If cells play dice, can we gamble our way out of cancer ?

Jorge M. Pacheco

atpgroup

Departamento de Matemática & Aplicações
Universidade do Minho
Centro de Matemática & Aplicações Fundamentais

http://www.ciul.ul.pt/~ATP/

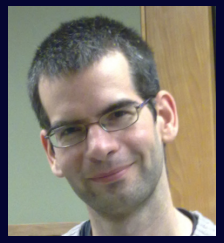
Third Workshop Dynamical Systems Applied to Biology and Natural Science - DSABNS 2012

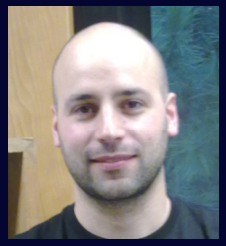
09-FEB-2012

atpgroup

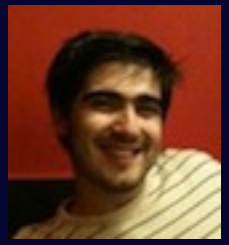
http://www.ciul.ul.pt/~ATP/







Francisco C. Santos
Sara Encarnação
Jeromos Vukov
Marta D. Santos
Pedro Neves

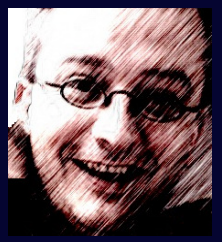

Marcos Gaudiano
Flávio Pinheiro
Ana Ribeiro
Vítor Vasconcelos
André Almeida

http://dl.dropbox.com/u/6053055/2012-02-09-TALK.pdf

atpgroup's collaborators



David Dingli (Mayo Clinic, USA)
Arne Traulsen (MPI Plön, DE)
Lucio Luzzatto (Inst. Tumori, Firenze, IT)



Tom Lenaerts (ULB, BE)
Tibor Antal (U. Edinburgh, UK)
Martin Nowak (Harvard, USA)

cancer

- cancer is a consequence of multicellularity
- cellular genome is under permanent attack (environmental or metabolic genotoxic agents) } mutations
- DNA replication machinery is not perfect

- many mutations are neutral
- others → malignant tranformation → clonal development
- risk of mutation: μ rate, # cells@risk, cell-lifetime

tissue architecture

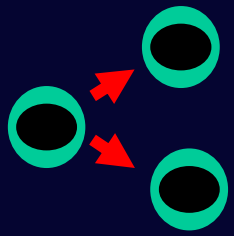
- tissue architecture has evolved
- most tissue cells have a ↘ lifetime & a ↗ turnover

  → minimize impact of mutations
- many tissues evolved a hierarchical structure

  → tree-like structure
- at the root of the tree are the tissue-specific stem-cells

- example: hematopoiesis
- stem-cell concept was developed in hematopoiesis and has
- extended to many other tissues
- tissue *resilience* relies on ↘ # & ↘ turnover of stem cells

hematopoietic stem cells (HSC)

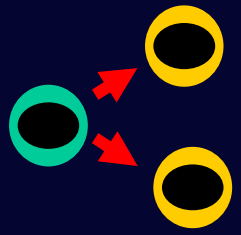


self-renewal :

for how long ?

(Hayflick hypothesis,

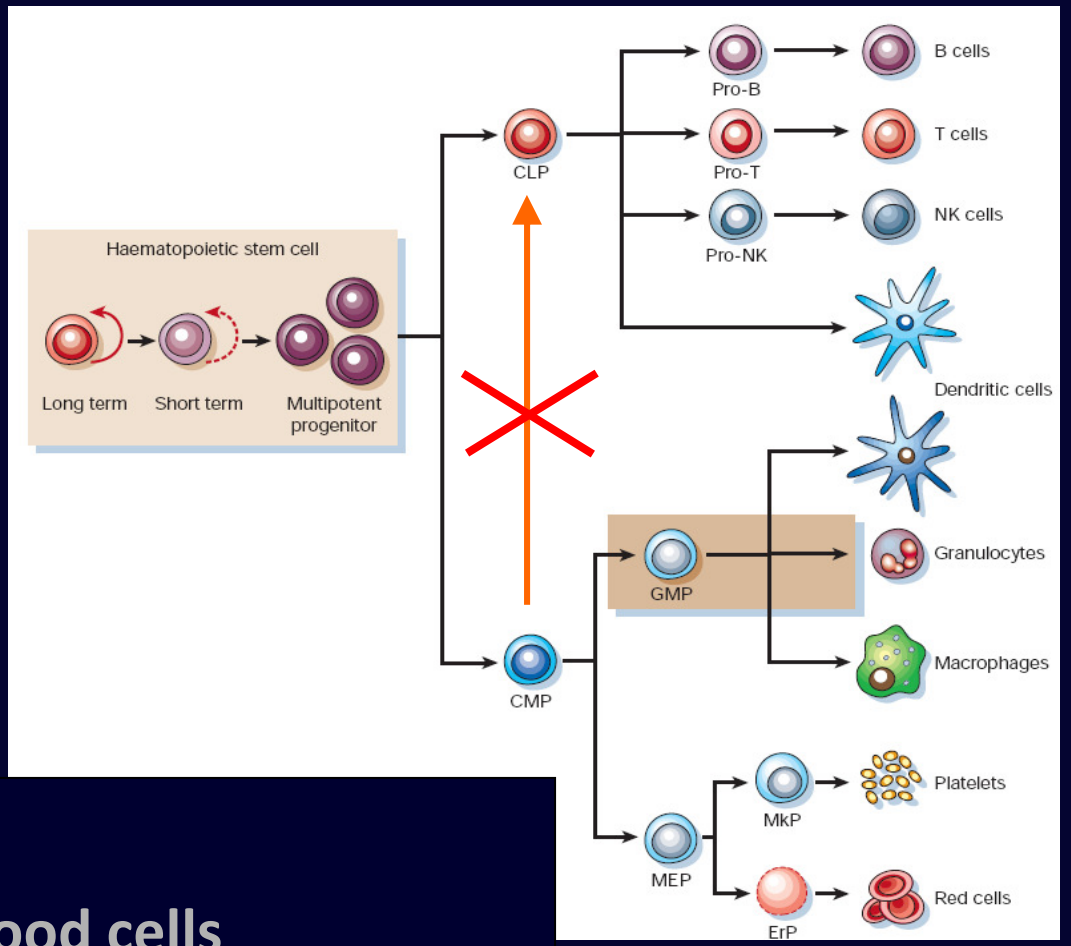
telomere shortening)



differentiation :

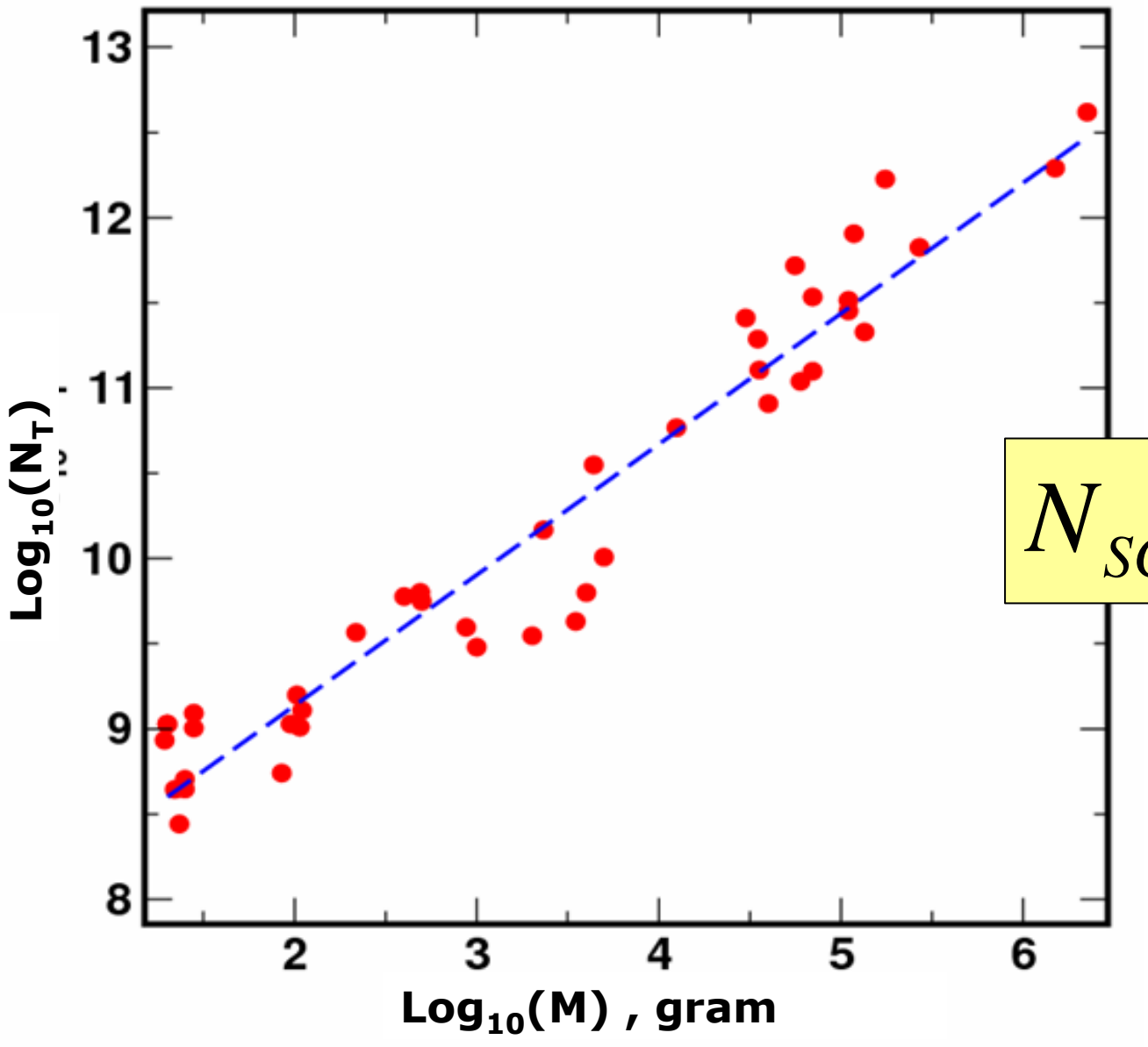
capacity to differentiate

into all other types of blood cells



stemness *is a matter of degree – you have to stand at the* ***root*** *of the* ***hematopoietic tree***

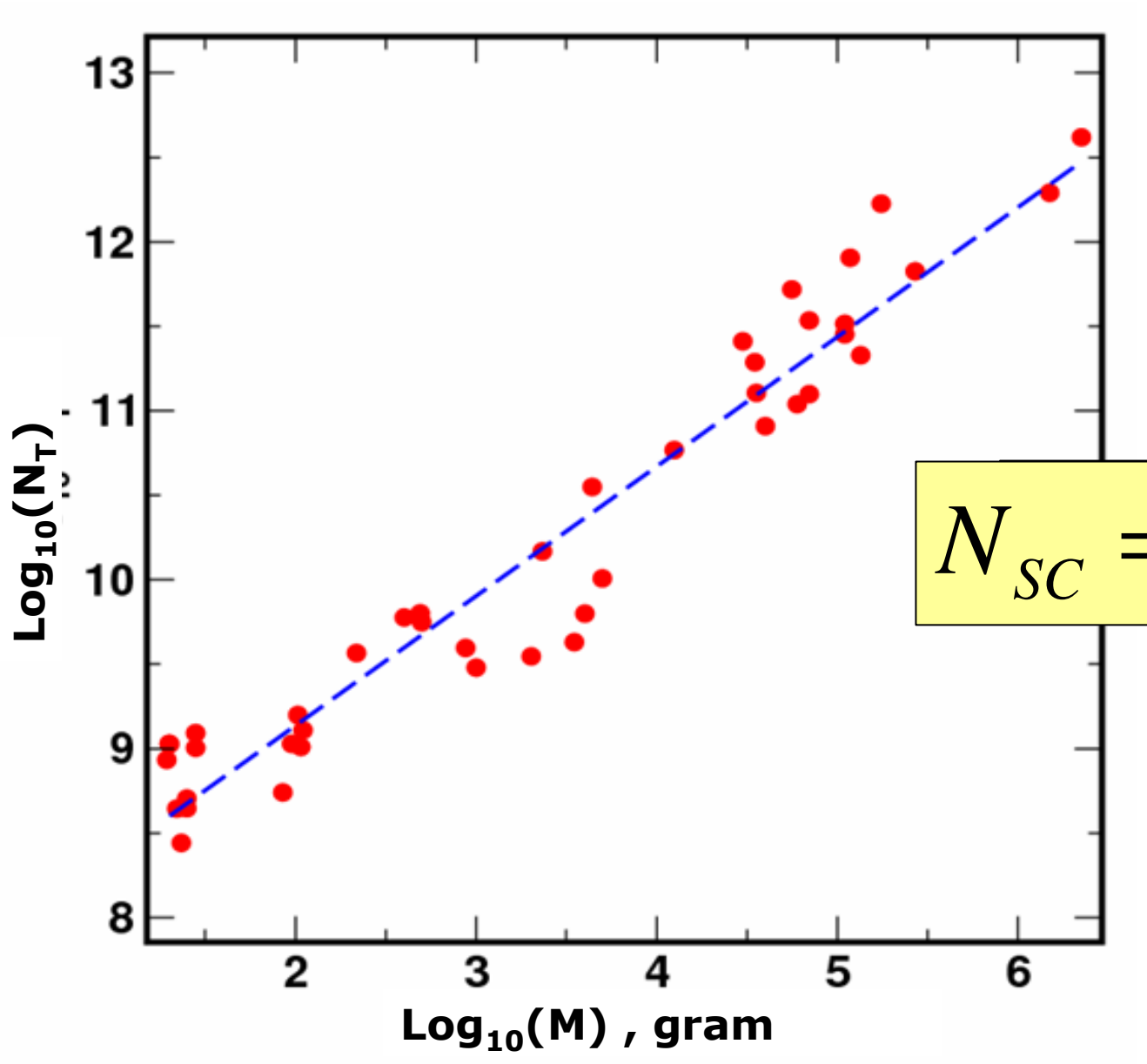
allometric scaling of hematopoiesis in land mammals



$$N_{SC} \sim M^{3/4}$$

Dingli & Pacheco, *PLoS ONE*, 2006

allometric scaling of hematopoiesis in land mammals



?

$$N_{SC} = N_0 \, M^{3/4}$$

Dingli & Pacheco, *PLoS ONE*, 2006

allometric scaling of hematopoiesis in land mammals

use experimental estimates for cats for calibration (fix N_0):
under normal conditions, ≥ 40 ! (*Abkowitz et al, Blood, 2002*)

what	model predictions ×	experimental data
HSC in humans *cat = 40*	385	~400 *(Buescher et al, J Clin Invest, 1985)*
rate HSC division *cat post-TRX = 8 week^{-1}*	60 week $^{-1}$	~ 52-104 week $^{-1}$ *(Rufer, et al, J Exp Med, 1999)*
human post-transplant *cat = 13*	111	~ 116 *(Nash et al, Blood, 1988)*
mouse	1	1 *(Abkowitz et al, PNAS , 1995)*
rate macaques	23 week^{-1}	23 week^{-1} *(Shepherd et al, Blood , 2007)*
rate baboons	36 week^{-1}	36 week^{-1} *(Shepherd et al, Blood , 2007)*

Dingli & Pacheco, *PLoS ONE*, 2006

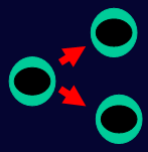
the hematopoietic *tree*

- *in humans ~ 400 HSC divide each 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 ?*

