the evolutionary dynamics of hematopoiesis
(in health & disease)

Jorge M. Pacheco

atpgroup

http://dl.dropbox.com/u/6053055/SP2016-3-of-5.pdf

ICTP SAIFR | International Centre for Theoretical Physics
South American Institute for Fundamental Research

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UNIVERSIDADE ESTADUAL PAULISTA
"JÚLIO DE MESQUITA FILHO"

layout

wednesday – 11:15 – 12:30

- hematopoiesis : from HSC to circulating blood
- a continuous *math* model for the hematopoietic tree
- analytic solution of the model
- the *standard model* (SM) of hematopoiesis
- analytical solution of the SM
- getting the parameters of the SM from EXP
- the importance of numbers :

continuous $\otimes$ *stochastic* descriptions

from HSC to circulating blood cells

Dingli, Traulsen & Pacheco, *PLoS-ONE*, 2007

the hematopoietic *tree*

- *in humans ~ 400 HSC divide once per year;*
- *but : daily output of bone marrow ~ 3.5 x 10^{11} cells !!!*

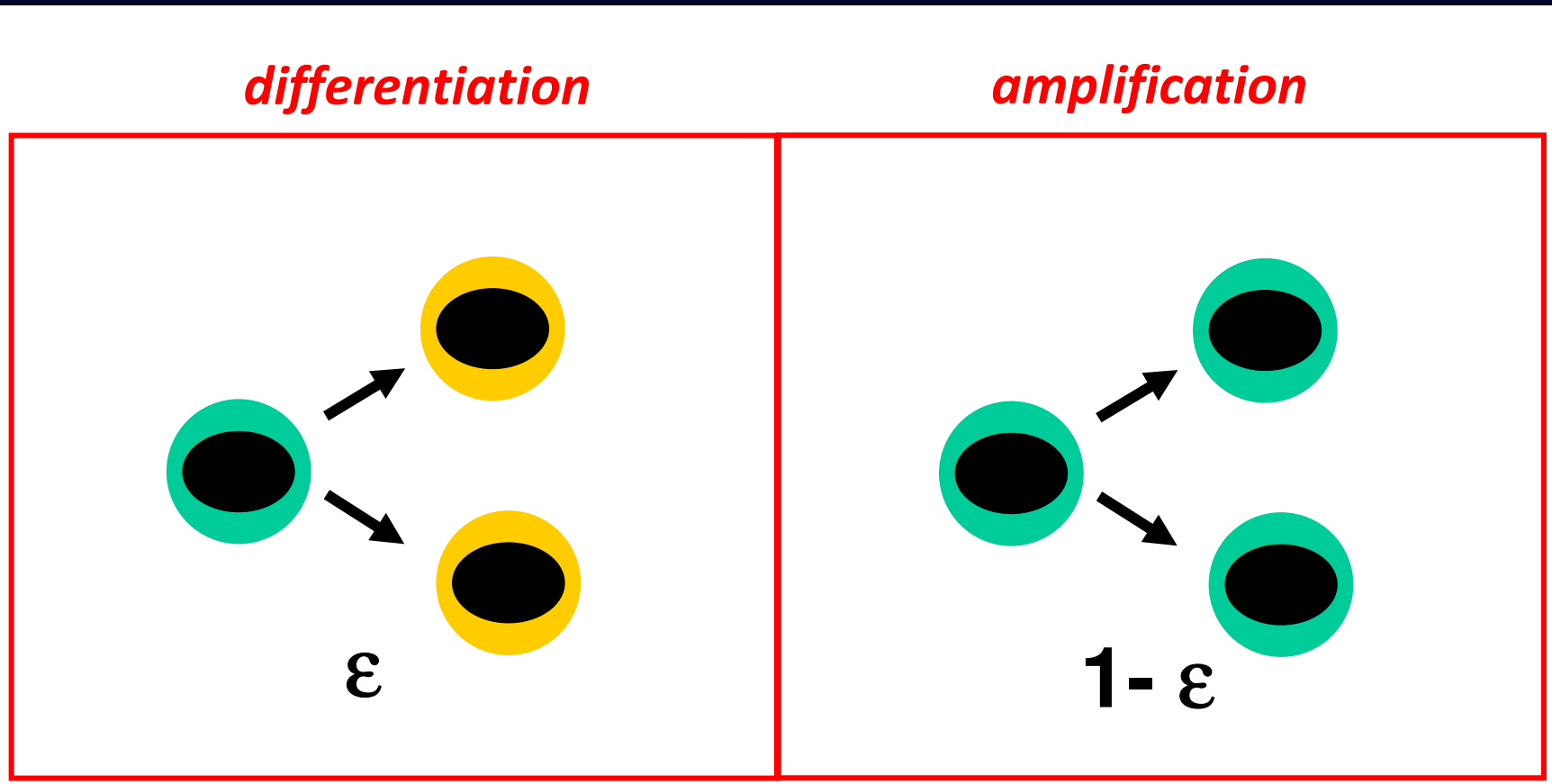
how to explain this enormous amplification given the slow replication rate of HSC ?

- *one must consider :*

differentiation

amplification

the hematopoietic *tree*



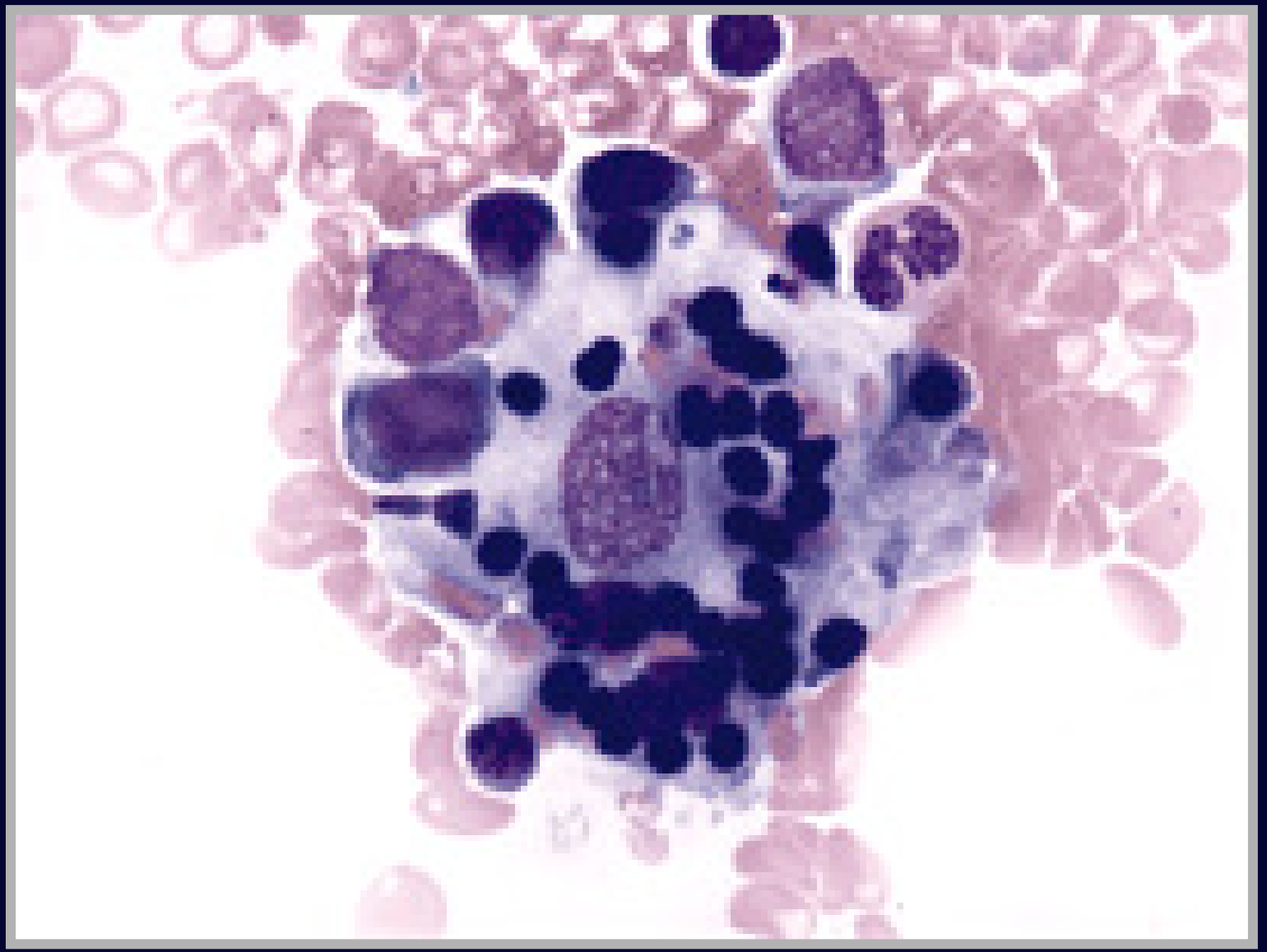
Dingli, Traulsen & Pacheco, *PLoS-ONE*, 2007

this is a simplified statistical treatment; other possibilities exist; for details see

Dingli, Traulsen & Michor, *PLoS-CB* (2007) *& Lecture 5*

the hematopoietic *tree*

let us consider a **compartmentalized** struture of the **bone-marrow**



the hematopoietic *tree*

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the hematopoietic *tree*

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the hematopoietic *tree*

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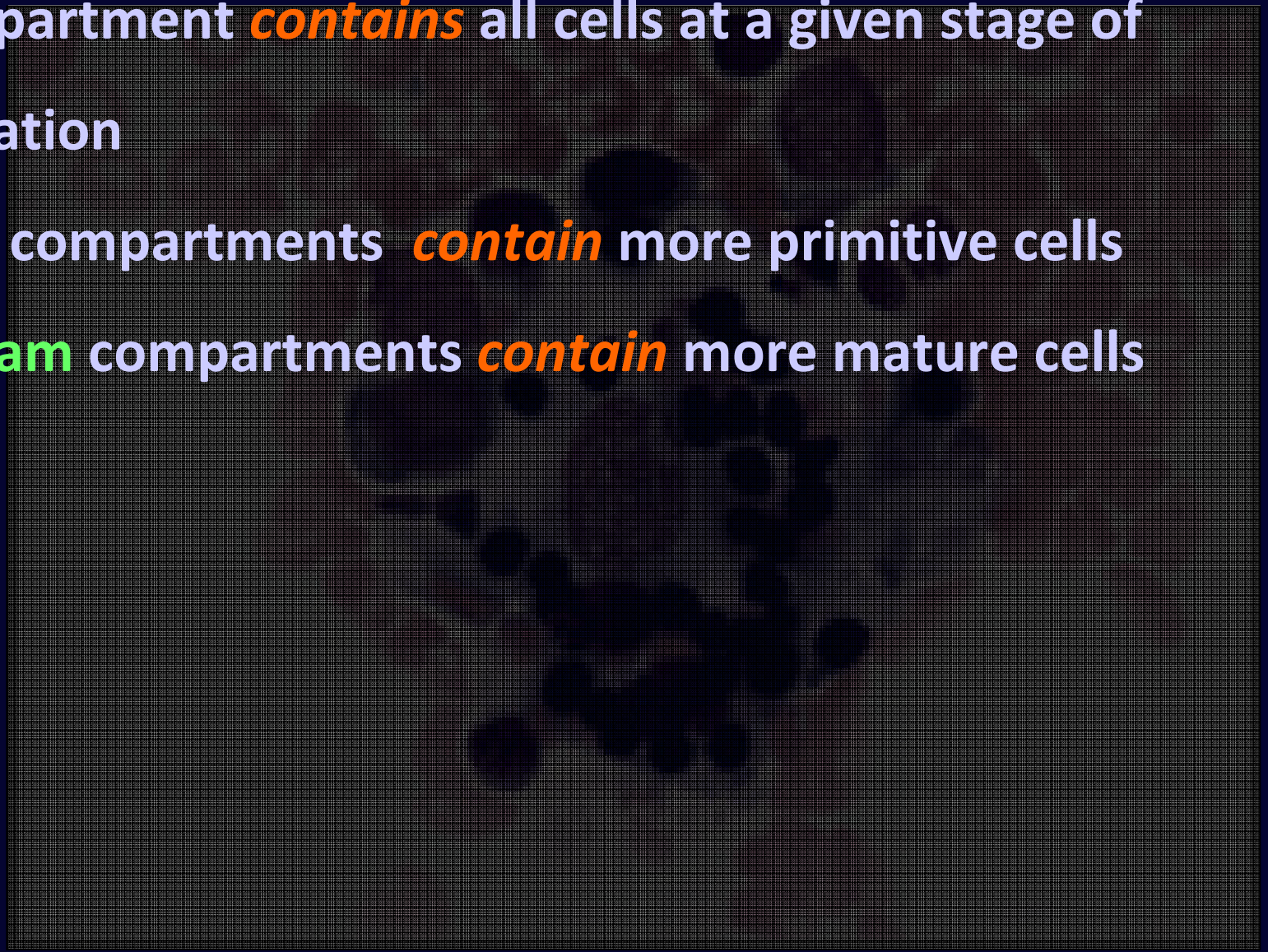

