the evolutionary dynamics of hematopoiesis
(in health & disease)

Jorge M. Pacheco

atpgroup

http://dl.dropbox.com/u/6053055/SP2016-4-of-5.pdf

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

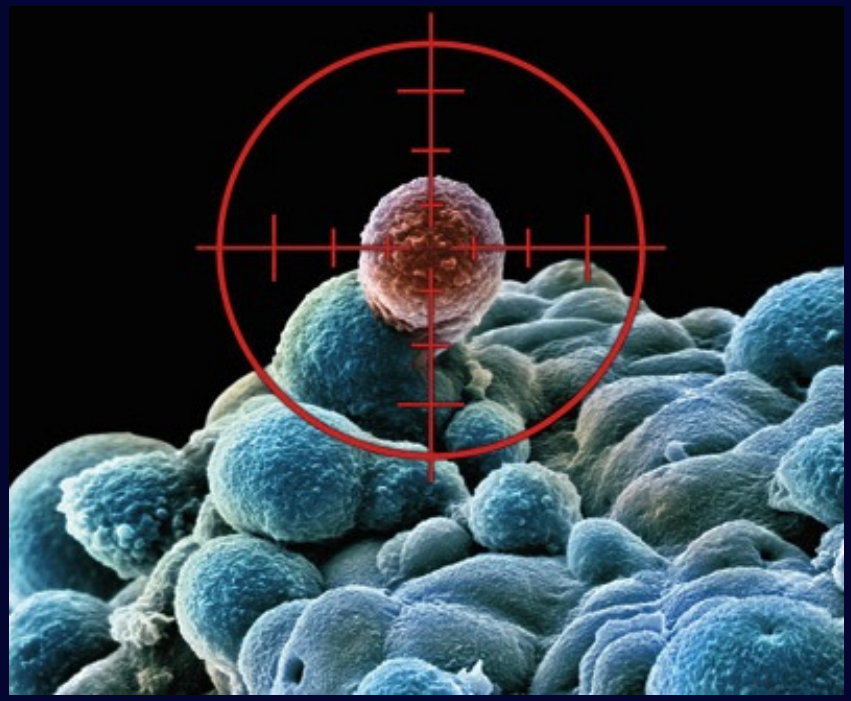
unesp
UNIVERSIDADE ESTADUAL PAULISTA
"JÚLIO DE MESQUITA FILHO"

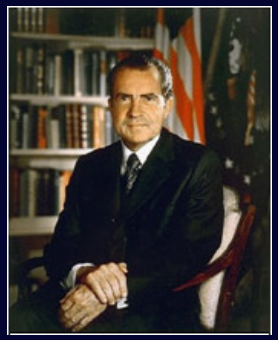
layout

thursday – 11:15 – 12:30

- hematopoiesis : from **health** to **disease**
- modeling (rare) diseases using the *standard model* (**SM**)
- some predictions of the **SM**
- stochastic effects in (the **SM** of) hematopoiesis

war on cancer





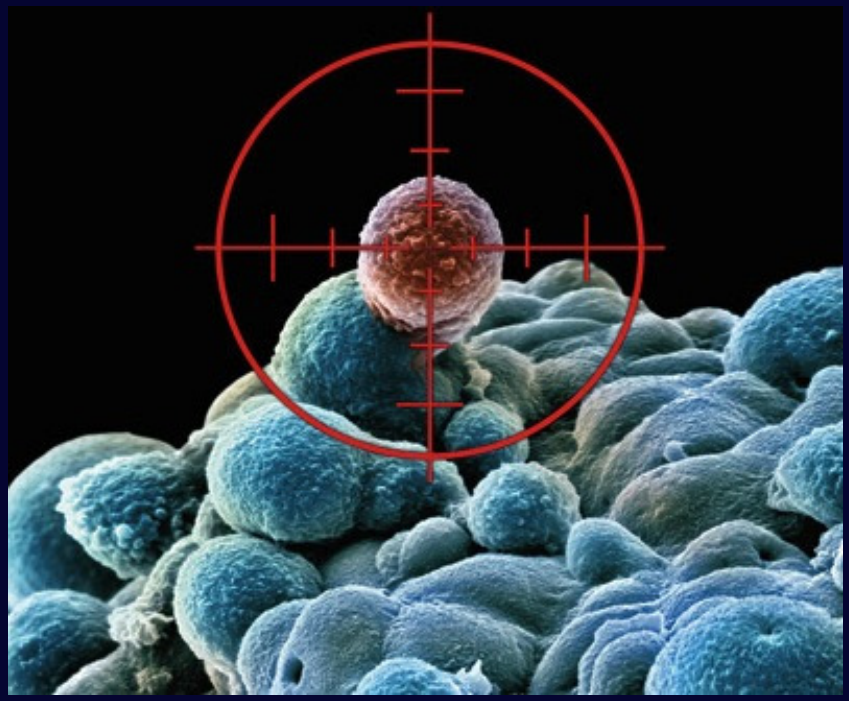
1971 (23/Dec) National Cancer Act (Richard Nixon)