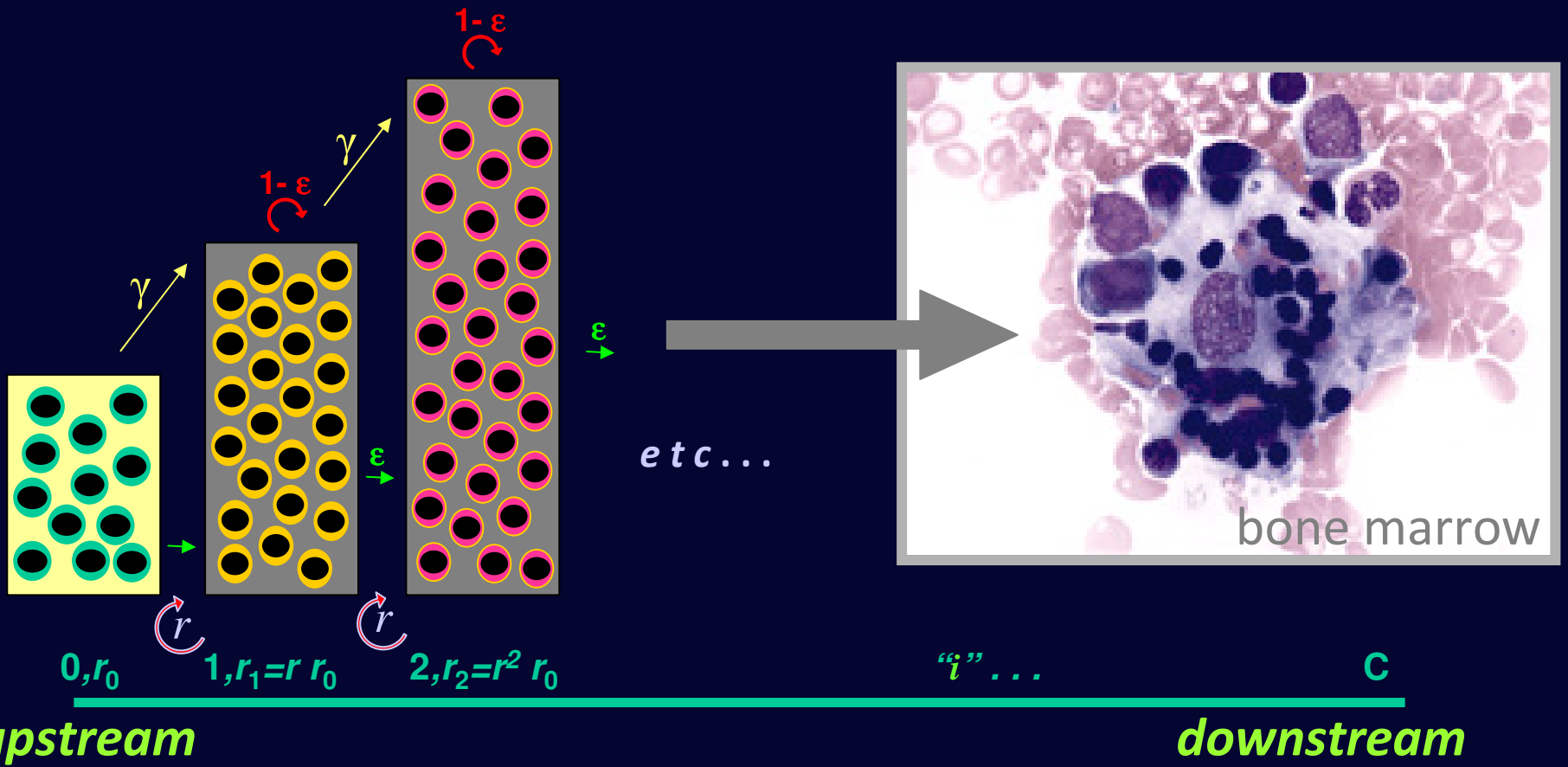
- *one must consider :*

differentiation  ε

amplification  1- ε

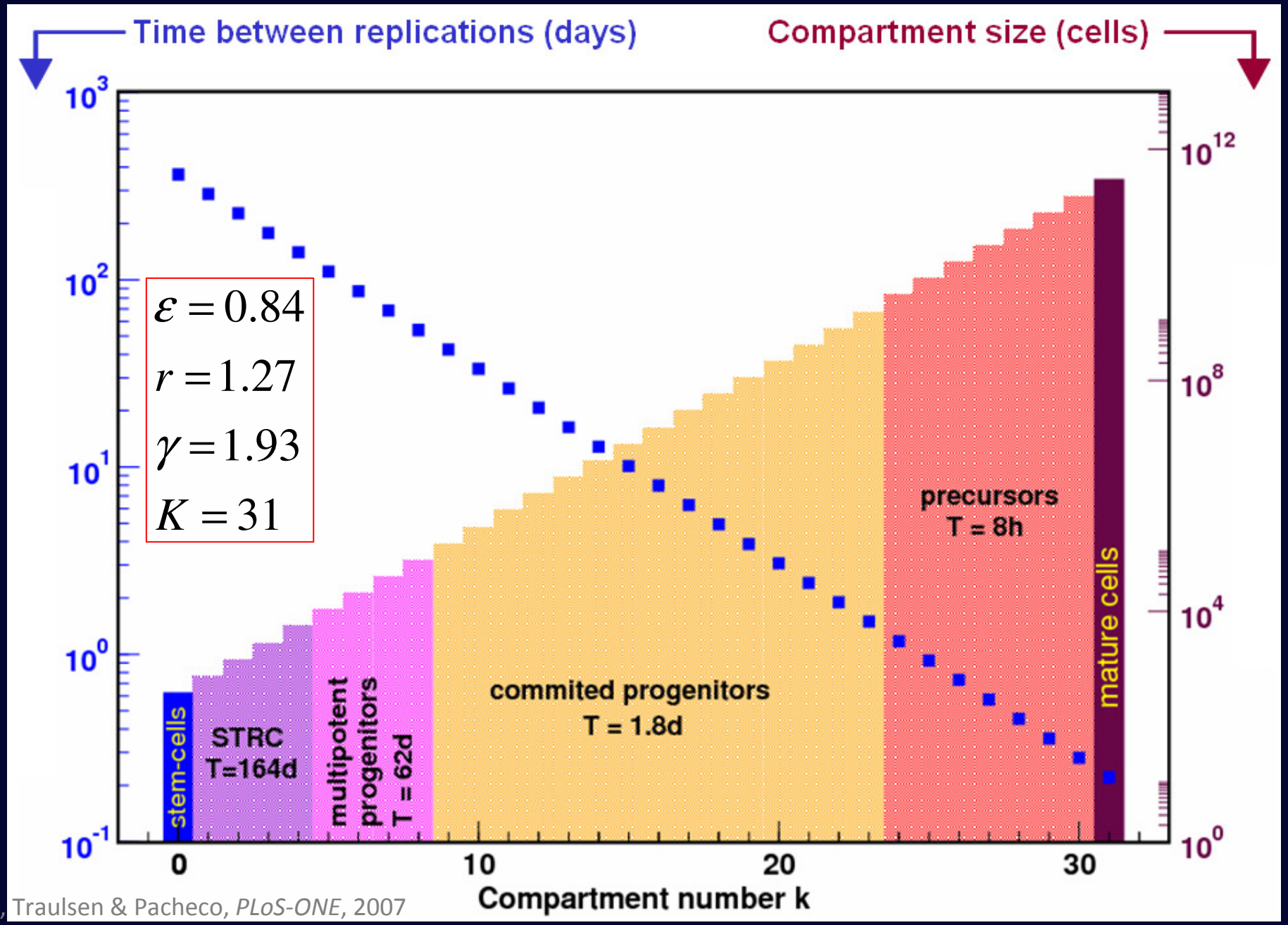
the hematopoietic *tree*

- *we consider a compartmentalized struture in which cells from upstream compartments flow into downstream compartments , under stationary flux conditions;*



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

the hematopoietic *tree*

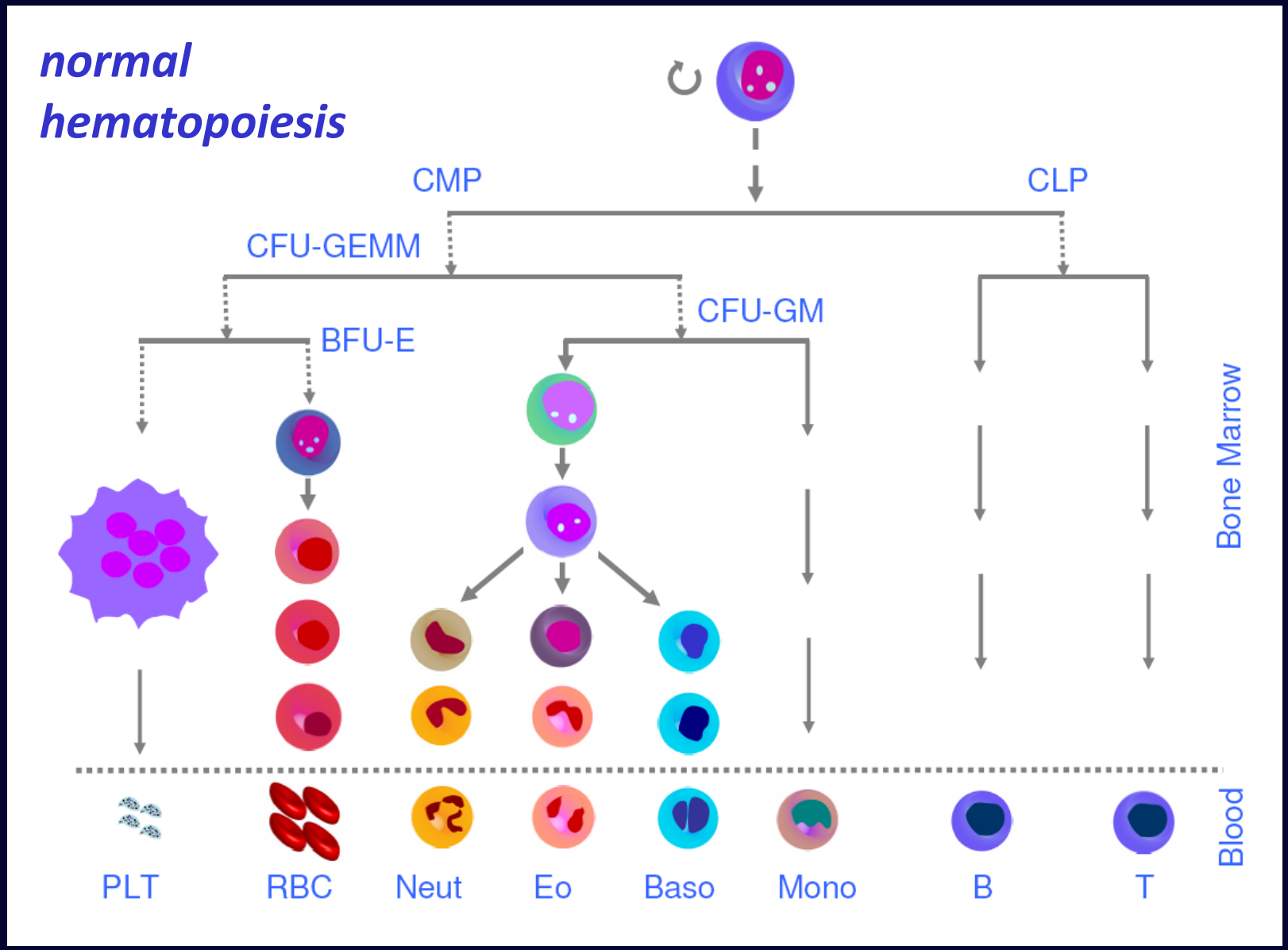


Dingli, Traulsen & Pacheco, *PLoS-ONE*, 2007

D I S E A S E

trouble

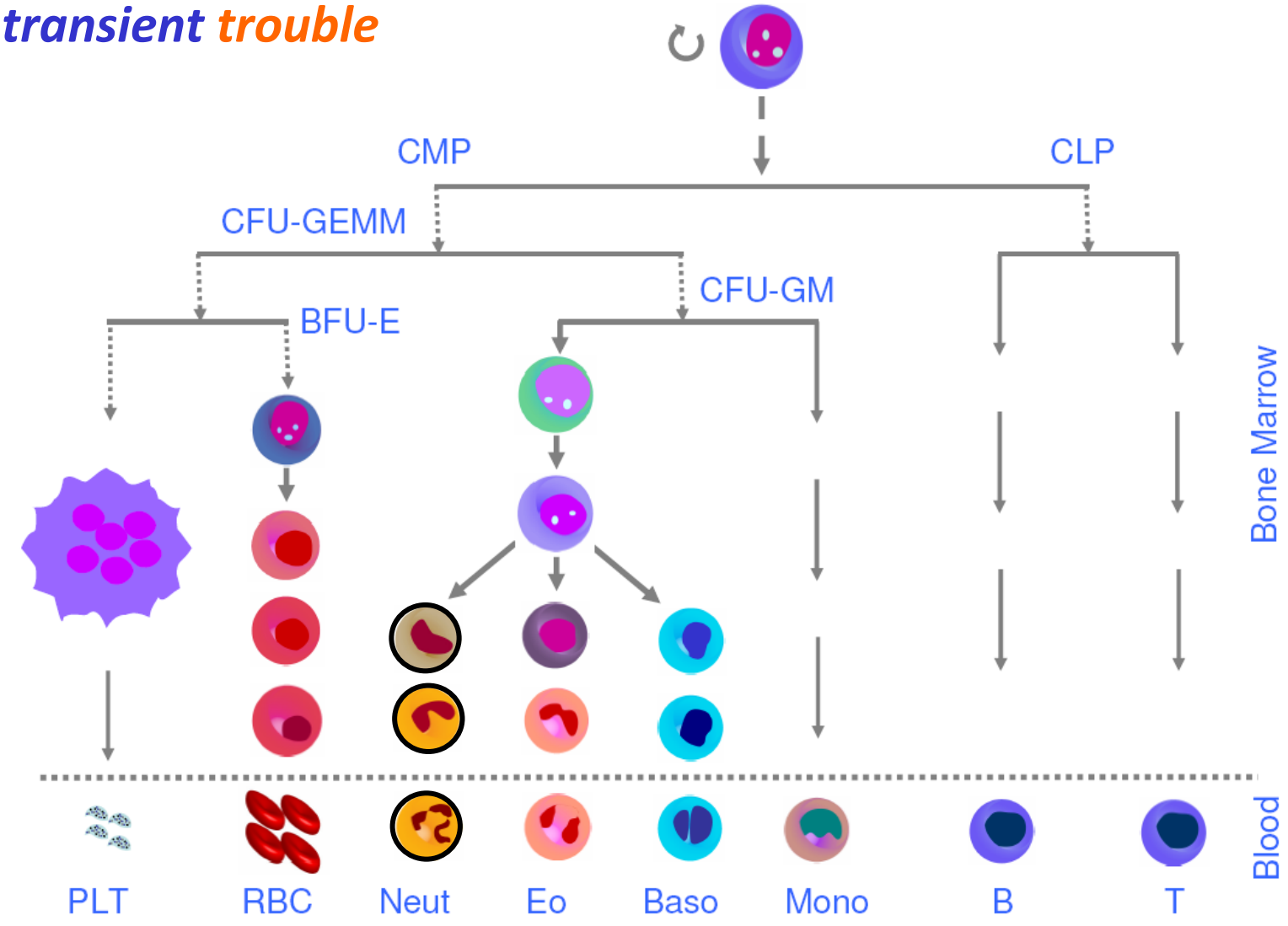
normal : $10^{-7} < \mu < 10^{-6}$ ***per cell per replication***



trouble

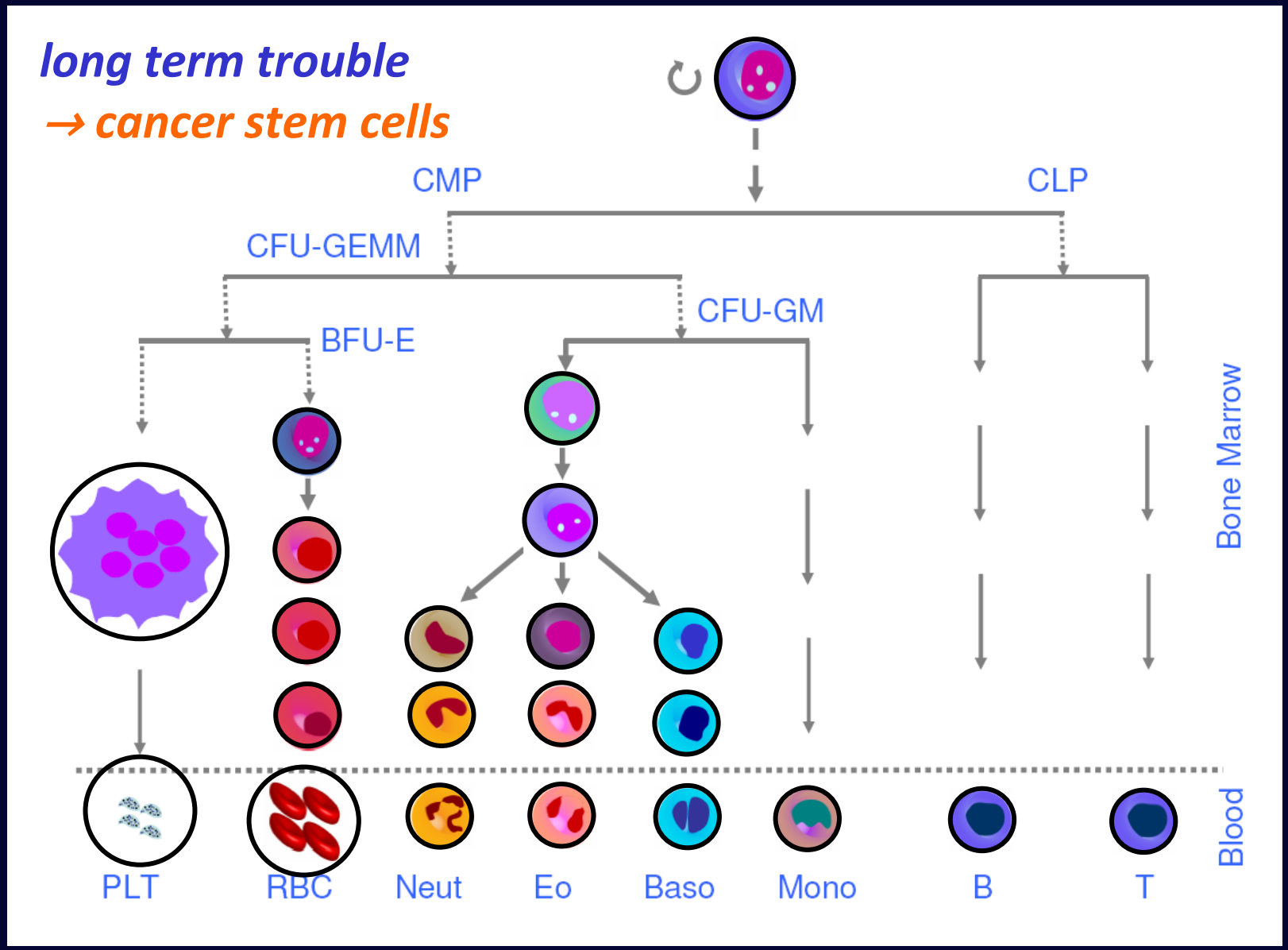
normal : $10^{-7} < \mu < 10^{-6}$ ***per cell per replication***

transient trouble

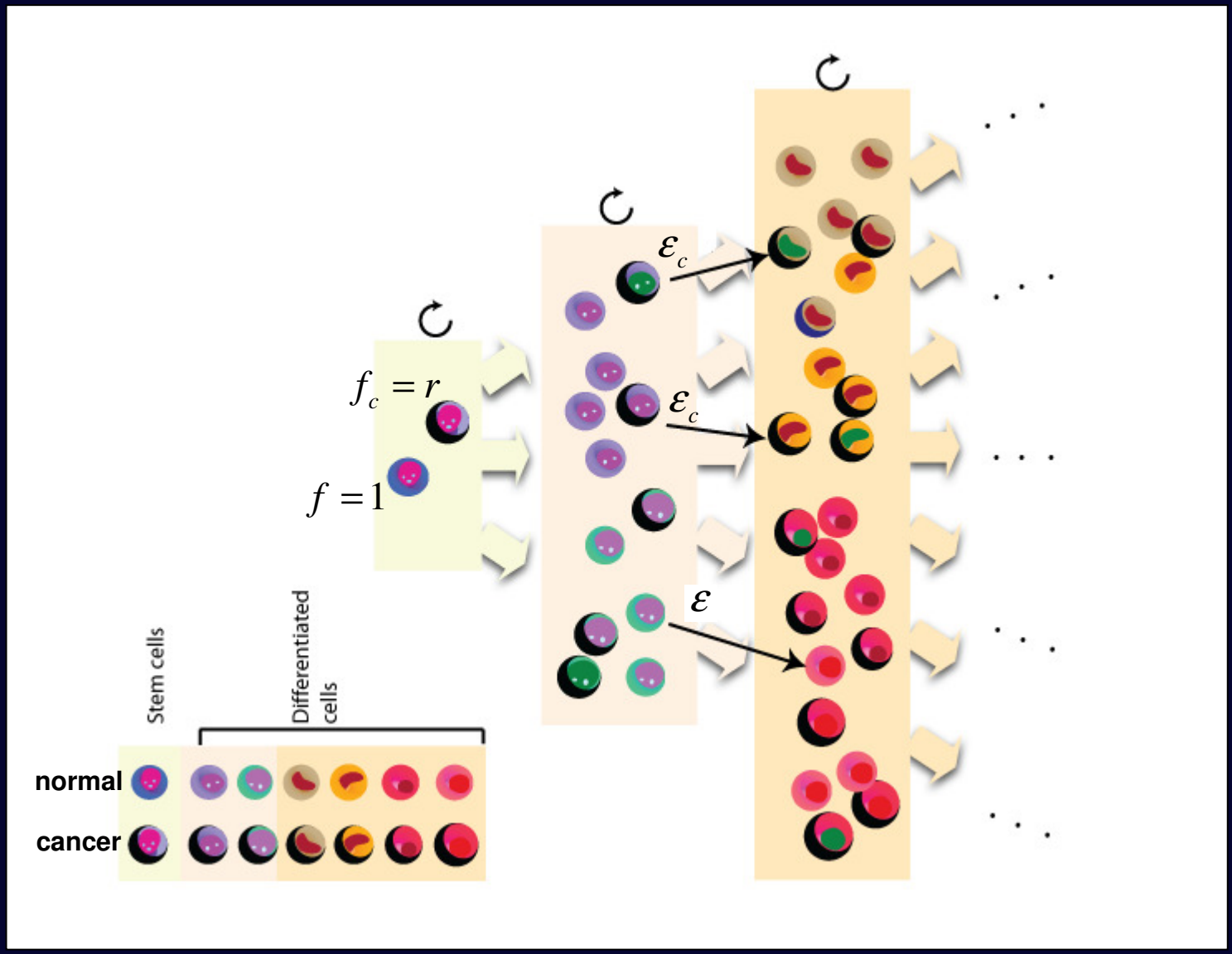


trouble

normal : $10^{-7} < \mu < 10^{-6}$ ***per cell per replication***



troubled hematopoiesis



cancer dynamics becomes a multi-scale ecology of cell competition

starting upstream with a small number of HSC & CSC and getting downstream into very large numbers of cells of all kinds

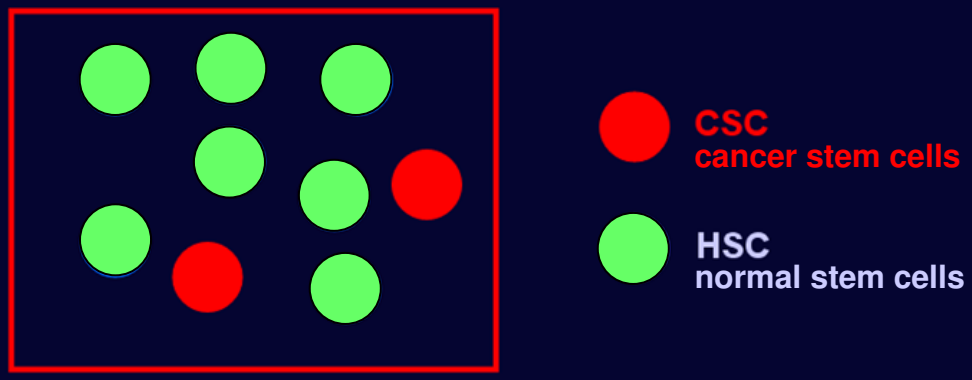
the mathematics of Darwinian cell selection

