Multi-scale and hybrid models in cell dynamics

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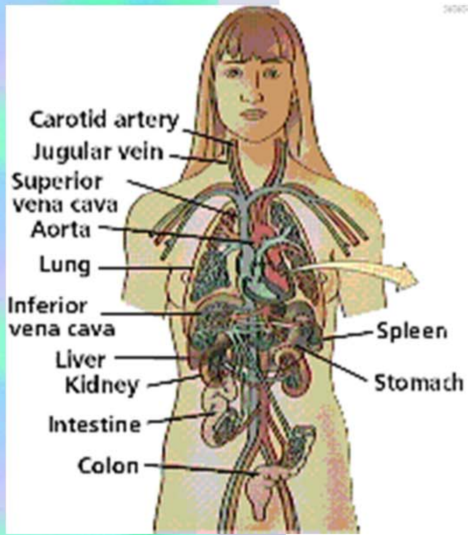
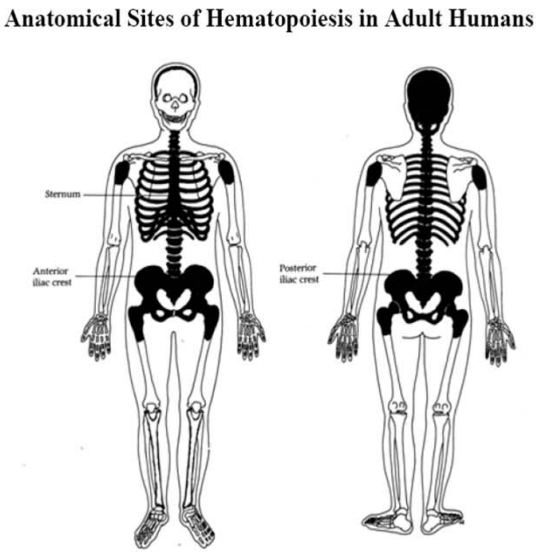
Moscow, November 2014

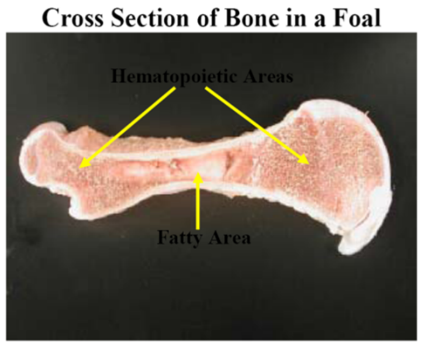
Outline

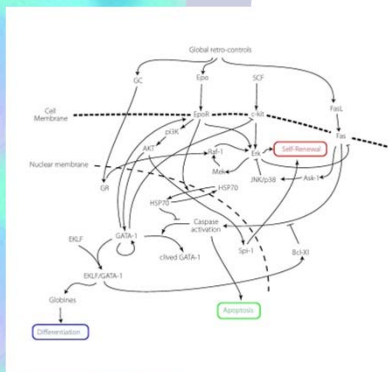
- Multi-scale and hybrid modelling in biology
- Deformable cell model (blood cells, plants)
- Hematopoiesis and blood diseases

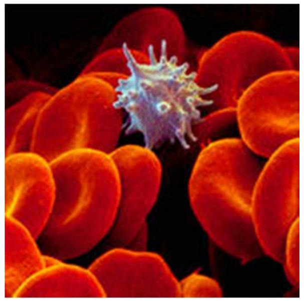
Multi-scale modelling in biology and medicine

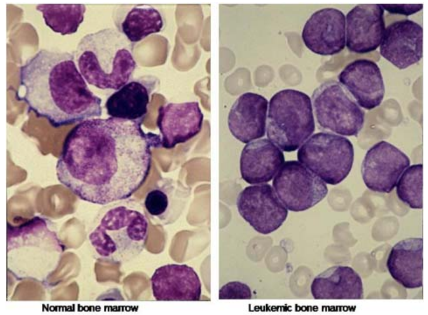




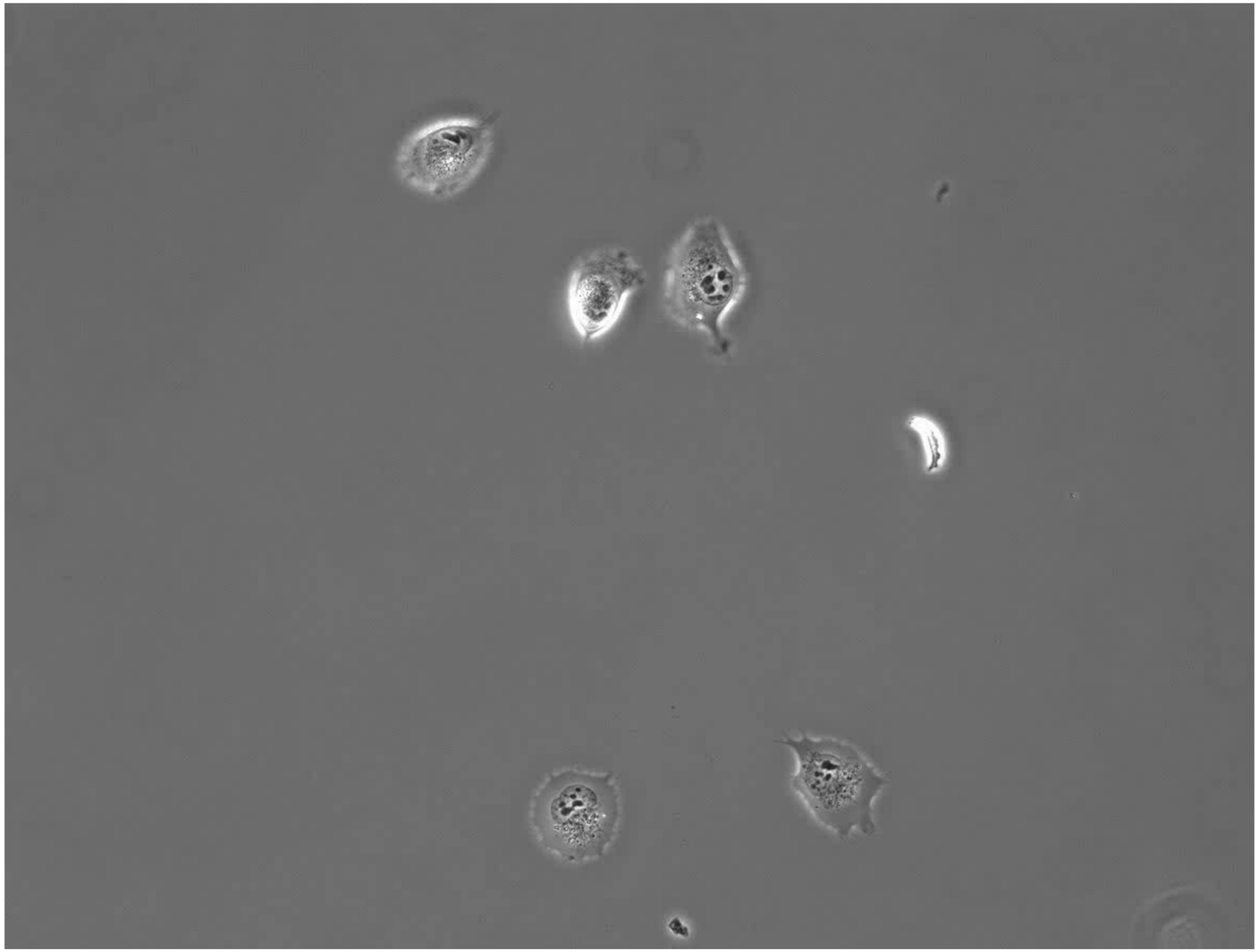




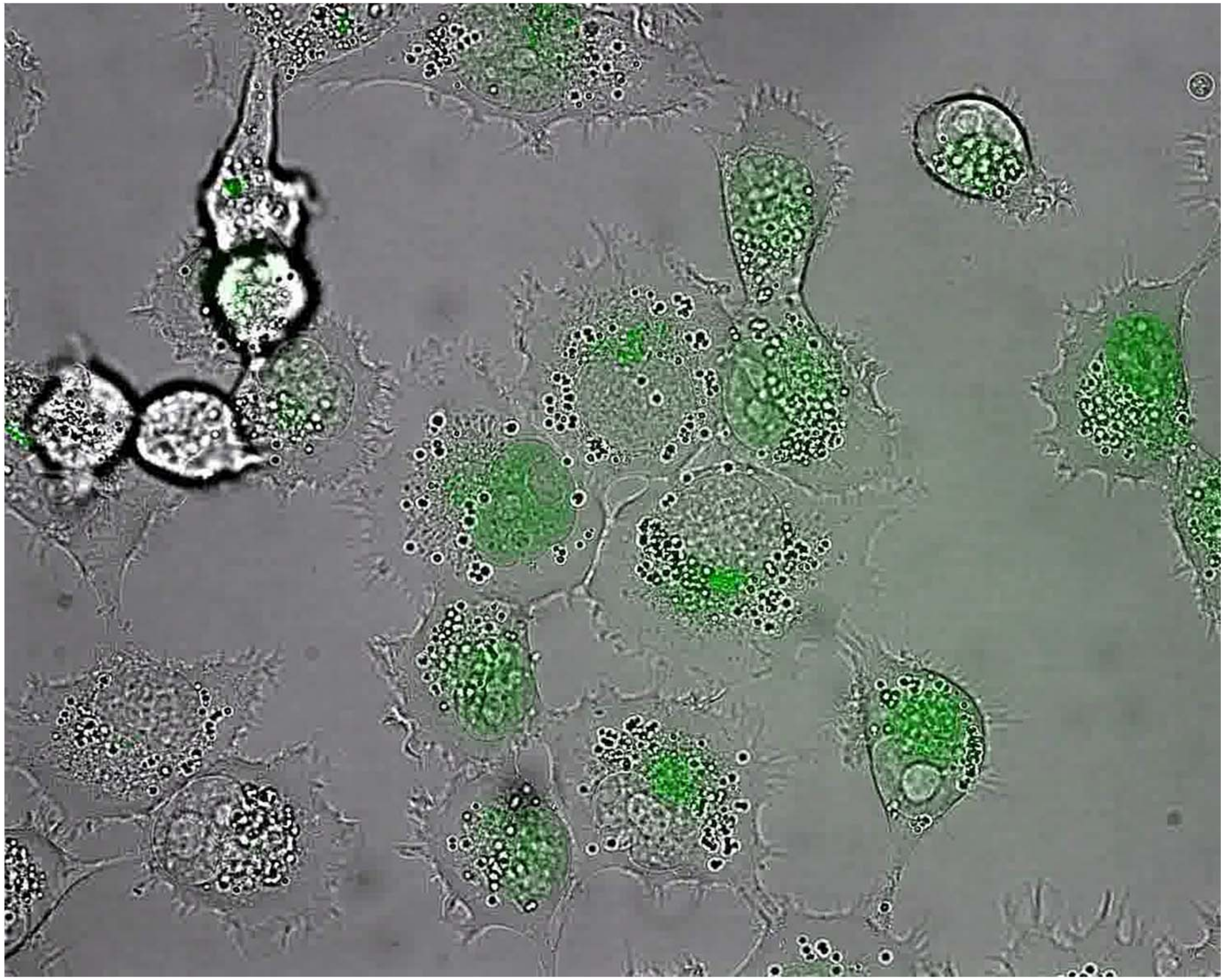




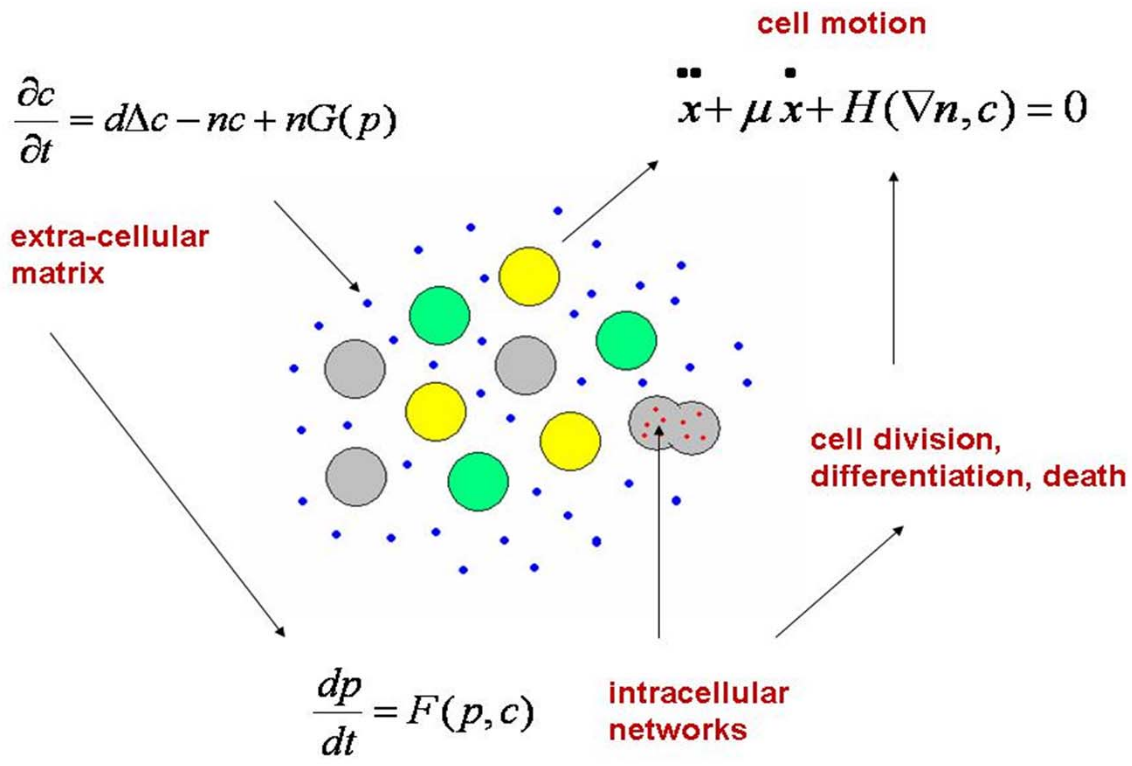
Concise cell biology for mathematicians: cell motion and division



