The Role of PEDF in Bone Mineralization

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Equations

$$\frac{dx_1}{dt} = -k_1 x_1 \quad \text{(collagen matrix [molecules/vol])} \tag{1}$$

$$\frac{dx_2}{dt} = k_1 x_1 \quad \text{(Assembled collagen matrix [molecules/vol])} \tag{2}$$

$$\frac{dI}{dt} = v_1 x_1 - r_1 x_2 I \quad \text{(Inhibitor [molecules/vol])} \tag{3}$$

$$\frac{dN}{dt} = k_1 k_2 x_1 - r_3 \frac{dy}{dt} N \quad \text{(Nucleator [molecules/vol])} \tag{4}$$

$$\frac{dy}{dt} = k_3 \left(\frac{b}{b + I^a} \right) N \quad \text{(Hydroxyapatite [molecules/vol])} \tag{5}$$

The parameters

Rate constants :

- k_1 : collagen assembly
- k_2 : number of nucleators per crosslinked collagen
- k_3 : formation of hydroxyapatite molecules (mineralization)
- v_1 : production of inhibitor by immature matrix
- r_1 : degradation of inhibitor (increased by presence of assembled matrix)
- r_2 : use of nucleators by mineralized bone

Other parameters

- a, b : Hill function parameters

Nondimensionalized Equations

Scaled by $\hat{x} = 10^6$ molecules/μm^3 and $\hat{y} = 10^9$ molecules/μm^3 :

$$\dot{x_1} = -k_1 x_1 \tag{6a}$$

$$\dot{x_2} = k_1 x_1 \tag{6b}$$

$$\dot{I} = v_1 x_1 - \hat{r}_1 x_2 I \tag{6c}$$

$$\dot{N} = k_1 x_1 - \hat{r}_2 k_3 \frac{\hat{b}}{\hat{b} + I^a} N^2 \tag{6d}$$

$$\dot{y} = \hat{k}_3 \frac{\hat{b}}{\hat{b} + I^a} N \tag{6e}$$

where $\hat{r}_1 = r_1 \hat{x}, \quad \hat{b} = \frac{b}{\hat{x}^a}, \quad \hat{r}_2 = r_2 \hat{x}, \quad \hat{k}_3 = \frac{k_3 \hat{x}}{\hat{y}}.$

Linearization

Linearize four equations since y is decoupled :

$$\frac{d}{dt}\begin{pmatrix}\delta x_1\\ \delta x_2\\ \delta I\\ \delta N\end{pmatrix} = \begin{pmatrix}-k_1 & 0 & 0 & 0\\ k_1 & 0 & 0 & 0\\ \hat{v}_2 & -\hat{r}_1 I & -\hat{r}_1 x_2 & 0\\ \hat{k}_2 & 0 & -\hat{r}_3\hat{k}_3 N^2 \hat{H}' & 0\end{pmatrix}\begin{pmatrix}\delta x_1\\ \delta x_2\\ \delta I\\ \delta N\end{pmatrix}$$

where $\hat{H}(x) := \frac{\hat{b}}{\hat{b}+I^n}$, $\hat{H}' := \frac{d\hat{H}}{dI}$

Sensitive Parameters

Parameters which affect time to mineralization

- k_1 [collagen maturation]
- r_1 [inhibitor decay]
- v_1 [inhibitor production]

Parameters which affect degree of mineralization

- k_1 [collagen maturation]
- r_1 [inhibitor decay]
- k_3 [mineralization]
- $x_1(t_0)$ [initial collagen]
- r_2 [nucleator reduction]

