Pattern Formation & Signaling

3/2/15

Jasmine Otto

things we’ll cover

- signals that give rise to structural patterns
- structural patterns that are recognized as signals
- mathematical models of these things

http://www.eb.tuebingen.mpg.de/de/forschung/emeriti/hans-meinhardt/periodic.html

models of biological pattern formation

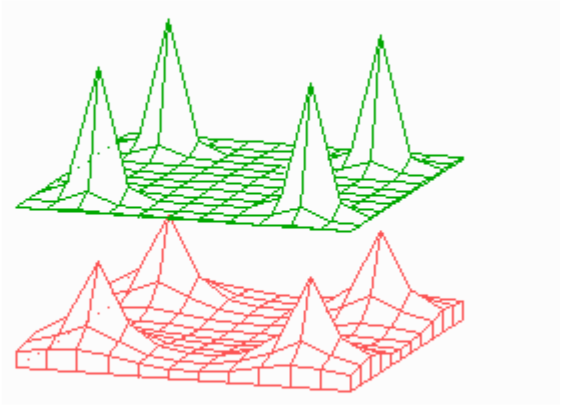
(Hans Meinhardt, Alfred Gierer)

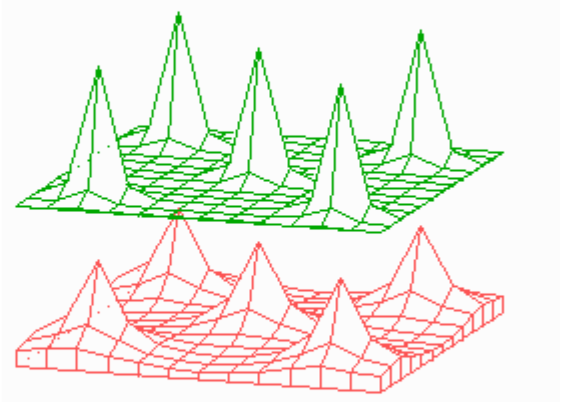
activator / inhibitor dynamics

periodic formations - uniform insertion

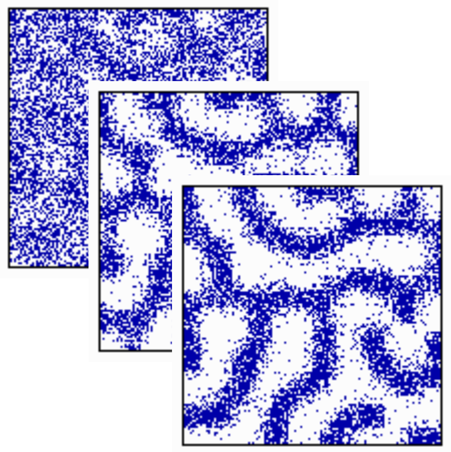
unless inhibited, insert a maxima

each maxima inhibits the formation of another maxima nearby





uniform pattern formation



periodic formations - stripes

idea: require large activated patches,

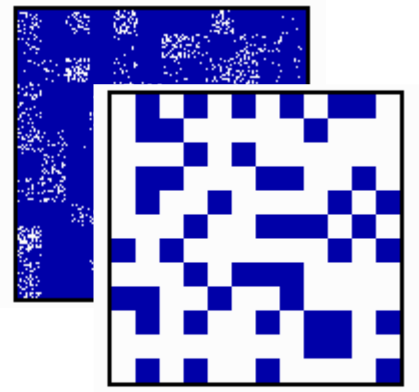
yet that every activated cell have inactivated neighbors

activator self-catalyzes

does so at superlinear rate, but saturates at a threshold concentration

cells must dump inhibitor into neighbors to become active

uniform pattern formation cont'd



if activator does not diffuse,

the two types of cell appear (with fixed ratio) in clumps

positioning of clumps and stripes depends on source density

(which kicks off signal-molecule production)

which should be distributed uniformly but at random

examples of pattern formation

e.g. Drosophila
(recruitment from the ectoderm to the peripheral nervous system)