2008 The Economist

*" … the fear of disease has transferred itself to cancer. How to prevent it, and how to treat it if prevention has failed, fills the health pages of the newspapers. How this or that celebrity won or lost his or her battle with it seems to fill much of the rest. The **military metaphor** is not confined to newspapers … "*

war on cancer

the philosophy of war on cancer for the last 44 years

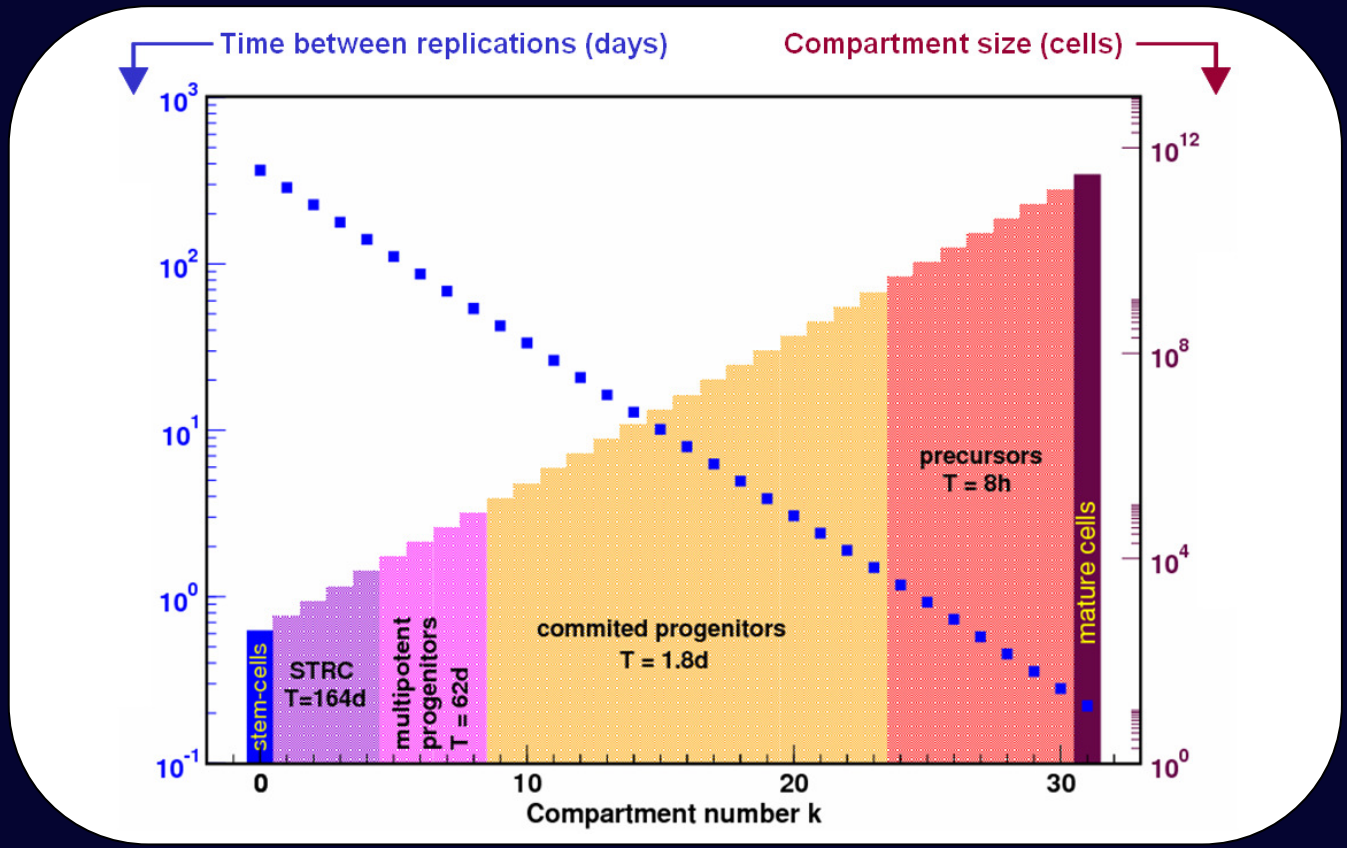


cure cancer = kill every cancer cell !

war on cancer

is this feasible ?

- the example from **hematopoiesis** (study of all aspects of the formation of blood cellular components, and their function)



- *we replace ~ 3.5 x 10^{11} blood cells every day (1%)*

war on cancer

what are we looking for ?

- several leukemias (blood cancers) originate from mutations of Hematopoietic Stem Cells (**HSC** ➔ **CSC**)