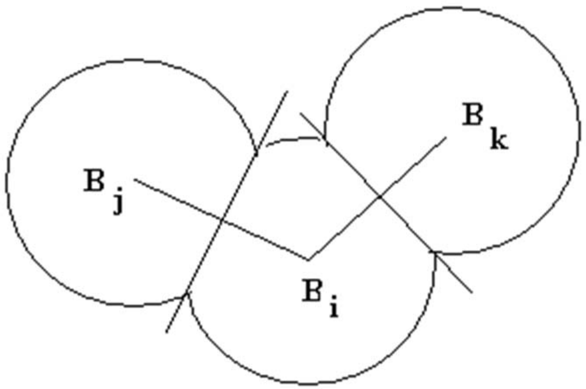
Apoptosis



Hybrid models



Mechanical interaction



Forces:

Potential

Dissipation

Adhesion

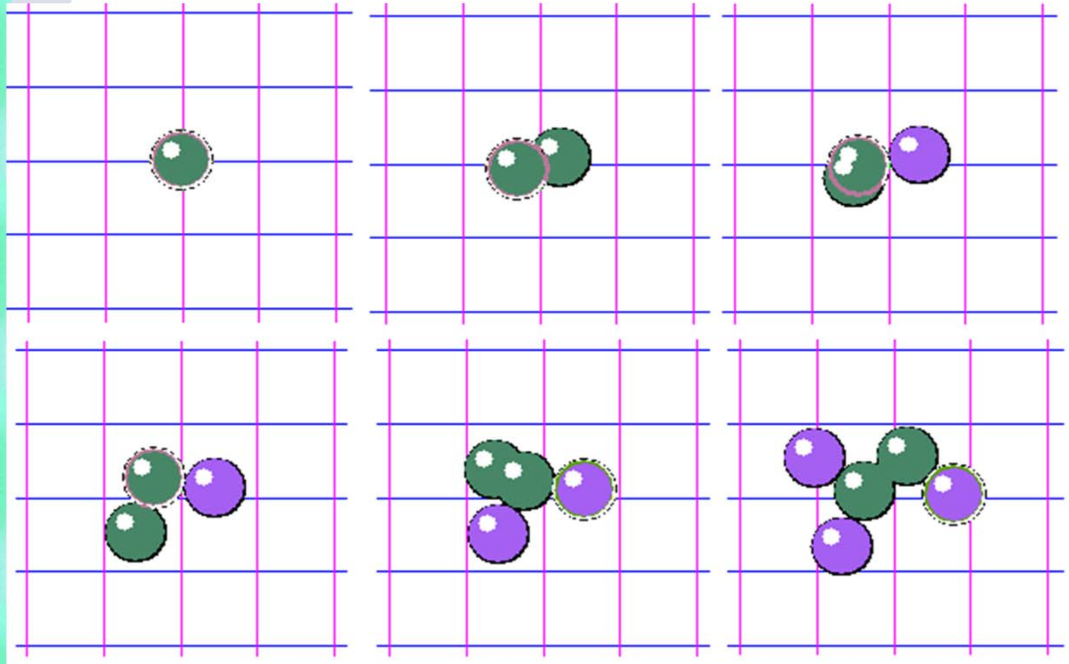
Chemotaxis

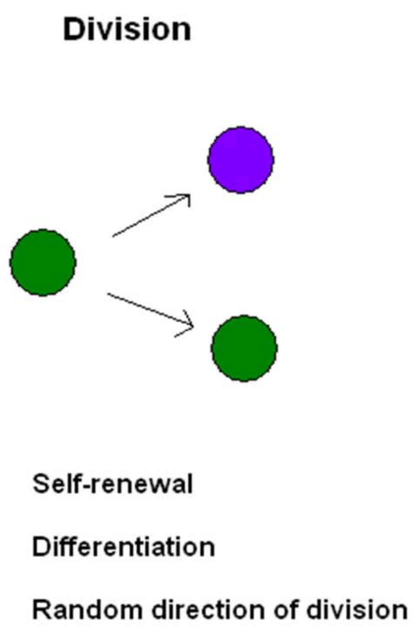
Random

Cells are replaced by points; Newton's second law:

$$m\ddot{x}_i + F^P + F^D + F^R = 0$$

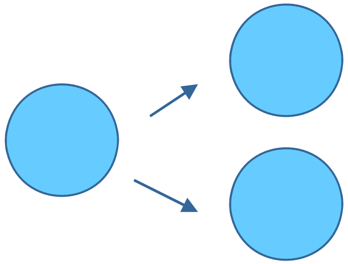
Cell division (Here and below: all software done by N. Bessonov)



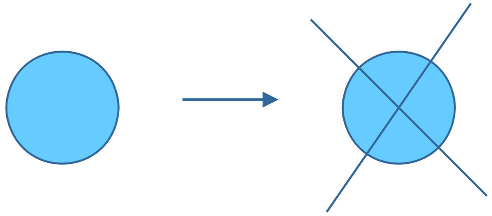


Cell division determines their random motion

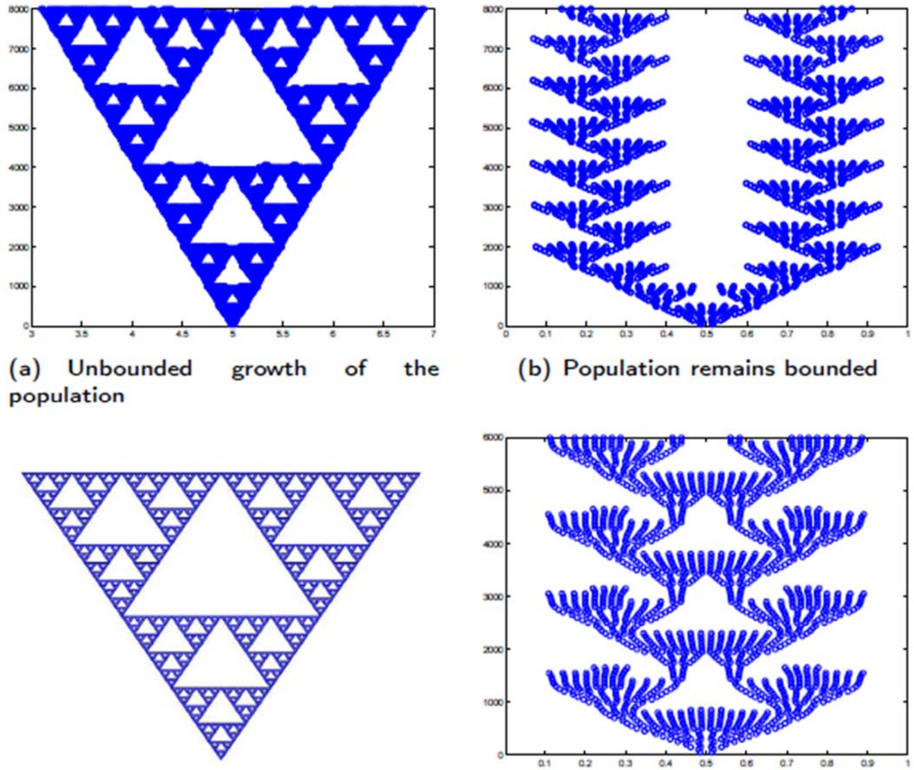
Proliferation and apoptosis



Ui > Ucr



Vi > Vcr



(a) Unbounded growth of the population

(b) Population remains bounded

(c) Tapis de Serpinskii - ensemble fractal

(d) Population remains bounded

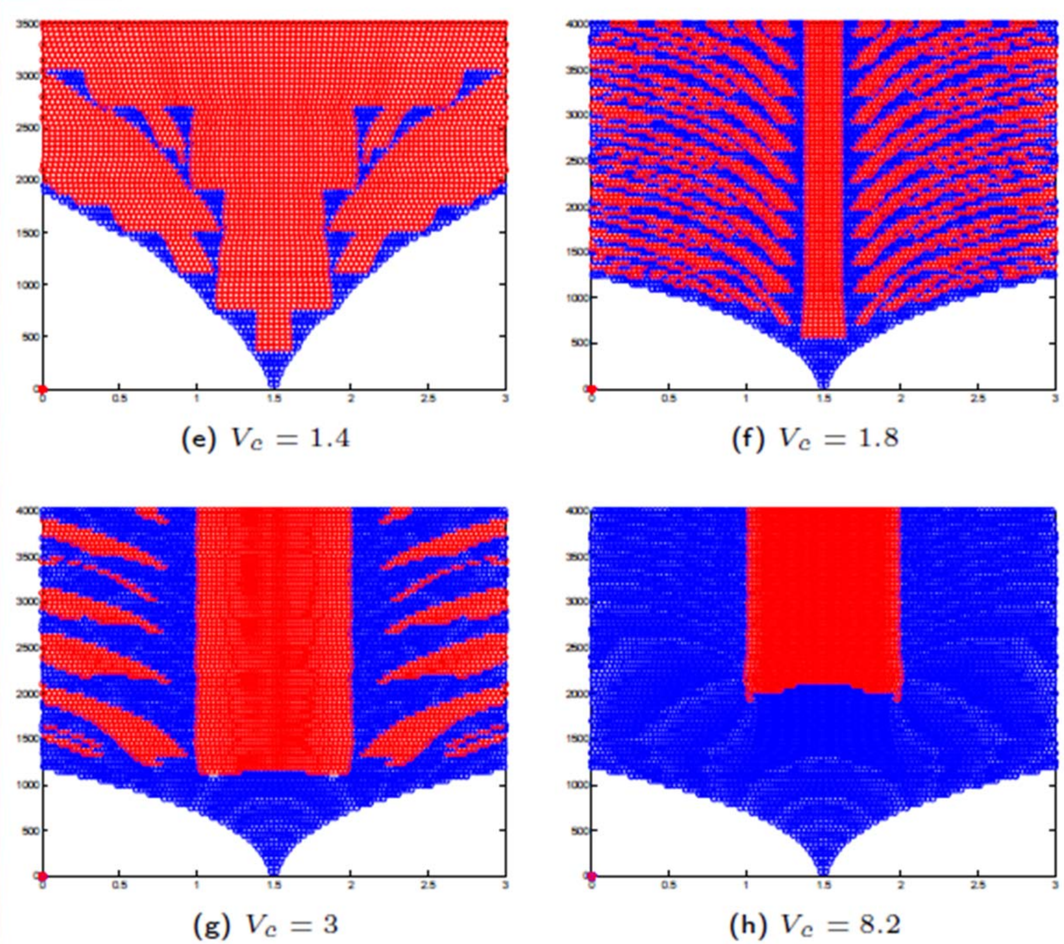
Extracellular regulation

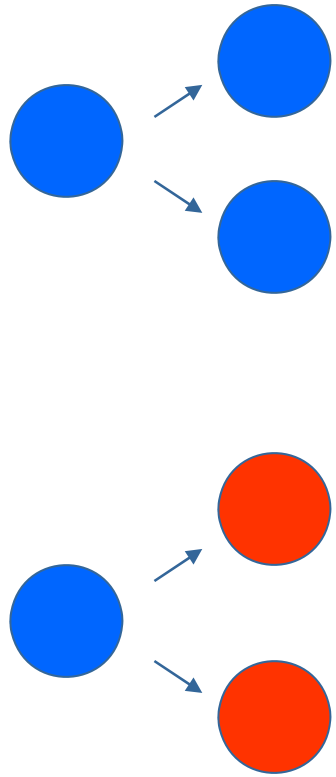
$$\begin{cases} \frac{du}{dt} = d_1 \frac{\partial^2 u}{\partial x^2} + b_1 c - q_1 u \\ \frac{dv}{dt} = d_2 \frac{\partial^2 v}{\partial x^2} + b_2 c - q_2 v \end{cases}$$

