

# Modeling Bone Mineralization in Osteogenesis Imperfecta Type VI

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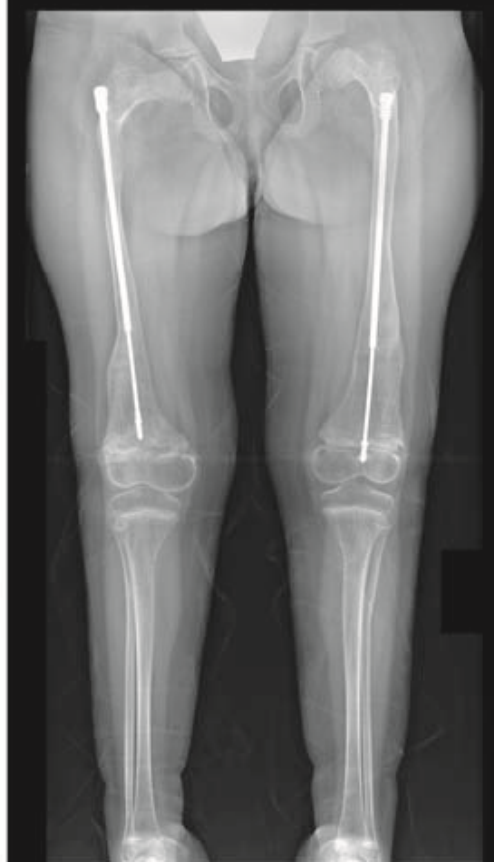
# Osteogenesis Imperfecta Type VI

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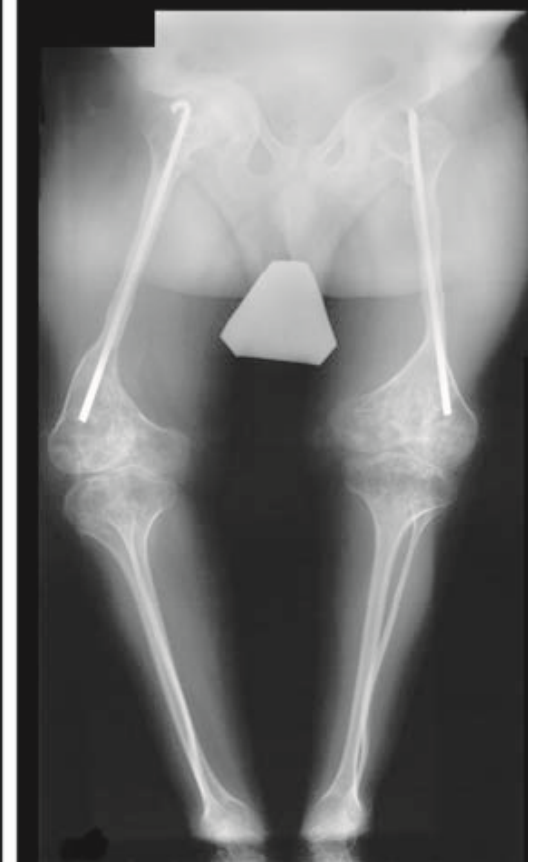
Hereditary disorder characterized by brittle bones