the hematopoietic *tree*

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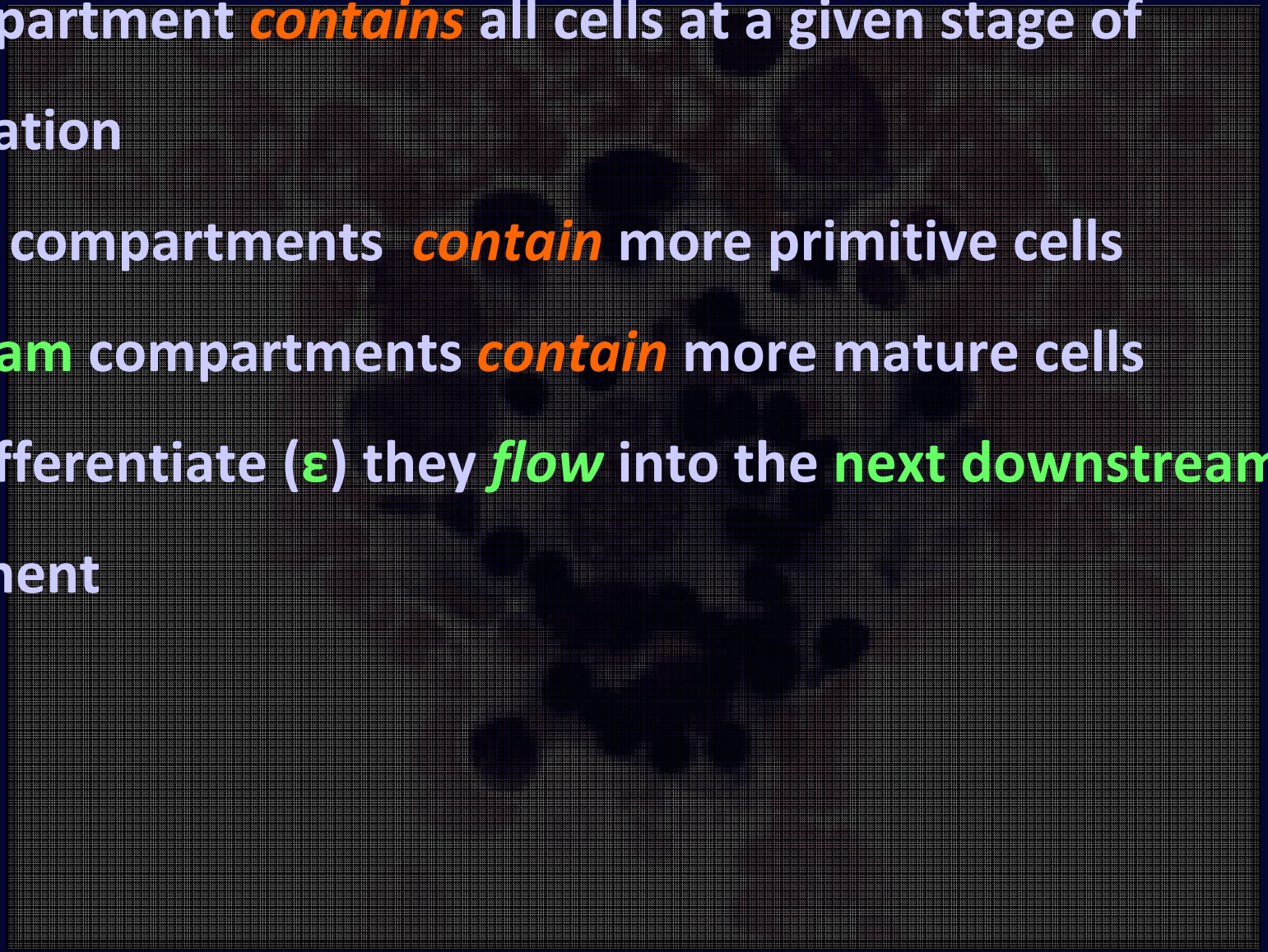

the hematopoietic *tree*

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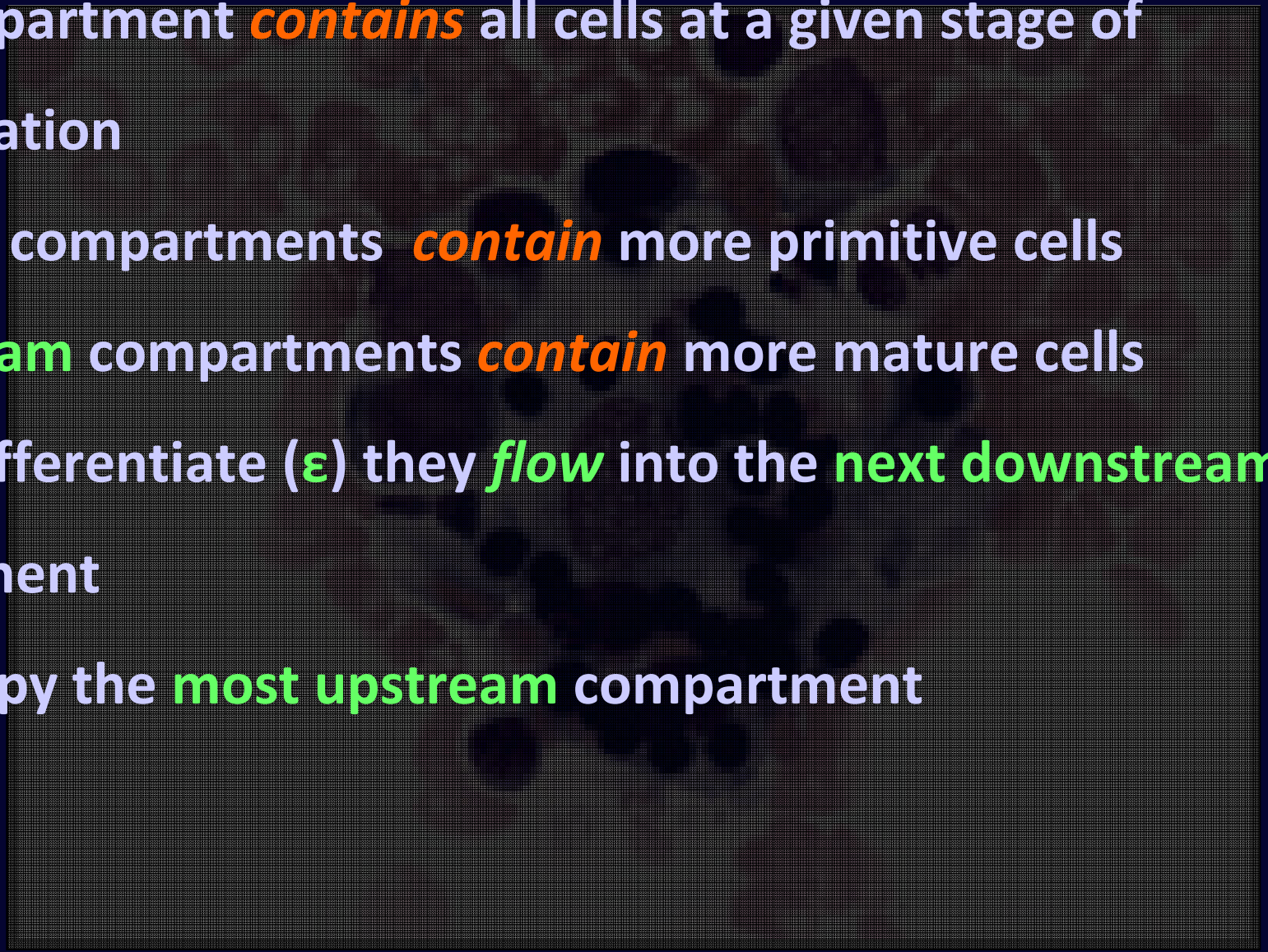
- **HSC** occupy the **most upstream** compartment



the hematopoietic *tree*

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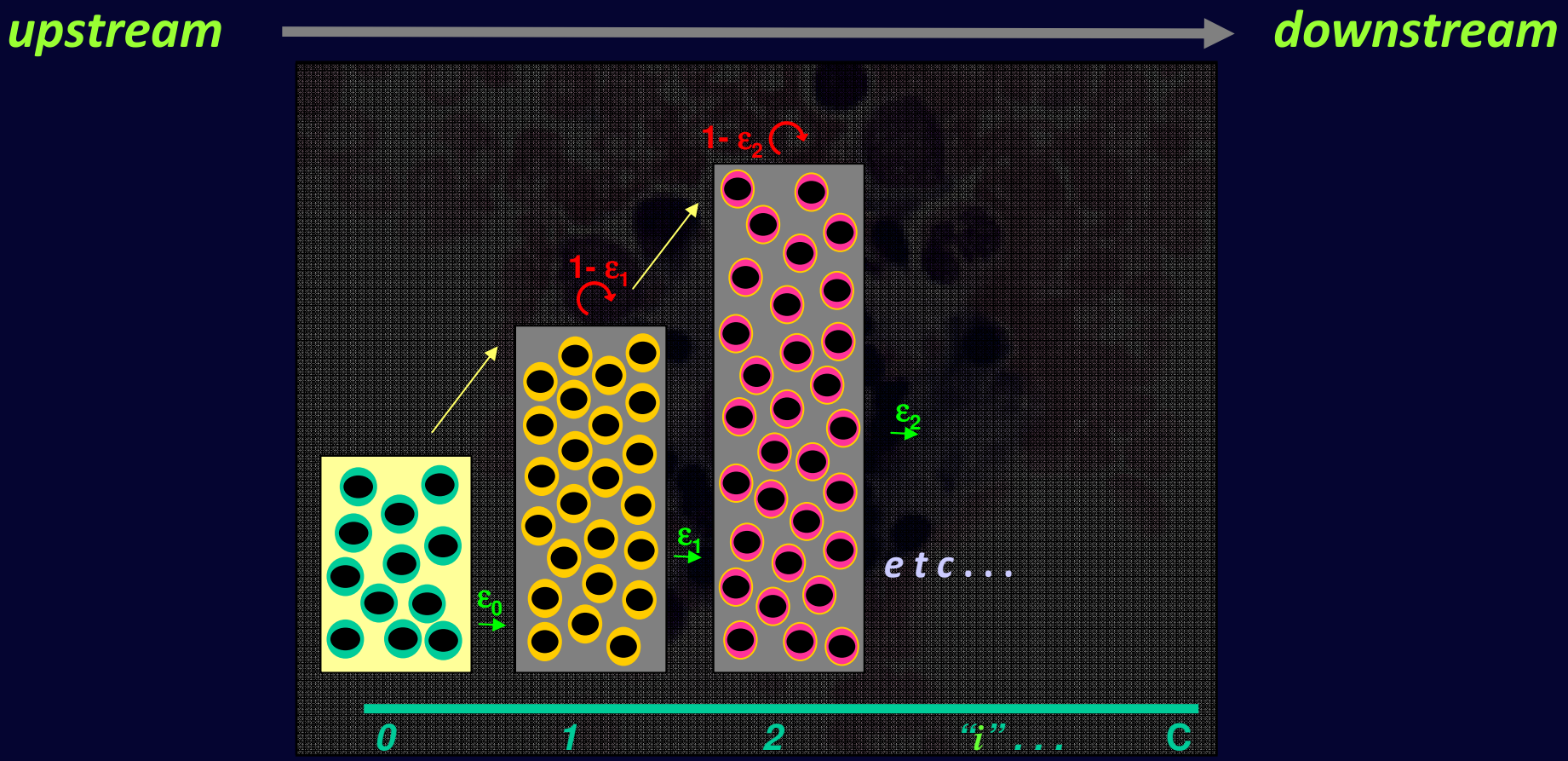
- as cells differentiate (ε) they ***flow*** into the **next downstream** compartment
- HSC occupy the **most upstream** compartment
- cells that differentiate in the last (**most downstream**) compartment are sent into the **circulating blood stream**

the hematopoietic *tree*



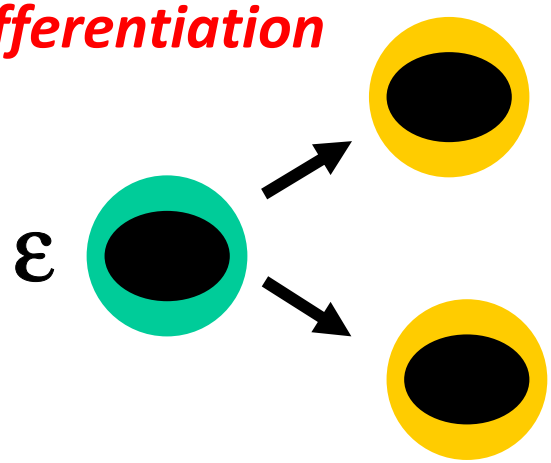
replication rate	r_0	r_1	r_2	*etc...*
differentiation *prob.*	ε_0	ε_1	ε_2	*etc...*

Dingli, Traulsen & Pacheco, *PLoS-ONE*, 2007

doing the math . . .

