A review of mathematical modeling of bone remodeling from a systems biology perspective

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SUPPLEMENTARY MATERIAL

1 Supplementary tables

Tables S1–S3 provide summary descriptions of the mathematical models of bone remodeling reviewed in the manuscript. Table S1 considers those that follow the power law approach. Table S2 considers those that follow the mass action kinetics approach. Table S3 considers those that do not follow the power law or mass action kinetics approaches used in the models in Tables S1 and S2.

Table S1: Mathematical models of bone remodeling that follow the power law approach. All models in the table include osteoblasts (OBL) and osteoclasts (OCL), except for Ryser et al. (2012) which only includes OCL, so these are not explicitly listed in the table. All the models also include the general autocrine and paracrine signals. † denotes that a model has a stochastic aspect. ^{d} denotes that a model is a system of delay differential equations (DDEs). Abbreviations: basic/bone multicellular unit (BMU), calcitonin (CT), insulin-like growth factor (IGF), interleukin-6 (IL-6), metastatic tumor (MT), multiple myeloma (MM), ordinary differential equations (ODEs), osteocytes (OCY), osteoprotegerin (OPG), parathyroid hormone-related protein (PTHrP), partial differential equations (PDEs), preosteoblasts (pOBL), preosteoclasts (pOCL), prostate cancer (PC), receptor activator of nuclear factor kappa-B (RANK), receptor activator of nuclear factor kappa-B ligand (RANKL), sclerostin (SCL), transforming growth factor beta (TGF-β), wingless-related integration site (Wnt).

Model	Cells	Signaling Mechanisms	Treatments	Motivation/Insights
ODEs				
Komarova et al. (2003)	-	-	-	1. Models the different dynamics of remodeling 2. Power law application to autocrine/paracrine signals 3. Simplified model shows complex dynamics
Komarova (2005)	-	-	PTH	1. Models the effect of PTH administration on bone cells 2. Points to the importance of correct dosing with PTH
Garzón-Alvarado (2012)	MT	IGF, PTHrP, TGF-β	-	1. Models two different MT types 2. Qualitative view of MT dynamics in bone
Liò et al. (2012)	Bacteria	RANKL	-	1. Develops a model for osteomyelitis 2. Model shows how bacteria population in osteomyelitis affects bone
Graham et al. (2013)	pOBL, OCY	Implied SCL	-	1. Focuses on the role of OCY in remodeling 2. Qualitative exploration of OCY and SCL as therapeutic targets
Jerez and Chen (2015)	-	Generalized external influence	-	1. Identifies areas of stability for Komarova et al. (2003) 2. Adds new OCL influencer to account for external inputs
Chen-Charpentier and Diakite (2016)	-	-	-	1. Adds a delay aspect to Komarova et al. (2003) to capture the signaling time 2. Explores the differences in dynamics of Komarova et al. (2003) and the delay model
Coelho et al. (2016)	pOBL, pOCL, MT	PTH	Anti-cancer, bisphosphonates, denosumab	1. Focuses on how PTH and other therapies interact with a bone metastatic environment 2. Provides insight on the possibility of anti-resorptive treatments to prevent tumor growth