activator: Achaete-Scute

inhibitor: Delta, which stimulates Notch

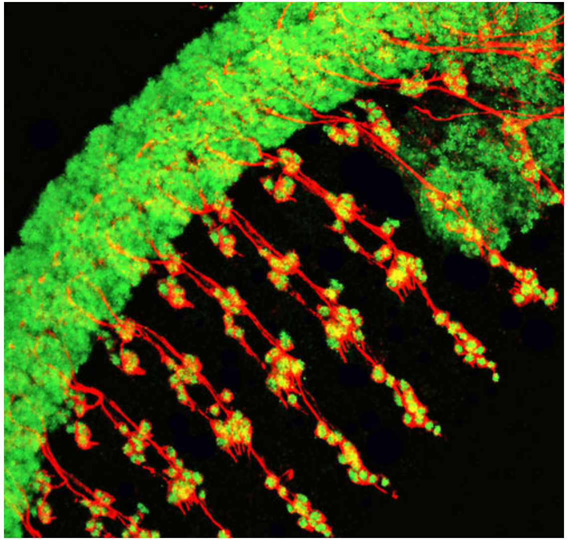
e.g. feather patterns

activators: FGF-4, sonic hedgehog

inhibitors: BMP-2, BMP-4

regions in which these genes are being transcribed can be identified

but finding the range over which the molecules diffuse is also important



Drosophila embryonic neurons
(Xin Xu via Princeton Department of Molecular Biology)

Fledgling Blue Jay
Photo by and (c)2009 Derek Ramsey (Ram-Man), under GFDL v.1.2

http://www.birds.cornell.edu/AllAboutBirds/studying/feathers/color/document_view
http://en.wikipedia.org/wiki/Structural_coloration

feather coloration

pigments: melanins (black, reddish browns, pale yellows - these provide durability, hence their use on wingtips)

carotenoids (bright red, orange, yellow - acquired from plants)

porphyrins (pink, browns, reds, greens - these fluoresce red under UV)

structural colors

iridescent - e.g. hummingbird gorgets

(diffraction grating - micro-prisms)

blue - e.g. jays, bluebirds, buntings

(deformed matrices - light scattering)

(Muhammad Mahdi Karim (www.micro2macro.net) via Wikipedia)

feather coloration, cont’d

red-green-blue can be mapped to hue-saturation-value (hue only, pictured)

extended spectrum

- some birds can see ultraviolet light, as a consequence of being tetra- or penta-chromats
- (and having four or five colors presumably provides them with a much different experience of color than ours)

other forms of structural coloration

- butterflies - diffraction grating, photonic crystals, selective mirrors
- sea mouse - crystal fibres
- marble berries - spiral coils
- cephalopods - reflectin-containing chromatophores

phototropism

(shoots grow towards light)

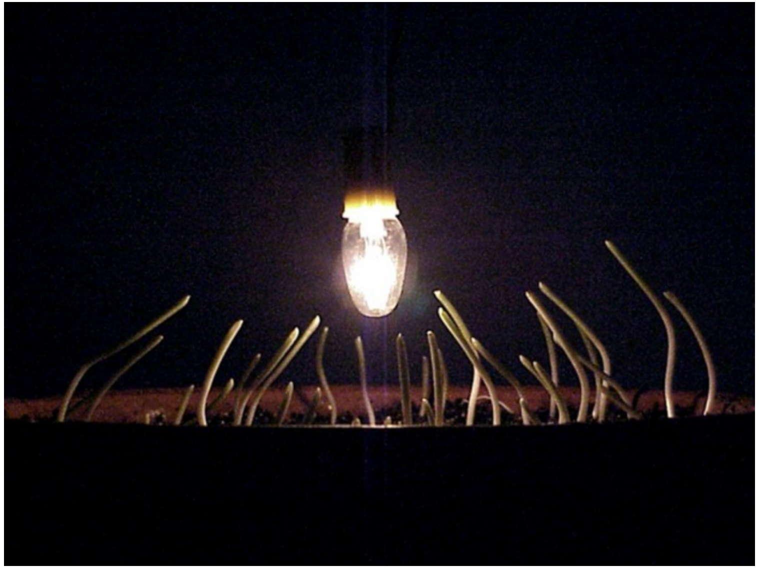
auxin is produced at the shoot tip

auxin is transported away from the light source by PIN proteins

(activated by D6PK protein kinase)

auxin travels between cells, accumulates on the shaded side of the plant

these cells elongate, and the plant bends towards the light source



attribution uncertain

http://www.plantcell.org/content/25/5/1674.full via http://www.sciencedaily.com/releases/2013/05/130528105946.htm

plant sensory organelles

(Willige et. al.)

