



Mathematical formulations for bone remodelling

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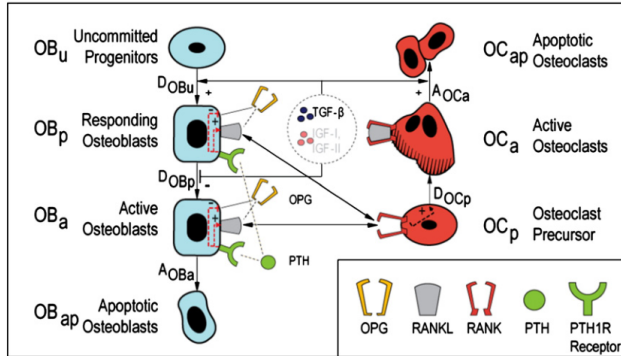


Figure: Proposed cell population model by Pivonka et al. [2008] that shows a basic multicellular unit (BMU). The BMU contains osteoblastic cells (OBs) and osteoclastic cells (OC) at different maturation steps including various molecules that influence the differentiation process.

K - RANK, L - RANKL, O - OPG, T - TGF- β , P - PTH

dynamic bone cell population model by Lemaire et al. [2004]

- RANK-RANKL-OPG pathway to regulate OCa formation
- PTH injection to regulate OBp, OBa formation

$$\frac{dC_{OBp}}{dt} = D_{OBp} \cdot \pi_T - \frac{D_{OBa}}{\pi_T} \cdot C_{OBp} \quad (1a)$$

$$\frac{dC_{OBa}}{dt} = \frac{D_{OBa}}{\pi_T} C_{OBp} - A_{OBa} \cdot C_{OBa} \quad (1b)$$

$$\frac{dC_{OCa}}{dt} = D_{OCa} \cdot \pi_L(I_L, I_O, I_P) - D_A \cdot \pi_T \cdot C_{OCa} \quad (1c)$$

C_α - concentration of α , D_α - differentiation rate of α , π_β - proportion of occupied β receptors, A_α - apoptosis rate of α , I_β - injection rate of β

dynamic bone cell population model by Pivonka et al. [2008]

- bone volume as new variable
- RANK-RANKL-OPG pathway expression (by TGF- β) for OBp, OBa
- TGF- β rate equation depending on bone resorption

$$\frac{dC_{OBp}}{dt} = D_{OBu} \cdot \pi_{a,OBu}^T(C_T) - D_{OBp} \cdot \pi_{r,OBp}^T(C_T) \cdot C_{OBp} \quad (2a)$$

$$\frac{dC_{OBa}}{dt} = D_{OBp} \cdot C_{OBp} \cdot \pi_{r,OBp}^T(C_T) \cdot C_{OBp} - A_{OBa} \cdot C_{OBa} \quad (2b)$$

$$\frac{dC_{OCa}}{dt} = D_{OCp} \cdot \pi_{a,OCp}^L(I_O, I_P) - A_{OCa} \cdot \pi_{a,OCp}^T(C_T) \cdot C_{OCa} \quad (2c)$$

$$\frac{dBV}{dt} = -k_r \cdot [C_{OCa} - C_{OCa}(t_0)] + k_f \cdot [C_{OBa} - C_{OBa}(t_0)] \quad (2d)$$

$\pi_{a/r,\beta}^\alpha$ - activation(a)/repression(r) function of α binding β , t_0 - initial state, BV - bone volume, $k_{r/f}$ - resorption/formation rate

multiscale mechanobiological femur model by Lerebours et al. [2016]

- material properties on tissue scale based on remodeling process at cellular scale
- stress/strain on microstructural scale based on macroscopic Euler-Bernoulli beam theory

stress/strain at tissue level

$$\sigma_{11} = \mathbb{C}_{1111} \cdot \varepsilon_{11}, \sigma_{22} = \mathbb{C}_{1122} \cdot \varepsilon_{11}, \sigma_{33} = \mathbb{C}_{1133} \cdot \varepsilon_{11} \quad (3)$$

$$\varepsilon_{11}(x_2, x_3) = \varepsilon_1(\mathbb{C}, \mathbf{N}, \mathbf{M}) - \kappa_3(\mathbb{C}, \mathbf{N}, \mathbf{M}, t) \cdot x_2 + \kappa_2(\mathbb{C}, \mathbf{N}, \mathbf{M}) \cdot x_3 \quad (4)$$