9 months

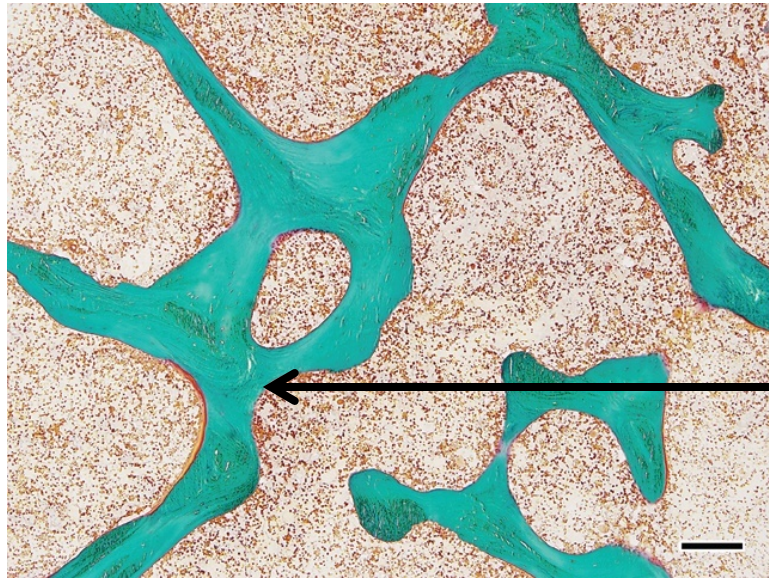


8 years



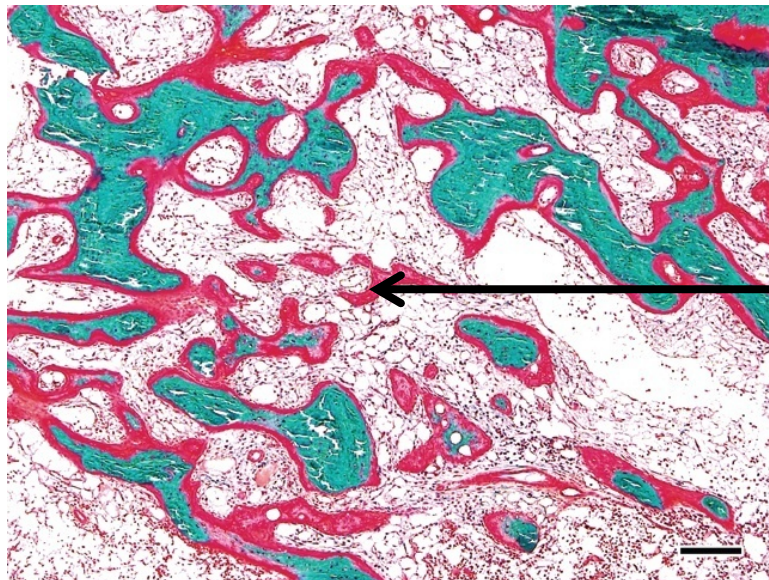
21 years

# OI Type VI – Mineralization delay



**Green** – mineralized bone  
**Red** – unmineralized bone  
(osteoid)

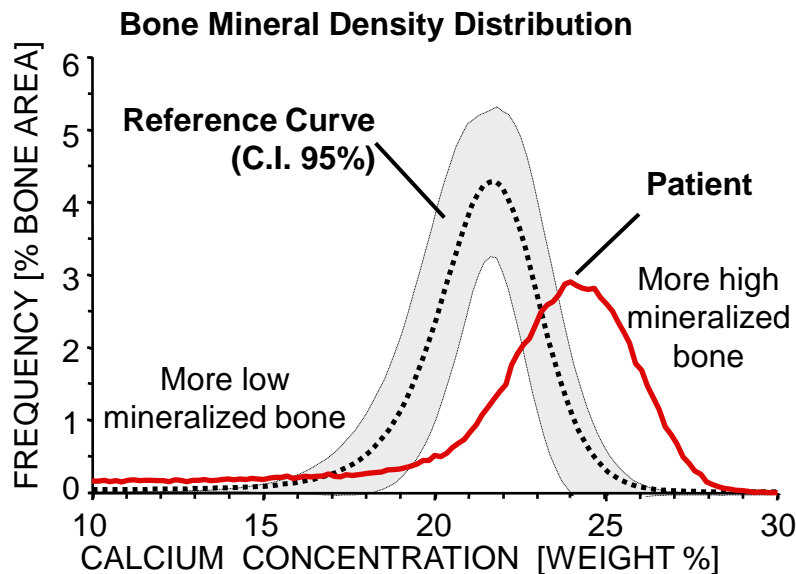
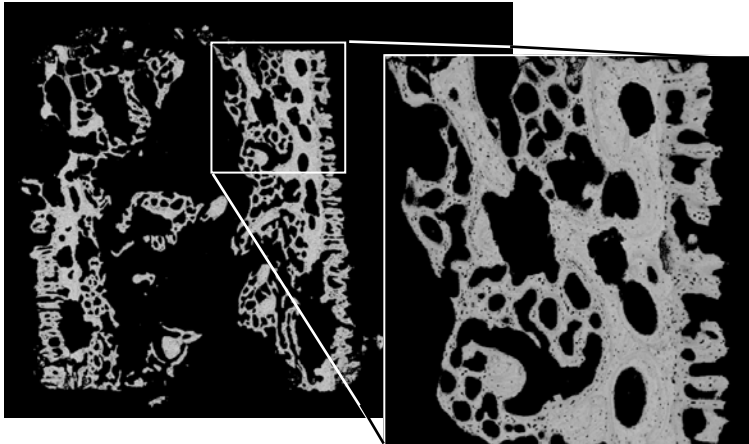
Normal histology  
**No red**