how was the light source detected?

phototropins contain a photosensory LOV (light-oxygen-voltage) domain

phot1 autophosphorylates when excited by blue light

this triggers a pathway involving several other proteins

(eventually PIN proteins are inactivated?)

gravitropism appears to also be mediated by auxin transport,

but in response to statoliths (organelles containing starch grains).

gravitropism

(shoots grow away from gravity)

statoliths fall towards the bottoms of cells

(auxin transport occurs?)

auxin accumulates on the lower side of the plant

in response, these cells expand, and the plant curves upwards

multiple auxin transport mechanisms exist:

knocking out some abolishes only gravitropism

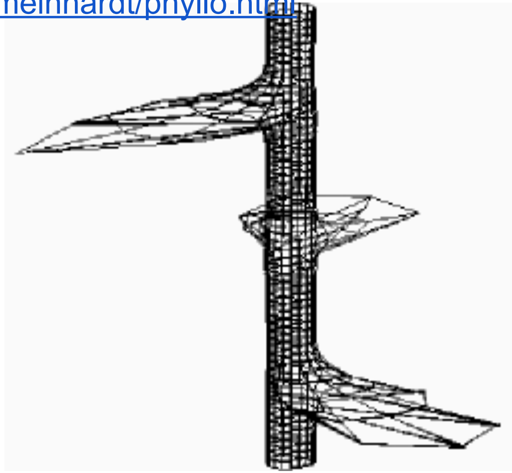
knocking out others abolishes only phototropism

(Kleuske via Wikipedia)

http://www.eb.tuebingen.mpg.de/de/forschung/emeriti/hans-meinhardt/phyllo.html

leaf arrangement

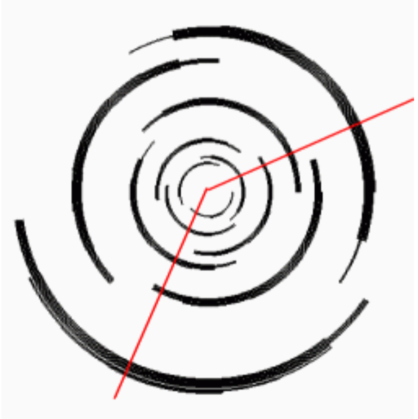
(Meinhardt, Gierer)



spiral patterns do not arise if only a single inhibitor is present, because the system lacks memory

so we introduce a long-duration inhibitor to our model

auxin is known to be necessary for leaf initiation; it is our activator.



"In a wide range of parameters, there is a tendency to initiate leaves with an angular spacing of 137°, the golden angle."

this, therefore, is (one possible) stable configuration.

leaf arrangement

regardless of initial conditions, the dynamical system will converge towards an equilibrium

if the equilibrium is unstable, periodic behavior results

if the equilibrium is stable, the dynamical system ends up sitting there

the golden angle equilibrium appears to be stable with respect to (w.r.t.) angle, though not w.r.t time (= position along shoot)

but surprisingly, this equilibrium is also stable w.r.t parameter values

Addtl' Topics

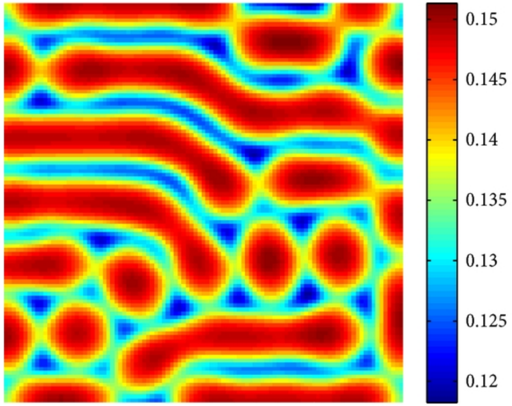
models of bacterial growth

(Xinze Lian, Guichen Lu, and Hailing Wang)

http://www.hindawi.com/journals/aaa/2014/149801/

“two reaction-diffusion equations of a predator-prey type
with a Holling Type III functional response”

i.e. prey and predator cells diffuse across the space,
and are predated on at a rate that increases slowly w.r.t prey density
for low and high densities, and quickly otherwise