war on cancer

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- each one of us in this room has $\approx 10^{13}$ blood cells, a tiny fraction of which ($\approx 4 \times 10^{2}$) are **HSC**; in early stages of blood-cancers, **CSC** (Cancer Stem Cell) are but a small fraction (≈ 1) of the **HSC** population.

war on cancer

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- is killing a **CSC** as hard as finding a needle in a haystack ?

war on cancer

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- is killing a **CSC** as hard as finding a needle in a haystack ?

not even close !!!

war on cancer

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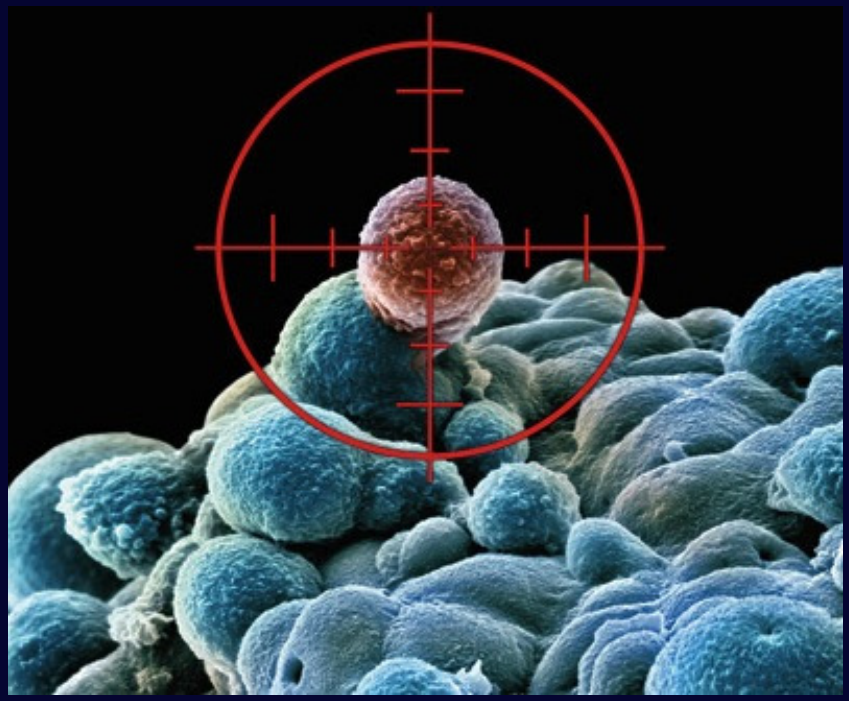
- is killing a **CSC** as hard as finding a needle in a haystack ?