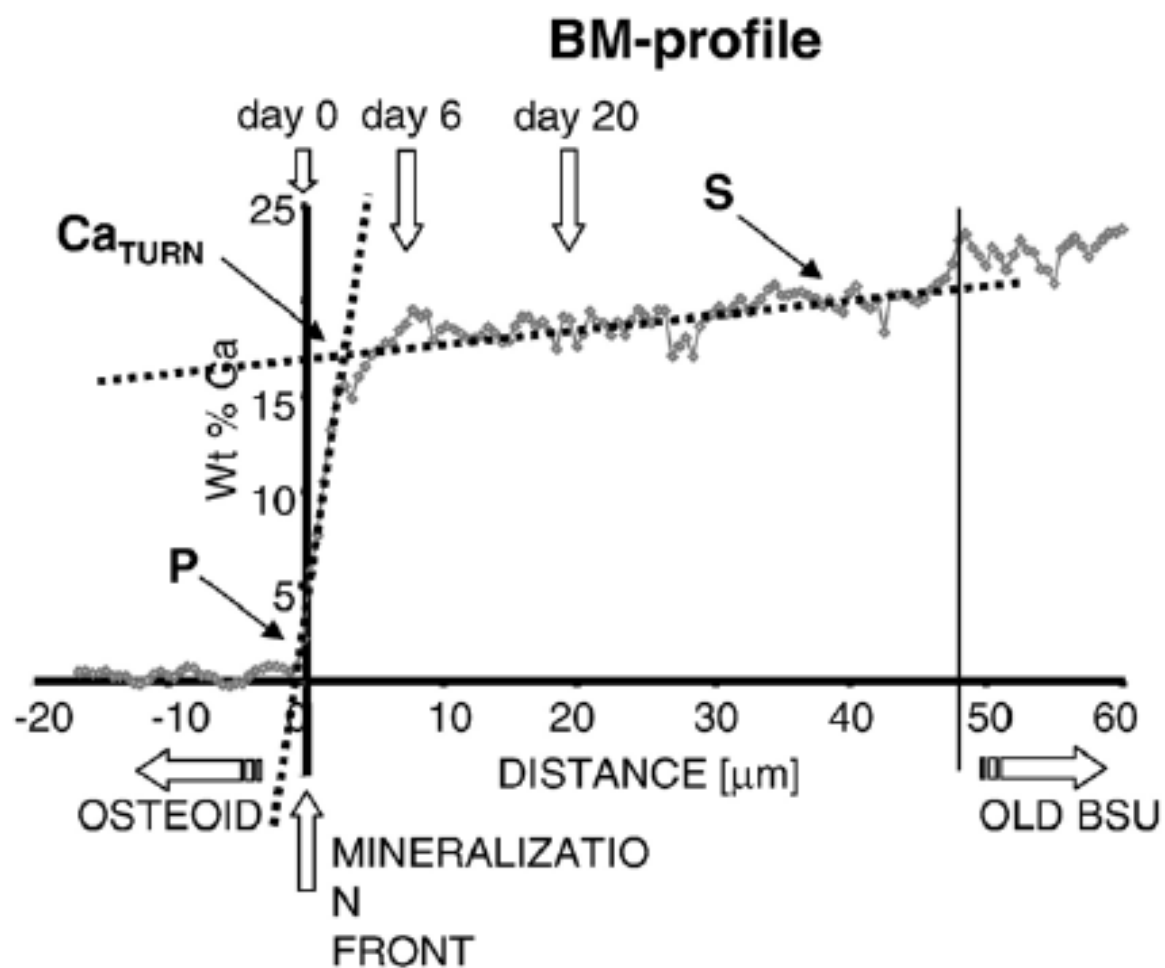
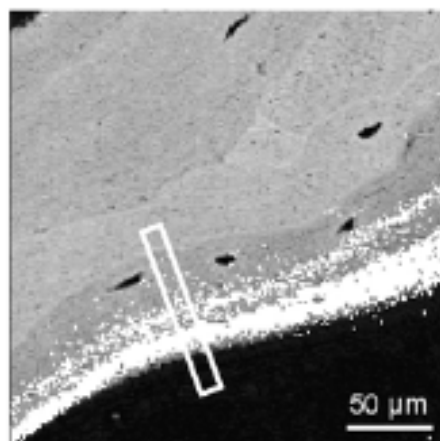
Patient histology  
**Lots of red**

