Organic templating of inorganic materials
Bone-mimetic materials

Last time:	interfacial biomineralization and biomimetic inorganic chemistry
Today:	biological strategies for inorganic templating by organic materials Biomimetic organic template materials Bone-mimetic materials
Reading:	S. Mann, 'Biomineralization: Principles and Concepts of Bioinorganic Materials Chemistry,' Ch. 6, pp. 89-102 (2001)
Supplementary Reading:	Excerpt from Allen and Thomas 'The Structure of Materials'- pp. 135-138 on Miller indices to describe crystal planes

ANNOUNCEMENTS:

Last time

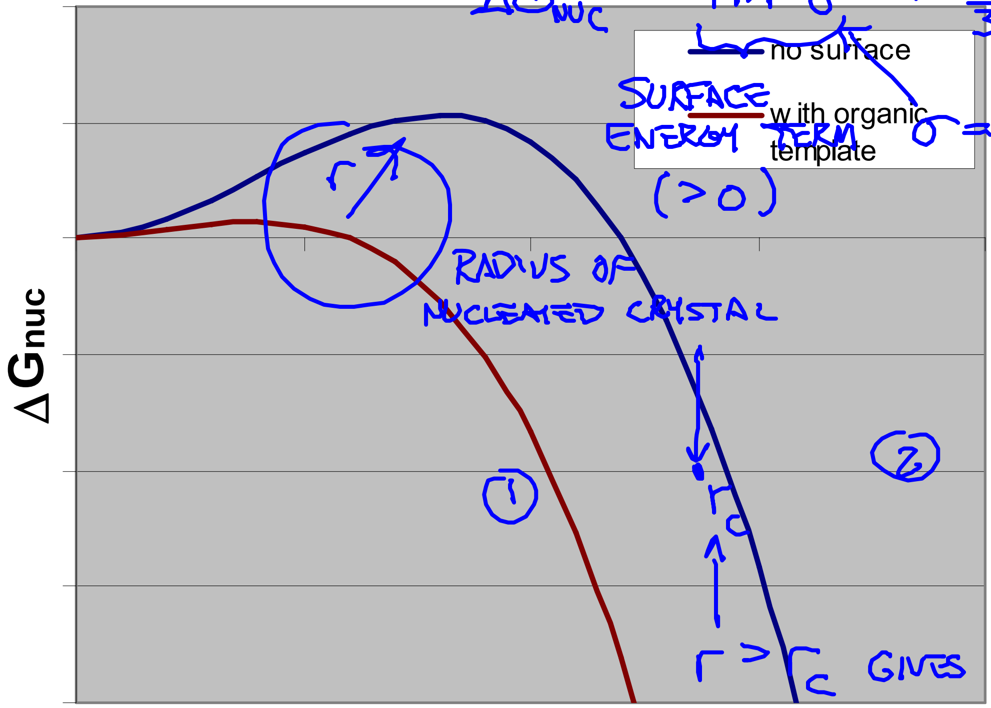
FREE ENERGY OF NUCLEATION:

$$\Delta G_{NUC} = \underbrace{4\pi r^2 \sigma}_{\text{SURFACE ENERGY TERM } (>0)} + \overbrace{\frac{4}{3}\pi r^3 \frac{\Delta \bar{G}_{FORM}}{\bar{V}}}^{\text{BULK FORMATION TERM } (<0)}$$

$\Delta \bar{G}_{FORM}$ ← FREE ENERGY CHANGE TO NUC. NEW PHASE

$\bar{V}$ ← MOLAR VOL. NEW PHASE

σ = SURFACE ENERGY $[J/m^2]$



RADIUS OF NUCLEATED CRYSTAL

$r > r_c$ GIVES SPONTANEOUS GROWTH OF NEW PHASE

PLOT SHOWS

$\sigma_1 = \frac{1}{2}\sigma_2$

- High affinity between ions and organic surface groups lowers the free energy barrier to nucleation

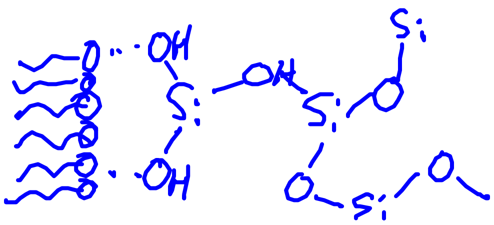
UNSATISFIED BONDS IF FORMED IN SOLUTION

- (shown left is effect of 50% reduction in surface energy)

Controlled nucleation and growth vs. preferential nucleation and growth

- Organic templates can preferentially nucleate inorganics without ordering or aligning the crystals

E.G. SILICA IN DIATOMS + RADIOLARIANS:



NO STRONG ORDER TO RECOGNITION SITES

- Templated crystal growth requires both recognition of individual molecules and a larger underlying lattice to drive ordered nucleation

- Obtaining periodicity in organic templates:

SECONDARY STRUCTURES OF POLYPEPTIDES: α-HELICES (nm SCALE)

β-SHEETS

↓

AT LARGER LENGTH SCALES, CELLS PROVIDE CONTROLLED DEPOSITION ← 2NDARY, TERTIARY, QUATERNARY STRUCTURES HELP PROVIDE 'LATTICE'

Charge distribution effects on templated nucleation

Table removed due to copyright reasons.
Please see: Table 1 in Mann, et al. 1993.

