NON-EQUILIBRIUM THERMODYNAMICS OF HETEROGENEOUS GROWING BIOSYSTEMS

Natalya Kizilova

Department of Theoretical and Applied Mechanics

Kharkov National University

Ukraine

Outline

1. Biological growth: definition, types, properties
2. Experiments with growing plant materials (leaves)
3. Experiment-based mathematical model of growing continuum. Parameter identification.
4. Biological growth in tissue engineering. Experimental technologies and models.
5. A mixture model of the inhomogeneous growing tissue. Application to the tissue growth in the degradable scaffold
6. Conclusions

Growth = irreversible changes in the mass (volume, size) of an object provided by new mass accumulation

Tissues=cells + extracellular solid matter + interstitial liquid

Plant cells = immovable cells + rigid cellular walls

Animal cells = movable (migrating) cells + extracellular solids and liquids

I: cell growth and divisions

II: extracellular matter production and self-assembling

Biosystems are

- open TD systems with are in permanent mass and energy exchange with environment (circulatory, respiratory, excretory systems; outer and internal surfaces)

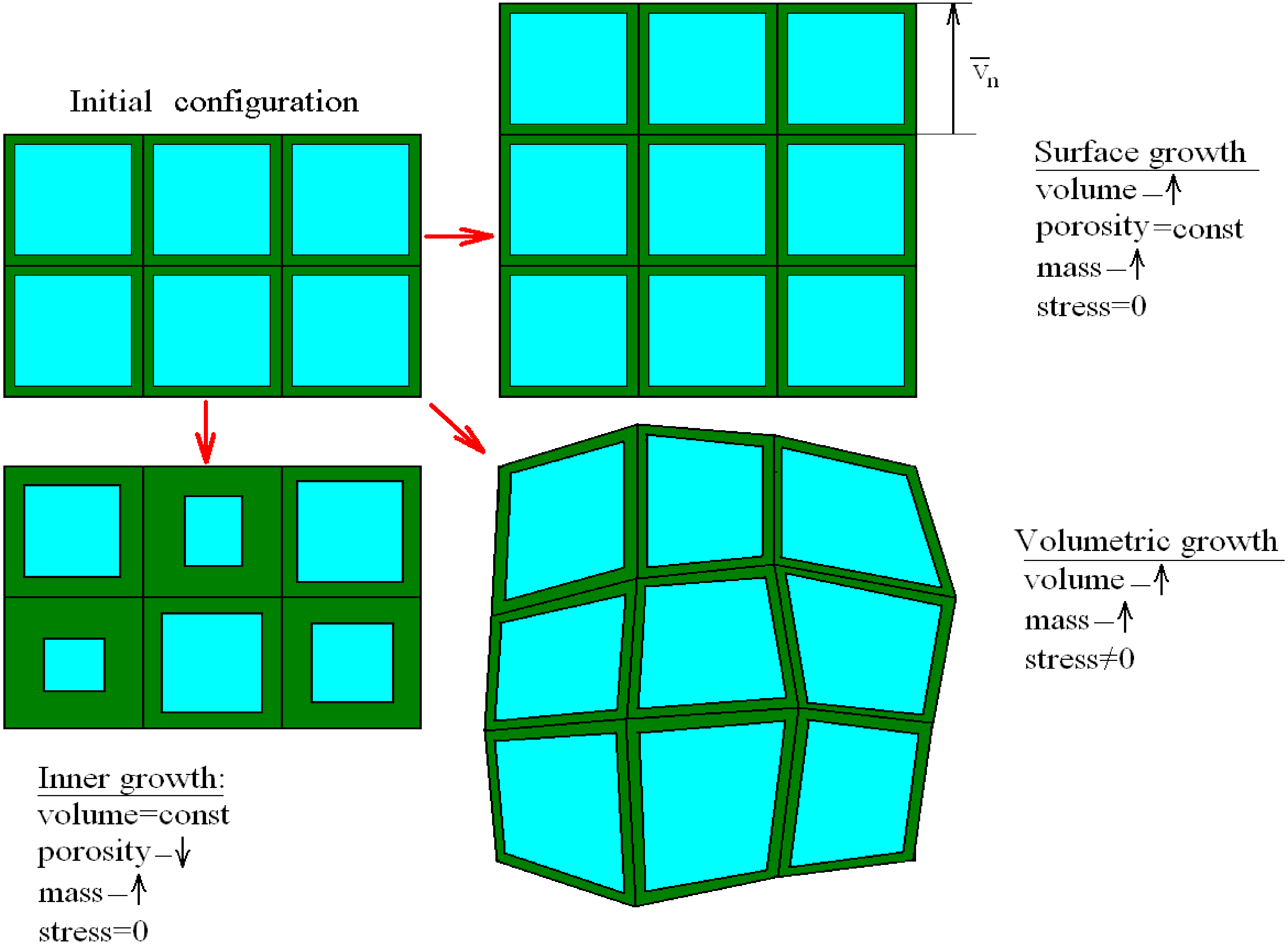
- in permanent non-equilibrium (NE) state working against equilibrium; supporting non-zero gradients and corresponding fluxes; exhibiting complex cross-related phenomena

- non-uniform systems (cell types, gradient fields) at permanent dynamical loading (gravity, muscle contractions, flow oscillations, electric impulses)

- active systems (parameter-dependent properties; local chemical and mechanical + central nervous and humoral systems)

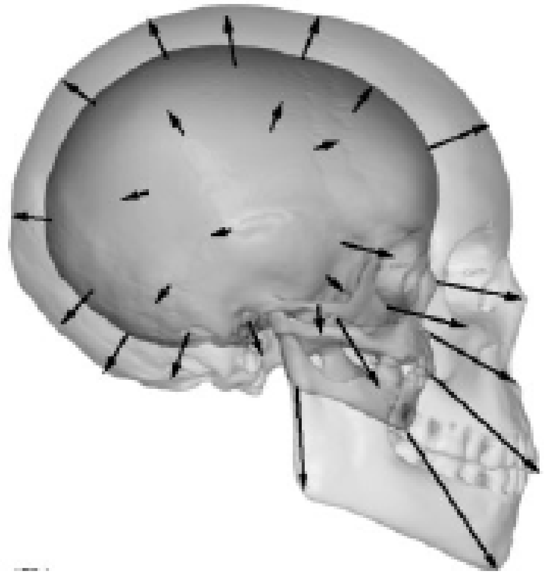
- optimal systems possessing maximal performance at given conditions (minimal energy expenses/entropy production)

