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Mathematical formulations for bone remodelling

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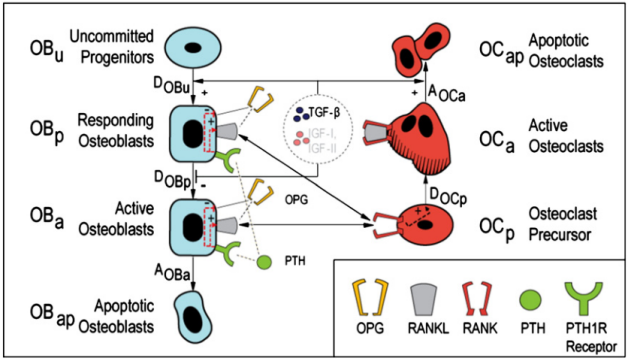

Figure: Proposed cell population model by Pivonka et al. [2008] that shows a basic multicellular unit (BMU). The BMU contains osteoblastic cells (OBs) and osteoclastic cells (OC) at different maturation steps including various molecules that influence the differentiation process.

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

$$\frac{\mathrm{d}C_{\mathrm{OBp}}}{\mathrm{d}t} = D_{\mathrm{OBp}} \cdot \pi_{\mathrm{T}} - \frac{D_{\mathrm{OBa}}}{\pi_{\mathrm{T}}} \cdot C_{\mathrm{OBp}} \tag{1a}$$

$$\frac{\mathrm{d}C_{\mathrm{OBa}}}{\mathrm{d}t} = \frac{D_{\mathrm{OBa}}}{\pi_{\mathrm{T}}} C_{\mathrm{OBp}} - A_{\mathrm{OBa}} \cdot C_{\mathrm{OBa}} \tag{1b}$$

$$\frac{\mathrm{d}C_{\mathrm{OCa}}}{\mathrm{d}t} = D_{\mathrm{OCa}} \cdot \pi_L(I_{\mathrm{L}}, I_{\mathrm{O}}, I_{\mathrm{P}}) - D_{\mathrm{A}} \cdot \pi_{\mathrm{T}} \cdot C_{\mathrm{OCa}} \tag{1c}$$

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

$$\frac{\mathrm{d}C_{\mathrm{OBp}}}{\mathrm{d}t} = D_{\mathrm{OBu}} \cdot \pi^{\mathsf{T}}_{\mathrm{a,OBu}}(C_{\mathsf{T}}) - D_{\mathrm{OBp}} \cdot \pi^{\mathsf{T}}_{\mathrm{r,OBp}}(C_{\mathsf{T}}) \cdot C_{\mathrm{OBp}} \tag{2a}$$

$$\frac{\mathrm{d}C_{\mathrm{OBa}}}{\mathrm{d}t} = D_{\mathrm{OBp}} \cdot C_{\mathrm{OBp}} \cdot \pi^{\mathsf{T}}_{\mathrm{r,OBp}}(C_{\mathsf{T}}) \cdot C_{\mathrm{OBp}} - A_{\mathrm{OBa}} \cdot C_{\mathrm{OBa}} \tag{2b}$$

$$\frac{\mathrm{d}C_{\mathrm{OCa}}}{\mathrm{d}t} = D_{\mathrm{OCp}} \cdot \pi^{\mathsf{L}}_{\mathrm{a,OCp}}(I_{\mathsf{O}}, I_{\mathsf{P}}) - A_{\mathrm{OCa}} \cdot \pi^{\mathsf{T}}_{\mathrm{a,OCp}}(C_{\mathsf{T}}) \cdot C_{\mathrm{OCa}} \tag{2c}$$

$$\frac{\mathrm{d}BV}{\mathrm{d}t} = -k_{\mathsf{r}} \cdot [C_{\mathrm{OCa}} - C_{\mathrm{OCa}}(t_0)] + k_{\mathsf{f}} \cdot [C_{\mathrm{OBa}} - C_{\mathrm{OBa}}(t_0)] \tag{2d}$$

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

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

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

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

stress/strain at cellular level

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

$$\mathbb{C} = f_{bm} \cdot \mathbb{C}^m_{bm} : \mathbb{A}_{bm} + [1 - f_{bm}] \cdot \mathbb{C}^m_{vas} : \mathbb{A}_{vas} \tag{6}$$

strain energy density

$$\Psi = \frac{1}{2}\boldsymbol{\varepsilon} : \mathbb{C} : \boldsymbol{\varepsilon} \tag{7}$$

$$\Psi^m == \frac{1}{2}\boldsymbol{\varepsilon}^m : \mathbb{C}^m_{bm} : \boldsymbol{\varepsilon}^m \tag{8}$$