(Mann et al. 1993)

Dictating crystal polymorph via lattice matching

Calcium carbonate ($CaCO_3$) crystal structures

calcite

aragonite

Images removed due to copyright reasons.
Please see: http://ruby.coloarado.edu/~smyth/min/minerals.html

(http://ruby.coloarado.edu/~smyth/min/minerals.html)

Charge distribution effects on templated nucleation

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Please see: Figure 4.20 in Mann, S. *Biomineralization: Principles and Concepts in Bioinorganic Materials Chemistry*.
New York, NY: Oxford University Press, 2001.

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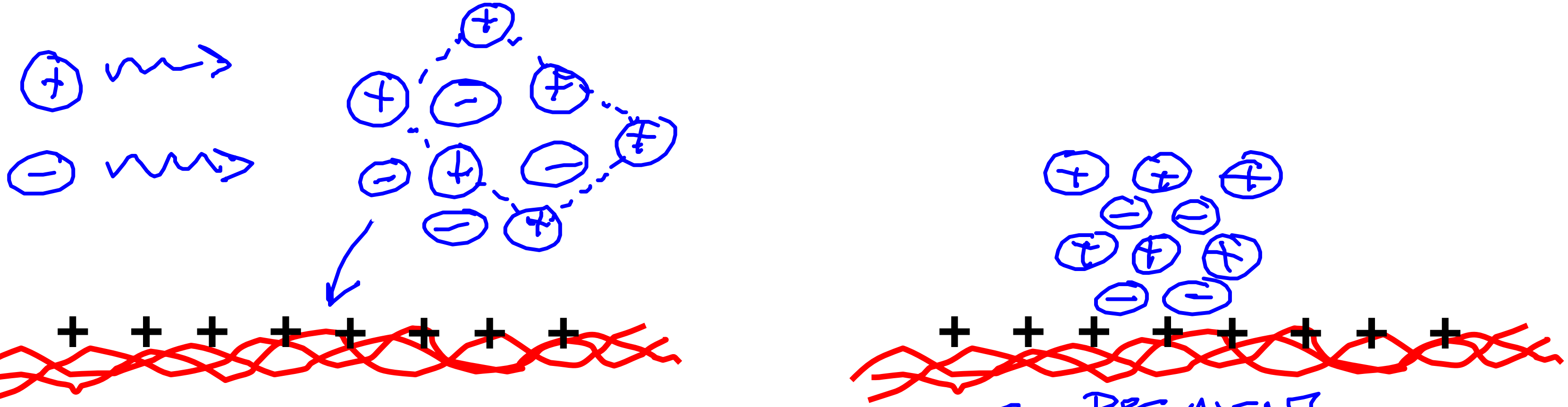
Please see: Figure 4.23 in Mann, S. *Biomineralization: Principles and Concepts in Bioinorganic Materials Chemistry*. New York, NY: Oxford University Press, 2001.

(Mann 2001)

2 mechanisms of surface-mediated nucleation:

① NUCLEUS BUILT AT SURFACE

② NUCLEUS FORMED IN SOLUTION IS SELECTED!



– NOT YET KNOWN WHICH MECHANISM IS MORE PREVALENT IN NATURE

Example of organic templating: nacre

Plate-like aragonite ($CaCO_3$) crystals form the inner layer of seashells:

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Please see: Mann, S. *Biomineralization: Principles and Concepts in Bioinorganic Materials Chemistry.*
New York, NY: Oxford University Press, 2001.

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Please see: Figure 6.38 in Mann, S. *Biomineralization: Principles and Concepts in Bioinorganic Materials Chemistry.*
New York, NY: Oxford University Press, 2001.

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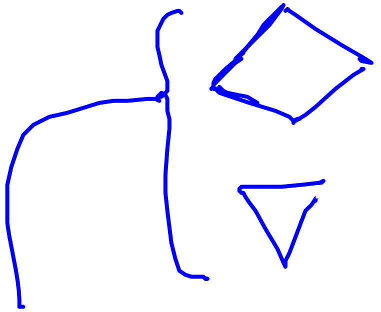
Please see: Figure 6.39 in Mann, S. *Biomineralization: Principles and Concepts in Bioinorganic Materials Chemistry*. New York, NY: Oxford University Press, 2001.

Building artificial nacre

NOT ORGANIC-TEMPLATE CRYSTAL GROWTH; RATHER, ORGANIC-TEMPLATED DEPOSITION OF PRE-FORMED INORGANIC CRYSTALS:

INORGANIC:

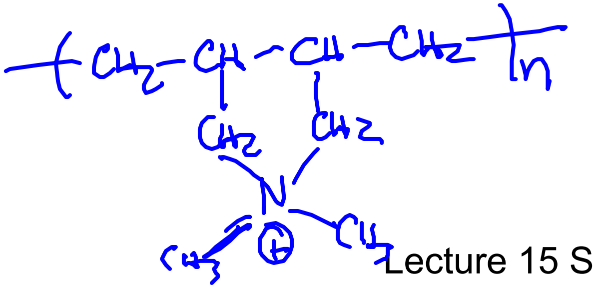
MONTMORILLONITE:


Al OCTAHEDRA w/ O

Si TETRAHEDRA w/ OXYGEN

NET (-) CHARGE OF SHEETS REQUIRES Na^+ INSERTION

ORGANIC: POLY(DIMETHYL AMMONIUM CHLORIDE)


$$-\!\!\left[CH_2-CH-CH-CH_2\right]_n$$

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Please see: Tang, Z.Y., N. A. Kotov, S. Magonov, and B. Ozturk. "Nanostructured Artificial Nacre." *Nature Materials* 2 (2003): 413-U8.