- there are only about $\approx 10^{9}$ straws in a haystack with
  100m x 100m x 10m

- thus, the prospect of killing every single cell seems unfeasible

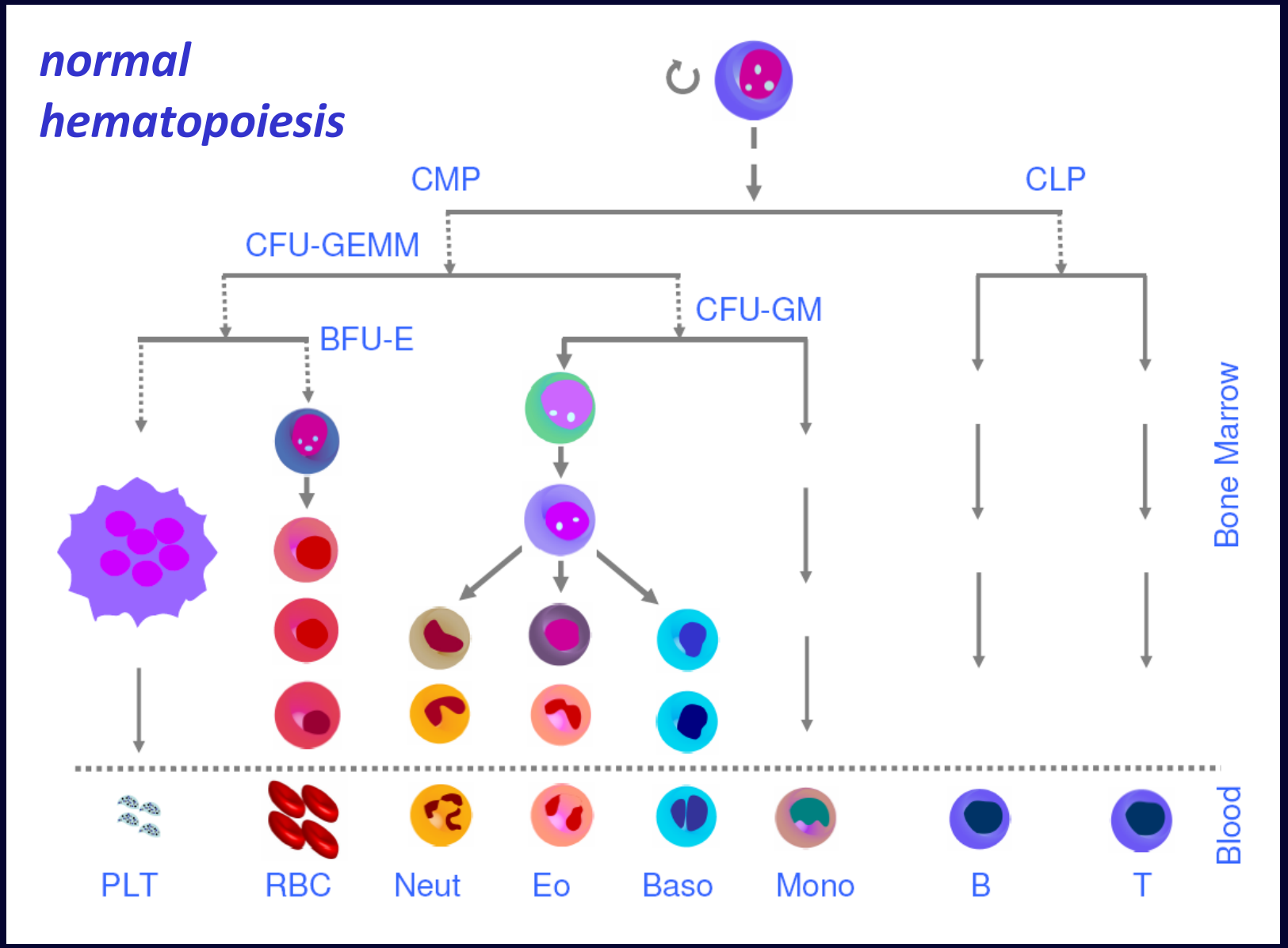
disease



trouble happens – how ?