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

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

- incorporation of Ψ into OC actication/repression function

$$\frac{\mathrm{d}C_{\mathrm{OBp}}}{\mathrm{d}t} = D_{\mathrm{OBu}} \cdot \pi^{\mathsf{T}}_{\mathrm{a,OBu}} \cdot C_{\mathrm{OBu}}(f_{bm}) - D_{\mathrm{OBp}} \cdot \pi^{\mathsf{T}}_{\mathrm{r,OBp}} \cdot C_{\mathrm{OBp}} + \mathcal{P}_{\mathrm{OBp}}(\Psi) \cdot C_{\mathrm{OBp}} \tag{9a}$$

$$\frac{\mathrm{d}C_{\mathrm{OBa}}}{\mathrm{d}t} = D_{\mathrm{OBp}} \cdot \pi^{\mathsf{T}}_{\mathrm{r,OBp}} \cdot C_{\mathrm{OBp}} - A_{\mathrm{OBa}} \cdot C_{\mathrm{OBa}} \tag{9b}$$

$$\frac{\mathrm{d}C_{\mathrm{OCp}}}{\mathrm{d}t} = D_{\mathrm{OCu}} \cdot \pi^{\mathsf{L}}_{\mathrm{a,OCu}}(\Psi, \beta_{\mathsf{L}}) \cdot C_{\mathrm{OBu}}(f_{bm}) - D_{\mathrm{OCp}} \cdot \pi^{\mathsf{L}}_{\mathrm{r,OCp}}(\Psi, \beta_{\mathsf{L}}) \cdot C_{\mathrm{OCp}} \tag{9c}$$

$$\frac{\mathrm{d}C_{\mathrm{OCa}}}{\mathrm{d}t} = D_{\mathrm{OCp}} \cdot \pi^{\mathsf{L}}_{\mathrm{a,OCp}}(\Psi, \beta_{\mathsf{L}}) \cdot C_{\mathrm{OCp}} - A_{\mathrm{OCa}} \cdot \pi^{\mathsf{T}}_{\mathrm{a,OCp}} \cdot C_{\mathrm{OCa}} \tag{9d}$$

$$\frac{\mathrm{d}f_{bm}}{\mathrm{d}t} = -k_{\mathsf{r}} \cdot C_{\mathrm{OCa}} + k_{\mathsf{f}} \cdot C_{\mathrm{OBa}} \tag{9e}$$

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

geometrical feedback

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

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

geometrical feedback

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

$\overline{C_\alpha}$ - 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

$$\frac{\mathrm{d}D}{\mathrm{d}t} = -k_a \cdot D \cdot F \tag{12a}$$

$$\frac{\mathrm{d}C_\mathrm{T}}{\mathrm{d}t} = \frac{F}{V_d} \cdot k_a \cdot D - k_e \cdot C_\mathrm{T} + \beta_\mathrm{T} \tag{12b}$$

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 $H_{\mathsf{P}}^{-}(C_{B2})$ to regulate OBa apoptosis from following ODEs

$$\frac{\mathrm{d}C_{R2}}{\mathrm{d}t} = \beta_{R2} - d_{R2} \cdot H_{R2}^{+}(C_{\mathsf{T}}) \cdot C_{R2} \tag{13a}$$

$$\frac{\mathrm{d}C_{pC}}{\mathrm{d}t} = \beta_{pC} \cdot H_{pC}^{+}(C_{\mathsf{T}}) - d_{pC} \cdot C_{pC} \tag{13b}$$

$$\frac{\mathrm{d}C_{B2}}{\mathrm{d}t} = \beta_{B2} \cdot C_{R2} \cdot C_{pC} - d_{B2} \cdot C_{B2} \tag{13c}$$

