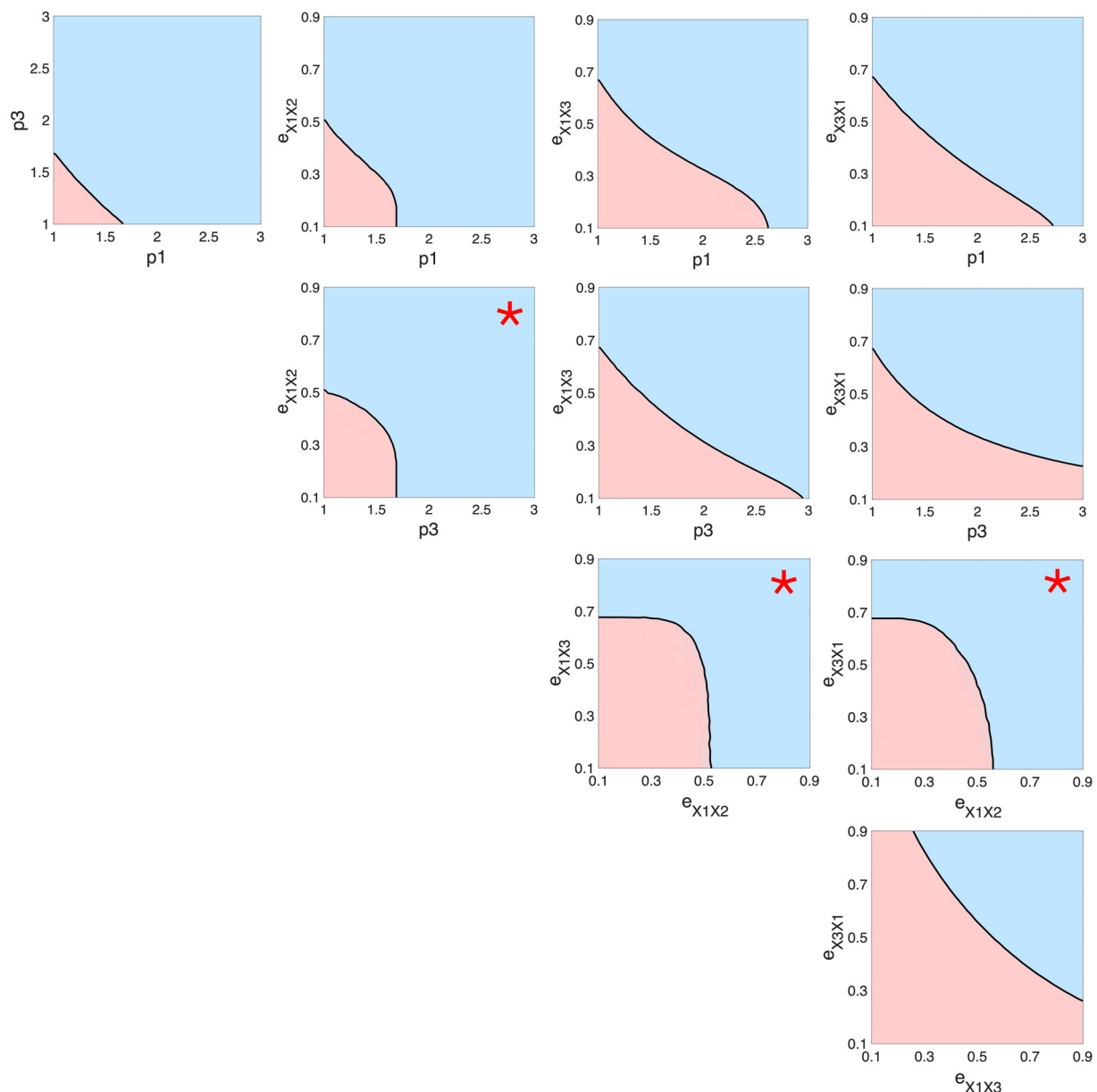


Figure 5. Two-parameter bifurcation diagrams of the bistable ODE system with the settings reported in Table 1. The bifurcation analysis was conducted on the parameters that were found to induce transition from bistability to monostability in the single-parameter bifurcation analysis (Figure 4). All remaining parameters were kept at their fixed (baseline) values. Each panel shows the regions of monostability (light blue) and bistability (pink) in the plane defined by the two varying parameters. The boundary line indicates the transition between the two dynamical regimes. The red stars indicate a subset of two-parameter diagrams showing bistable regions with a tendency toward rectangular shapes, indicating a certain degree of independence between the two parameters.

The importance of bifurcation parameters in controlling over the system's dynamics is illustrated in Figure 6. Starting from the settings shown in Figure 3 and listed in Table 1, two strategies can be pursued to shift the system away from the pathogenic state corresponding to the high- $X1/X3$, low- $X2$ equilibrium point.