Intracellular regulation

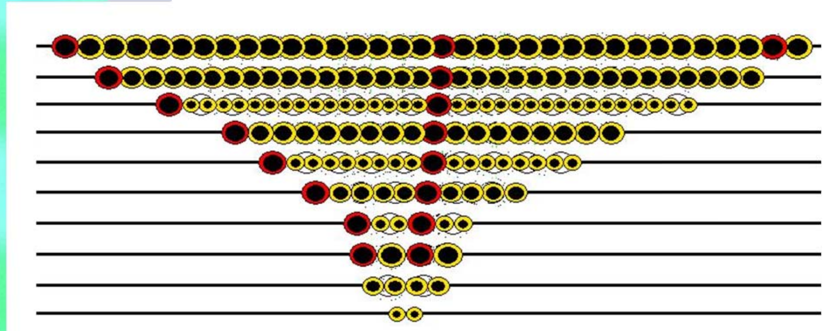
$$\begin{cases} \frac{du_i}{dt} = k_1^{(1)} u(x,t) - k_2^{(1)} u_i(t) + H_1 \\ \frac{dv_i}{dt} = k_1^{(2)} v(x,t) - k_2^{(2)} v_i(t) + H_2 \end{cases}$$

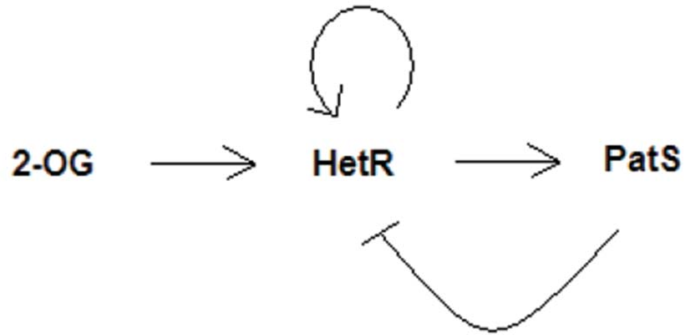
Proliferation and differentiation





Bacteria filament (anabaena)





$$
\begin{cases}
\frac{du_i}{dt} = H_u \\
\frac{dG_i}{dt} = H_g \\
\frac{dh_i}{dt} = k_1^{(h)} G_i(t) + k_2^{(h)} h_i^2(t) - k_3^{(h)} p_i(t) h_i(t) \\
\frac{dp_i}{dt} = d(p_{i-1} - p_i) + d(p_{i+1} - p_i) + k_1^{(p)} h_i(t) - k_2^{(p)} p_i(t)
\end{cases}
$$

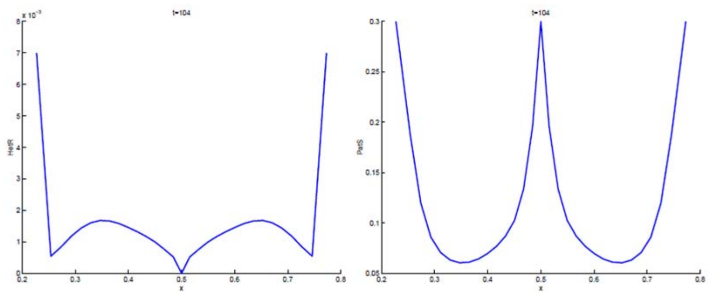


Figure 3: Concentrations of HetR (left) and of PatS (right) along the filament. Minima of HetR and maxima of PatS correspond to differentiated cells.