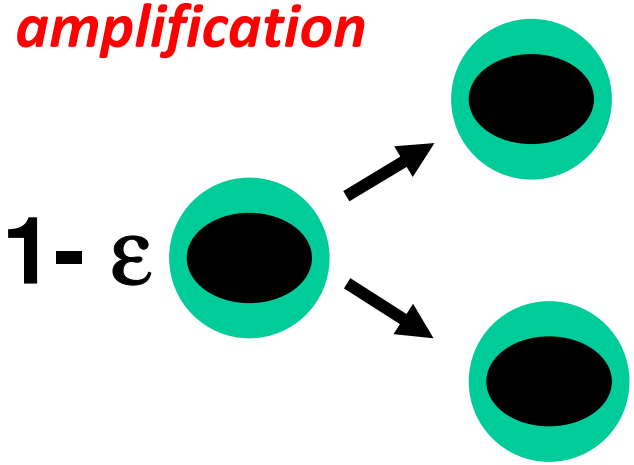
the hematopoietic *tree*

differentiation



comp-number	k-1	k
# cells before	N_{k-1}	N_k
# cells after	N_{k-1} -1	N_k+2

amplification



comp-number	k
# cells before	N_k
# cells after	N_k+1

the hematopoietic *tree*

- let us consider compartment "0" :

  we assume that the number N_0 of HSC remains constant

- let us consider compartment "1" :

  N_1 increases (per unit time) due to :

  self renewal : $(1-\varepsilon_1)N_1 r_1$

  in-flux from HSC *differentiation* (N_0) : $2\varepsilon_0 N_0 r_0$

  N_1 decreases (per unit time) due to :

  differentiation : $\varepsilon_1 N_1 r_1$

Dingli, Traulsen & Pacheco, *PLoS-ONE*, 2007

the hematopoietic *tree*

- let us consider compartment "1" :

we obtain

$$\dot{N}_1 = (1-\varepsilon_1)N_1 r_1 + 2\varepsilon_0 N_0 r_0 - \varepsilon_1 N_1 r_1$$

gain | loss

that is

$$\dot{N}_1 = 2\varepsilon_0 N_0 r_0 - (2\varepsilon_1 - 1)N_1 r_1$$

gain | net loss

finally

$$\dot{N}_1 = b_0 N_0 - d_1 N_1$$

Dingli, Traulsen & Pacheco, *PLoS-ONE*, 2007

the hematopoietic *tree*

- in general, for compartment "*i*" :

$$\dot{N}_i = b_{i-1} N_{i-1} - d_i N_i$$

with $b_i = 2\varepsilon_i r_i$ and $d_i = (2\varepsilon_i - 1) r_i$

- leading to a system of *C*+1 coupled (linear) ODEs

$$\dot{N}_0 = 0; \quad \dot{N}_i = b_{i-1} N_{i-1} - d_i N_i \ (i = 1, C)$$

Werner, Dingli, Lenaerts, Pacheco, Traulsen, *PLoS-CB*, 2011

the hematopoietic *tree*

with general solution

$$N_0(t) = N_{SC}$$

$$N_1(t) = N_0 \frac{r_0}{d_1}\left[1 - e^{-d_1 t}\right]$$

$$N_i(t) = N_0 \frac{r_0}{d_i}\prod_{k=1}^{i-1}\frac{b_k}{d_k}\left[1 - e^{-d_k t}\right] + N_0 r_0\left(\prod_{l=1}^{i-1} b_l\right)\sum_{k=1}^{i}\frac{(-1)^k}{d_k R_{k,i}}\left(e^{-d_k t} - e^{-d_i t}\right)$$

where

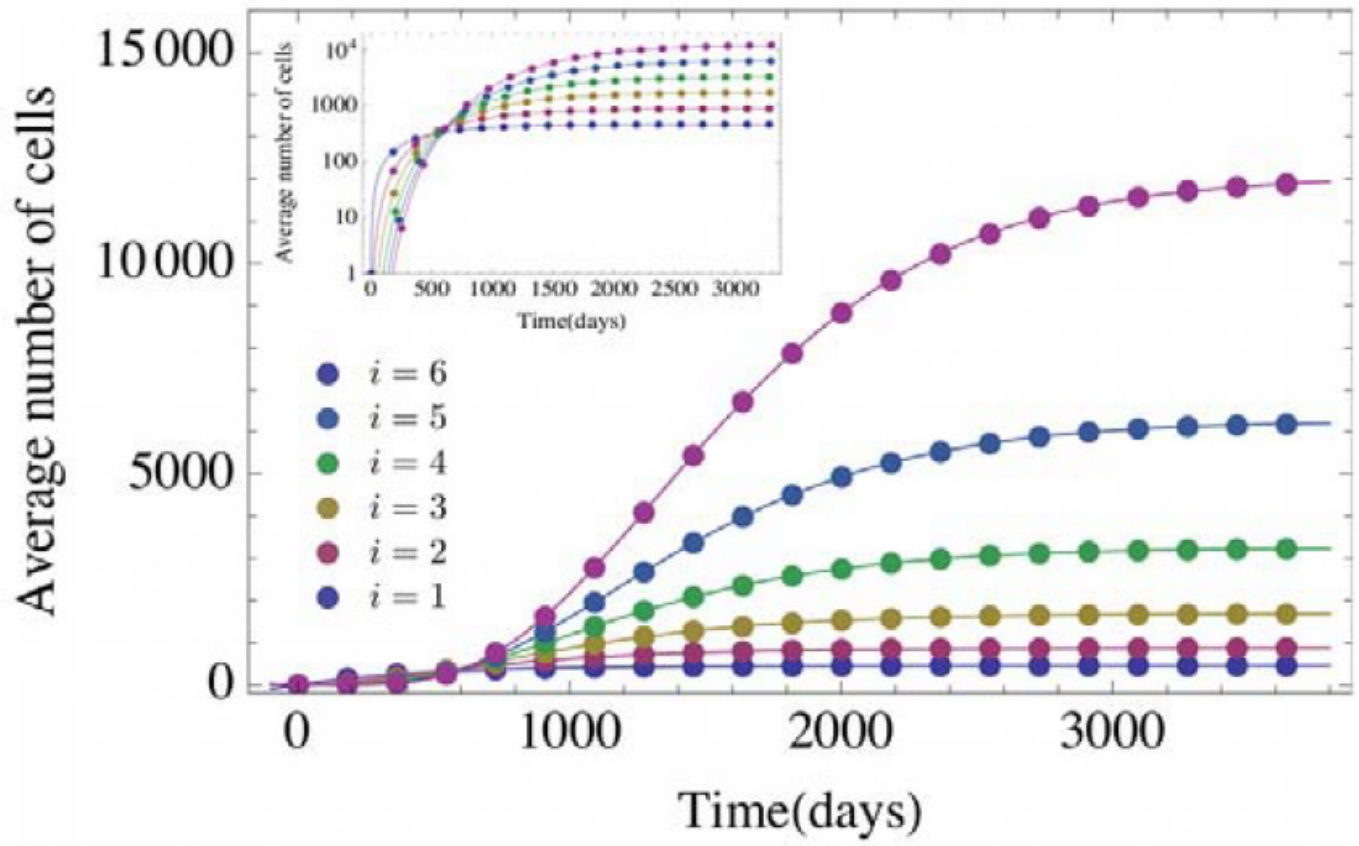
$$b_i = 2\varepsilon_i r_i$$

$$d_i = (2\varepsilon_i - 1) r_i$$

$$R_{k,i} = \prod_{l=1(l\neq k)}^{i}\left(d_k - d_l\right)$$

Werner, Dingli, Lenaerts, Pacheco, Traulsen, *PLoS-CB*, 2011

the hematopoietic *tree*



filling of the 1st 6 compartments using the parameters that will be derived in the following

the hematopoietic *tree*

in such a model, homeostasis means (flux-balance conditions)

$$\dot{N}_i(t) = 0 \quad (i = 0, \cdots, C)$$

leading to

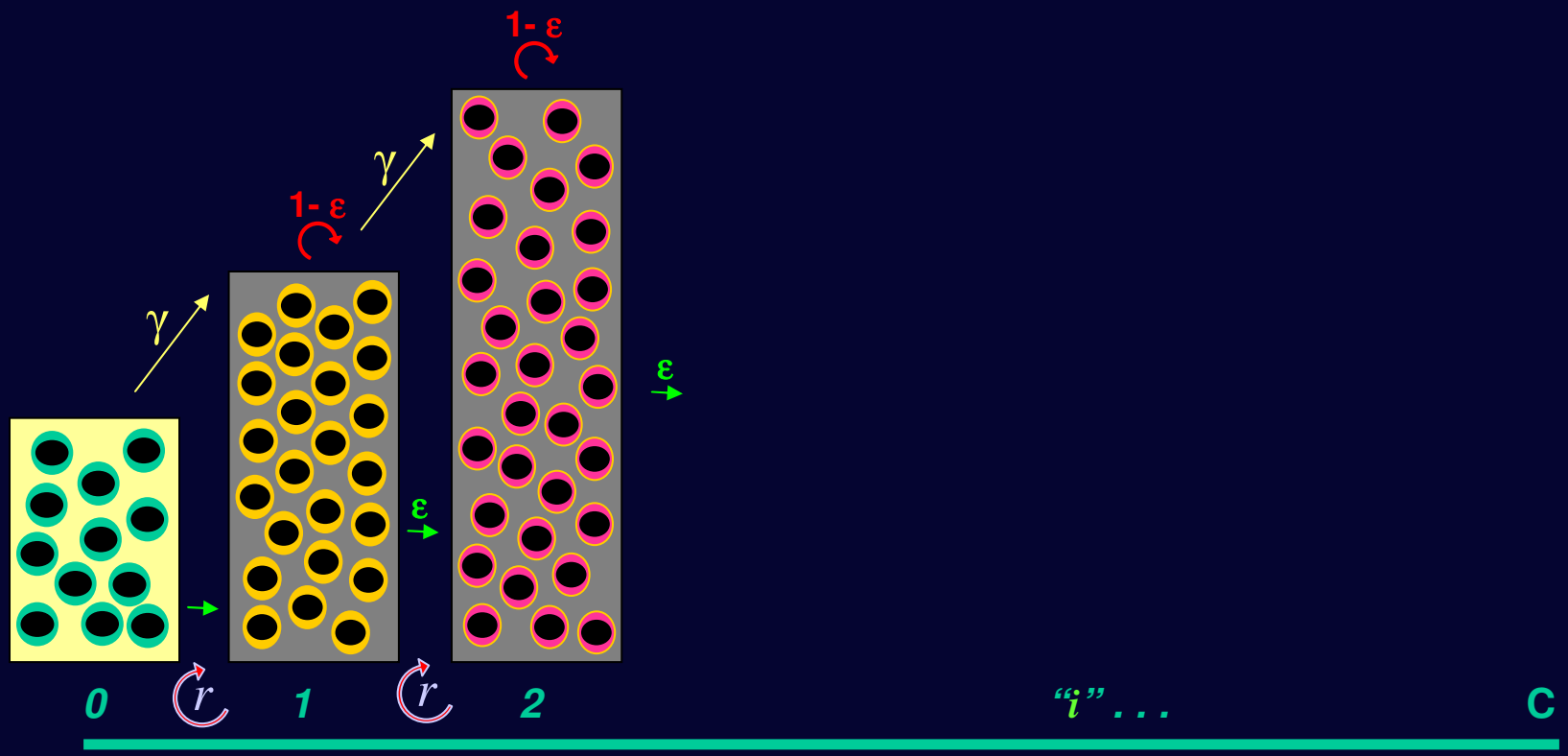
$$N_i(t) = N_0 \frac{r_0}{d_i} \prod_{k=1}^{i-1} \frac{b_k}{d_k}$$