Dingli, Traulsen & Pacheco, *Cell Cycle*, 2007

Dingli, Traulsen & Pacheco, *PRS**B** 275 (2008) 2389*

stochastic dynamics of *HSC*

stochastic model for humans :



- *SC population remains constant (400);*
- *HSC divide at normal rate (once per year);*
- *CSC divide at rate r x normal, where r = relative fitness ;*
- *when a cell divides, gives rise to two new identical cells;*
- *subsequently, 1 cell is randomly selected for export;*
- *HSC may suffer mutations and transform into CSC.*

Dingli, Traulsen & Pacheco, *Cell Cycle*, 2007

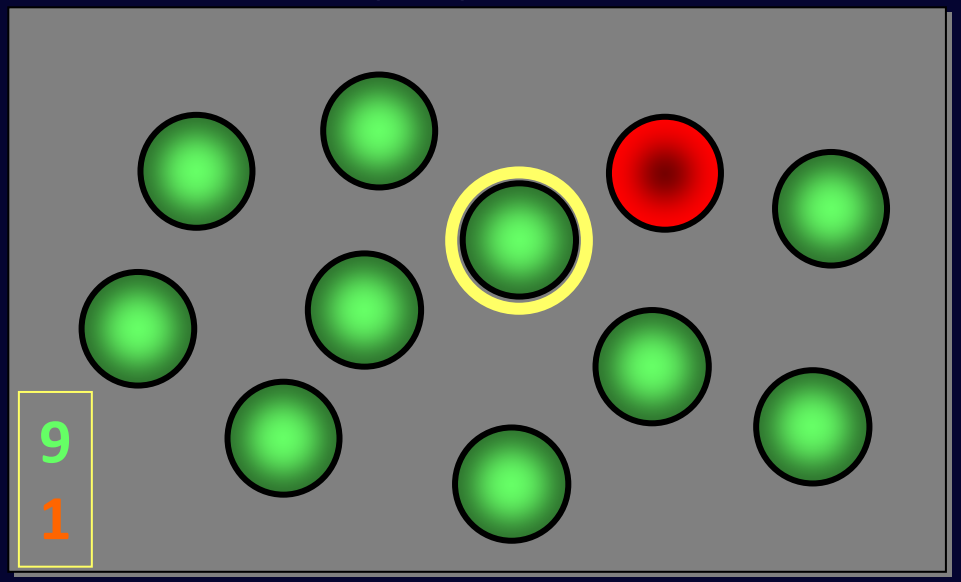
this stochastic model is known in
mathematics (& population genetics)
as a
Moran (birth-death) process

in each stochastic discrete event, either :
— nothing happens
— the number of cells of one of the types changes by ± 1

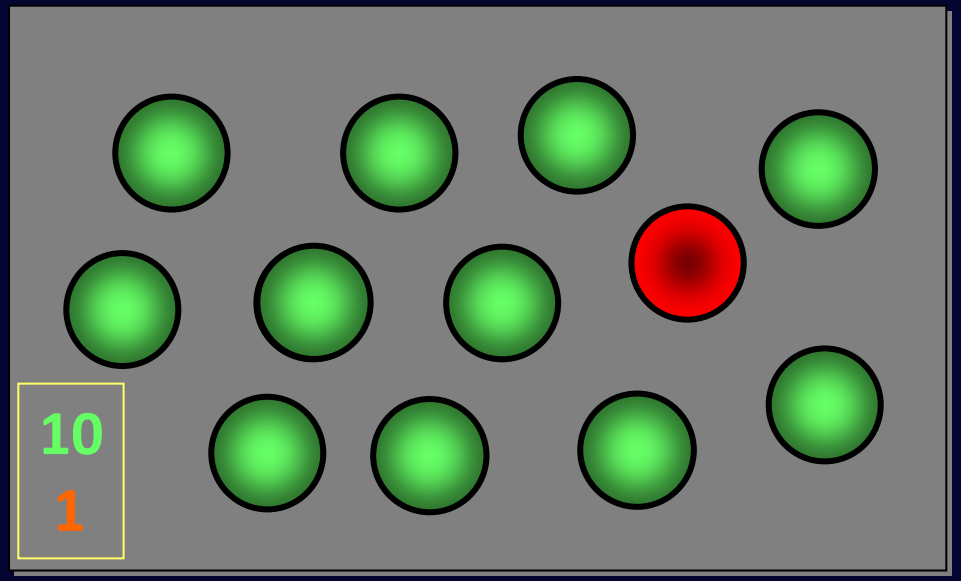
after N *events, one time step has elapsed*

example 1: 1 HSC is exported & nothing happens in SC pool

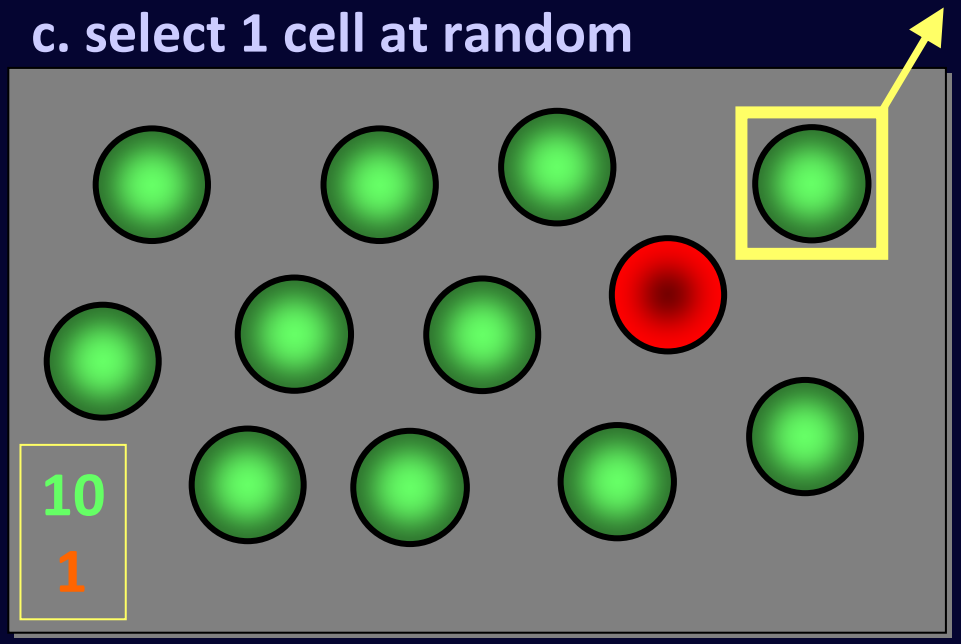
a. select 1 cell proportional to fitness



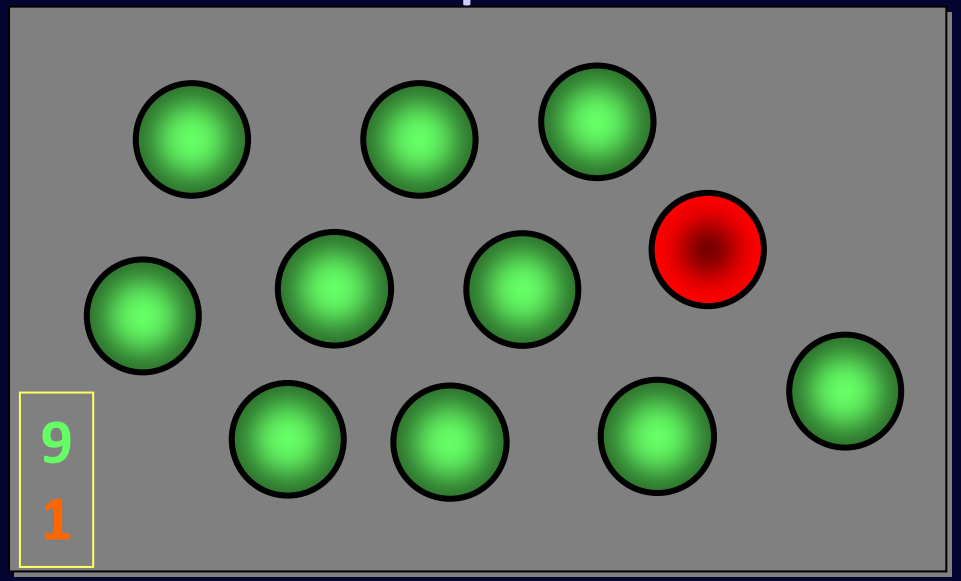
b. chosen cell replicates



c. select 1 cell at random

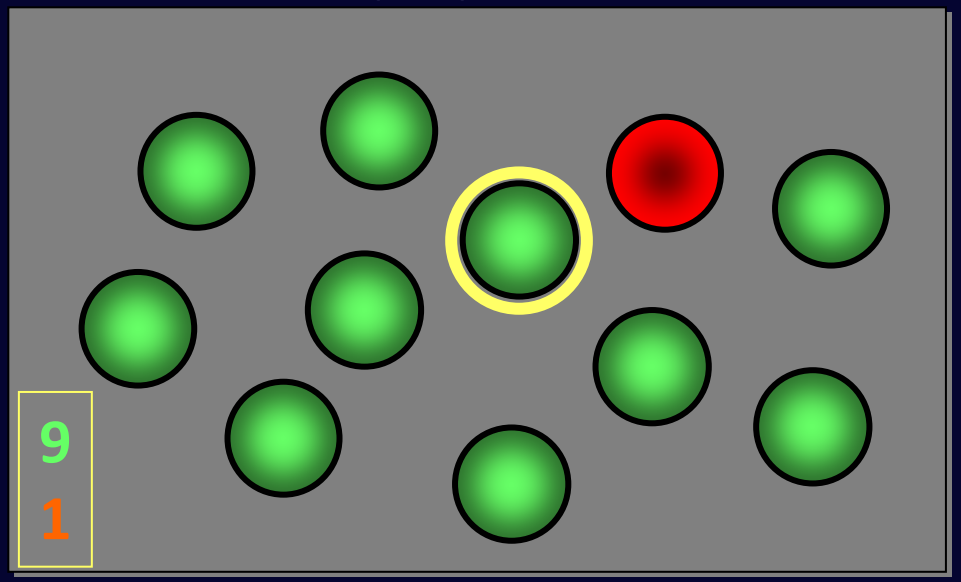


d. chosen cell is exported

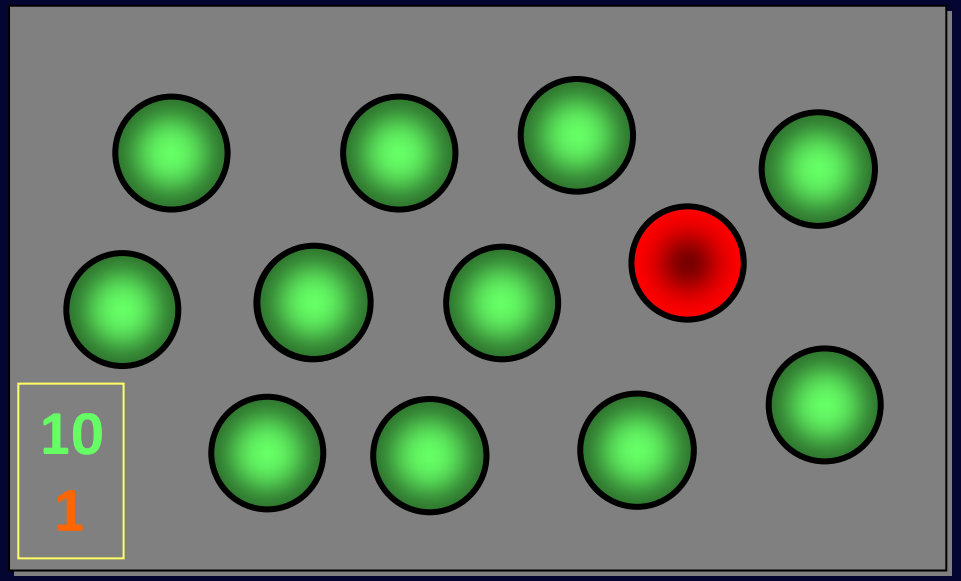


example 2: 1 CSC is exported & CSC-lineage gets extinct

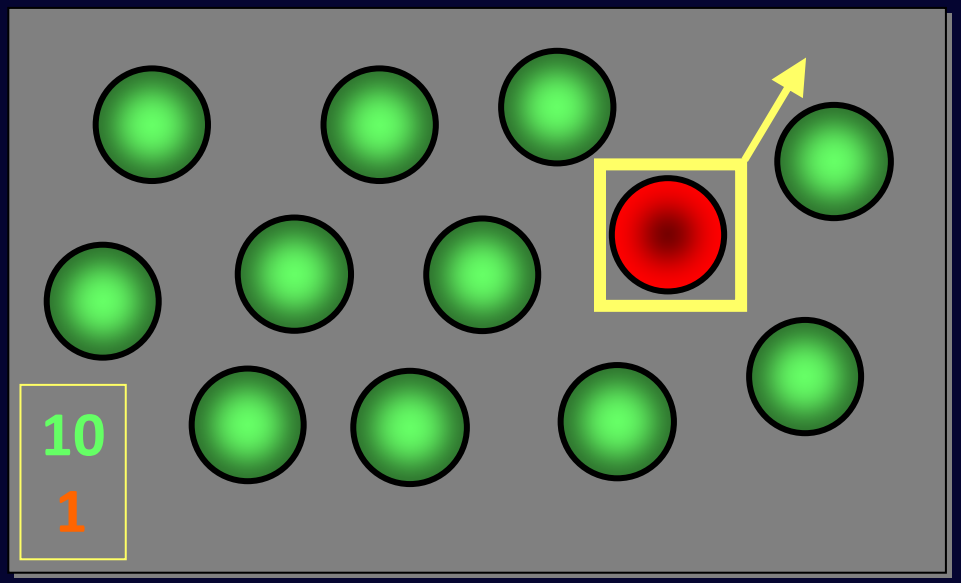
a. select 1 cell proportional to fitness



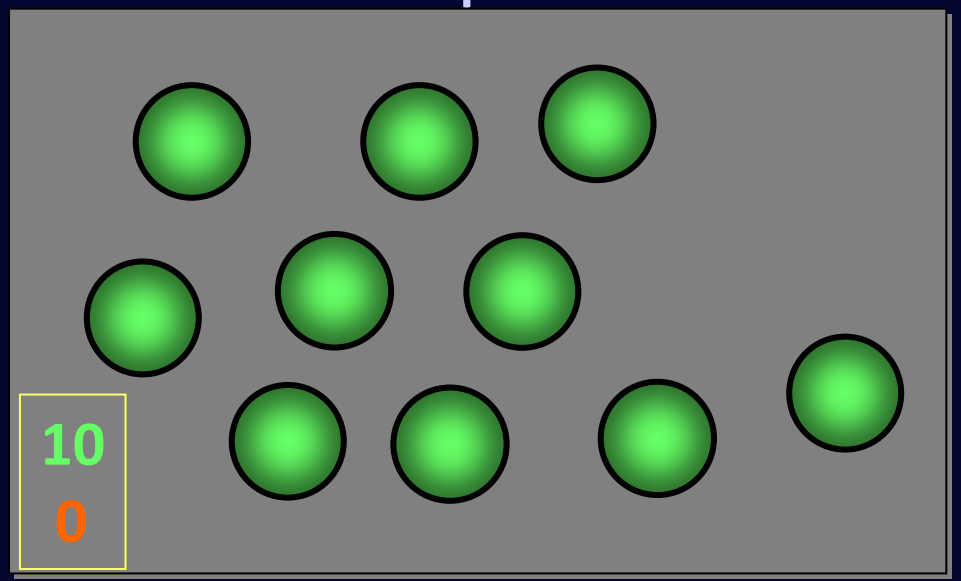
b. chosen cell replicates



c. select 1 cell at random

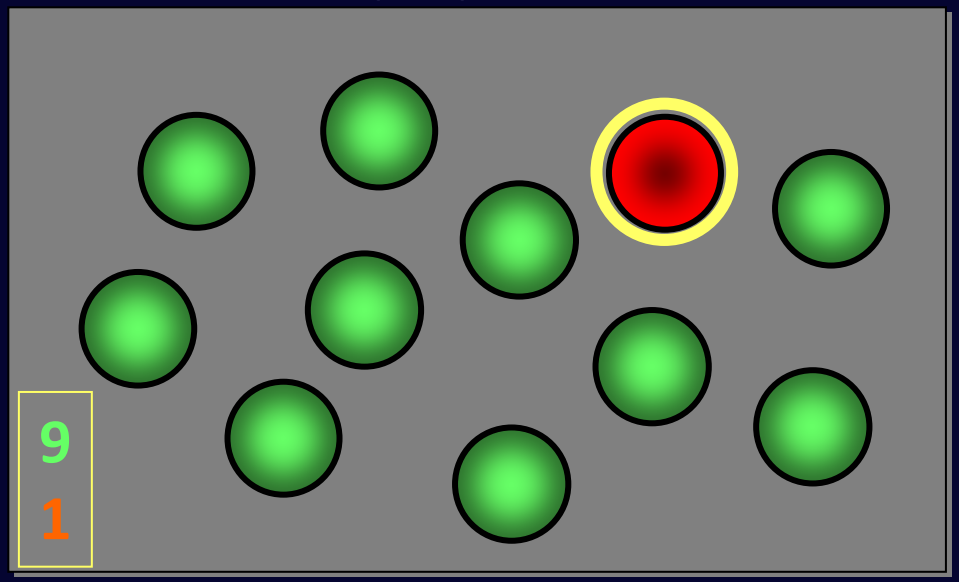


d. chosen cell is exported

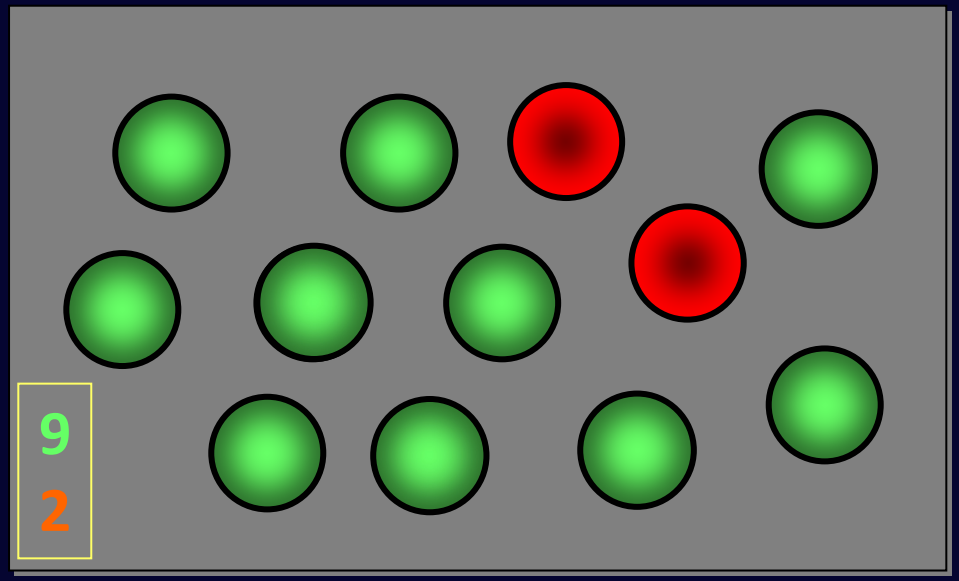


example 3: 1 HSC is exported & CSC number increases by 1

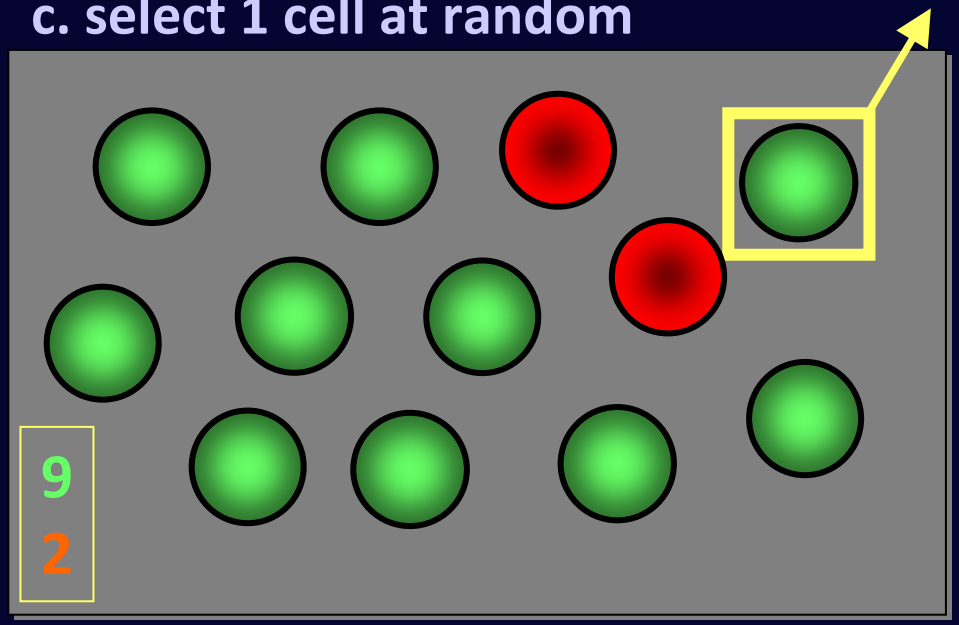
a. select 1 cell proportional to fitness



