Modelling of leukemia development in the bone marrow

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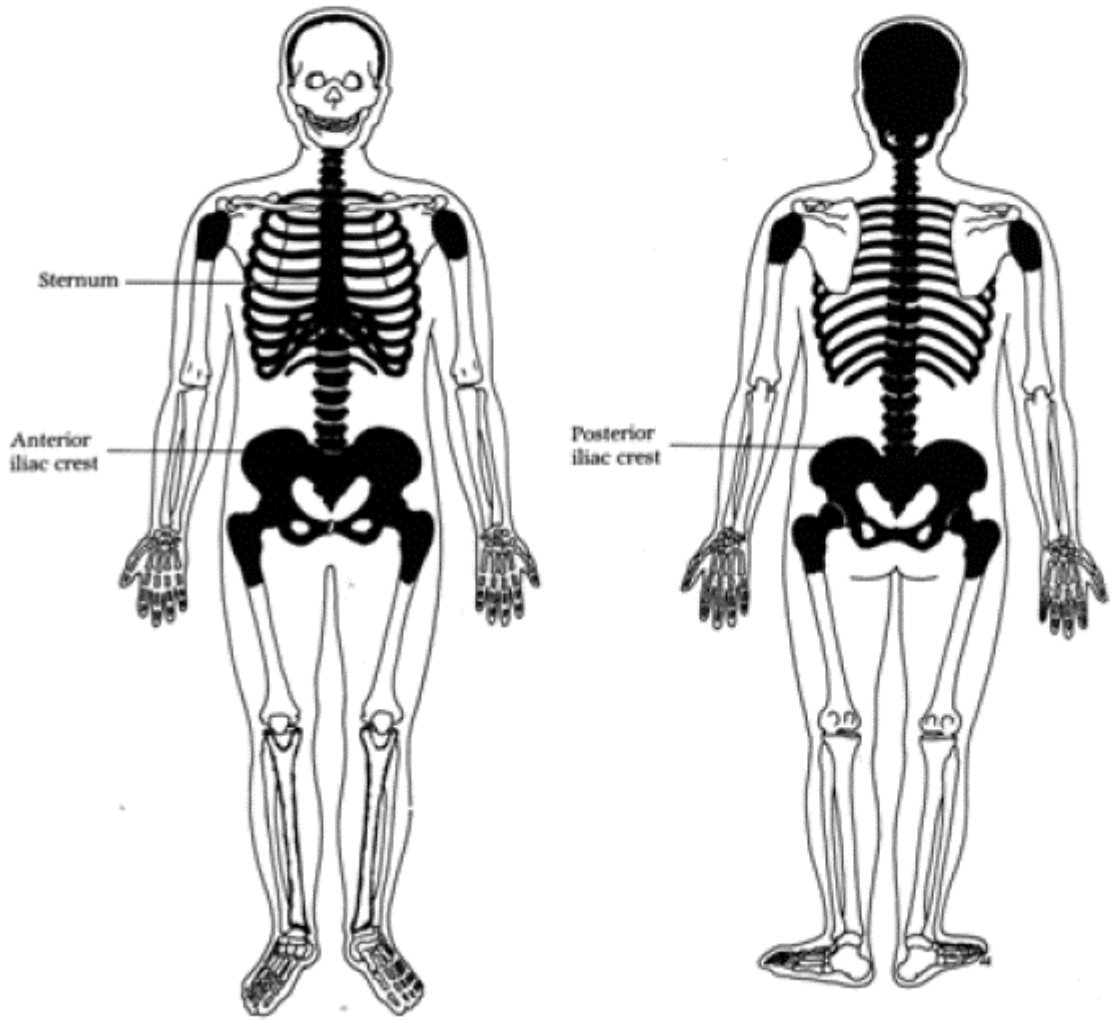
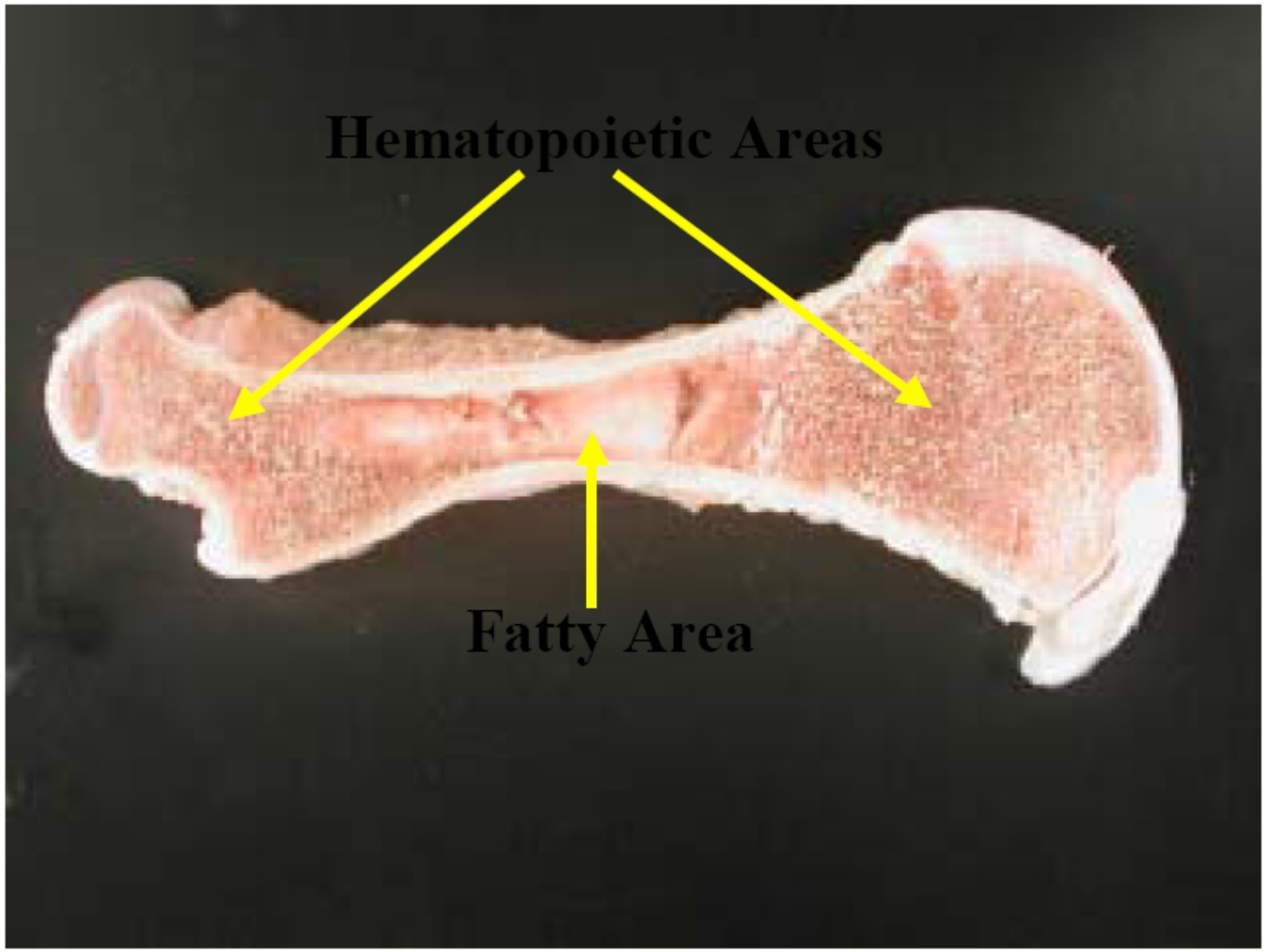
Plan of the presentation

- 1. About hematopoiesis
- 2. Leukemia dignostics with flow cytometry
- 3. Cellular modelling

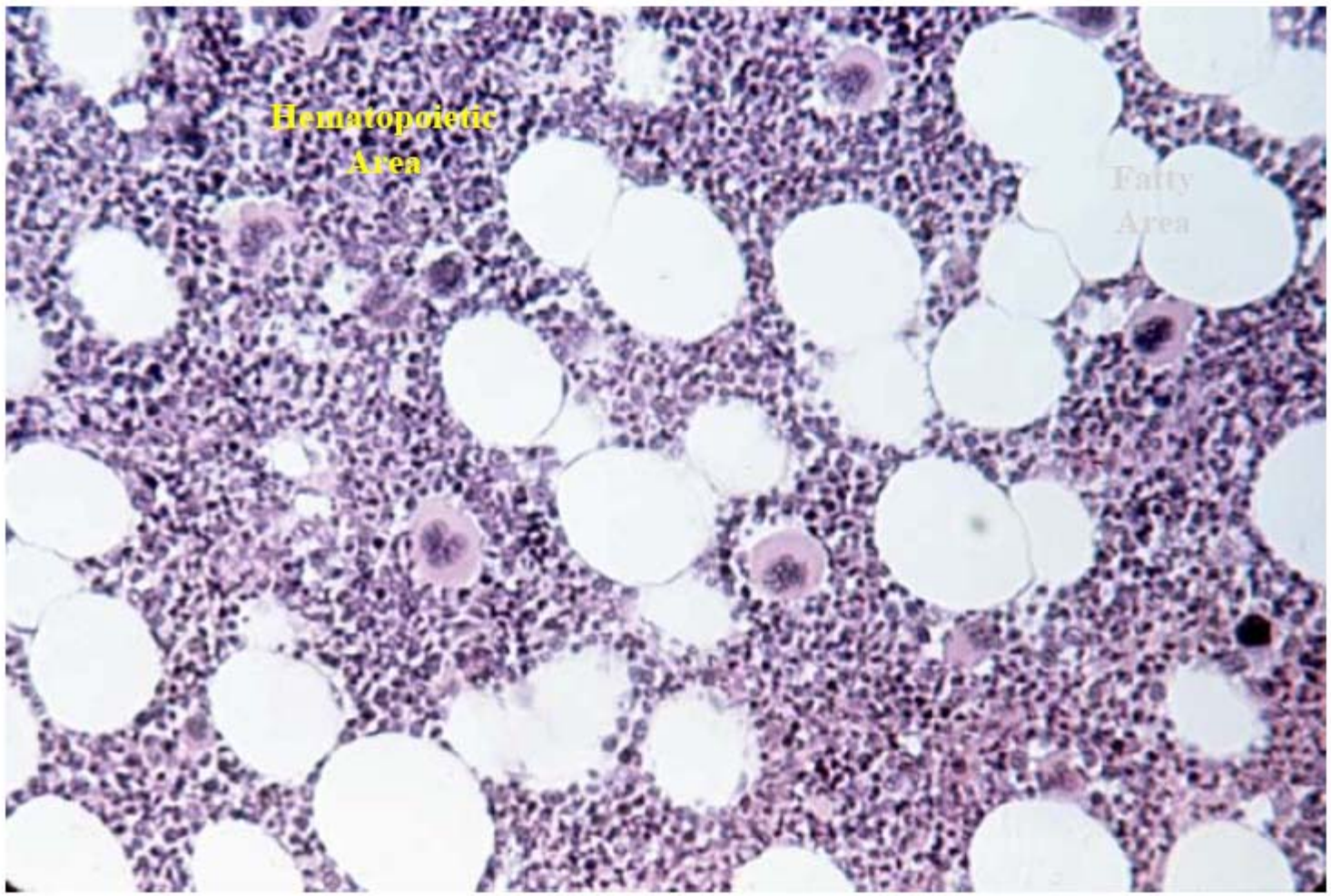
Anatomical Sites of Hematopoiesis in Adult Humans