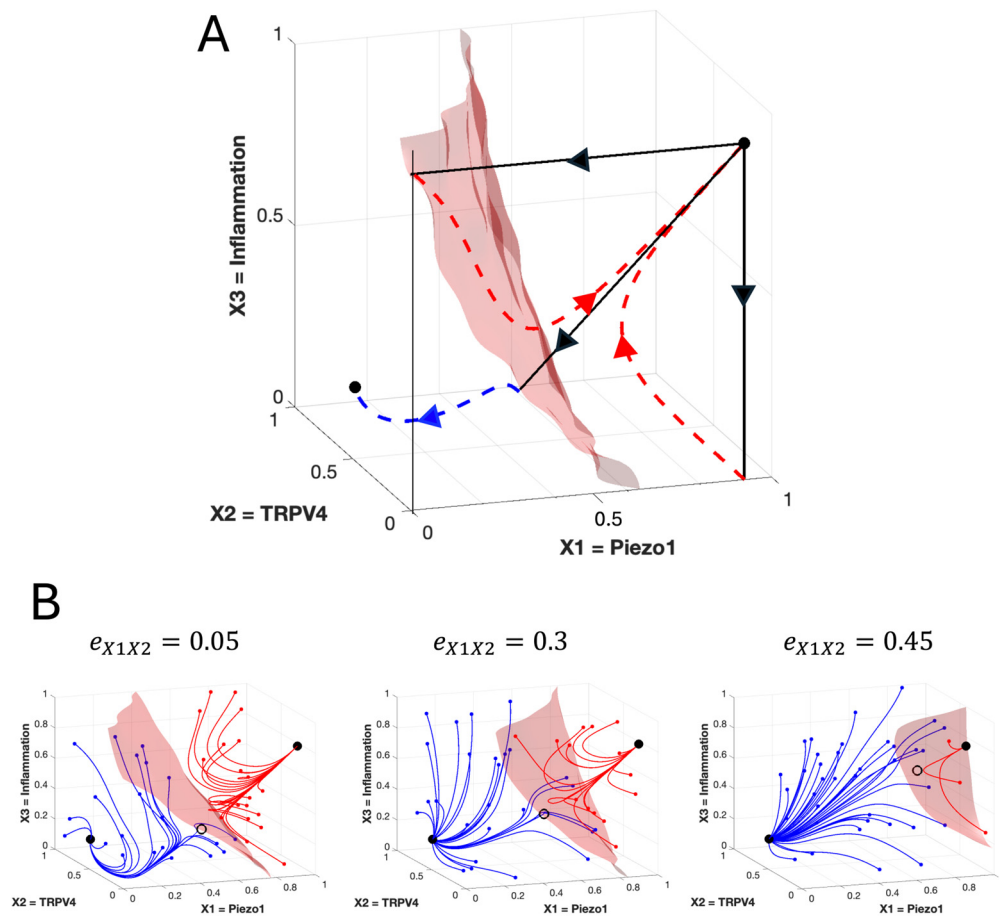


Figure 6. (A). Phase portrait of the system under the same settings as in Figure 3, illustrating three actions consisting of imposed stimuli and the consequent spontaneous trajectories starting from the high- $X1/X3$, low- $X2$ equilibrium point (upper right, black filled circle). The horizontal black line represents inhibition of $X1$ (*Piezo1*), reducing it to $X1 = 0$, and the vertical black line represents inhibition of $X3$ (*inflammation*), reducing it to $X3 = 0$, while the red trajectories return to the starting point. The diagonal black line represents combined inhibition of $X1$ and $X3$, crossing the decision boundary, while the blue trajectory flows toward the low- $X1/X3$, high- $X2$ (*TRPV4*) equilibrium point (lower left, black filled circle). (B). Phase portraits showing the rightward shift of the decision boundary for increasing values of the bifurcation parameter e_{X1X2} , which progressively enlarges the basin of attraction of the low- $X1/X3$, high- $X2$ equilibrium point while shrinking that of the other (symbols and lines as in Figure 3).

The first strategy involves acting directly on the system's variables. Inhibiting either *Piezo1* ($X1$) or *inflammation* ($X3$) alone is insufficient to cross the decision boundary. As a result, once the intervention ceases, the system spontaneously returns to the initial pathogenic equilibrium, since it remains within the same basin of attraction. In contrast, simultaneous reduction in both *inflammation* and *Piezo1* can push the system beyond the decision boundary, allowing it to evolve spontaneously toward the low- $X1/X3$, high- $X2$, non-pathogenic equilibrium point (Figure 6A). However, this type of intervention does not modify the intrinsic dynamical structure of the system, as indicated by the unchanged decision boundary. Consequently, the system remains susceptible to falling back into the pathogenic basin of attraction when exposed to specific stimuli.