(Tang et al. 2003)

Montmorillonite structures

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Please see: http://www.wwnorton.com/college/chemistry/chemconnections/Rain/pages/minerals.html

Building artificial nacre

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Please see: Tang, Z. Y., N. A. Kotov, S. Magonov, and B. Ozturk. “Nanostructured Artificial Nacre.” *Nature Materials* 2 (2003): 413-U8.

Mechanical properties of the biomimetic composite

(Tang et al. 2003)

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Please see: Tang, Z. Y., N. A. Kotov, S. Magonov, and B. Ozturk. "Nanostructured Artificial Nacre." *Nature Materials* 2 (2003): 413-U8.

Table removed for copyright reasons.

Please see: Table 1 in Tang, Z.Y., N. A. Kotov, S. Magonov, and B. Ozturk. "Nanostructured Artificial Nacre." *Nature Materials* 2 (2003): 413-U8 .

biomimetic nucleation of crystals with synthetic patterned organic surfaces

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Please see: Aizenberg, J. "Patterned Crystallization of Calcite in Vivro and in Vitro." *Journal of Crystal Growth* 211 (2000): 143-148.

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Please see: Figure 2 in Aizenberg, J. "Patterned Crystallization of Calcite in Vivro and in Vitro." *Journal of Crystal Growth* 211 (2000): 143-148.

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Please see: Figure 4 in Aizenberg, J. "Patterned Crystallization of Calcite in Vivro and in Vitro." *Journal of Crystal Growth* 211 (2000): 143-148.

Directed calcite crystal formation

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Please see: Aizenberg, J. "Patterned Crystallization of Calcite in Vivro and in Vitro." *Journal of Crystal Growth* 211 (2000) 143-148.

Structure of bone

Functions of organic components in bone:

1. Template formation of HA crystals at physiological concentrations of ions
2. Provide strength by forming an organic-inorganic composite

Bone as an example of organic templated-inorganic growth:
Mineralization in human bone

Crystallization of HA:

- Thermodynamically most stable form of Ca phosphate

← BUT, [illegible], DCDP
BRUSHITE
SHOULD
FORM FIRST
UNDER
PHYSIOLOGICAL
CONDITIONS

- Does not spontaneously crystallize in physiologic Ca/HPO4 concentrations
    - Forms metastable solutions well above the solubility product levels

Figure removed due to copyright reasons.

Please see: Figure 6 in Busch, S., U. Schwarz, and R. Kniep. "Morphogenesis and Structure of Human Teeth in Relation to Biomimetically Grown Fluorapatite-Gelatine Composites." *Chemistry of Materials* 13 (2001): 3260-3271.

(Busch et al. 2001)

2-component model of bone organic matrix

DETAILS OF BONE STRUCTURE HAVE BEEN DIFFICULT TO RESOLVE

— CONSTANT REMODELING!

HOW TO PROVIDE A PHYSICAL TEMPLATE TO NUCLEATE HA BUT ALSO A STRUCTURAL SUPPORT?

CURRENT SIMPLEST MODEL:

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Please see: Figure 6.4 in Mann, S. *Biomineralization: Principles and Concepts in Bioinorganic Materials Chemistry*. New York, NY: Oxford University Press, 2001.

2-component model of bone organic matrix

Human bone framework macromolecules:

Staggered arrangement of tropocollagen (triple helices) maximizes interfilament cross-links:

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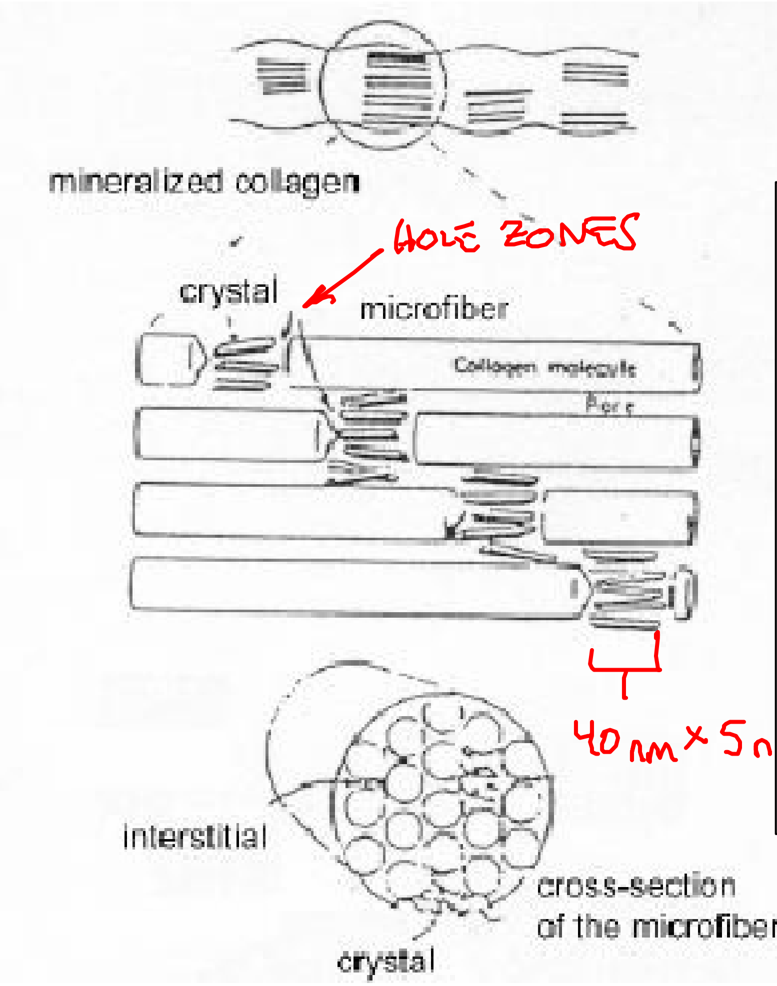
Please see: Figure 6.11 in Mann, S. *Biomineralization: Principles and Concepts in Bioinorganic Materials Chemistry*. New York, NY: Oxford University Press, 2001.