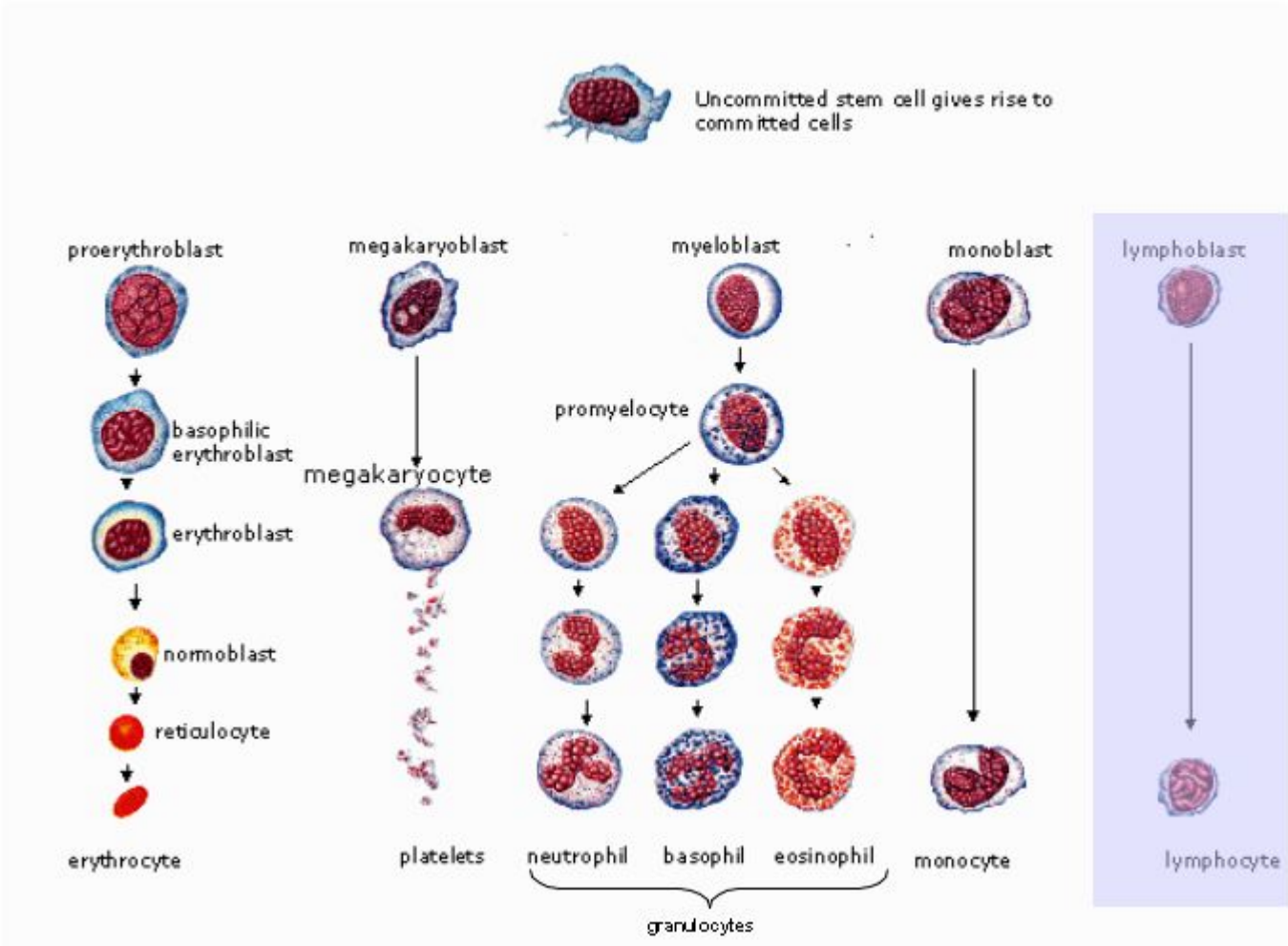
Cross Section of Bone in a Foal

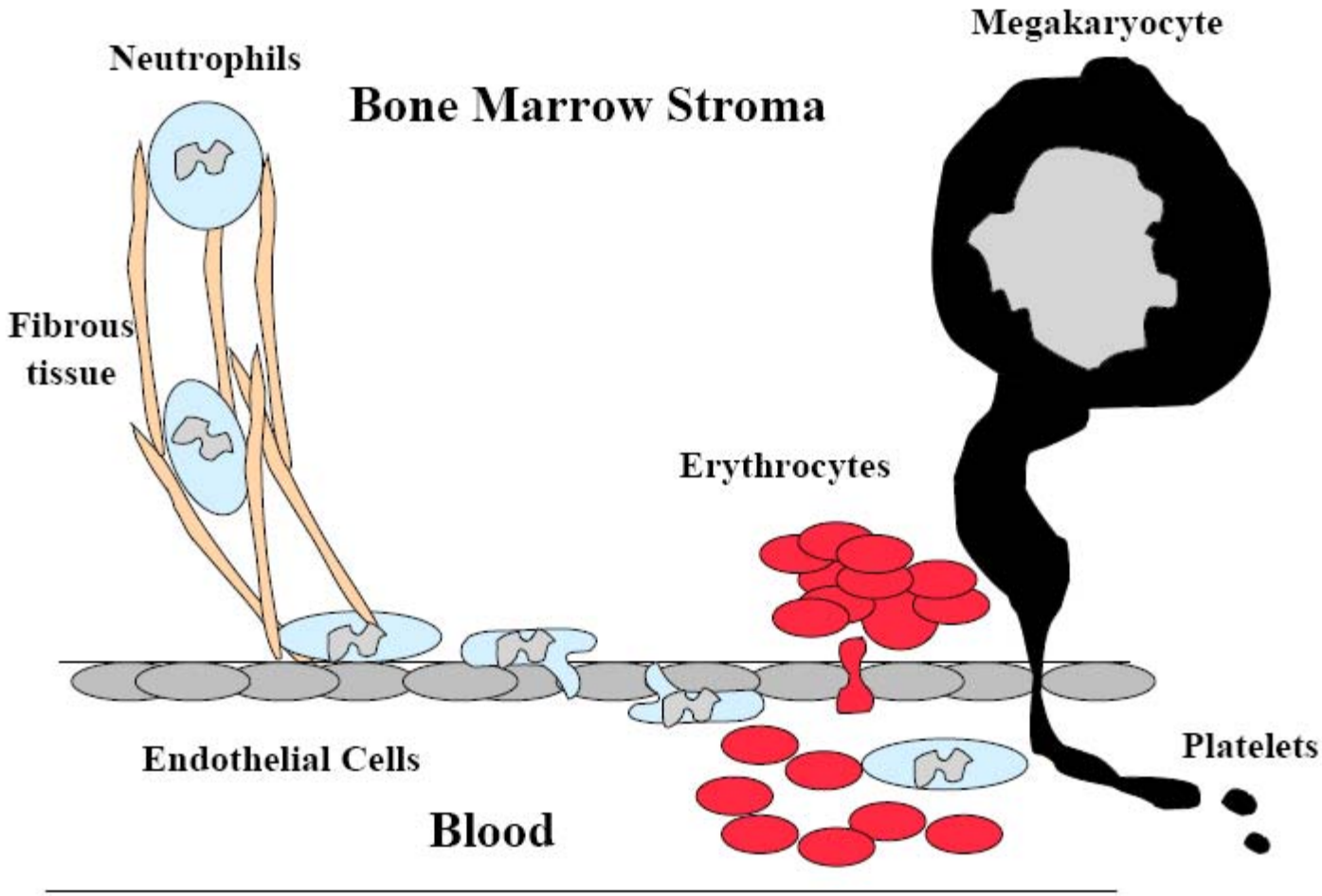


Microscopic Appearance of Bone Marrow



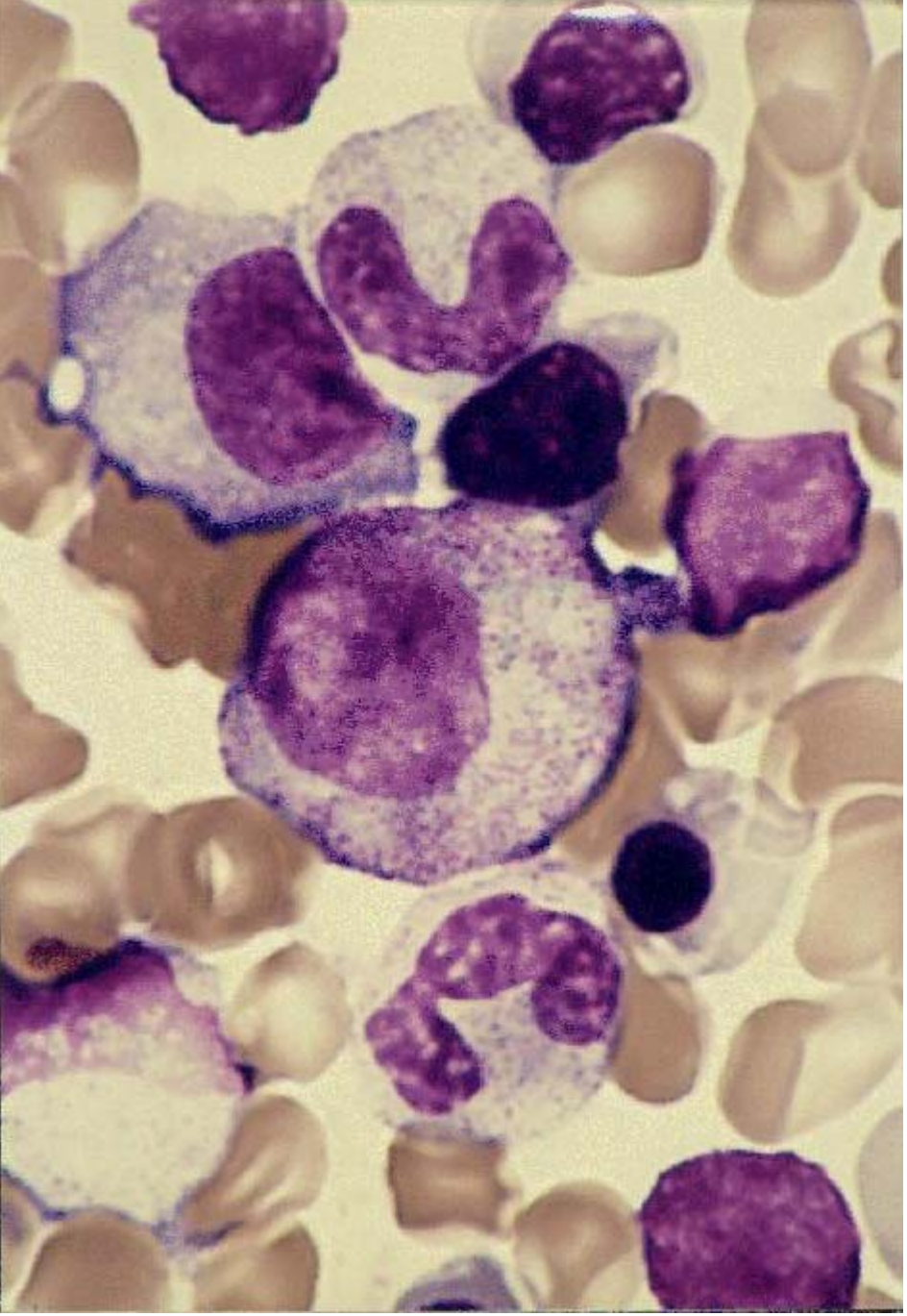
Hematopoiesis scheme



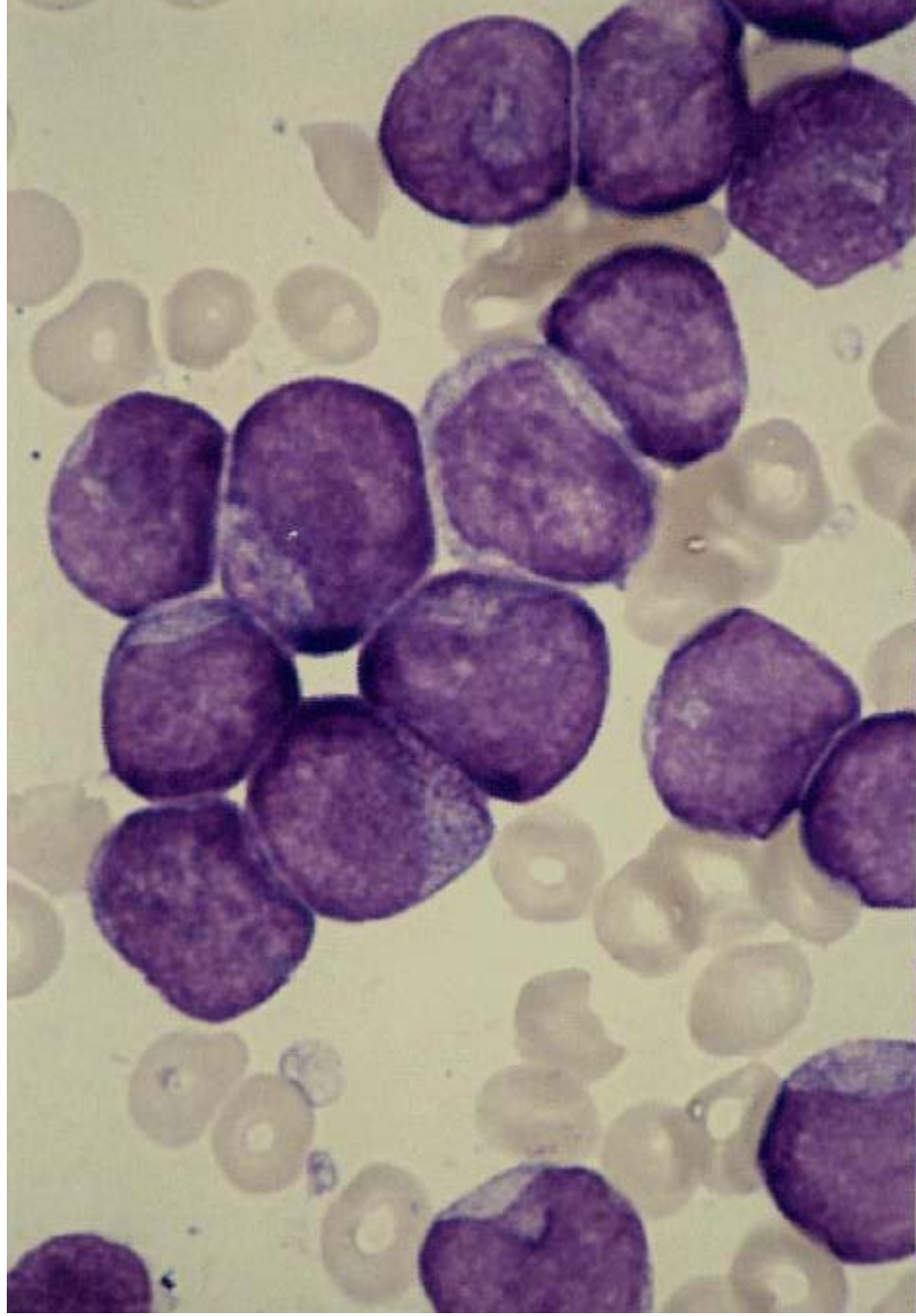

Megakaryocyte
Neutrophils
Bone Marrow Stroma
Fibrous tissue
Erythrocytes
Endothelial Cells
Platelets
Blood

Leukemia

- Begins with a single deficient cell
- More proliferation, less differentiation
- Classification and diagnostics