***trouble* happens**

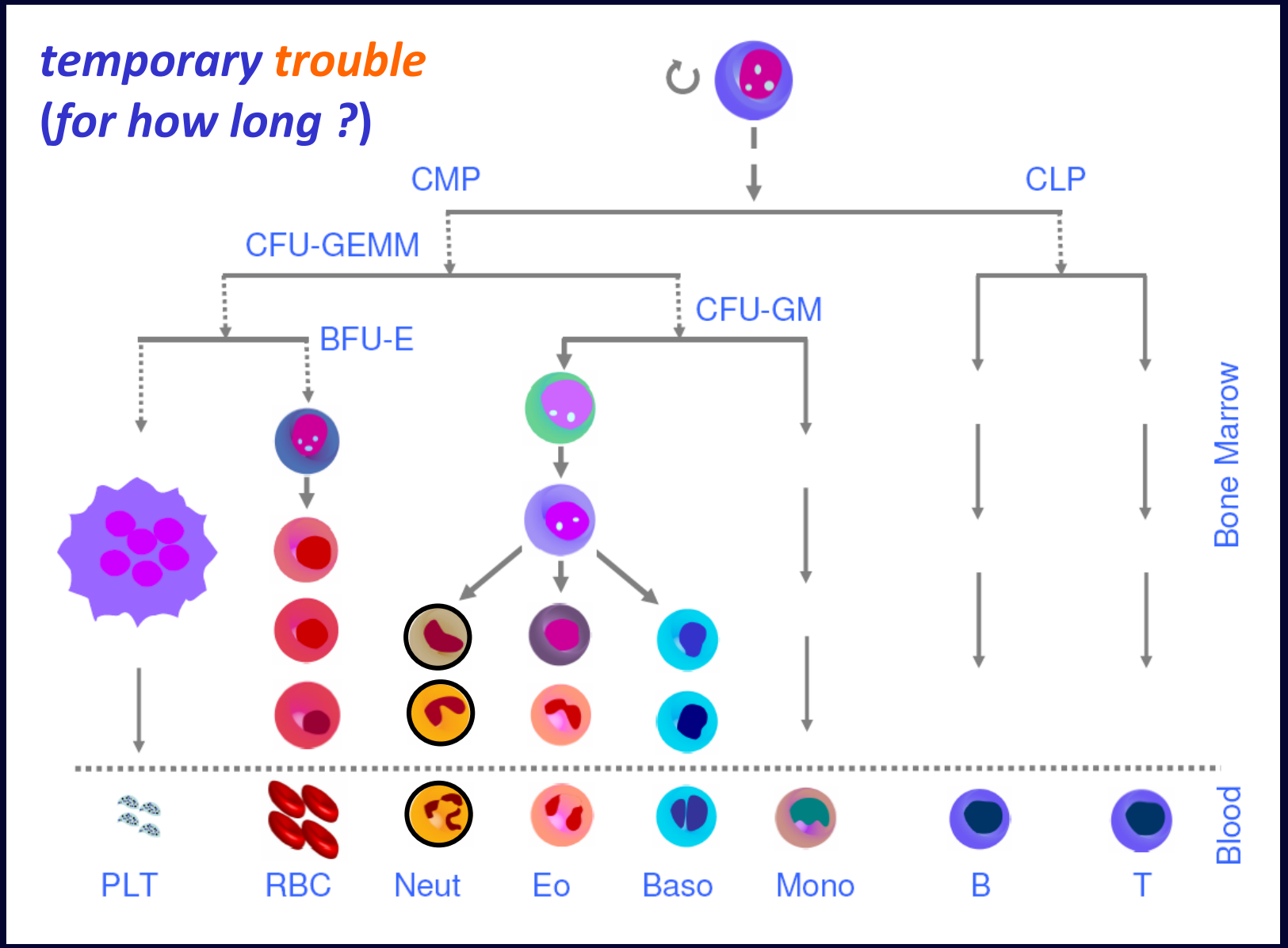
normal : $10^{-7} < \mu < 10^{-6}$ *per cell per replication*