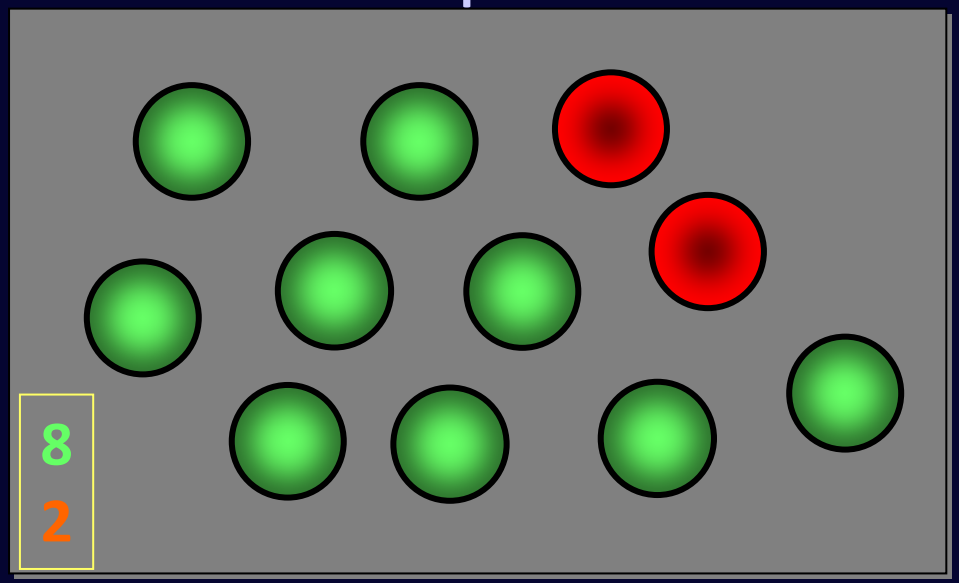
b. chosen cell replicates



c. select 1 cell at random

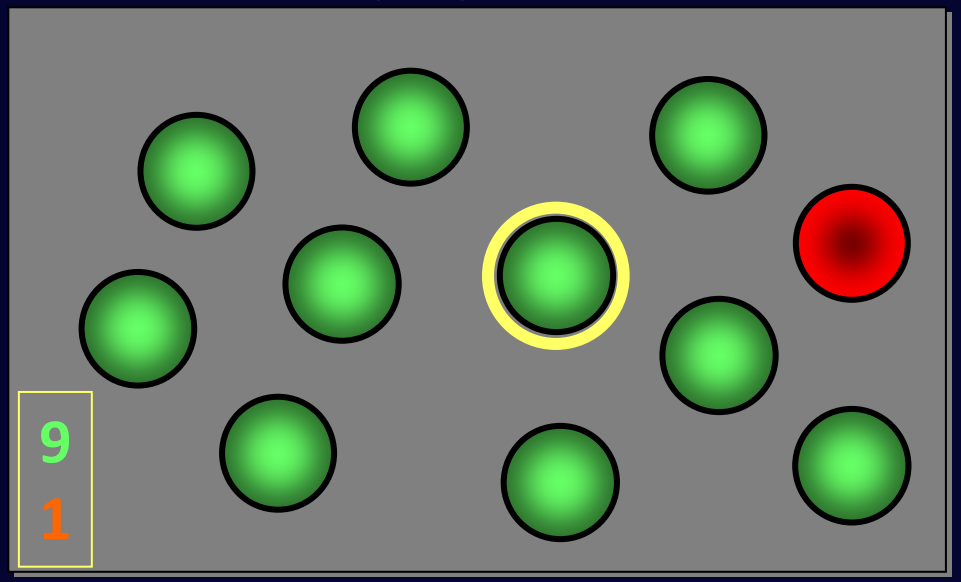


d. chosen cell is exported

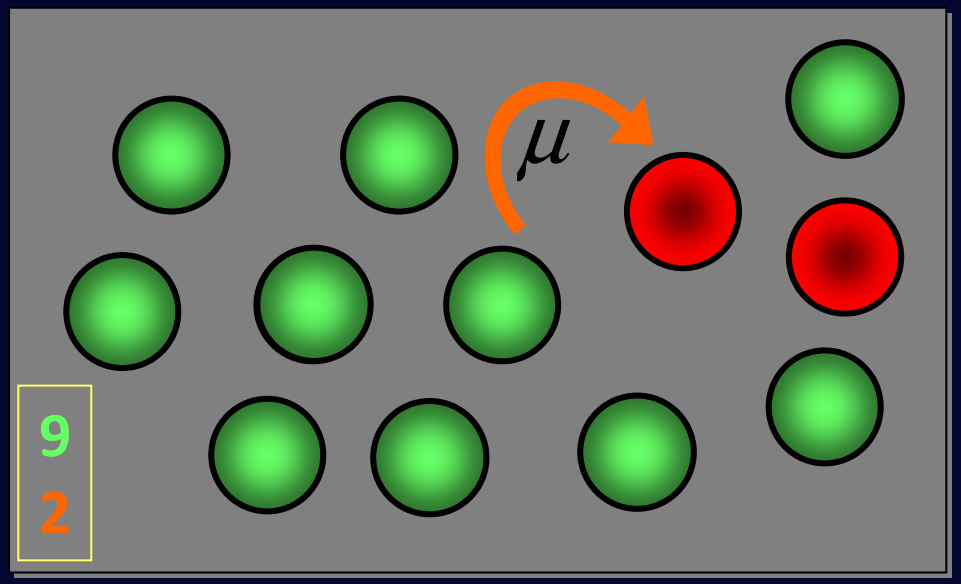


example 4: HSC mutations enter scene to make things worse

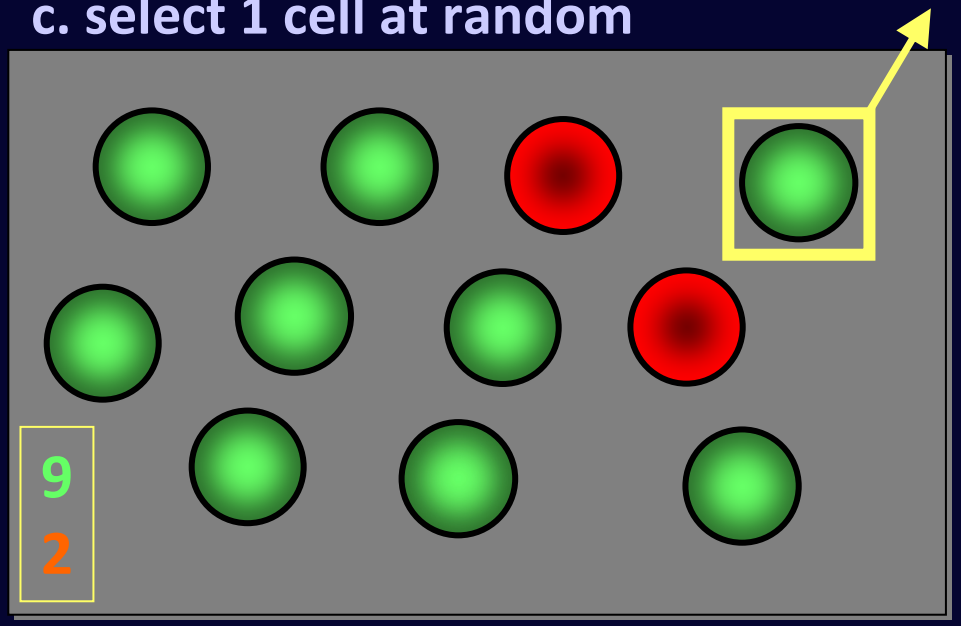
a. select 1 cell proportional to fitness



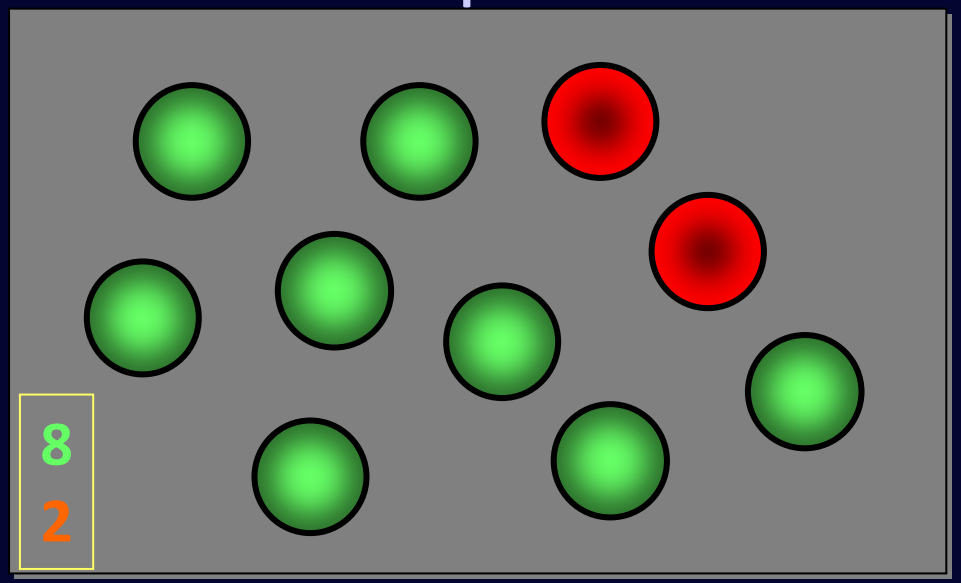
b. chosen cell replicates & mutates



c. select 1 cell at random

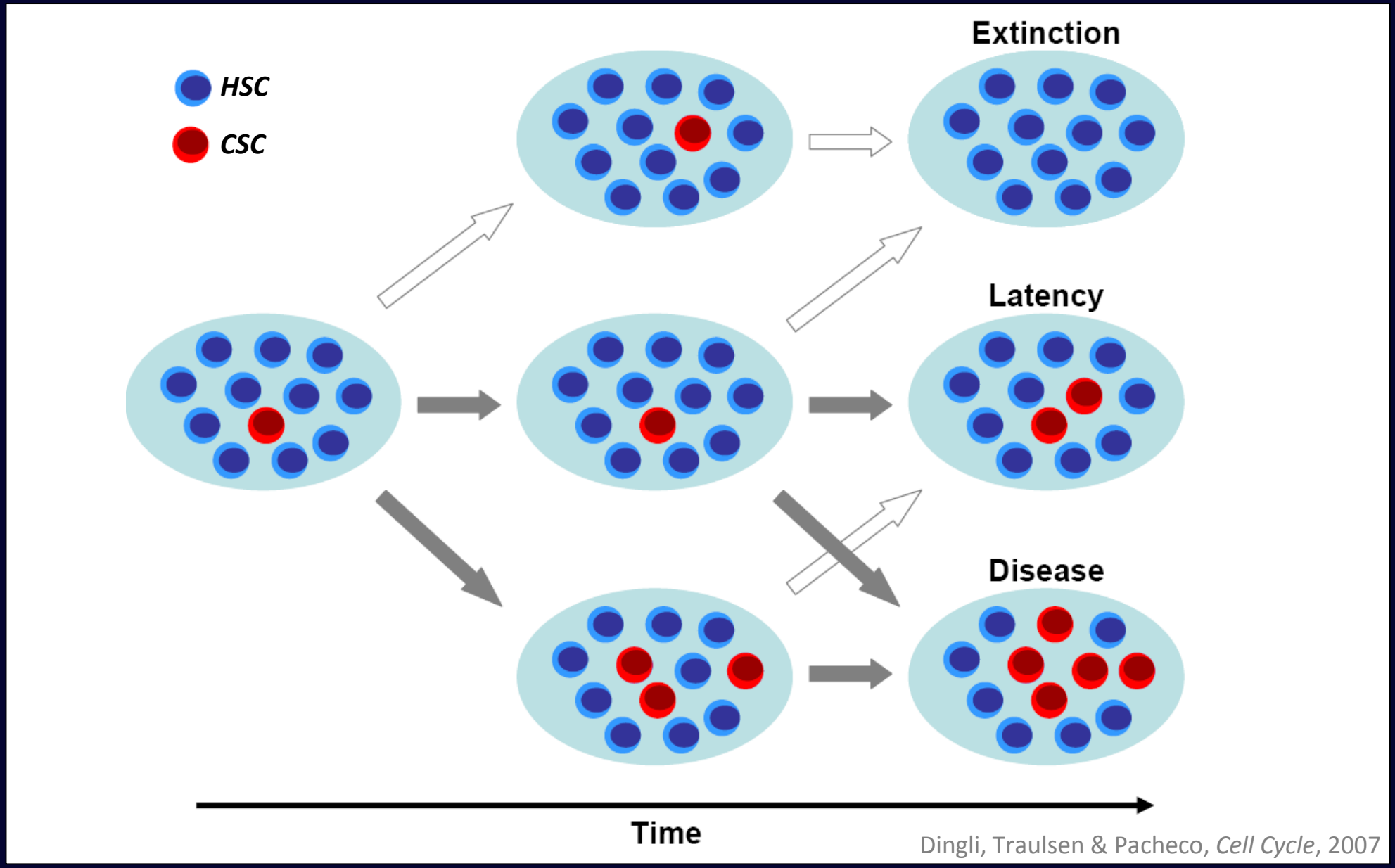


d. chosen cell is exported



stochastic dynamics of *HSC*

several possible scenarios :



Dingli, Traulsen & Pacheco, *Cell Cycle*, 2007

is the stochastic dynamics of cells an oddity ?

neutral evolution

&

PAROXYSMAL NOCTURNAL HEMOGLOBINURIA

Dingli, Luzzatto & Pacheco, *PNAS* 105 (2008) 18496

Motoo Kimura (木村 資生 Kimura Motoo, November 13, 1924 - November 13, 1994)

paroxysmal nocturnal hemoglobinuria

what is known :

- rare disease
- true stem-cell disorder since :
- it originates in the PIG-A gene of a HSC
- rate of PIG-A gene mutation is normal
- often BMF is later observed

conventional wisdom regarding disease development :

- a 2nd mutation leads to a fitness advantage of PNH cells → disease expansion (too rare an event)

  Dingli, Pacheco & Traulsen, *Physical Review E77* (2008) 021915

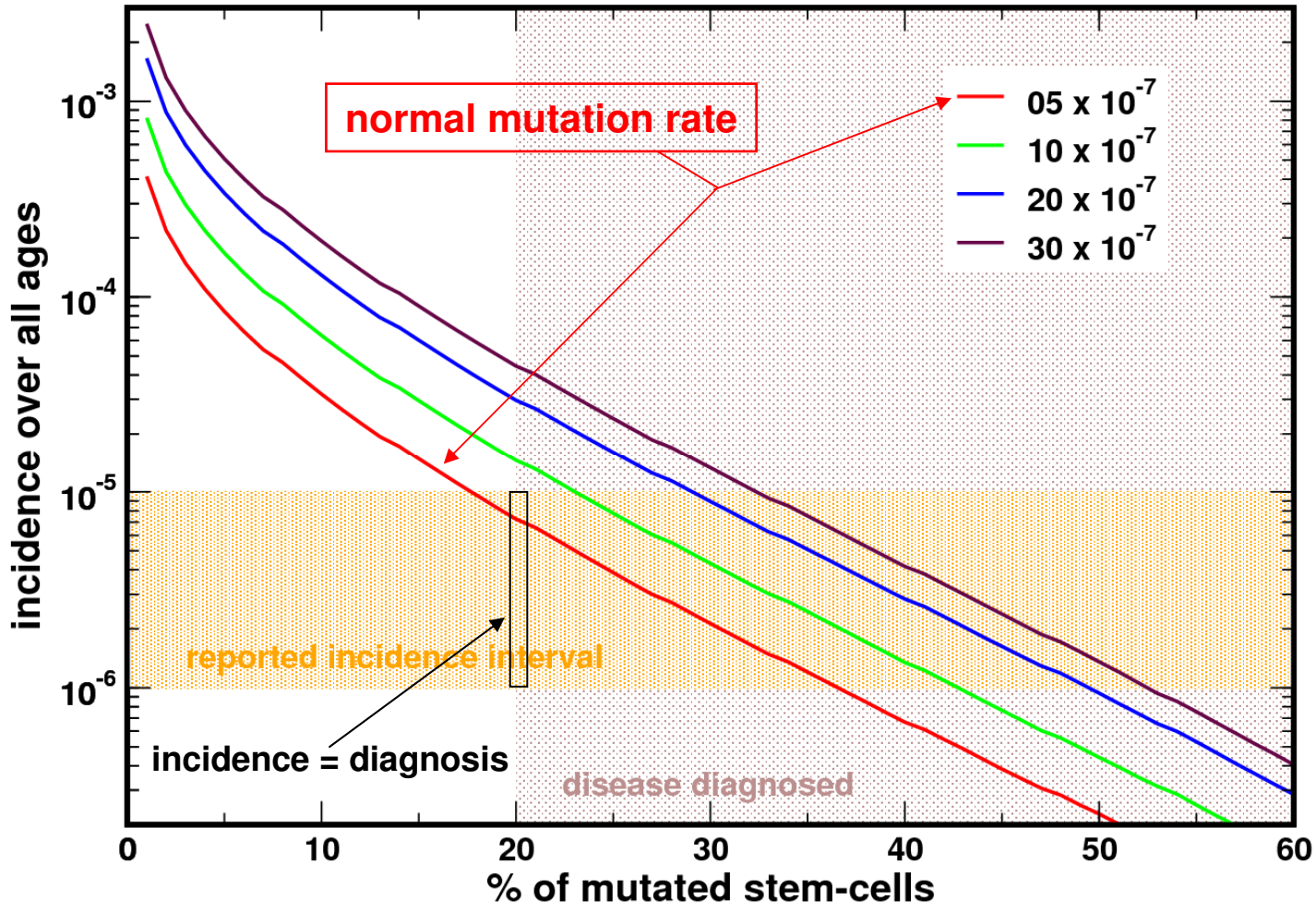
- *relative fitness advantage* of PNH cells due to an imunne attack to normal HSC → disease expansion

model features

disease development

- use $N_{SC} = 400$
- simulate HSC activity in virtual USA (10^9 virtual Americans)
- use normal mutation rate for HSC → PNH transformation
- assume *neutral drift* (r=1) between HSC & PNH cells
- fold data with CENSUS 2000 for USA population
- compare results with incidence data in *USA*

results



results above & other results suggest that it is not necessary to invoke a relative fitness difference to explain incidence of PNH

neutral evolution relies on the stochastic nature of cell behavior, & **PNH** shows us that, likely, many individuals suffer the PIG-A mutation but are never diagnosed PNH, as it is more likely for the mutant to become extinct than to evolve into a clone. This, in turn, suggests that the current way of approaching the (now over) 40-year old war-on-cancer, that is,

cure = ***kill-every-single-cancer-cell***

is perhaps not always the best; in fact, sometimes it maybe even unnecessary.