Size bars: 100µm

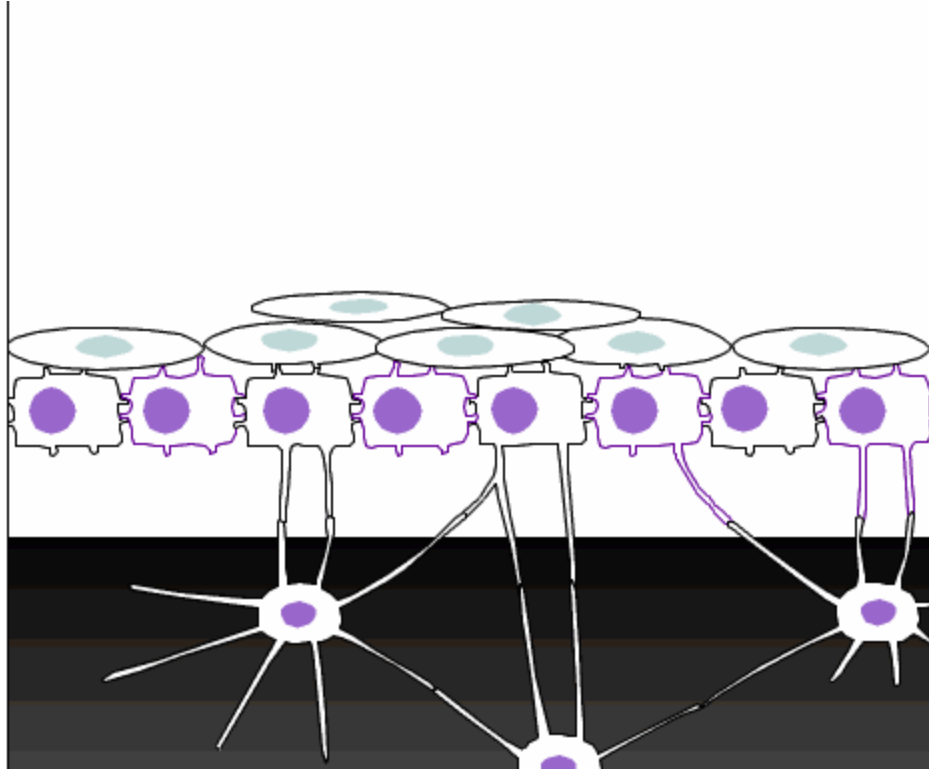
# OI Type VI – Increase in Material Bone Density