Table S1 continued from previous page

Model	Cells	Signaling Mechanisms	Treatments	Motivation/Insights
Jerez et al. (2018)†	-	Environmental randomness	-	1. Focuses on realistic variations in bone remodeling 2. Stochastic model shows a fluctuating periodic solution
Camacho and Jerez (2019)	MT	-	Denosumab, radiotherapy	1. Develops an optimal control model of MT in bone 2. Explores different treatment effectiveness for MT
Idrees et al. (2019)[d]	pOBL	IL-6, PTH	PTH	1. Combines Komarova et al. (2003) and Kroll (2000) into a DDEs model of PTH 2. Indicates that a larger dose of PTH is more effective
Javed et al. (2019)	-	Aging factor, RANKL	-	1. Focuses on the dynamics of bone remodeling through analysis of a bone remodeling model 2. Produces a stability analysis of bone remodeling
Idrees and Sohail (2020)	-	CT	CT	1. Explores the effects of dosed CT on bone remodeling 2. Points to the need to have intermittent dosing of CT
Miranda et al. (2020)	MT	-	Bisphosphonates, denosumab, paclitaxel, proteasome inhibitors	1. Explores the effects of several drugs on bone remodeling in the presence of an MT 2. Model considers drug resistance after prolonged treatment
Camacho and Jerez (2021)	MT	TGF-β, Wnt	Biphosphonates, chemotherapy	1. Directly models TGF-β and Wnt by removing OBL paracrine exponent 2. Explores treatment of MT with varying levels of TGF-β and Wnt
Islam et al. (2021)	pOBL, OCY	Wnt-10b, implied SCL	Butyrate, Wnt-10b	1. Determines if butyrate activation of Tregs accounts for bone volume increase seen from butyrate studies 2. Points to other influences of butyrate on bone remodeling
Cook et al. (2022)	pOBL, OCY	Wnt-10b, implied SCL	-	1. Explores the effect of Wnt-10b alterations on bone remodeling 2. Points to a previously unidentified indirect relation of Wnt-10b to OCL
PDEs				
Ryser et al. (2009)	-	OPG, RANKL	-	1. Focuses on the spatiotemporal dynamics of a BMU 2. Model predicts the movement of a BMU through bone

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Model	Cells	Signaling Mechanisms	Treatments	Motivation/Insights
Ayati et al. (2010)	MM	-	Parameters related to proteasome inhibitors	1. Focuses on the movement of cells and MM interactions 2. Spatial model of MM and bone allows for the exploration of treatment targets
Ryser et al. (2010)	-	OPG, RANKL	-	1. Captures the effects of RANKL and OPG fields on bone remodeling 2. Model explains how OBL and OCL communicate without direct contact
Graham and Ayati (2012)	-	-	-	1. Considers the geometrical aspects of bone remodeling 2. Produces a PDE version of Komarova et al. (2003) using a level set approach
Ryser et al. (2012)	pOCL, MT	Only autocrine, OPG, PTHrP, RANKL	-	1. Captures the effects of MT with fields of RANKL, OPG, and PTHrP 2. Points to different responses to varying levels of OPG
Ryser and Murgas (2017)	OCY	-	-	1. Applies evolutionary game theory to a spatial model that includes OCY 2. Highlights the impact of geometry on bone remodeling
Peyroteo et al. (2019)	-	-	-	1. Converts Komarova et al. (2003) into a spatiotemporal model 2. Compares the results of three different numerical techniques used to solve the same equation set
Baldonedo et al. (2021)	pOBL, OCY	Implied SCL	-	1. Extends into a spatiotemporal model 2. Compares two-dimensional model to original results of Graham et al. (2013)
Idrees and Sohail (2023)	MM	CT, PTH	Bisphosphonates, PTH, anti-cancer	1. Extends Ayati et al. (2010) to include PTH and CT 2. Shows the effects of select hormones and treatments in a cancer environment

Table S2: Mathematical models of bone remodeling that follow the mass action kinetics approach. All models in the table include osteoblasts (OBL), osteoclasts (OCL), osteoprotegerin (OPG), parathyroid hormone (PTH), receptor activator of nuclear factor kappa-B ligand (RANKL), and transforming growth factor beta (TGF-β) so these are not explicitly listed in the table. * denotes that a model has a biomechanical aspect. Abbreviations: basic/bone multicellular unit (BMU), calcium (Ca), dickkopf-related protein 1 (DKK1), insulin-like growth factor 1 (IGF-1), interleukin-6 (IL-6), macrophage colony-stimulating factor (MCSF), multiple myeloma (MM), nitric oxide (NO), N-telopeptide (NTX), ordinary differential equations (ODEs), osteocytes (OCY), parathyroid hormone-related protein (PTHrP), partial differential equations (PDEs), phosphate (PO_4), preosteoblasts (pOBL), preosteoclasts (pOCL), prostate cancer (PC), pharmacokinetic (PK), pharmacodynamic (PD), prostate-specific antigen (PSA), pulsed electromagnetic field (PEMF), small leucine-rich proteoglycans (SLRPs), sclerostin (SCL), semaphorin-3A (Sema3A), urokinase plasminogen activator receptor-associated protein (Endo180), vascular cell adhesion molecule 1 (VCAM1), very late antigen-4 (VLA4), wingless-related integration site (Wnt).