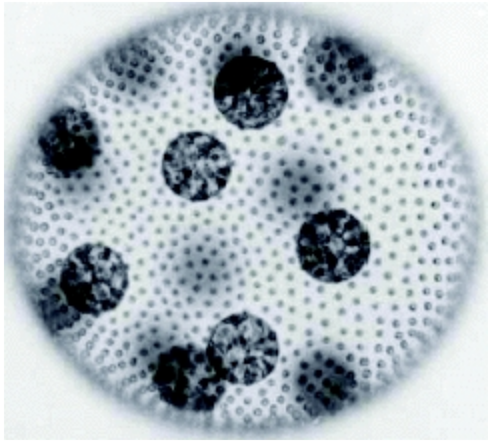


‘spots-stripes’ output

the goal, from a certain point of view
(Lab of Prof. Eshel Ben-Jacob of Tel-Aviv University, via MicrobeWiki)

communication in Volvox colonies

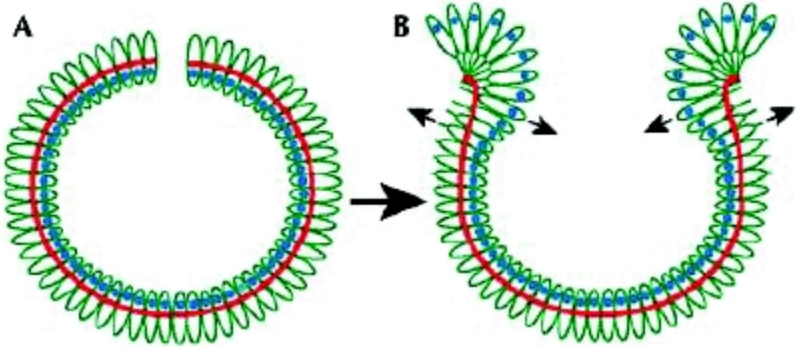
(Harold J. Hoops, Ichiro Nishii, and David L Kirk)



cytoplasmic bridges hold Volvox embryos
together during cleavage and inversion

(the red line in the diagram)

and disappear afterwards

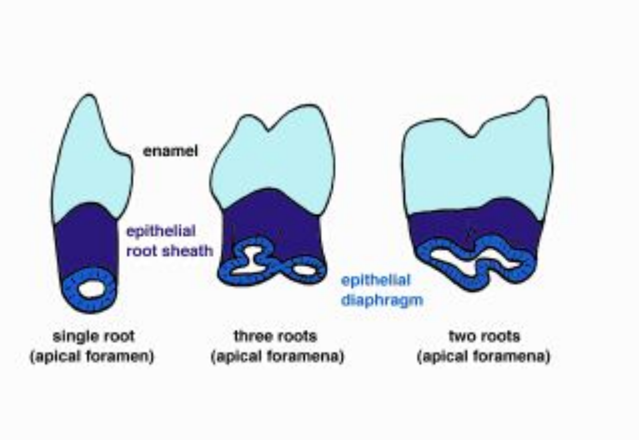


each cell of an 8-cell embryo is linked to
its neighbors by ˜250 bridges

following cleavage, there are 2^{11} or 2^{12} cells, and
an average cell is connected to its neighbors by about 25 bridges

http://dev.biologists.org/content/139/19/3487.full
http://www.uky.edu/~brmacp/oralhist/module3/lab/imgshtml/image40.htm

primate dentition



mammalian teeth

are specialized

are hard to replace

shape is determined by differential growth of the epithelial diaphragm cells

transplanting a tooth bud to a different site does not change what it develops into http://www.wwnorton.com/college/anthro/bioanth/ch7/chap7.htm