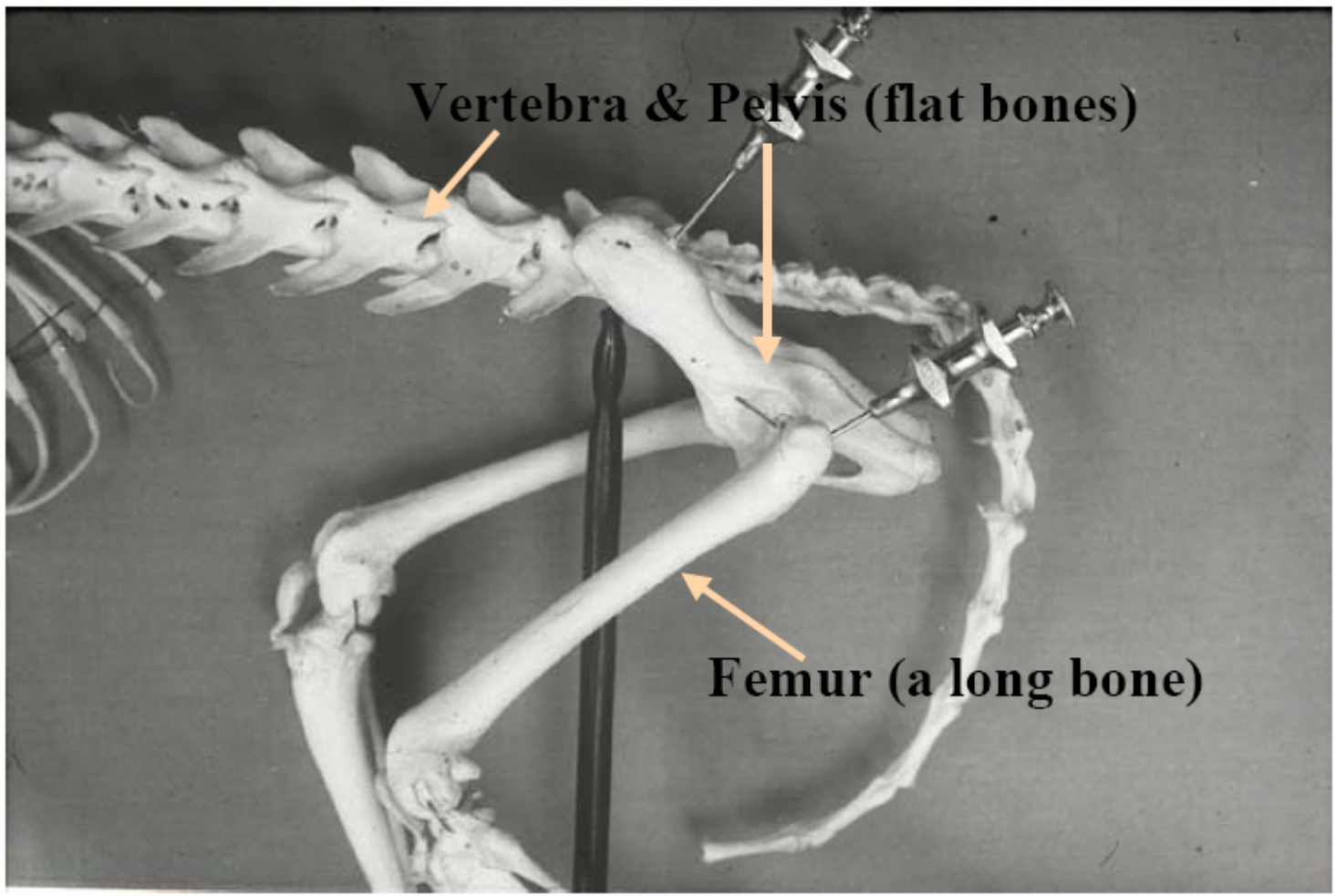


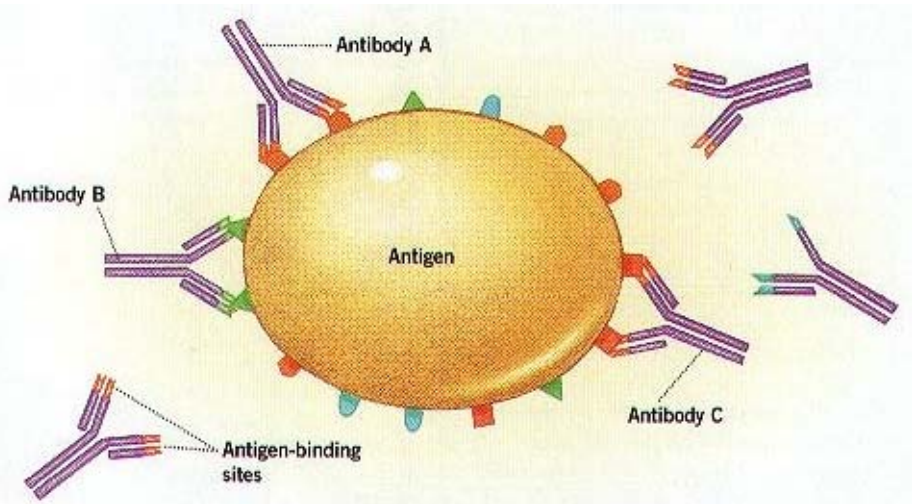
Normal bone marrow

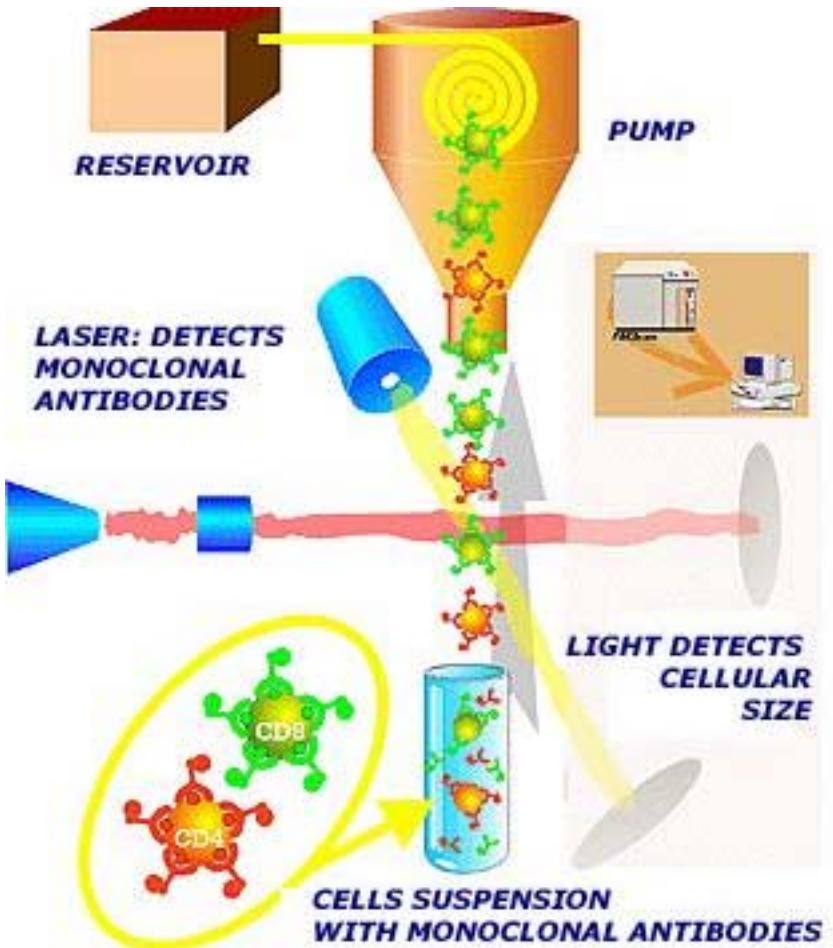


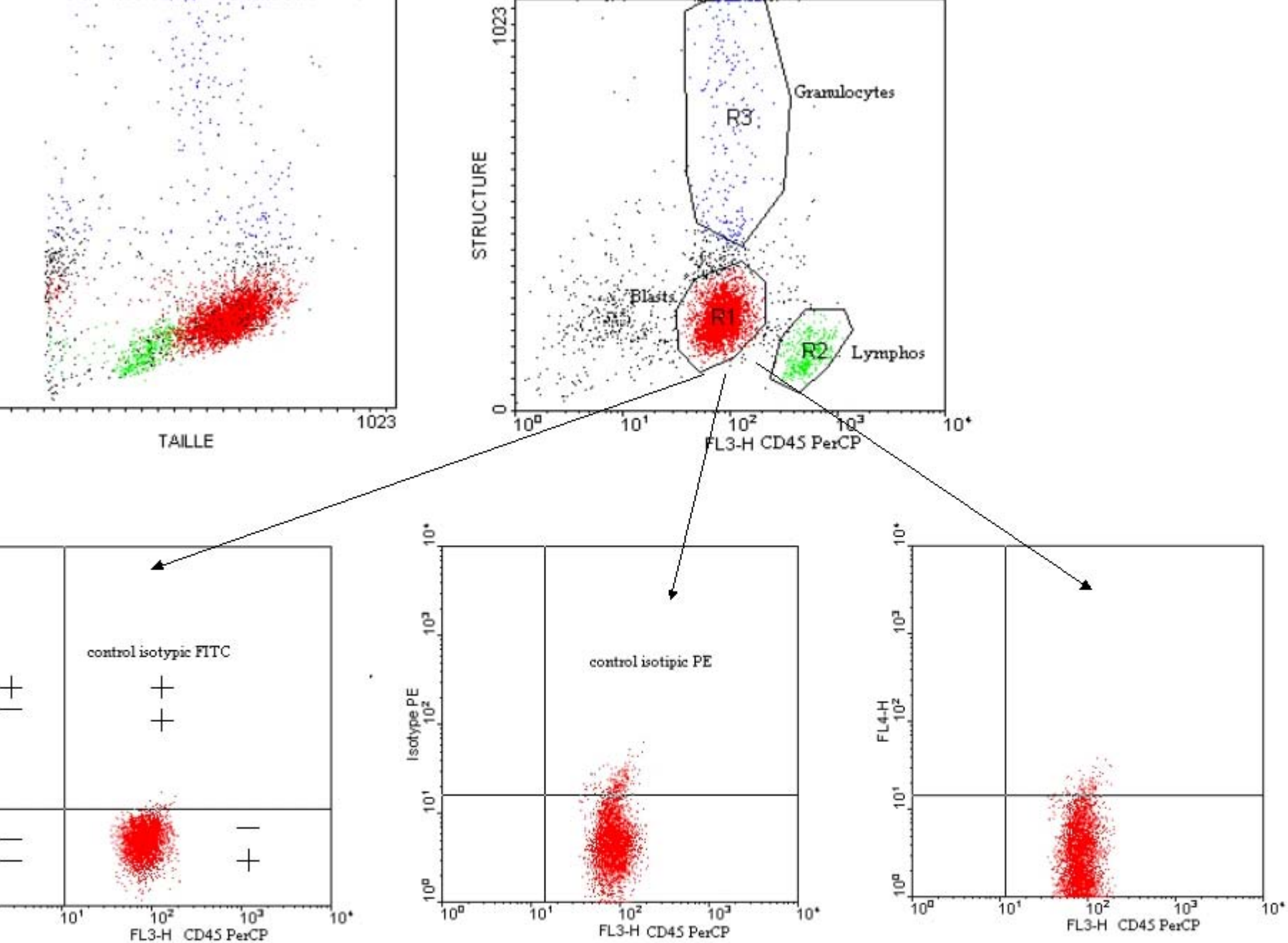
Leukemic bone marrow

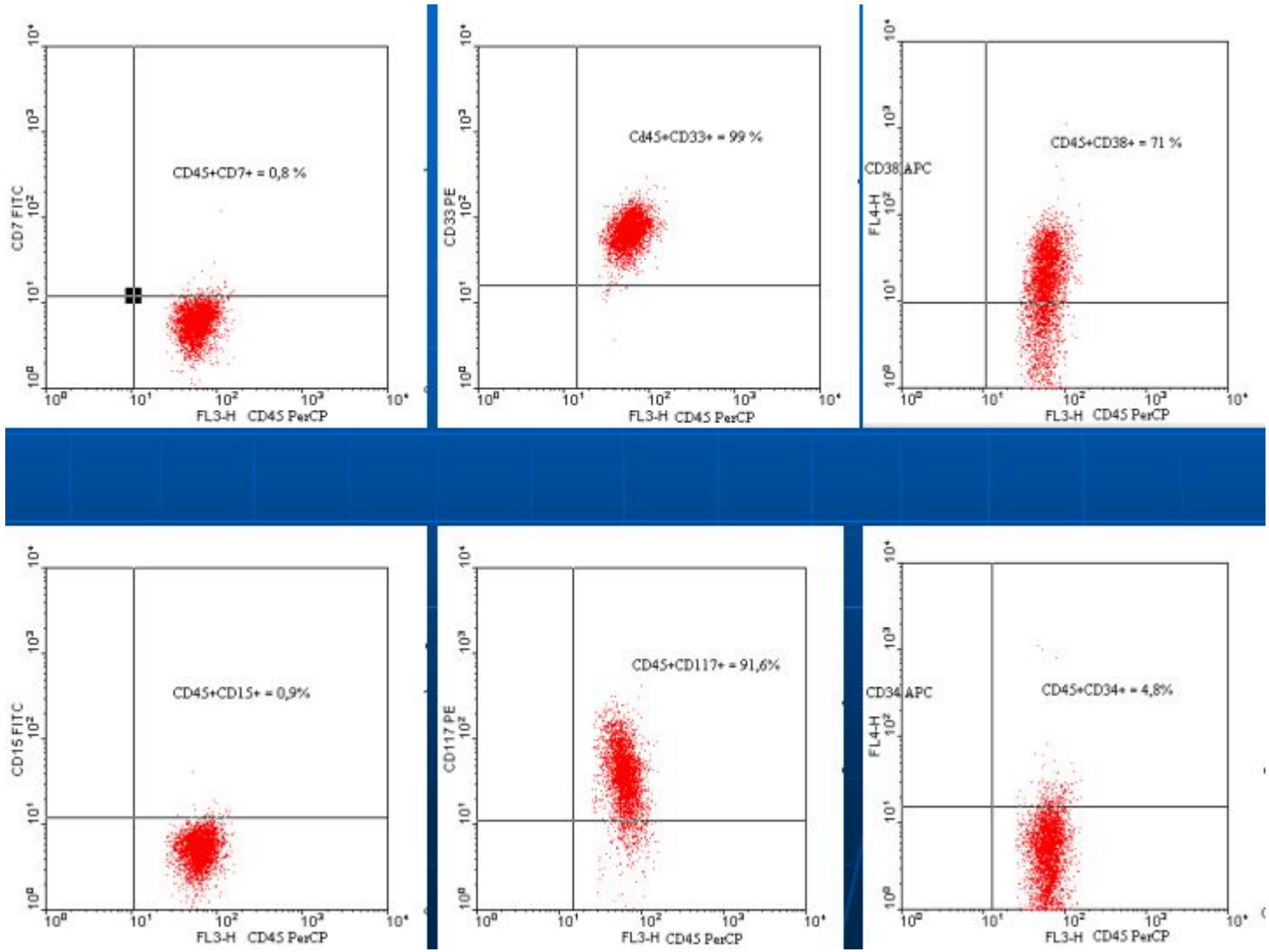
Iliac Crest and Femur Locations for Obtaining Bone Marrow Aspirates




Antibody A
Antibody B
Antigen
Antibody C
Antigen-binding sites

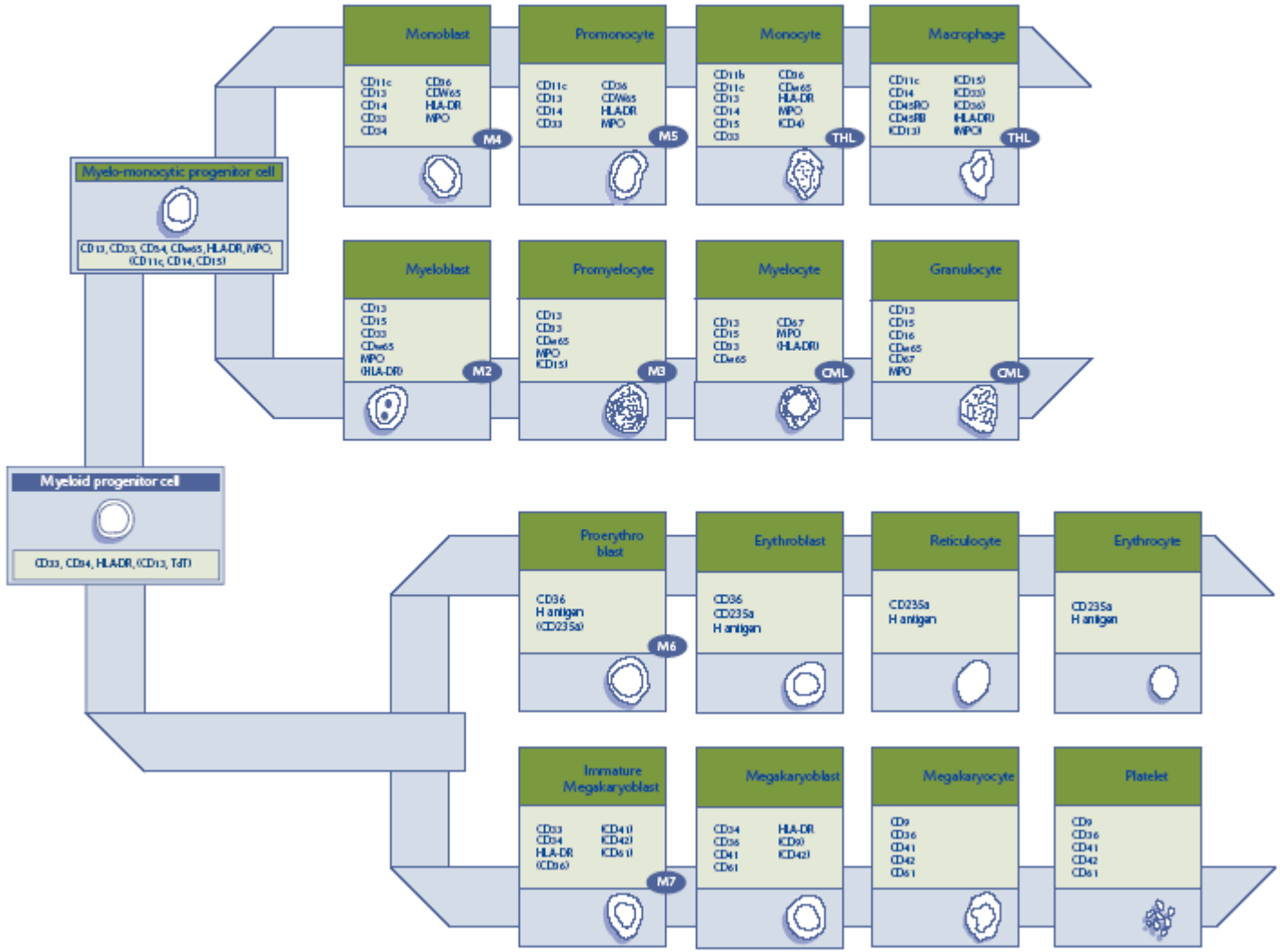

RESERVOIR
PUMP
LASER: DETECTS
MONOCLONAL
ANTIBODIES
LIGHT DETECTS
CELLULAR
SIZE
CD8
CD4
CELLS SUSPENSION
WITH MONOCLONAL ANTIBODIES

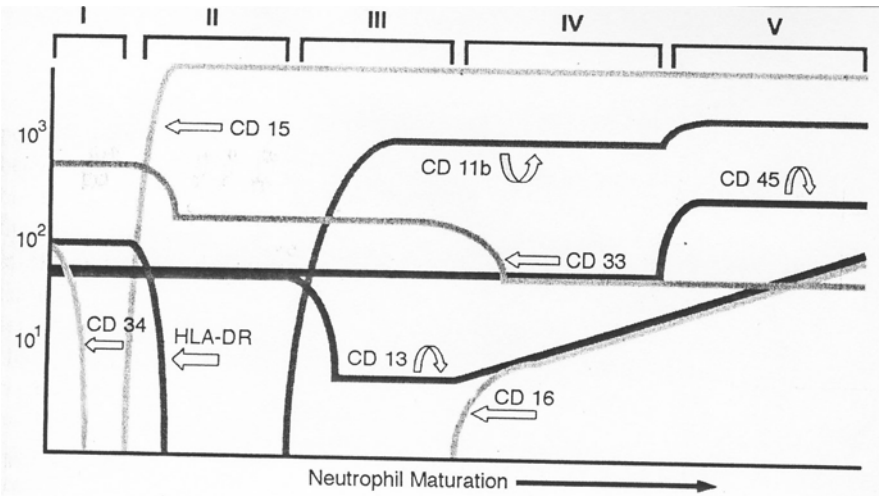

TAILLE
1023
STRUCTURE
1023
0
Granulocytes
R3
Blasts
R1
R2
Lymphos
10^0
10^1
10^2
10^3
10^4
FL3-H CD45 PerCP
control isotypic FITC
FL3-H CD45 PerCP
Isotype PE
control isotipic PE
FL3-H CD45 PerCP
FL4-H
FL3-H CD45 PerCP