***trouble* happens**

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

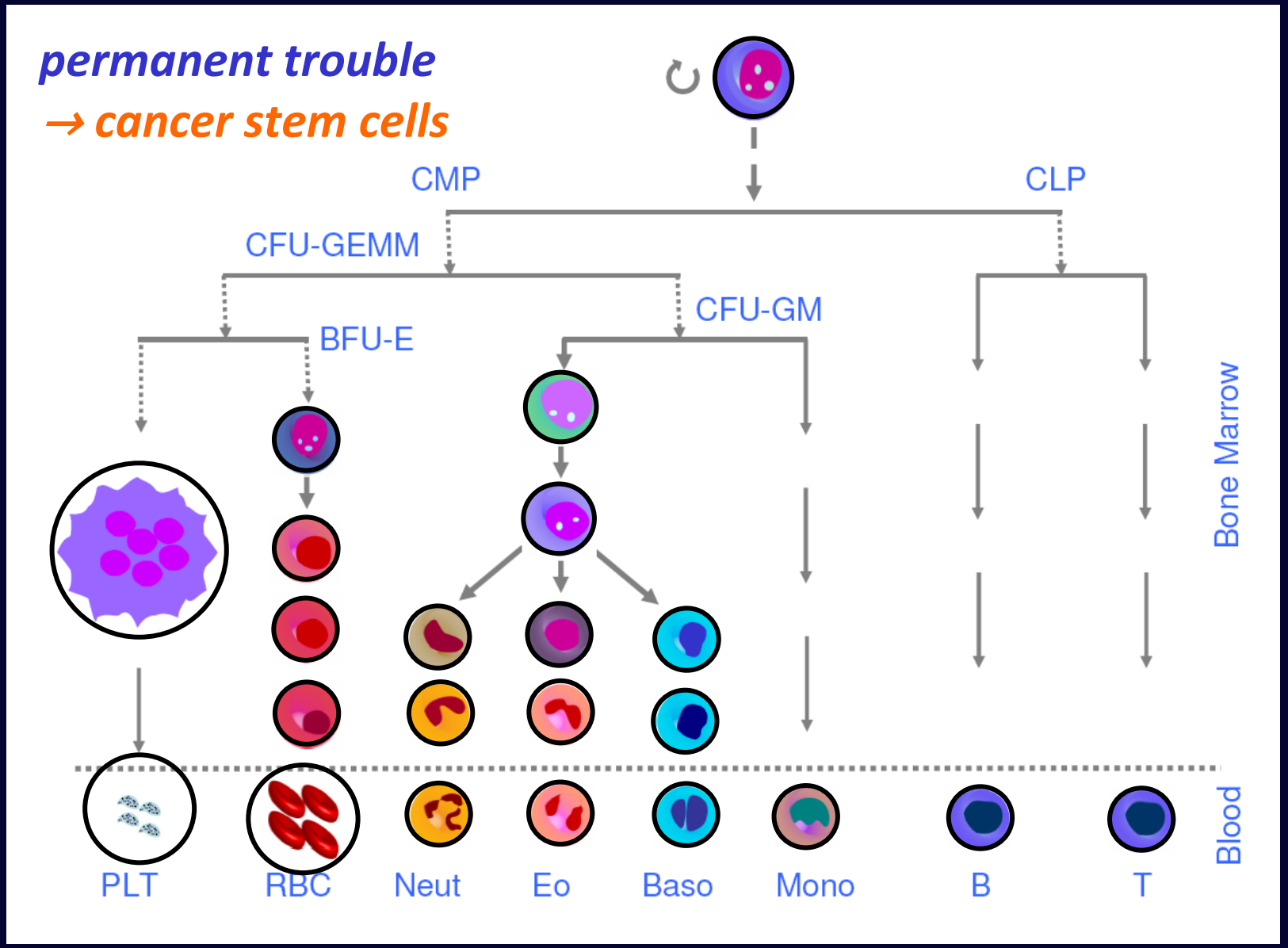
temporary trouble
(for how long ?)