http://www.chimpsanctuarynw.org/blog/2013/09/chimpanzee-smiles/

primate dentition, cont'd

size of canine teeth is correlated with male-male competition

smiling is intimidation,
if you show your upper teeth

intimidation is less dangerous than fighting

(Wade Tregaskis via Flickr)

assorted horns

(Valerius Geist)

http://www.jstor.org.proxy.cc.uic.edu/stable/4533157
http://rsbl.royalsocietypublishing.org/content/3/6/651
https://news.wsu.edu/2012/07/26/trigger-for-massive-animal-weapons-ornaments-uncovered

great variety in the horns of various species living in the same locale

only a few cases (musk oxen, moose) where horns are useful as defense

primarily used in male-male competition

(but also in female-female competition over food?)

curving patterns could be produced by unequal elongation on outside & inside

spiralling patterns could be produced by certain orienting dynamical systems in which the maximum continually escapes to an adjacent position

http://www.eb.tuebingen.mpg.de/de/forschung/emeriti/hans-meinhardt/orient.html

examples of bovine horns collected by roachpatrol @ tumblr

http://rsta.royalsocietypublishing.org/content/372/2029/20130372#sec-1
via http://www.wired.com/2013/01/living-crystal/

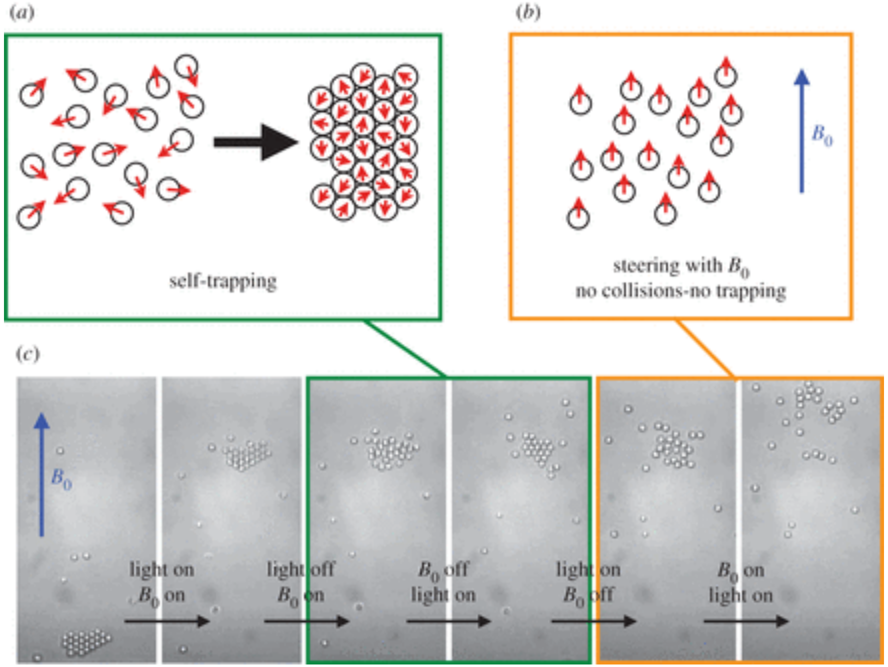
social patterns (flocking)

usually requires neural net(s),
but not always

light-activated colloids display flocking behavior

Brownian motion in the absence of hematite-exciting blue light

light causes the asymmetrical particles to self-propel (due to the chemical cloud released)



Skeletal Development

http://www.annualreviews.org.proxy.cc.uic.edu/doi/full/10.1146/annurev.cellbio.16.1.191

vertebrate skeletal development

(Bjorn R. Olsen, Anthony M. Reginato, and Wenfang Wang)

embryonic lineages,	which through **morphogenesis** produce
mesenchymal condensations,	which through **organogenesis** produce
rudimentary bone,	which undergoes continuous remodelling

three embryonic lineages

craniofacial, arising from the cranial neural crest

axial, arising from paraxial mesoderm

appendicular, arising from lateral plate mesoderm

each undergoes separate morphogenesis

morphogenesis (making the plans)

morphogenesis occurs according to the transcription factors present, e.g.,

the products of Hox (homeobox) genes, PAX (paired box) genes,

and the BMPs (bone morphogenetic proteins
a.k.a. cytokines, metabologens)

