Bayesian Joint Modeling of Bone Mineral Density And Repeated Time-To-Fracture Event For Multiscale Bone Systems Model Extension

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Background

· Physiologically-based multiscale systems (PBMS) model describes cellular mechanisms and bone dynamics in bone-related diseases.[1,2]

· Fracture rate considered as most meaningful endpoint affected by disease progression and drug intervention.[3]

Objectives

To develop a model simultaneously characterizing bone mineral density (BMD) and fracture risk based on time since final menstrual period (FMP).

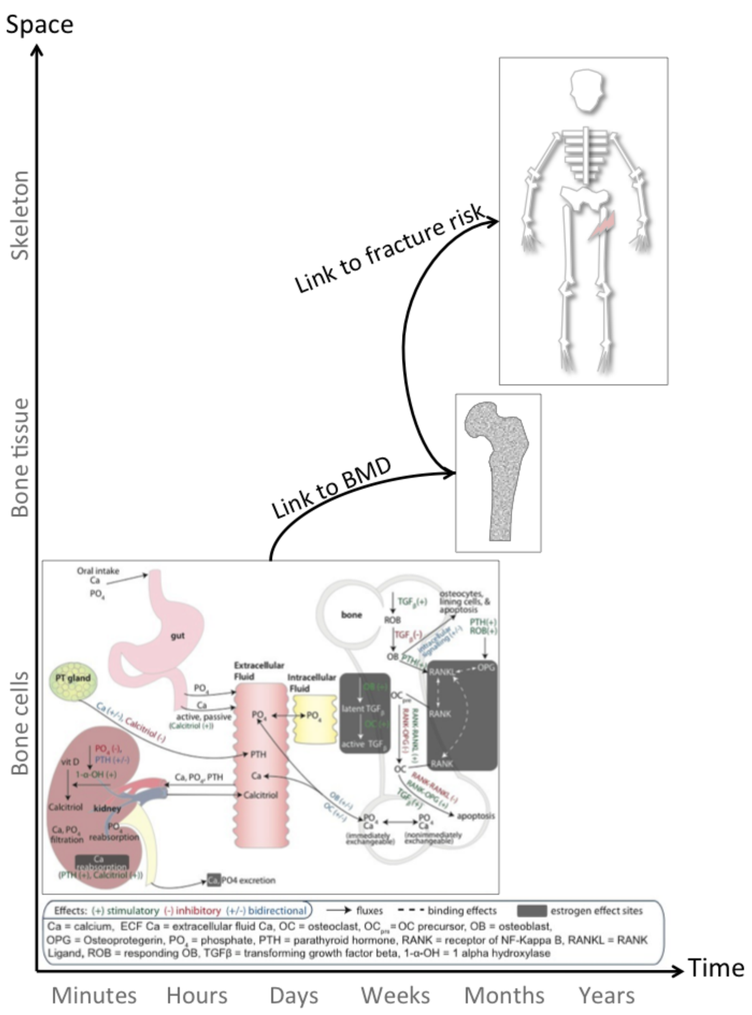

Fig. 1: Multiscale bone systems model extension to fracture risk

Methods

Data

· 2005-2008 NHANES[4] demographics, dual energy X-ray absorptiometry, body measures, osteoporosis, and reproductive health datasets.

· 1605 postmenopausal ♀ of 63 (95% inter-percentiles (IP) 27–85) yr mean age and 45 (95% IP 26–57) yr mean FMP age; 1 femoral neck BMD measure and 0–5 (204 total) fracture events each.