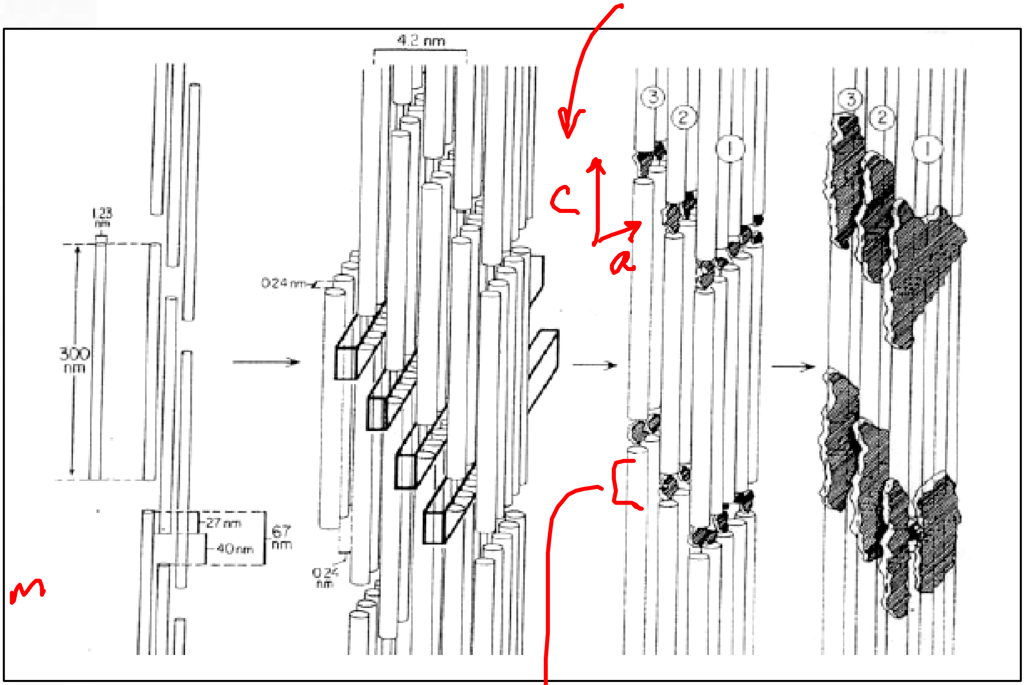
Mineralization in human bone



HOLE ZONES

40 nm × 5 nm

CRYSTAL AXES



CRYSTALS LIE w/ FLAT FACE ⊥ TO [1$\bar{1}$0] AXIS → SELECTED CRYSTAL ORIENTATION

Second role of the organic component in bone: strengthening the inorganic matrix

	HA + protein	HA alone
Relative Tensile strength:	1	$\boxed{\sim 0.03}$
Relative Modulus:	1	~1

(MANN p. 90)