Werner, Dingli, Lenaerts, Pacheco, Traulsen, *PLoS-CB*, 2011

the standard model (**SM**)

the hematopoietic *tree*

- *let us considerably simplify our compartmentalized struture by assuming that* :



Dingli, Traulsen & Pacheco, *PLoS-ONE*, 2007

the hematopoietic *tree*

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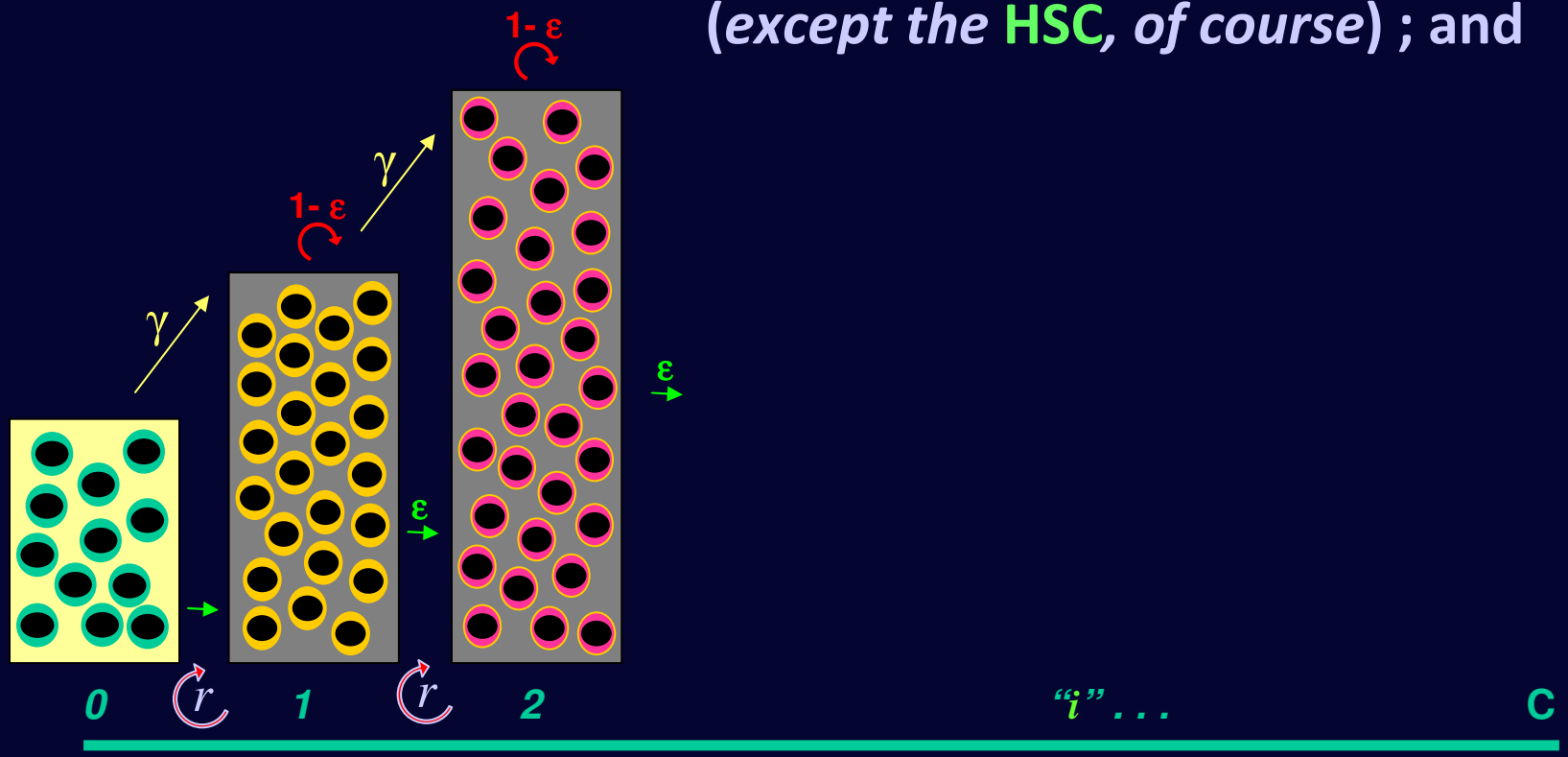
ε is the same for all compartments (except the HSC, of course) ; and



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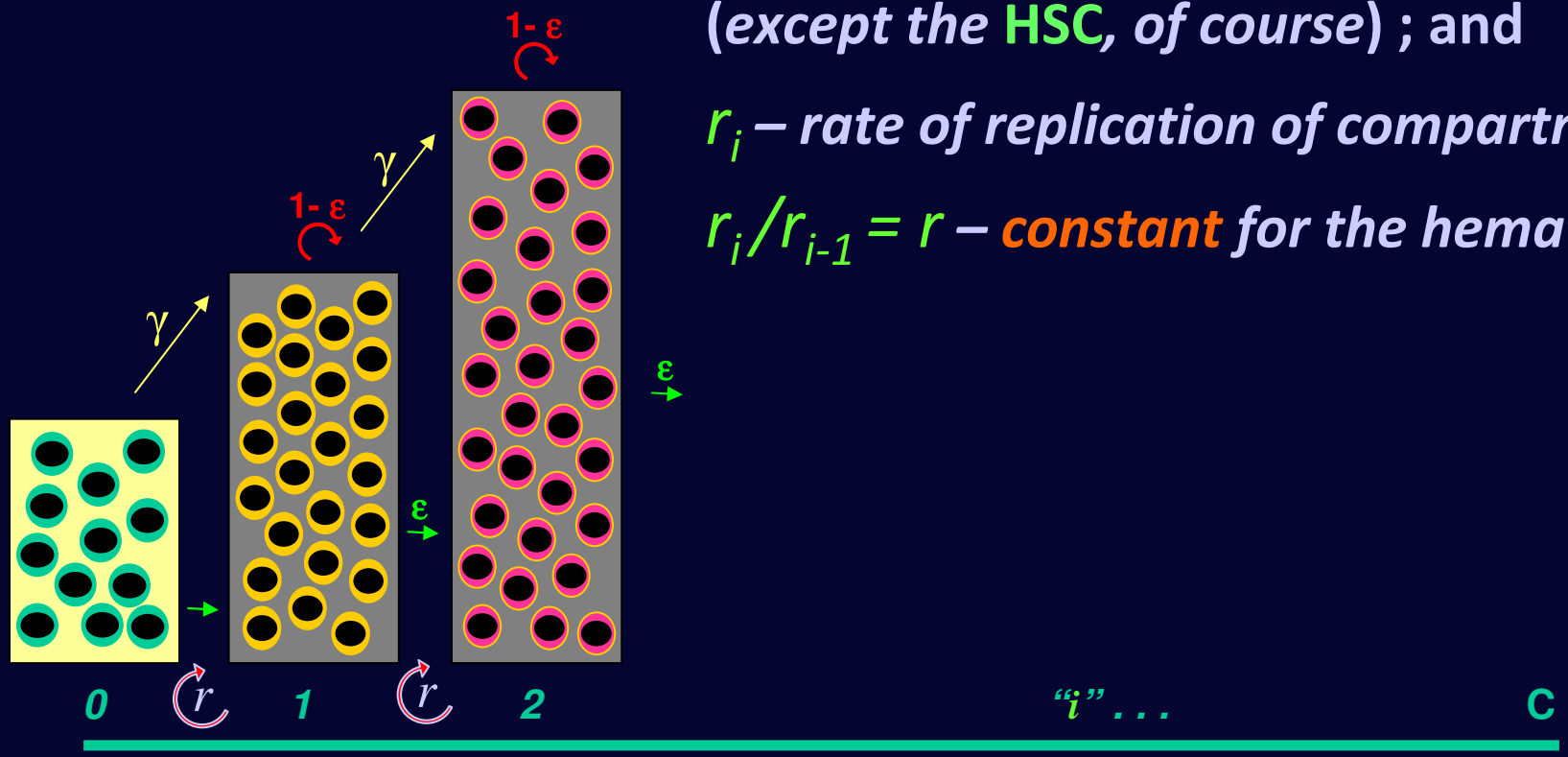
the hematopoietic *tree*

❖ *let us considerably simplify our compartmentalized struture by assuming that* :

ε *is the same for all compartments* (*except the* **HSC**, *of course*) ; and

r_i – *rate of replication of compartment "i" ;*

$r_i / r_{i-1} = r$ – *constant for the hematopoietic tree*



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the hematopoietic *tree*

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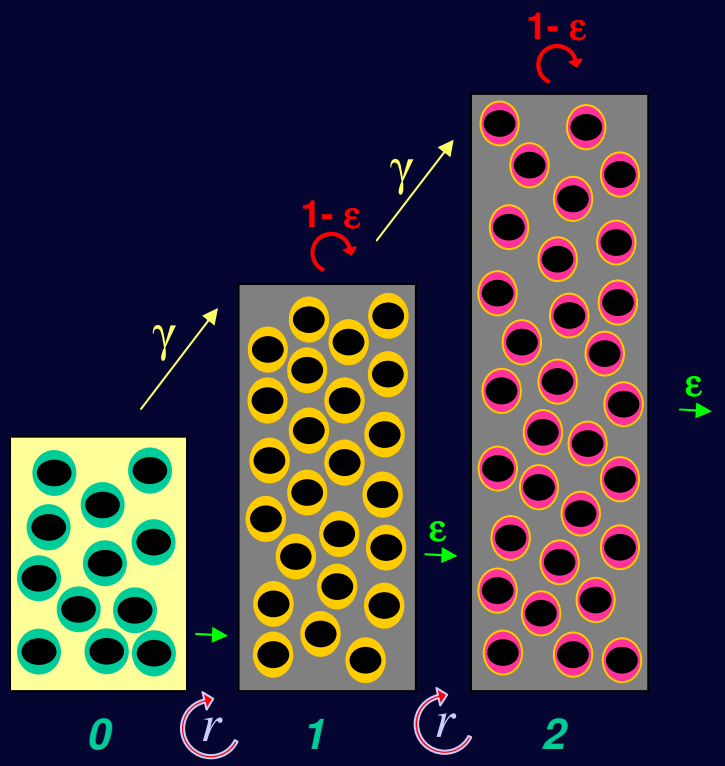

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---

we know r_0 (HSC) → all we need to know is *r*

$\varepsilon \neq \varepsilon_0$? *possible, because*

$\varepsilon_0 = 0.5$ (it must be)

Dingli, Traulsen & Pacheco, *PLoS-ONE*, 2007

the hematopoietic *tree*

and the general solution remains

$$N_0(t) = N_{SC}$$

$$N_1(t) = N_0 \frac{r_0}{d_1}\left[1 - e^{-d_1 t}\right]$$

$$N_i(t) = N_0 \frac{r_0}{d_i}\prod_{k=1}^{i-1}\frac{b_k}{d_k}\left[1 - e^{-d_k t}\right] + N_0 r_0\left(\prod_{l=1}^{i-1} b_l\right)\sum_{k=1}^{i}\frac{(-1)^k}{d_k R_{k,i}}\left(e^{-d_k t} - e^{-d_i t}\right)$$

where the coefficients simplify now to

$$b_i = 2\varepsilon\, r_0 r^i$$

$$d_i = (2\varepsilon - 1) r_0 r^i$$

$$R_{k,i} = (2\varepsilon - 1)^{i-1}\prod_{l=1(l\neq k)}^{i}\left(r^k - r^l\right)$$