***trouble* happens**

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

permanent trouble
→ cancer stem cells



***trouble* happens**

***CSC** are cancer cells that stand at the root of the tree*

***however* :**

***CSC** "co-evolve" with normal **HSC** in the bone marrow*

*often a small fraction of **CSC** in the **SC** population leads to **trouble***

***CSC** × **HSC** co-evolution can be viewed as a species competition*

***trouble* happens**

***given the small number of active* HSC *in (e.g.) humans* :**

hematopoiesis becomes stochastic in nature

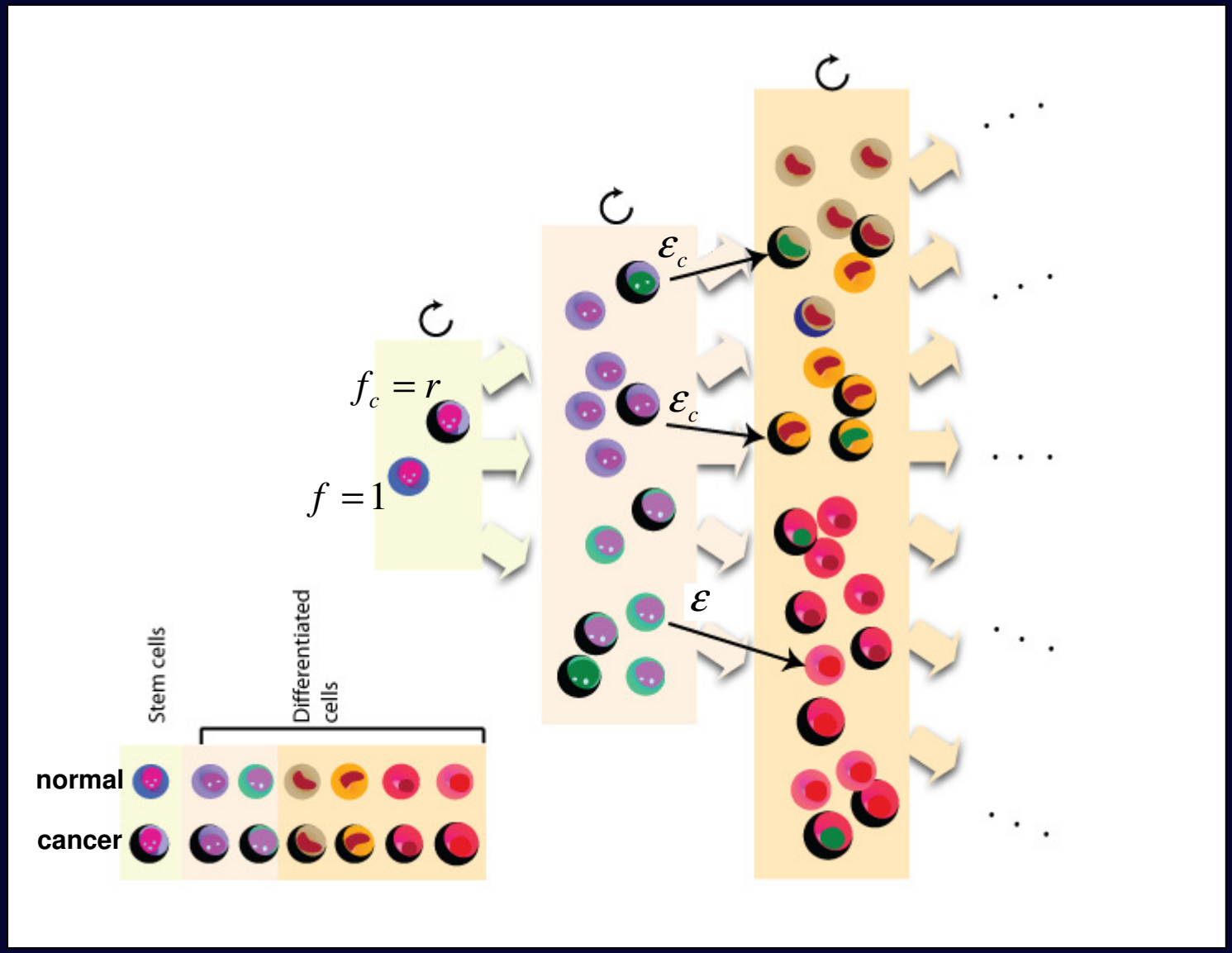
Abkowitz, J. L., Catlin, S. N. & Guttorp, P. *Evidence that hematopoiesis may be a stochastic process in vivo*. Nature Medicine 2, 190-7 (1996)