σ - macro stress, ε - macro strain, \mathbb{C} - macro stiffness tensor, \mathbf{N} - normal force, \mathbf{M} - bending moment

stress/strain at cellular level

$$\boldsymbol{\varepsilon}^m = \mathbb{A}_{bm}(f_{bm}) : \boldsymbol{\varepsilon}, \boldsymbol{\sigma}^m = \mathbb{B}_{bm}(f_{bm}) : \boldsymbol{\sigma} \quad (5)$$

$$\mathbb{C} = f_{bm} \cdot \mathbb{C}_{bm}^m : \mathbb{A}_{bm} + [1 - f_{bm}] \cdot \mathbb{C}_{vas}^m : \mathbb{A}_{vas} \quad (6)$$

strain energy density

$$\Psi = \frac{1}{2} \boldsymbol{\varepsilon} : \mathbb{C} : \boldsymbol{\varepsilon} \quad (7)$$

$$\Psi^m = \frac{1}{2} \boldsymbol{\varepsilon}^m : \mathbb{C}_{bm}^m : \boldsymbol{\varepsilon}^m \quad (8)$$

$\boldsymbol{\sigma}^m$ - micro stress, $\boldsymbol{\varepsilon}^m$ - micro strain, f_{bm} - BV/TV, $\mathbb{A}_{bm}/\mathbb{A}_{vas}$ - matrix/vascular strain concentration tensor, \mathbb{B}_{bm} - stress concentration tensor, $\mathbb{C}_{bm}^m/\mathbb{C}_{vas}^m$ - matrix/vascular stiffness tensor, Ψ^m - strain energy density

dynamic bone cell population model by Lerebours et al. [2016]

- incorporation of Ψ into OC activation/repression function

$$\frac{dC_{OBp}}{dt} = D_{OBu} \cdot \pi_{a,OBu}^T \cdot C_{OBu}(f_{bm}) - D_{OBp} \cdot \pi_{r,OBp}^T \cdot C_{OBp} + \mathcal{P}_{OBp}(\Psi) \cdot C_{OBp} \quad (9a)$$

$$\frac{dC_{OBa}}{dt} = D_{OBp} \cdot \pi_{r,OBp}^T \cdot C_{OBp} - A_{OBa} \cdot C_{OBa} \quad (9b)$$

$$\frac{dC_{OCp}}{dt} = D_{OCu} \cdot \pi_{a,OCu}^L(\Psi, \beta_L) \cdot C_{OBu}(f_{bm}) - D_{OCp} \cdot \pi_{r,OCp}^L(\Psi, \beta_L) \cdot C_{OCp} \quad (9c)$$

$$\frac{dC_{OCa}}{dt} = D_{OCp} \cdot \pi_{a,OCp}^L(\Psi, \beta_L) \cdot C_{OCp} - A_{OCa} \cdot \pi_{a,OCp}^T \cdot C_{OCa} \quad (9d)$$

$$\frac{df_{bm}}{dt} = -k_r \cdot C_{OCa} + k_f \cdot C_{OBa} \quad (9e)$$

\mathcal{P}_{OBp} - proliferation rate of OBp cells, β_L - RANKL production rate,

geometrical feedback

- $\forall f_{bm} \in [0, 1] : \text{find } C_{OCu}(f_{bm}) \text{ and } C_{OBu}(f_{bm}) \text{ s.t}$

$$k_f \cdot \overline{C_{OBa}}(C_{OBu}(f_{bm}), C_{OCu}(f_{bm})) = k_r \cdot \overline{C_{OCa}}(C_{OBu}(f_{bm}), C_{OCu}(f_{bm})) \quad (10)$$

geometrical feedback

$$\beta_L(\Psi) = \begin{cases} -\kappa \cdot \mu(\Psi), & \text{if } \mu(\Psi) \leq 0 \\ 0 & \text{else} \end{cases}, \mathcal{P}_{OBp}(\Psi) = P_{OBp} + \begin{cases} 0, & \text{if } \mu(\Psi) \leq 0 \\ P_{OBp} \cdot \lambda \cdot \mu(\Psi), & \text{if } \mu(\Psi) \in (0, \frac{1}{\lambda}) \\ P_{OBp}, & \text{else} \end{cases} \quad (11)$$

$\overline{C_\alpha}$ - steady state concentration of α , μ - normalised Ψ difference, P_{OBp} - proliferation term of OBp cells, λ - conduction strength

pharmacokinetics(PK)/pharmacodynamics(PD) model by Lavaill et al. [2020]

- PTH concentration from PK model
- incorporation of dual PTH action + mech. feedback into cell population model

PK model

- obtain C_T as external from following ODEs

$$\frac{dD}{dt} = -k_a \cdot D \cdot F \quad (12a)$$

$$\frac{dC_T}{dt} = \frac{F}{V_d} \cdot k_a \cdot D - k_e \cdot C_T + \beta_T \quad (12b)$$