Werner, Dingli, Lenaerts, Pacheco, Traulsen, *PLoS-CB*, 2011

the hematopoietic *tree*

then, under stationary conditions :

$$2\,\varepsilon_{i-1}\,N_{i-1}\,r_0\,r^{i-1} = (2\varepsilon_i - 1)N_i\,r_0\,r^i$$

we define

$$\frac{N_i}{N_{i-1}} = \gamma \equiv \frac{1}{r}\frac{2\varepsilon}{2\varepsilon - 1}$$

such that growth implies

$$N_i > N_{i-1} \Rightarrow \frac{2\varepsilon}{2\varepsilon - 1} > r \Leftrightarrow \gamma > 1$$

the hematopoietic *tree*

Fixing the parameters ε, r & C (using lab data) :

- *During polymorphonuclear leukocyte production, ≈ 10^{10} myeloblasts expand and produce ≈ 1.4×10^{11} myelocytes in 4 differentiation steps*

$$\gamma = \left(\frac{1.4\times10^{11}}{10^{10}} \right)^{1/4} \approx 1.93$$

- *γ provides the net cell amplification between consecutive compartments; thus, knowledge of N_0 & bone-marrow output leads to*

$$C = \frac{Log\left(\frac{3.5\times10^{11}}{400} \right)}{Log(1.93)} \approx 31$$

Dingli, Traulsen & Pacheco, *PLoS-ONE*, 2007

the hematopoietic *tree*

Fixing the parameters ε, r & C (using lab data) :

- *precursors of granulocytes may replicate up to ≈ 5 times per day ;*
  HSC *replicate, on average, once per year; thus*

$$r = \left(\frac{5/1}{1/365} \right)^{1/31} \approx 1.27$$

from where we obtain

$$\varepsilon = \frac{r \cdot \gamma}{2(r \cdot \gamma - 1)} \approx 0.84$$

during hematopoiesis, and during replication, cells ***contribute more to differentiation than to their own amplification in each compartment.***

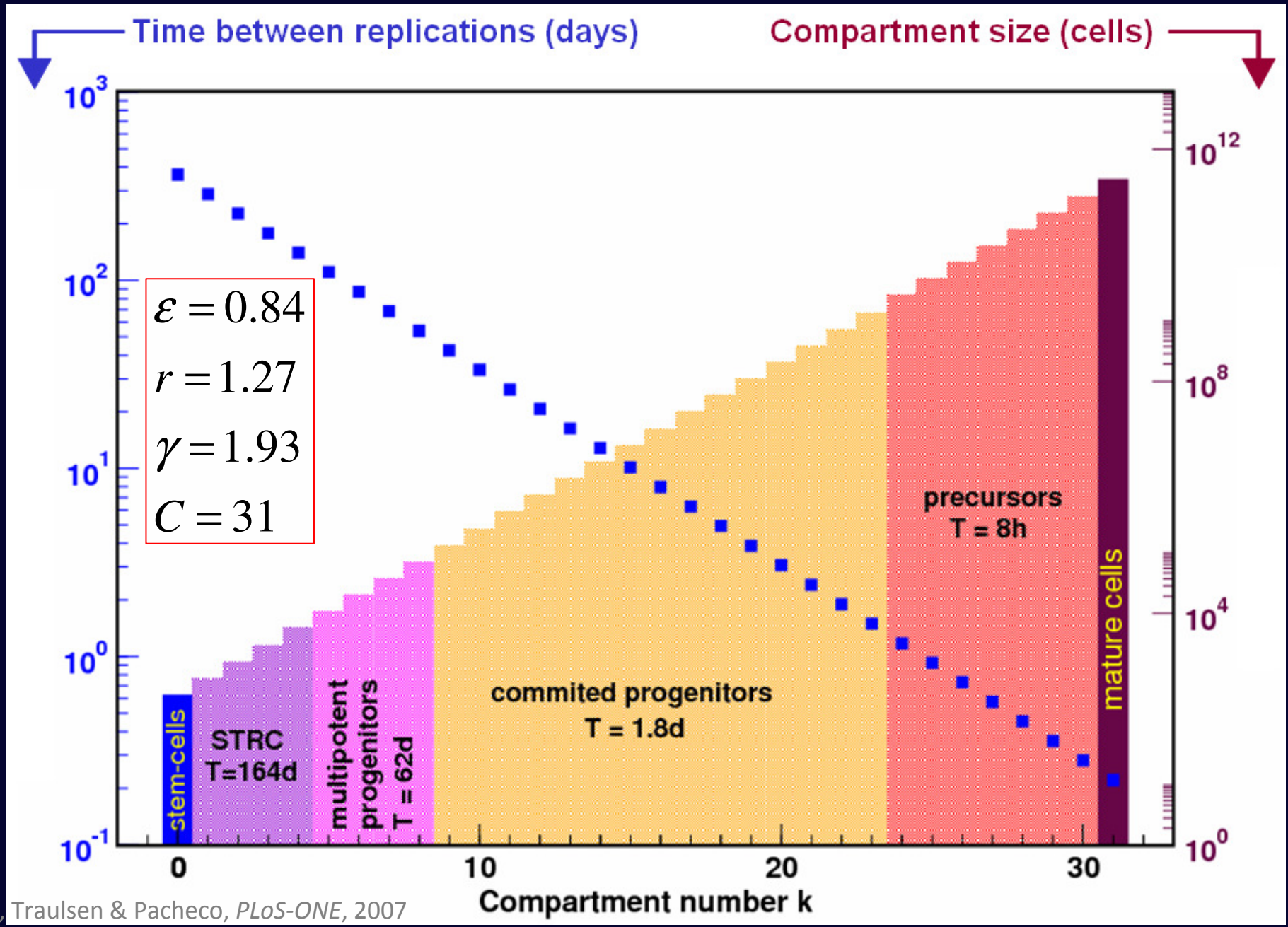
Dingli, Traulsen & Pacheco, *PLoS-ONE*, 2007

the hematopoietic *tree*

- ***ε = 0.5*** *means compartment "i" does not need input from upstream compartments* (**HSC**)*;*

- ***ε = 1.0*** *means there is no chance of increasing the flux on demand (hemorrage, etc.) ;*

the hematopoietic *tree*



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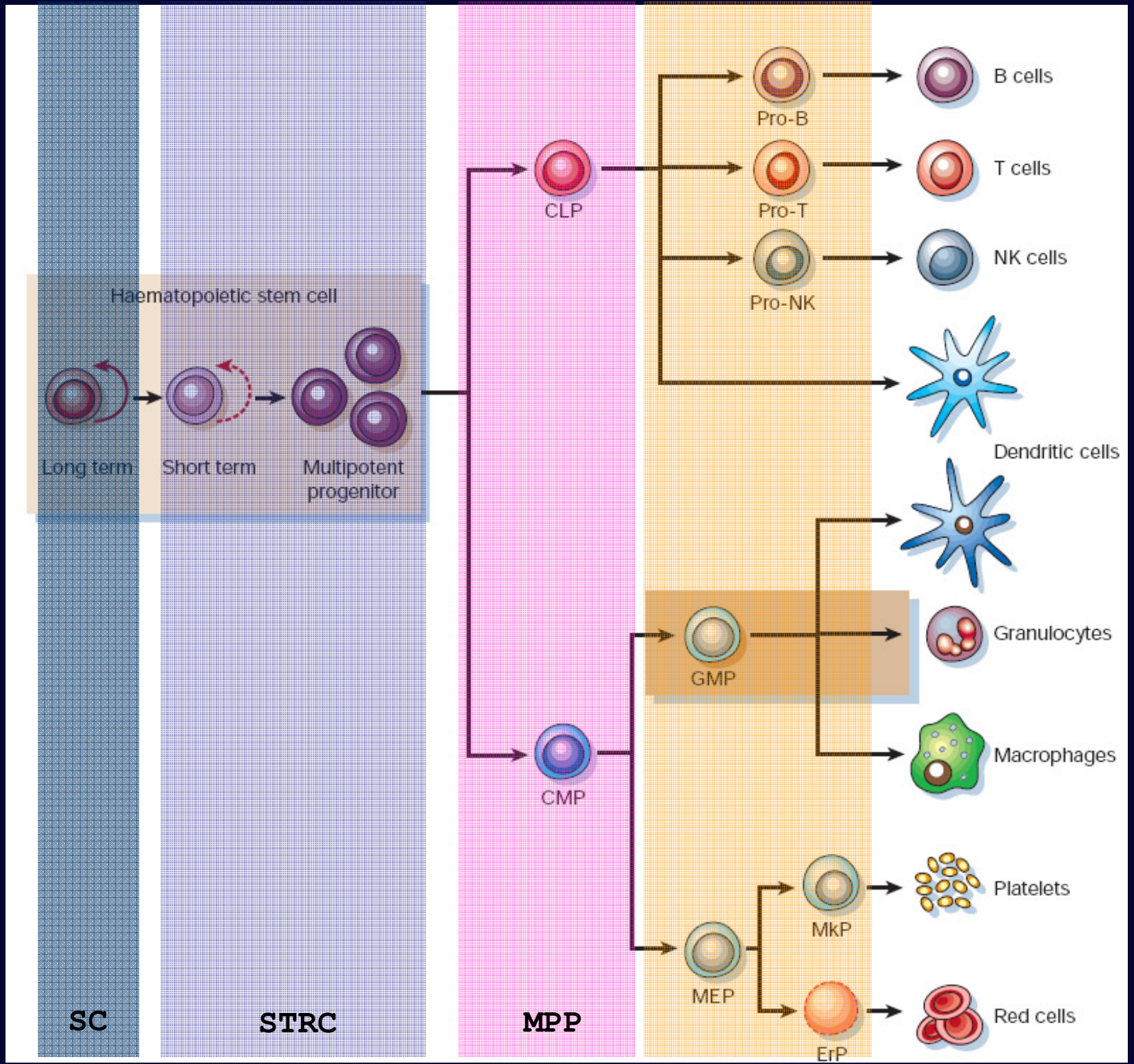
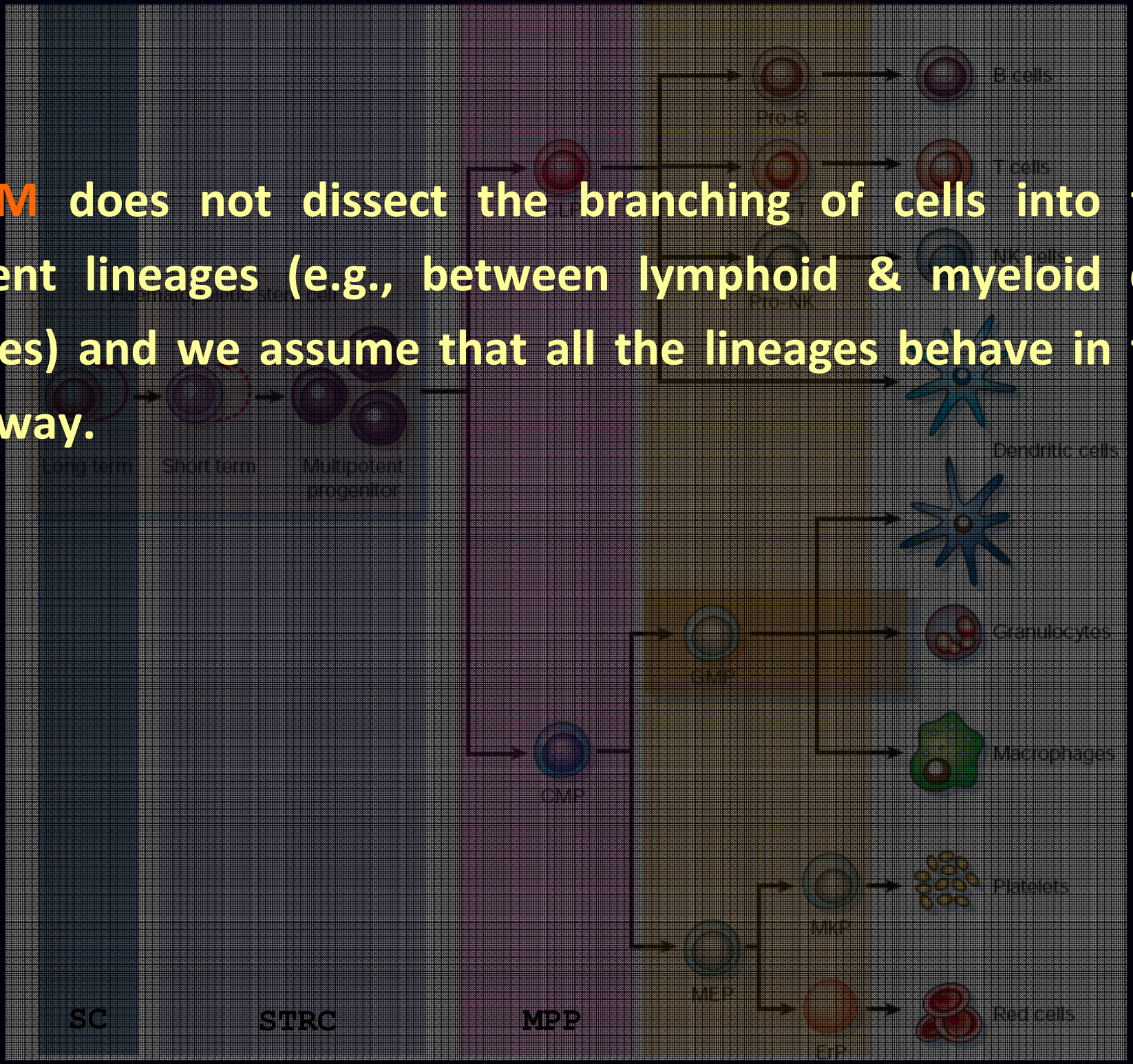

Haematopoietic stem cell
Long term
Short term
Multipotent progenitor
CLP
CMP
Pro-B
Pro-T
Pro-NK
GMP
MEP
MkP
ErP
B cells
T cells
NK cells
Dendritic cells
Granulocytes
Macrophages
Platelets
Red cells
SC
STRC
MPP

the SM does not dissect the branching of cells into the different lineages (e.g., between lymphoid & myeloid cell lineages) and we assume that all the lineages behave in the same way.