progenitor driven
CHRONIC MYELOID LEUKEMIA

Dingli, Traulsen, Lenaerts & Pacheco,

Clinical Leukemia 2 (2008) 133

BioEssays 32 (2010) 1003

Cancer Letters 294 (2010) 43

Genes and Cancer 1, 4 (2010) 309-315

Haematologica 95 (2010) 900-907

BMC Biology 9(2011) 41

Cell Cycle 10 (2011) 1540

PLoS-CB 7 (2011) e1002290

Chronic Myeloid Leukemia

what is known :

- Hematopoietic stem cell disorder
- Initial event: Philadelphia chromosome
- ? HSC are enough to drive chronic phase ?
- clonal expansion and myeloproliferation
- stem cell derived but progenitor cell driven
- *abl*-kinase inhibitors very effective

CML dynamics

- **Q-RT-PCR data from patients treated with *imatinib***
- **2 data sets available**
  - Michor *et al, Nature*, 2005
  - Roeder *et al, Nature Medicine*, 2006
  - other data recently available for ***nilotinib***
- **data fitting**

model features

disease development

- use existing model of hematopoiesis
- how to get from HSC origin to progenitor driven disease ?
- bone marrow expansion $\longrightarrow \varepsilon_{CML} < \varepsilon_0$

treatment

- how does *imatinib* work ?
- does *imatinib* induce cell death?
- how many cells are responding to *imatinib* ?

model constraints

disease development

- time from initial insult to diagnosis is 3.5 – 6 years
- progenitor cell expansion >14%
- total number of active HSC is *not* increased
- daily bone marrow output is ~ 3 x normal

treatment

- *imatinib* leads to $\varepsilon_{IMAT} > \varepsilon_0 > \varepsilon_{CML}$
- *imatinib* does not affect HSC
- at any time a fraction *z* of cells responds to *imatinib*

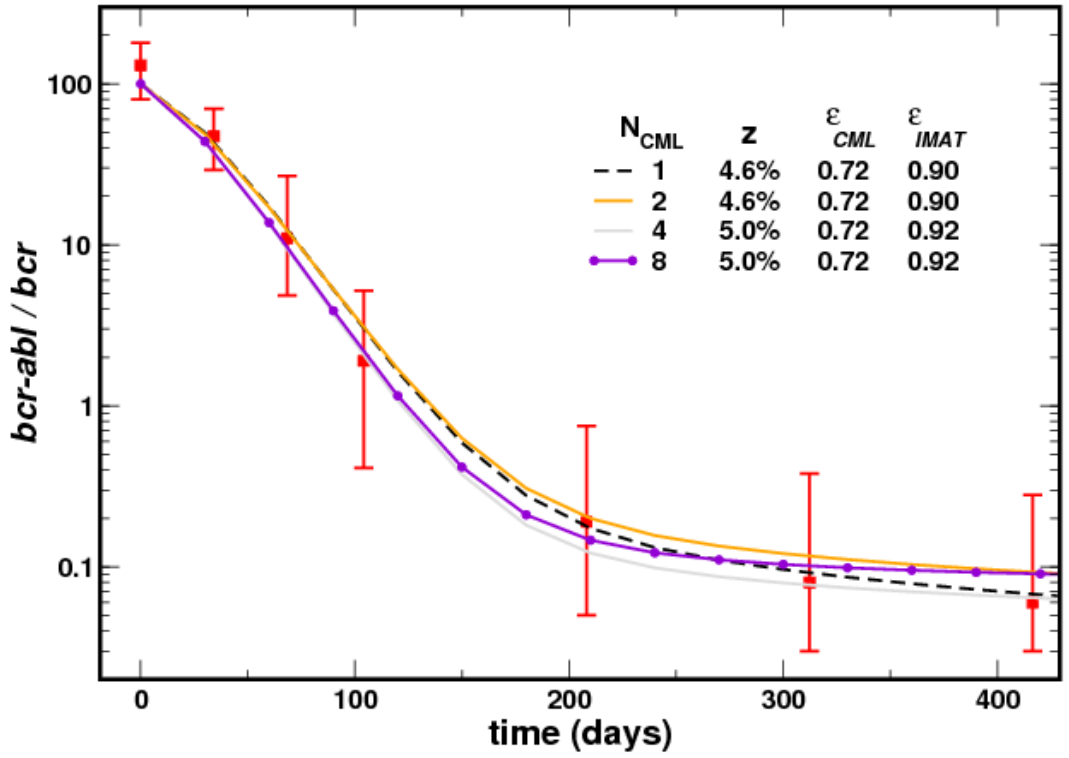
CML dynamics under *imatinib*

we define (deterministic model . . .)

output rate from compartment “i” $d_i = (2\varepsilon - 1) r_i$

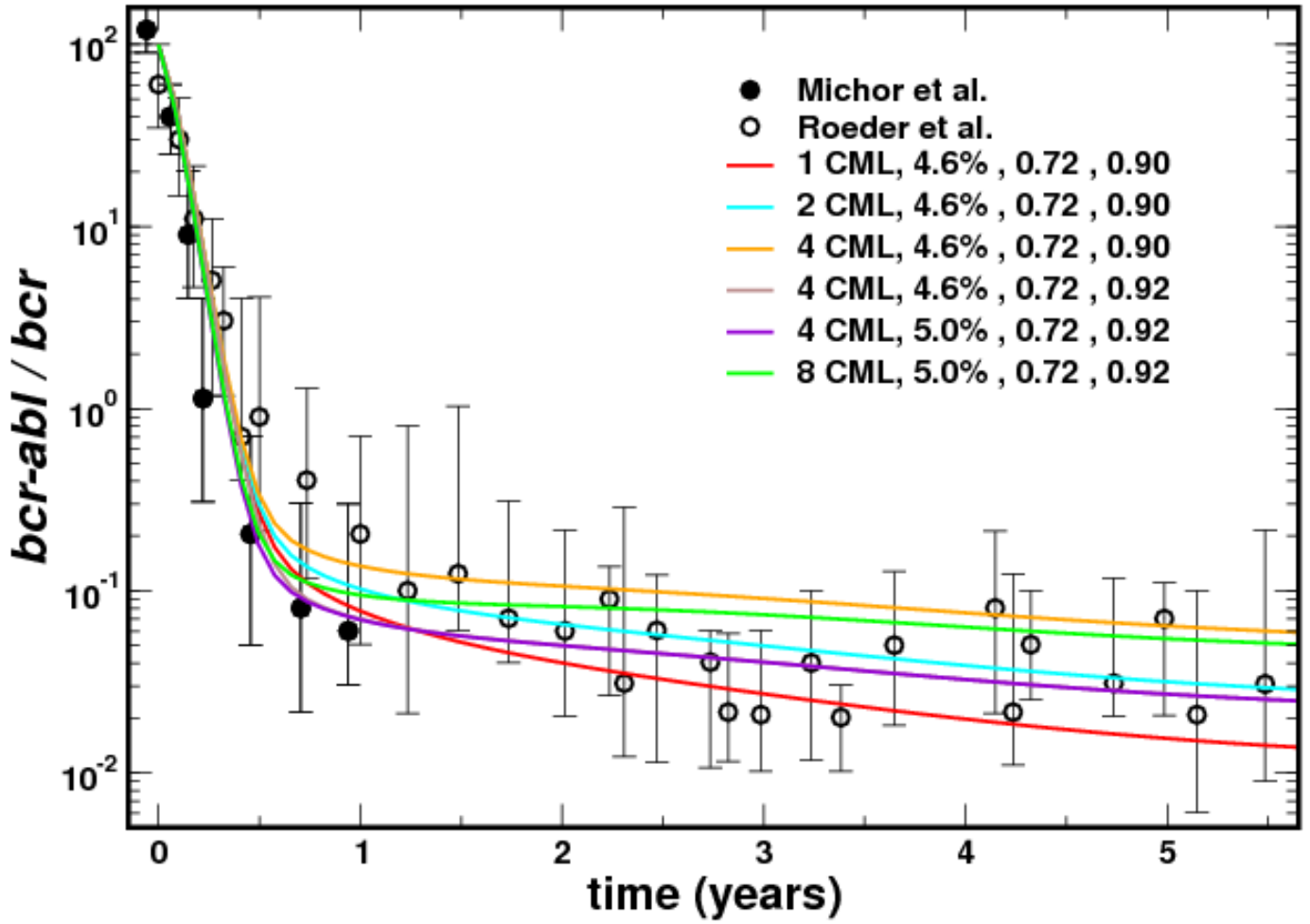
input rate from compartment “i-1” $b_{i-1} = 2 \cdot \varepsilon \cdot r_{i-1}$

$$\frac{d}{dt} N_i^{CML} = (1-z) \cdot \left[b_{i-1}^{CML} \cdot N_{i-1}^{CML} - d_i^{CML} \cdot N_i^{CML} \right] + z \cdot \left[b_{i-1}^{IMAT} \cdot N_{i-1}^{CML} - d_i^{IMAT} \cdot N_i^{CML} \right]$$



fit to Michor *et al.* data

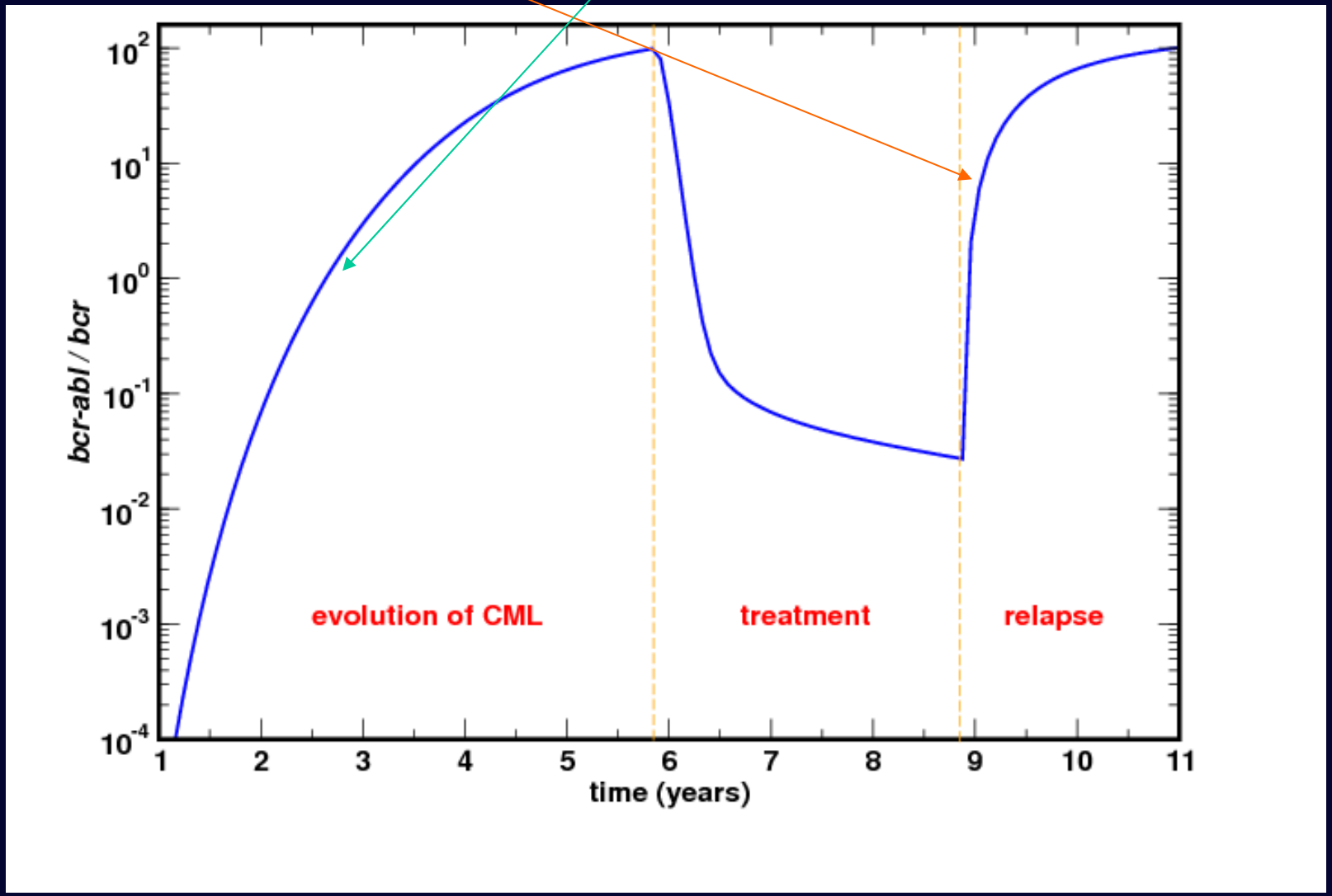
results



Dingli, Traulsen & Pacheco, *Clinical Leukemia* 2 (2008) 133

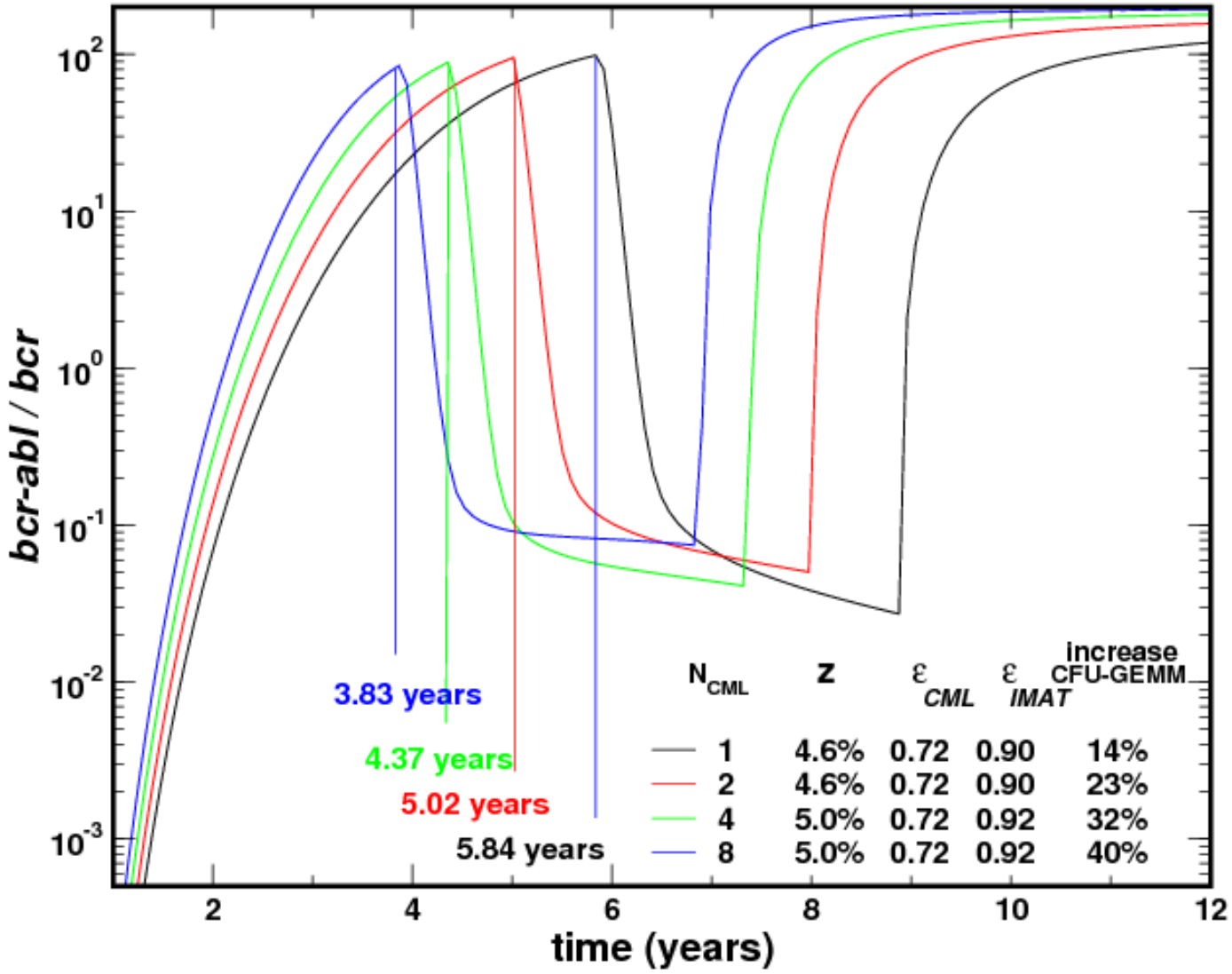
features

up to now, the # HSC driving the disease is constant in time & their dynamics is deterministic; when treatment is stopped, treated cells *wake up* and relapse is much faster than normal disease progression



Dingli, Traulsen & Pacheco, *Clinical Leukemia* 2 (2008) 133

features



Dingli, Traulsen & Pacheco, *Clinical Leukemia* 2 (2008) 133

features of CML

- CML is driven by a small number of neoplastic stem cells
- *imatinib* reduces the fitness of the neoplastic cells
- many CML progenitors persist
- only a fraction of CML cells are responding to therapy at any time
- relapse is driven by CML progenitors not just HSC

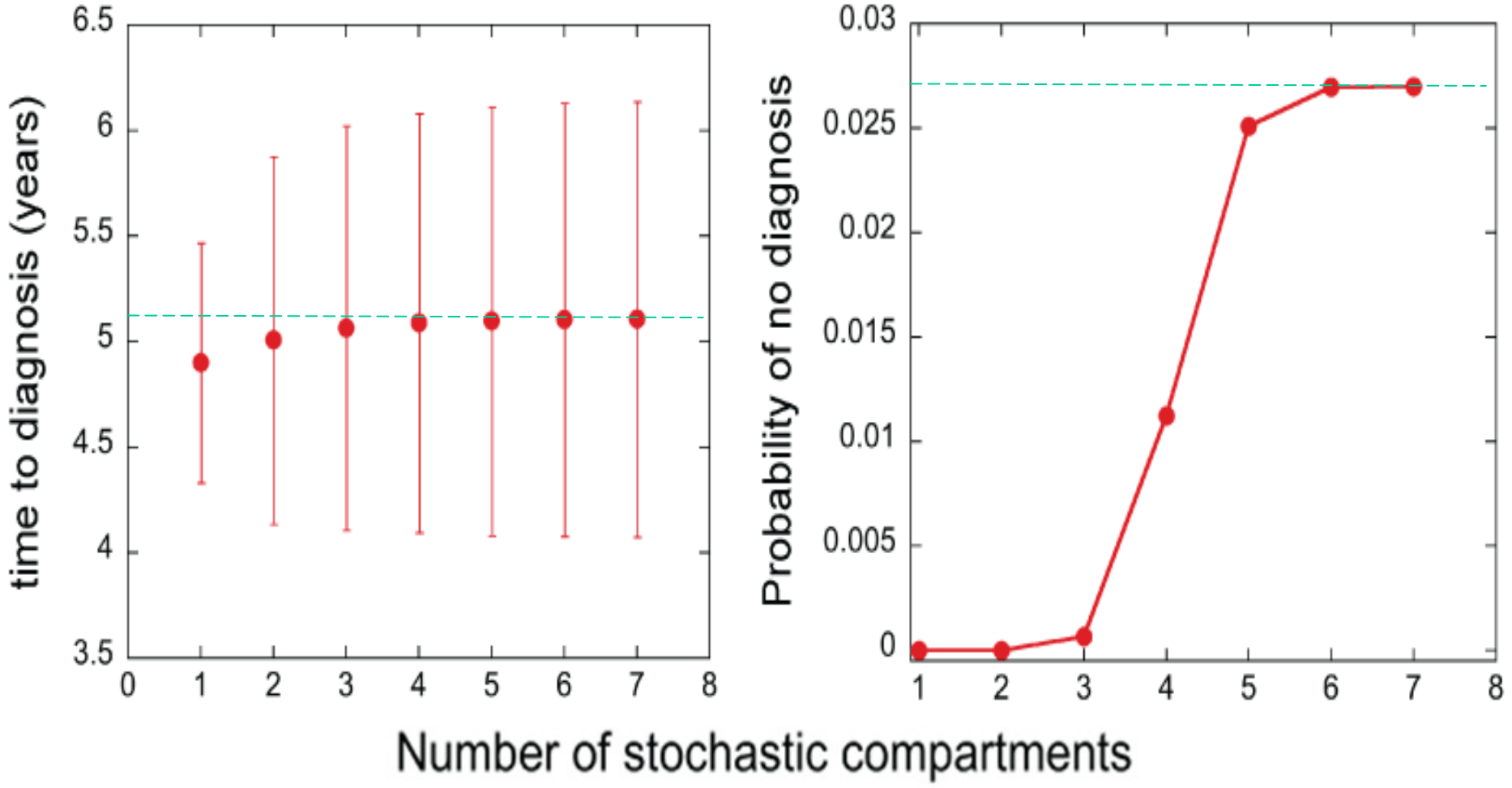
but **:**

- hematopoiesis is sochastic in nature, hence

what is the impact of stochastic effects on CML dynamics ?