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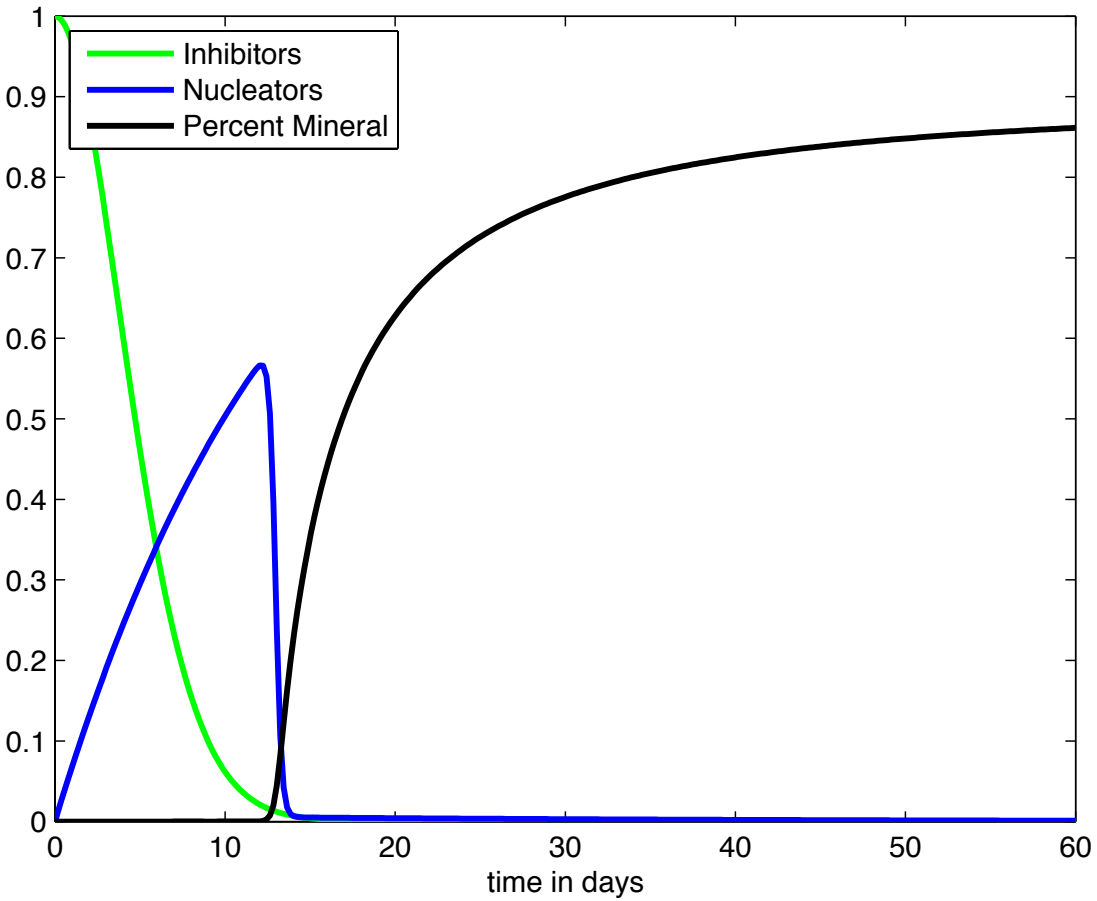
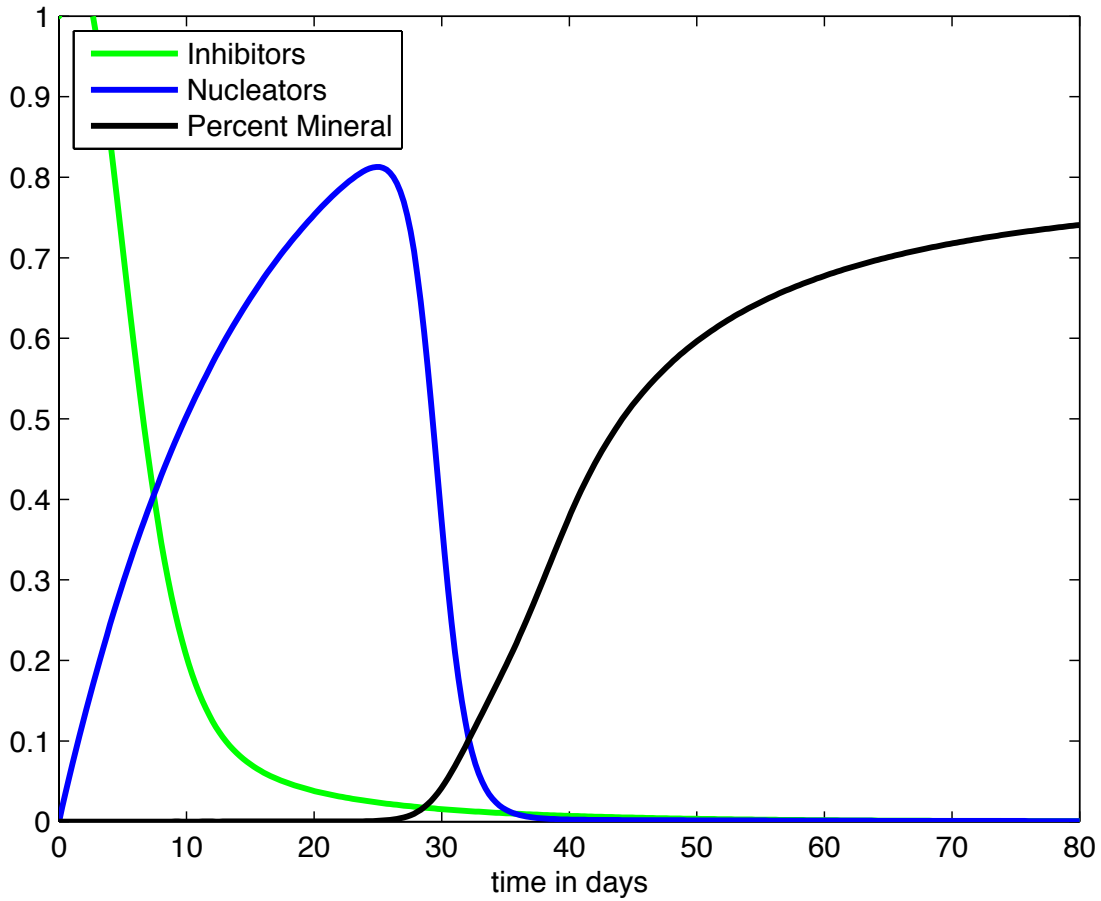
Changing inhibitor production