Model	Cells	Signaling Mechanisms	Treatments	Motivation/Insights
ODEs				
Lemaire et al. (2004)	pOBL	-	Generic anti-resorptive, generic bone formation	1. Mechanistic model of bone remodeling explores diseased states 2. Points to formation therapies that increase the amount of pOBL
Pivonka et al. (2008)	pOBL	-	-	1. Focuses on the implications of the RANKL/OPG relationship 2. Updates the receptor-ligand relationship presented by Lemaire et al. (2004) 3. Model is most responsive when pOBLs express RANKL and OPG is expressed by OBLs
Marathe et al. (2008)	pOBL	-	Denosumab	1. Develops a model that shows bone remodeling response to denosumab in MM patients 2. Model connects denosumab response through experimentally measurable NTX
Peterson and Riggs (2010)	pOBL	Ca, PO_4	PTH	1. Focuses on the systemic factors in bone remodeling and Ca homeostasis 2. Multicompartment model connects to bone, gut, kidneys, and parathyroid
Pivonka et al. (2010)	pOBL	-	-	1. Determines if Pivonka et al. (2008) can represent diseases related to RANKL/OPG 2. Points to dual therapies being best at treating the represented bone diseases

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Model	Cells	Signaling Mechanisms	Treatments	Motivation/Insights
Marathe et al. (2011)	pOBL	-	Denosumab, ibandronate	1. Characterizes the action of denosumab and ibandronate 2. Explores the action of these drugs on osteoporotic bone remodeling
Schmidt et al. (2011)	-	-	Estrogen, glucocorticoids, vitamin D	1. Reduces Lemaire et al. (2004) to a smaller but dynamically similar system 2. Shows that, on the timescale of disease progression modeling, OBL and OCL are sufficient for bone remodeling dynamics
Wang et al. (2011)	pOBL, MM	IL-6, VCAM1, VLA4	-	1. Focuses on the MM feedback mechanisms resulting in bone lesions 2. Points to only needing two feedback mechanisms for MM to progress
Buenzli et al. (2012b)	pOBL, PC	PSA, PTHrP, Wnt	-	1. Captures OBL production through pOBL proliferation 2. Model shows how pOBL proliferation could be affected by signals such as Wnt and PTH
Peterson and Riggs (2012)	pOBL	Ca, PO_4	Denosumab	1. Extends Peterson and Riggs (2010) to include denosumab treatment 2. Explores the effect of start-stop-restart treatment regimens
Ross et al. (2012)	pOBL	-	PTH	1. Adds PTH action on osteoblasts to Lemaire et al. (2004) 2. Model exhibits the catabolic and anabolic behavior of PTH
Wang and Qin (2012)	pOBL	-	PEMF	1. Extends Pivonka et al. (2008) to respond to PEMFs 2. Identifies parameter sets that represent the physiological response to PEMF
Scheiner et al. (2013)*	pOBL	-	-	1. Combines bone cell populations and mechanical strains into one model 2. Model depicts bone loss over time
Pivonka et al. (2013)*	pOBL, pOCL	MCSF (assumed constant)	-	1. Focuses on the impact of bone microstructure density 2. A mechano-chemo-biological model links to the geometrical structure of bone
Post et al. (2013)	-	Estrogen	Ca placebo, tibolone	1. Compares clinical data of osteoporosis to model (Schmidt et al., 2011) 2. Identifies two types of responders to Tibolone