CD45+CD7+ = 0,8 %
CD7 FITC
FL3-H CD45 PerCP
Cd45+CD33+ = 99 %
CD33 PE
FL3-H CD45 PerCP
CD45+CD38+ = 71 %
CD38 APC
FL4-H
FL3-H CD45 PerCP
CD45+CD15+ = 0,9%
CD15 FITC
FL3-H CD45 PerCP
CD45+CD117+ = 91,6%
CD117 PE
FL3-H CD45 PerCP
CD45+CD34+ = 4,8%
CD34 APC
FL4-H
FL3-H CD45 PerCP

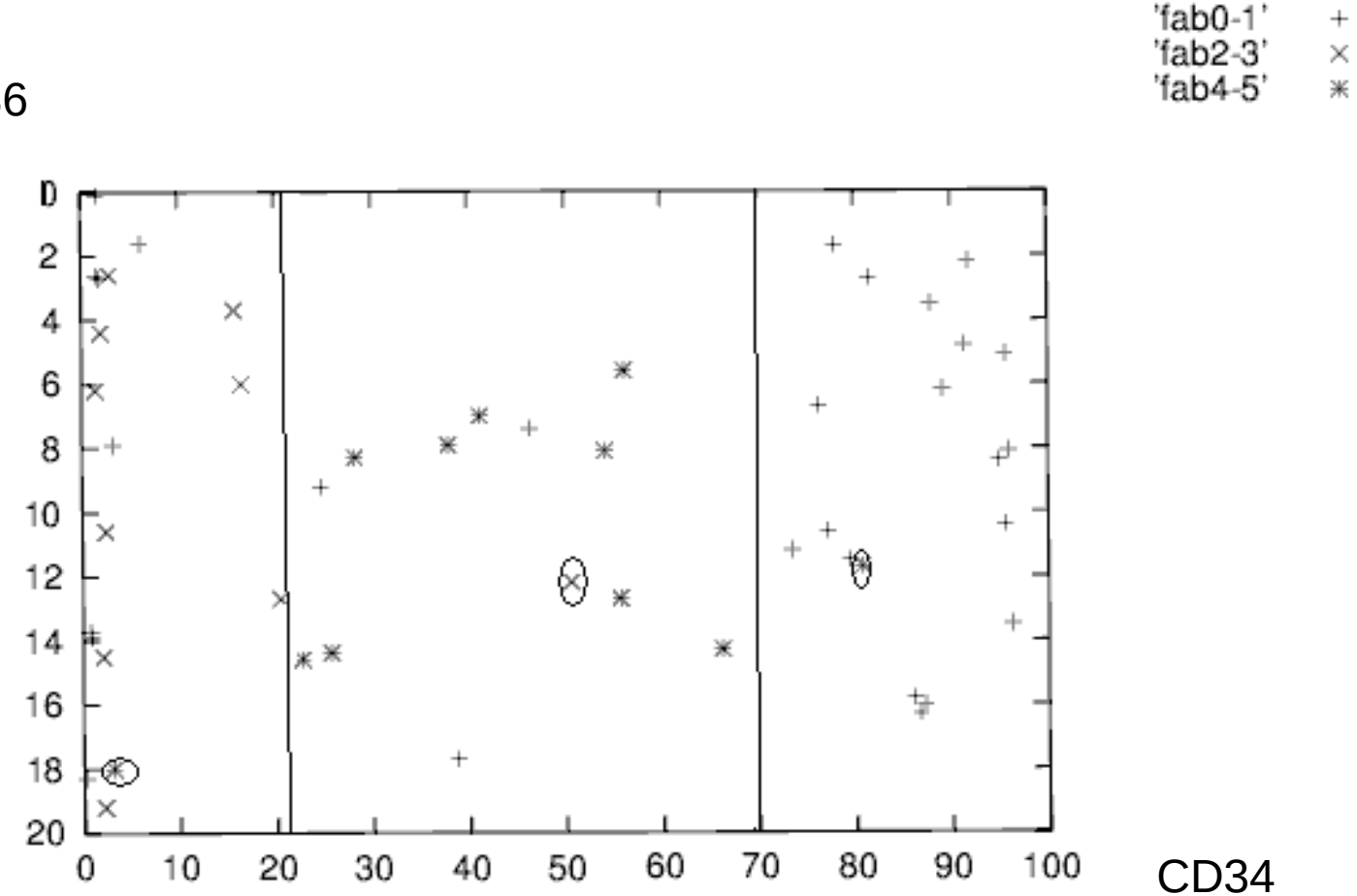
Myeloid Cell Differentiation

Figure 1 Hypothetical scheme of myeloid cell differentiation and the corresponding leukemias and non-Hodgkin lymphomas.

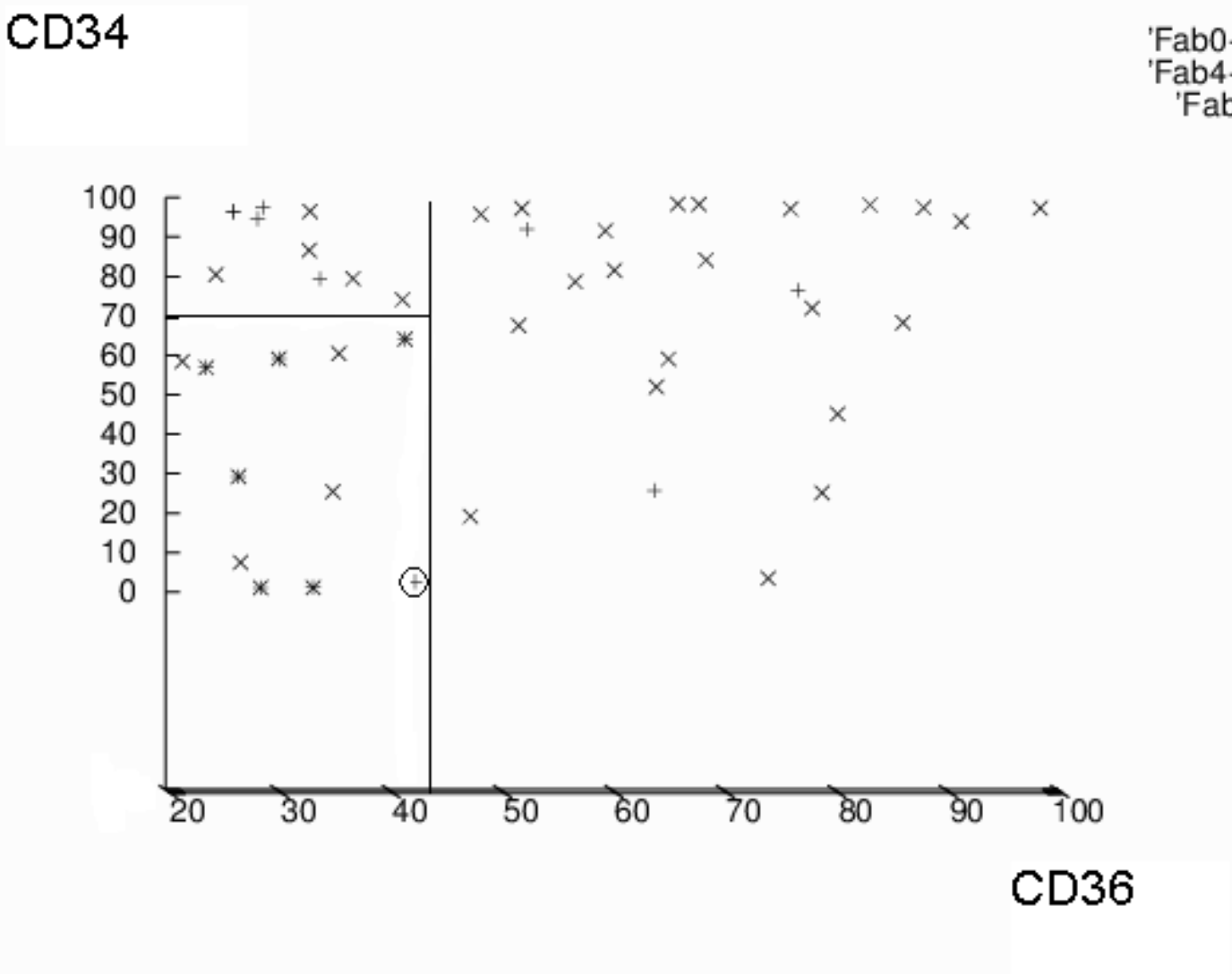



I
II
III
IV
V
10^3
10^2
10^1
CD 15
CD 11b
CD 45
CD 33
CD 34
HLA-DR
CD 13
CD 16
Neutrophil Maturation

CD36


'fab0-1'
'fab2-3'
'fab4-5'
0
2
4
6
8
10
12
14
16
18
20
0
10
20
30
40
50
60
70
80
90
100

CD34

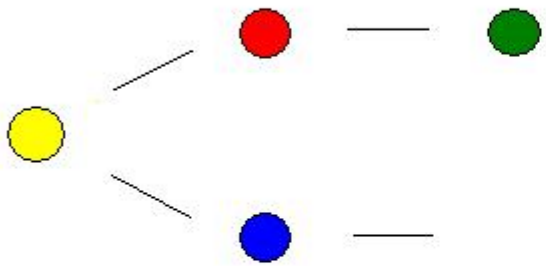

CD34
'Fab0-1'
'Fab4-5'
'Fab2'
100
90
80
70
60
50
40
30
20
10
0
20
30
40
50
60
70
80
90
100
CD36

Modelling Hematopoiesis

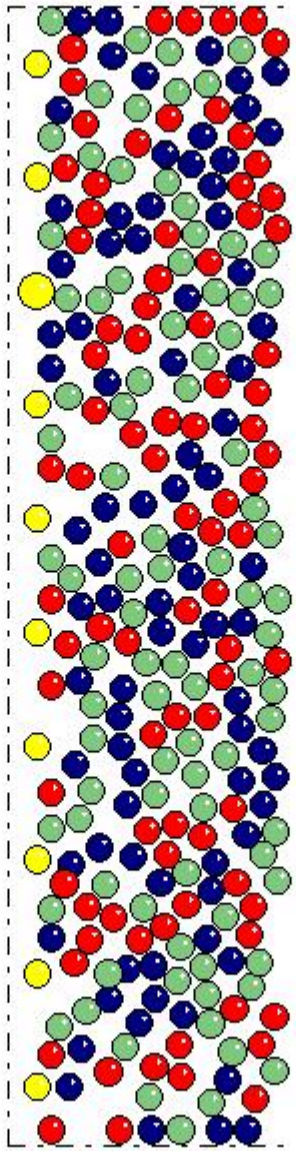
- ODE
- ODE with delay
- Reaction-diffusion equations
- Cellular modelling

Mackey, Adimy, Rudnicki, Loeffler

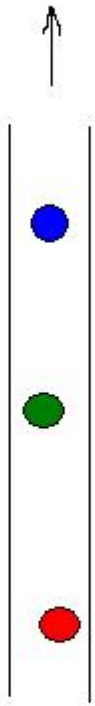
Modelling Hematopoiesis



Proliferation
Differentiation
Apoptosis



Bone marrow



Blood vessel

Cells move pushed by other cells

Normal hematopoiesis: myeloid lineage

New

Parent	Chld1	Chld2	Chld3	Chld4	Time of...	+/- Tim...	Radius ...
A0	A0	B1	E1	F1	10	2	0.01
B1	C1	D1	-	-	200	40	0.01
C1	C2	-	-	-	200	40	0.01
C2	C3	-	-	-	200	40	0.01
C3	C4	-	-	-	200	40	0.01
C4	-	-	-	-	1e+020	2	0.01
D1	D2	-	-	-	200	40	0.01
D2	D3	-	-	-	200	40	0.01
D3	D4	-	-	-	200	40	0.01
D4	-	-	-	-	1e+020	2	0.01
E1	E2	-	-	-	200	40	0.01
E2	E3	-	-	-	200	40	0.01
E3	E4	-	-	-	200	40	0.01
E4	-	-	-	-	1e+020	2	0.01
F1	F2	-	-	-	200	40	0.01
F2	F3	-	-	-	200	40	0.01

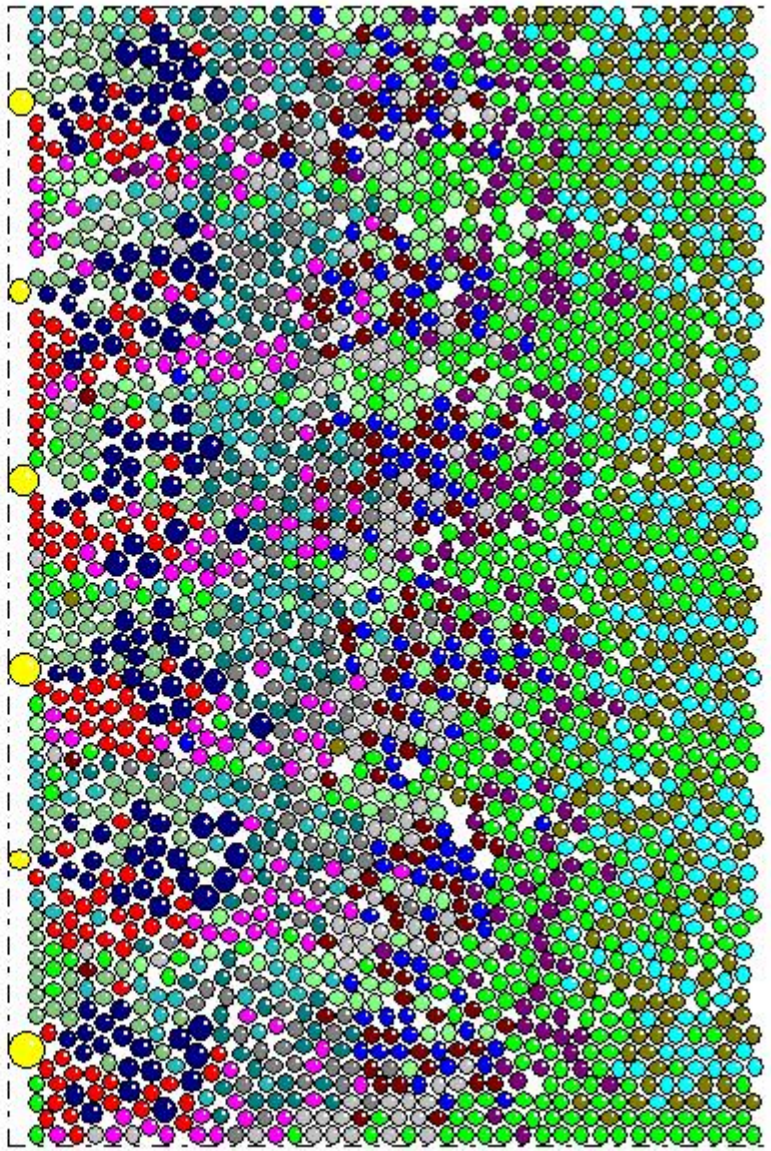
x= 0.4
y= 0.6
New area

Paint f() g()
Paint A0,A1,...