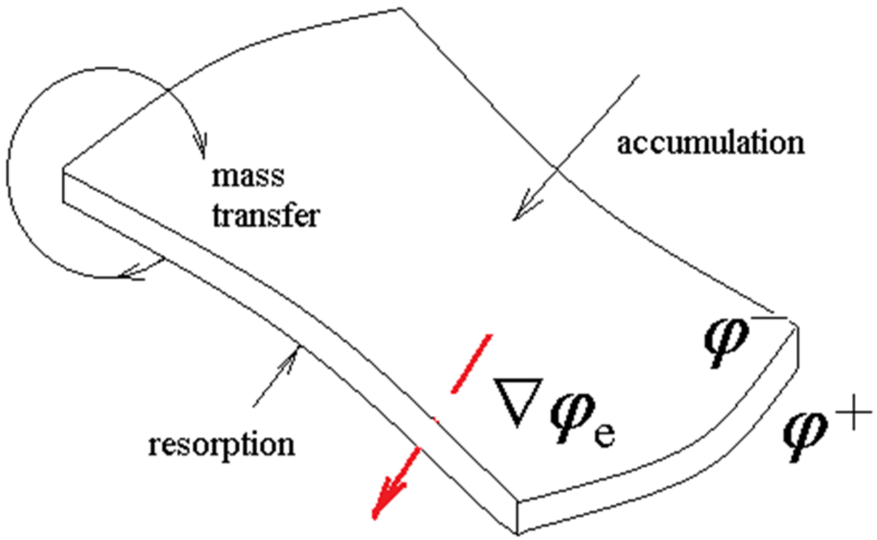
Growth types:



Surface growth

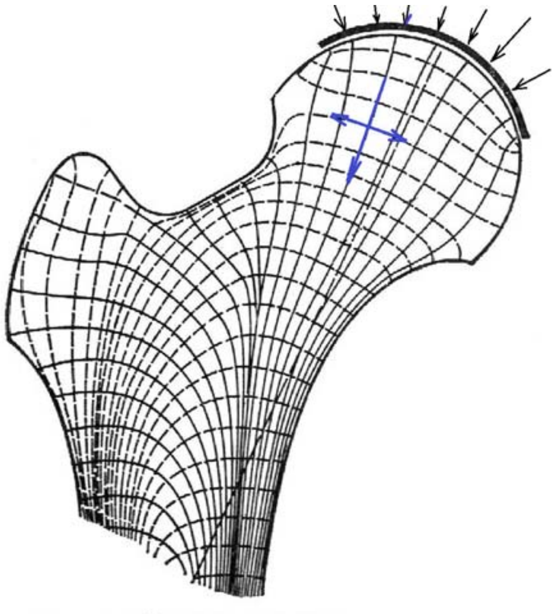
- Mass accumulation/resorbtion at external surfaces
- Coupling of dissolution-crystallization
- Driven by $\nabla c_a, \nabla \varphi_e, \ldots$
- Features: growth anisotropy; non-uniformity
- TD consideration: solidification fronts
- Examples: bones, skull, tree trunks. branches, shoots

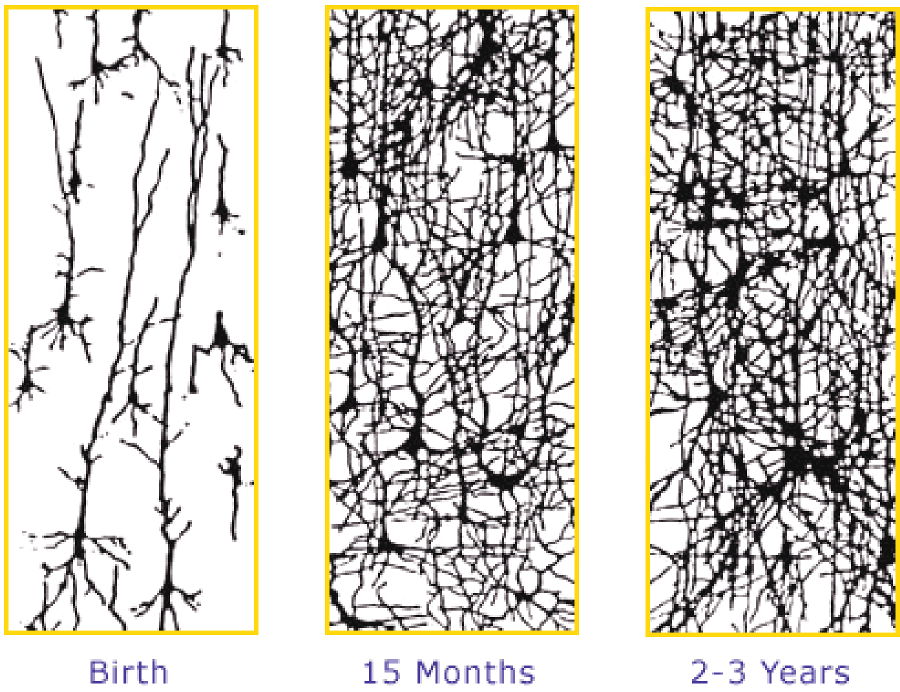




Inner growth (remodeling)

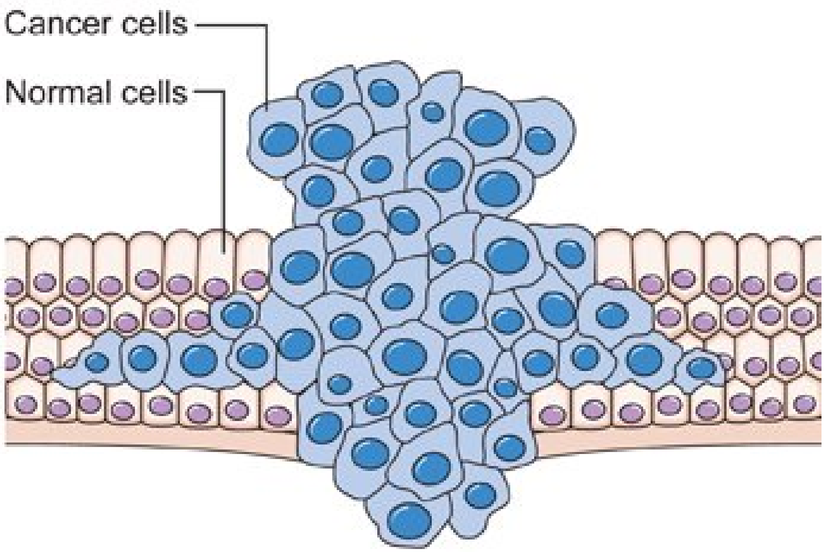
- Mass increase/decrease in each point
- Non-zero stress field
- Examples: plant leaves and roots, inner organs, tumors
- Features: anisotropic growth; residual stresses