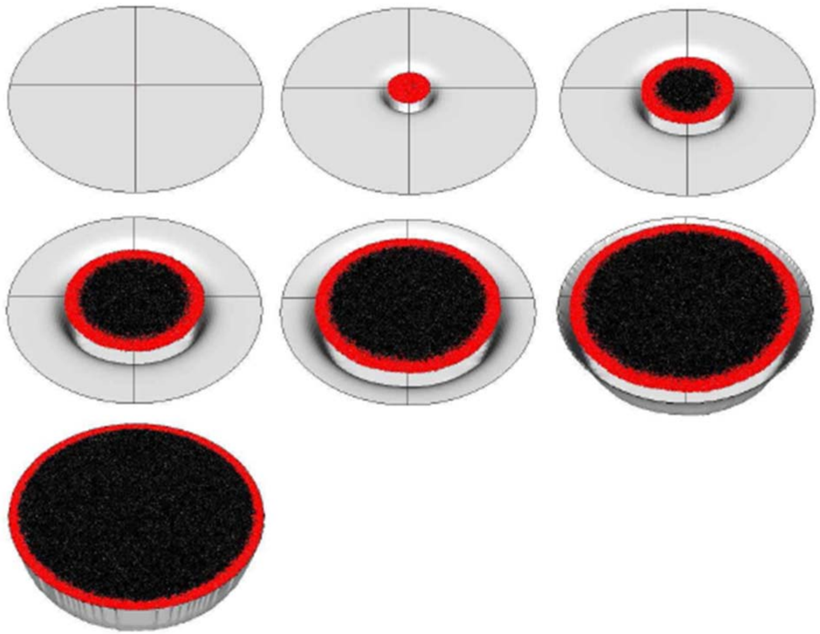
Tumor growth

$$\frac{\partial u}{\partial t} = D\,\Delta u - kcu$$

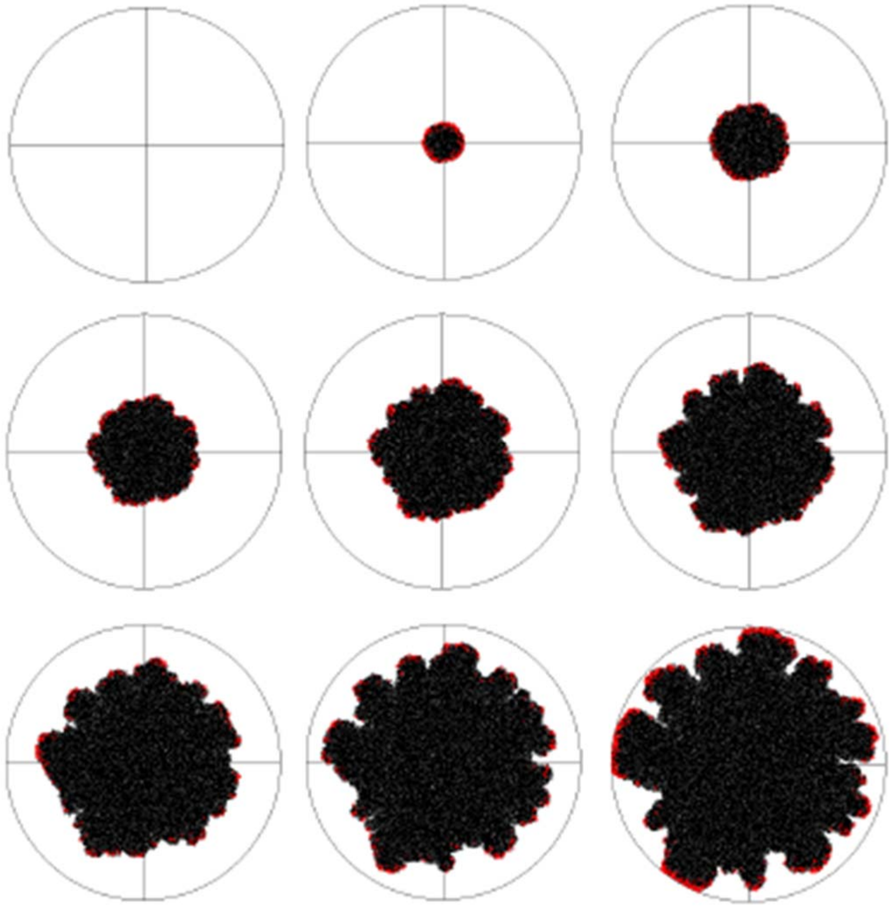
Nutrients

$$\frac{du_i}{dt} = k_1 u(x_i, t) - k_2 u_i$$

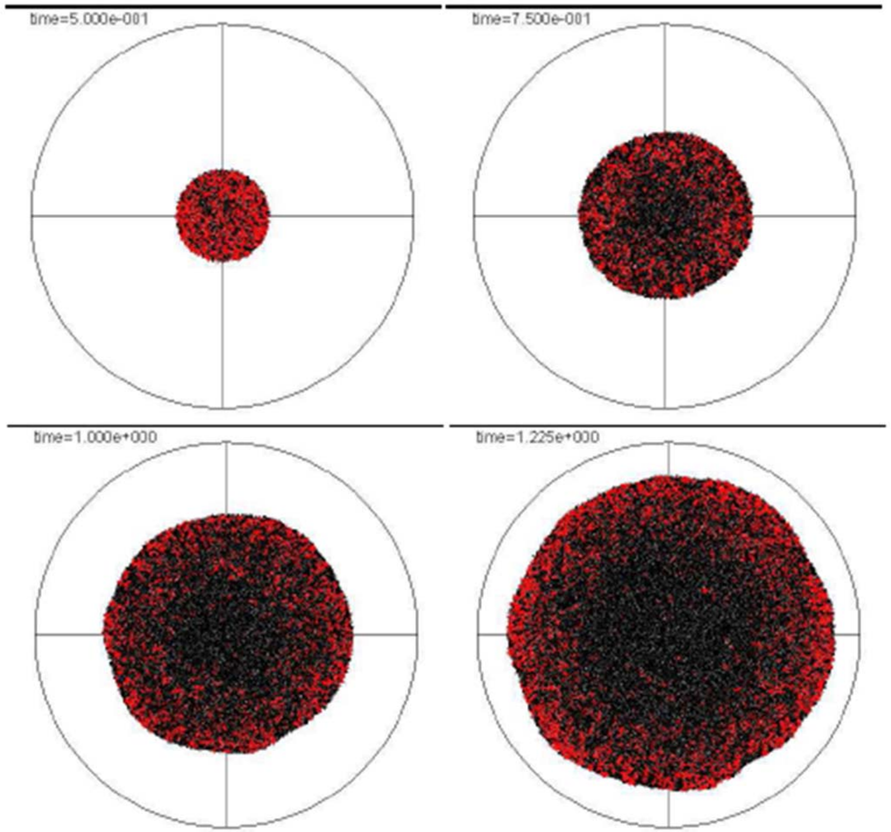
Intra-cellular concentration



Asymmetric growth

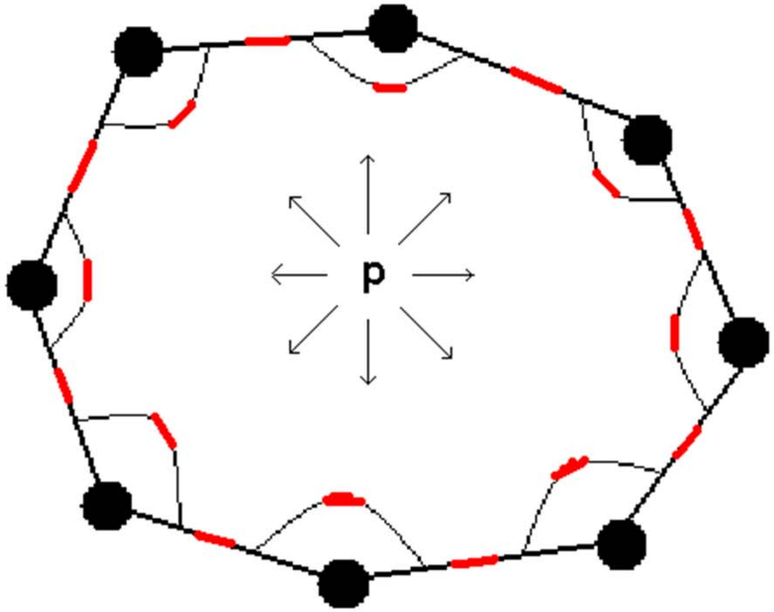


Dividing and dormant cells can be mixed

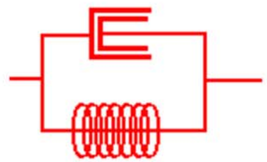


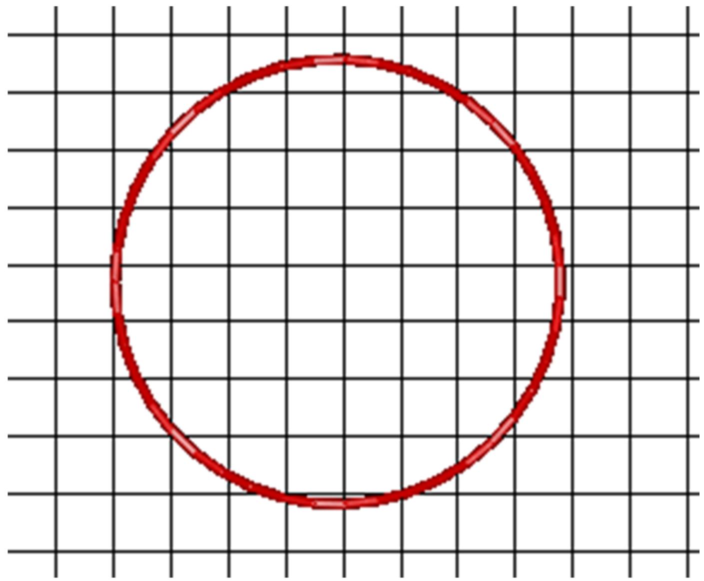
Deformable cell model

Cells are not exactly mathematical points: elastic cell model

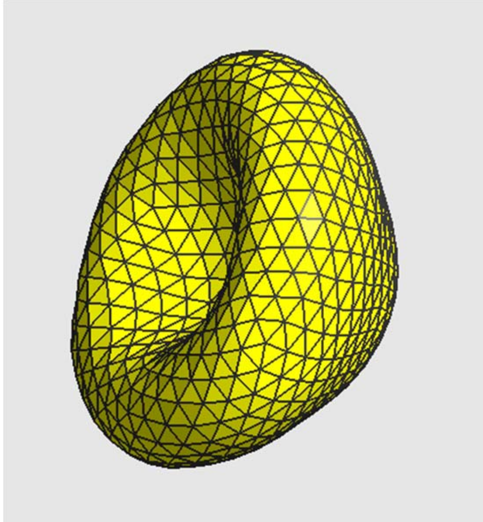


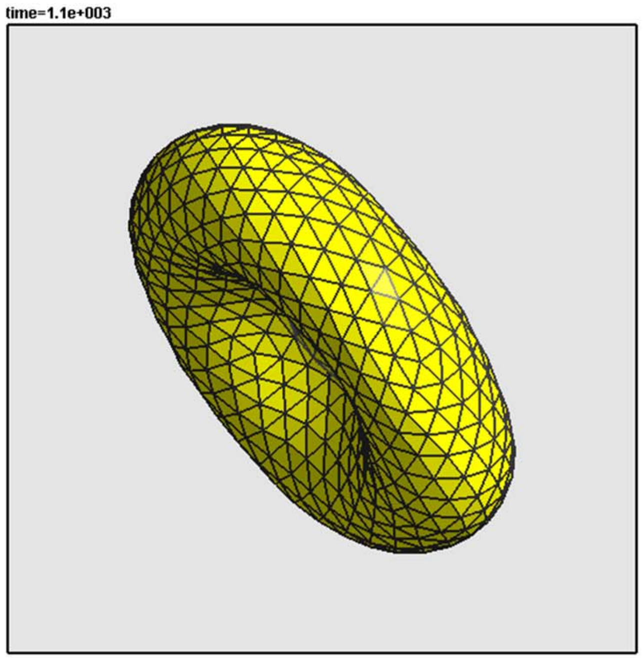
$$p \sim \frac{V_0}{V} - 1$$



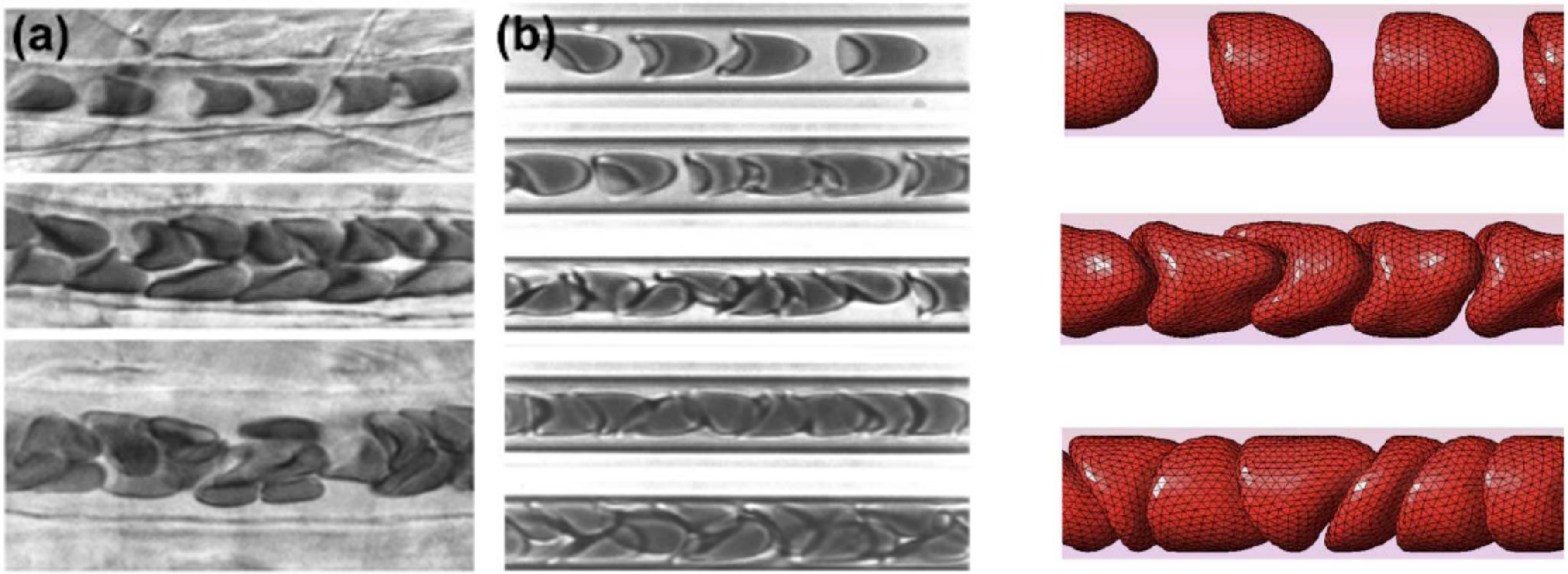


Erythrocyte 3D