Force = max...min
Apply
max= 1
min= 0

density of A0= 0.2
A0 is fixed
f=a4,g=0/f=0,g=b4 Posle zapolenija

f0= 0
g0= 0



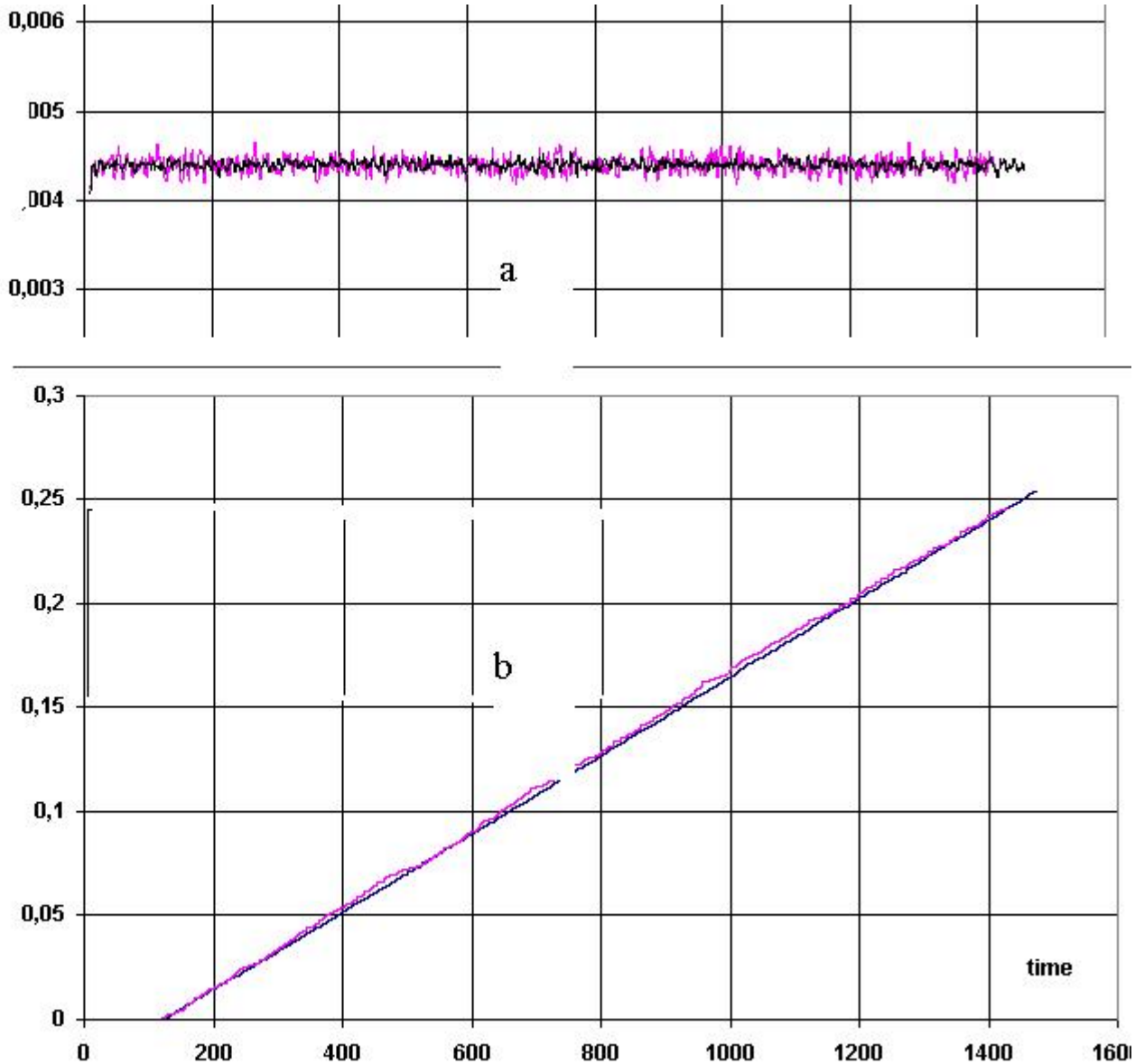

3

Convergence

with respect to cell size

a) Total number of cells

b) Cells leaving the marrow



Development of leukemia

New

Parent	Chld1	Chld2	Chld3	Chld4	Time of...	+/- Tim...	Radius ...
E1	E2	-	-	-	200	40	0.01
E2	E3	-	-	-	200	40	0.01
E3	E4	-	-	-	200	40	0.01
E4	-	-	-	-	1e+020	2	0.01
F1	F2	-	-	-	200	40	0.01
F2	F3	-	-	-	200	40	0.01
F3	-	-	-	-	200	40	0.01
F4	-	-	-	-	1e+020	2	0.01
X	X	X	-	-	10	2	0.01
-	-	-	-	-	0	0	0
-	-	-	-	-	0	0	0
-	-	-	-	-	0	0	0
-	-	-	-	-	0	0	0
-	-	-	-	-	0	0	0
-	-	-	-	-	0	0	0
-	-	-	-	-	0	0	0

x= 0.4

y= 0.6

New area

Paint f() g()

Paint A0,A1,...