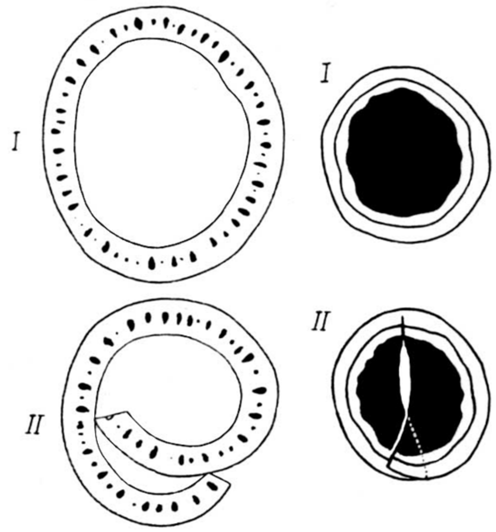




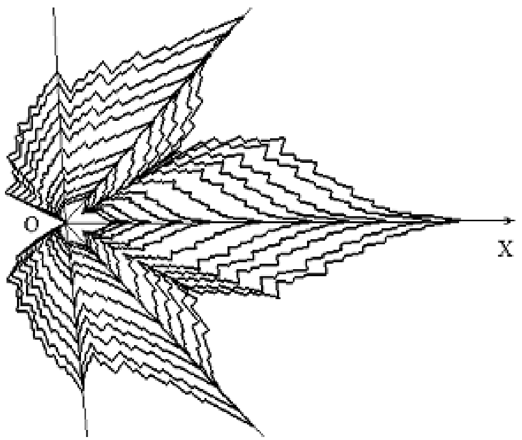
Volume growth

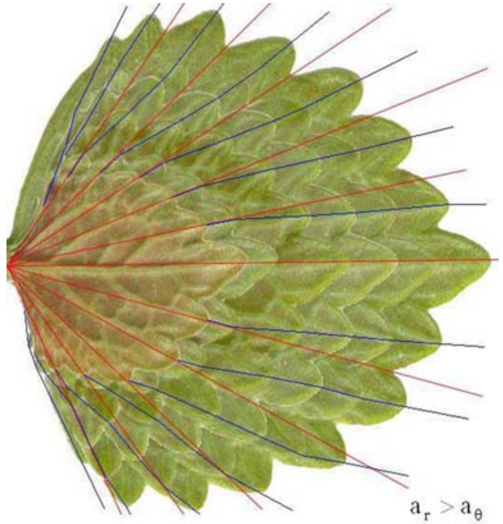
- Mass increase/decrease in each point
- Non-zero stress field
- Examples: plant leaves and roots, inner organs, tumors
- Features: anisotropic growth; residual stresses

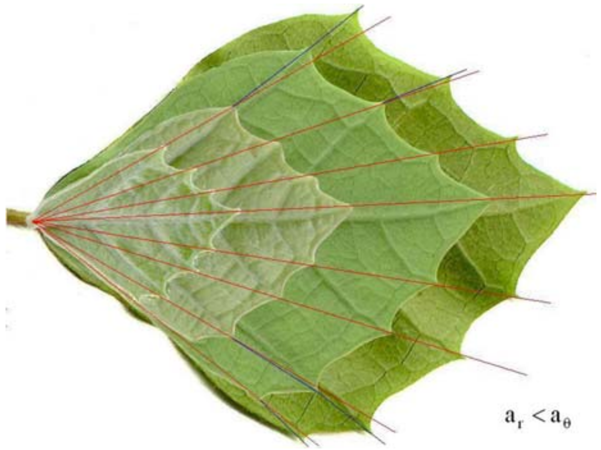




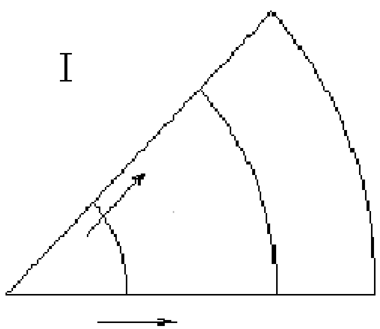
Experimental study of plant leaf growth at zero stress conditions



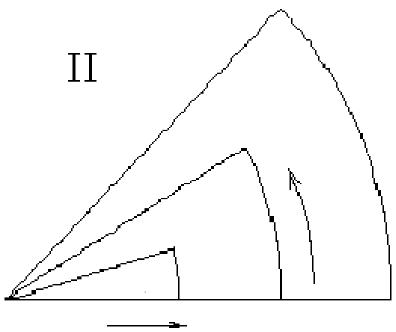




I



II



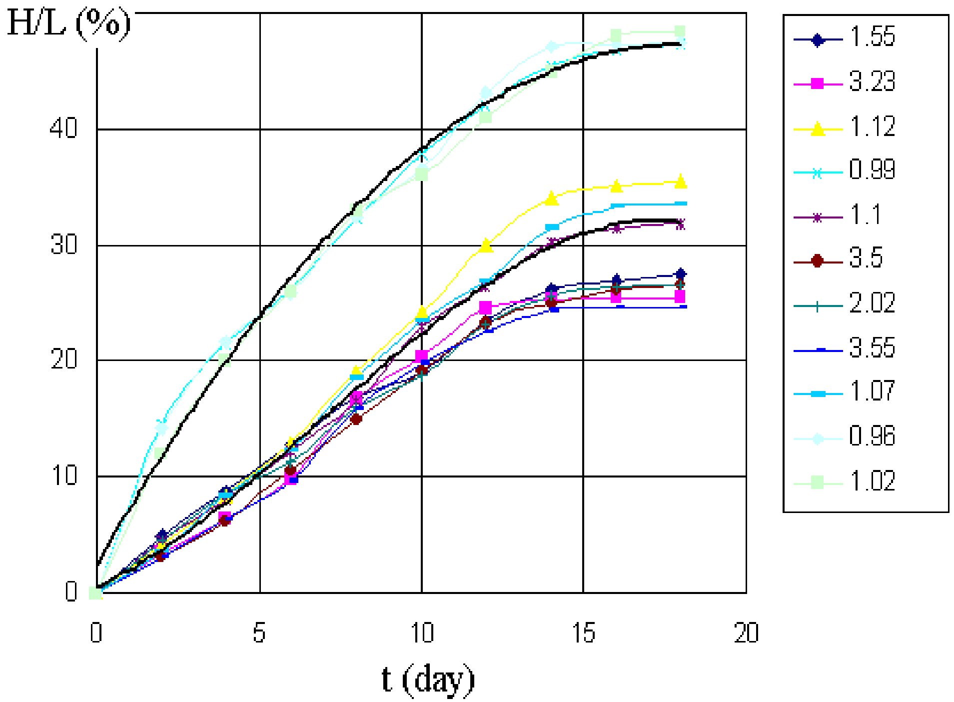
$$\vec{v} = (v_r, v_\theta)$$

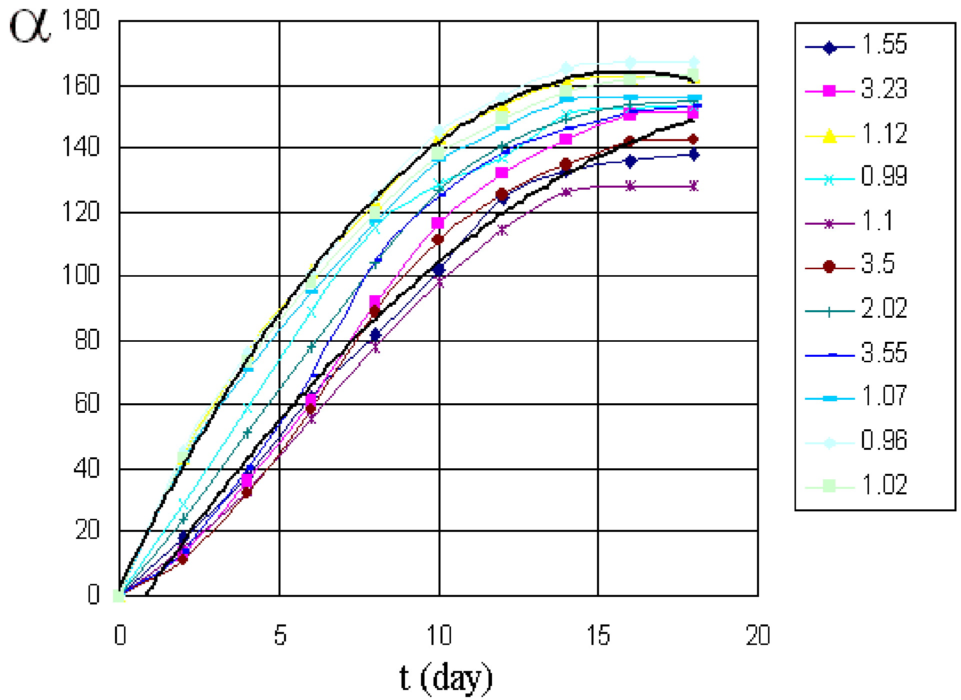
$$\begin{cases} v_r = a_r(t) r \\ v_\theta = 0 \end{cases}$$