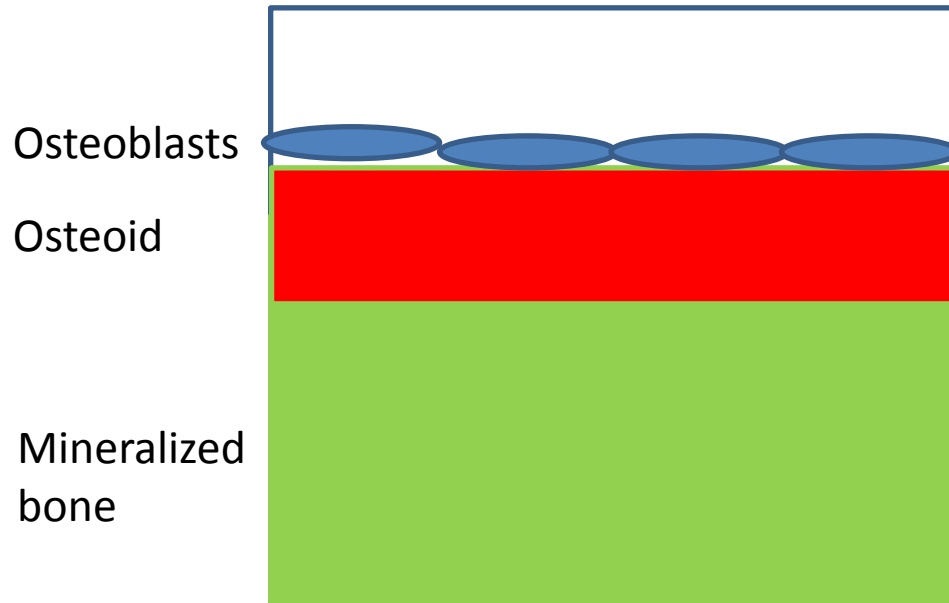
| Patient                                   | Sex | CaPeak z-score |
|---|-----|----------------|
| <i>Patients from Glorieux et al, 2002</i> |     |                |
| 1   | M   | +8.7           |
| 2   | M   | +5.7           |
| 3   | F   | +2.7           |
| 4   | M   | +10.0          |
| 5   | M   | +5.0           |
| 6   | F   | +9.0           |
| 7   | M   | +6.7           |
| 8   | M   | +9.3           |
| <i>New Patients</i>                       |     |                |
| 9   | M   | +8.7           |
|   |     |                |
| <b>Mean:</b>                              |     | <b>+7.3</b>    |