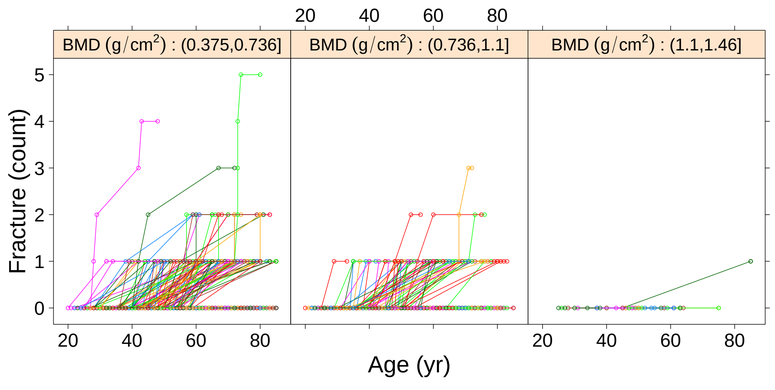

Fig. 2: Number of fractures since FMP per observed BMD strata

Models

BMD: Piecewise linear model from literature[5]

$\mathrm{BMD}(t) = \mathrm{b} + \mathrm{s_{tr}} \times t_{-1,2\mathrm{yr}} + \mathrm{s_{po}} \times t_{2,5\mathrm{yr}} + \mathrm{s_{fi}} \times t_{5,\infty\mathrm{yr}}$

Included covariates: BMI, ethnicity, and FMP_{age}.

Fracture risk: Repeated time-to-event model[6,7]

$\mathrm{S}(t) = \mathrm{e}^{-(\int_{t_{j-1}}^{t_j} \mathrm{h}(u)du)^{\alpha}}$

Investigated covariates: observed BMD, BMD(t), FMP_{age}, and *time* ($\alpha \neq 1$, Weibull distribution).

Software

WinBUGS, BlackBox[8], R (deSolve, mrgSim).

Results

Evaluation w.r.t. NHANES data

BMD: Retrospective prediction, from examination time to FMP, through fracture time point(s).

Structural parameter estimates:
$\mathrm{b} = 0.84, \mathrm{s_{tr}} = -1.66, \mathrm{s_{po}} = -0.85, \mathrm{s_{fi}} = -0.34$
(close to reported literature values[5]).

Centered covariate effects added on all parameters.

Random effect included as residual variability:
$\sigma = 0.131$ (95% credible interval (CI) 0.127–0.136).

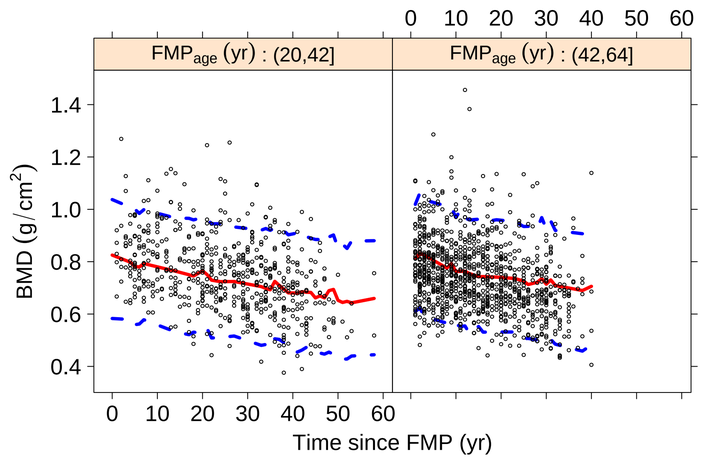

Fig. 3: Posterior predictive distributions obtained from BMD fit

Fracture risk: Time-varying hazard reflects increase due to time-dependent BMD decline in final model.