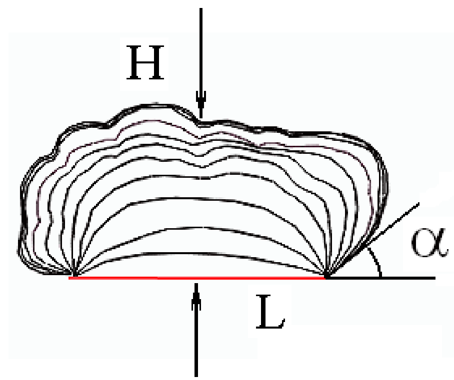
$$\begin{cases} v_r = a_r(t) r \\ v_\theta = a_\theta(t) r\theta \end{cases}$$

Experimental study of plant leaf growth at mechanical restrictions

Leaf blade deflection and boundary angle measurements







Experiment-based conclusions:

- Extraction/compression stimulates/oppresses growth in the corresponding direction
- Growth rate at zero-stress conditions is a function of time and concentrations of growth factors/regulators
- Growth rate at nonzero-stress conditions is a function of stress tensor components
- New material accumulates according to principals of the stress tensor providing the lightweight design
- Stress-induced elongation of cells (endothelial cells in vessel wall, skeletal muscle cells, conducting vessels)

Mathematical modeling of growing continua

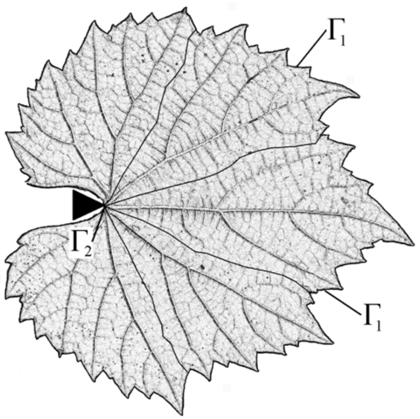
$$\frac{\partial \boldsymbol{\rho}}{\partial t} + \mathrm{div}(\boldsymbol{\rho}\vec{v}) = q$$

$$\hat{e} = \hat{A}(t) + \hat{B}\hat{\boldsymbol{\sigma}} + (\hat{E})^{-1} d\hat{\boldsymbol{\sigma}} / dt$$

$$\mathrm{div}\hat{\boldsymbol{\sigma}} = 0$$

$$\hat{e} = \frac{1}{2}\left(\frac{\partial v_i}{\partial x_k} + \frac{\partial v_k}{\partial x_i}\right)$$

$$\vec{\boldsymbol{\sigma}}_n\Big|_{\Gamma_1} = 0, \qquad \vec{v}\Big|_{\Gamma_2} = 0$$



$$\frac{\partial v_x}{\partial x} = A_{xx}$$

$$\frac{\partial v_y}{\partial y} = A_{yy} \quad \Rightarrow \quad \frac{\partial^2 A_{xx}}{\partial y^2} + \frac{\partial^2 A_{yy}}{\partial x^2} = 2\frac{\partial^2 A_{xy}}{\partial x \partial y}$$

$$\frac{\partial v_x}{\partial y} + \frac{\partial v_y}{\partial x} = 2A_{xy}$$

$$\frac{\partial^2 A_{ii}}{\partial x_j^2} + \frac{\partial^2 A_{jj}}{\partial x_i^2} = 2\frac{\partial^2 A_{ij}}{\partial x_i \partial x_j}, \qquad i, j = 1,2,3 \quad A_{ii} = \frac{\partial^2 \boldsymbol{\Theta}}{\partial x_i^2}, \qquad A_{ij} = \frac{\partial^2 \boldsymbol{\Theta}}{\partial x_i \partial x_j}$$

Growth viscosity tensor, Beltrami-Michell equations, growth problem formulation

$$e_{ik} = A_{ik} + B_{iklm}\sigma_{lm}$$

$$B = \begin{pmatrix} B_{11} & B_{12} & B_{13} & 0 & 0 & 0 \\ B_{21} & B_{22} & B_{23} & 0 & 0 & 0 \\ B_{31} & B_{32} & B_{33} & 0 & 0 & 0 \\ 0 & 0 & 0 & B_{44} & 0 & 0 \\ 0 & 0 & 0 & 0 & B_{55} & 0 \\ 0 & 0 & 0 & 0 & 0 & B_{66} \end{pmatrix},$$

$$\frac{\partial^2(B_{ii}\sigma_{ii} + B_{ij}\sigma_{jj} + B_{ik}\sigma_{kk})}{\partial x_j^2} + \frac{\partial^2(B_{ji}\sigma_{ii} + B_{jj}\sigma_{jj} + B_{jk}\sigma_{kk})}{\partial x_i^2} = $$

$$= 2\frac{\partial^2(B_{mm}\sigma_{ij})}{\partial x_i \partial x_j}$$

$$i, j, k = 1,2,3;\ m = i + 3$$

$$\frac{\partial}{\partial x_i}\left[\frac{1}{b}\sum_{m=1}^{3}\left(\frac{\partial v_m}{\partial x_m} - A_{mm}\right)\right] + \frac{\partial}{\partial x_j}\left[\frac{1}{2B_{pp}}\left(\frac{\partial v_i}{\partial x_j} + \frac{\partial v_j}{\partial x_i} - A_{ij}\right)\right] +$$

$$+ \frac{\partial}{\partial x_k}\left[\frac{1}{2B_{qq}}\left(\frac{\partial v_i}{\partial x_k} + \frac{\partial v_k}{\partial x_i} - A_{ik}\right)\right] + F_i = 0$$

$$i, j, k = 1,2,3, \quad q = 9 - i - k, \quad p = 9 - i - j$$

$$\operatorname{div}\hat{\sigma} + \vec{F} = 0$$

$$\vec{\sigma}_n\big|_\Gamma = \vec{\sigma}^*$$

$$\vec{v}\big|_\Gamma = 0$$

$$b = \det|b_{ik}|$$

$$b_{ik} = \begin{vmatrix} B_{11} & B_{12} & B_{13} \\ B_{21} & B_{22} & B_{23} \\ B_{31} & B_{32} & B_{33} \end{vmatrix}$$

Conclusions

- In spite of different shape, size, physiology, evolutionary age, etc… the narrow limits for growth parameters have been found