The second strategy involves acting on the bifurcation parameters. For example, increasing the parameter e_{X1X2} , which represents the threshold of the Hill-type effect of $X1$ (*Piezo1*) on $X2$ (*TRPV4*), reduces the size of the pathogenic basin of attraction. This makes it much easier to drive the system out of the high- $X1/X3$, low- $X2$ equilibrium state, and correspondingly harder for it to fall into the pathogenic basin when residing in the low- $X1/X3$, high- $X2$, non-pathogenic equilibrium state (Figure 6B).

4. Discussion

4.1. Mechanistic and Translational Control of OA Pathogenesis

Several studies in Systems Biology have focused on analyzing biological processes as nonlinear dynamical systems. In this context, biological changes have been interpreted as a system's ability to "decide" between different outcomes when its nonlinear dynamics allow for multistability. Therefore, if biological changes correspond to transitions from one equilibrium point to another, then multistability is a necessary condition for their occurrence. The acquisition of multistable behavior is thus a prerequisite for such transitions [48].

Bifurcation parameters act as the driving forces behind transitions from monostability to multistability at specific bifurcation points. They are therefore critical factors that enable biological changes in response to appropriate stimuli. This concept has also been extended to pathogenesis, where transitions from physiological to pathological conditions are interpreted as shifts between different equilibrium points [13]. Within this framework, modeling a pathogenic process using a nonlinear dynamic system and identifying the critical bifurcation factors represents the most effective approach to planning optimal interventions. Such analysis is supposed to reveal the most promising therapeutic targets, thereby guiding more precise and effective drug design and treatments.