transcription factors activate suites of genes, leading to cell differentiation

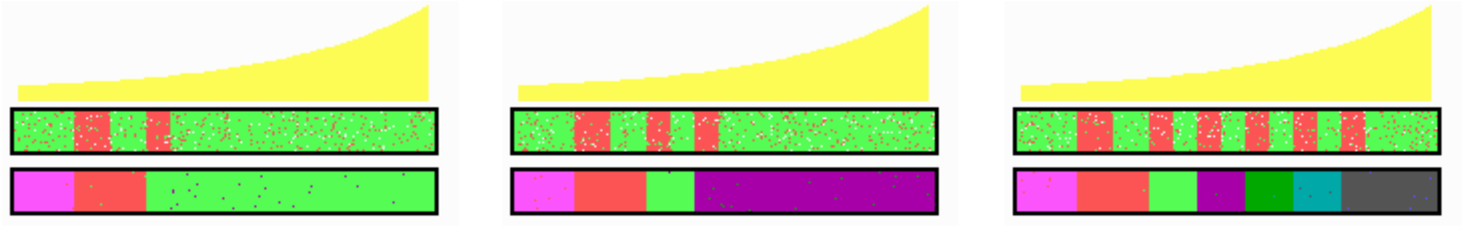
somites

(Meinhardt, Gierer)

http://www.eb.tuebingen.mpg.de/de/forschung/emeriti/hans-meinhardt/somites.html

How are the Hox genes associated with specific regions along the axial skeleton?

Their activation is tied to a segment clock, an oscillating system driven by a pre-existing gradient.



proteins involved

(Olsen, Reginato, & Wang)

axial patterning

bone morphogenetic protein (BMP) action requires the Sonic hedgehog (Shh) protein

absence → no sclerotome (bone somite) development
→ no vertebrae, dorsolateral ribs, distal limbs formed

limb patterning

- sonic hedgehog, Hoxd genes
  - mutations → a variety of polydactylies and syndactylies
- cartilage-derived morphogenetic protein 1 (CDMP1)
  - mutations → brachydactyly type C and acromesomelic dysplasias
- noggin, a BMP-binding molecule
  - mutations → proximal symphalangism

proteins involved (T-box genes)

limb patterning cont'd

- certain T-box transcription factors
  - mutations → abnormalities of limb bones
    - → heart or breast issues (Holt-Oram or ulnar-mammary syndrome)

- TBX5 is expressed in developing forelimbs but not hindlimbs.
- TBX4 is expressed only in the developing leg.
  - mutations in Pitx1, an upstream regulator of Tbx4
    - → mouse hindlimbs resemble forelimbs
    - → cleft palate and pituitary changes
  - misexpression of Pitx1 in chick wing buds
    - → wings resemble legs

organogensis (building the house)

differentiation occurs in mesenchymal condensations (formed by morphogenesis)

organogenesis is controlled by

- transcription factors, cytokines, growth factors, and extracellular matrix molecules (esp. collagens)

osteoblasts require Cbfa1 to form

- a transcription factor
- targets the promoters of several bone proteins
  - incl' osteocalcin, bone sialoprotein, alkaline phosphatase, type I collagen
- absence → mice develop a cartilage skeleton, but no bones

lamellar bone organogenesis

endochondral ossification:

differentiation into chondrocytes

which promote calcification of the matrix

via glycogen & phosphatase secretion

and then die off, allowing osteoprogenitor cells to invade

analgen are cartilage models of the future bones

after bone formation, cartilage remains only at the articular surface

intramembranous ossification:

differentiation into osteocytes occurs directly

lamellar bone structure

at the growth plate of long bones, time is mapped to space:

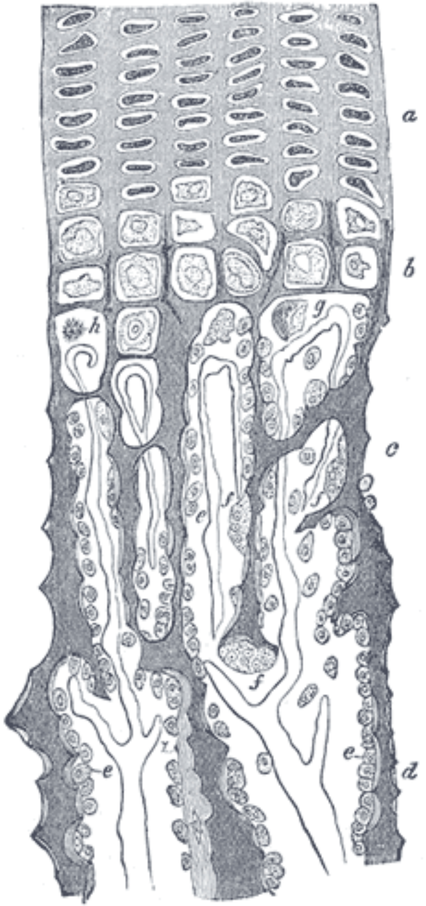
resting cartilage →

chondrocyte proliferation →

chondrocyte maturation (hypertrophy, glycogen & phosphatase secretion) →

calcification (chondrocytes die due to lack of diffusion, leaving cavities) →

ossification (osteoprogenitor cells invade)



Slide 80 from Gray’s Anatomy, via Wikipedia.
a. Flattened cartilage cells. b. Enlarged cartilage cells.
c, d. Newly formed bone. e. Osteoblasts. f. Giant cells or osteoclasts.

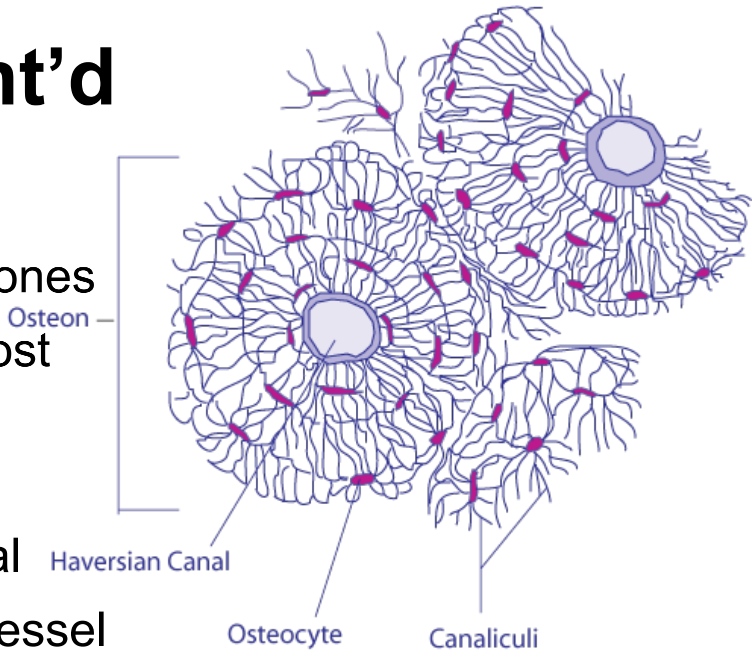
http://onlinelibrary.wiley.com/doi/10.1111/j.1469-7580.2011.01398.x/full

lamellar bone structure cont'd

haversian system (osteon)

- functional unit of compact bone, esp. long bones
- osteons vary by taxon, but are present in most mammals [?]

- osteons are laid down around a central canal
- which is hollowed out surrounding a blood vessel



(Edit by BDB of a plate from Gray's Anatomy of the Human Body, via Wikipedia)

but there are also drifting, branched, and clustered forms of osteons

- hence, 3D rendering via micro-computed tomography (micro-CT)

osteons

in humans, in idealized form:

concentric layers of **lamellae**, surrounding the haversian canal, through which pass the blood vessels and nerves

interstitial lamellae (resorbed osteons) occupy the space between the cylindrical osteons

each osteon contains lacuna, in which living osteocytes are present

between the lacuna are canaliculi, through which the osteocytes' processes interface

collagen fibers are arranged parallel to each other within each layer

Volkmann's canals connect the osteons and periosteum transversely

proteins involved

chondrocyte differentiation is controlled [?] by the transcription factor SOX9

L-Sox5 and Sox6 are coexpressed with Sox9 at all chondrogenic sites
→ they likely cooperatively activate Col2a1, which encodes collagen type II