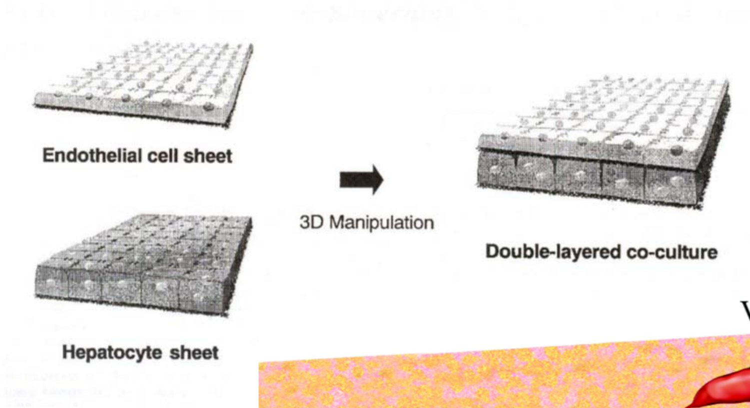
$$\boldsymbol{\sigma}^* \sim 0.03 - 0.05 \text{ MPa}$$

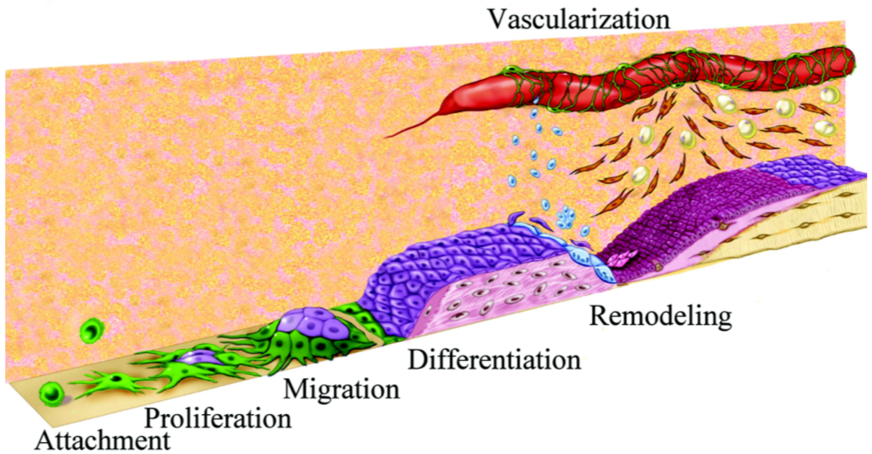
$$A^* \sim 0.5 - 3 \text{ mm / day}$$

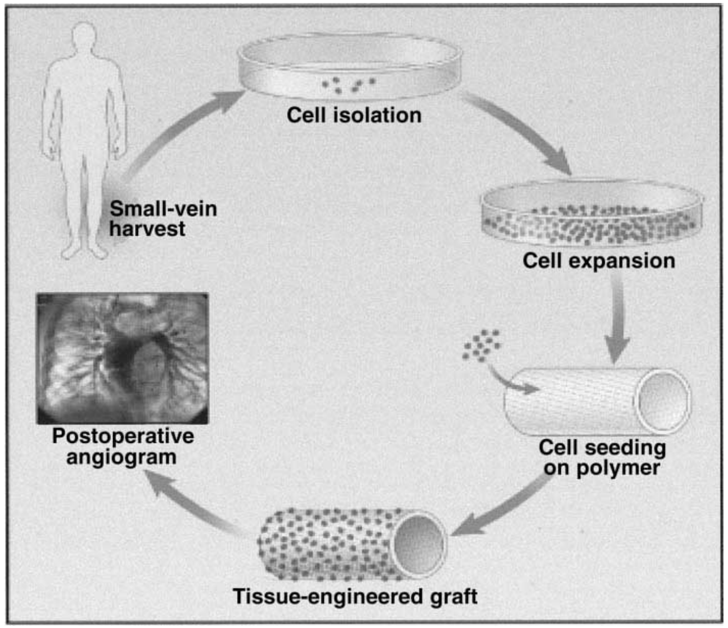
$$B^* \sim 0.1 - 1\,(\text{Pa} \cdot \text{s})^{-1}$$

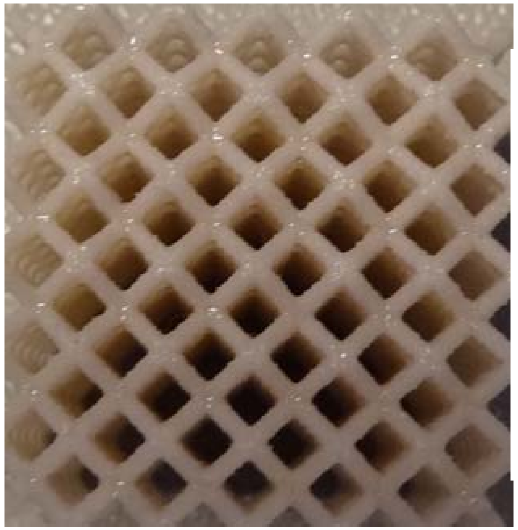
- Transportation systems have the same principles of design (dependences between the lengths, diameters, branching angles, drianage areas) which corresponds to the model of optimal pipeline providing homogenous flow delivery at minimum energy expences.

