
Figures and figure supplements

Modeling osteoporosis to design and optimize pharmacological therapies comprising multiple drug types

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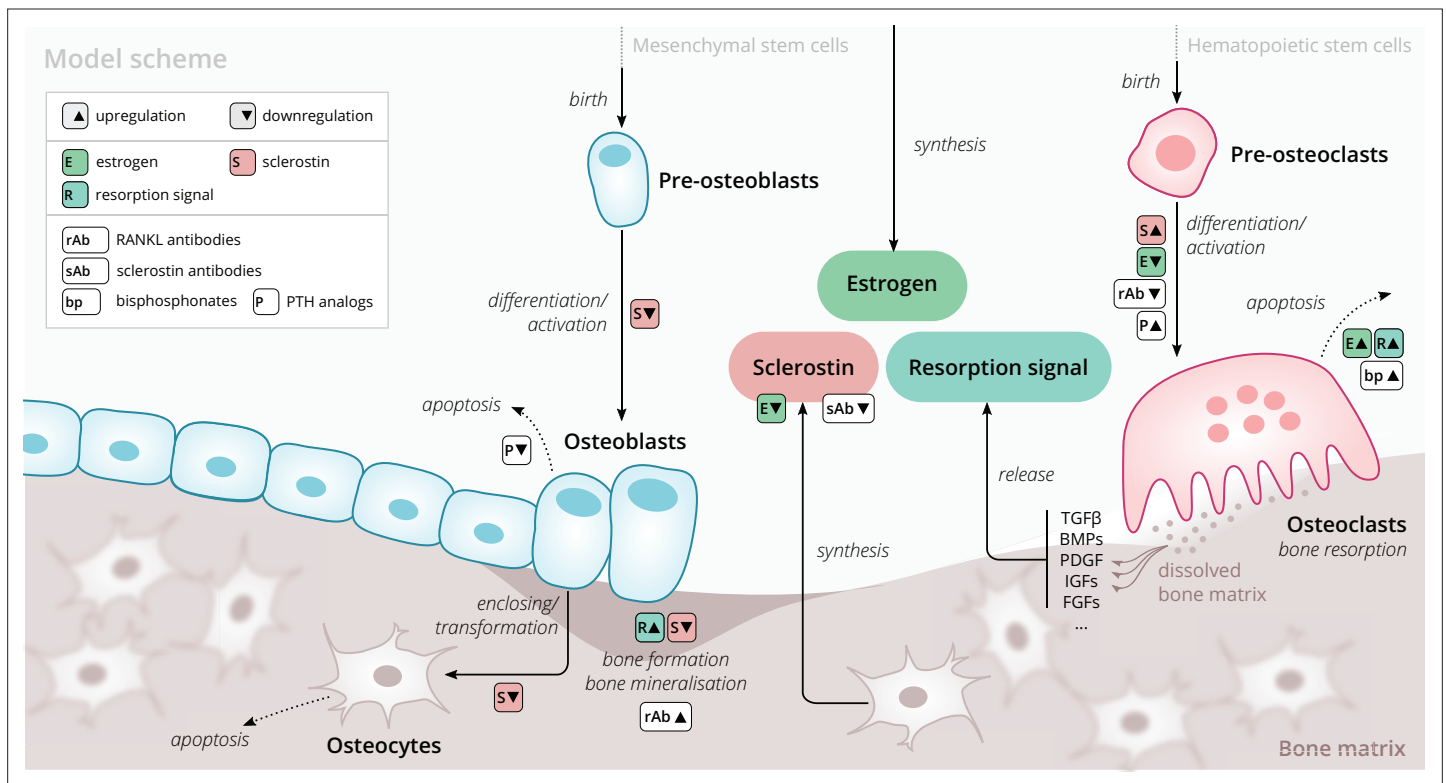


Figure 1. Schematic of the osteoporosis model describing the cell dynamics and signaling pathways within a 'representative bone remodeling unit (BRU)'. Regulatory interactions between different model components are indicated by colored boxes (see legend). TGFβ, transforming growth factor beta; BMP, bone morphogenetic protein; PDGF, platelet-derived growth factor; IGF, insulin-like growth factor; FGF, fibroblast growth factor.