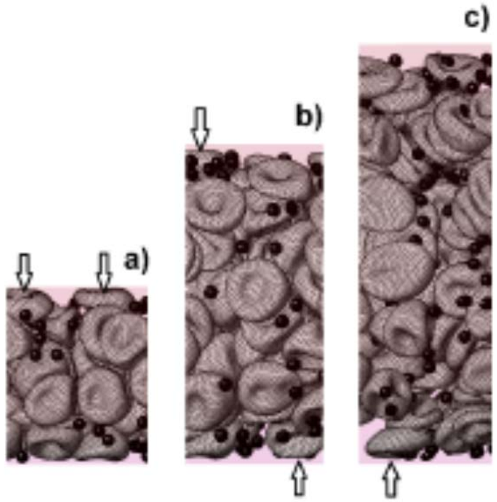


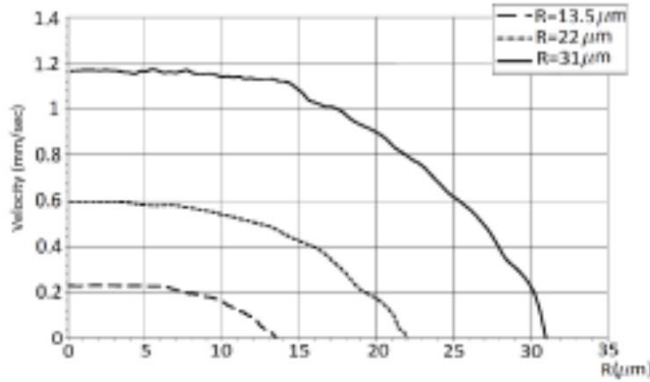


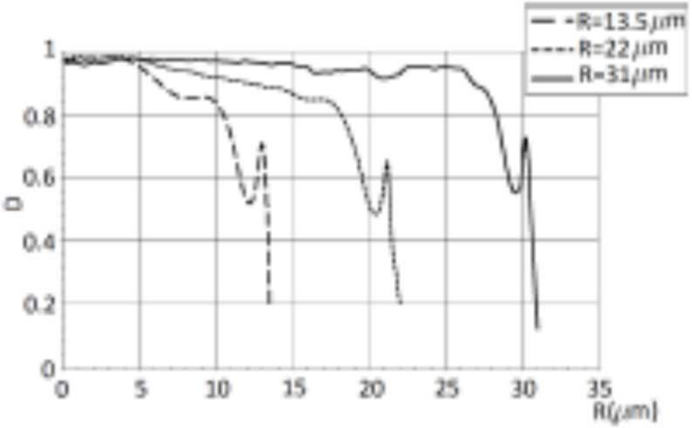
Blood flow in vivo, in vitro, in silico

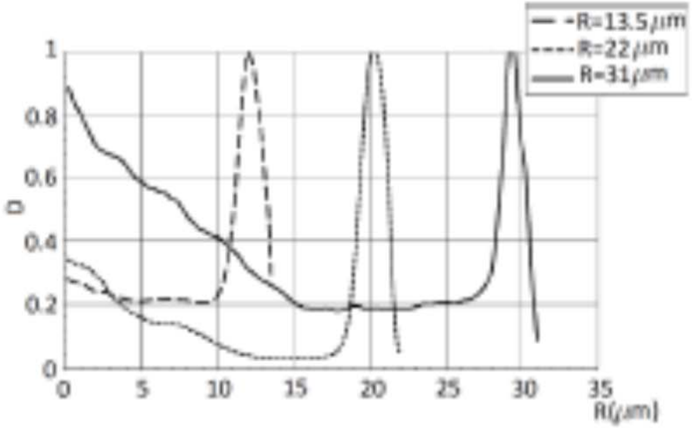


Cell distribution in flow

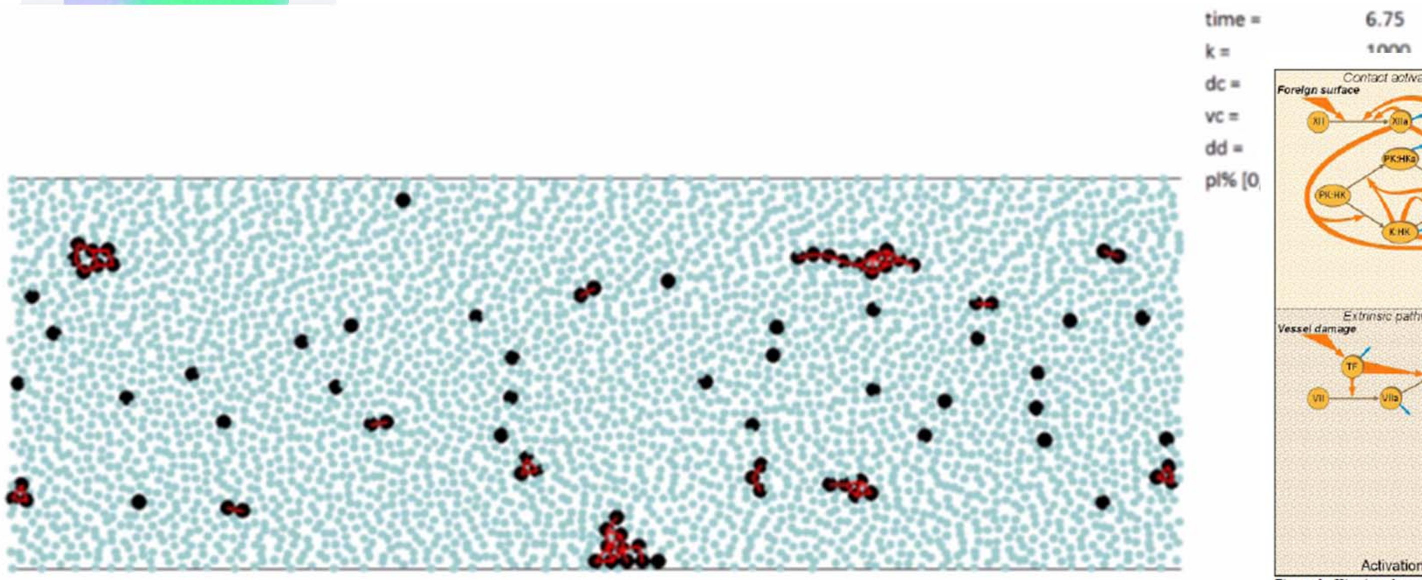








Blood coagulations



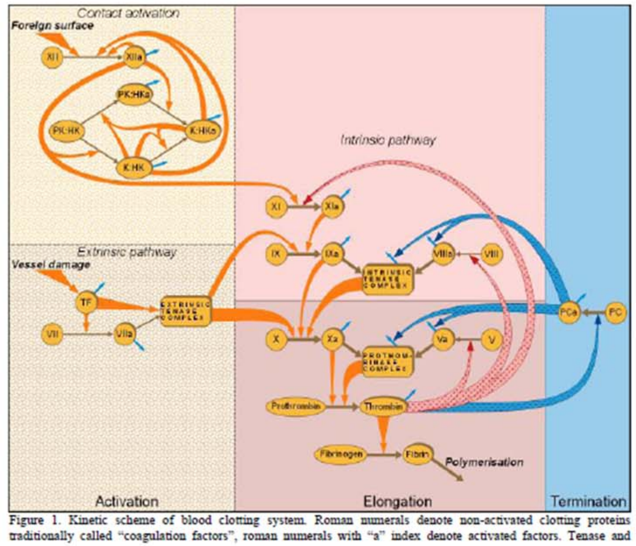
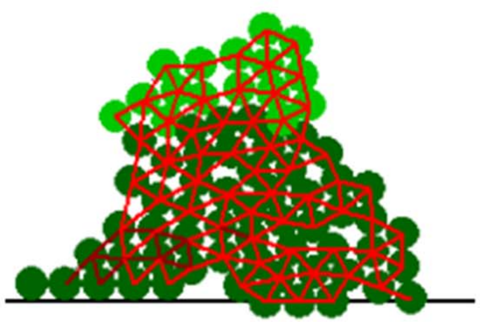
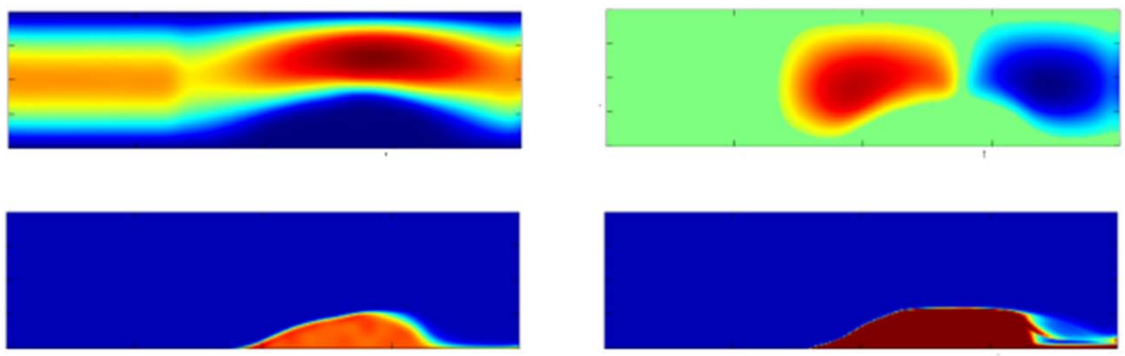
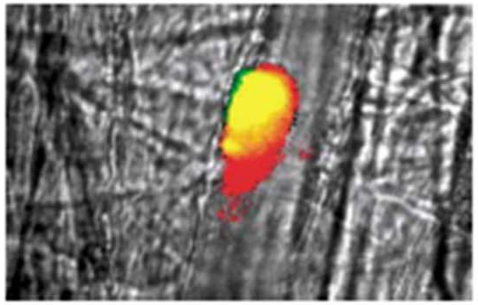


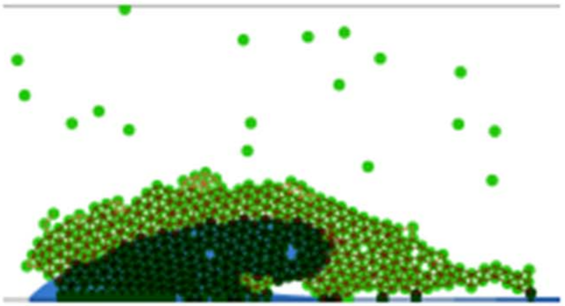
Figure 1. Kinetic scheme of blood clotting system. Roman numerals denote non-activated clotting proteins traditionally called "coagulation factors", roman numerals with "a" index denote activated factors. Tenase and