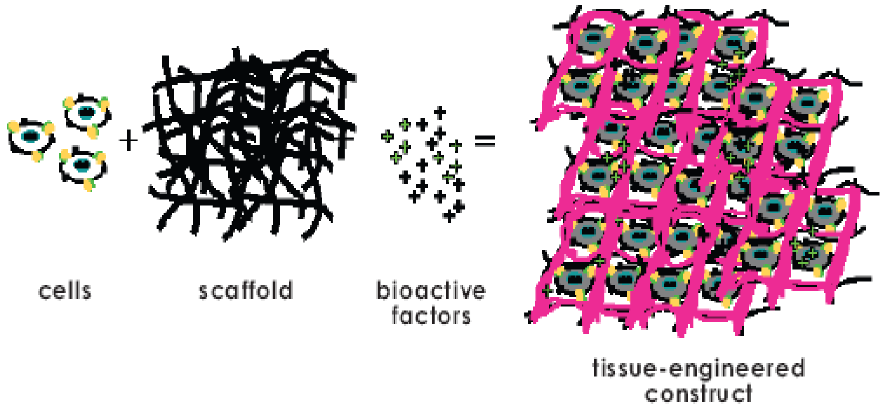
Biological growth in tissue engineering







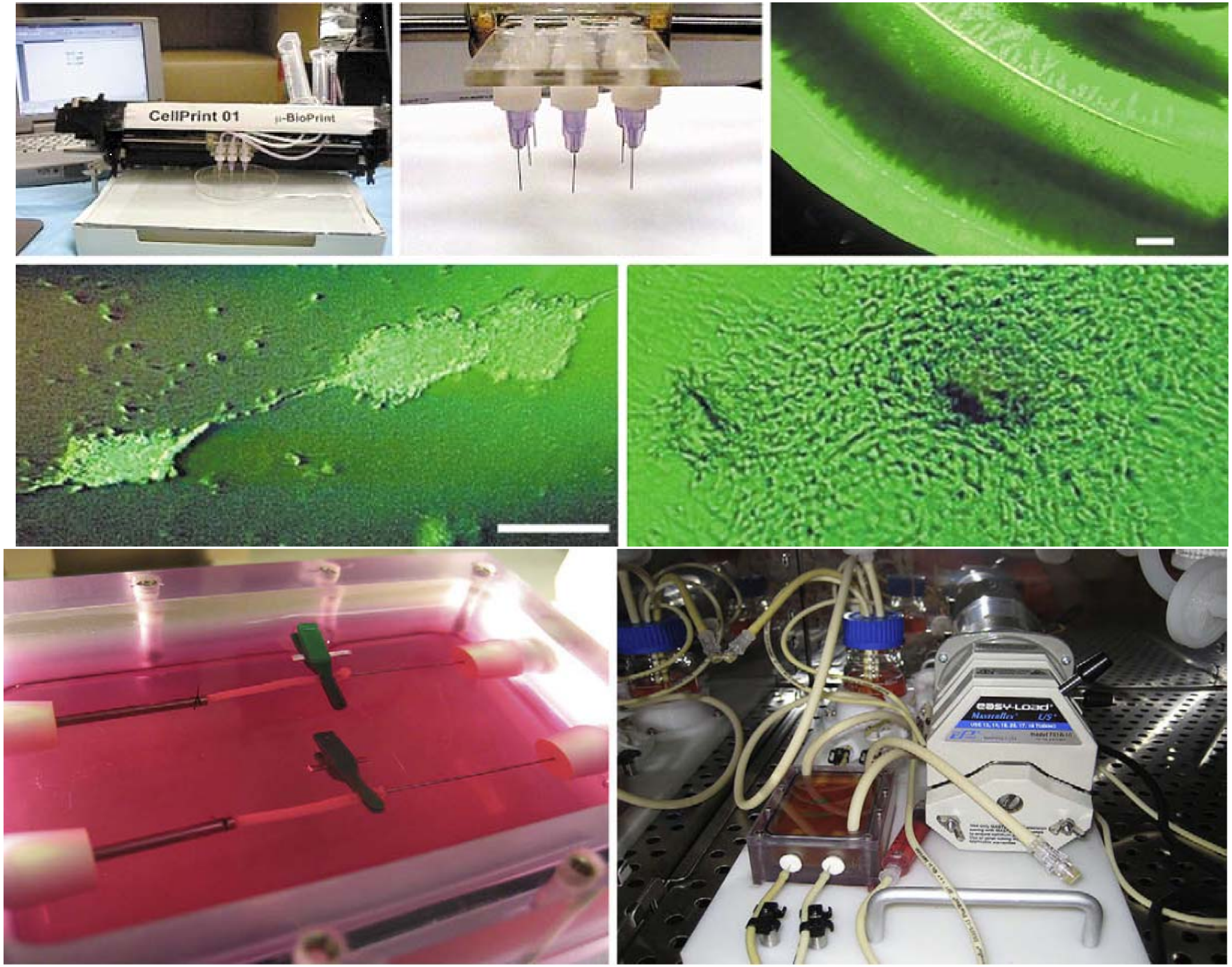




Successful laboratory and clinical reports on tissue engineering of:

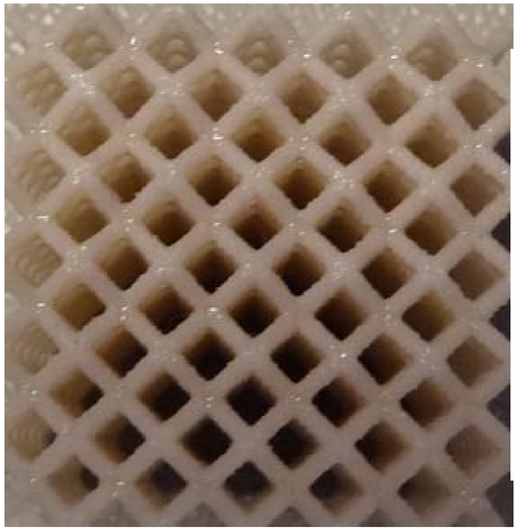
blood and lymphatic vessels [Shin'oka T., et al, 2001]
heart valves [Sodian R., et al, 2000]
cardiac tissue [Carrier R.L., et al, 1999]
bone and cartilage [Vacanti C.A., et al, 1994]
tendon [Cao D., et al, 2006]
skin [Parenteau N.L., et al, 1991]
liver [Kim T.H., et al, 2000]
stomach [Maemura T., et al, 2003]
intestine [Choi R.S., et al, 1998]
bladder [Oberpenning F., et al, 1998]
skeletal muscle [Geris L., et al, 2001]
nerves [Fansa H., et al, 2003]

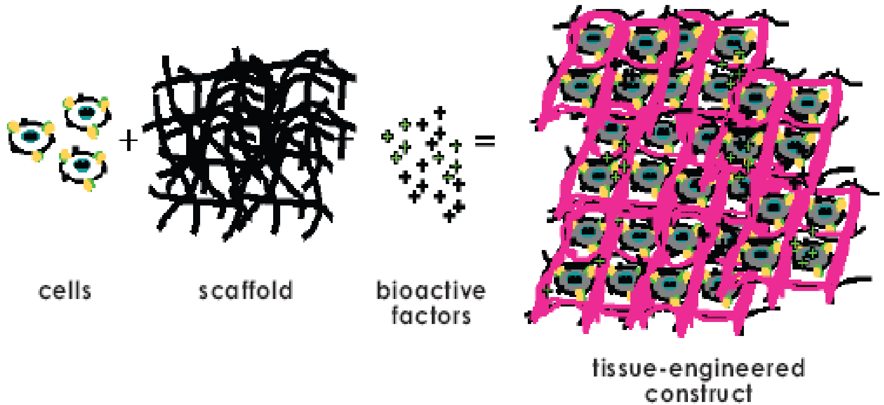
3D tissue and organ printing



Polymer and metal scaffolds with regular structure

- Role of geometry (strength, lightweight design, porosity, shape of pores, adequate pore sizes for easy penetration of the growing cells/structures)
- Role of material (biocompatibility and non-toxicity; controlled degradation kinetics corresponding to the new tissue formation).





Diffusion models of growth

$$\frac{\partial C}{\partial t} + \nabla \cdot \vec{J}_C = \boldsymbol{\alpha} C$$

$$\frac{\partial b}{\partial t} + \nabla \cdot \vec{J}_b = \boldsymbol{\beta} - \boldsymbol{\gamma} C b$$