D - PTH dose, k_a - absorption rate, F - bioavailability, V_d - distribution volume, k_e - elimination rate, β_T - PTH production rate

PD model

- obtain repressor function $H_P^-(C_{B2})$ to regulate OBa apoptosis from following ODEs

$$\frac{dC_{R2}}{dt} = \beta_{R2} - d_{R2} \cdot H_{R2}^+(C_T) \cdot C_{R2} \quad (13a)$$

$$\frac{dC_{pC}}{dt} = \beta_{pC} \cdot H_{pC}^+(C_T) - d_{pC} \cdot C_{pC} \quad (13b)$$

$$\frac{dC_{B2}}{dt} = \beta_{B2} \cdot C_{R2} \cdot C_{pC} - d_{B2} \cdot C_{B2} \quad (13c)$$

$R2$ - Runx2, pC - pCREB, $B2$ - Bcl-2, β - production rate, d - degradation rate, H - regulation function

dynamic cell population model by Lavaill et al. [2020]

- catabolic PTH action in $\pi_{a,OCp}^L$, anabolic PTH action in A_{OBa}
 - Ψ based on Lerebours et al. [2016]
- geometrical and mechanical feedback from (11)

$$\frac{dC_{OBp}}{dt} = D_{OBu} \cdot \pi_{a,OBu}^T \cdot C_{OBu} - D_{OBp} \cdot \pi_{r,OBp}^T \cdot C_{OBp} + \mathcal{P}_{OBp} \cdot C_{OBp} \quad (14a)$$

$$\frac{dC_{OBa}}{dt} = D_{OBp} \cdot \pi_{r,OBp}^T \cdot C_{OBp} - A_{OBa} \cdot H_P^- \cdot C_{OBa} \quad (14b)$$

$$\frac{dC_{OCa}}{dt} = D_{OCp} \cdot \pi_{a,OCp}^L \cdot C_{OCp} - A_{OCa} \cdot \pi_{a,OCp}^T \cdot C_{OCa} \quad (14c)$$

$$\frac{df_{bm}}{dt} = -k_r \cdot C_{OCa} + k_f \cdot C_{OBa} \quad (14d)$$

continuum mechanical model for bone turnover by Sansalone et al. [2021]

- bone turnover: resorption \rightarrow formation \rightarrow mineralisation
- three distinct phases: porosity (p), mineralised bone (m), unmineralised bone (u)

kinematics

$$\dot{f}_u = \dot{f}_u^{\text{OB}} + \dot{f}_u^{\text{OC}} + \dot{f}_u^{\chi} \quad (15a)$$

$$\dot{f}_m = \dot{f}_m^{\text{OC}} + \dot{f}_m^{\chi} \quad (15b)$$

$$\dot{f}_p = 1 - \dot{f}_u - \dot{f}_m \quad (15c)$$

$(\dot{*}) = \frac{d(*)}{dt}$, OB - formation mechanism, OC - resorption mechanism, χ - mineralisation mechanism, f_{α}^{β} - vol. fraction of phase α due to mechanism β

balance equations

$$\operatorname{div}(\boldsymbol{\sigma}) + \mathbf{b} = \mathbf{0} \text{ in } \mathcal{B}_0 \text{ with } \boldsymbol{\sigma} \cdot \mathbf{n} = \mathbf{t} \text{ in } \partial\mathcal{B}_0 \quad (16a)$$

$$\overset{i}{\mathbf{T}} + \overset{o}{\mathbf{T}} = \mathbf{0} \text{ in } \mathcal{B}_0 \quad (16b)$$

$$\overset{i}{\lambda}_u^{\text{OB}} + \overset{i}{\lambda}_u^{\text{OB}} = 0 \text{ in } \mathcal{B}_0 \quad (16c)$$

$$\overset{i}{\lambda}_u^{\text{OC}} + \overset{i}{\lambda}_u^{\text{OC}} = 0 \text{ in } \mathcal{B}_0 \quad (16d)$$

$$\overset{i}{\lambda}_m^{\text{OB}} + \overset{i}{\lambda}_m^{\text{OB}} = 0 \text{ in } \mathcal{B}_0 \quad (16e)$$

$$[\overset{i}{\lambda}_m^{\text{X}} - \overset{i}{\lambda}_u^{\text{X}}] + [\overset{o}{\lambda}_m^{\text{X}} - \overset{o}{\lambda}_u^{\text{X}}] = 0 \text{ in } \mathcal{B}_0 \quad (16f)$$