$R2$ - 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 $\pi^{\mathsf{L}}_{\mathsf{a,OCp}}$, anabolic PTH action in A_{OBa}
- Ψ based on Lerebours et al. [2016]
- geometrical and mechanical feedback from (11)

$$\frac{\mathrm{d}C_{\mathsf{OBp}}}{\mathrm{d}t} = D_{\mathsf{OBu}} \cdot \pi^{\mathsf{T}}_{\mathsf{a,OBu}} \cdot C_{\mathsf{OBu}} - D_{\mathsf{OBp}} \cdot \pi^{\mathsf{T}}_{\mathsf{r,OBp}} \cdot C_{\mathsf{OBp}} + \mathcal{P}_{\mathsf{OBp}} \cdot C_{\mathsf{OBp}} \tag{14a}$$

$$\frac{\mathrm{d}C_{\mathsf{OBa}}}{\mathrm{d}t} = D_{\mathsf{OBp}} \cdot \pi^{\mathsf{T}}_{\mathsf{r,OBp}} \cdot C_{\mathsf{OBp}} - A_{\mathsf{OBa}} \cdot H^{-}_{\mathsf{P}} \cdot C_{\mathsf{OBa}} \tag{14b}$$

$$\frac{\mathrm{d}C_{\mathsf{OCa}}}{\mathrm{d}t} = D_{\mathsf{OCp}} \cdot \pi^{\mathsf{L}}_{\mathsf{a,OCp}} \cdot C_{\mathsf{OCp}} - A_{\mathsf{OCa}} \cdot \pi^{\mathsf{T}}_{\mathsf{a,OCp}} \cdot C_{\mathsf{OCa}} \tag{14c}$$

$$\frac{\mathrm{d}f_{bm}}{\mathrm{d}t} = -k_{\mathsf{r}} \cdot C_{\mathsf{OCa}} + k_{\mathsf{f}} \cdot C_{\mathsf{OBa}} \tag{14d}$$

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

$$\dot{f}_u = \dot{f}_u^{\mathrm{OB}} + \dot{f}_u^{\mathrm{OC}} + \dot{f}_u^{\chi} \tag{15a}$$

$$\dot{f}_m = \dot{f}_m^{\mathrm{OC}} + \dot{f}_m^{\chi} \tag{15b}$$

$$\dot{f}_p = 1 - \dot{f}_u - \dot{f}_m \tag{15c}$$

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

balance equations

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

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

$$\overset{i}{\lambda}{}^{\text{OB}}_{u} + \overset{i}{\lambda}{}^{\text{OB}}_{u} = 0 \text{ in } \mathcal{B}_0 \tag{16c}$$

$$\overset{i}{\lambda}{}^{\text{OC}}_{u} + \overset{i}{\lambda}{}^{\text{OC}}_{u} = 0 \text{ in } \mathcal{B}_0 \tag{16d}$$

$$\overset{i}{\lambda}{}^{\text{OB}}_{m} + \overset{i}{\lambda}{}^{\text{OB}}_{m} = 0 \text{ in } \mathcal{B}_0 \tag{16e}$$

$$[\overset{i}{\lambda}{}^{\chi}_{m} - \overset{i}{\lambda}{}^{\chi}_{u}] + [\overset{o}{\lambda}{}^{\chi}_{m} - \overset{o}{\lambda}{}^{\chi}_{u}] = 0 \text{ in } \mathcal{B}_0 \tag{16f}$$

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

temporal change of bone phases

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

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

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

$$\dot{f}_m^{\chi} = \frac{f_u \cdot f_m}{\overline{d}^{\chi}} \cdot [(\overset{o\chi}{\lambda}_m - \overset{o\chi}{\lambda}_u) - \Delta\lambda^{\mathrm{mech}}(\mathbb{C}, \varepsilon) - \Delta\lambda^{\mathrm{chem}}(\mu_p, \mu_m, \mu_u)] \tag{17d}$$

$\overline{d}$ - turnover ressistance, α - unit stimuli, S_V - specific surface, $\lambda_{u/m}^{\mathrm{mech/chem}}$ - 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

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

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

$$C_{\mathrm{P}} = \begin{cases} \gamma_1 \text{ if } (n-1)\cdot T \leq t \leq (n-1)\cdot T + \tau_1 \\ \gamma_0 \text{ if } (n-1)\cdot T + \tau_1 \leq t \leq (n-1)\cdot T + \tau_1 + \tau_0 \end{cases} \tag{19}$$

cellular responsiveness α_R

$$\alpha_R = \frac{\alpha_T}{\alpha_{T_{\text{step}}}} \cdot \frac{\alpha_T}{T} \tag{20}$$

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

$\gamma_{0/1}$ - 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

$$\underset{\gamma_1,\tau_1}{\text{argmin}}\ [\alpha_R(C_{\text{P}}^{gl} - \alpha_R^{ref})]^2 \tag{22}$$

Predict optimal dosing pattern

$$\underset{D}{\text{argmin}}\ [\alpha_R^{\text{inj}}(D) - (\alpha_R^{ref} - \alpha_R^{ill})]^2 \tag{23}$$

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

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