$$\vec{J}_b = -D_b \nabla b$$

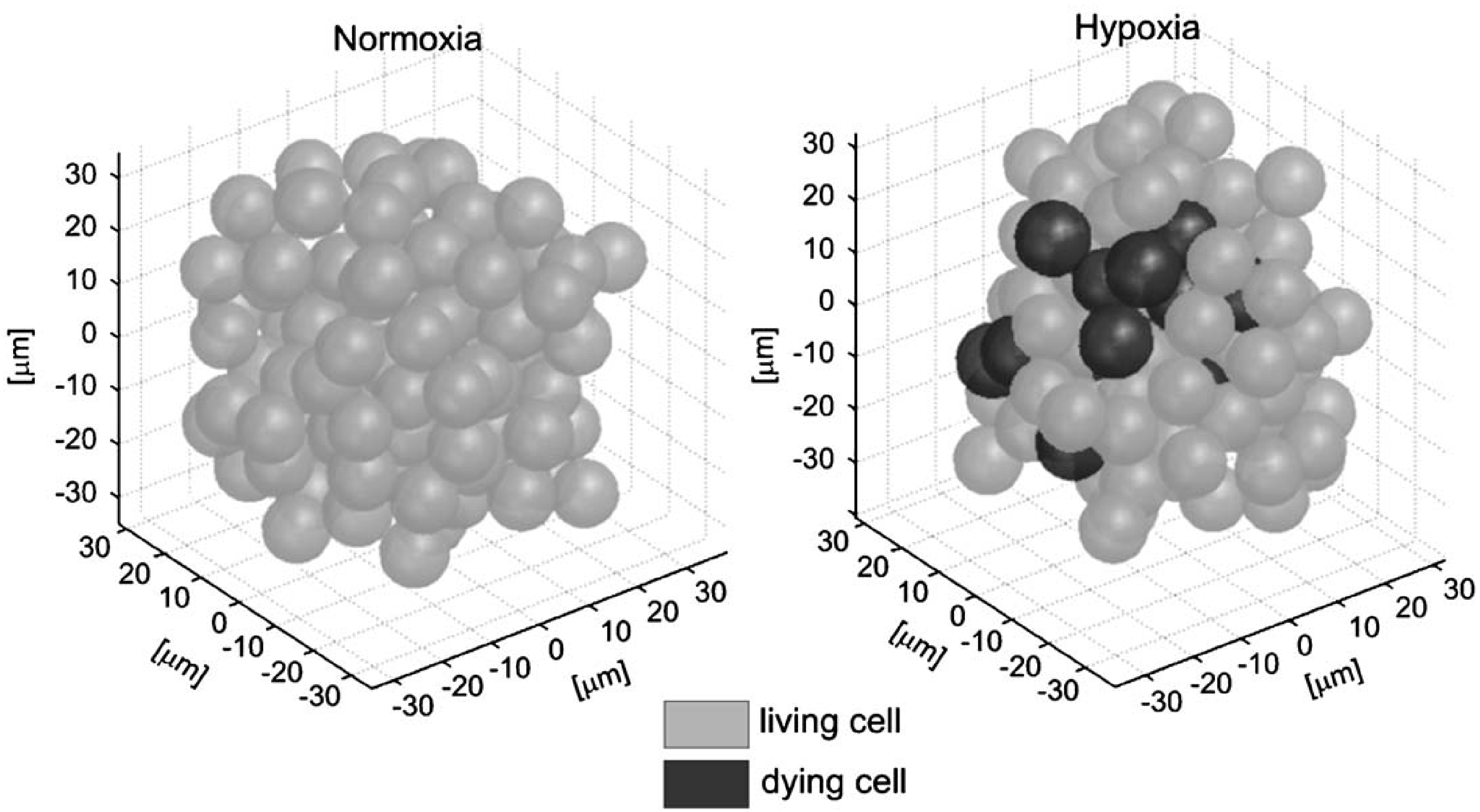
$$\vec{J}_C = -D_C \nabla C + f(b) \nabla b$$

$$D_C = D_C(\boldsymbol{\gamma}, b, \boldsymbol{\rho}, R, \boldsymbol{\mu}, \boldsymbol{\xi}(T)) = \frac{\boldsymbol{\xi\gamma} b}{\boldsymbol{\rho} R} \cdot F\left(\frac{\boldsymbol{\xi\gamma} b}{6\boldsymbol{\pi\mu\rho} R} \right)$$

Particle dynamic growth models

$$m^{(j)}\frac{d^2\vec{r}^{(j)}}{dt^2} = k_a(\vec{r}_S - \vec{r}^{(j)}) - 6\pi R\mu\frac{d\vec{r}^{(j)}}{dt} + \sum_{k\neq j} k_r \frac{\vec{r}^{(j)} - \vec{r}^{(k)}}{\left|\vec{r}^{(j)} - \vec{r}^{(k)}\right|^n} + \frac{d\vec{r}_{rm}^{(j)}}{dt}$$

adhesion drag repulsion random walks



A multi-phase model of the growing inhomogeneous tissue

Solid phases: 1 – cells of different types

2 - vessel walls, connective tissues, airways

3 – extracellular matrix

Liquid phases: 4 – intracellular liquids

5 – extracellular (tissue) liquid

6 – delivering liquid

Components: 1 - nutrition (glucose, O_2, …)

2 – growth factors, …

Mass balance equations

$$\frac{\partial \rho^{\alpha}}{\partial t} + \mathrm{div}\left(\rho^{\alpha}\vec{v}^{\alpha}\right) = \theta^{\alpha}$$

$$\rho\frac{dC^{\alpha\beta}}{dt} = -\mathrm{div}\vec{J}^{\alpha\beta} + \theta^{\alpha\beta} + M^{\beta}\sum_{\gamma} k_{\gamma}^{\alpha}\nu_{\gamma}^{\alpha\beta}$$

$$\vec{J}^{\alpha\beta} = \rho C^{\alpha\beta}(\vec{v}^{\alpha\beta} - \vec{v})$$

Momentum balance equations

$$\frac{\partial \rho^{\alpha} v^{\alpha k}}{\partial t} + \nabla_j (\rho^{\alpha} v^{\alpha k} v^{\alpha j}) = \nabla_j p^{\alpha kj} + R^{\alpha k} + M^{\alpha k} + \rho^{\alpha} f^{\alpha k}$$

$$M^{\alpha k} = \sum_{\alpha \neq \beta} \theta^{\beta} v^{\alpha\beta k}$$

$$\sum_{\alpha} (R^{\alpha k} + M^{\alpha k}) = 0$$

Energy balance equations

$$\frac{\partial \boldsymbol{\rho}^{\boldsymbol{\alpha}} \mathrm{E}^{\boldsymbol{\alpha}}}{\partial \mathrm{t}} + \nabla_{\mathrm{j}} (\boldsymbol{\rho}^{\boldsymbol{\alpha}} \mathrm{v}^{\boldsymbol{\alpha}\mathrm{k}} \mathrm{E}^{\boldsymbol{\alpha}}) = \nabla_{\mathrm{j}} \mathrm{Q}^{\boldsymbol{\alpha}\mathrm{j}} + \mathrm{v}_{\mathrm{k}}^{\boldsymbol{\alpha}} \left(\mathrm{R}^{\boldsymbol{\alpha}\mathrm{k}} + \boldsymbol{\rho}^{\boldsymbol{\alpha}} \mathrm{f}^{\boldsymbol{\alpha}\mathrm{k}} \right) + \mathrm{N}^{\boldsymbol{\alpha}} + \mathrm{W}^{\boldsymbol{\alpha}}$$

$$\mathrm{N}^{\boldsymbol{\alpha}} = \sum_{\boldsymbol{\alpha} \neq \boldsymbol{\beta}} \boldsymbol{\theta}^{\boldsymbol{\beta}} \mathrm{E}^{\boldsymbol{\alpha\beta}}$$

$$\sum_{\boldsymbol{\alpha}} (\mathrm{v}_{\mathrm{k}}^{\boldsymbol{\alpha}} \mathrm{R}^{\boldsymbol{\alpha}\mathrm{k}} + \mathrm{N}^{\boldsymbol{\alpha}} + \mathrm{W}^{\boldsymbol{\alpha}}) = 0$$

