A Negative feedback model for a mechanism based description of longitudinal observations: application for bone turnover biomarkers.

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Introduction

In modern medicine the initial diagnosis of an abnormal metabolic condition is based on blood borne measurements often involving multiple biomarkers. The biomarkers concentrations themselves would not be sufficient for providing a mechanism based description of mode of action. Estimates of clearance rates are the minimum requirement for a mechanism based description of longitudinal observations.

Methods

A minimal negative feedback model is proposed for the description of longitudinal observations in clinical trials for treatment of osteoporosis in postmenopausal women (Fig. 1B). The data for this work was obtained from the published literature [2]. The study's subjects were women 42 to 82 years of age who all had had hysterectomy. There were four treatment groups, placebo, alendronate, conjugated estrogen (CE) and alendronate plus CE. In the extended year (third year) the treatments were switched to placebo except for alendronate plus CE which either did not change or switched to placebo.

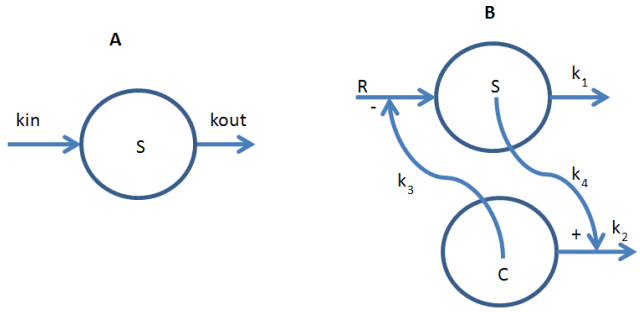

Figure 1 *(A). A single compartment biomarker disappearance model. (B) Extended biomarker clearance or indirect therapeutic indicator model with its controller C, all fluxes are positive. Note that k_4S and k_3C are control fluxes and depending on their sign can be regarded as production or disappearance rates. [1].*

The differential equations describing the above basal concentration (s) is shown in (1)

$$\frac{dc}{dt} = -k_2 c + k_4 s \qquad \frac{ds}{dt} = -k_1 s - k_3 c \qquad \textbf{(1)}$$

The two first order differential equations in (1) is transformed into a second order describing the above basal concentration of a biomarker .

$$\frac{d^2 s}{dt^2} + (k_1 + k_2)\frac{ds}{dt} + (k_1 k_2 + k_3 k_4)s = 0 \qquad \textbf{(2)}$$

The equation in (2) is made equivalent to standard second order differential equation describing a mechanical servo mechanism, with the above basal values as step input (the forcing term).

$$\frac{d^2 s}{dt^2} + 2\zeta\omega_n \frac{ds}{dt} + \omega_n^2 s = (forcing - term)\omega_n^2 \qquad \textbf{(3)}$$

With the assumption that all rate constants for the negative feedback model are equal, ζ will become 0.707 and only ω_n need to be estimated. In the model (Figure 1B) changes in k_4 controls the levels of the biomarker *s*. For linkage of biomarkers changes in *c* from baseline modulates the k_4 of other biomarkers in the causal pathway (Figure 3).

$$\Delta(BAP\ k_4) = linkage\ (\Delta\ \ BMD\ \ controller) \qquad \textbf{(4)}$$

Results

The ω_n was estimated for BMD and Bone-specific Alkaline Phosphatase (BAP) using least squares (nlm() function in R [3]). A simulation of the results are shown in Figure 2.

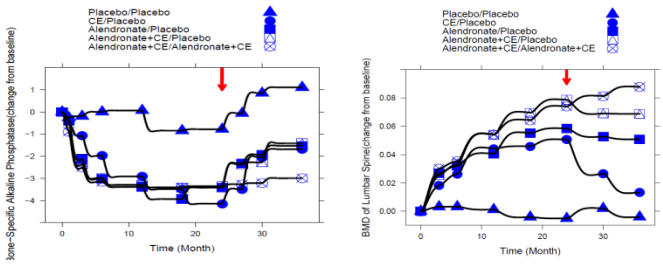

Figure 2, *Simulation of above basal BMD and BAP using equation 3.*

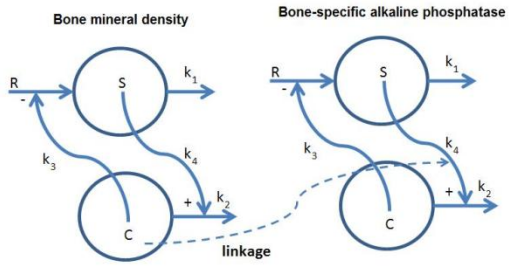

Figure 3. *Linkage of BMD and BAP models.*

Having estimated the clearance rate the production rate of the biomarker is the product of clearance rate by the corresponding biomarker values. The biomarkers concentrations could also be simulated by inducing changes in k_4 (Fig. 4A). The value of linkage parameter was determined by simulating the linked BMD and BAP models (Fig. 4B). The value of linkage parameters in Figure 4B were 70 (CE),80 (Alendronate),100 (Alendronate +CE) and 100 (Alendronate +CE).

During the extension period the value of linkage was reduced by 0% (CE), 70% (Alendronate), 60% (Alendronate +CE) and 0% (Alendronate +CE).

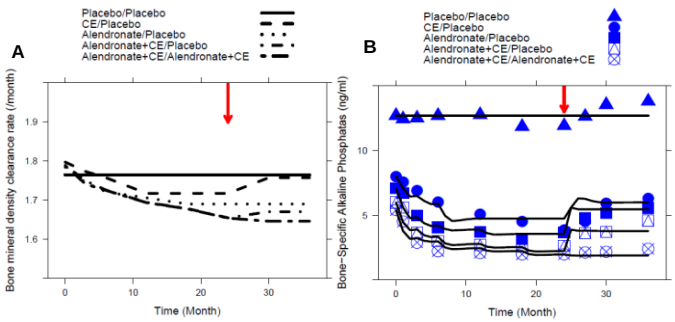

Figure 4 *(A) Simulation of BMD by reducing k_4 of BMD. (B) Simulation of model linkage by adjustment of linkage parameter equation (4).*

Conclusions

The linked negative feedback models support a mechanism based simulation of clinical trials efficacy whereby trial's outcome can be anticipated. At first a value for the clearance rate of measured biomarkers are assumed. The initial values for the clearance rates are from the literature or exploratory observations. The anticipation begins by simulating the primary measure after start of a clinical trial (in this case BMD) by inducing changes in ***k_4***. The subsequent linking (cascading) of models would set the linkage parameter value. The longitudinal estimation of the linkage parameters using a cascade of negative feedback models are more sensitive to changes in drug effect as the clearance rate of biomarkers has been taken into account.

References:

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