Proteins which regulate growth of hydroxyapatite *in* VIVO

PROTEINS AT HOLE ZONES MAY PLAY COMPLEX ROLES

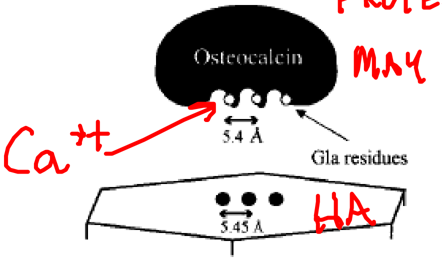
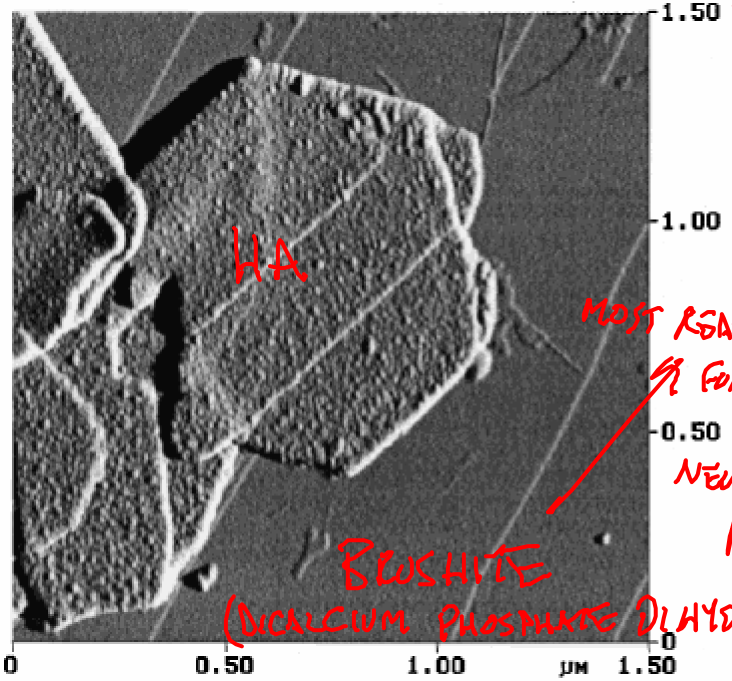
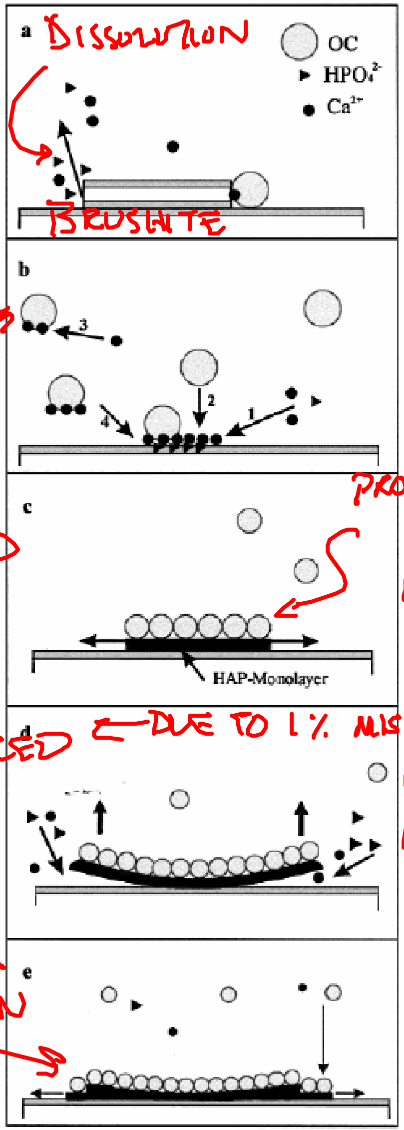


Figure 1. Schematic representation of the osteocalcin–HAP interaction. Ca^{2+} ions are represented as black dots. The corresponding distances between Gla residues of osteocalcin and Ca^{2+} sites of the HAP (0001) planes, respectively, are indicated. (Redrawn from ref. 16.)



MOST READILY FORMED AT NEUTRAL pH

Figure 5. SFM image of precipitated hexagonal, apatite-like crystals on the DCPD (010) face after 1 h of incubation with osteocalcin-containing buffer. Only the apatite-like crystals are covered with osteocalcin molecules (amplitude image).



OC BINDS Ca++

NUCLEATION OF HA W/ORIENTED GROWTH

PROTEIN BINDING LIMITS VERTICAL GROWTH

STRESS-INDUCED DELAMINATION ← DUE TO 1% MISMATCH IN PROTEIN POCKETS VS HA XTAL STRUCTURE

NEW HA NUCLEATION AT GAPS

Figure 9. Four-step model for the dissolution–reprecipitation mechanism of DCPD to HAP under the influence of osteocalcin. The main steps are dissolution of DCPD (a), osteocalcin-activated nucleation of HAP on the DCPD (010) face (b), lateral growth of HAP crystals by blocking the (0001) HAP face by osteocalcin (c), stress-induced delamination along the water–HAP interface, and further HAP formation in the developed thin gaps at the water apatite interface, resulting in a characteristic growth pattern (d, e).

Structural hierarchy in bone

‘plywood’ arrangement of mineralized collagen sheets

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Please see: Figure 8.1 in Mann, S. *Biomineralization: Principles and Concepts in Bioinorganic Materials Chemistry*. New York, NY: Oxford University Press, 2001.