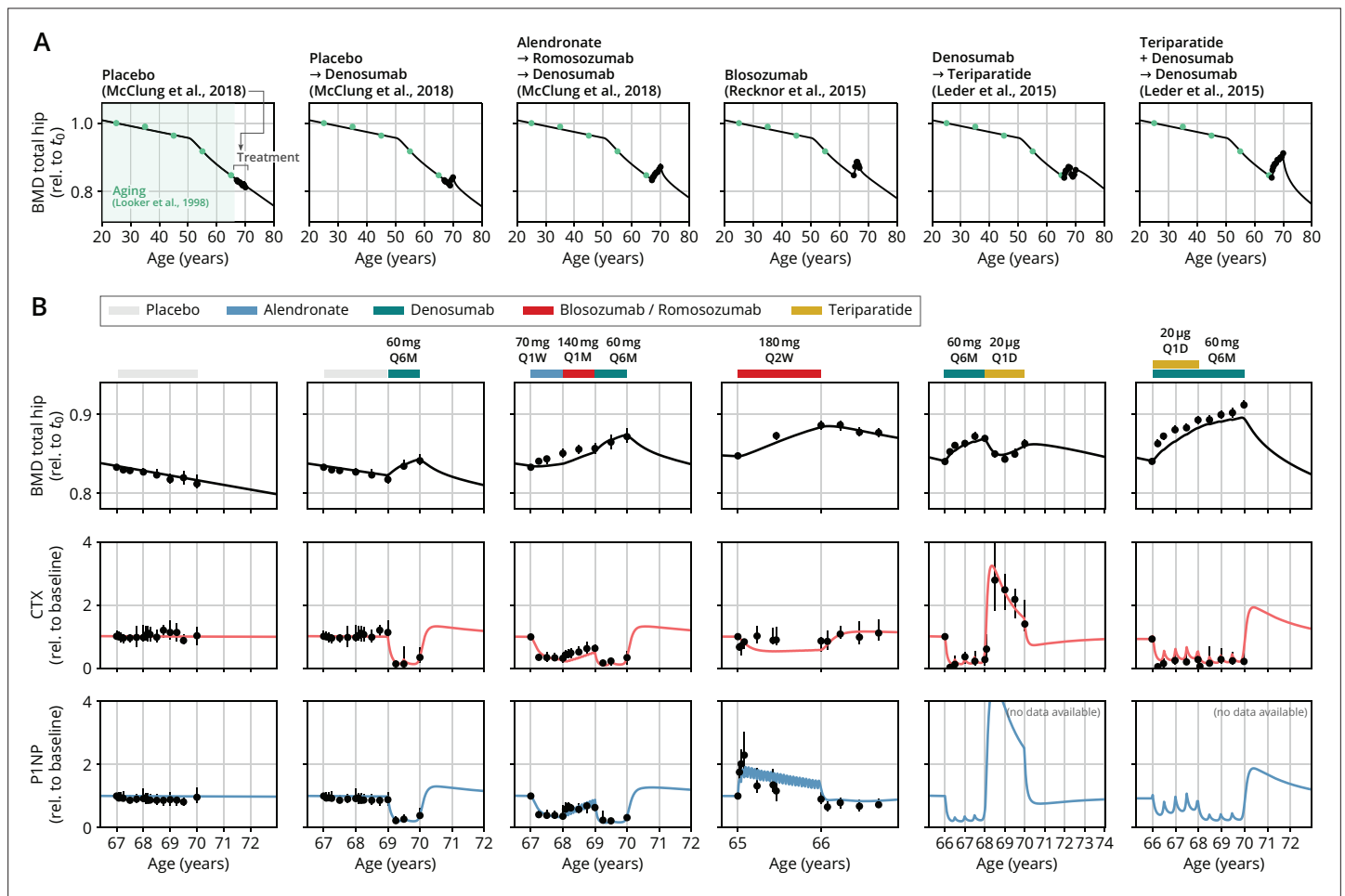


Figure 2. With a single set of parameters, the calibrated model can quantitatively predict the effects of various drugs in different dosing regimens, alone and in combination. **(A)** Comparison of simulated total hip bone mineral density (BMD, black curves) and clinical data (dots), including aging behavior (green dots) and treatment behavior (black dots) of various sequential drug treatments, including denosumab, romosozumab, alendronate, and teriparatide. Hybrid aging/treatment datasets were created combining data from *Looker et al., 1998* (aging dataset, green dots in panel **A**; in total $N = 3251$ subjects 20 years and older), as well as *Recknor et al., 2015* (blosozumab 180 mg Q2W: $N = 25$), *McClung et al., 2018* (placebo/deno.: $N = 18$, alendro./romo./deno.: $N = 21$), and *Leder et al., 2015* (deno./teri.: $N = 27$, teri. + deno./deno.: $N = 23$) (treatment datasets, black dots in panels **A** and **B**) as indicated, see 'Methods.' **(B)** Zoom