To develop a hypothetical OA pathogenic model, we focused on Piezo1-TRPV4-inflammation interactions, assumed as a minimal mechanotransduction-inflammatory subsystem capable of generating closed-loop nonlinear dynamics in OA cartilage. From a modeling perspective, this closed-loop architecture is sufficient to generate multistability and regime shifts. The first outcome of our mathematical analysis was that the loop model can exhibit either monostable or bistable behavior. In the bistable regime, one of the equilibrium points can be interpreted as the pathogenic state, as it corresponds to high Piezo1 activity and elevated inflammation. Accordingly, we explored modulatory interventions capable of driving the system away from the basin of attraction of the pathogenic equilibrium, thereby shifting it toward the low Piezo1 and low inflammation equilibrium. The phase portrait of the bistable condition clearly shows that, starting from the pathogenic equilibrium, reducing the variable $X3$ alone (*inflammation*) is insufficient to move the system out of its basin of attraction. Thus, our model provides a mechanistic explanation for the limited clinical efficacy of anti-inflammatory treatments and viscosupplementation [49,50]. In contrast, combining reduction of variable $X1$ (Piezo1 inhibitors) with reduction of variable $X3$ (anti-inflammatory interventions), appears to be a substantially more effective strategy.

No clinically available inhibitors of Piezo1 have been developed to date but some inhibitors have been identified and investigated in preclinical OA models. Among them, the peptide GsMTx4, derived from tarantula spider venom, has been shown to attenuate OA progression in animal models by blocking Piezo1-mediated Ca^{2+} influx, thereby reducing chondrocyte apoptosis and preserving cartilage matrix integrity [30]. In addition, the antimalarial sesquiterpene lactone artemisinin [51], extracted from *Artemisia annua* (sweet wormwood), has emerged as a promising inhibitor that suppresses Piezo1 activation, downregulates the expression of Piezo1-induced matrix-degrading enzymes, and mitigates OA-like pathology in preclinical studies [52].

However, our analysis suggests that the focus of preclinical and clinical research should be redirected toward alternative strategies. In our mathematical model, Piezo1 is represented as an ODE variable. Hence, as discussed above, its modulation can effectively displace the system from a noxious regime but does not alter the system's intrinsic dynamics. In contrast, bifurcation parameters that control the transition to bistability constitute particularly attractive therapeutic leverage points, since their modulation could hinder the onset of the pathogenic regime. Such an effect is represented in the dynamical system by the compression or elimination of the pathogenic basin of attraction, thereby transforming the system from bistable to monostable. Specifically, the parameter e_{X1X2} , which controls the bifurcation points largely independently of the other parameters, could represent the most promising therapeutic target. Pharmacological modulation of this parameter could prevent the transition to the bistable regime while minimizing unintended interference with other regulatory mechanisms.

While our model indicates precise directions of interventions, the problem remains as how to identify the biological counterparts of the detected targets. The e_{X1X2} parameter represents the threshold of the inhibitory effect of the variable $X1$ (*Piezo1*) on $X2$ (*TRPV4*). However, the mechanism of interplay between the biological agents represented in our model has not been sufficiently disclosed. Reported signal transduction pathways involved in the interplay between Piezo1 and inflammatory cytokines (mainly IL-1 β , IL-6, and TNF- α) are Piezo1 transcriptional activation and the enhancement of mechanosensitivity by p38 MAPK/NF- κ B [27], as well as the upregulation of cytokines by Piezo1 through P38 MAPK/CREB [53], NLRP3 inflammasome/caspase-1 [54], and cGAS-STING pathways [55]. In addition, various other mechanisms are involved in mechanotransduction and the consequent interplay among Piezo1, inflammatory cytokines, and TRPV4 [56]. In summary, deeper investigation of these mechanisms is needed to enable targeted interventions aimed at manipulating the activation thresholds and self-limiting properties of the aforementioned agents.

4.2. Model Limitations and Strengths

The present model does not seek to capture the full complexity of the molecular pathways involved in OA. Rather, it identifies a minimal mechanistic core that is sufficient to reproduce the key dynamical features of the disease onset, thus pointing to possible critical targets for therapeutic intervention. As stated above, we developed a theoretical loop model of OA pathogenesis based on literature data from preclinical studies conducted in *in vitro* and *in vivo* models. By contrast, no clinical studies or clinical practice data are currently available to support the model. Hence, all deductions derived from the model depend on the assumed network topology and on the choice of functional forms. Specifically, the role of bifurcation parameters in shaping the pathogenesis process, as well as the possibility of exploiting them for disease management, await experimental verification. However, some drugs could be considered for testing the OA model in a clinical setting, at least on a provisional basis. Considering Piezo1 as a potential target, compounds such as GsMTx4 or Dooku1 are preferential candidates, but they have not yet been developed into clinically viable drugs [57]. Artemisinin is a well-known antimalarial drug already approved for human use, but no regulatory agency has approved it for use in OA.