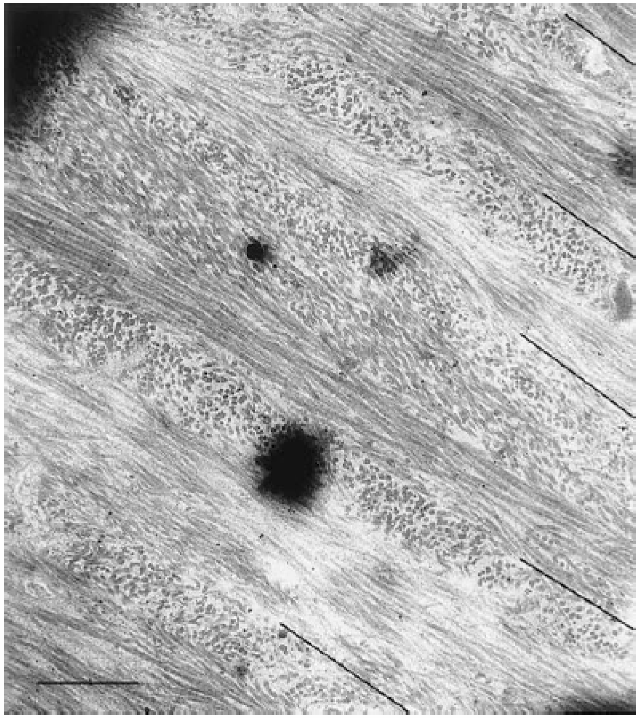

FIG. 2. A TEM micrograph of a vitrified section of a demineralized 2-year-old rat tibia midshaft cut transverse to the long axis of the bone. The section is not stained. The black areas are due to crystalline ice on the surface of the section. The sloping lines demarcate the boundaries between successive lamellar units, which are arbitrarily located adjacent to the sublayer with collagen fibrils in the plane of the section. The differing lengths of the sectioned fibrils reflect the angles at which they are aligned relative to the section surface. The sectioning itself probably introduces some disorder. Note too that the boundaries between lamellar units are not straight, but undulate. Scale bar, 1 μm.

Assembly of the superstructure

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Please see: Figure 8.2 in Mann, S. *Biomineralization: Principles and Concepts in Bioinorganic Materials Chemistry*. New York, NY: Oxford University Press, 2001.

Mimicking bone structure/organic-templated assembly

Issues in bone tissue engineering relevant to biomimetic materials synthesis

Solid metal implants used for bone replacement (e.g., Ti hip implants):

- Do no match mechanical props of natural bone (much stiffer than bone)
  - Drives stress shielding and subsequent bone resorption
- Do not integrate with surrounding tissue
  - Failure of implant-tissue adhesion can lead to loosening of implants

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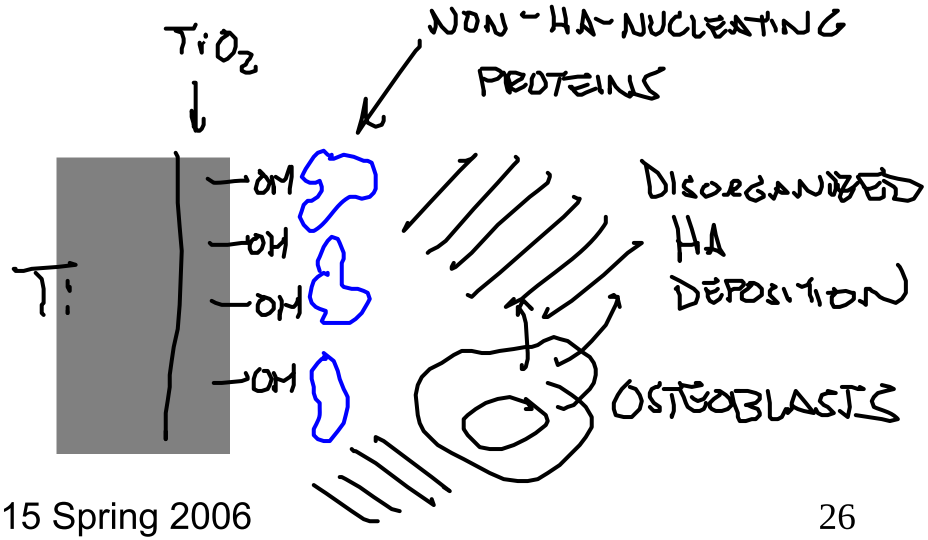
Please see: Trident® System at
http://www.stryker.com/jointreplacements/sites/trident/patient/pat_tech.php

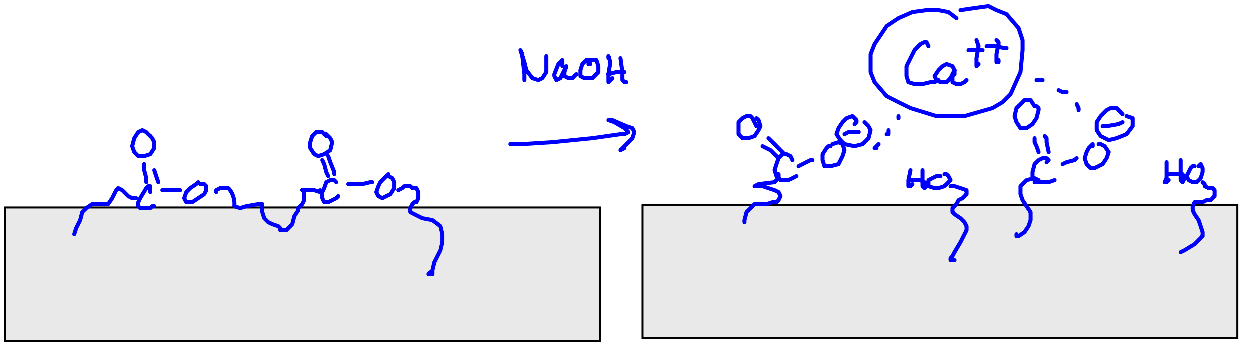
http://www.stryker.com/jointreplacements/sites/trident/patient/pat_tech.php



Strategies to augment bone-biomaterial integration

Introduction of HA-nucleating charged groups on degradable polymer surfaces:

PLGA:



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Please see: Murphy, W. L., and D. J. Mooney. "Bioinspired Growth of Crystalline Carbonate Apatite on Biodegradable Ploymer Substrata." *Journal of the Americal Chemical Society* 124 (2002): 1910-1917.