into the treatment regions shown in panel **(A)** including BMD (black) and baseline changes of the bone resorption marker C-terminal telopeptide (CTX, red) and the bone formation marker procollagen type 1 amino-terminal propeptide (P1NP, blue). Colored bars above the plots indicate the medication scheme (see legend). Data points show population averages; average types and error bar types as reported in the respective original publication. In both panels, BMD is displayed as a fraction of its value at $t_0 = 25$ years.

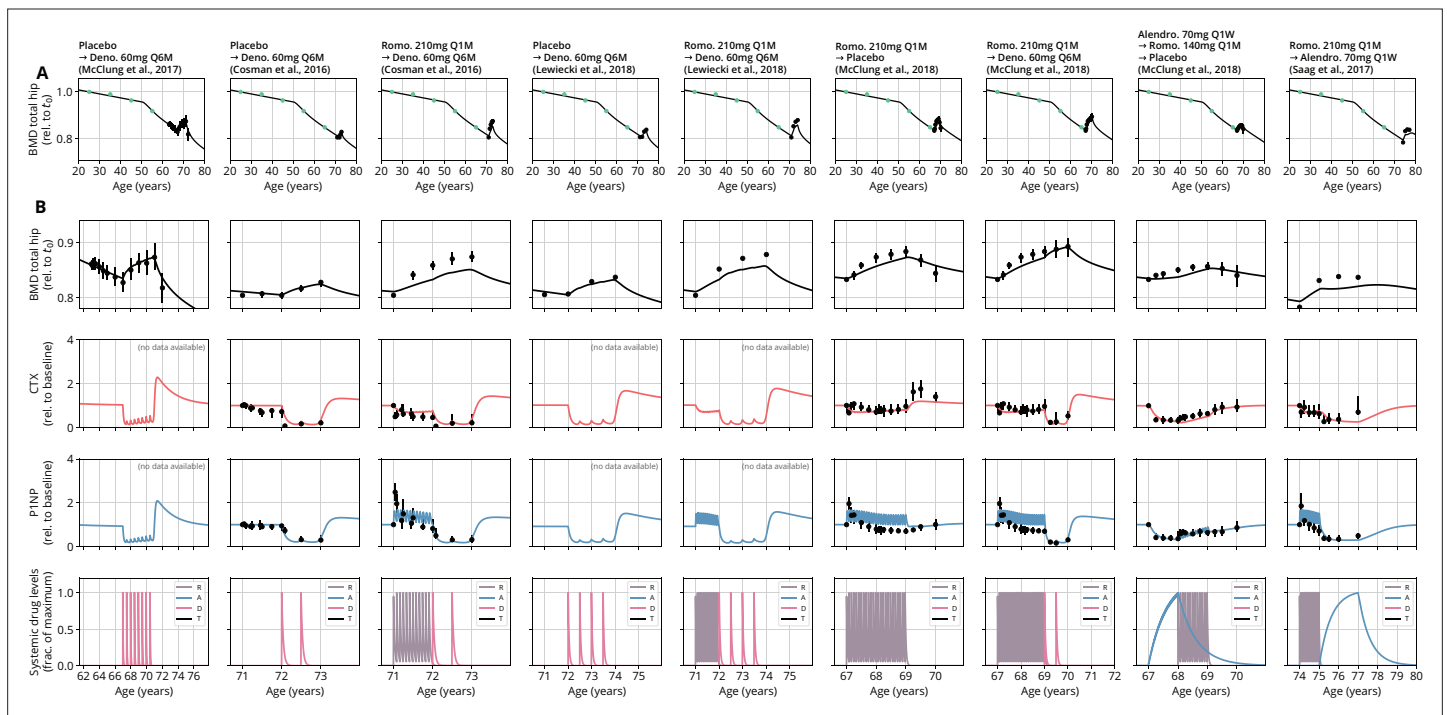


Figure 2—figure supplement 1. Continuation of **Figure 2** comparing model predictions and clinical data from various studies, all conventions identical. See **Appendix 3—table 2** for a list of data sources and **Appendix 3—table 3** for goodness-of-fit measures. Dosing: mg, milligrams; mcg, micrograms; Q x M, dose administered every x months; Q x W, every x weeks; Q x D, every x days; R, romosozumab; A, alendronate; D, denosumab; T, teriparatide.