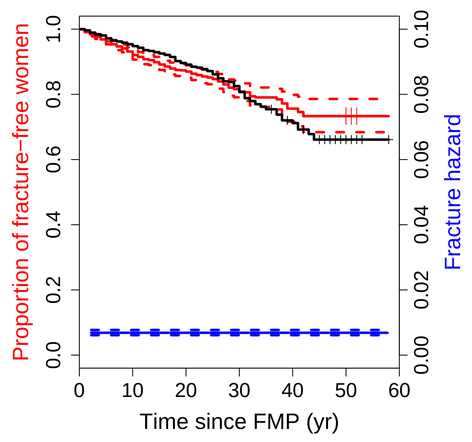

Fig. 4: Simulation with constant hazard

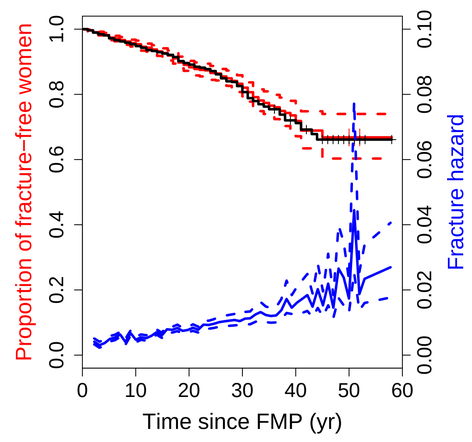

Fig. 5: Simulation with final model

$\mathrm{h}(t) = \mathrm{e}^{\theta_h \times (1 + \theta_{BMD} \times (\mathrm{BMD}(t) - \overline{\mathrm{BMD}}))}$
$(\overline{\mathrm{BMD}} = 0.8\ g/cm^2, \alpha = 1)$

$\theta_h = -5.5$ (95%CI −5.49 – −5.54),
$\theta_{BMD} = 1.5$ (95%CI 1.49–1.52)

$\mathrm{h}(t)$ accumulates from $t_0 = \mathrm{FMP}$.
$\Delta\mathrm{DIC}(\mathscr{M}_{constant} - \mathscr{M}_{varying}) = 30$

FMP_{age} and *time* indirect covariates with dynamically predicted BMD *vs.* direct with observed BMD.