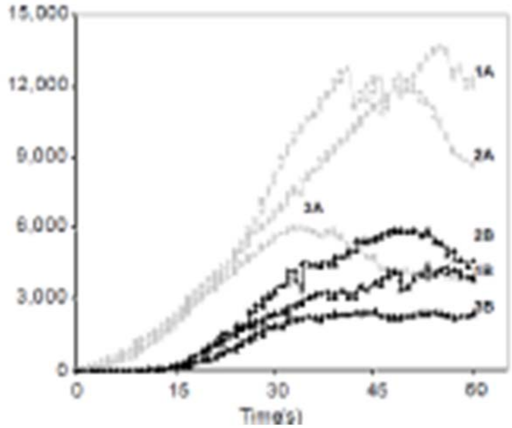


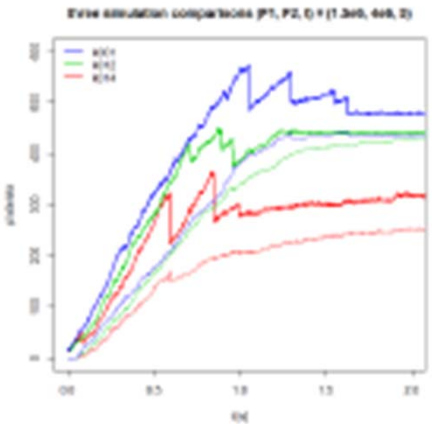


Clot growth

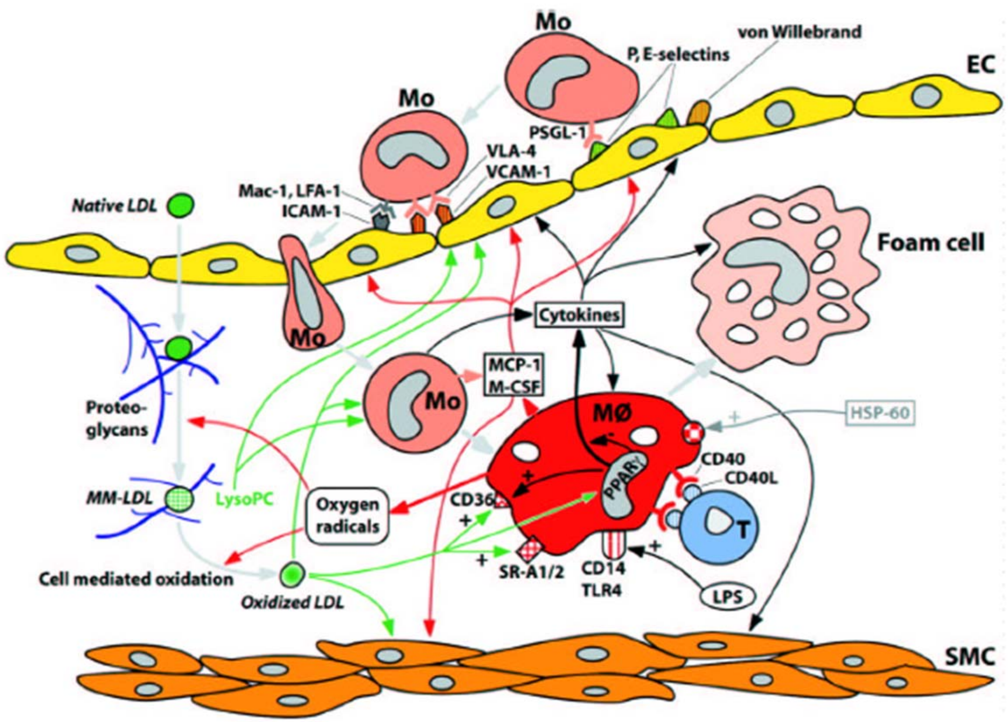


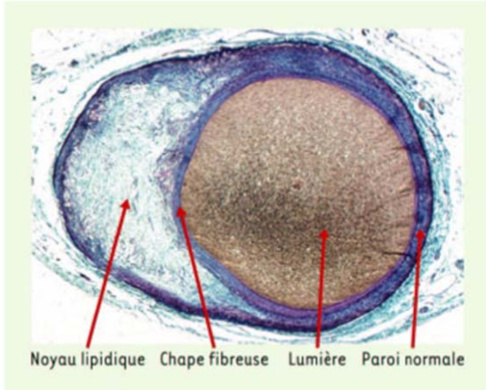


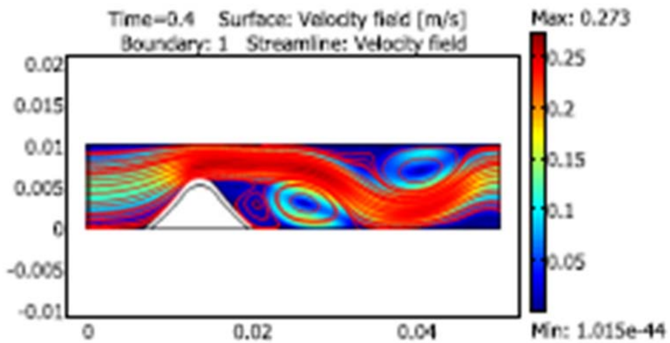




Atherosclerosis



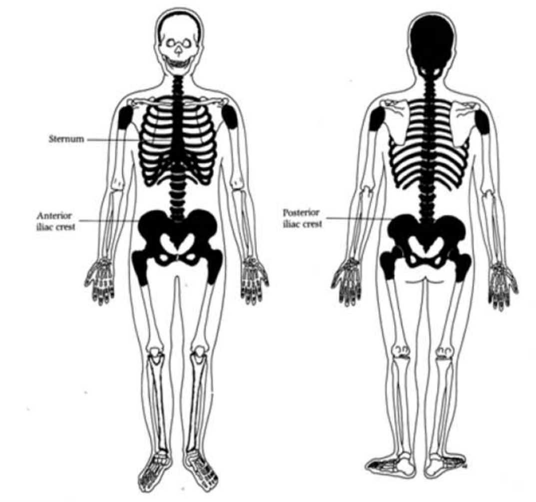




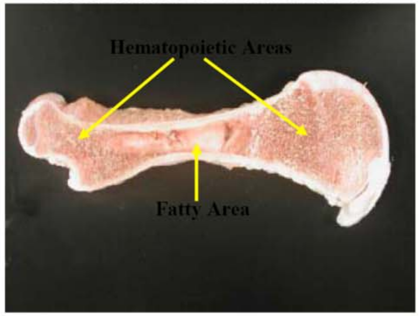
Hematopoiesis and blood diseases

Hematopoiesis: blood cell production in the bone marrow

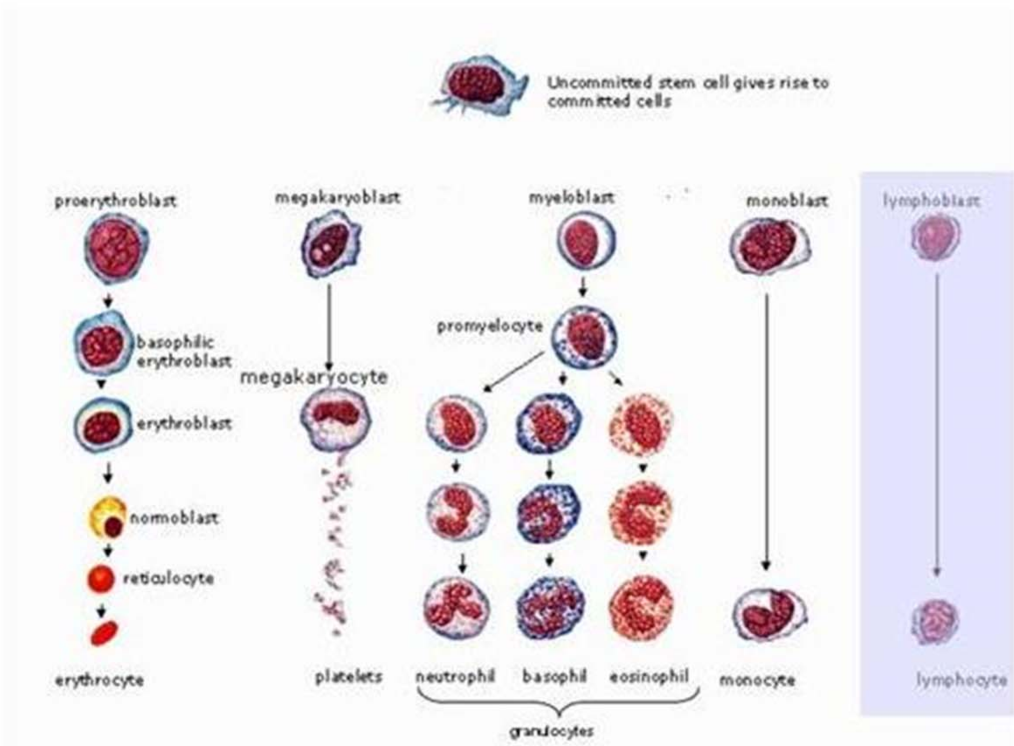
Anatomical Sites of Hematopoiesis in Adult Humans