stochasticity in CML

. . . stochastic dynamics of 10^{12} cells is unfeasible

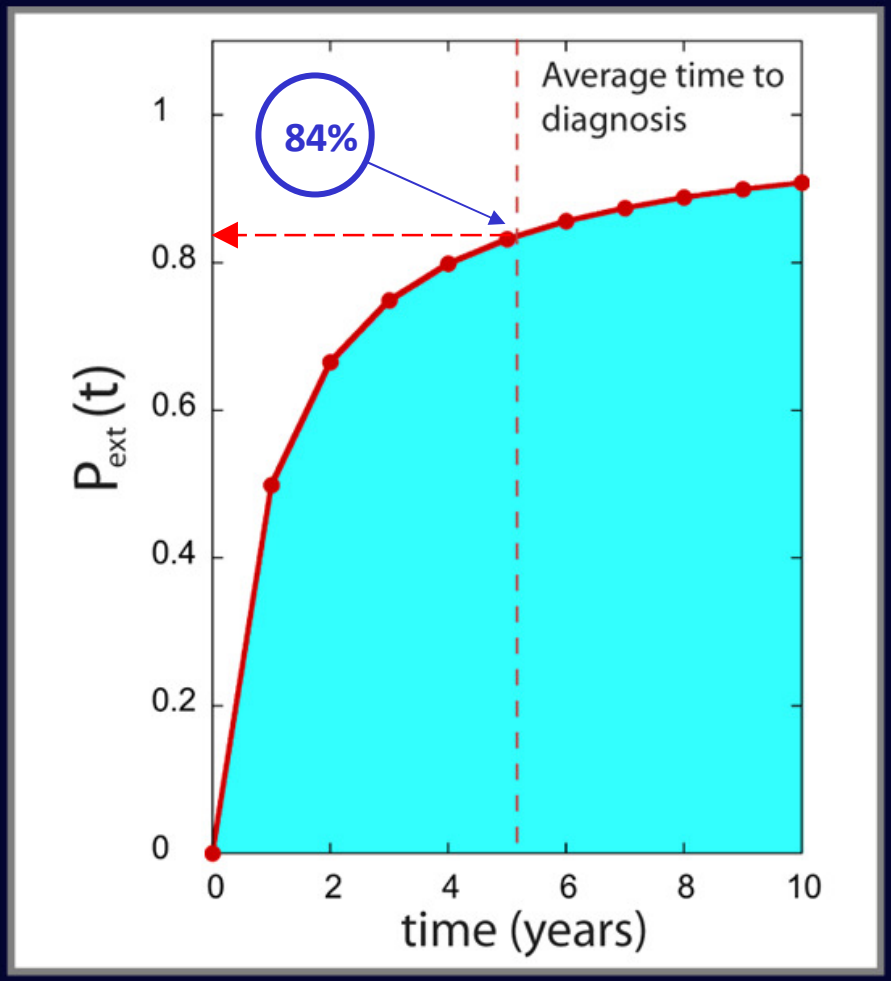


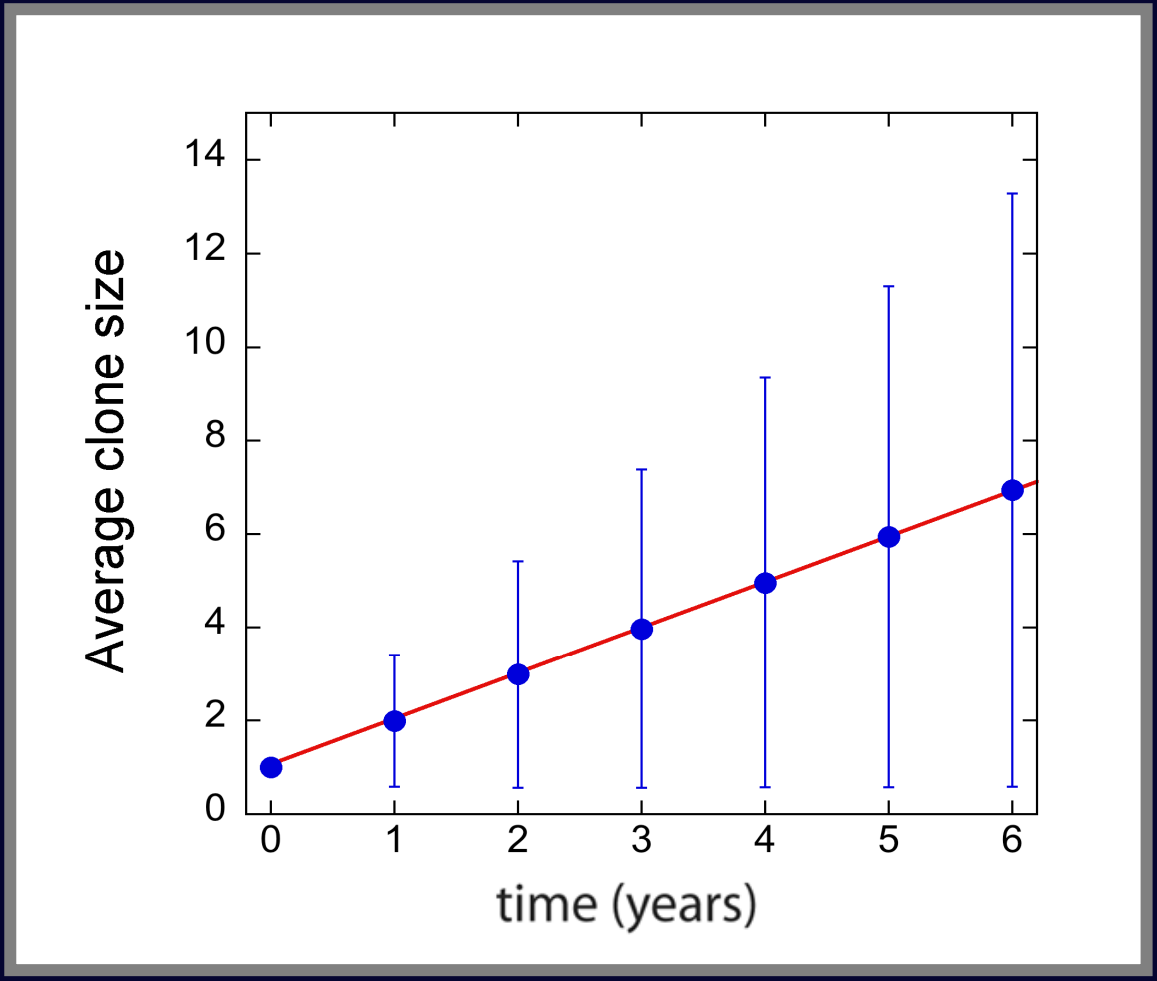
Tom Lenaerts et al. (Haematologica 95 (2010) 900-907)

stochasticity in CML

in 84% of individuals, CSC population goes extint before diagnosis

in 16% of individuals, CSC population grows, on average, 1 per year



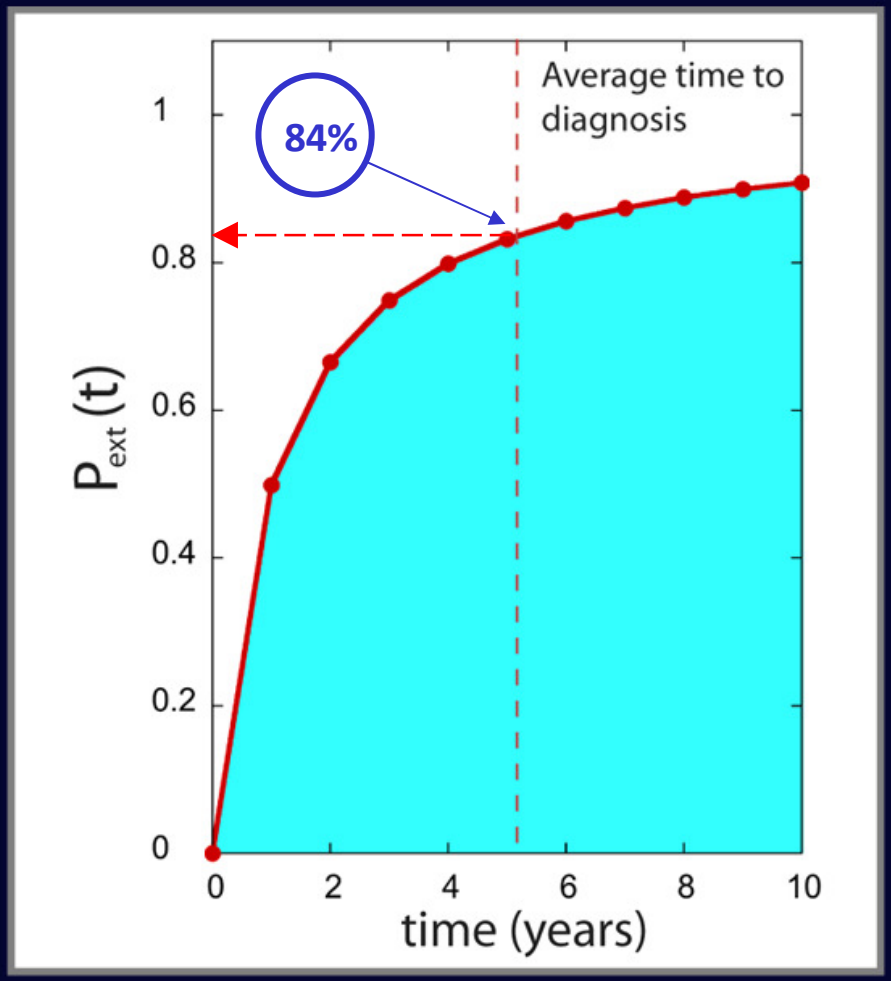


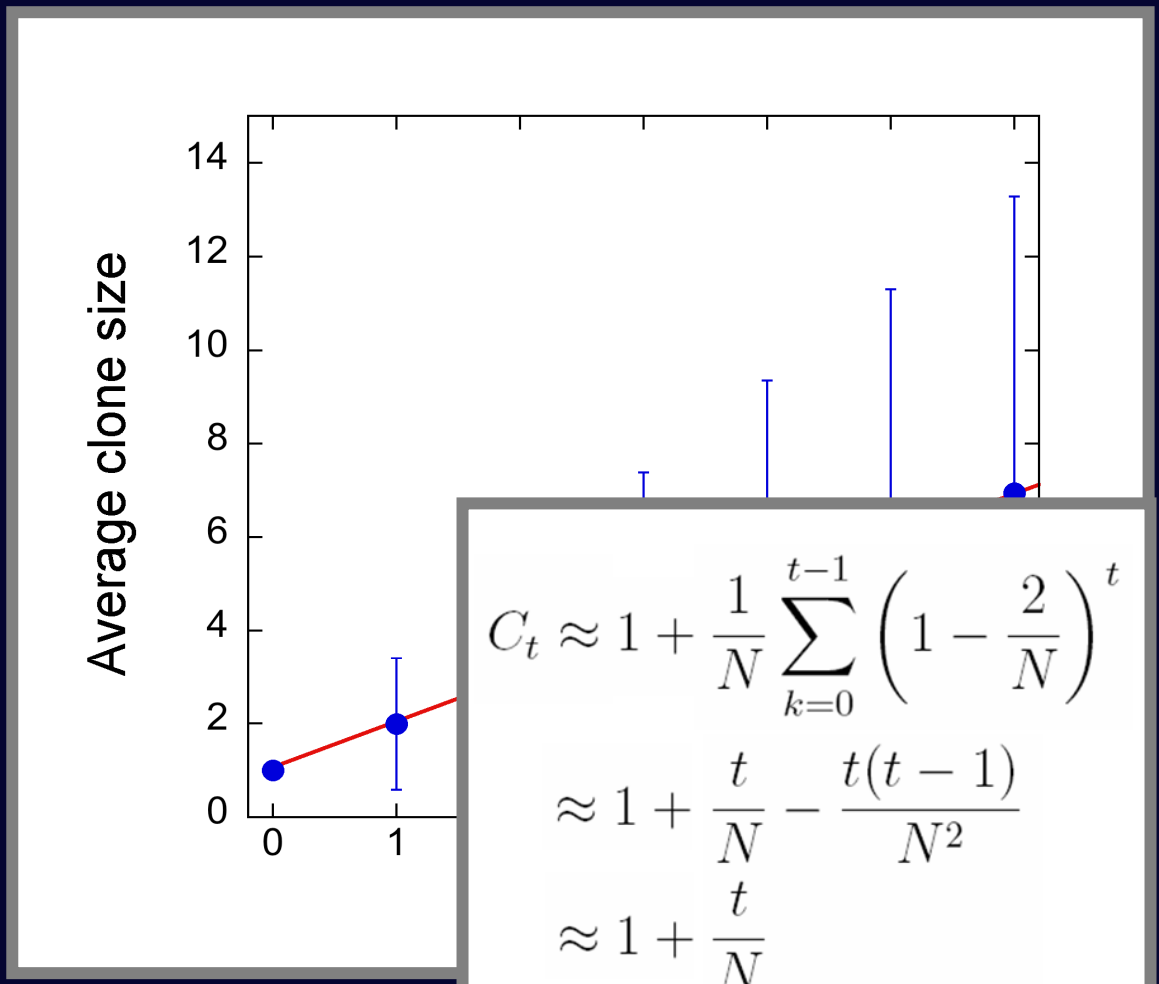
Tom Lenaerts et al. (Haematologica 95 (2010) 900-907)

stochasticity in CML

in 84% of individuals, CSC population goes extint before diagnosis

in 16% of individuals, CSC population grows, on average, 1 per year





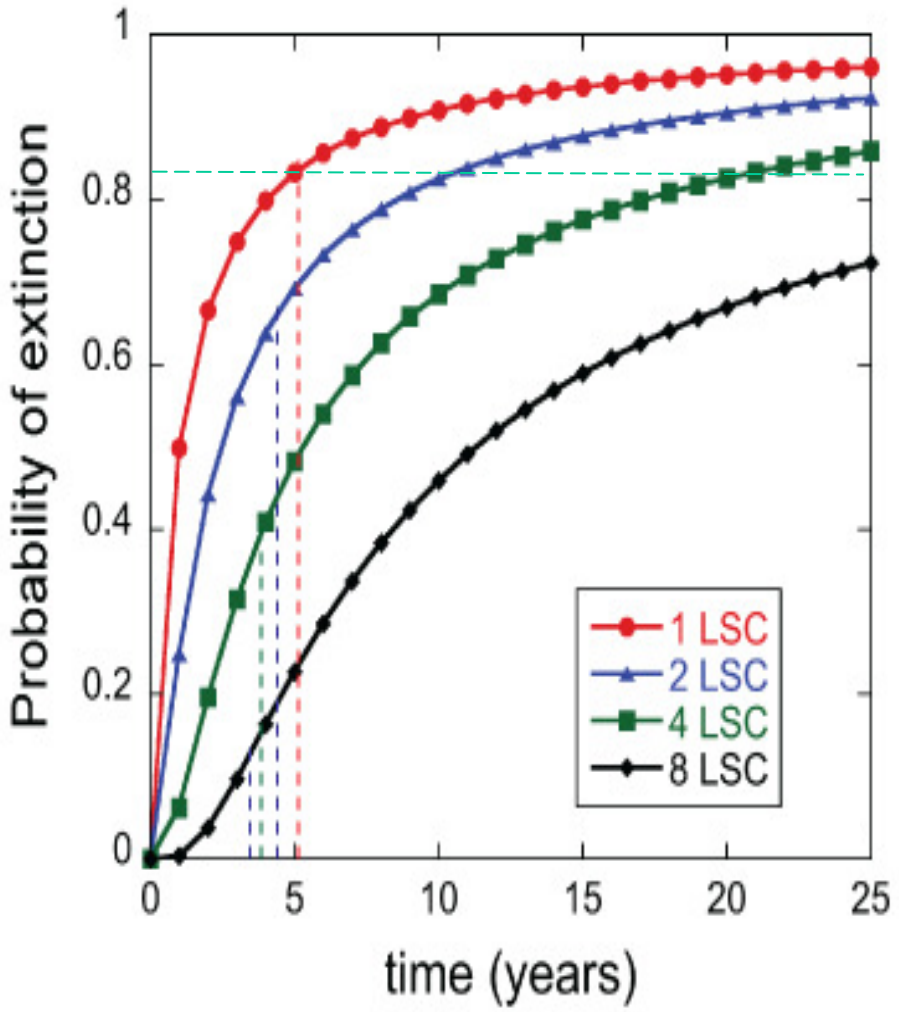
$$C_t \approx 1 + \frac{1}{N}\sum_{k=0}^{t-1}\left(1-\frac{2}{N}\right)^t$$