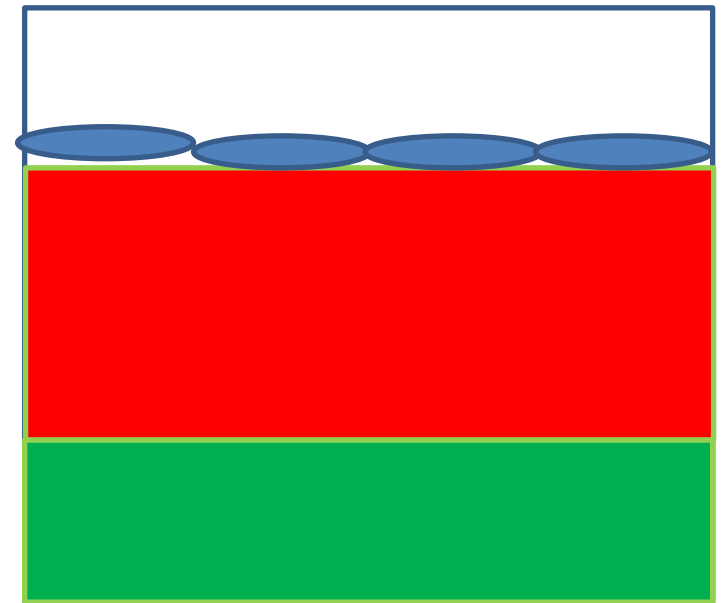
# Mineralization schematics



## Normal

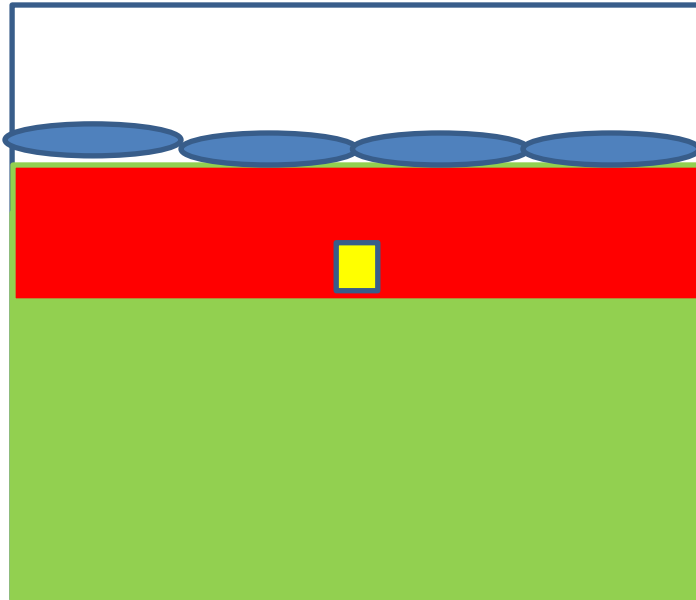


## OI type 6

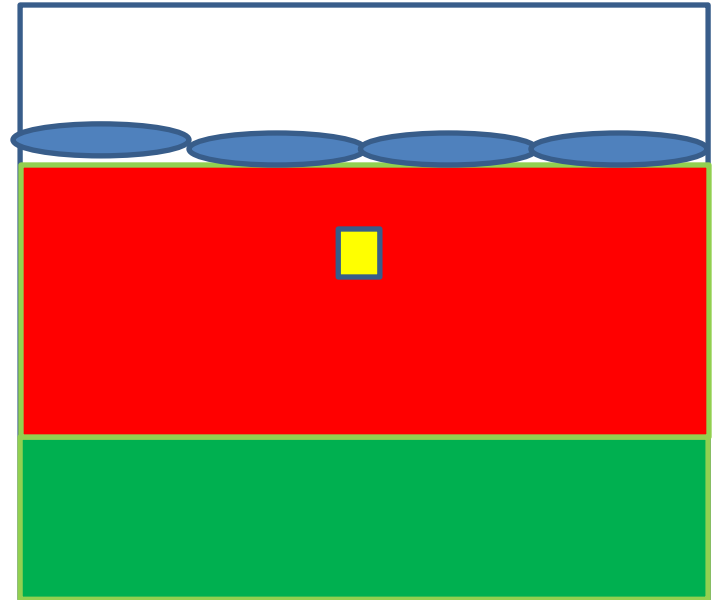


# Approach 1

Normal



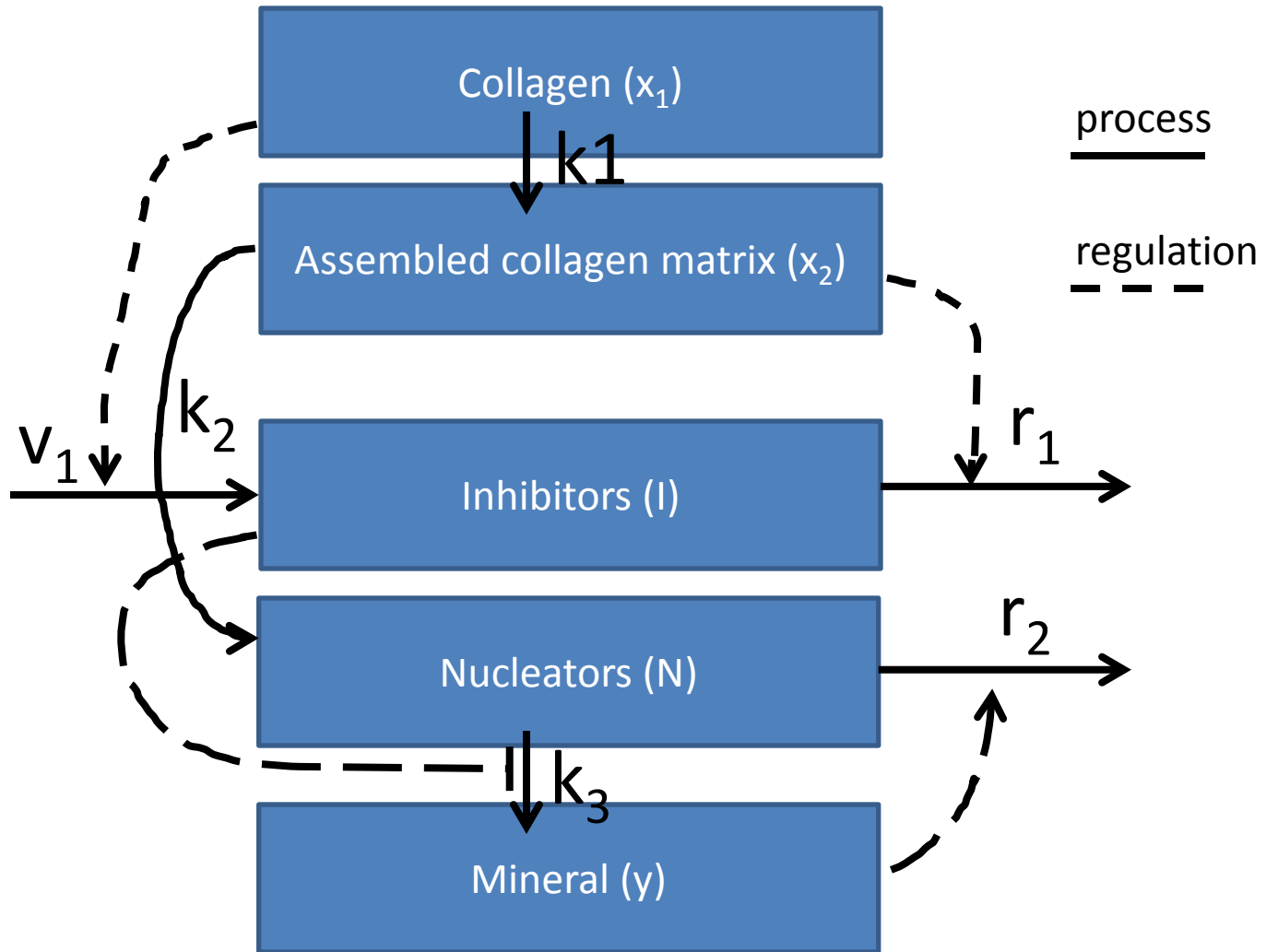
OI type 6



Selected a uniform region of collagen matrix  
Modeled changes in time within this small region



# Model schematics



# Model assumptions

- Collagen matrix is produced by osteoblasts in a naïve form that requires further maturation into a fully assembled mature collagen matrix.
- Inhibitors of the mineralization are produced in the space near the cells and their availability is proportional to the amount of naïve collagen.
- Inhibitors are degraded, their degradation is stimulated by the presence of fully assembled collagen matrix.
- Nucleators arise in the assembled collagen, each collagen molecule gives rise to one nucleator. Nucleators are removed from the system when mineralization occurs.
- The rate of mineralization is directly proportional to the number of nucleators and is inversely related to the amount of inhibitors.