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Model	Cells	Signaling Mechanisms	Treatments	Motivation/Insights
Ji et al. (2014)	pOBL, MM	IL-6, SLRPs, VCAM1, VLA4	-	1. Focuses on MM dynamics with bone remodeling 2. Simulations of tumor removal show why bone rarely heals
Scheiner et al. (2014)*	pOBL	-	Denosumab	1. Alters Scheiner et al. (2013) to a postmenopausal state 2. Explores the effect of denosumab on diseased state
Berkhout et al. (2015)	-	Estrogen	Ca placebo	1. Applies a reduced model (Schmidt et al., 2011) to postmenopausal populations 2. Demonstrates that the model is relevant for multiple placebo populations
Lee and Okos (2016)	pOBL	Ca, IGF-1	-	1. Adds IGF-1 to Pivonka et al. (2010) 2. Explores how different perturbations to the parameters affect bone remodeling
Eudy et al. (2015)	pOBL, OCY	Ca, PO_4, SCL, Wnt (assumed constant)	Romosozumab	1. Explores the effects of OCY-produced SCL on the remodeling cycle 2. Alteres Peterson and Riggs (2010) to show how SCL and SCL-blockers interact with bone remodeling
Berkhout et al. (2016)	-	Estrogen	Alendronate (bisphosphonate)	1. Focuses on the long-term use of alendronate 2. Utilizes Schmidt et al. (2011) and adds PK/PD information for alendronate
Farhat et al. (2017)	pOBL, PC	Ca, DKK1, PSA, PTHrP, Wnt	-	1. Focuses on how PC interrupts the bone remodeling balance 2. Blocking Wnt with DKK1 might prevent tumor growth
Ross et al. (2017)	pOBL	Ca, PO_4	Bisphosphonate, generic RANKL inhibitor	1. Combines several models of bone remodeling to get a multicompartment model 2. Explores the action of anabolic and antiresorptive compounds on bone
Hasegawa and Duffull (2018)	pOBL	Ca, PO_4	Denosumab	1. Reduces Peterson and Riggs (2010) to a simple model 2. Reduced model captures long-term results
Pastrama et al. (2018)*	pOBL	-	-	1. Creates a model that considers the size and shape of BMU channel 2. Model has different concentration equations than Lemaire et al. (2004) 3. Explores different mechanical factors

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Model	Cells	Signaling Mechanisms	Treatments	Motivation/Insights
Ji et al. (2019)	pOBL	-	Intracrine signaling	1. Develops a model that includes RANK 2. Investigates how OCLs respond to RANK activation
Lemaire and Cox (2019)	pOBL	SCL, Wnt (assumed constant)	Denosumab, PTH, romosozumab	1. Focuses on the dynamics of cells with PTH and antibody treatments 2. Shows two coexisting pathways for PTH regulation
Martin et al. (2019)*	pOBL, OCY	NO, SCL, Wnt (assumed constant)	-	1. Focuses on the biochemical response of a biomechanical stimulus 2. Model includes many commonly overlooked aspects
Martínez-Reina and Pivonka (2019)*	pOBL	-	Denosumab	1. Focuses on the long-term effects of denosumab 2. Model depicts the mineralization process 3. Suggests that the response to denosumab cannot be captured without alterations to the mineralization process
Trichilo et al. (2019)	pOBL	Intracrine signaling	PTH	1. Shows the dual action of administered PTH 2. Considers separate populations of existing OBLs and derived OBLs 3. Suggests that bone modeling might also be affected by administered PTH
Zhang and Mager (2019)	pOBL, MM	DKK1	Bortezomib, dexamethasone	1. Explores the optimal relationship between bortezomib and dexamethasone treatment 2. Identifies a potential regimen of drugs that is effective for treating MM while also preventing skeletal side effects
Ashrafi et al. (2020)*	pOBL	-	-	1. Derives a mechano-chemo-biological model using Lemaire et al. (2004) and various biomechanical models 2. Presents a new mechanotransduction approach that connects mechanical stimulus to a BMU
Bahia et al. (2020)*	pOBL	-	Bisphosphonate	1. Creates a mechano-chemo-biological model that includes PKPD and mechanical strain information information 2. Model shows bone response to pharmacological and mechanical influences