Additional equations (active movement, structure formation, aggregation, …)

$$\frac{\partial \Gamma^{\alpha\beta}}{\partial t} + (\vec{v}^{\alpha\beta} \cdot \nabla)\Gamma^{\alpha\beta} = Z_{+}^{\alpha\beta}(C^{\alpha\beta}, \vec{v}^{\alpha\beta}, \ldots) - Z_{-}^{\alpha\beta}(C^{\alpha\beta}, \vec{v}^{\alpha\beta}, \ldots)$$

$$\frac{\partial n}{\partial t} + \mathrm{div}(n\vec{v}^{1}) = G$$

Internal energy

$$U^{\boldsymbol{\alpha}} = \begin{cases} U^{\boldsymbol{\alpha}}(S^{\boldsymbol{\alpha}}, C^{\boldsymbol{\alpha}}), \boldsymbol{\alpha} = 4-6 & \text{(liquid phases)} \\ U^{\boldsymbol{\alpha}}(S^{\boldsymbol{\alpha}}, C^{\boldsymbol{\alpha}}, \boldsymbol{\varepsilon}_{kj}^{\boldsymbol{\alpha}}), \boldsymbol{\alpha} = 1-3 & \text{(solid phases)} \end{cases}$$

$$T^{\boldsymbol{\alpha}} = \frac{\partial U^{\boldsymbol{\alpha}}}{\partial S^{\boldsymbol{\alpha}}}, \boldsymbol{\mu}^{\boldsymbol{\alpha}} = \frac{\partial U^{\boldsymbol{\alpha}}}{\partial C^{\boldsymbol{\alpha}}}, \boldsymbol{\sigma}_{kj}^{\boldsymbol{\alpha}} = \frac{\partial U^{\boldsymbol{\alpha}}}{\partial \boldsymbol{\varepsilon}_{kj}^{\boldsymbol{\alpha}}}$$

Entropy balance equation

$$\frac{\partial S}{\partial t} + \nabla_j G^j = \boldsymbol{\sigma}_S, \; S = \frac{1}{\boldsymbol{\rho}} \sum_{\boldsymbol{\varepsilon}} \boldsymbol{\rho}^{\alpha} S^{\alpha}$$

$$\boldsymbol{\sigma}_S = \sum_n X^n Y^n$$

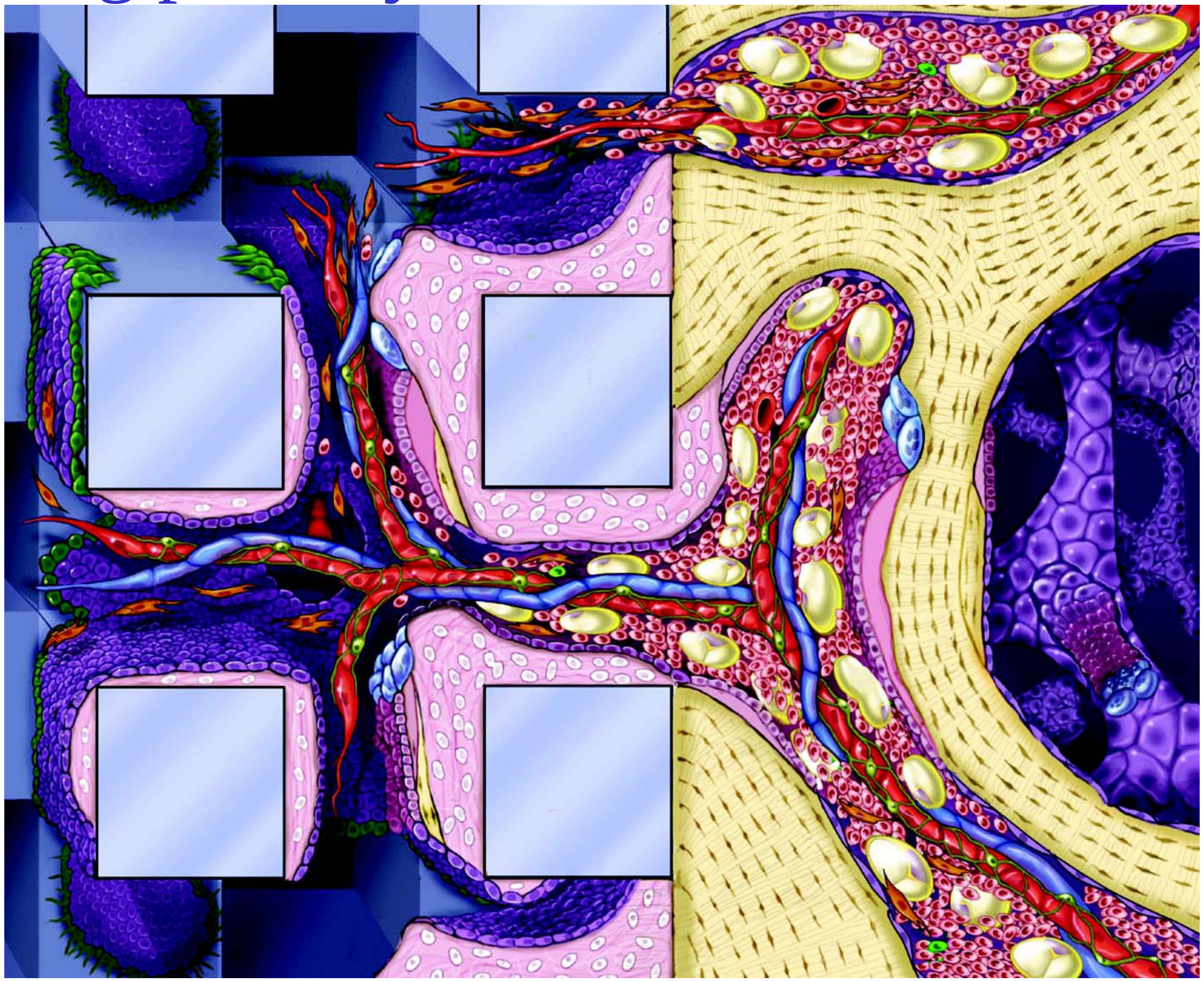
$$p^{\gamma kj} = -pC_\gamma g^{kj} + \boldsymbol{\Lambda}_\gamma^{kjpq} \nabla_p v_q^\gamma, \quad \boldsymbol{\gamma} = 4-6$$

$$p^{\gamma kj} = p^{kj} - pC_\gamma g^{kj} + \boldsymbol{\Lambda}_\gamma^{kjpq} \nabla_p v_q^\gamma, \quad \boldsymbol{\gamma} = 1-3$$

$$R_k^\gamma = p\nabla_k C_\gamma - k_\gamma (v_k^\gamma - v_k) + \boldsymbol{\lambda}_\gamma \nabla_k \boldsymbol{\mu}^\gamma$$

$$J_k^\gamma = -D\nabla_k \boldsymbol{\mu}^\gamma + \boldsymbol{\lambda}_\gamma (v_k^\gamma - v_k)$$

Cell proliferation, migration, adhesion, interaction, vascularization in a biodegradable scaffold can be studied as slow flow through a porous media with increasing porosity



Conclusions

1. Biological growth is a complex phenomena that can be described and understood on the concepts of NET of open systems
2. Mixture models based on Onsager theory are useful for slow normal growth and tissue engineering problems while they are failed in some special occasions
3. Tissue engineering technologies need development of the TD theory enable to describe non-uniform multicellular growth at mechanical load and chemical regulation conditions; control over tissue anisotropy, vascularisation and innervation