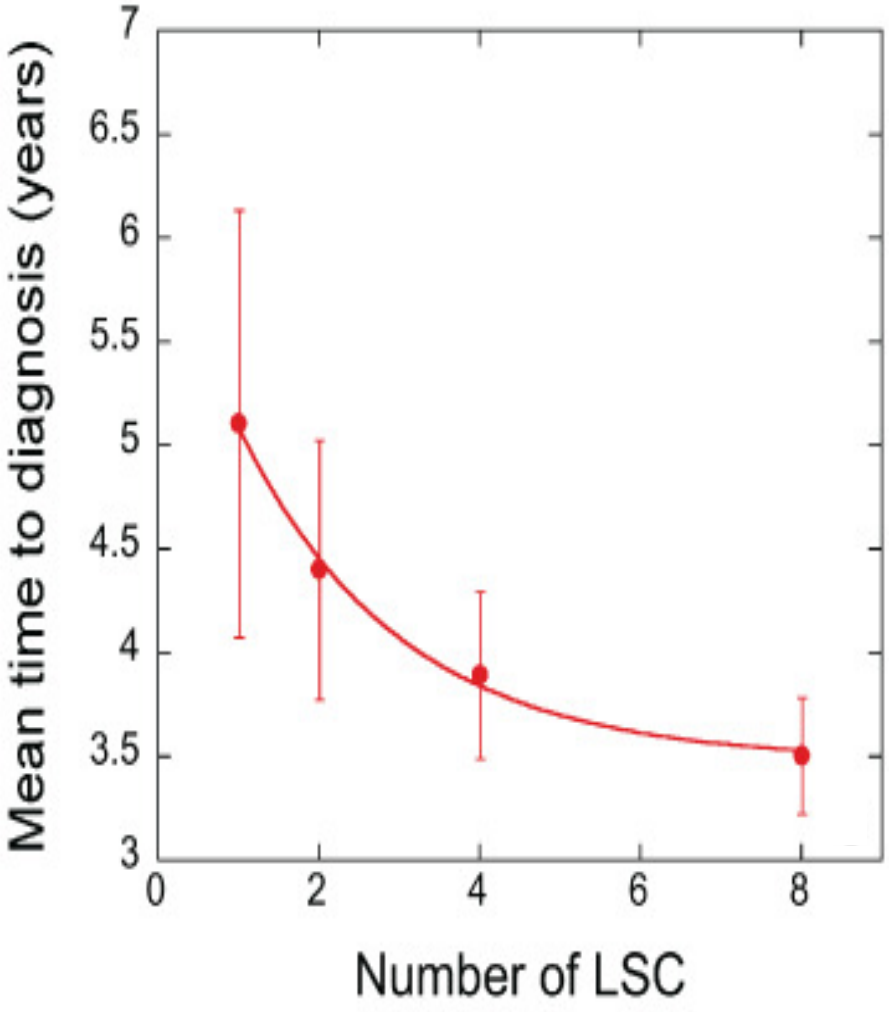
$$\approx 1 + \frac{t}{N} - \frac{t(t-1)}{N^2}$$

$$\approx 1 + \frac{t}{N}$$

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

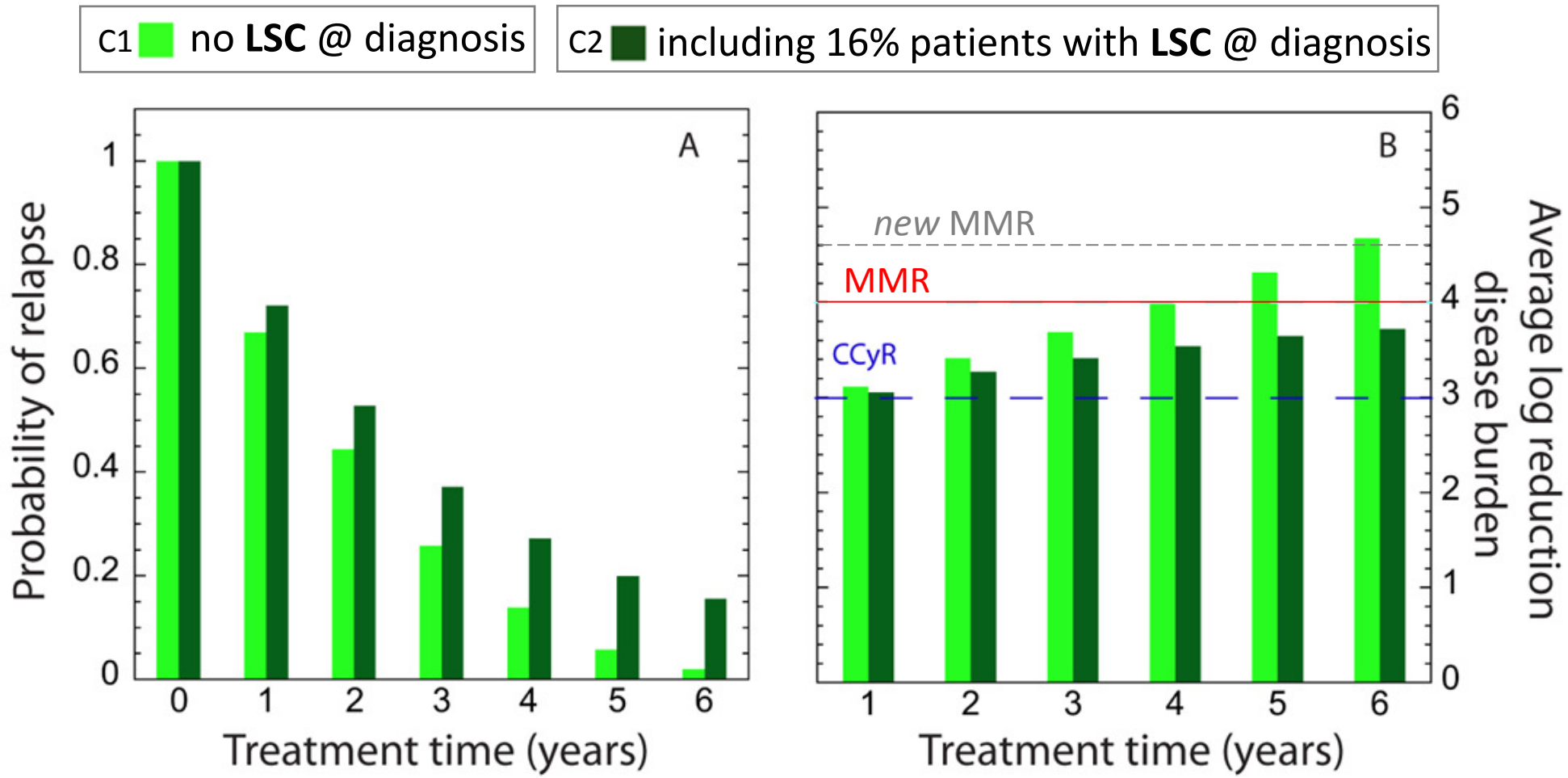
stochasticity in CML





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

stochasticity in CML



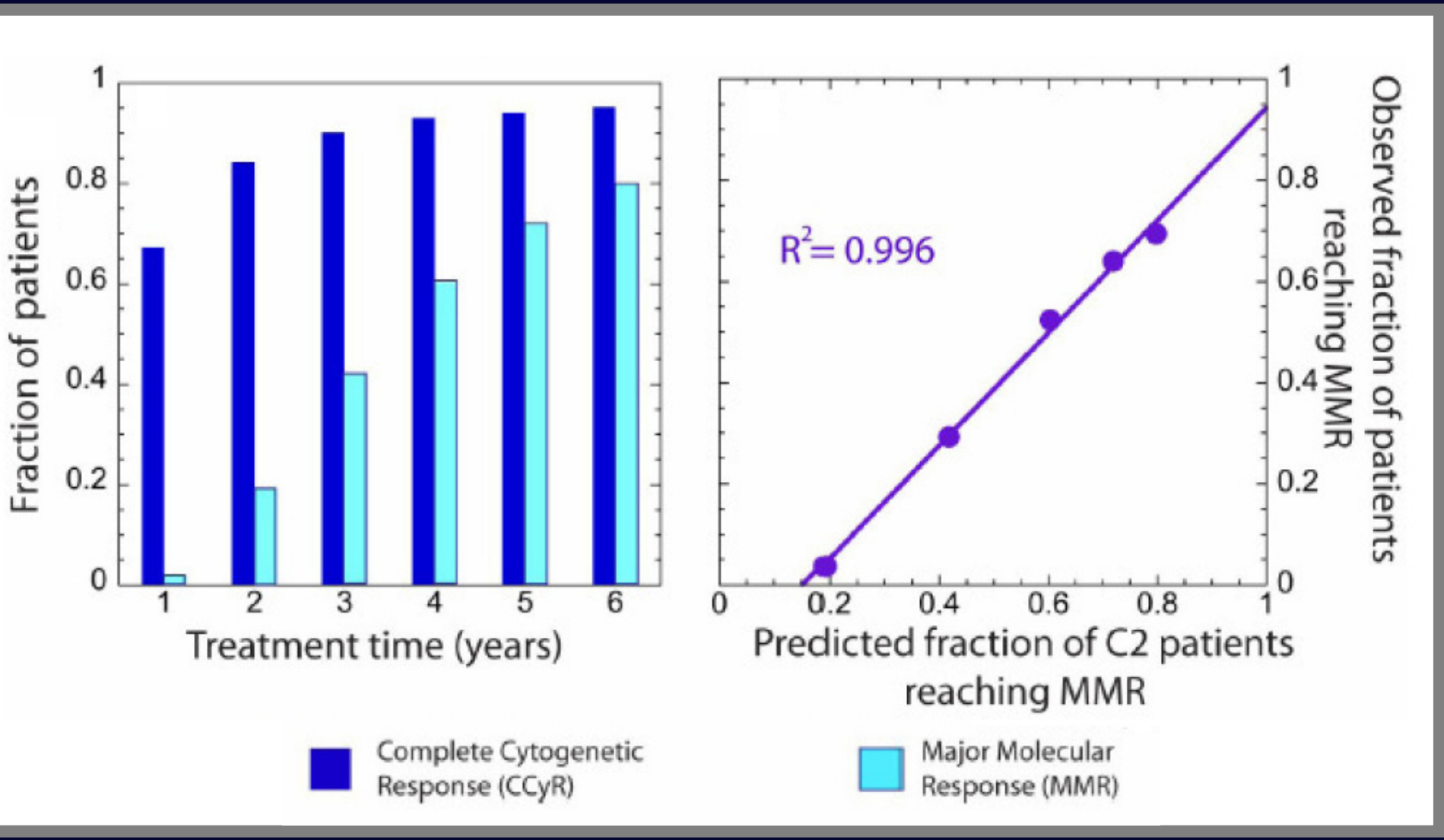
despite *NOT* affecting directly CSC,

imatinib + natural selection can cure the majority of CML patients

ongoing: development of *resistance mutations* . . .

stochasticity in CML

treatment with TKI-inhibitors helps an individual to stay alive and live his eveyday life while natural selection helps him getting rid of the cause of the disease; however, it takes years for one to gamble his way out of cancer.

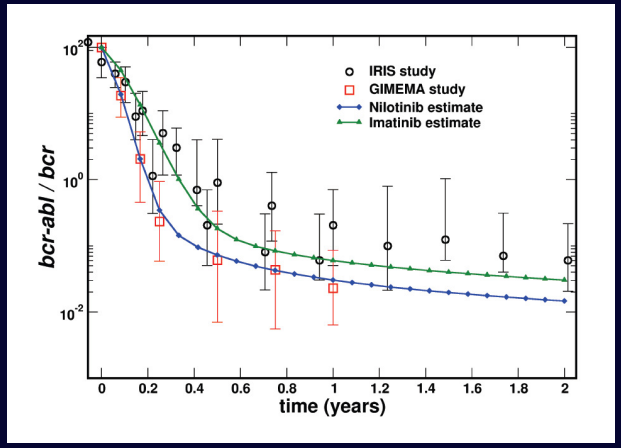


cancer ecology & CML treatments

Lenaerts *et al.*, Cell Cycle 10 (2011) 1540-1544

different therapeutic power of TKI-inhibitors

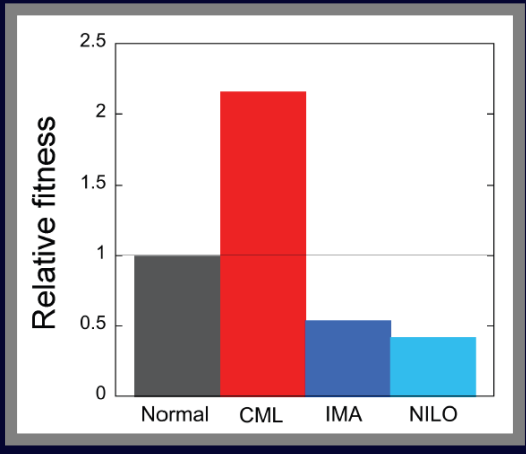
- CML can be successfully treated with different TKI-inhibitors
- *imatinib* & *nilotinib* lead to distinct disease progression curves



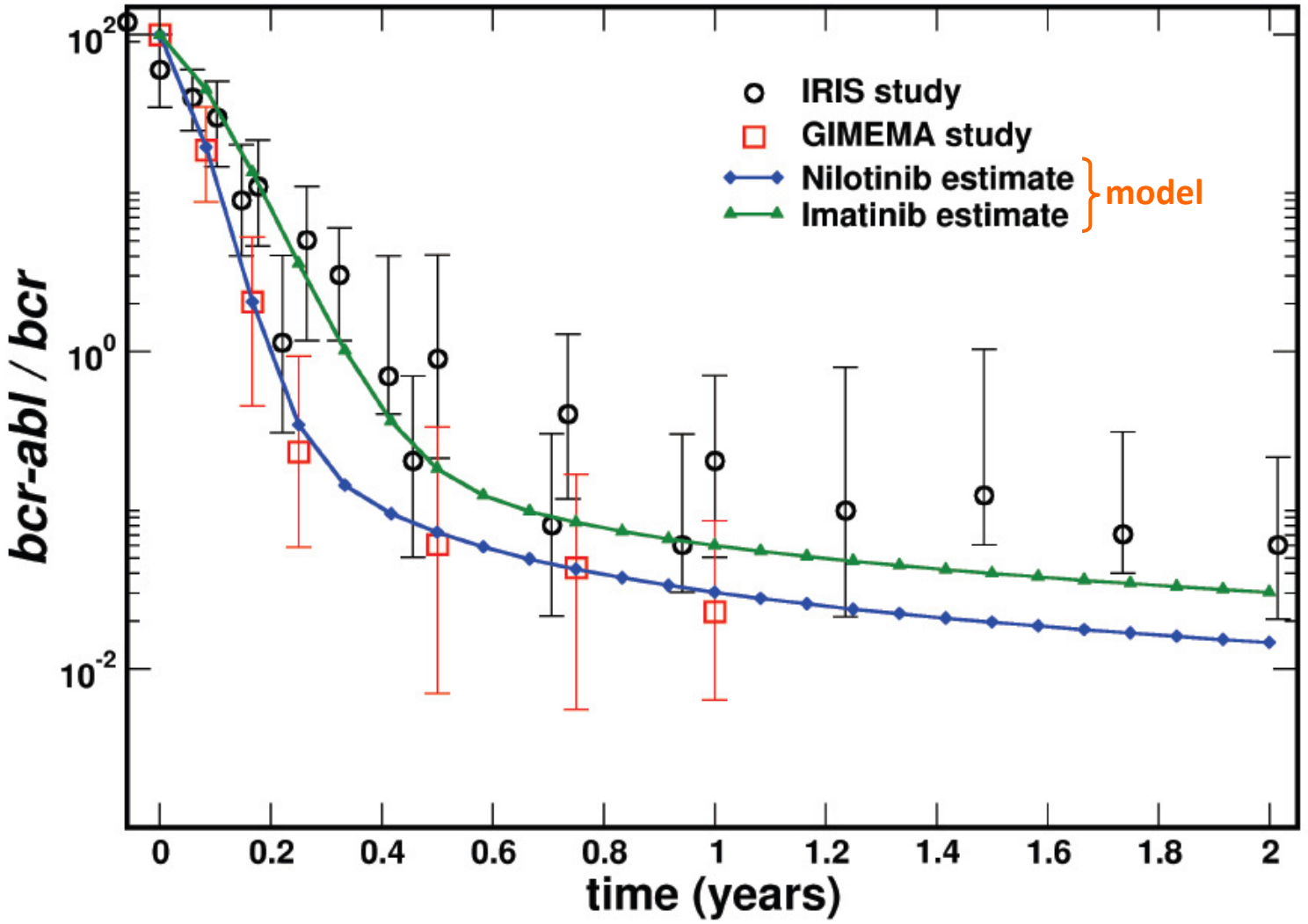
- however, *in-vitro* studies show no apparent difference between *imatinib* & *nilotinib*

what's going on ?

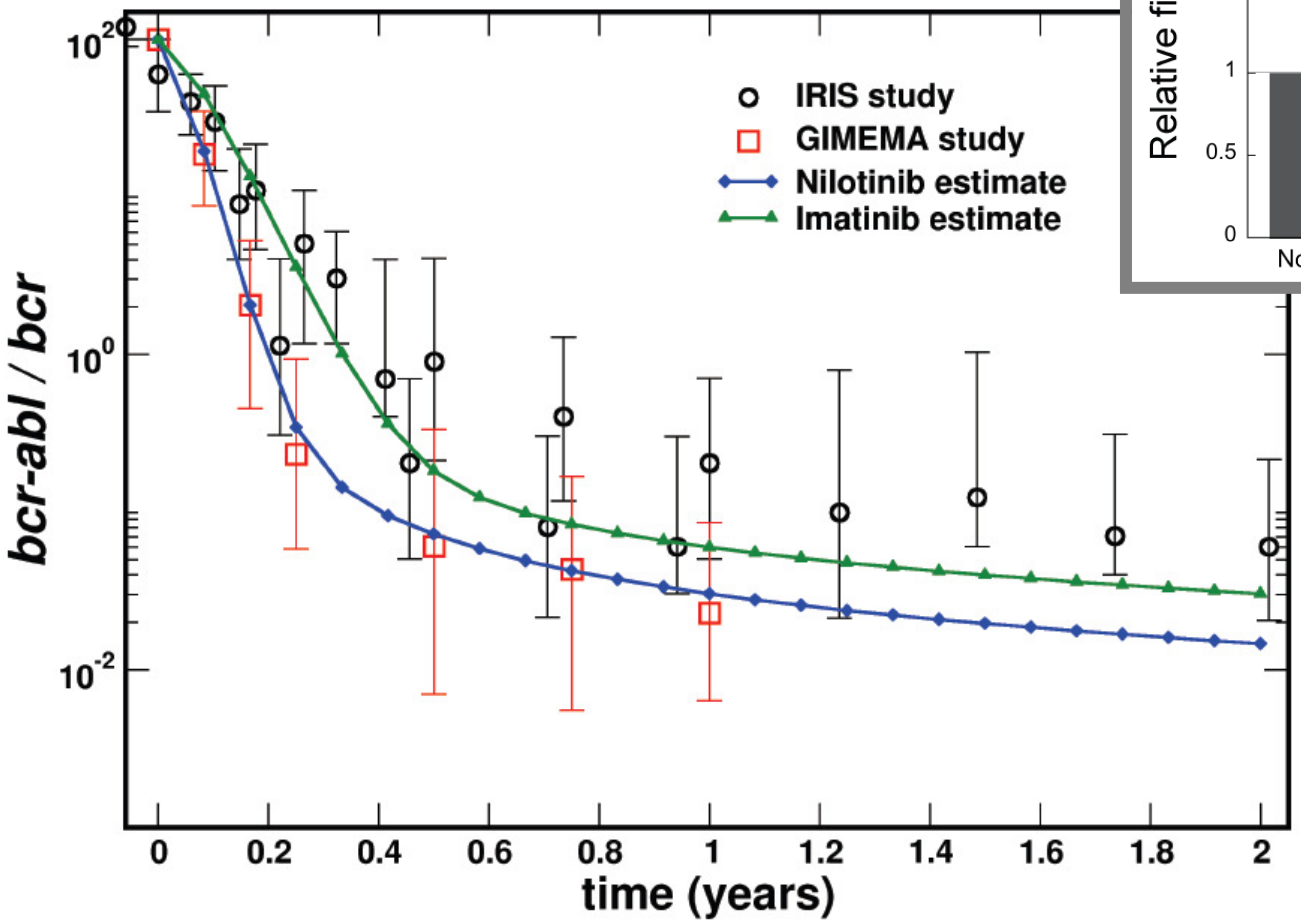
- *in-vitro* studies do not incorporate the ecology of cell competition that occurs *in-vivo*.