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(Murphy and Mooney, 2001)

Strategies to augment bone-biomaterial integration

Introduction of HA-nucleating charged groups on degradable polymer surfaces:

HA growth on hydrolyzed PLGA films
after 7 days: ← RELATIVELY SLOW MINERAL GROWTH

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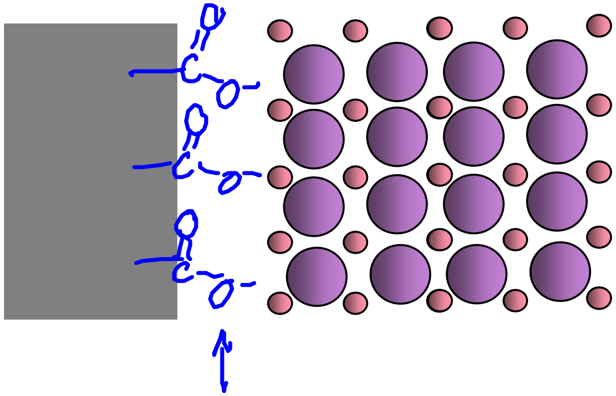
Please see: Murphy, W. L., and D. J. Mooney. "Bioinspired Growth of Crystalline Carbonate Apatite on Biodegradable Ploymer Substrata." *Journal of the Americal Chemical Society* 124 (2001): 1910-1917.



LIMITED ADHESION STRENGTH AT THIS FLAT INTERFACE.

(Murphy and Mooney, 2001)

DELAMINATION OF INORGANIC CRYSTALS IS A SERIOUS ISSUE FOR SURFACE-MODIFIED IMPLANTS

Strategies to augment bone-biomaterial integration

Introduction of HA-nucleating charged groups on hydrogels:

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Please see: Song, J., E. Saiz, and C. R. Bertozzi. "A New Approach to Mineralization of Biocompatible Hydrogel Scaffolds: An Efficient Process Toward 3-Dimensional-Bonelike Composites." *Journal of the American Chemical Society* 125 (2003): 1236-1243.

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Strategies to augment bone-biomaterial integration

Introduction of HA-nucleating charged groups on hydrogels:

Amorphous calcium phosphate nucleated by hydrogel surface

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Journal of the American Chemical Society 125 (2003): 1236-1243.

(Song et al. 2003)

Modifying the growing structure of HA crystals

BONE CRYSTAL GROWTH CAN BE ALTERED BY PROTEIN BINDING TO CRYSTAL FACES:

Images removed due to copyright reasons.

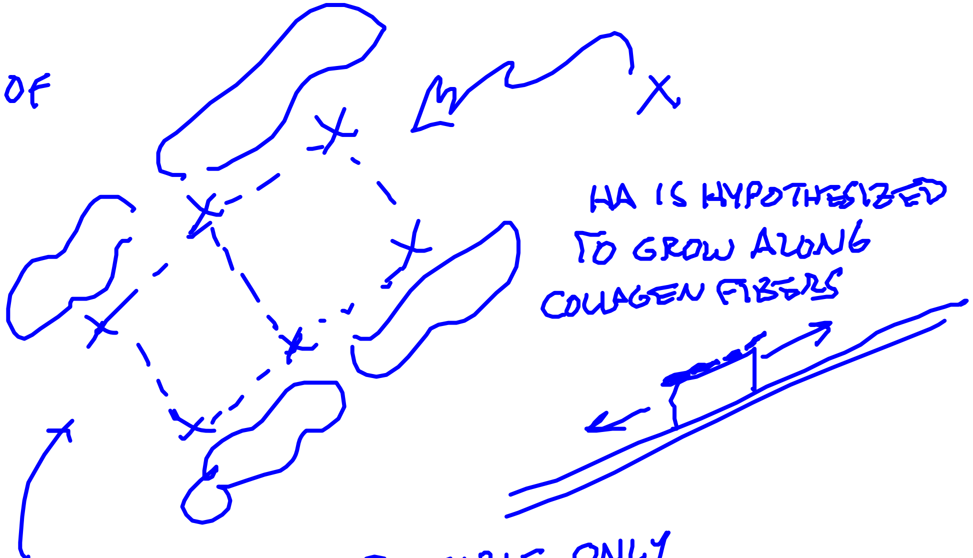
Please see: Liu, Y., E. B. Hunziker, N. Randall, K. de Groot, and P. Layrolle. "Proteins Incorporated Into Tbiomimetically Prepared Calcium Phosphate Coatings Modulate their Mechanical Strength and Dissolution Rate." *Biomaterials* 24 (2003): 65-70.

BOVINE SERUM ALBUMIN

0% BSA

MODIFICATION OF HA CRYSTAL GROWTH

0.1 ng/mL BSA



HA IS HYPOTHESIZED TO GROW ALONG COLLAGEN FIBERS

ION ADDITION POSSIBLE ONLY AT OPEN ENDS

10 ng/mL BSA

(Liu et al. 2003)

Self-assembling bone-mimetic materials

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Please see: Figures 1A, 1B, 1C in Hartgerink J. D., E. Beniash, and S. I. Stupp. "Peptide-Amphiphile Nanofibers: A Versatile Scaffold for the Preparation of Self-Assembling Materials." *Proceedings of the National Academies of Science USA* 99 (2002): 5133-8.