Ihh and PTHrP (whose production Ihh promotes) promote chondrocyte proliferation

insufficient # proliferating growth plate chondrocytes
(relative to the size of the hypertrophic zone)
→ dwarfism

excessive # proliferating growth plate chondrocytes

→ dwarfism also
(the rate of hypertrophy is decreased either way)

FGFR3 inhibits chondrocyte proliferation

bone structure

contrast lamellar bone with woven bone

- which occurs at insertions, sutures, and during development / repair
- whose collagen fibers are arranged haphazardly

extracellular matrix molecules include:

- type I and type II collagens
  - mutations → a variety of skeletal and cartilage disorders, respectively

- various minor collagens (types IX thru XII)
  - in regulatory (not mechanical) roles, perhaps

http://www.scientificamerican.com/article/how-are-seashells-created/

calcium in bones

contrast: **bone** vs. **shell**, coral, & chromaveolates

i.e. calcium phosphate vs. calcium carbonate

e.g. turtle bone (beneath the keratin scutes) is comprised of

protein + hydroxyapatite

which is mostly calcium phosphate (some calcium carbonate)

entombed osteocytes → growth from within, not from the mantle

protein matrix binds calcium ions, directing calcification

(crystal formation)

https://scholar.google.com/scholar?q=calcium+carbonate+deposition

calcium in bones, cont'd

calcium carbonate may form calcite or aragonite

depends on the exact protein matrix

calcium phosphate does not vary in this manner

searches for calcium phosphate were unproductive

has been used as a material for bone grafts

implanted titanium sometimes accumulates deposited calcium phosphate

(incidentally, pearly nacre is iridescent because aragonite platelets form diffraction grating)

bone remodelling

(M. Doblaré, J.M. García)

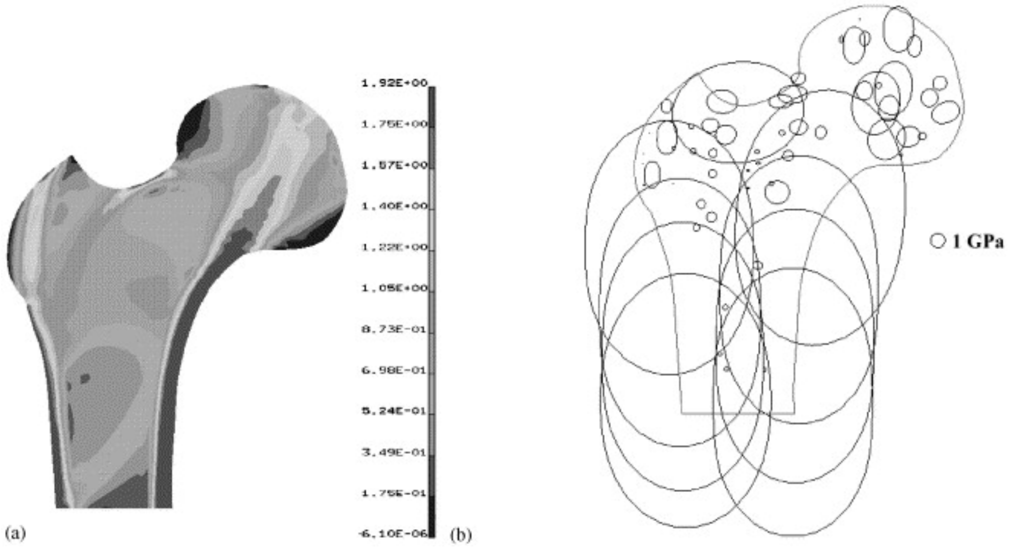
http://www.sciencedirect.com.proxy.cc.uic.edu/science/article/pii/S0021929001001786

continuous throughout life

both organic and mineral components are removed and re-added

non-uniform density arises mechanistically

through remodelling in accordance with loads borne



Density and stress surface distribution after 300 days (anisotropic damage-repair model).