Force = max...min

Apply

max= 1

min= 0

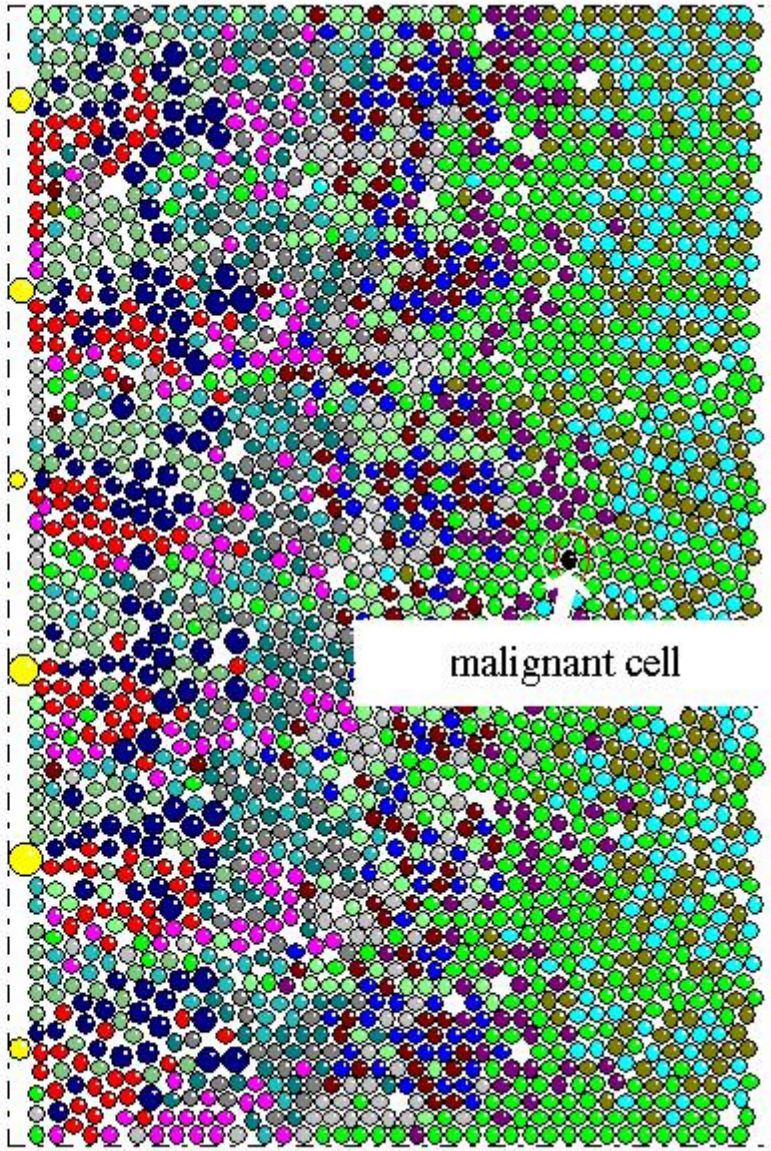
density of A0= 0.2

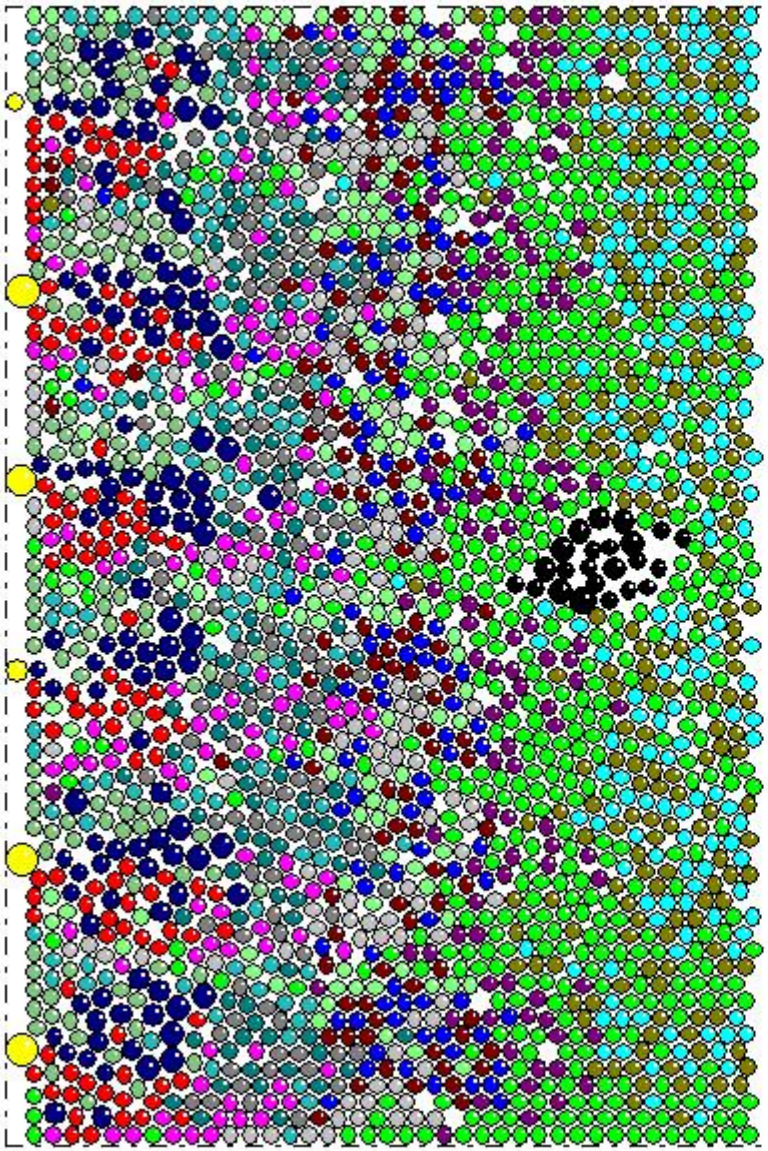
A0 is fixed

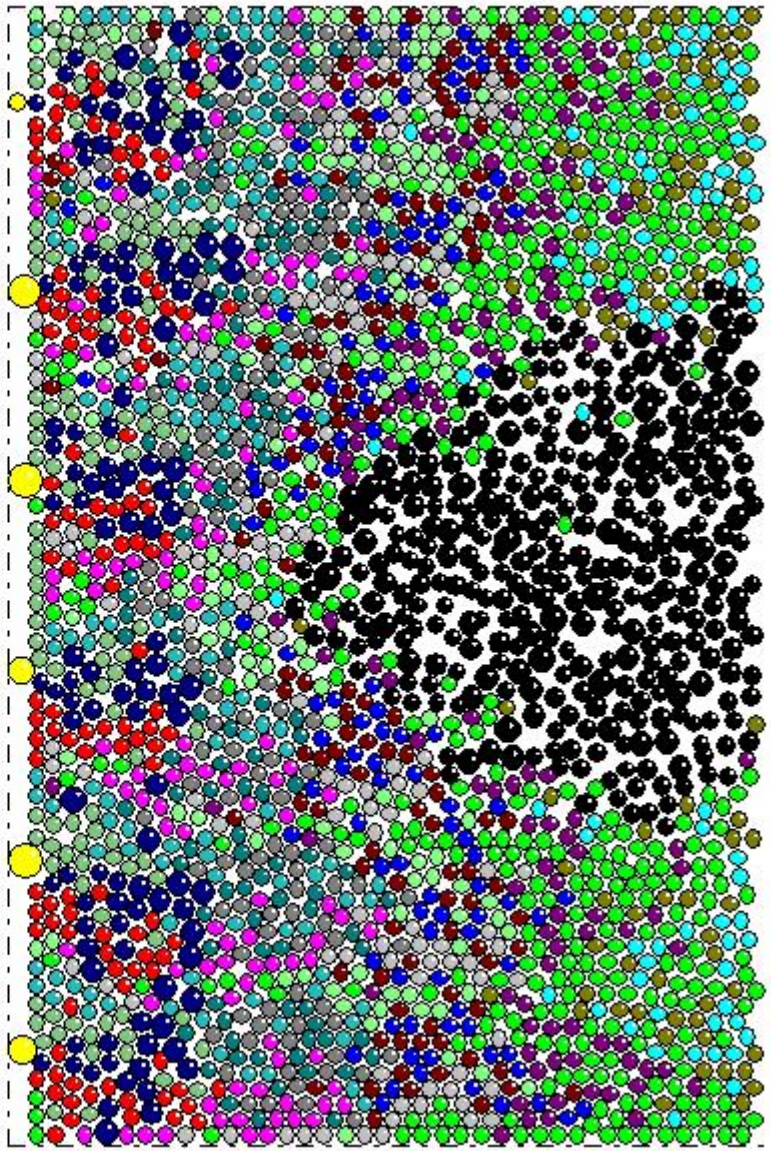
f=a4,g=0/f=0,g=b4 Posle zapolenija

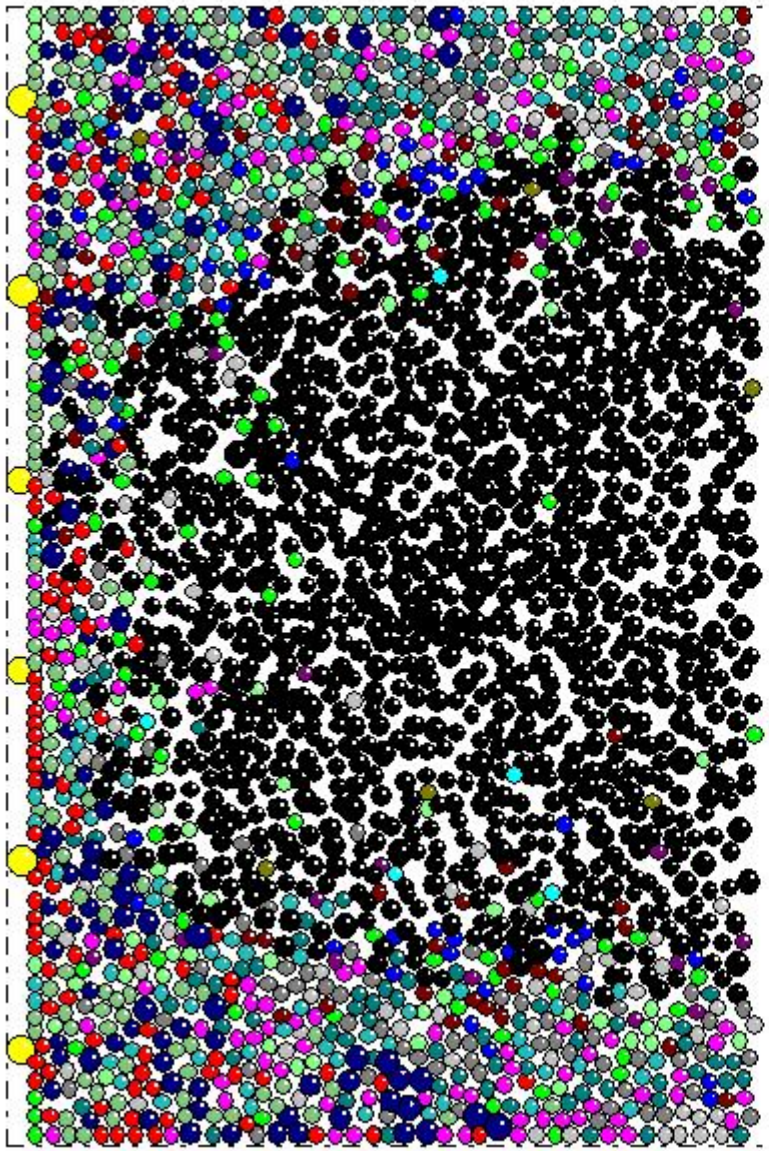
f0= 0

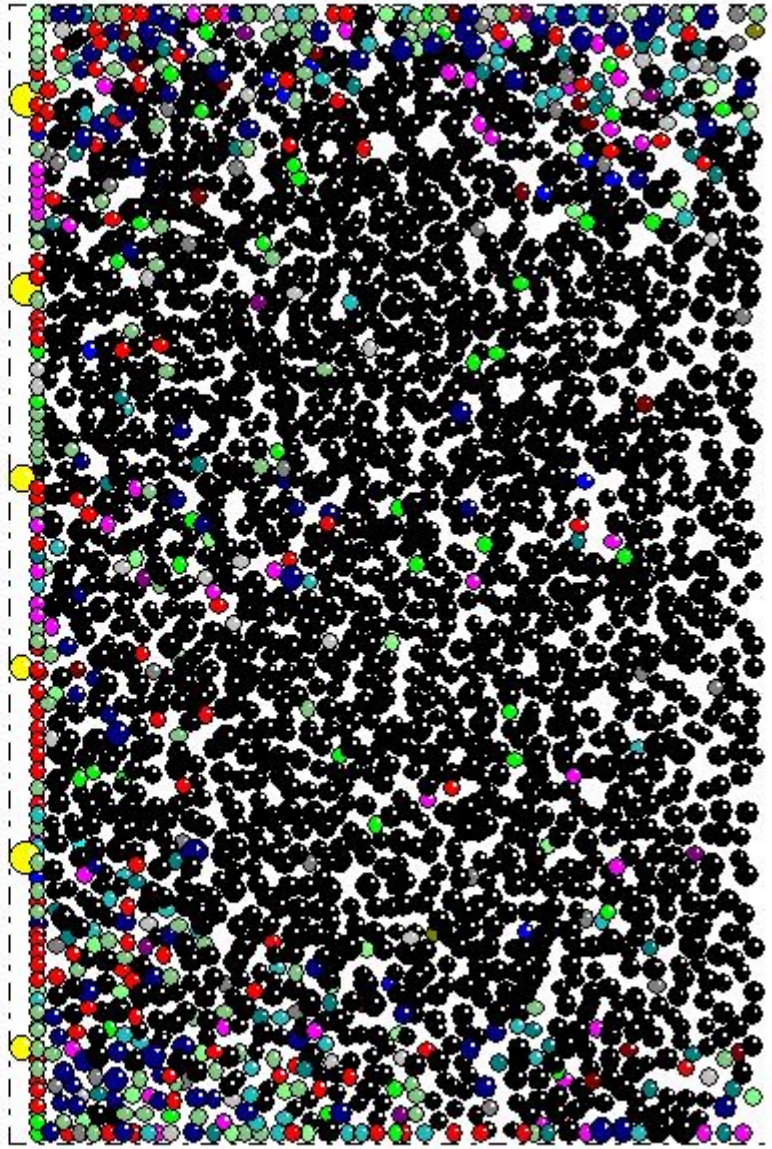
g0= 0

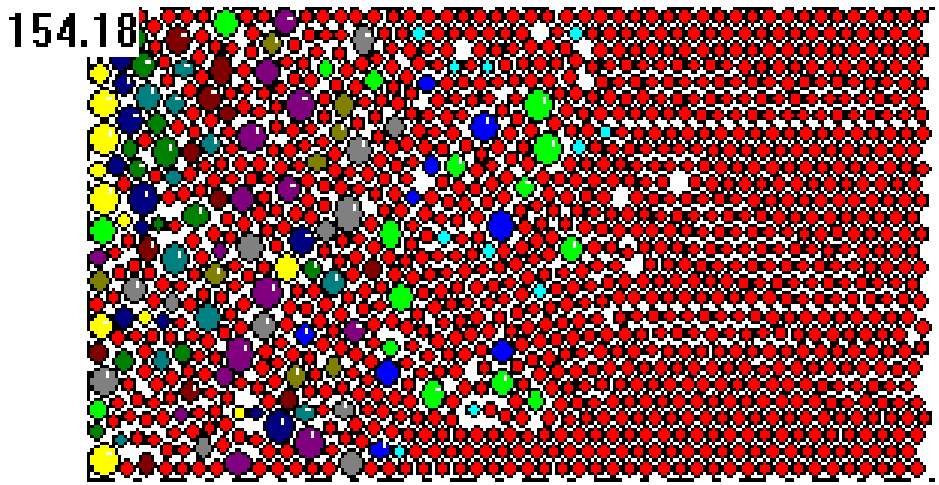








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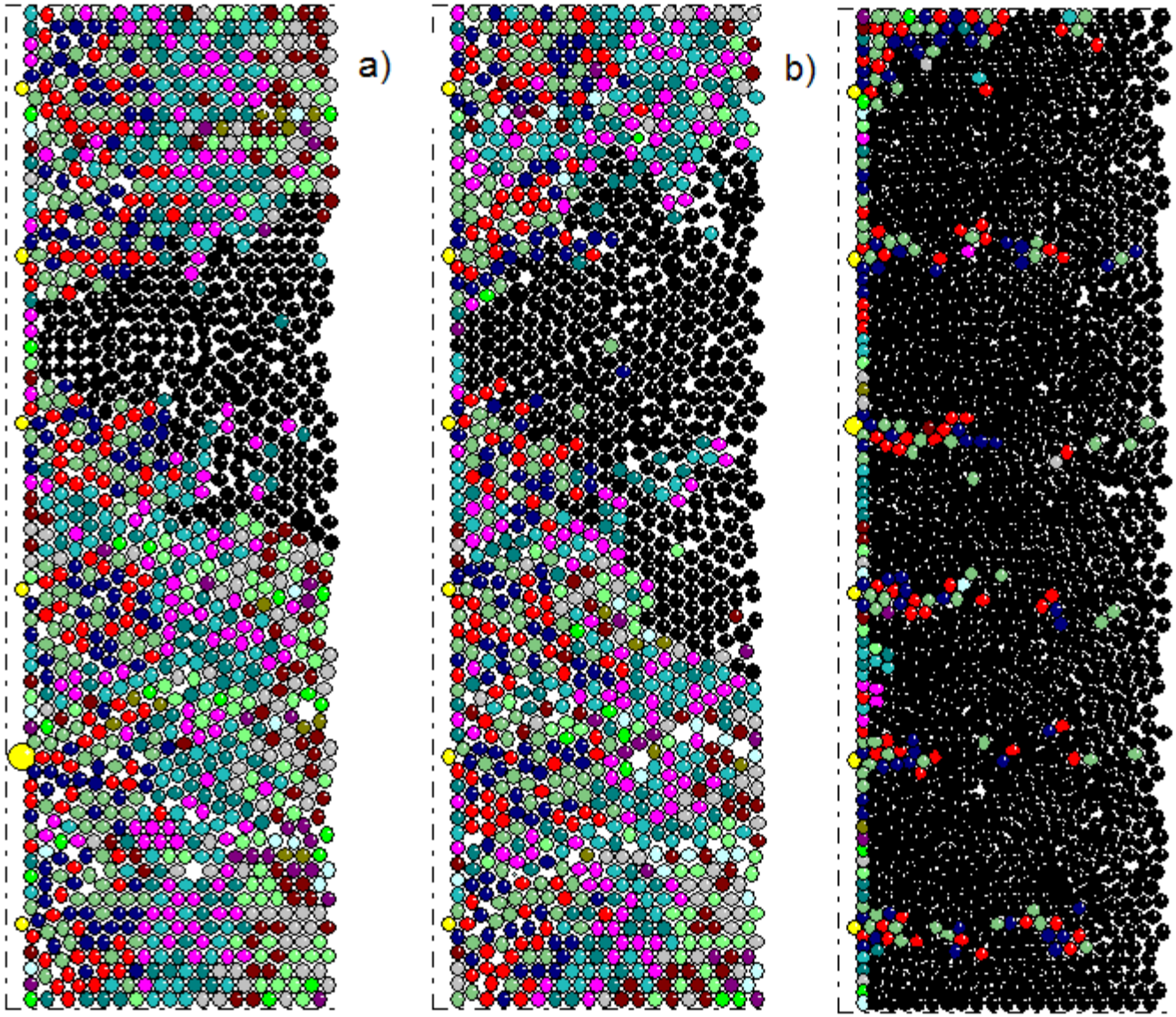
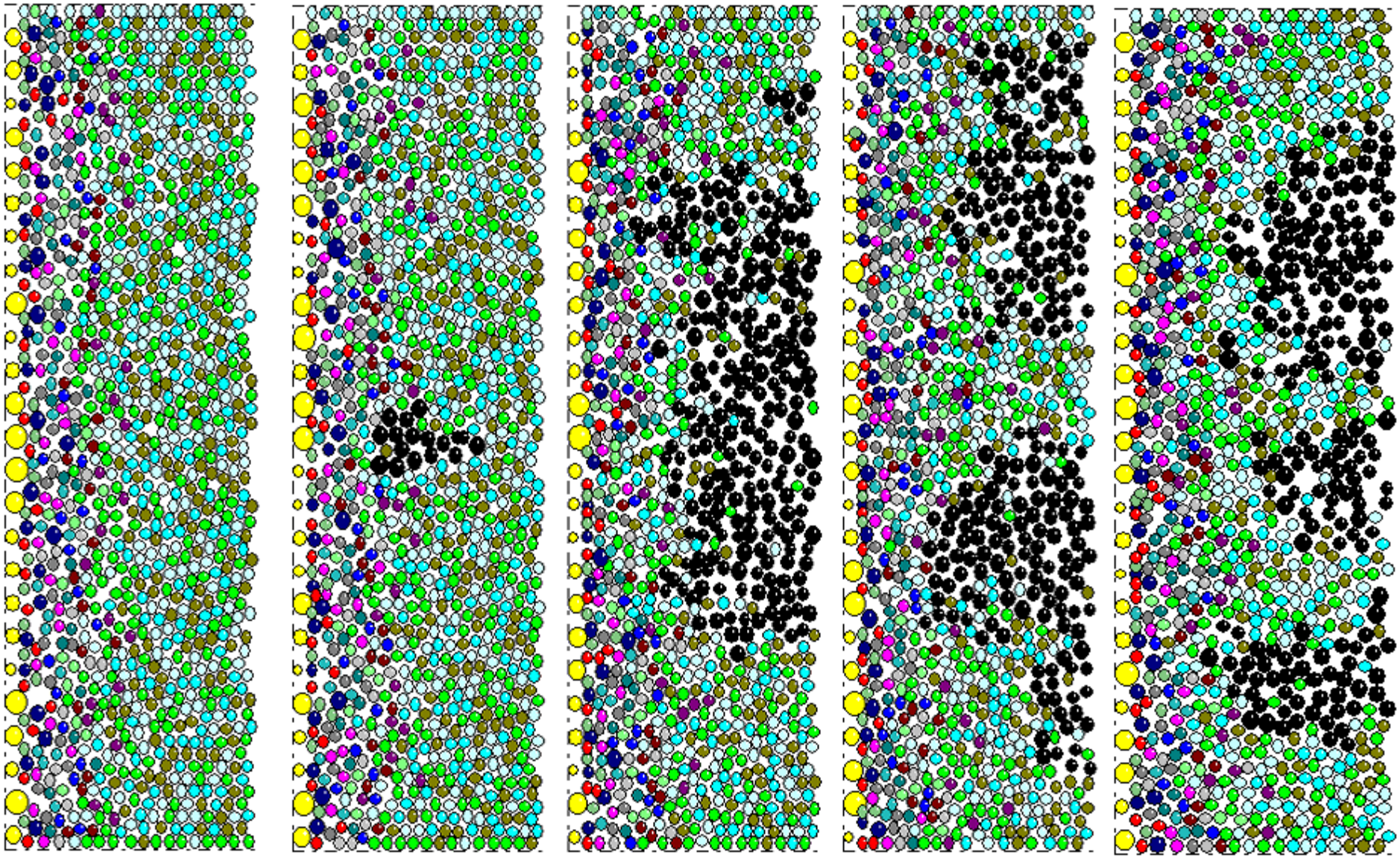


Proliferation time for black cells

a) 100

b) 50

c) 20



Leukemia stem cells

New

Parent	Chld1	Chld2	Chld3	Chld4	Time of...	+/- Tim...	Radius ...
E2	E3	-	-	-	200	40	0.01
E3	E4	-	-	-	200	40	0.01
E4	-	-	-	-	200	2	0.01
F1	F2	-	-	-	200	40	0.01
F2	F3	-	-	-	200	40	0.01
F3	F4	-	-	-	200	40	0.01
F4	-	-	-	-	200	2	0.01
X	X	X1	-	-	10	2	0.01
X1	X1	X2	-	-	10	2	0.01
X2	X3	X3	-	-	10	2	0.01
X3	X4	X4	-	-	10	2	0.01
X4	X5	X5	-	-	10	2	0.01
X5	-	-	-	-	1000	40	0.01
-	-	-	-	-	0	0	0
-	-	-	-	-	0	0	0
-	-	-	-	-	0	0	0

x= 0.3

y= 0.6

New area

Paint f() g()

Paint A0,A1,...