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Model	Cells	Signaling Mechanisms	Treatments	Motivation/Insights
Ji et al. (2020)	pOBL, PC	Endo180, IL-6, SLRPs, VCAM1	-	1. Couples bone cells with tumor cells to explore disease development feedback 2. Explores the effects of various levels of TGF-β on Endo180 expression
Lavaill et al. (2020)*	pOBL	Intracrine signaling	PTH	1. Develops a mechanistic model of PTH treatment that includes mechanical feedback 2. Simulations suggest that a combination of PTH and mechanical loading is most effective
Martin et al. (2020)*	pOBL, OCY	NO, SCL, Wnt (assumed constant)	Romosozumab	1. Extends Martin et al. (2019) to include romosozumab 2. Model indicates need for other treatment after discontinuation of romosozumab
Larcher and Scheiner (2021)*	pOBL	-	-	1. Reduces the number of parameters in Scheiner et al. (2013) 2. Develops a framework for analyzing and reducing complex bone models
PDEs				
Buenzli et al. (2011)	pOBL	-	-	1. Focuses on the emergence of a BMU 2. Provides spatial understanding of how signaling factors cause cells to activate and migrate
Buenzli et al. (2014)	pOBL	-	-	1. Extends Buenzli et al. (2011) to include the formation phase 2. Points to the initiation and termination of a BMU to be much faster than other phases
Lerebours et al. (2016)*	pOBL, pOCL	-	-	1. Focuses on site-specific dynamics of bone 2. Bone loss from osteoporosis or disuse is dependent on site-specific dynamics
Kameo et al. (2020)*	OCY	SCL, Sema3A	Anti-RANKL antibody, anti-SCL antibody, Sema3A, bisphosphonate	1. Develops a platform of cell and organ interactions for in silico experiments 2. Highlights the importance of considering dual function molecules
Calvo-Gallego et al. (2023)*	pOBL, pOCL, OCY	-	-	1. Develops a spatiotemporal simulation of normal bone remodeling by extending Martínez-Reina and Pivonka (2019) 2. Shows that TGF-β helps coordinate the cycle

Table S3: Mathematical models of bone remodeling that do not follow either the power law or mass action kinetics approaches. Almost all the models in the table include osteoblasts (OBL) and osteoclasts (OCL), so these are not explicitly listed in the table. The exceptions are Akchurin et al. (2008), which only includes OCL, and Nutini et al. (2021) and Taylor-King et al. (2020), which exclude OCL. * denotes that a model has a biomechanical aspect. ^{d} denotes that a model is a system of delay differential equations. Abbreviations: agent-based models (ABMs), autocrine and paracrine (A&P) signaling, bone-derived factors (BDF), basic/bone multicellular unit (BMU), calcitonin (CT), dickkopf-related protein 1 (DKK1), hematopoietic stem cells (HSC), macrophage colony-stimulating factor (MCSF), mesenchymal stem cells (MSC), ordinary differential equations (ODEs), osteocytes (OCY), osteoprotegerin (OPG), parathyroid hormone (PTH), parathyroid hormone-related protein (PTHrP), partial differential equations (PDEs), preosteoblasts (pOBL), preosteoclasts (pOCL), prostate cancer (PC), receptor activator of nuclear factor kappa-B ligand (RANKL), sclerostin (SCL), transforming growth factor beta (TGF-β), wingless-related integration site (Wnt).