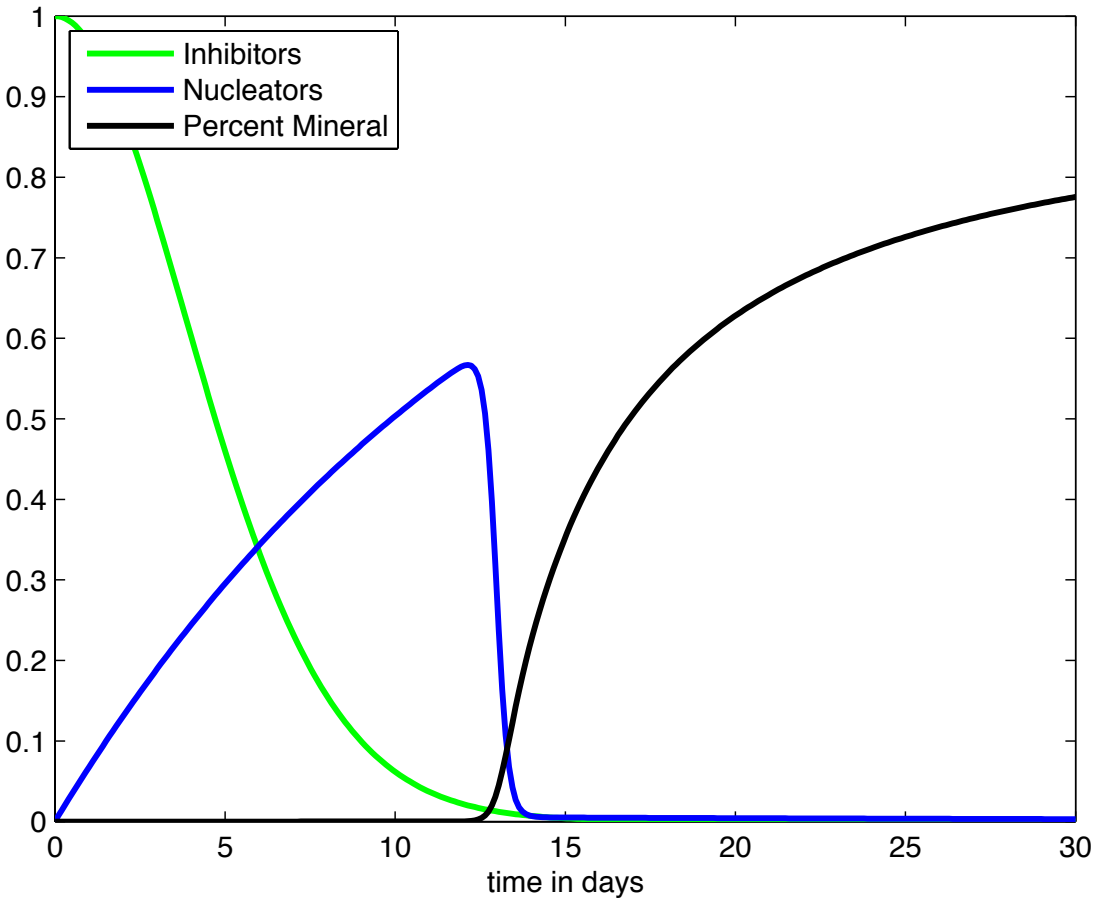
Model of healthy bone

Changing inhibitor production



Effect of v_1 increase (x100)