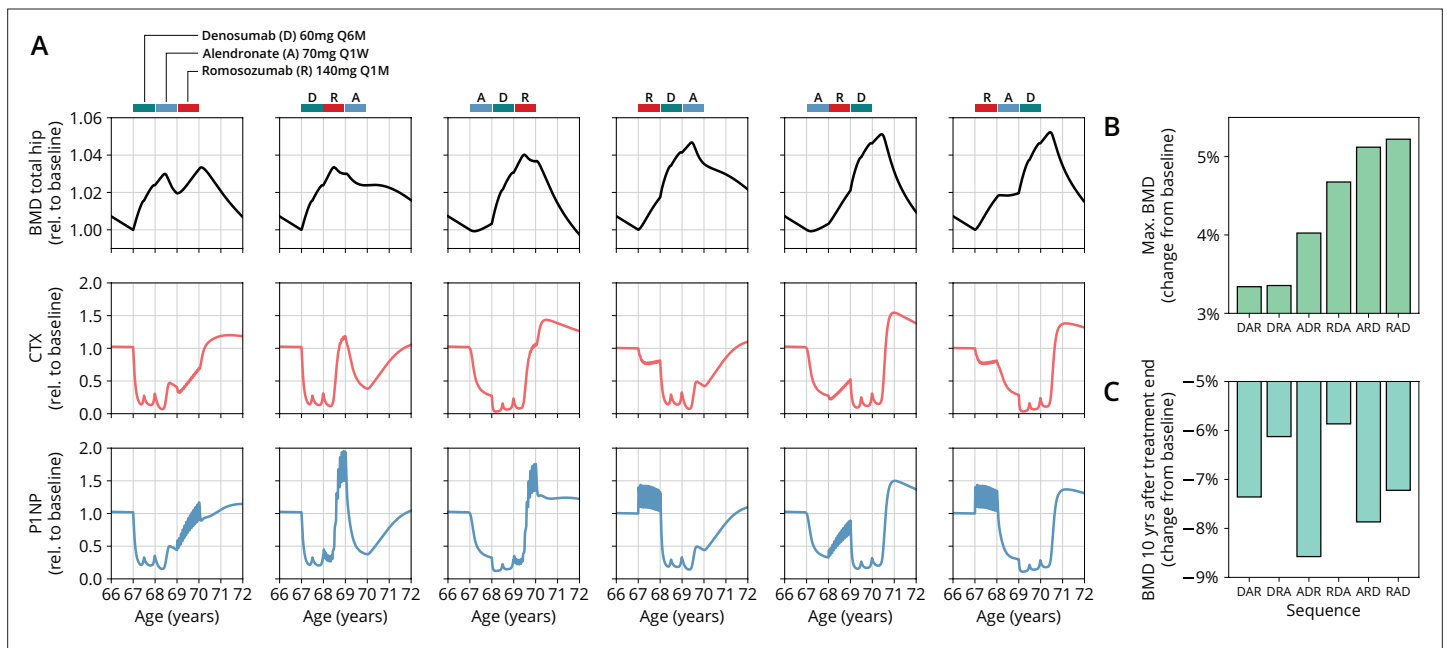
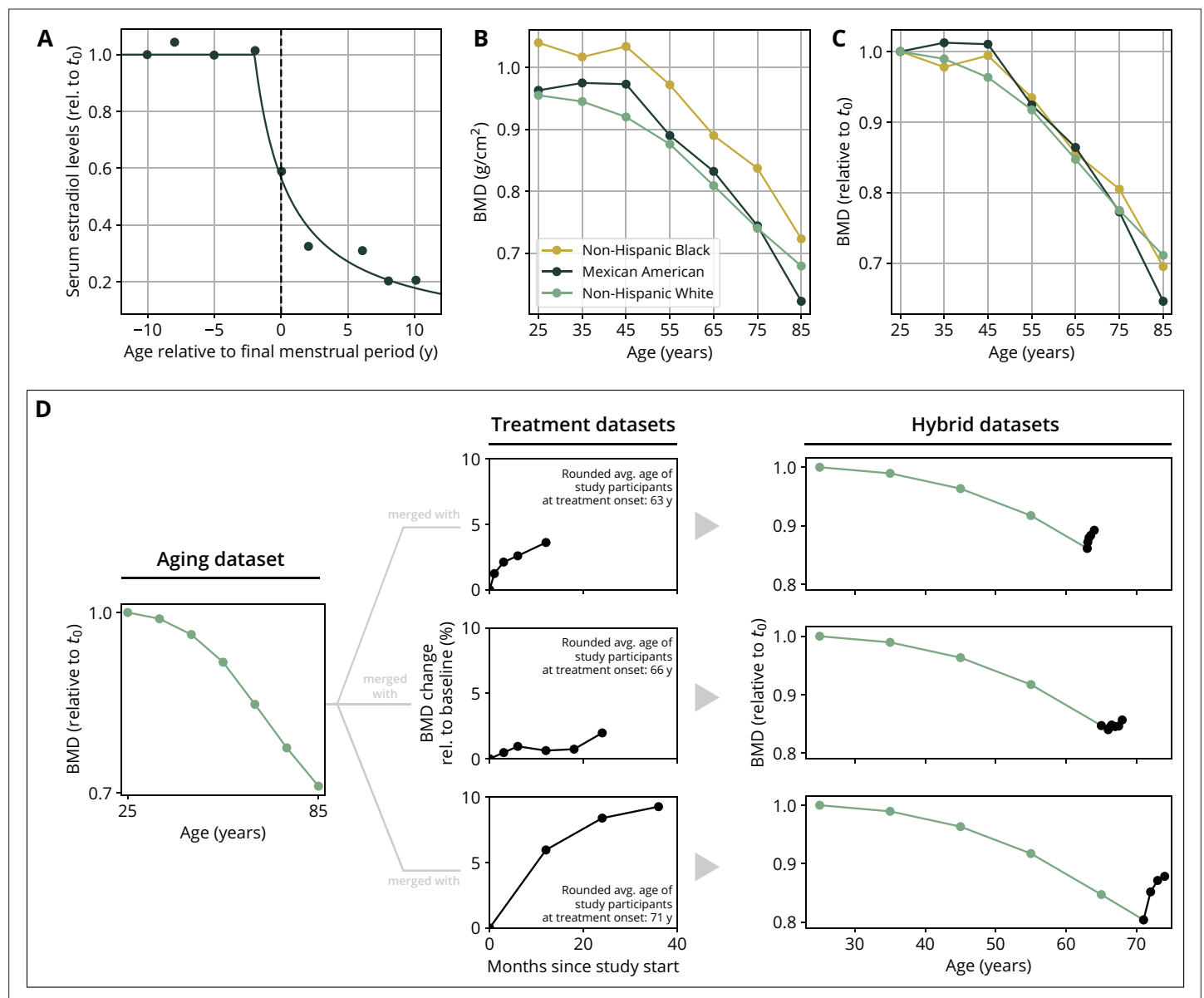