Cross Section of Bone in a Foal

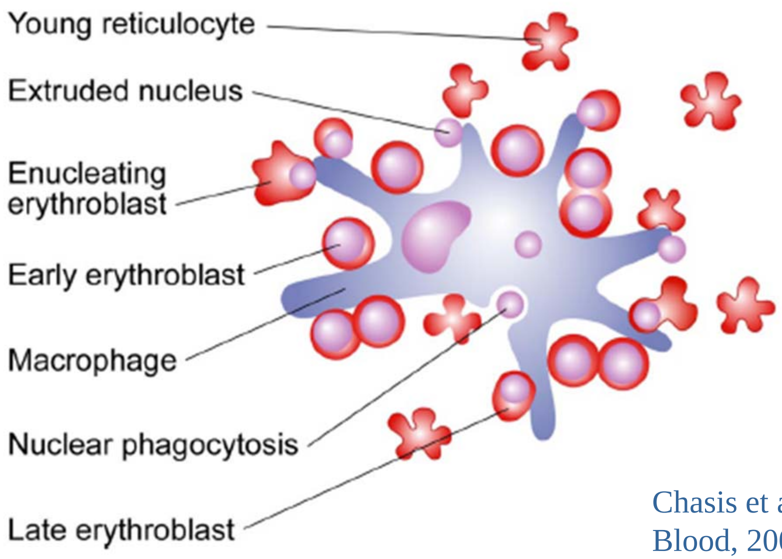


Hematopoiesis scheme



Millions of blood cells produced every second

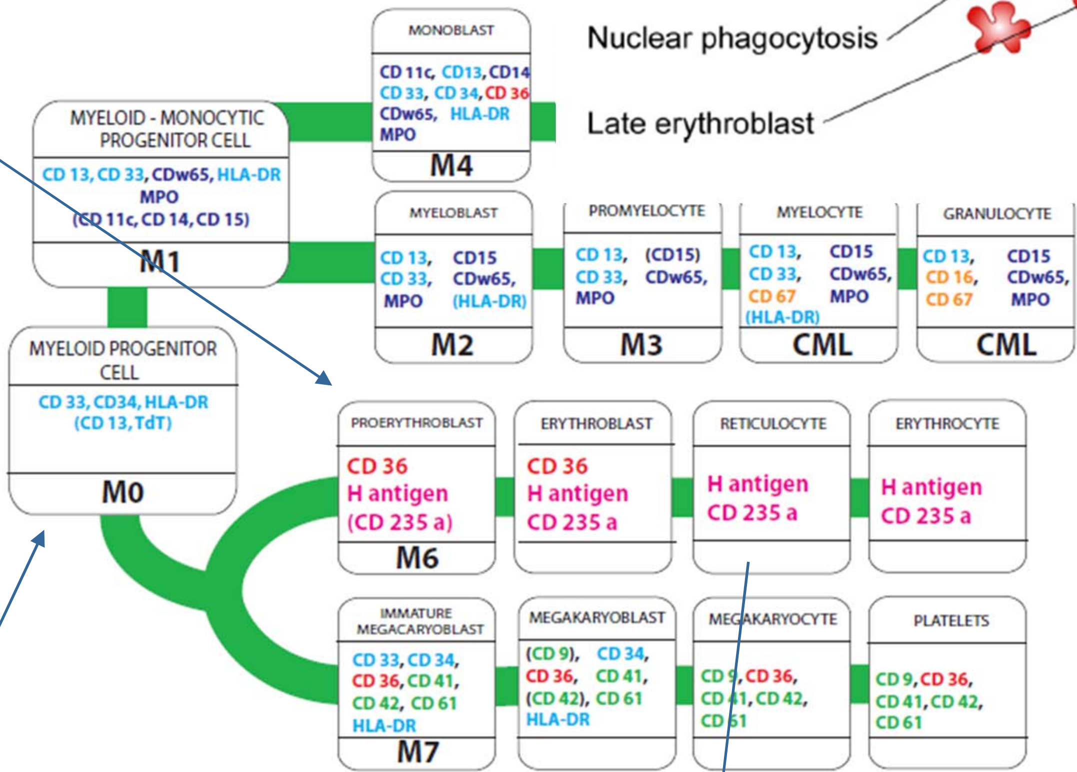
Erythropoiesis



Chasis et al. Blood, 2008

Erythroleukemia

Stem cells



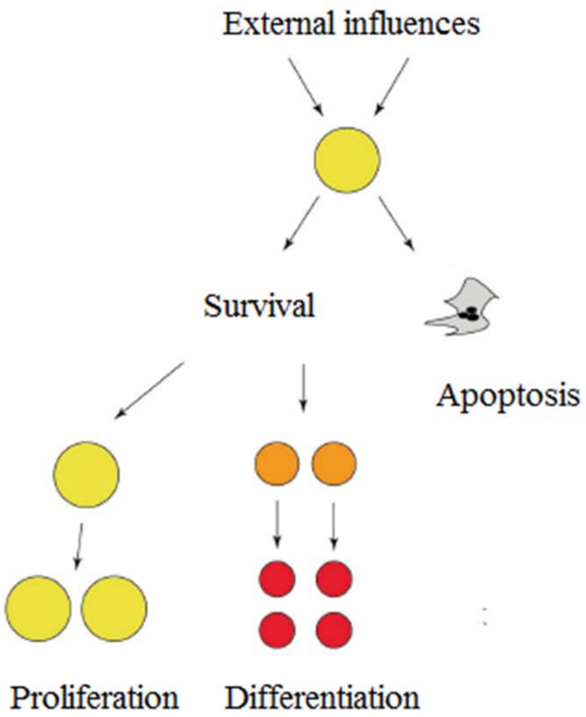
Blood flow

Self-renewal, differentiation, apoptosis

Fas-ligand

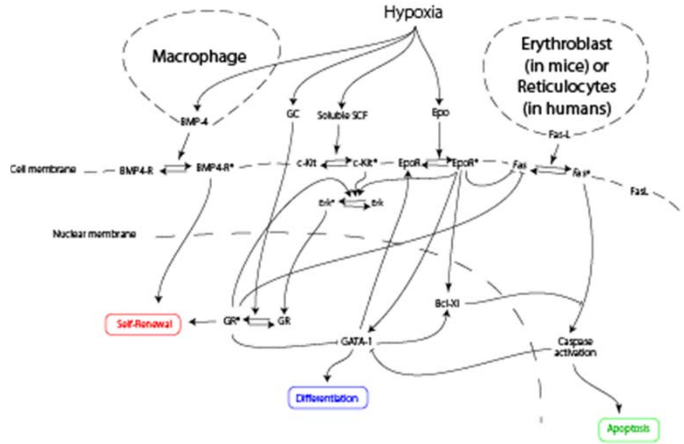
Feedback by erythropoietin

Intracellular and extracellular regulation of erythroid progenitors



$$\frac{\partial F_L}{\partial t} = D_1 \Delta F + W_1 - \sigma_1 F_L,$$

$$\frac{\partial G}{\partial t} = D_2 \Delta G + W_2 - \sigma_2 G.$$

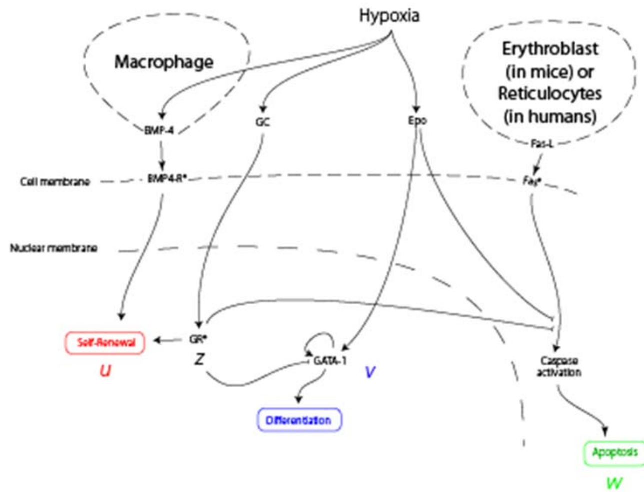


$$\frac{dz}{dt} = a_0,$$

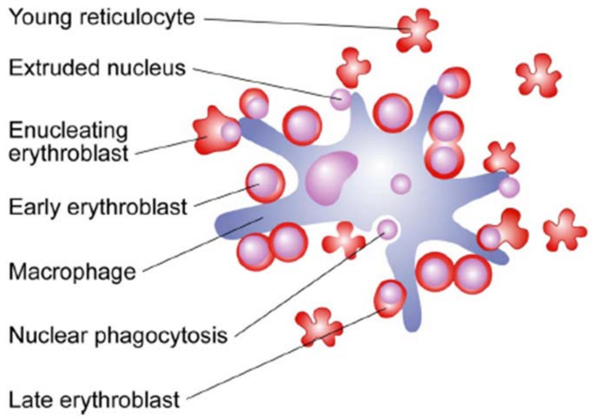
$$\frac{du}{dt} = a_1 + b_1 z,$$

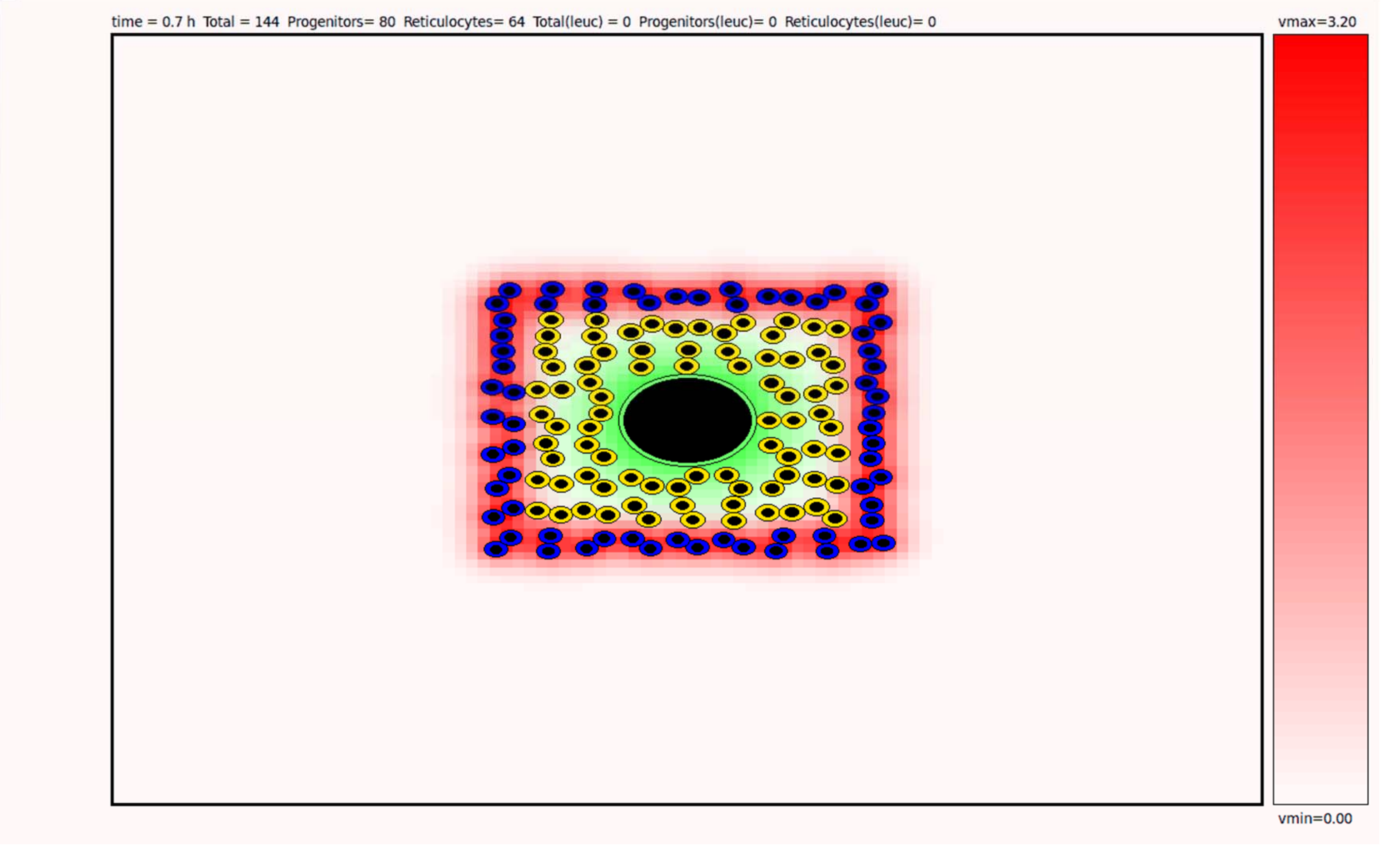
$$\frac{dv}{dt} = a_2 - b_2 z v,$$

$$\frac{dw}{dt} = a_3 - b_3 z w.$$

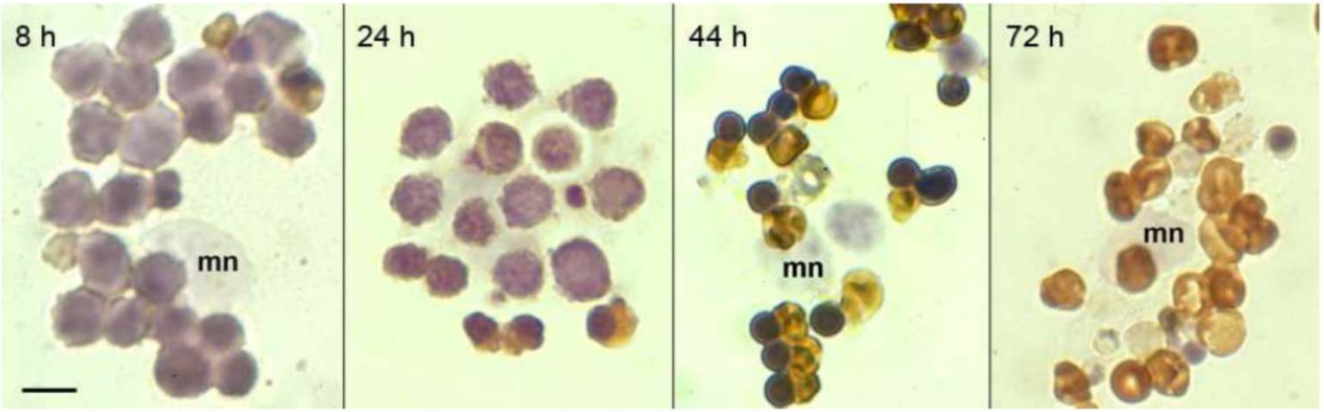


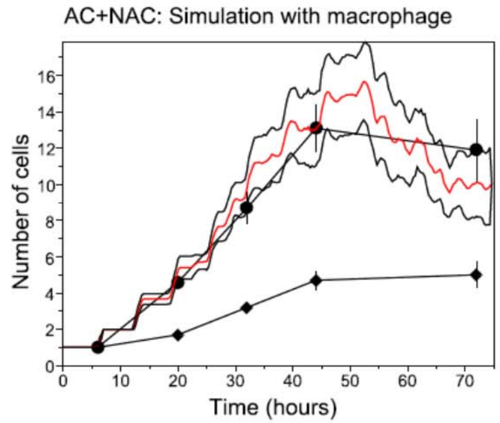
Erythroblastic islands

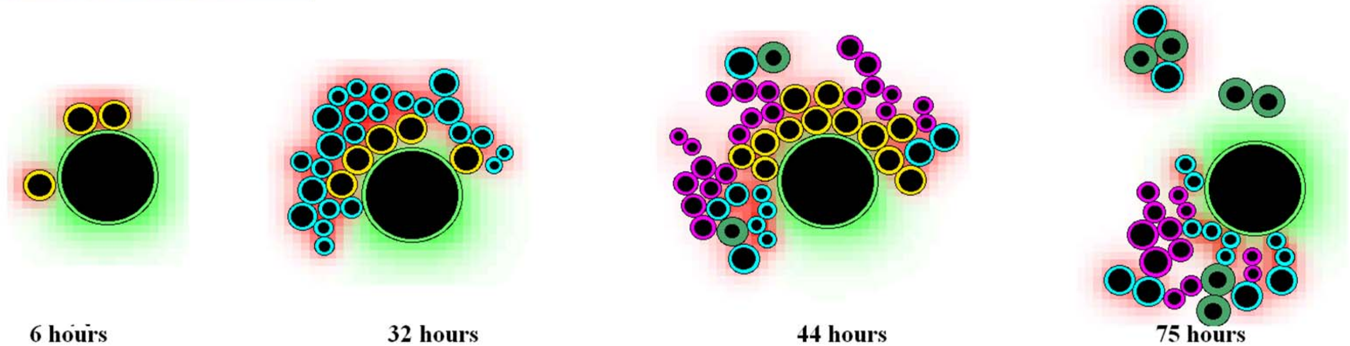


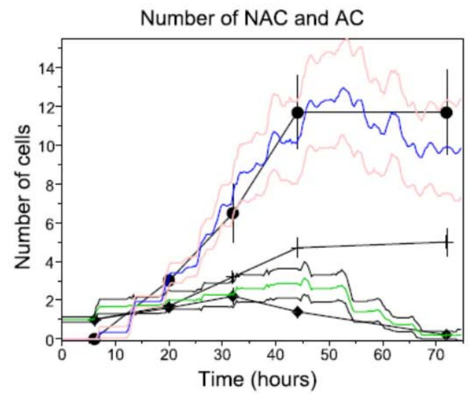


Erythroblastic islands

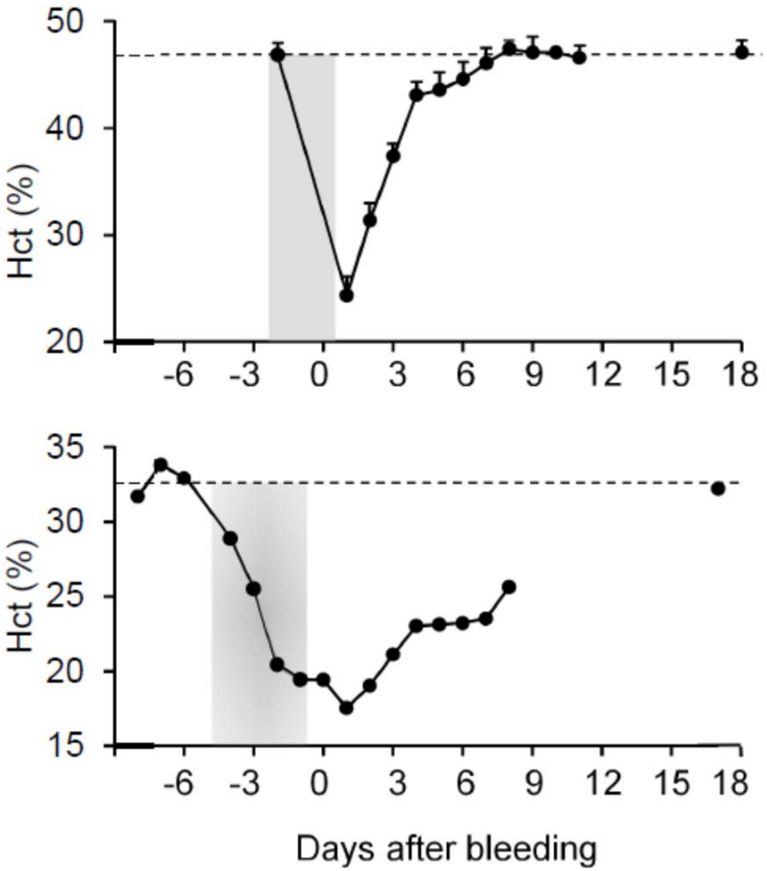


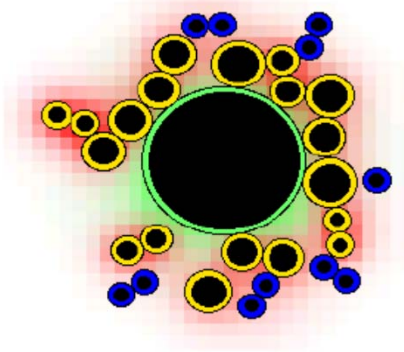


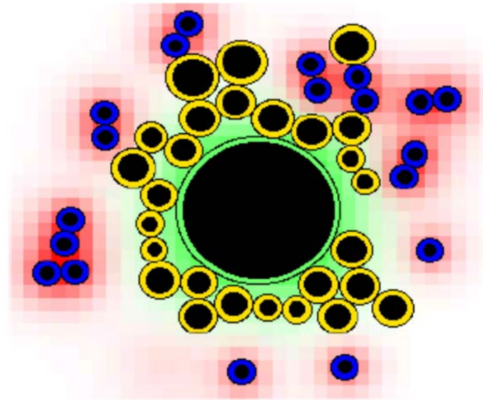


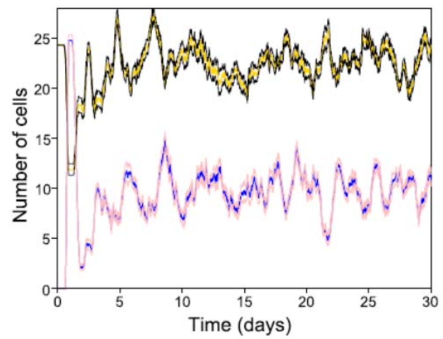


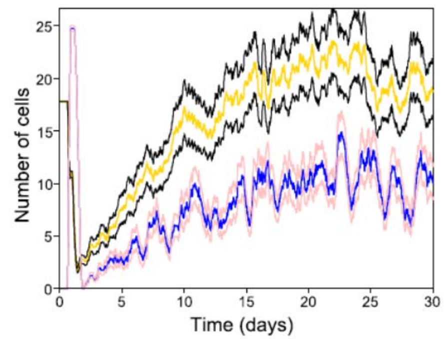
Man versus mouse





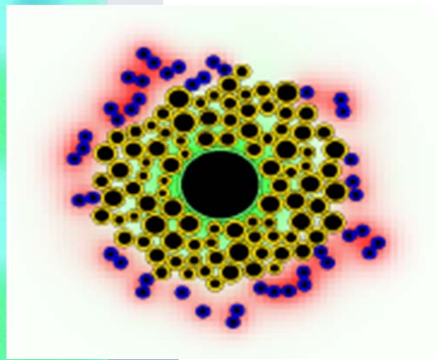






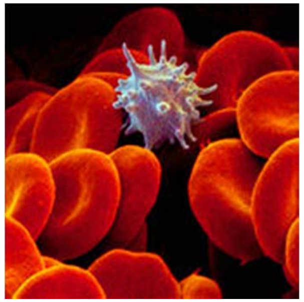
Anemia (in vivo mice bleeding)