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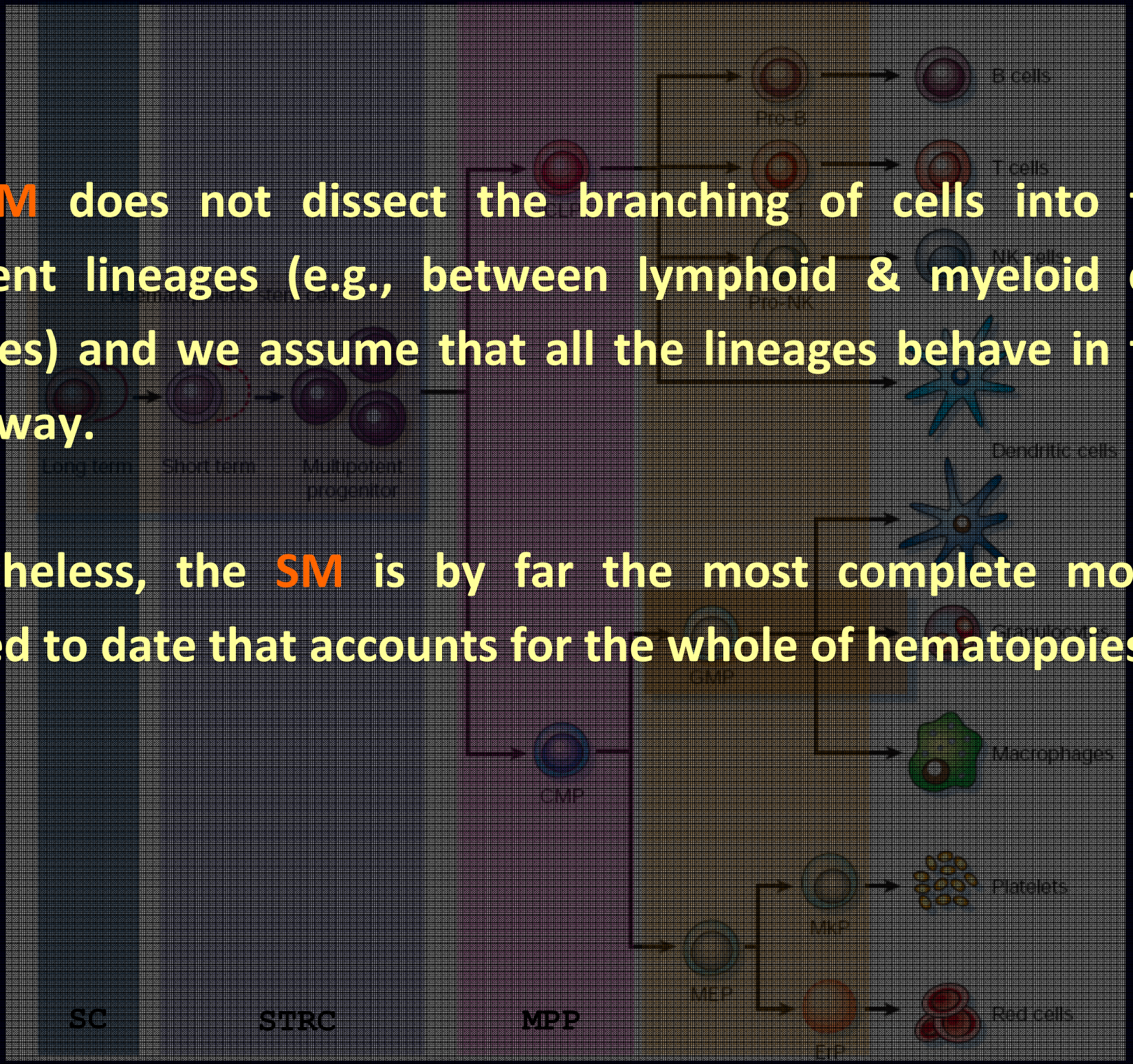

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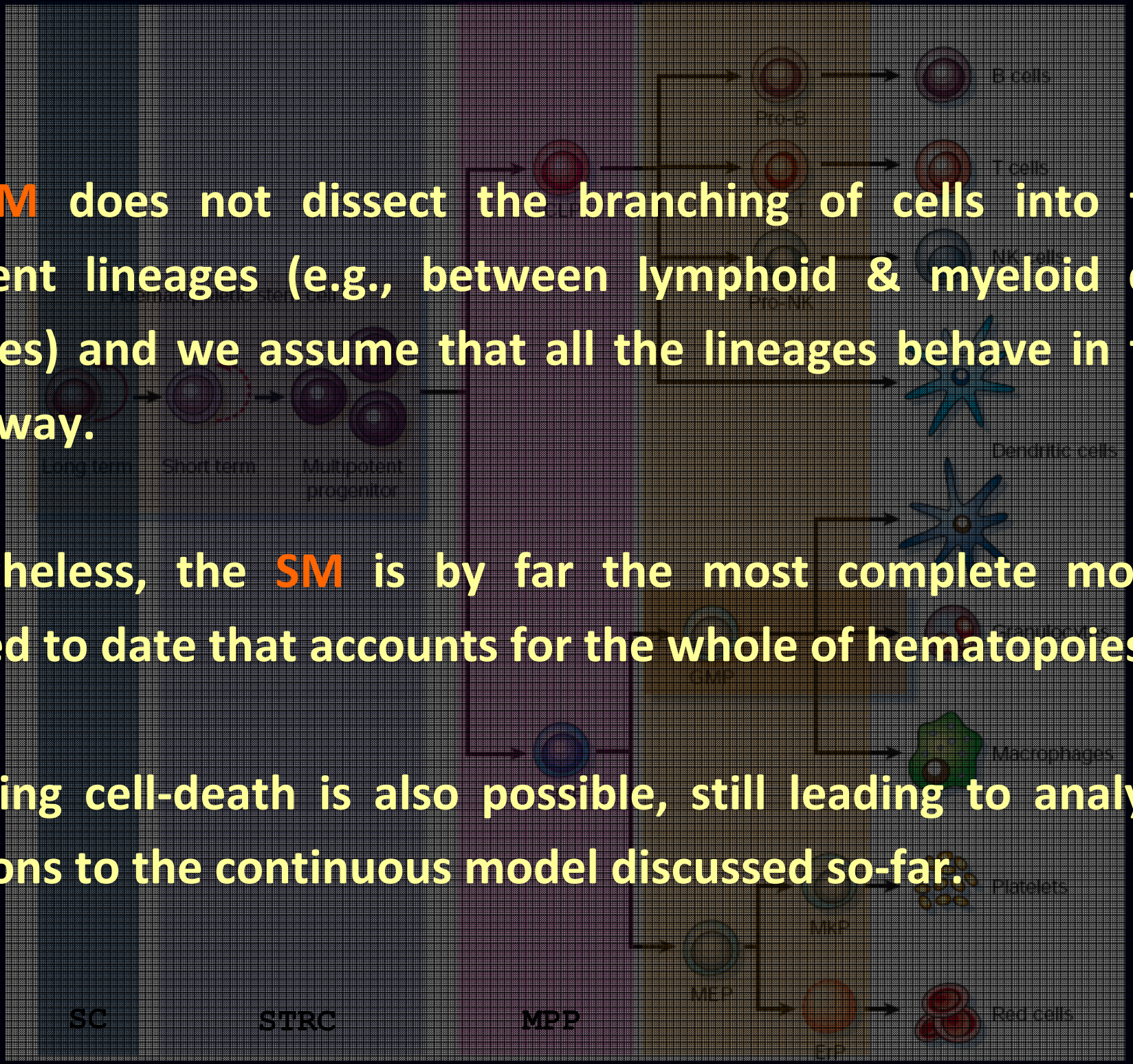
including cell-death is also possible, still leading to analytic solutions to the continuous model discussed so-far.



the hematopoietic *tree*

some predictions of the model :

- ***number of compartments** connecting stem-cells and circulating blood cells ; **number of mitotic events is never below 31** → we can look at **telomeres** (Lecture 5)*

- ***size, replication rate & average time a given cell type contributes to hematopoiesis ;***

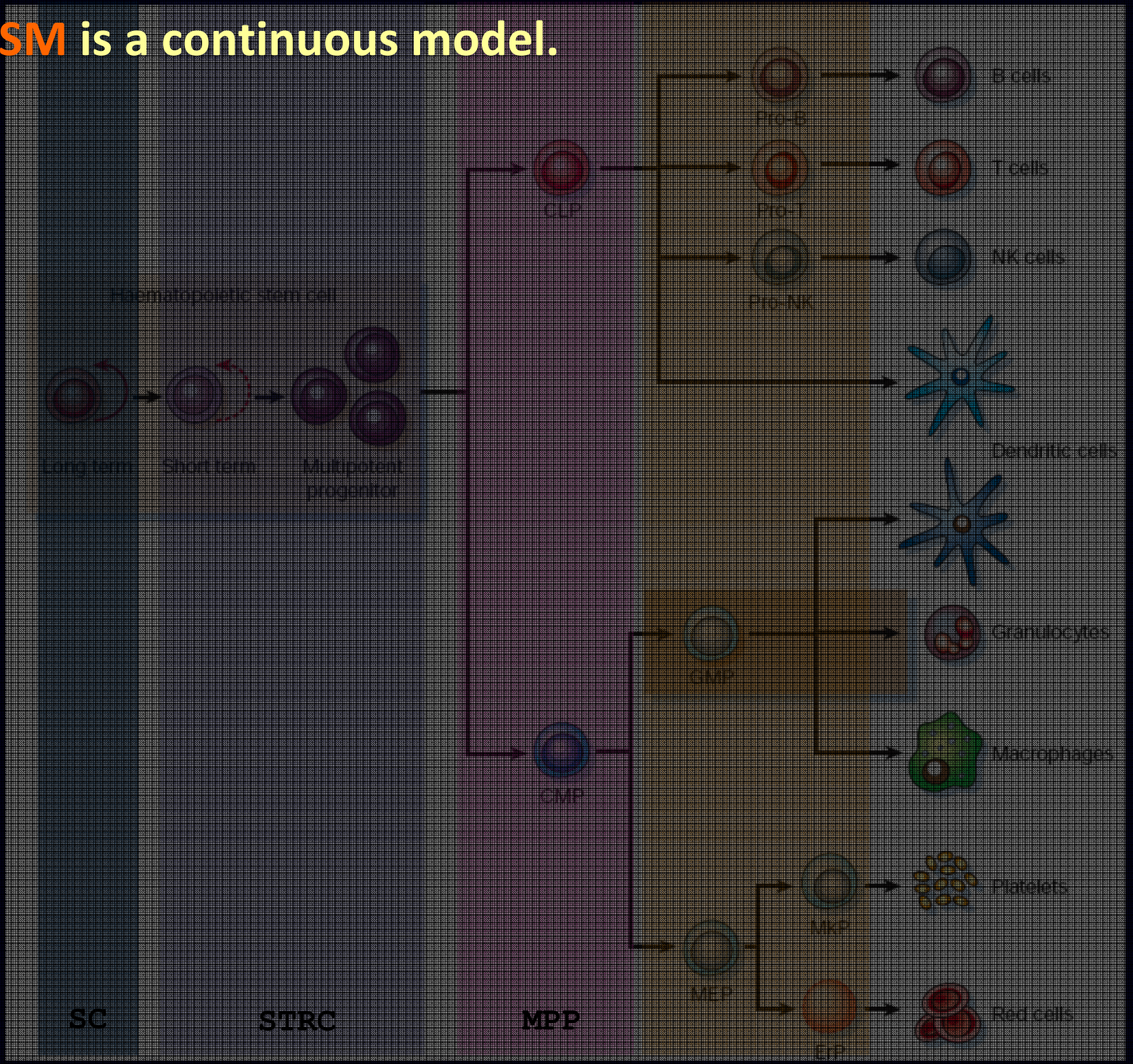
$$5 \leq \text{compartment (CFU-GEMM)} \leq 8$$

the (weighted) average time they contribute to hematopoiesis is then 61-120 days.