Force = max...min

Apply

max= 1

min= 0

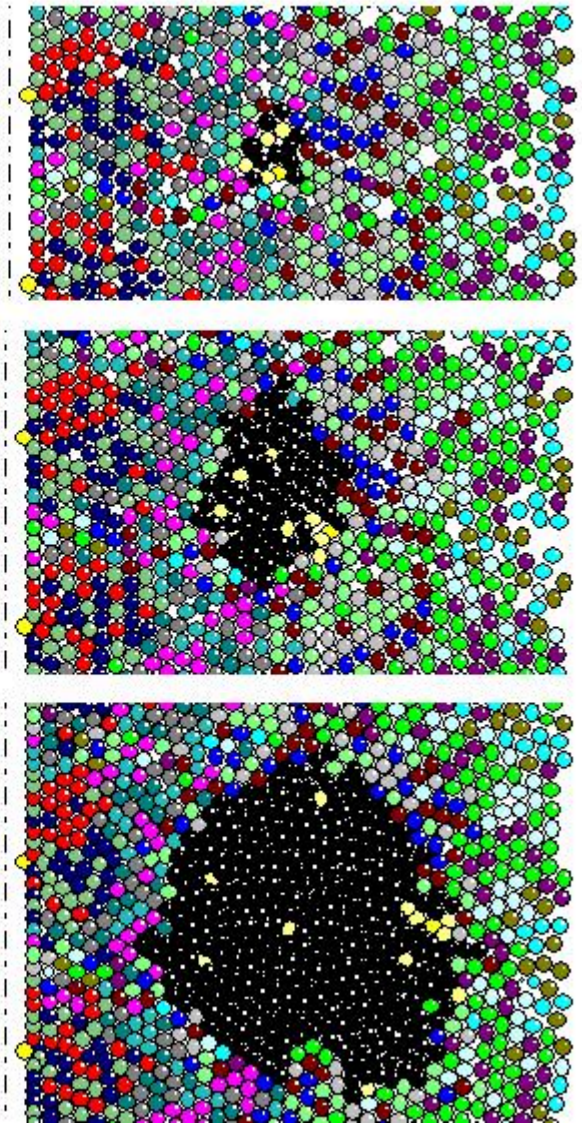
density of A0= 0.2

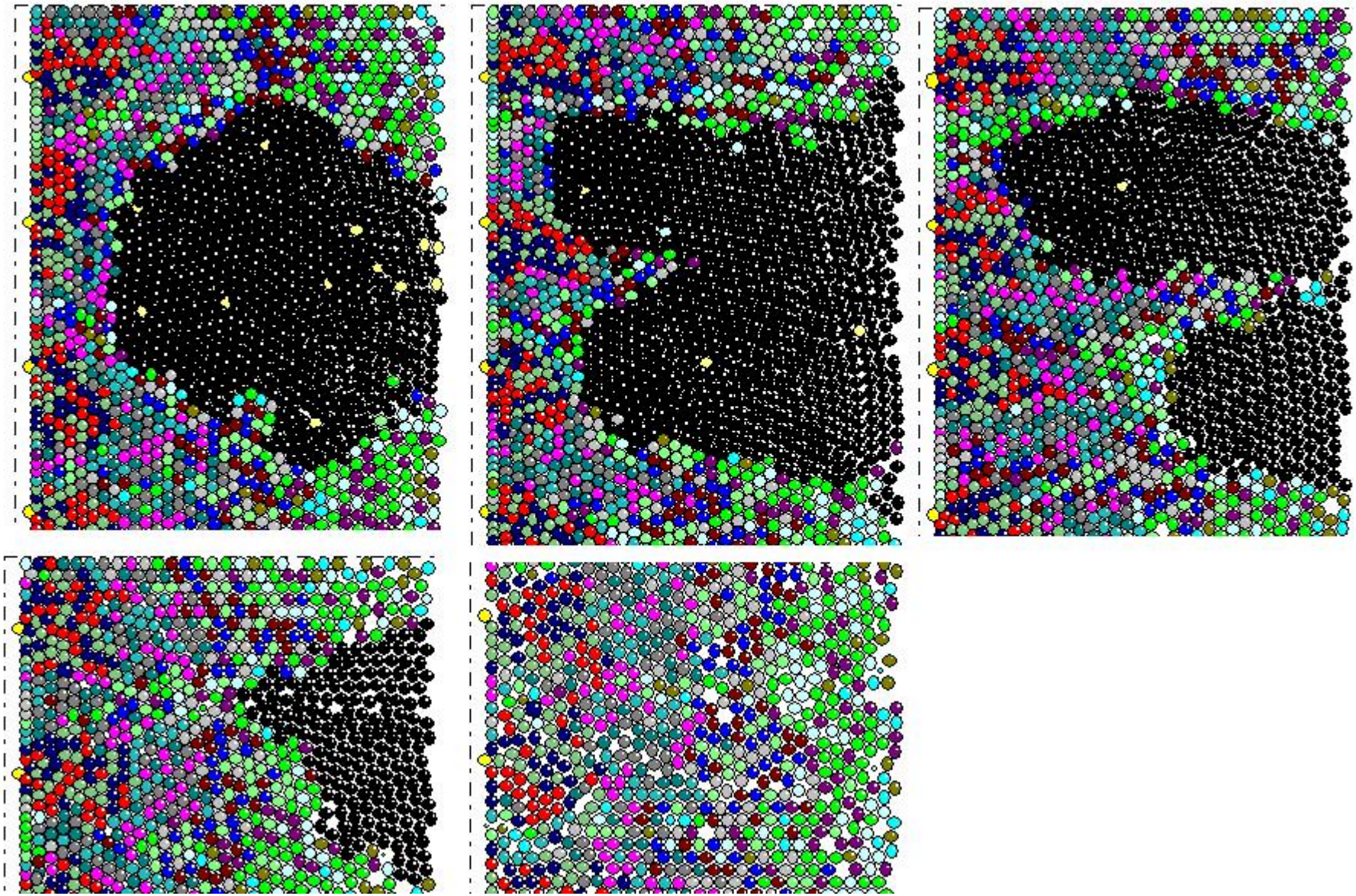
f=a4,g=0/f=0,g=b4 Posle zapolenija

f0= 0

g0= 0

Iskystvennaja vjazkost (0...1)= 0.1

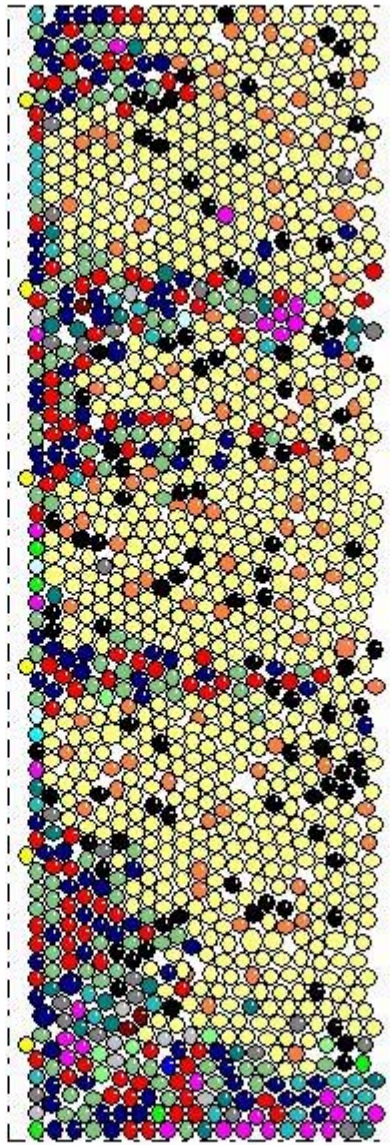


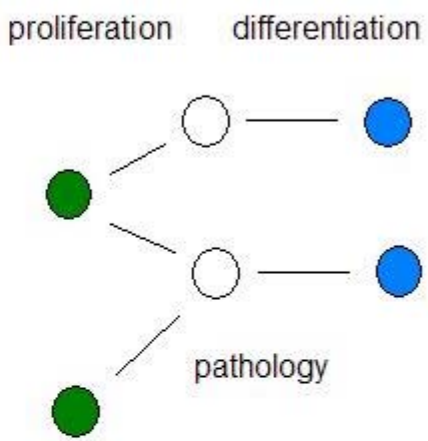


Another proliferation rate

Parent	Chld1	Chld2	Chld3	Chld4	Time of...	+/- Tim...	Radius ...
D1	D2	-	-	-	200	40	0.01
D2	D3	-	-	-	200	40	0.01
D3	D4	-	-	-	200	40	0.01
D4	-	-	-	-	200	2	0.01
E1	E2	-	-	-	200	40	0.01
E2	E3	-	-	-	200	40	0.01
E3	E4	-	-	-	200	40	0.01
E4	-	-	-	-	200	2	0.01
F1	F2	-	-	-	200	40	0.01
F2	F3	-	-	-	200	40	0.01
F3	F4	-	-	-	200	40	0.01
F4	-	-	-	-	200	2	0.01
X	X	X1	-	-	5	2	0.01
X1	X	X2	-	-	100	2	0.01
X2	X3	-	-	-	200	2	0.01
X3	X4	-	-	-	200	2	0.01

0.2
0.6
New area
Paint f() g()
Paint A0,A1,...
Force = max...min
Apply
max= 1
min= 0
ensity of A0= 0.2
f=a4,g=0/f=0,g=b4 Posle zapolenija
0
g0= 0
Iskystvennaja vjazkost (0...1)= 0.1





Leukemic hemapotoiesis Is not known. Modelling allows us to study its Influence on leukemia development

Mulitplication of leukemia stem cells

Parent	Chld1	Chld2	Chld3	Chld4	Time of...	+/- Tim...	Radius ...
D1	D2	-	-	-	200	40	0.01
D2	D3	-	-	-	200	40	0.01
D3	D4	-	-	-	200	40	0.01
D4	-	-	-	-	200	2	0.01
E1	E2	-	-	-	200	40	0.01
E2	E3	-	-	-	200	40	0.01
E3	E4	-	-	-	200	40	0.01
E4	-	-	-	-	200	2	0.01
F1	F2	-	-	-	200	40	0.01
F2	F3	-	-	-	200	40	0.01
F3	F4	-	-	-	200	40	0.01
F4	-	-	-	-	200	2	0.01
X	X	X1	-	-	10	2	0.01
X1	X	X2	-	-	100	2	0.01
X2	X3	-	-	-	200	2	0.01
X3	X4	-	-	-	200	2	0.01

0.2

0.6

New area

Paint f() g()

Paint A0,A1,...

Force = max...min

Apply

max= 1

min= 0

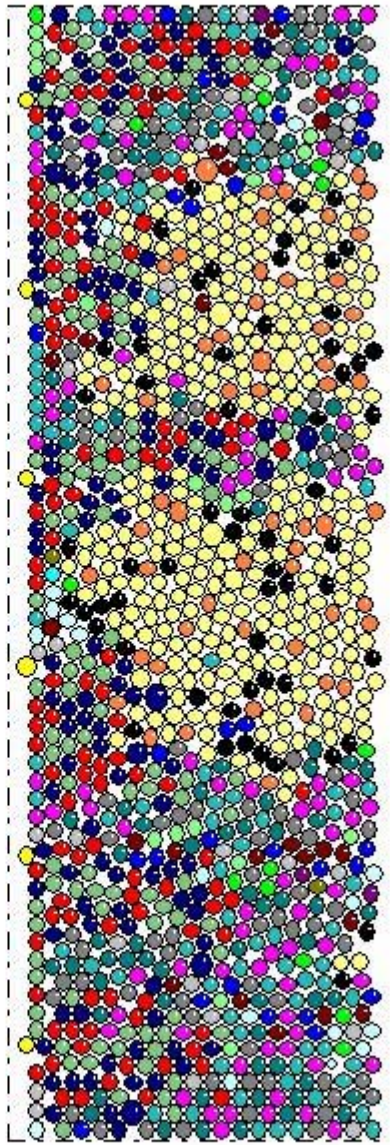
ensity of A0= 0.2

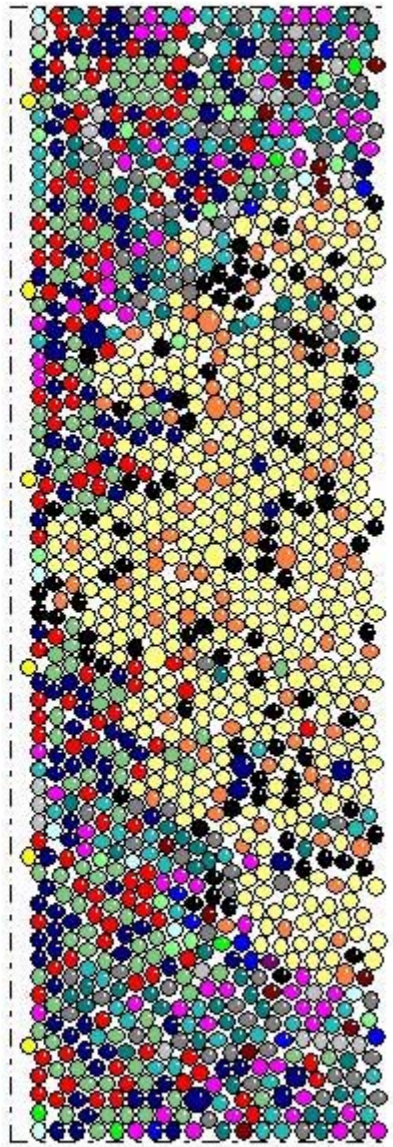
f=a4,g=0/f=0,g=b4 Posle zapolenija

0

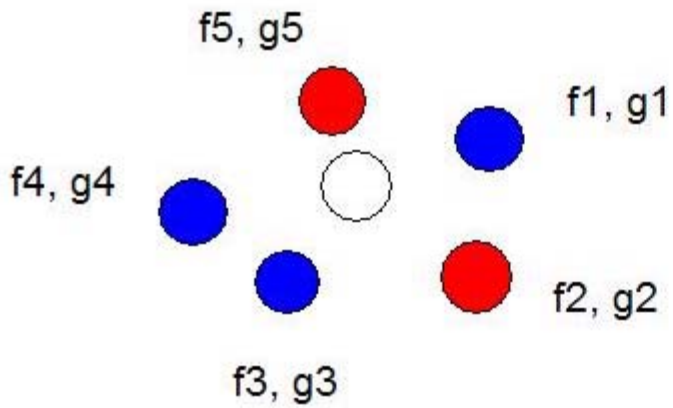
g0= 0

Iskystvennaja vjazkost (0...1)= 0.1





Cell communication



1. Cell childhood (what colour to choose?)

$df/dt = a (F - f)$, $dg/dt = a (G - g)$

F = average of fi, G = average of gi

Critical condition: f = f* or g = g*

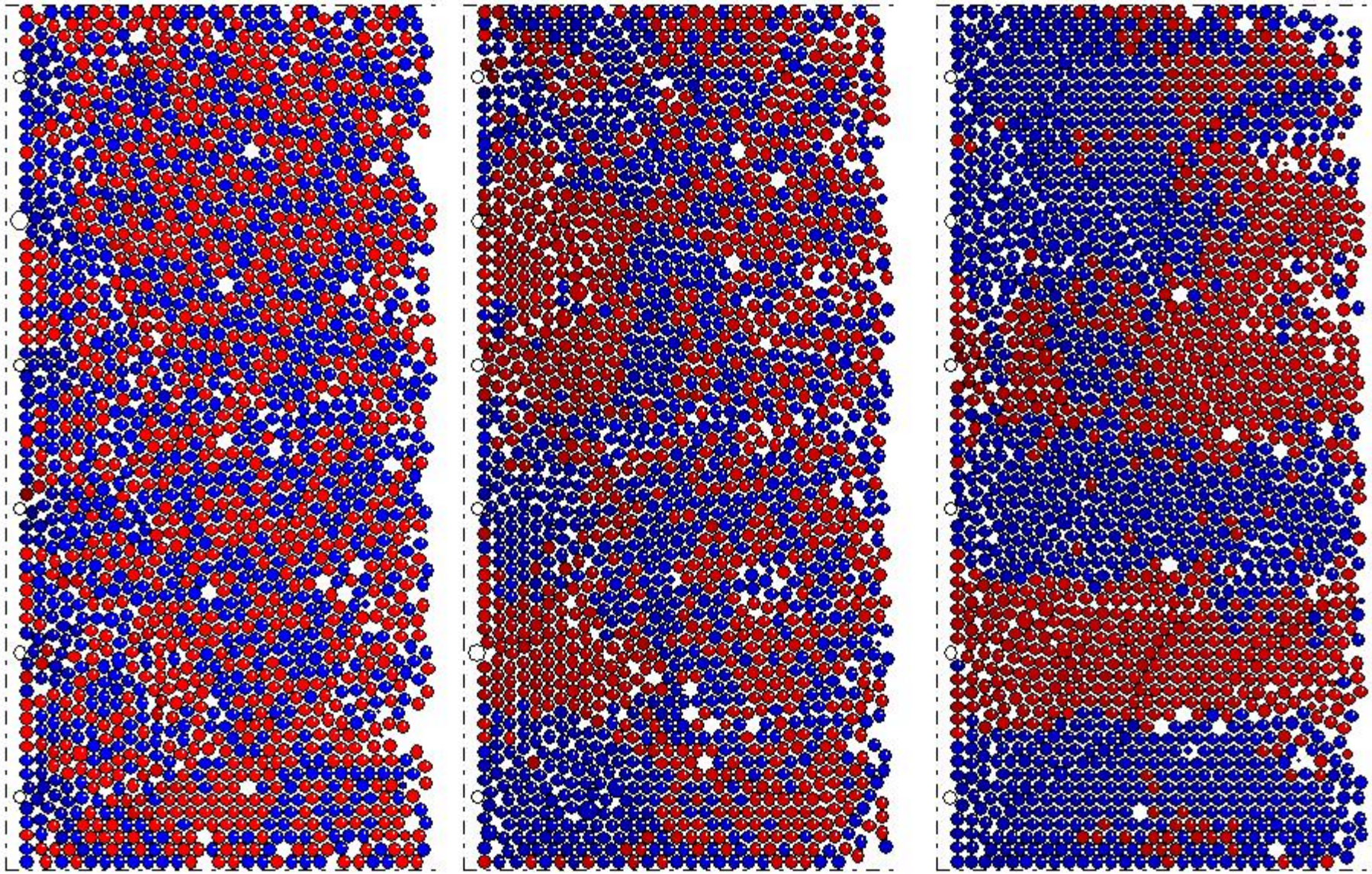
2. Adult life

Blue: $df/dt = P(f,g^*)$, $g = g^*$

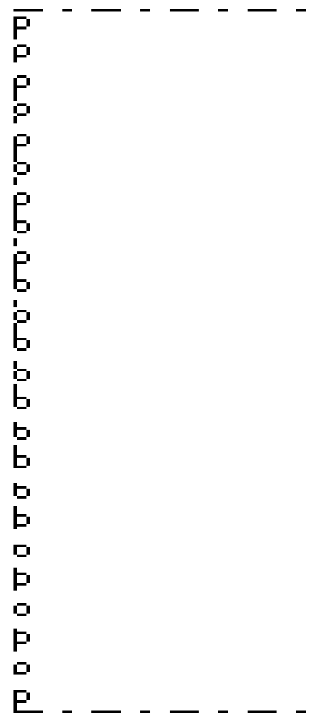
Red: $dg/dt = Q(f^*,g)$, $f = f^*$

g

f



1



tial | Output | Run | Help | void

ent	Chld1	Chld2	Chld3	Chld4	Time of...	+/- Tim...	Radius ...
A0	A0	B1	E1	F1	10	0	0.01
B1	-	-	-	-	200	0	0.01
C1	C2	-	-	-	10	2	0.01
C2	C3	-	-	-	10	2	0.01
C3	C4	-	-	-	10	2	0.01
C4	-	-	-	-	1e+020	2	0.01
D1	D2	-	-	-	10	2	0.01
D2	D3	-	-	-	10	2	0.01
D3	D4	-	-	-	10	2	0.01
D4	-	-	-	-	1e+020	2	0.01
E1	-	-	-	-	200	0	0.01
E2	E3	-	-	-	10	2	0.01
E3	E4	-	-	-	10	2	0.01
E4	-	-	-	-	1e+020	2	0.01
F1	-	-	-	-	200	0	0.01
F2	F3	-	-	-	10	2	0.01

0.1

0.6

ew area

Shell -> "X"

Paint f() g()

Paint A0,A1,...