Bone marrow
(erythroblastic island)



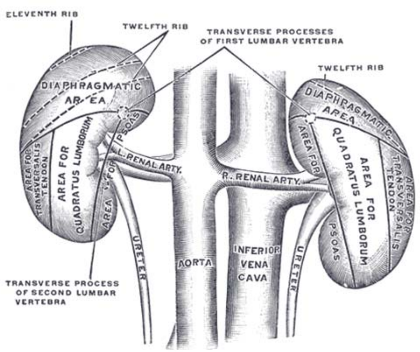
erythrocytes

Blood circulation



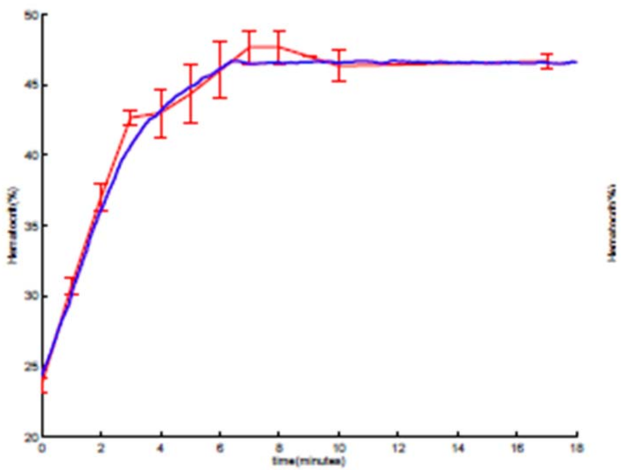
Bleeding (lack of
hemaglobine)

Erythropoietine
(decreases
apoptosis)



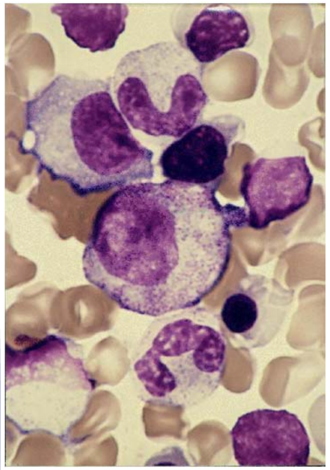
Kidneys

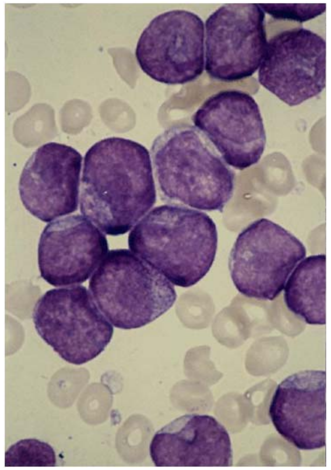
Hematocrite restoring
after anemia



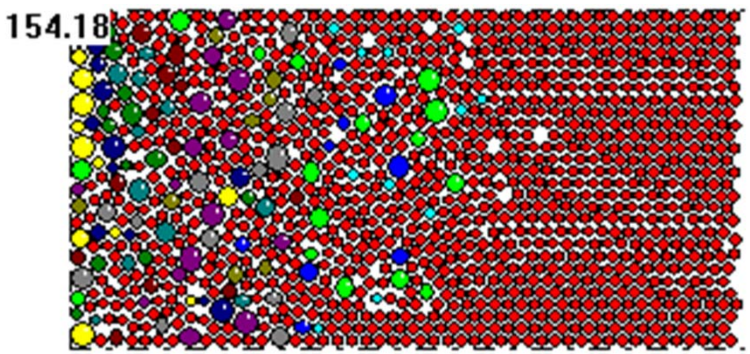
Leukemia modelling and treatment

Leukemia and personalized medicine





Normal bone marrow   Leukemic bone marrow



- ~1/1000 live with leukemia or in remission
- Five year relative survival rate: 14% in 1960, 54% in 2005
- Possible causes: radiation, chemicals, but mostly unknown
- Median patient age at diagnosis 66 years; 27% of all cancer cases for children

Cf. reaction-diffusion equations

Treatment with ara-c

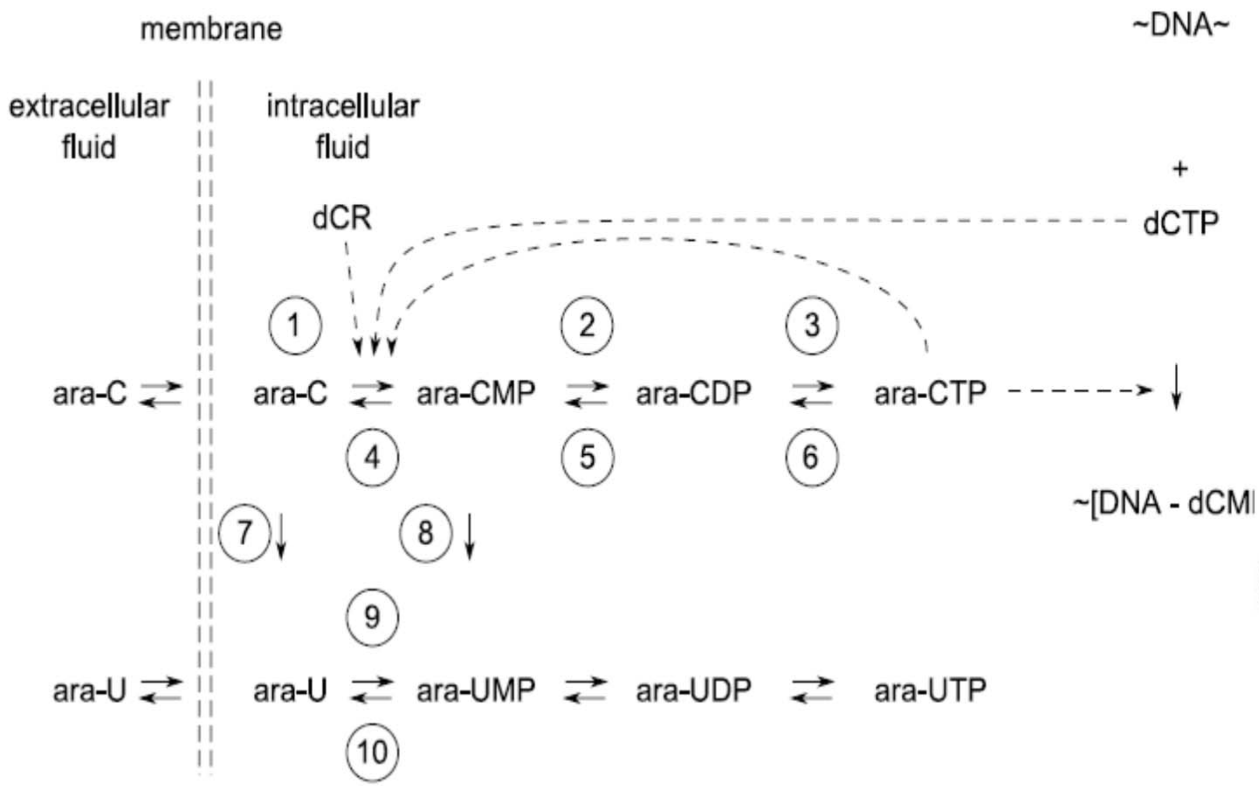
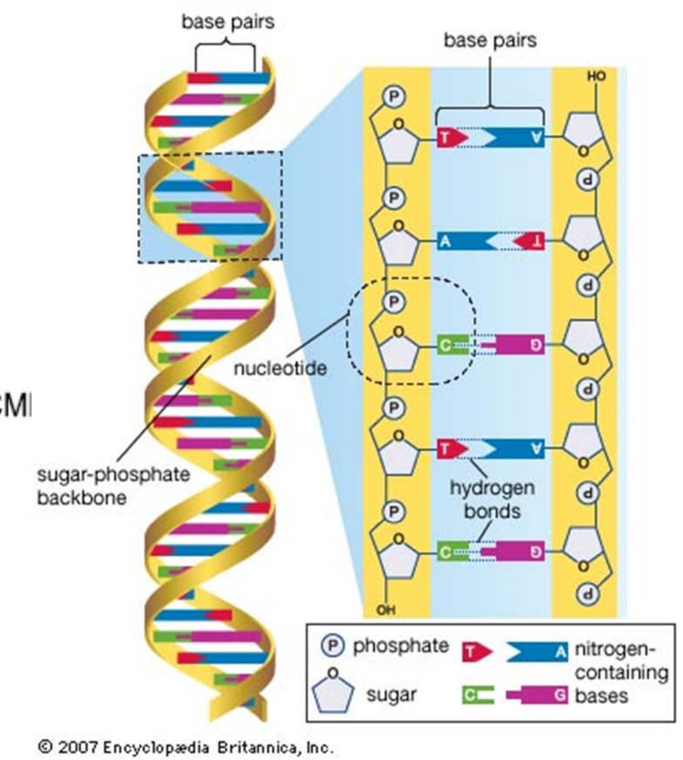


FIGURE 44 – The metabolism of AraC, adapted from [76].



Pharmacokinetics

Extra-cellular ara-c

$$\frac{dv_i}{dt} = k_1^{(v)} v(x,t) - k_2^{(v)} v_i(t) - (r_p - r_{dp} + r_{da})$$

Intra-cellular ara-c

$$r_p = \frac{V_k}{1 + \frac{K_m K_a}{v_i}}$$

Phosphorylation

$$r_{dp} = \frac{V_{dp}}{1 + \frac{\alpha K_{dp}}{v_i^a}}$$

Dephosphorylation

$$r_{da} = \frac{V_{da}}{1 + \frac{K_{da}}{v_i}}$$

Deamination

$$\frac{dv_i^a}{dt} = \widetilde{\alpha}(r_p - r_{dp})$$

Intra-cellular ara-ctp

Efficiency of treatment for different protocols

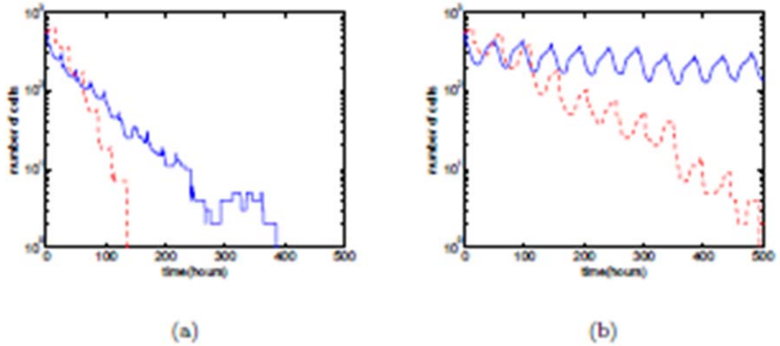


FIG. 3.5. *Evolution in time of the total number of cells with Ara-C administrated at 1 a.m. (upper curve) or at 1 p.m. (lower curve). Left: Interval between administrations is 24 hours. Right: Interval between administrations is 48 hours.*

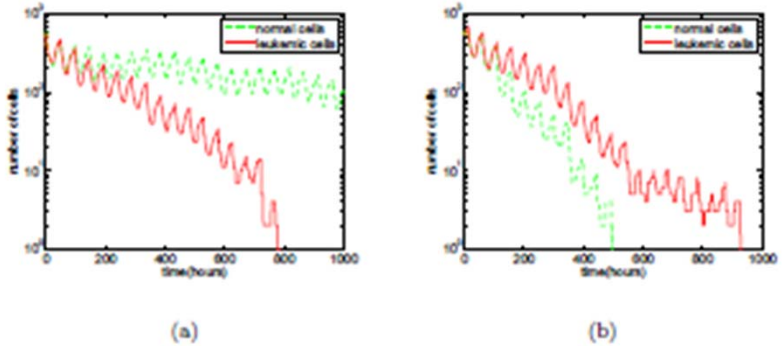


FIG. 3.6. *Evolution in time of the total number of normal cells (green line) and leukemic cells (red line) with Ara-C administrated every 48 hours at 1 a.m. (left) and at 1 p.m. (right).*

Discussion

- The choice of cell fate (self-renewal, differentiation, apoptosis):

  intracellular regulation (probably simplest and generic)

  local and global extracellular regulation

  the model may not be unique

  parameters

  control self-renewal (the last choice, local regulation)

- Cancer cell evolution
- The role of stochasticity