Model	Cells	Signaling Mechanisms	Treatments	Motivation/Insights
ODEs				
Moroz et al. (2006)*	OCY	A&P	-	1. Redevelops the A&P signaling to be more physiological and includes OCYs 2. Inclusion of OCYs allows for the entire remodeling cycle to be considered
Moroz and Wimpenny (2007)*	OCY	A&P	-	1. Adjusts Moroz et al. (2006) to include Hill function signaling for OCYs 2. Points to Hill functions as the preferred way to capture the complexity of remodeling
Akchurin et al. (2008)	Monocytes	RANKL	-	1. Captures the dynamic conversion of OCLs to monocytes 2. Kinetically models the conversion using *in vito* data
Ji et al. (2012)	-	-	-	1. Develops a predator-prey model that represents bone remodeling 2. Explores the population relationship of OBL and OCL in diseases
Buenzli (2015)	OCY	-	-	1. Develops a model of OCY generation and burial 2. Points to OCY burial being related to the infilling of the bone and the number of OCYs present
Proctor and Gartland (2016)*	pOBL, pOCL, OCY, HSC, MSC	Intracrine signaling, MCSF, OPG, PTH, RANKL, TGF-β, Wnt	-	1. Develops a model that includes mechanical and circadian rhythm influences 2. Explores the impact of mechanical loading and the timing of medical interventions

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Model	Cells	Signaling Mechanisms	Treatments	Motivation/Insights
Chaiya and Rattanakul (2017)[d]	-	CT, PTH	Estrogen	1. Focuses on the effects of different hormones on bone remodeling 2. Shows that bone remodeling is highly sensitive to estrogen levels
Javed et al. (2018)	pOBL, pOCL	OPG, RANKL, SCL	Denosumab, estrogen	1. Develops a model that includes major influencers of osteoporosis 2. Model corroborates experimental results that point to denosumab repressing OCLs
Javed et al. (2020)	-	CT, OPG, RANKL	CT	1. Develops a model to explore CT as a therapeutic 2. CT alone can not provide treatment for osteoporosis
Zhao and Zhang (2019)	-	Generic signaling, PTH, PTHrP	PTHrP	1. Develops a simplified model of PTH influence on bone remodeling 2. Points to the benefit of utilizing bioengineered scaffolds for treating osteoporosis
Nutini et al. (2021)*	OCY	DKK1, OPG, RANKL, SCL	-	1. Models the SCL action on bone remodeling 2. Explores actions of mechanical stimulus and SCL
Jorg et al. (2022)	pOBL, pOCL, OCY	Estrogen, Generic signaling, SCL	Bisphosphonates, denosumab, PTH, romosozumab	1. Utilizes clinical data to develop a model of osteoporosis 2. Captures the dynamics of several treatment methods
ABMs & PDEs				
van Oers et al. (2008)*	OCY	-	-	1. Focuses on the cavities made by a BMU 2. Shows how OCLs move towards areas of OCY death
Buenzli et al. (2012a)	-	-	-	1. Shows the movement of OCLs and the corresponding bone resorption 2. Predicts the shape of the developed cavity
Araujo et al. (2014)	pOBL, pOCL, MSC, PC	BDF, RANKL, TGF-β	Anti-RANKL antibody, bisphosphonates	1. Focuses on the interactions occurring in the PC bone microenvironment 2. Includes distinct phases of bone calcium degradation and solidification 3. Shows efficacy of bisphosphonates

Table S3 continued from previous page

Model	Cells	Signaling Mechanisms	Treatments	Motivation/Insights
Arias et al. (2018)	pOBL, pOCL, OCY	Generic signaling	-	1. Determines the simplest model that can replicate remodeling 2. Points to a connection between the depth of OCY damage and OCL lifespan 3. Shows that a BMU can respond to a variety of damage regions
Taylor-King et al. (2020)	pOBL, OCY	-	Zolendrate (bisphosphonate)	1. Develops a model to depict the interconnectedness of OCYs 2. Explores how OCY network changes with cancer and bisphosphonates

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