Even more critically, if the interaction mechanisms between Piezo1 and TRPV4 are to be targeted, as suggested by our analysis, further preclinical studies would be required to quantitatively explore these mechanisms and their nonlinear dynamics. Subsequent research should aim to identify suitable pharmacological targets within these interactions while minimizing side effects. Consequently, appropriate compounds should be selected as potential candidates for the development of anti-OA drugs.

Despite its limitations, our model demonstrates strengths in predicting and confirming various clinical aspects of OA. First, as stated above, the system dynamics in phase space explain why, despite the involvement of inflammatory agents in the pathogenic mechanism, targeting these agents alone yields very limited therapeutic efficacy.

Second, the model aligns with the established role of aging in promoting OA onset. In fact, inflammaging (a chronic low-grade inflammation state) has been included within aging hallmarks and contributes to the pathogenesis of age-related diseases, including OA [58]. Moreover, aging is associated with disrupted diurnal glucocorticoid (GC) rhythms and chronically elevated GC activity, particularly in the joints [59]. This imbalance results in detrimental actions of endogenous GCs on both osteoblast and chondrocytes, leading to OA progression [60]. In addition, a direct role of endogenous GCs on articular Piezo1 cannot be excluded, since studies have demonstrated that dexamethasone upregulates Piezo1 expression in macrophages via activation of serum/GC-regulated kinase 1 (SGK1) [61].

Third, the model is consistent with the combined effects of aging and menopause in determining the female prevalence of OA among older people. This epidemiological feature has been attributed to the intersection of aging and estrogen deficiency [62]. Estrogens have been shown to exert protective effects on cartilage. Consistently, postmenopausal women with OA undergoing hormone replacement therapy experience reduced joint pain and inflammation. Estrogen receptor alpha (ER α) appears to play a role in modulating chondrocyte aging, as its expression in chondrocytes derived from OA patients becomes dysregulated with advancing age [63]. Estrogen-related receptors (ERRs) are also implicated in OA pathogenesis: although they do not directly bind estrogens, ERRs can modulate estrogen signaling and contribute to cartilage degradation [64,65]. Finally, and more directly relevant to our model, activation of the G protein-coupled estrogen receptor (GPER) suppresses Piezo1 and reduces mechanical stress-induced apoptosis of OA chondrocytes [66]. In summary, the combined effect of aging and estrogen decline accelerates both inflammation and Piezo1 activation, which, in our model, corresponds to a transition toward the pathogenic equilibrium.

5. Conclusions

We developed a mathematical model of OA pathogenesis inspired by the concept that all biological processes, including diseases, can be represented as nonlinear dynamical systems composed of closed-loop interactions among functional agents. This framework aligns well with the emerging view that OA results from impaired mechanotransduction in articular chondrocytes [67]. Accordingly, the model was constructed around the interactions among the mechanoreceptors TRPV4 and Piezo1 and key inflammatory mediators.

While the model reflects the current understanding of OA, it is inevitably limited by the absence of direct clinical validation. Nevertheless, the model remains consistent with epidemiological and clinical features of the disease. The mathematical analysis precisely identifies the parameters governing the system's dynamics, suggesting that, if the model is valid, their biological counterparts represent potential therapeutic targets.

In conclusion, despite its limitations, the overall balance of strengths and weaknesses supports the value of this model as a framework worthy of further investigation in preclinical and clinical contexts, with the potential to guide the development of effective treatments for a currently unmet medical need.

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