(Hartgerink et al. 2001)

Mineralization of synthetic template fibers

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Please see: Figures 4 A, B, C, D in Hartgerink, J. D., E. Beniash, and S. I. Stupp. "Peptide-Amphiphile Nanofibers: A Versatile Scaffold for the Preparation of Self-Assembling Materials." *Proceedings of the National Academies of Science U.S.A.* 99 (2002): 5133-8.

Further Reading

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2. Weiner, S., Traub, W. & Wagner, H. D. Lamellar bone: structure-function relations. *J Struct Biol* **126**, 241-55 (1999).
3. Busch, S., Schwarz, U. & Kniep, R. Morphogenesis and structure of human teeth in relation to biomimetically grown fluorapatite-gelatine composites. *Chemistry of Materials* **13**, 3260-3271 (2001).
4. Fincham, A. G., Moradian-Oldak, J. & Simmer, J. P. The structural biology of the developing dental enamel matrix. *Journal of Structural Biology* **126**, 270-299 (1999).
5. Moradian-Oldak, J., Paine, M. L., Lei, Y. P., Fincham, A. G. & Snead, M. L. Self-assembly properties of recombinant engineered amelogenin proteins analyzed by dynamic light scattering and atomic force microscopy. *Journal of Structural Biology* **131**, 27-37 (2000).
6. Liu, Y., Hunziker, E. B., Randall, N. X., de Groot, K. & Layrolle, P. Proteins incorporated into biomimetically prepared calcium phosphate coatings modulate their mechanical strength and dissolution rate. *Biomaterials* **24**, 65-70 (2003).
7. Habibovic, P., Barrere, F., van Blitterswijk, C. A., de Groot, K. & Layrolle, P. Biomimetic hydroxyapatite coating on metal implants. *Journal of the American Ceramic Society* **85**, 517-522 (2002).
8. Flade, K., Lau, C., Mertig, M. & Pompe, W. Osteocalcin-controlled dissolution-reprecipitation of calcium phosphate under biomimetic conditions. *Chemistry of Materials* **13**, 3596-3602 (2001).
9. Murphy, W. L. & Mooney, D. J. Bioinspired growth of crystalline carbonate apatite on biodegradable polymer substrata. *Journal of the American Chemical Society* **124**, 1910-1917 (2002).
10. Song, J., Saiz, E. & Bertozzi, C. R. A new approach to mineralization of biocompatible hydrogel scaffolds: An efficient process toward 3-dimensional bonelike composites. *Journal of the American Chemical Society* **125**, 1236-1243 (2003).
11. Hartgerink, J. D., Beniash, E. & Stupp, S. I. Peptide-amphiphile nanofibers: a versatile scaffold for the preparation of self-assembling materials. *Proc Natl Acad Sci U S A* **99**, 5133-8 (2002).
12. Hartgerink, J. D., Beniash, E. & Stupp, S. I. Self-assembly and mineralization of peptide-amphiphile nanofibers. *Science* **294**, 1684-8 (2001).

Further Reading

1. Mann, S. *Biomineralization: Principles and Concepts in Bioinorganic Materials Chemistry* (Oxford Univ. Press, New York, 2001).
2. Mann, S. Molecular Tectonics in Biomineralization and Biomimetic Materials Chemistry. *Nature* **365**, 499-505 (1993).
3. Tang, Z. Y., Kotov, N. A., Magonov, S. & Ozturk, B. Nanostructured artificial nacre. *Nature Materials* **2**, 413-U8 (2003).
4. Brott, L. L. et al. Ultrafast holographic nanopatterning of biocatalytically formed silica. *Nature* **413**, 291-3 (2001).
5. Aizenberg, J., Black, A. J. & Whitesides, G. M. Control of crystal nucleation by patterned self-assembled monolayers. *Nature* **398**, 495-498 (1999).
6. Aizenberg, J. Patterned crystallization of calcite in vivo and in vitro. *Journal of Crystal Growth* **211**, 143-148 (2000).
7. Whaley, S. R., English, D. S., Hu, E. L., Barbara, P. F. & Belcher, A. M. Selection of peptides with semiconductor binding specificity for directed nanocrystal assembly. *Nature* **405**, 665-8 (2000).
8. Kriven, W. M., Kwak, S. Y., Wallig, M. A. & Choy, J. H. Bio-resorbable nanoceramics for gene and drug delivery. *Mrs Bulletin* **29**, 33-37 (2004).
9. Choy, J. H., Kwak, S. Y., Park, J. S., Jeong, Y. J. & Portier, J. Intercalative nanohybrids of nucleoside monophosphates and DNA in layered metal hydroxide. *Journal of the American Chemical Society* **121**, 1399-1400 (1999).
10. Khan, A. I., Lei, L. X., Norquist, A. J. & O'Hare, D. Intercalation and controlled release of pharmaceutically active compounds from a layered double hydroxide. *Chemical Communications*, 2342-2343 (2001).