# Summary and Conclusions

- We identified a number of parameters that can affect either mineralization delay or degree of mineralization.
- A single parameter ( $k_1$ ) describing the rate of matrix maturation emerged as capable of both, increasing the mineralization delay and degree of mineralization.
- This is consistent with the experimental observations of similar histological phenotypes in two different conditions associated with delayed collagen assembly: 1) mutations within the C-propeptide cleavage site on collagen type I; 2) mutations in BMP-1, that cleaves C-propeptide from collagen type I.

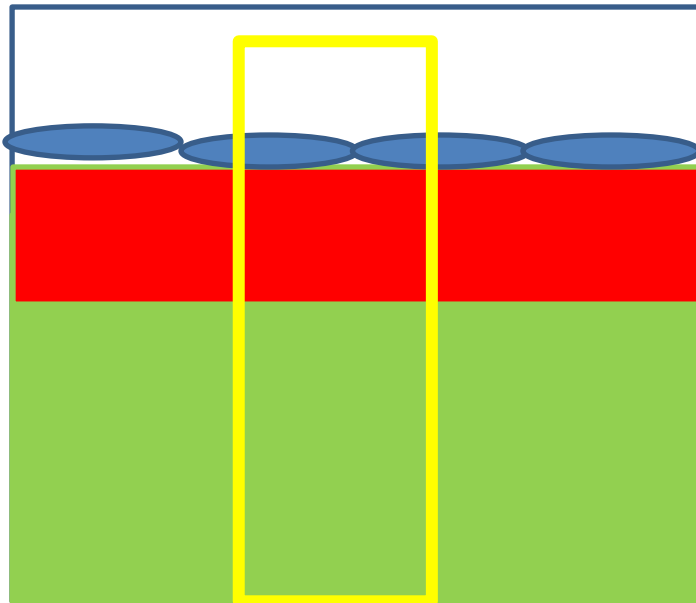
**PEDF likely regulates the C-propeptide cleavage of collagen type I**

# Future work

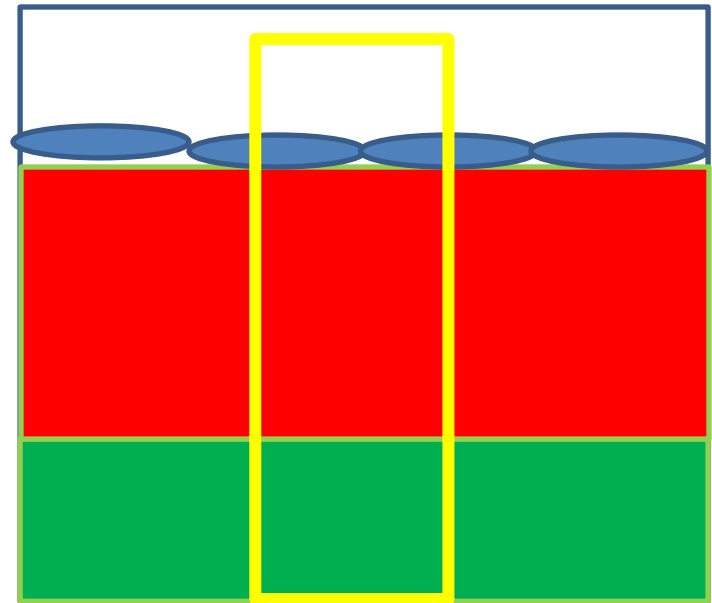
1. To define and track physical space occupied by collagen, non-collagenous proteins, water, and mineral.
2. To introduce additional source of nucleators to describe inter-fibrillar mineralization.
3. To better define parameters and validated assumptions using available or new experimental data.

## Approach 2

Normal



OI type 6



Selected a larger region ( $\sim 30 \mu\text{m}$ ) of collagen matrix, linked to the cells on top  
Modeled progression of the mineralization front