Simulation with PBMS model

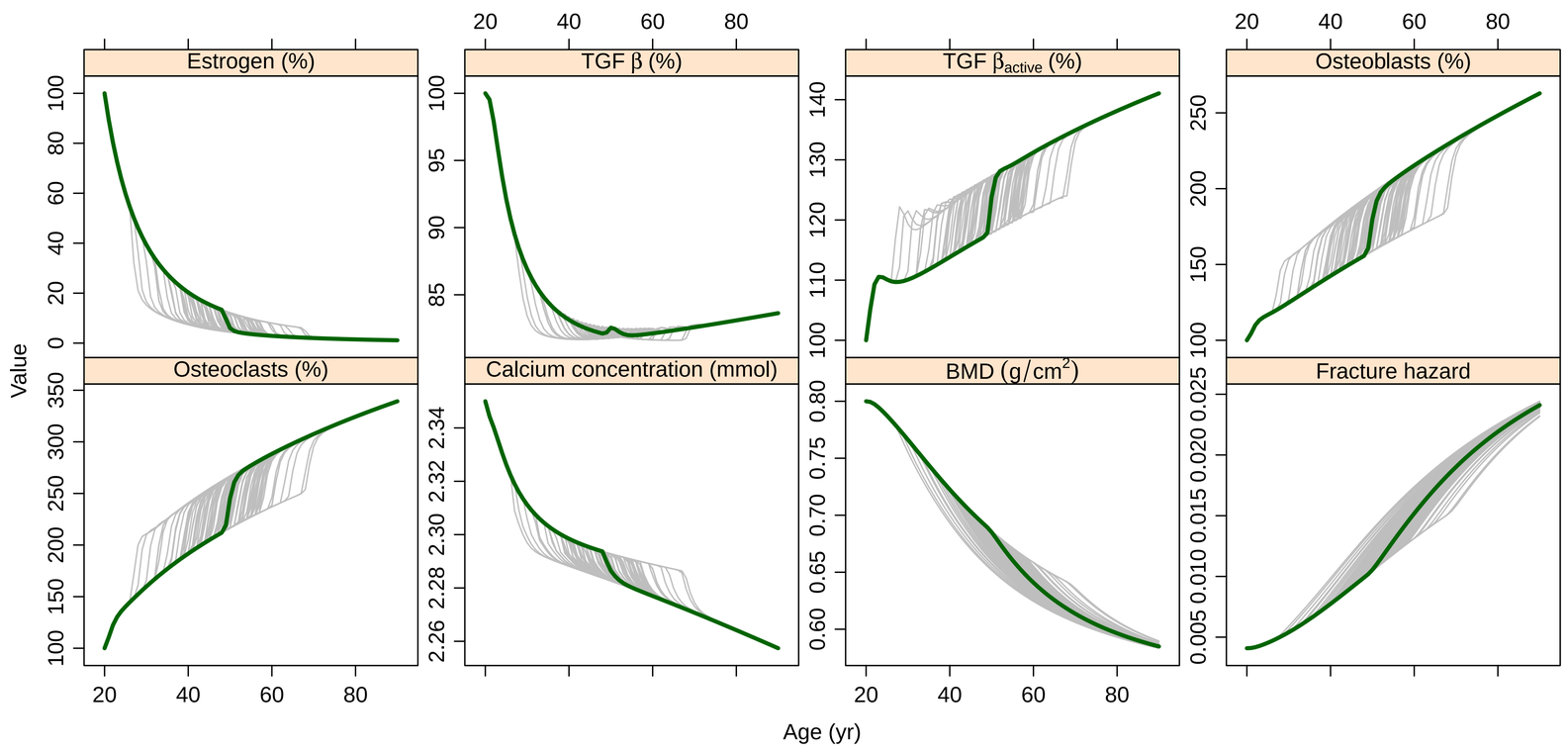

Fig. 6: Estrogen, bone remodeling factors and markers, calcium, BMD and fracture risk time-courses for 100 ♀ with FMP at 50 yr (SD 8)

Piecewise BMD model predictions resembled those based on the mechanistic model[2] reflecting the estrogen loss effect on a series of bone markers.

PBMS model extended to reflect changes in expected fracture-free time driven by bone markers.

Developed model spans several magnitudes in time and space: slow changes in survival can be predicted from more rapid changes in bone markers.

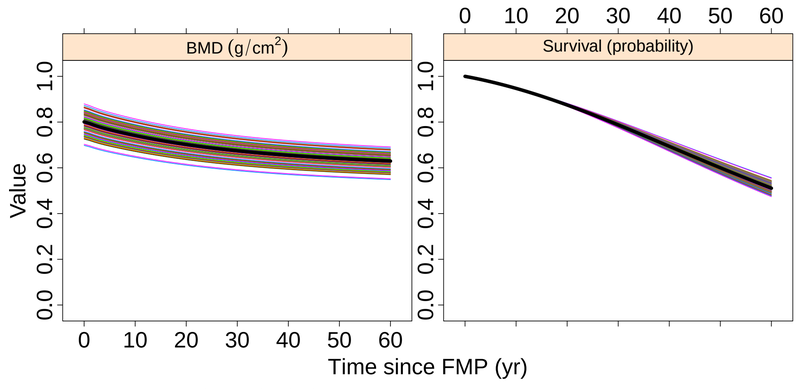

Fig. 7: BMD and probability to not experience fractures for 100 ♀ with BMD of 0.8 g/cm^2 (SD 0.04) at FMP

Conclusions

· Simultaneous modeling of BMD time-course and repeated time-to-fracture events from publicly available data enabled the characterization of the fracture risk in > 1500 postmenopausal ♀.

· Next steps include, among others, testing drug effects from previously explored therapeutics, performing external evaluation with estrogen therapy, and including uncertainty in deterministic model.

· This model will be made available in the data and model library METAMODL™.

References

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[6] Garnett C & Holford NHG. 5th International Symposium on Measurement and Kinetics of In Vivo Drug Effects. The Netherlands, 2006.
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