Changing mineralization rate



Model of healthy bone

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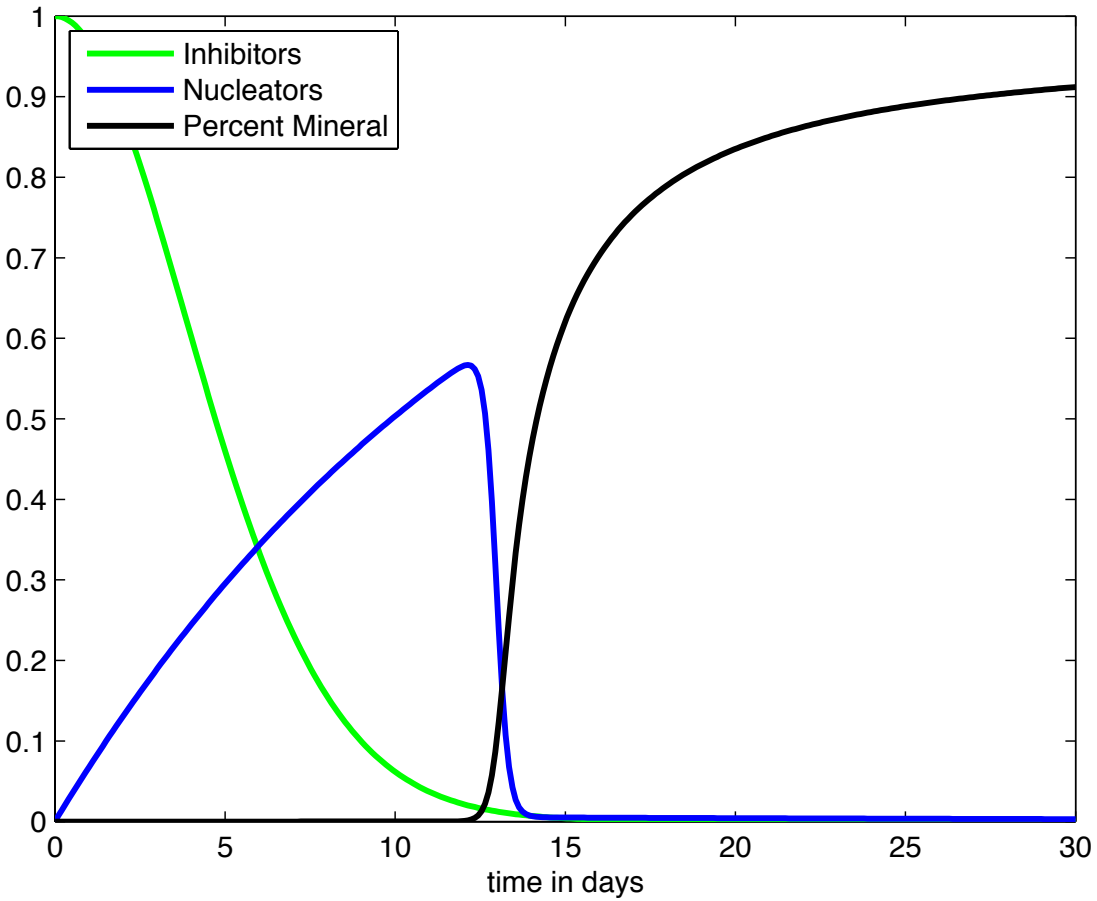
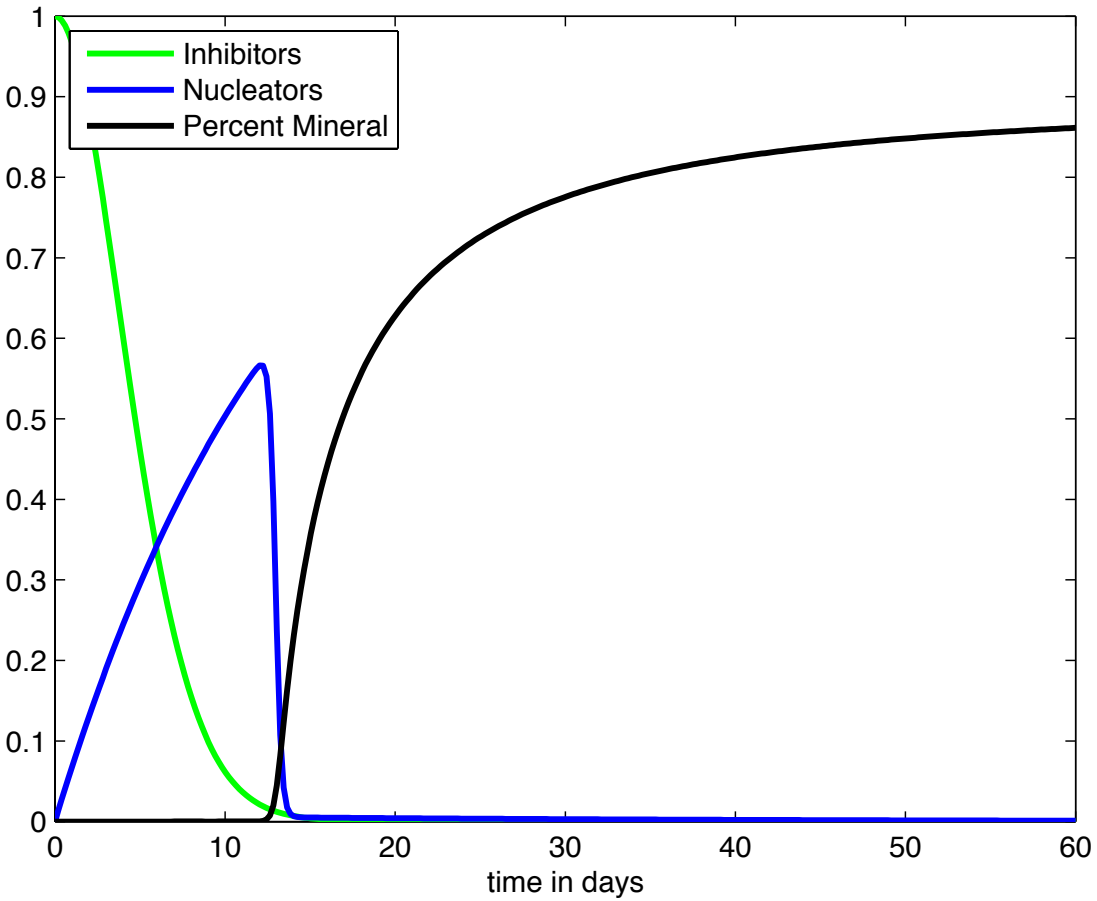