\mathbf{b} - body force, \mathbf{t} - surface traction, \mathbf{n} - surface normal, \mathcal{B}_0 - reference body, \mathbf{T} - rotary remodelling tensor, λ_α^β - remodelling force in phase α due to mechanism β , i/o - inner/outer

temporal change of bone phases

$$\dot{f}_u^{\text{OB}} = \frac{C_{\text{OB}}}{\bar{d}_u^{\text{OB}}} \cdot [\alpha_u^{\text{OB}} \cdot S_V - \lambda_u^{\text{mech}}(\mathbb{C}, \varepsilon) - \lambda_u^{\text{chem}}(\mu_p, \mu_m, \mu_u)] \quad (17a)$$

$$\dot{f}_u^{\text{OC}} = \frac{C_{\text{OC}}}{\bar{d}_u^{\text{OC}}} \cdot [\alpha_u^{\text{OC}} \cdot f_u \cdot (f_p - f_p^{\min}) - \lambda_u^{\text{mech}}(\mathbb{C}, \varepsilon) - \lambda_u^{\text{chem}}(\mu_p, \mu_m, \mu_u)] \quad (17b)$$

$$\dot{f}_m^{\text{OC}} = \frac{C_{\text{OC}}}{\bar{d}_m^{\text{OC}}} \cdot [\alpha_m^{\text{OC}} \cdot f_m \cdot (f_p - f_p^{\min}) - \lambda_m^{\text{mech}}(\mathbb{C}, \varepsilon) - \lambda_m^{\text{chem}}(\mu_p, \mu_m, \mu_u)] \quad (17c)$$

$$\dot{f}_m^{\chi} = \frac{f_u \cdot f_m}{\bar{d}^{\chi}} \cdot [(\lambda_m^{\text{OX}} - \lambda_u^{\text{OX}}) - \Delta \lambda^{\text{mech}}(\mathbb{C}, \varepsilon) - \Delta \lambda^{\text{chem}}(\mu_p, \mu_m, \mu_u)] \quad (17d)$$

\bar{d} - turnover resistance, α - unit stimuli, S_V - specific surface, $\lambda_{u/m}^{\text{mech/chem}}$ - generalised mech./chem. turnover force in phase u/m

two-state receptor ligand binding model for PTH by Martonová et al. [2023]

- PTH1R regulates skeletal development and transduces stimuli from PTH
- modelling activation of PTH1R

$$\begin{bmatrix} \dot{r}_a \\ \dot{c}_a \\ \dot{c}_i \end{bmatrix} = \begin{bmatrix} -k_1 - k_r \cdot C_P & k_{-r} & 0 & k_{-1} \\ k_r \cdot C_P & -k_2 - k_{-r} & k_{-2} & 0 \\ 0 & k_2 & -k_{-2} - k_{-d} & k_d \cdot C_P \end{bmatrix} \cdot \begin{bmatrix} r_a \\ c_a \\ c_i \\ 1 - (r_a + c_a + c_i) \end{bmatrix} \quad (18)$$

r_a - active receptor fraction, $c_{i/a}$ - inactive/active ligand-receptor complex fraction, k_i - kinematic parameters

PTH concentration

- Obtain separate C_P values due to internal secretion and external drug dosing

$$C_P = \begin{cases} \gamma_1 & \text{if } (n-1) \cdot T \leq t \leq (n-1) \cdot T + \tau_1 \\ \gamma_0 & \text{if } (n-1) \cdot T + \tau_1 \leq t \leq (n-1) \cdot T + \tau_1 + \tau_0 \end{cases} \quad (19)$$

cellular responsiveness α_R

$$\alpha_R = \frac{\alpha_T}{\alpha_{T_{\text{step}}}} \cdot \frac{\alpha_T}{T} \quad (20)$$

$$\alpha_T = \int_0^T [\alpha(r_a, c_a, c_1, r_i) - \alpha_0] dt \text{ with } T = \tau_0 + \tau_1 \quad (21)$$

$\gamma_{0/1}$ - PTH concentration due to tonic/pulsatile glandular secretion, $\tau_{0,1}$ - off-/on-phase, n - pulses, $\alpha_{T_{\text{step}}}$ - integrated activity, α - scaled activity

Predict optimal pulsatile pattern

$$\operatorname{argmin}_{\gamma_1, \tau_1} [\alpha_R(C_P^{gl} - \alpha_R^{ref})]^2 \quad (22)$$

Predict optimal dosing pattern

$$\operatorname{argmin}_D [\alpha_R^{inj}(D) - (\alpha_R^{ref} - \alpha_R^{ill})]^2 \quad (23)$$

C_P^{gl} - plasma PTH concentration, $\alpha_R^{ref/ill}$ healthy/unhealthy cellular responsiveness

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