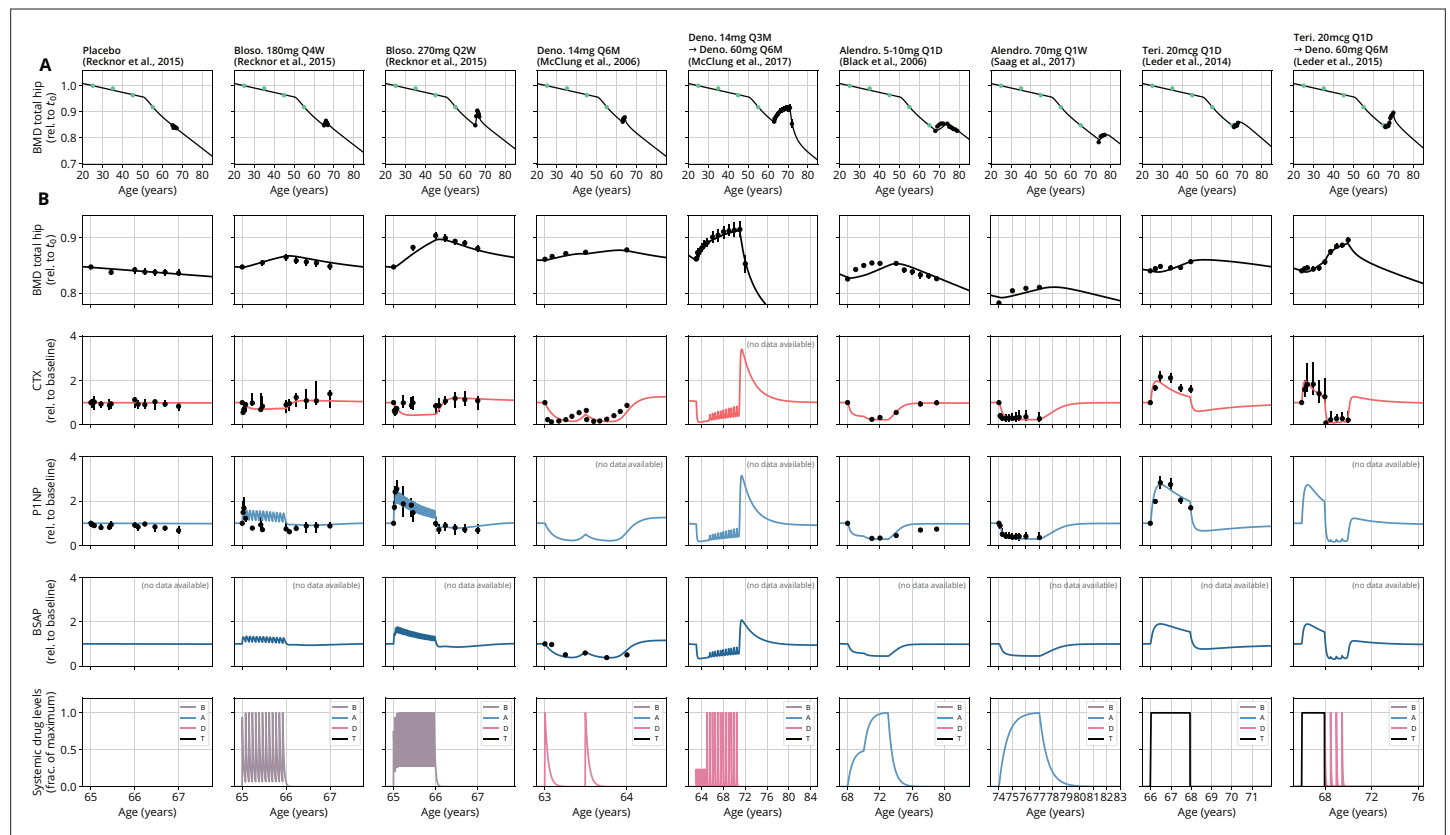