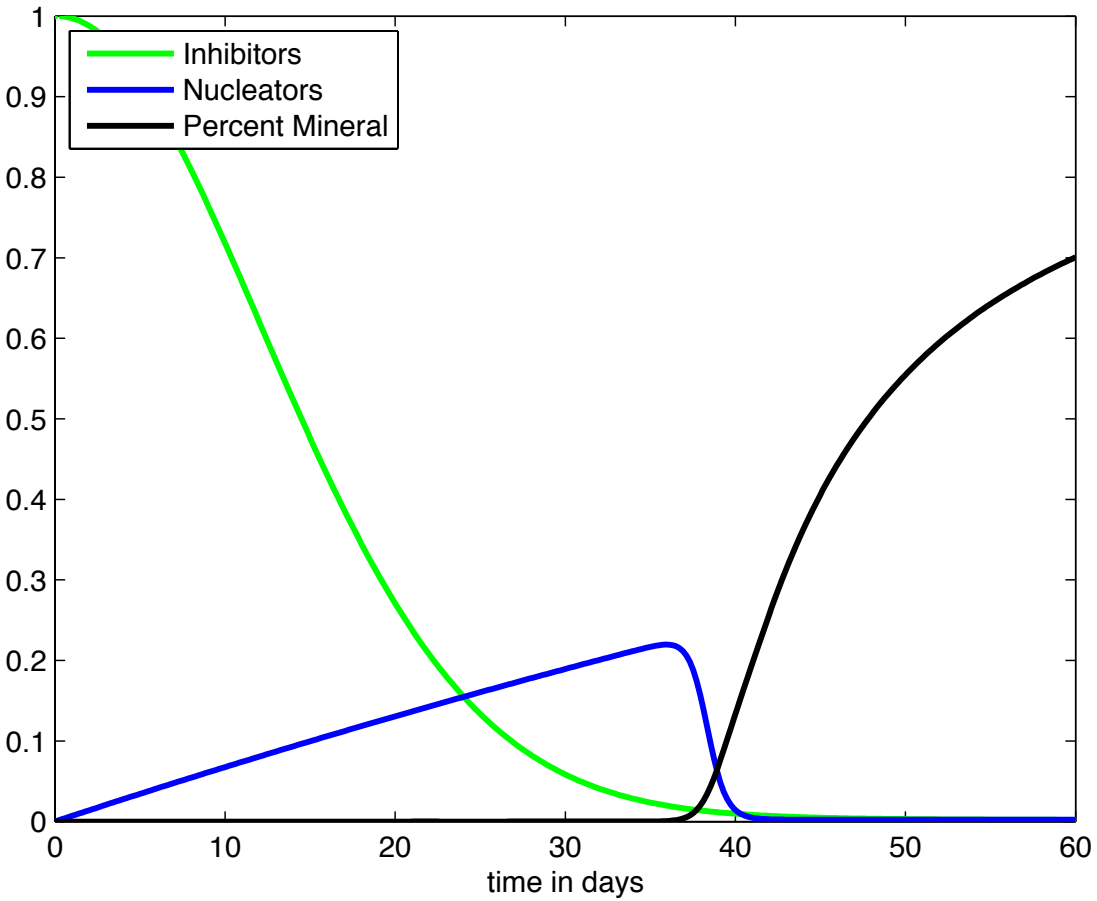
Effect of k_3 increase (3x)