Force = max...min

Apply

max= 1

min= 0

ty of A0= 0.5

A0 is fixed

DblClk here

dt = 0.005

Stop any 1 step

time= 1.0060e+003

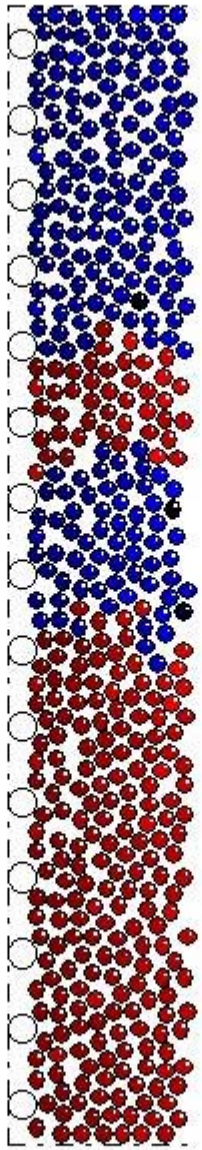
f0=	0	a5=	0.01
g0=	0	b5=	0.01
a1=	1	a6=	0
b1=	1	b6=	0
a4=	3	a7=	0
b4=	3	b7=	0
sigma=	1	a8=	0.01
		b8=	0.01
		a9=	0
		b9=	0

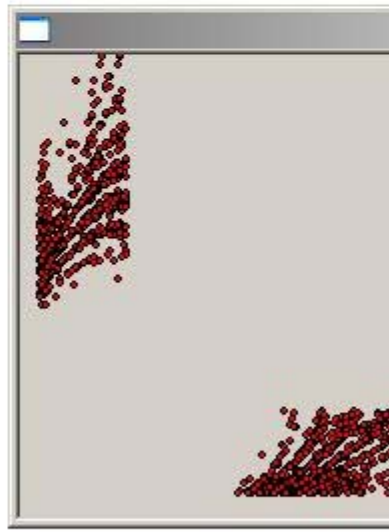
F=(f+f)/2

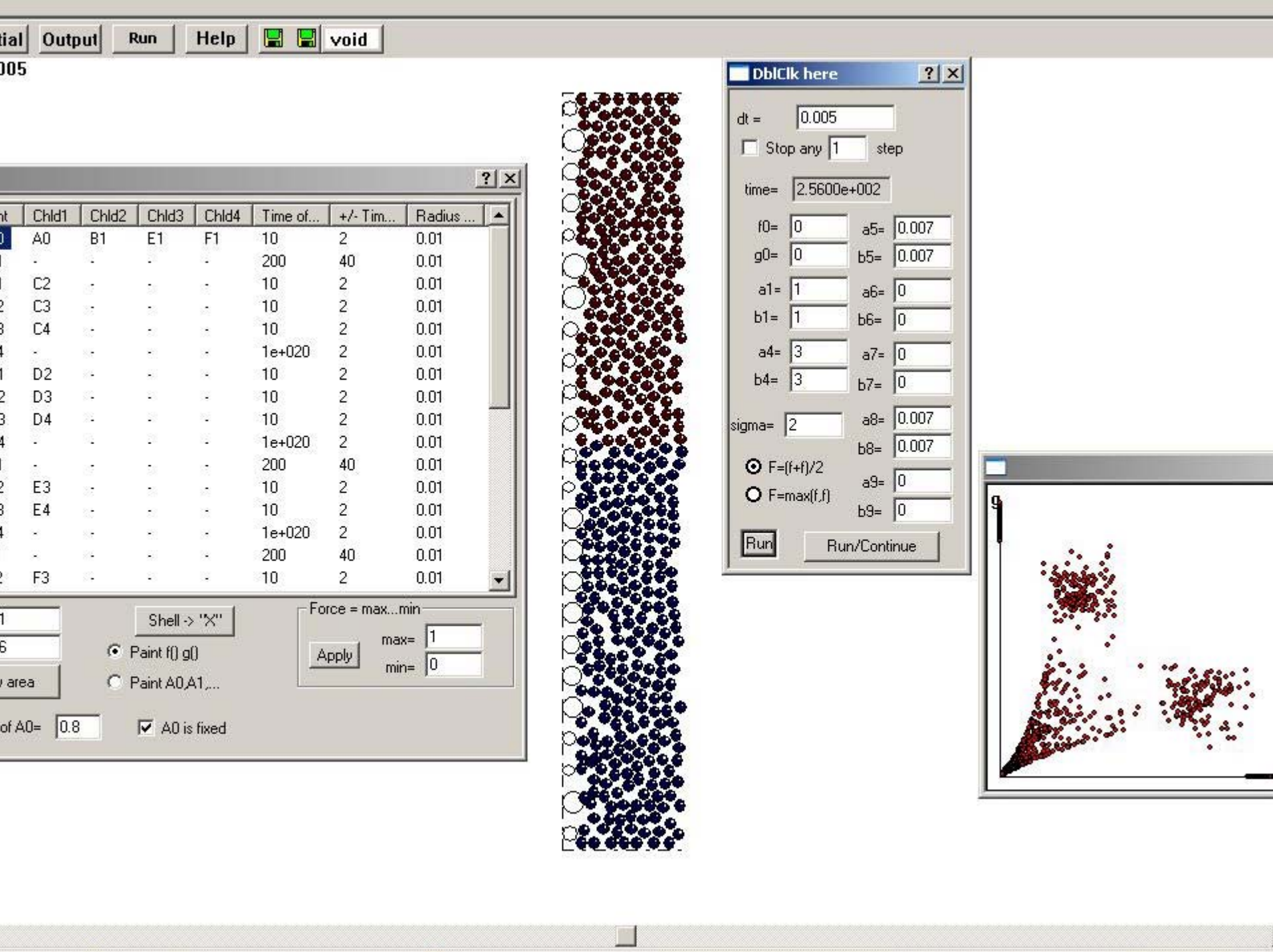
F=max(f,f)

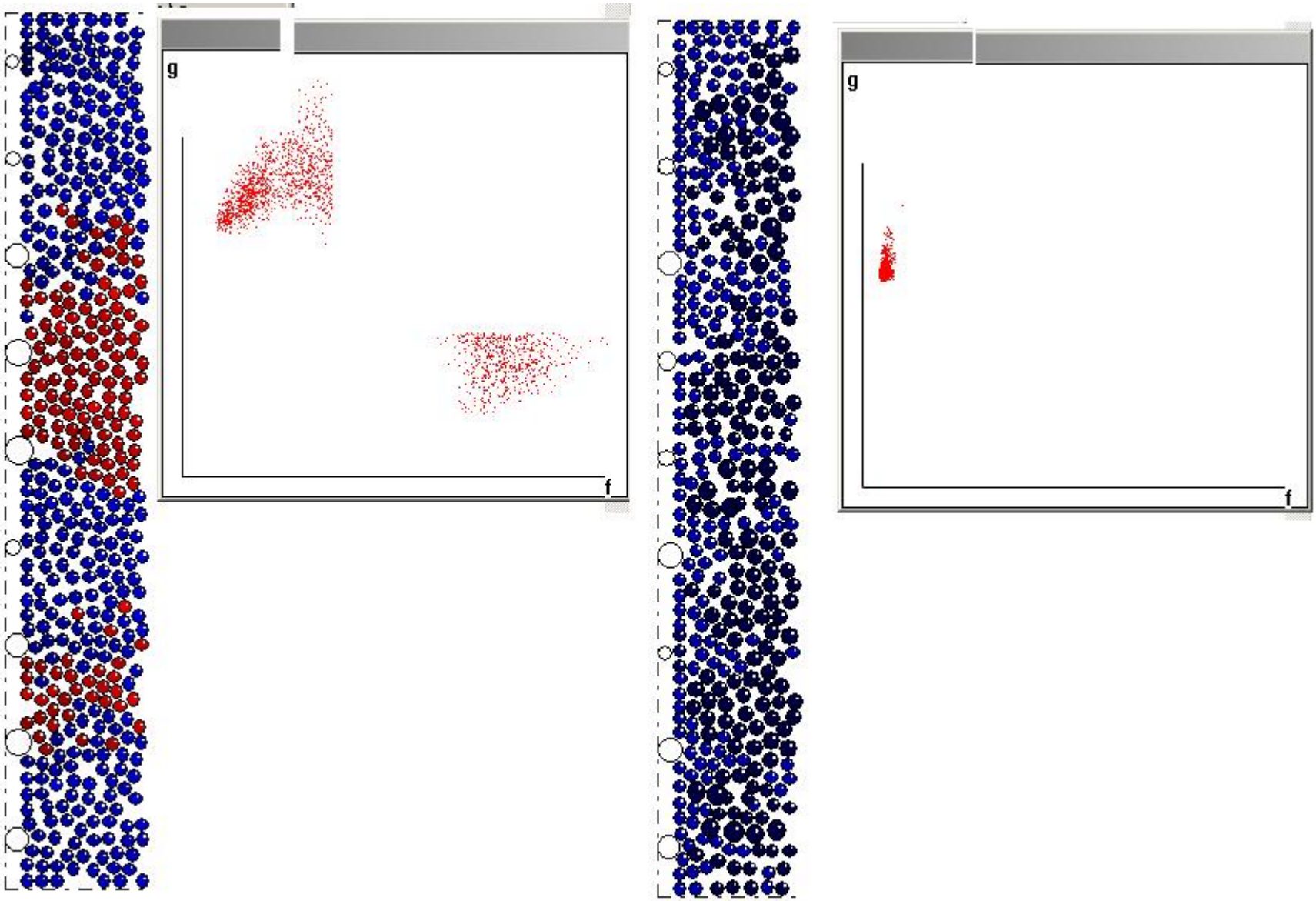
Run

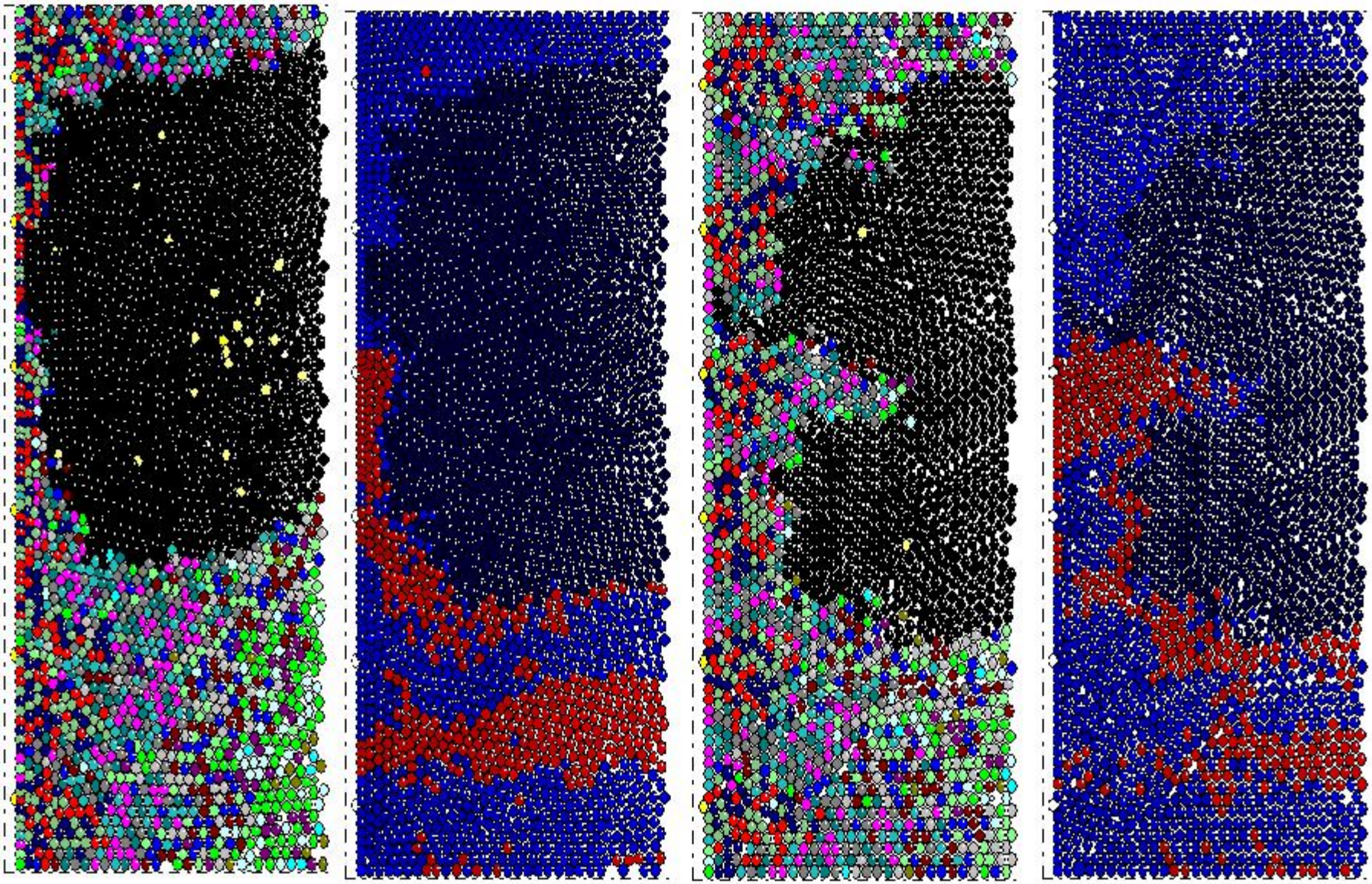
Run/Continue






tial
Output
Run
Help
void
005
Chld1
Chld2
Chld3
Chld4
Time of...
+/- Tim...
Radius ...
A0 B1 E1 F1 10 2 0.01
- - - - 200 40 0.01
C2 - - - 10 2 0.01
C3 - - - 10 2 0.01
C4 - - - 10 2 0.01
- - - - 1e+020 2 0.01
D2 - - - 10 2 0.01
D3 - - - 10 2 0.01
D4 - - - 10 2 0.01
- - - - 1e+020 2 0.01
- - - - 200 40 0.01
E3 - - - 10 2 0.01
E4 - - - 10 2 0.01
- - - - 1e+020 2 0.01
- - - - 200 40 0.01
F3 - - - 10 2 0.01
Shell -> "X"
Paint f() g()
Paint A0,A1,...
Force = max...min
Apply
max= 1
min= 0
of A0= 0.8
A0 is fixed
DblClk here
dt = 0.005
Stop any 1 step
time= 2.5600e+002
f0= 0
g0= 0
a1= 1
b1= 1
a4= 3
b4= 3
sigma= 2
F=(f+f)/2
F=max(f,f)
a5= 0.007
b5= 0.007
a6= 0
b6= 0
a7= 0
b7= 0
a8= 0.007
b8= 0.007
a9= 0
b9= 0
Run
Run/Continue


g
f
g
f



Some mathematical questions

- ODE on moving cells
- Existence and stability of stationary solutions, pattern formation
- Passing to continuous medium equations

Conclusions

Leukemia development in the bone marrow is determined by

- leukemic hematopoiesis
- cell communication and external signals

Both are not sufficiently studied and understood and are very (too ?) complex for modelling