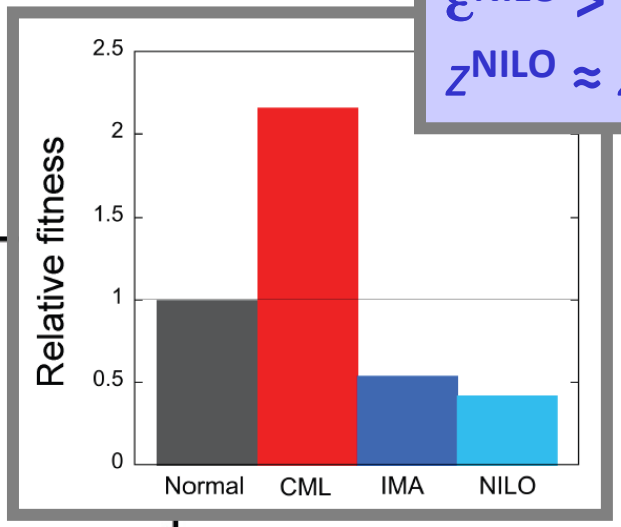


imatinib ⊗ nilotinib



imatinib ⊗ nilotinib





$\varepsilon^{NILO} > \varepsilon^{IMAT}$

$z^{NILO} \approx z^{IMAT}$

imatinib ⊗ nilotinib

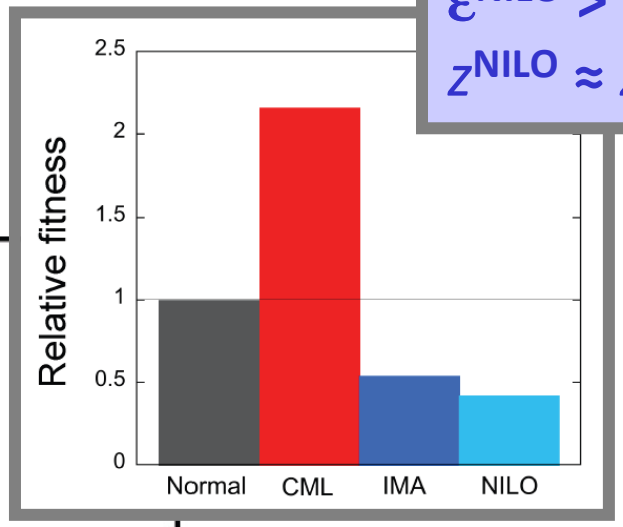
in vitro **: *no* differences**

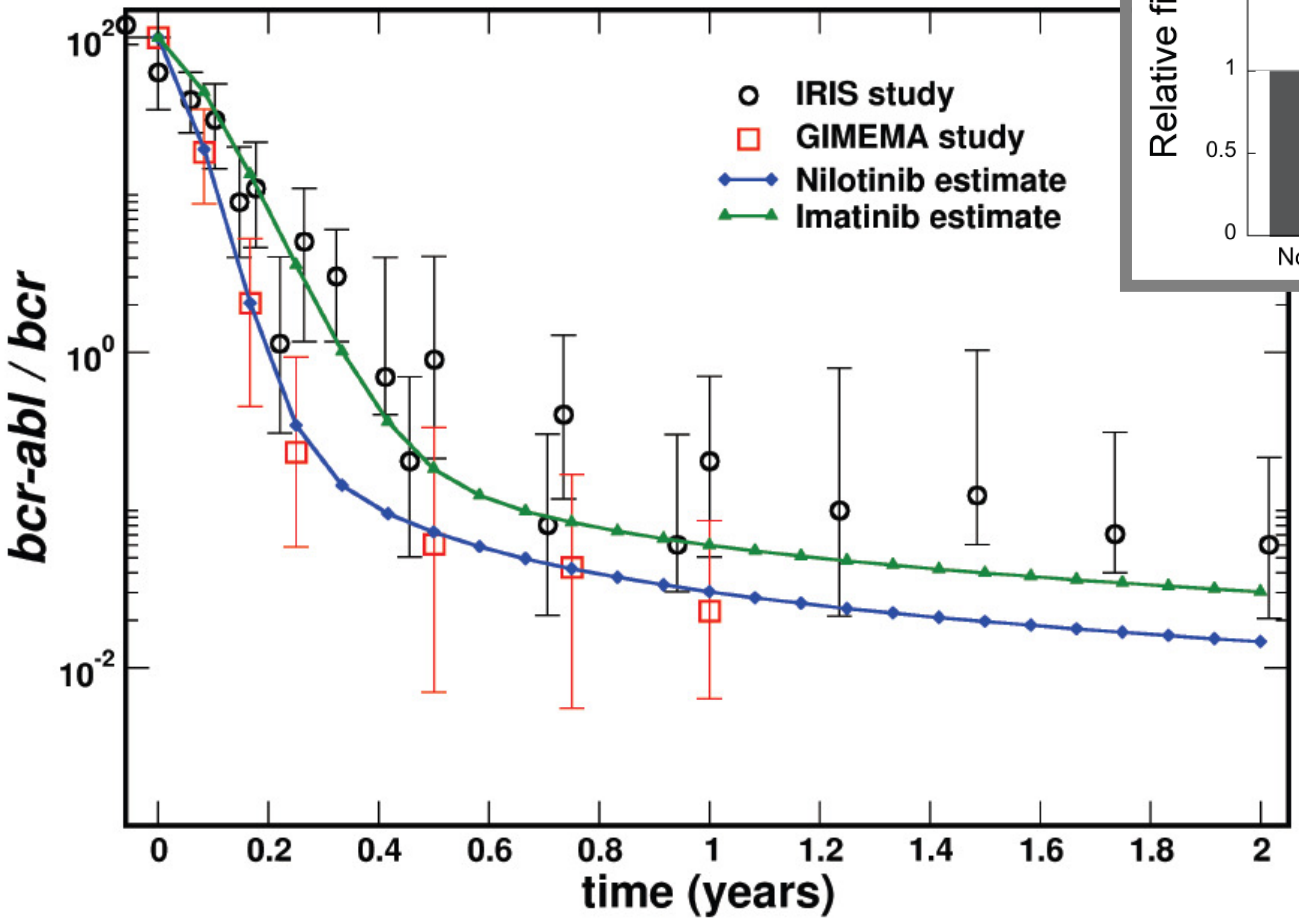
in vivo **: *important* differences**

(ecology of cancer cells is important)

$\varepsilon^{NILO} > \varepsilon^{IMAT}$

$z^{NILO} \approx z^{IMAT}$





conclusions

- *hematopoiesis results from the slow replication of a limited number of active stem-cells which scales allometrically with the mass of an adult mammal as* $N_{SC} \sim M^{3/4}$

- *the small number of HSC together wih their slow replication rate protect hematopoiesis from long-term trouble.*

- *the paradigm of stochastic behaviour – neutral evolution – suggests that PNH does not result from any* 2^{nd} *mutation or immune system attack – it results from the unlikely event of a rare-mutation in a small population at a normal mutation rate.*

- *stochastic effects have measurable consequences in disease progression, and lead to variabilities in the time to progression of stem-cell derived diseases; in CML, and in the absence of resistance mutations, stochastic effects let TKI-inhibitors cure most patients.*

- *such a broad vision of hematopoiesis paves the way to study blood diseases (e.g., PNH, CML, CN) as well as the detailed microscopic description of response to therapies, such as those associated with TKI-inhibitors (imatinib, nilotinib, dasatinib, etc.)* **not to mention studying the development of mutations which are resistant to treatment (** *ongoing . . .* **)**


end

selected references

allometric scaling of hematopoiesis

Allometric scaling of the hematopoietic stem cell pool accross mammals
David Dingli, J. M. Pacheco
PLoS ONE 1 (2006) e2

Acquired hematopoietic stem cell disorders and mammalian size
J. Viana Lopes, Jorge M. Pacheco, David Dingli
Blood 110 (2007) 4120-4122.

Dynamics of Hematpoiesis across Mammals
David Dingli, Arne Traulsen, Jorge M. Pacheco
Proceedings Royal Society B275 (2008) 2389-2392

The allometry of chronic myeloid leukemia
Jorge M. Pacheco, Arne Traulsen, David Dingli
Journal of Theoretical Biology 259 (2009) 635-640

Compartmental Architecture and Dynamics of Hematopoiesis
David Dingli, Arne Traulsen, J. M. Pacheco
PLoS ONE 2(4) (2007) e345

Ontogenic growth of the haematopoietic stem cell pool in humans
David Dingli, J. M. Pacheco,
Proceedings Royal Society B274 (2007) 2479

Dynamics of Hematpoiesis across Mammals
David Dingli, Arne Traulsen, Jorge M. Pacheco
Proceedings Royal Society B275 (2008) 2389-2392

Cyclic neutropenia in mammals
Jorge M. Pacheco, Arne Traulsen, Tibor Antal, David Dingli
American Journal of Hematology 83 (2008) 920

selected references

CML

Tyrosine kinase inhibitor therapy can cure chronic myeloid leukemia without hitting leukemic stem cells
Tom Lenaerts, Jorge M. Pacheco, Arne Traulsen, David Dingli
Haematologica 2009 (accepted)

The allometry of chronic myeloid leukemia
Jorge M. Pacheco, Arne Traulsen, David Dingli
Journal of Theoretical Biology 259 (2009) 635-640

Chronic Myeloid Leukemia: Origin, Development, Response To Therapy, And Relapse
David Dingli, Arne Traulsen, Jorge M. Pacheco
Clinical Leukemia 2 (2008) 133-139

Tyrosine kinase inhibitor therapy can cure chronic myeloid leukemia without hitting leukemic stem cells
Tom Lenaerts, Jorge M. Pacheco, Arne Traulsen, David Dingli
Haematologica 95 (2010) 900-907

Reproductive fitness advantage of BCR–ABL expressing leukemia cells
Arne Traulsen, Jorge M. Pacheco, David Dingli
Cancer Letters 294 (2010) 43-48

Somatic mutations and the hierarchy of hematopoiesis
Arne Traulsen, Jorge M. Pacheco, Lucio Luzzatto,David Dingli
BioEssays 32 (2010) 1003-1008

Evolutionary Dynamics of Chronic Myeloid Leukemia
David Dingli, Arne Traulsen, Tom Lenaerts, Jorge M. Pacheco
Genes and Cancer 1, 4 (2010) 309-315

Stochastic dynamics and the evolution of mutations in stem cells
David Dingli and Jorge M. Pacheco
BMC Biology 9 (2011) 41

Explaining the in vivo and in vitro differences in leukemia therapy
T. Lenaerts, F. Castagnetti, A. Traulsen, J.M. Pacheco, G. Rosti & D. Dingli
Cell Cycle 10 (2011) 1540-1544

Evolutionary Dynamics of Mutations in Hematopoietic Stem Cells and Beyond
David Dingli, Arne Traulsen and Jorge M. Pacheco
Stem Cells and Cancer Stem Cells,
Volume 3, Chapter 11 (2012, accepted)(Springer Science)

Dynamics of mutant cells in hierarchical organized tissues
Benjamin Werner, David Dingli, Tom Lenaerts, Jorge M. Pacheco, Arne Traulsen
PLoS-Computational Biology 7 (2011) e1002290

selected references

cyclic neutropenia

Cyclic neutropenia in mammals
Jorge M. Pacheco, Arne Traulsen, Tibor Antal, David Dingli
American Journal of Hematology 83 (2008) 920

Progenitor Cell Self-renewal and Cyclic Neutropenia
David Dingli, Tibor Antal, Arne Traulsen, Jorge M. Pacheco
Cell Proliferation 42 (2009) xxxx-xxxx

multiple myeloma

Cancer phenotype as the outcome of an evolutionary game between normal and malignant cells
David Dingli, F. A. Chalub, F. C. Santos, S. Van Segbroeck, Jorge M. Pacheco
British Journal of Cancer (2009) (accepted)

Single versus multiple transplants for multiple myeloma: Insights from in vivo and in silico studies
David Dingli, J. M. Pacheco, M. A. Gertz,
Blood 108 (2006) 458 .

In vivo and in silico studies on single versus multiple transplants for multiple myeloma
David Dingli, J. M. Pacheco, Angela Dispenzieri, Suzanne Hayman, Shaji Kumar, Martha Lacy, Dennis Gastineau, Morie Gertz
Cancer Science 98 (5) (2007) 734–739

Depth of response and outcome in multiple myeloma
David Dingli, J. M. Pacheco, Grzegorz S. Nowakowski, Shaji Kumar, Angela Dispenzieri, Suzanne Hayman, Martha Lacy, Dennis Gastineau, Morie Gertz
Journal of Clinical Oncology 25 (2007) 4933-4937

The serum M-spike and transplant outcome in patients with multiple myeloma
David Dingli, J. M. Pacheco, Angela Dispenzieri, Suzanne Hayman, Shaji Kumar, Martha Lacy, Dennis Gastineau, Morie Gertz
Cancer Science 98 (7) (2007) 1035–1040

paroxysmal nocturnal hemaglubinuria

Neutral evolution in paroxysmal nocturnal hemoglobinuria
David Dingli, Lucio Luzzatto, Jorge M. Pacheco
Proceedings of the National Academy of Sciences (USA) 105 (2008) 18496

On the origin of multiple mutant clones in paroxysmal nocturnal hemoglobinuria
Arne Traulsen, J. M. Pacheco, David Dingli
Stem Cells 25 (2007) 3081-3084

scaling considerations

Dingli, Traulsen & Pacheco, *PRS**B** 275 (2008) 2389*

scaling relations so-far . . .

- *number of **HSC** in adult mamals :*

$$N_{SC} \approx 16.55\, M^{3/4}$$

- *number of **HSC** during human ontogeny :*

$$N_{SC} \approx 5.5\, m(t)$$

- *specific basal metabolic rate :*

$$B_c \approx 2.9\, M^{-1/4} \quad (\ year^{-1}\ )$$

- *average life-span :*

$$L \approx 8.6\, M^{1/4} \quad (\ year\ )$$

([M] = kg)

implications . . .

Hayflick hypothesis **(*1961*):**

cells undergo a limited number of divisions during their lifespan

from the scaling relations, each cell divides

$$N \sim rate \times lifespan \sim M^{-1/4} \times M^{1/4} \sim M^{0}$$

that is, constant & independent of the mammalian species **:**

a mouse-HSC and an elephant-HSC replicate, on average, the same number of times during the ~2-year and the ~70-year lifespans of the mouse and elephant, respectively; humans are the exception, as we live much longer than lifespan estimate.

scaling across mammals

in

CYCLIC NEUTROPENIA

Dingli, Antal, Traulsen & Pacheco, Cell Proliferation (in press)
Pacheco, Traulsen, Antal & Dingli, American Journal of Hematology, 83 (2008) 920

cyclic neutropenia

Dingli, Antal, Traulsen & Pacheco, Cell Proliferation (in press)
Pacheco, Traulsen, Antal & Dingli, American Journal of Hematology, 83 (2008) 920

features

- rare congenital disorder
- → oscillations of neutrophil count

model

- biological defect is the same in mammals
- architecture of hematopoiesis is invariant across mammals
- allometric scaling should relate period of oscillations

results :

$$\frac{T_H}{T_D} = \left(\frac{M_H}{M_D}\right)^{1/4}$$

→

species	*mouse*	*macaque*	*dog*	*baboon*	*human*
mass (*kg*)	0.025	5	13	40	70
period (*days*)	3	10-11	14	17-18	19-21
sampling period (hours)	<18	63	84	105	120

cyclic neutropenia

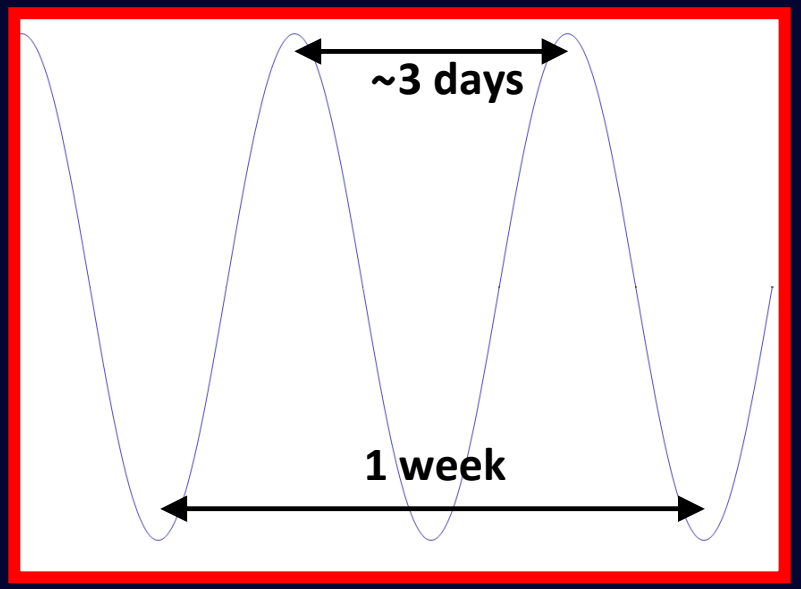
our model predicts a period of ~3 days for CN in mice
this is a direct consequence of metabolic rate of mice
does CN occur in mice ?

Grenda *et al.* Blood 100 (2002) 3221–3228

"Mice expressing a neutrophil elastase mutation derived from patients with severe congenital neutropenia have normal granulopoiesis"

- *there is a study on mice which claims there is no CN*
- *is that true ?*
- *what did they do ?*
- *they measured neutrophil count every week . . .*

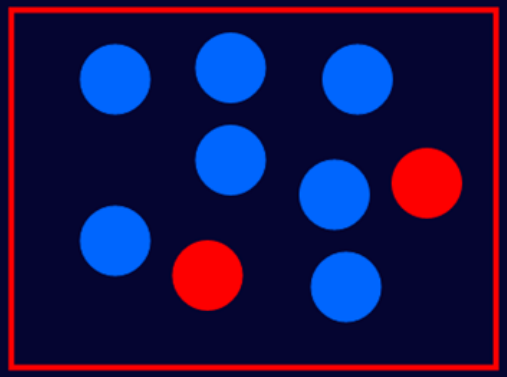
- *because sampling period is a multiple of CN period, they ever observe oscillations*



stochastic protection

THE MOST ROBUST MAMMAL

protection : the *best* of mammals



*combine allometric scaling with stochastic dynamics to determine the **mammal** **which is best protected** against acquired hematopoietic stem-cell disorders.*

scaling of lifespan: $L \sim M^{1/4}$ ↗

mass specific metabolic rate : $B_c \sim M^{-1/4}$ ↘

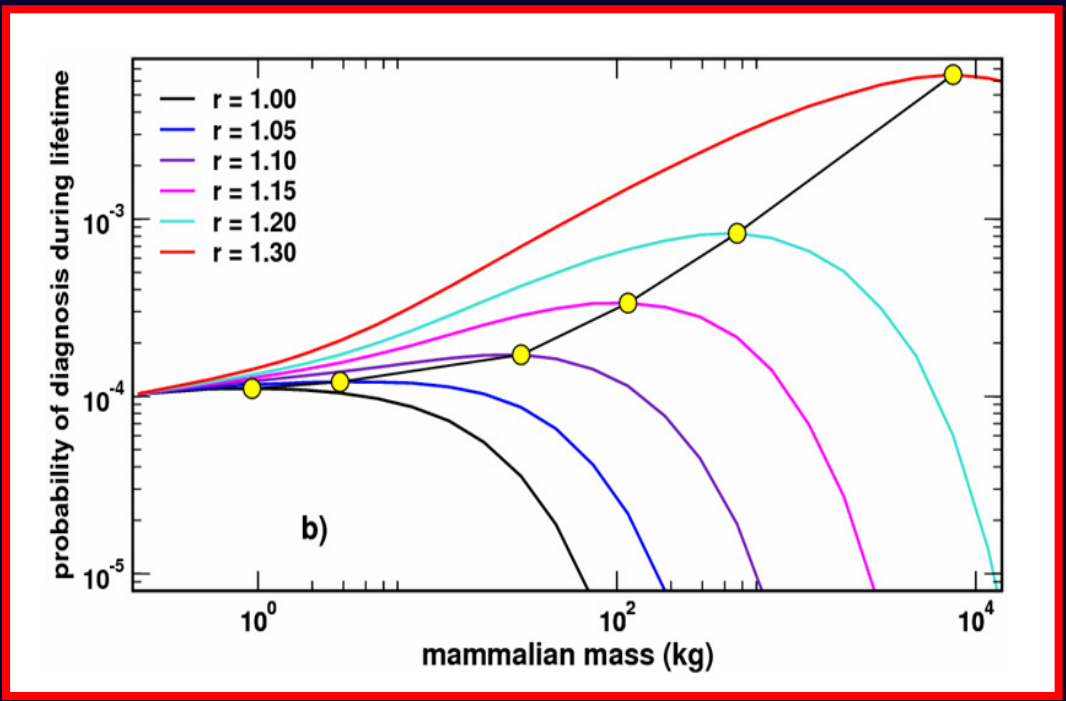
size of active SC pool : $N_{SC} \sim M^{3/4}$ ↗

prob. mutation HSC → CSC : $\mu \sim 10^{-6}$ **p/ replication** →

Lopes, Dingli, & Pacheco, *Blood* 110 (2007) 4120 - 4122

protection : the *best* of mammals

- ***r** is very difficult to determine experimentally;*
  unfortunately, it is consensual that, in general, r is large (>1.5) ;
- ***when r ~ 1, large mamals are more protected than small mammals;***
- ***when r > 1.3, small mammals are more protected, since the probability for the organism to acquire cancer mutations is minimized;***
- ***a small active HSC pool minimizes the risk of mutations; once mutations occur, the path to full blown disease opens up easily (whenever r >1).***



***r* =1.05 : *prob*(mouse) = *prob*(M=18 kg)**

***r* =1.10 : *prob*(mouse) = *prob*(M=125 kg)**

***r* =1.15 : *prob*(mouse) = *prob*(M=870 kg)**

***r* =1.20 : *prob*(mouse) = *prob*(M=5800 kg)**

Lopes, Dingli, & Pacheco, *Blood* 110 (2007) 4120 - 4122