→ *this is what is identified experimentally in the lab*

(Araten et al, **PNAS**, 1999)

the SM is a continuous model.



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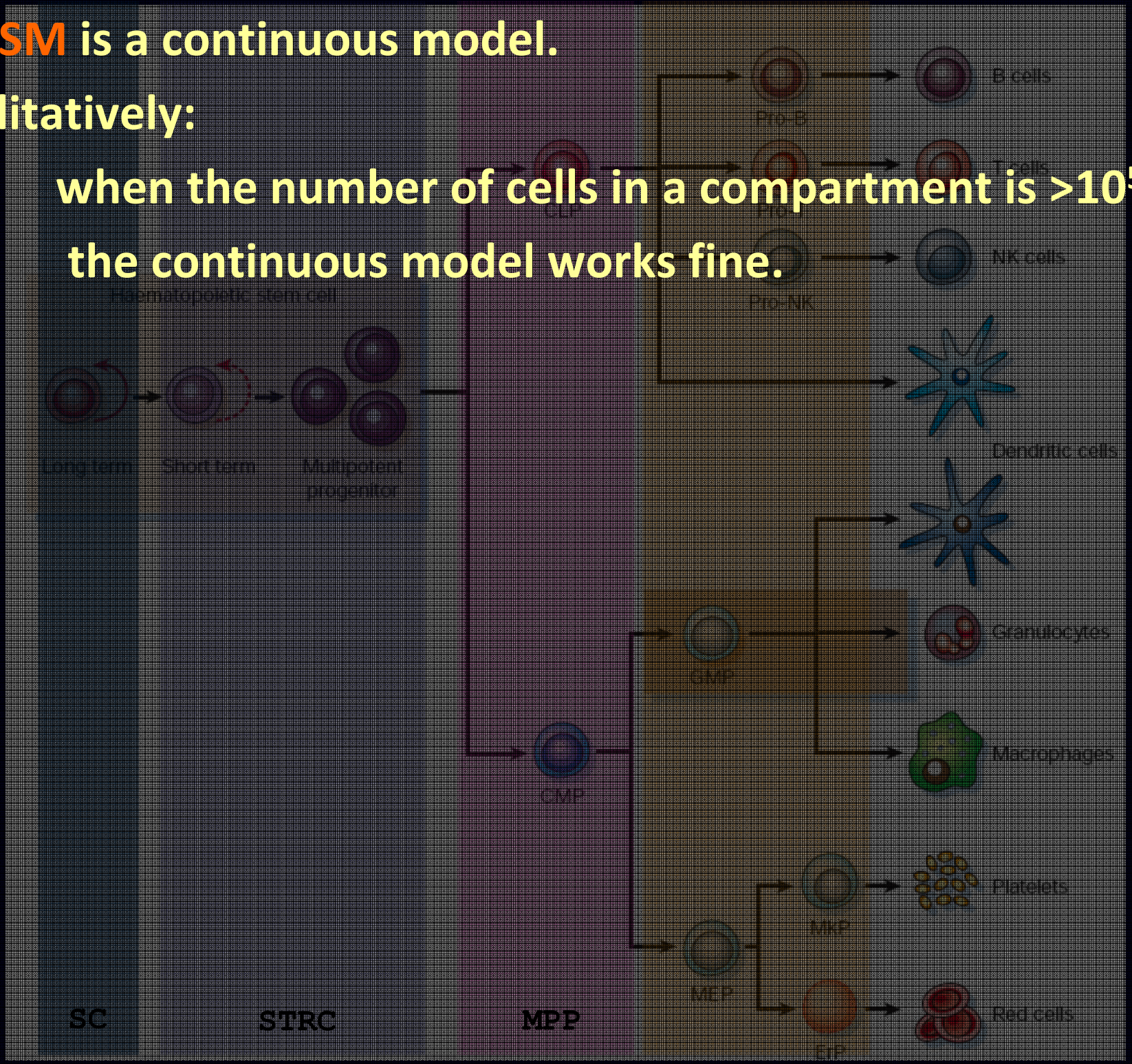
qualitatively:

when the number of cells in a compartment is $>10^5$

the continuous model works fine.



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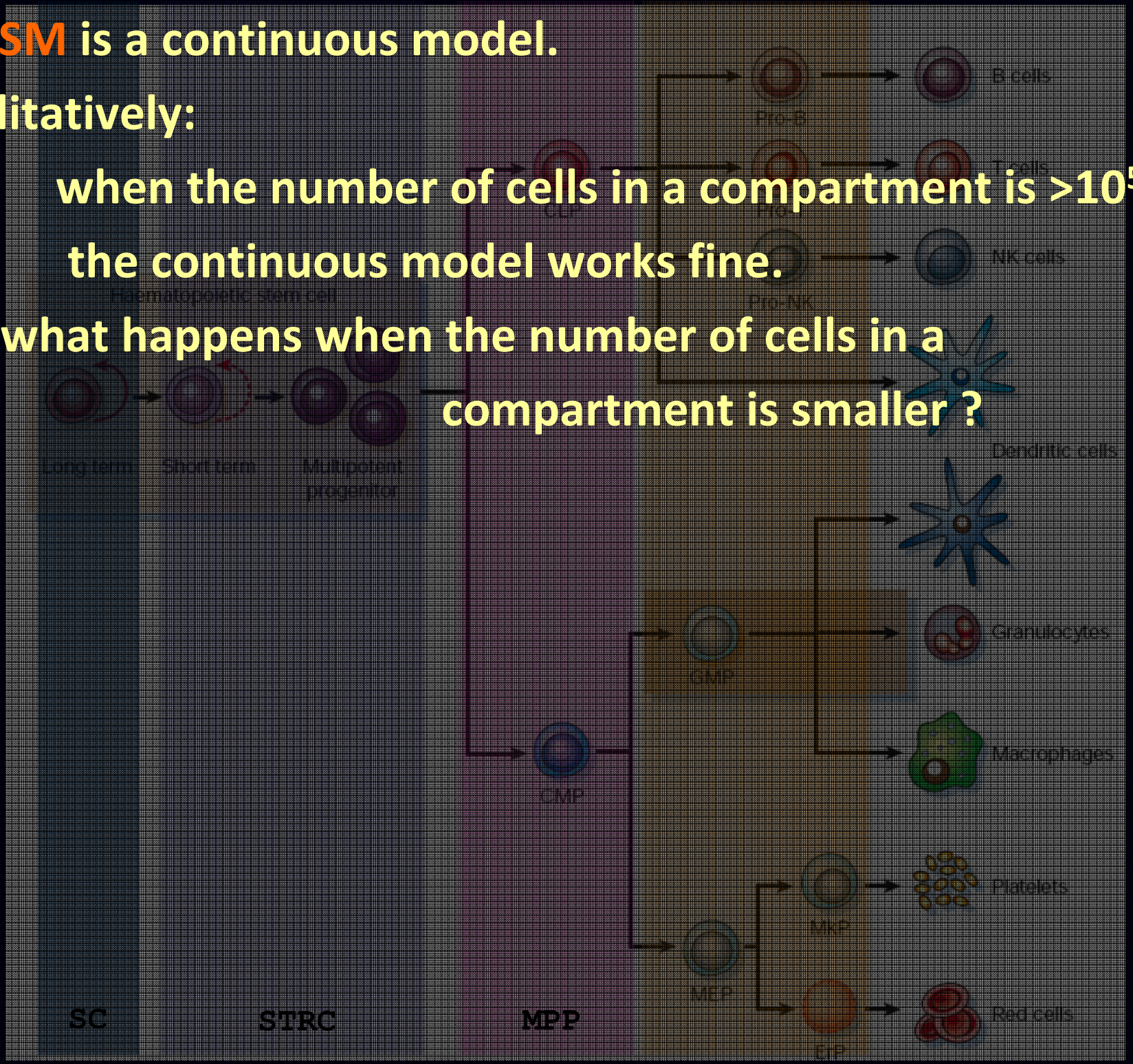

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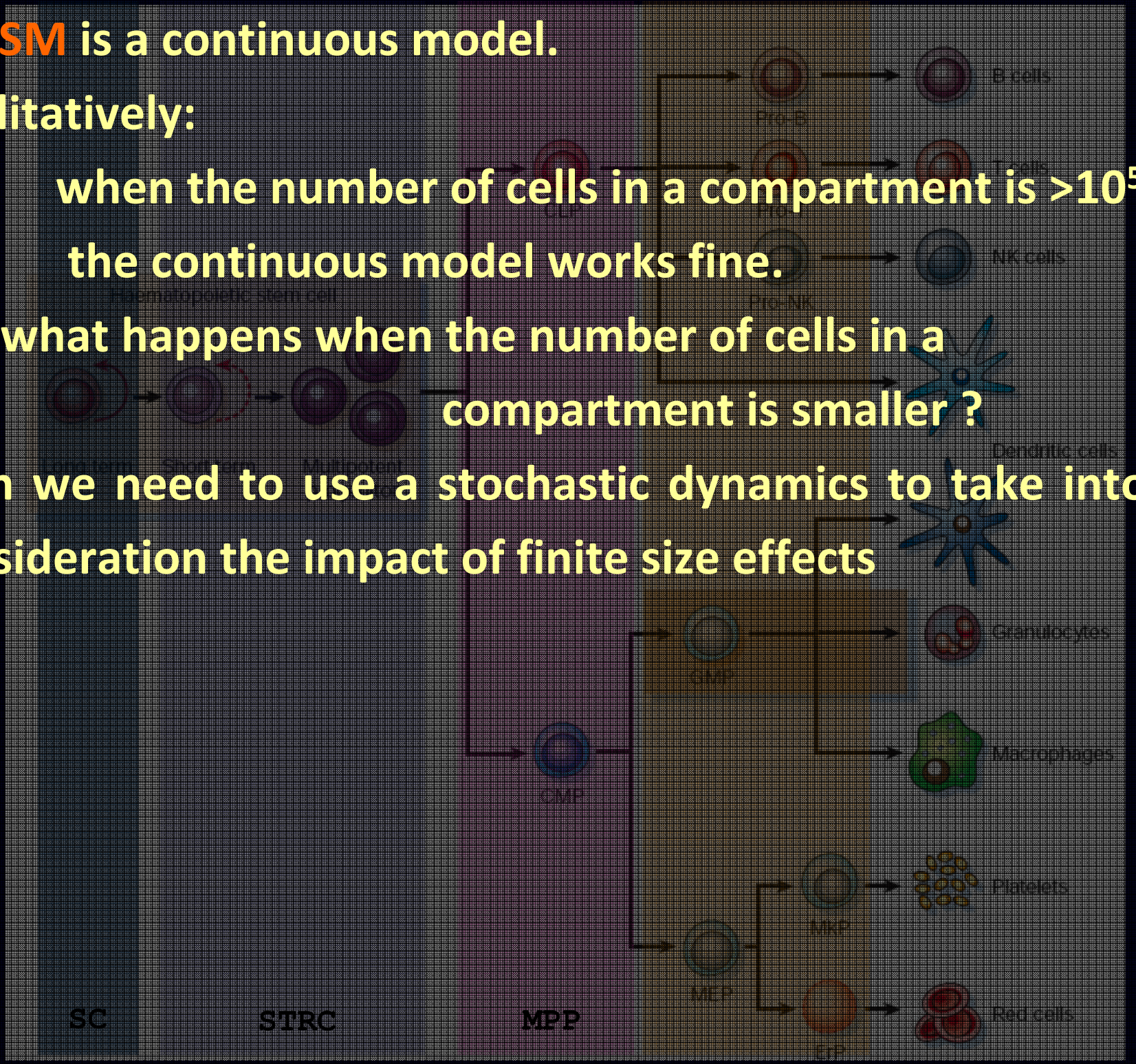