Changing collagen assembly rate



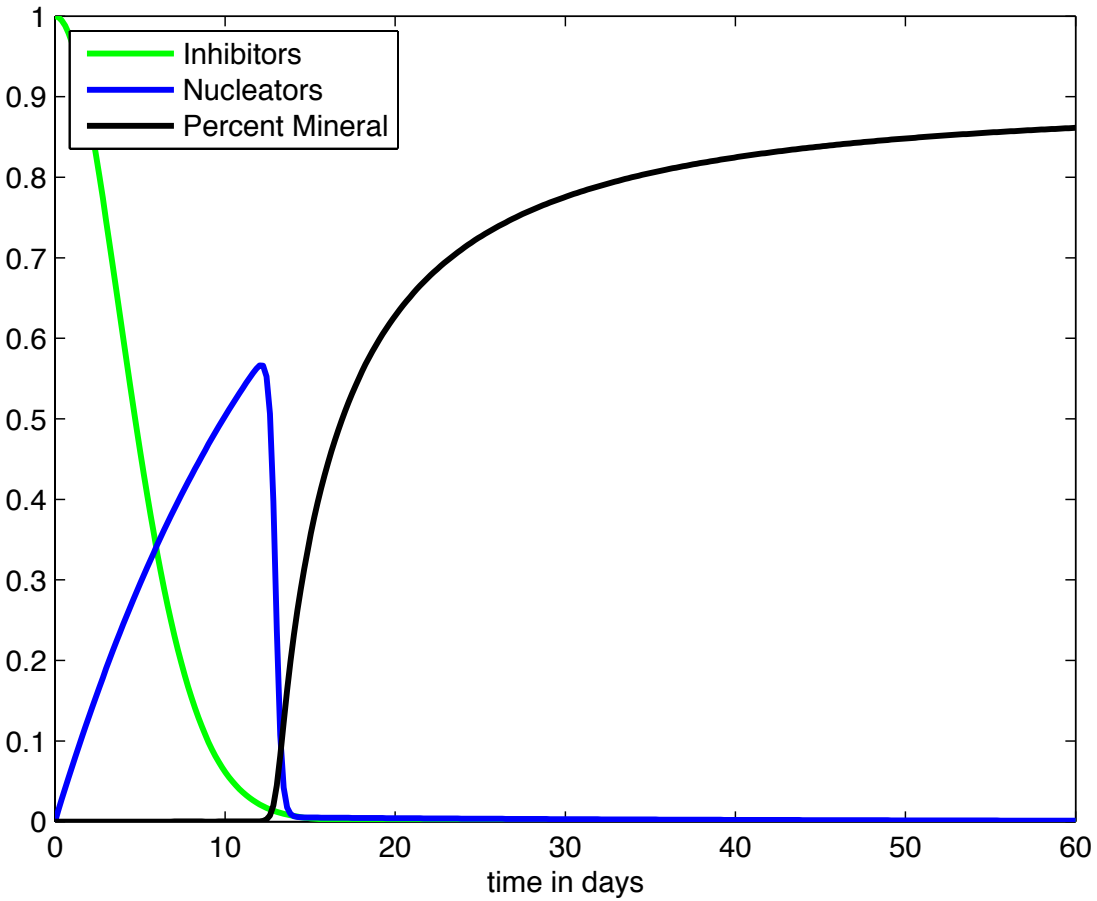
Model of healthy bone

Changing collagen assembly rate



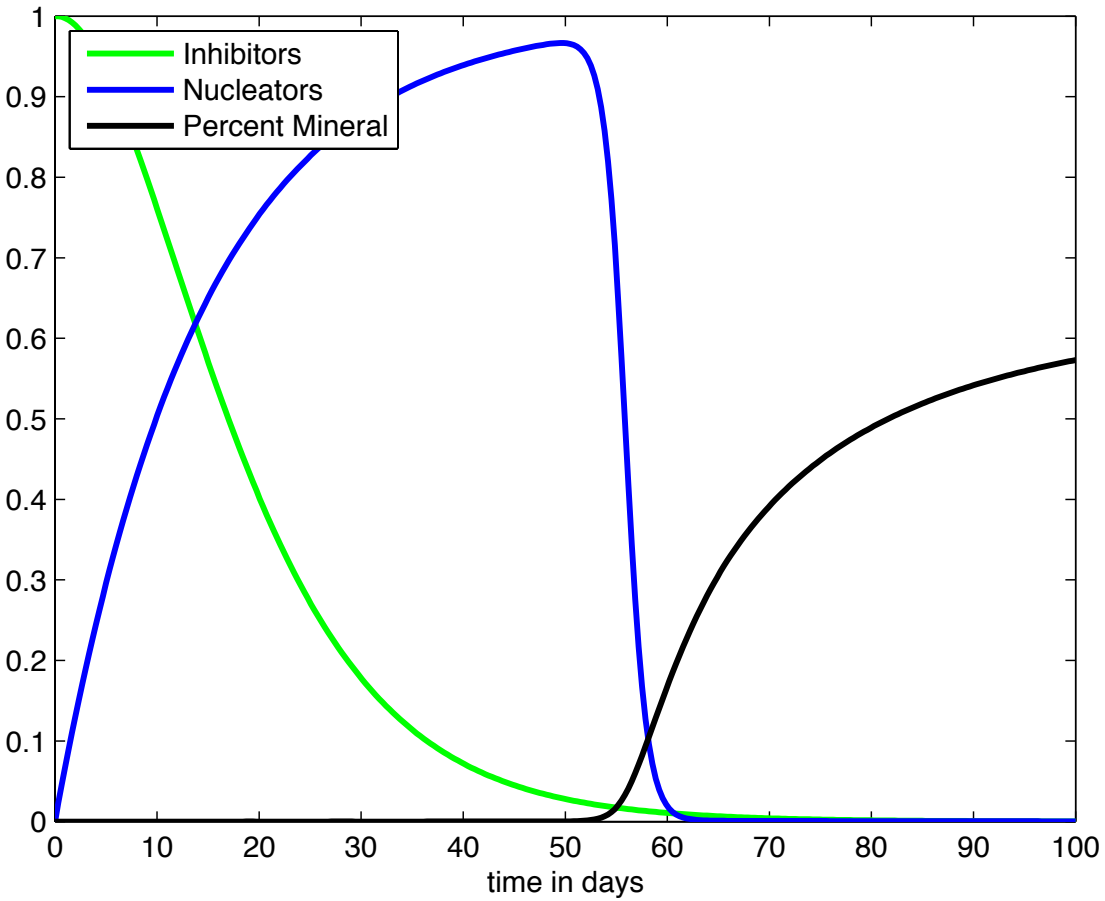
Effect of k_1 increase $(\div 10)$

Changing rate of inhibitor degradation



Model of healthy bone

Changing rate of inhibitor degradation



Effect of r_1 decrease $(\div 10)$