Figure 3. The model predicts differential outcomes for different sequences of the same drugs at constant total medication load. **(A)** Simulated progression of bone mineral density (BMD) and C-terminal telopeptide (CTX) and procollagen type 1 amino-terminal propeptide (P1NP) concentrations for different sequences (columns) of the three drugs denosumab (D), alendronate (A), and romosozumab (R) as indicated. Simulated treatment starts at age 67. The total amount of drug administered is identical among columns. Clinical results on the sequence ARD (column 5) were reported in **McClung et al., 2018**, see also **Figure 2**. **(B)** Maximum simulated BMD (relative to baseline at treatment start) achieved during the course of treatment for different drug sequences. **(C)** Simulated BMD 10 years after treatment end (relative to baseline at treatment start) for different drug sequences.



Appendix 1—figure 1. Parameterization of the aging behavior and creation of hybrid aging/treatment datasets for model calibration and validation. (A) Age dependence of estradiol serum levels. Clinical data (dots) modified from *Sowers et al., 2008*. The curve shows a fit of the function given by *Equation 18* to determine the parameter τ_e (*Appendix 3—table 4*). (B) Bone mineral density (BMD) age dependence for different ethnic groups as indicated. Data modified from *Looker et al., 1998*; reported age bin averages have been used to represent the center of the age bin. (C) BMD age dependence shown in panel (B), where all curves have been normalized to their earliest value ($t_0 = 25$ y). (D) Schematic of how hybrid aging/treatment datasets were generated by merging the same aging dataset with different treatment datasets; for details, see 'Methods.'



Appendix 3—figure 1. Calibration datasets comparing model predictions and clinical data from various studies. All conventions identical to **Figure 2**. Drug administrations are provided in the bottom row. See **Appendix 3—table 2** for a list of data sources and **Appendix 3—table 3** for goodness-of-fit measures. Dosing: mg, milligrams; mcg, micrograms; Q x M, dose administered every x months; Q x W, every x weeks; Q x D, every x days; B, blosozumab; A, alendronate; D, denosumab; T, teriparatide.