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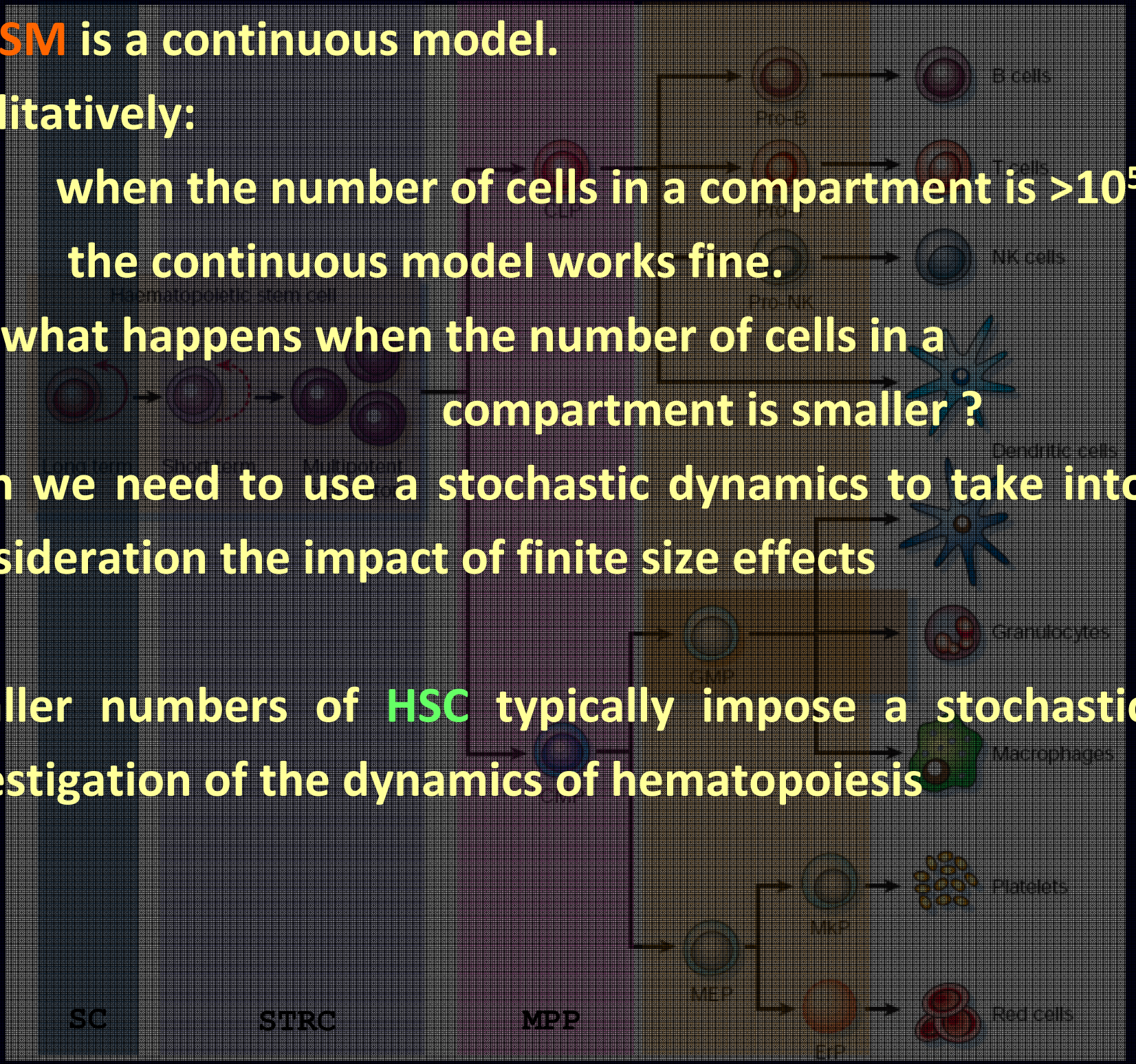
smaller numbers of HSC typically impose a stochastic investigation of the dynamics of hematopoiesis



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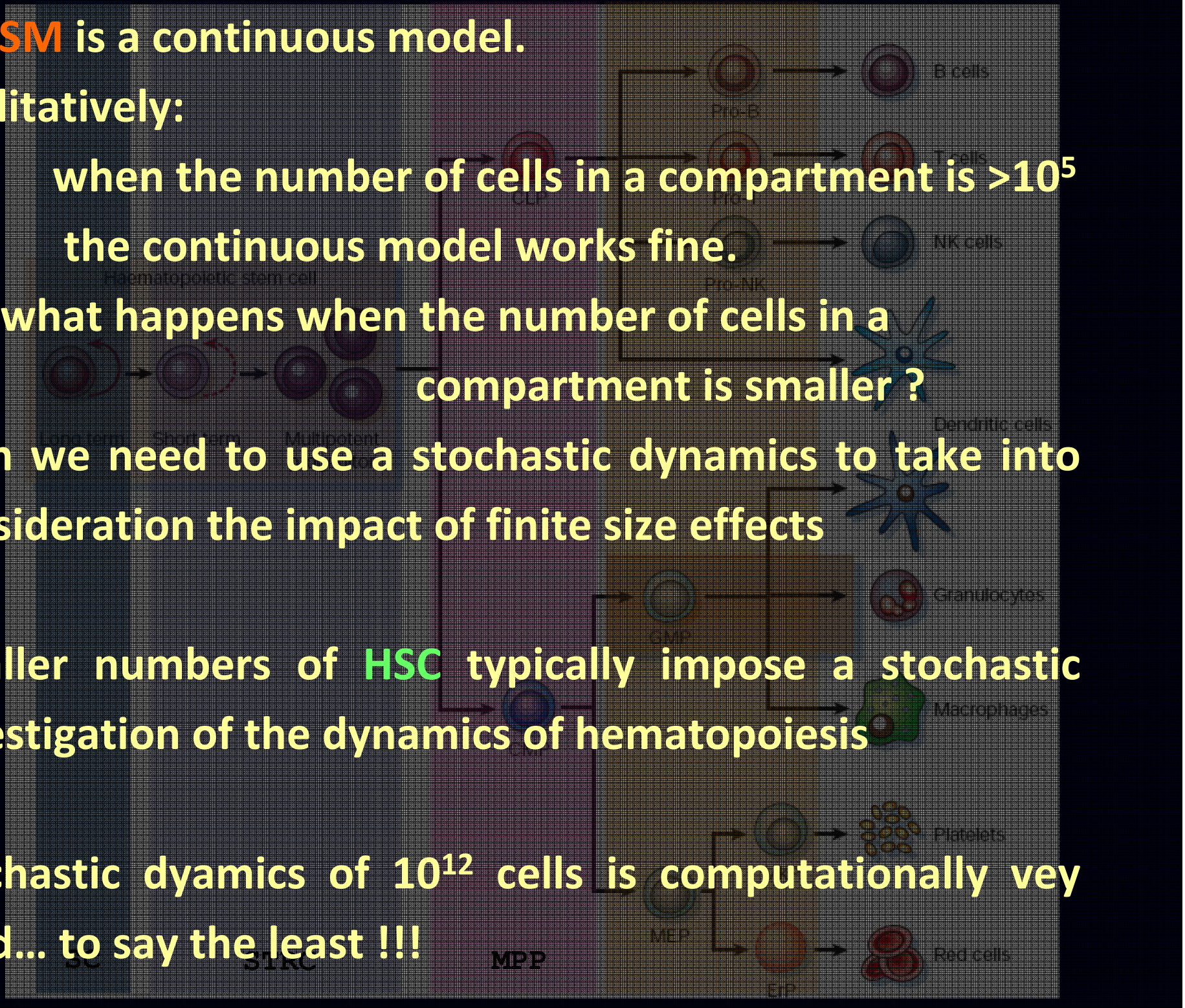
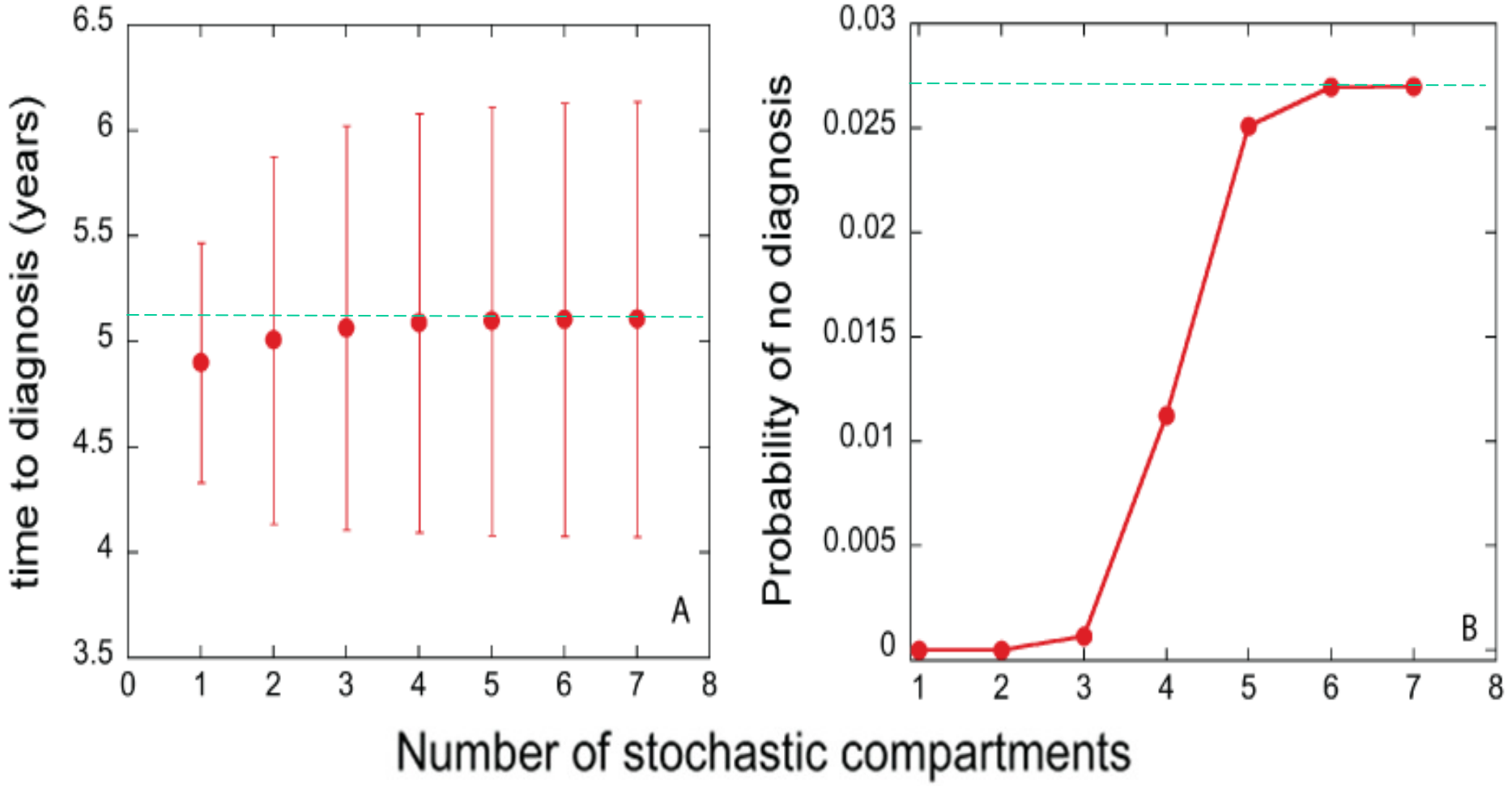
stochastic dyamics of 10^{12} cells is computationally vey hard... to say the least !!!



stochasticity in CML



Tom Lenaerts et al., Haematologica 95 (2010) 900-907