CSC ✕ HSC ***competition may only end when one wipes out the other***

CSC ✕ HSC ***competition is driven by natural selection, driven by the relative fitness difference between cell types***

will stochastic effects allow us to understand features associated with hematopoietic disorders ?

troubled hematopoiesis



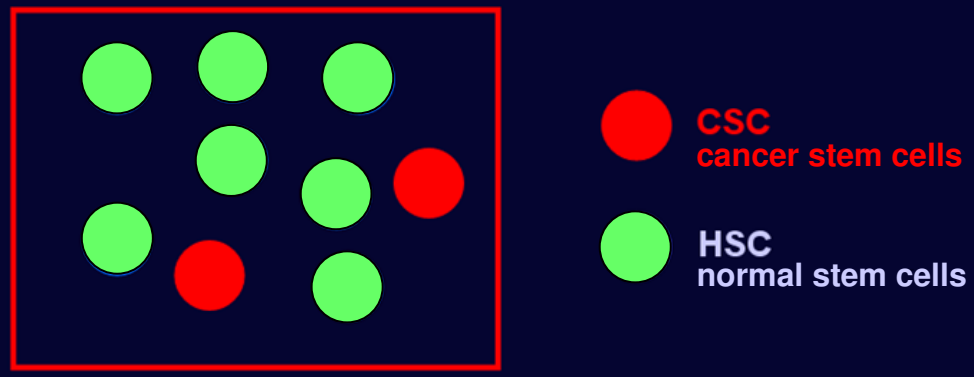
simple stochastic math of cell populations

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 (to, e.g., another compartment);*
- HSC *may suffer mutations and transform into CSC.*

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

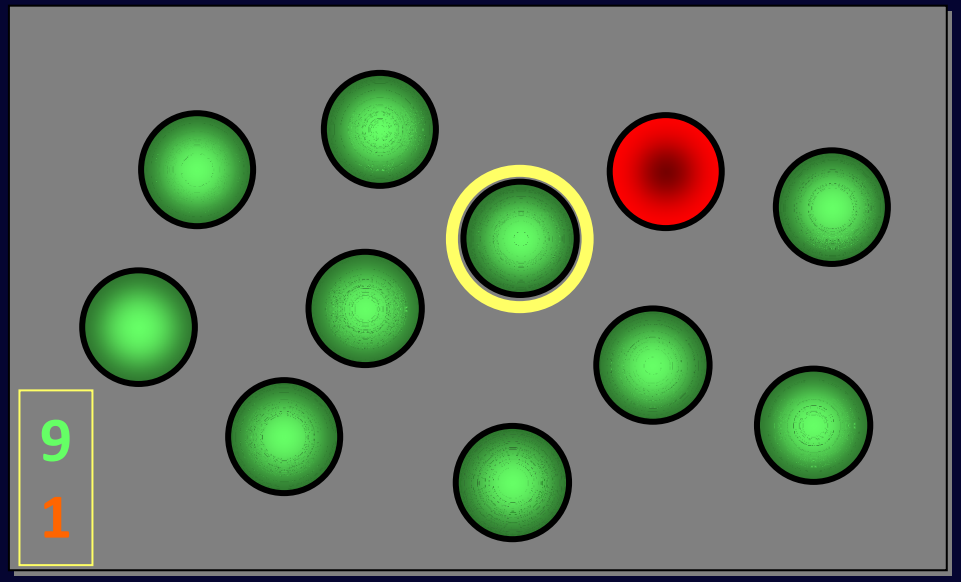
this stochastic model is known in
mathematics (& population genetics)
as a
Moran (birth-death) process

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

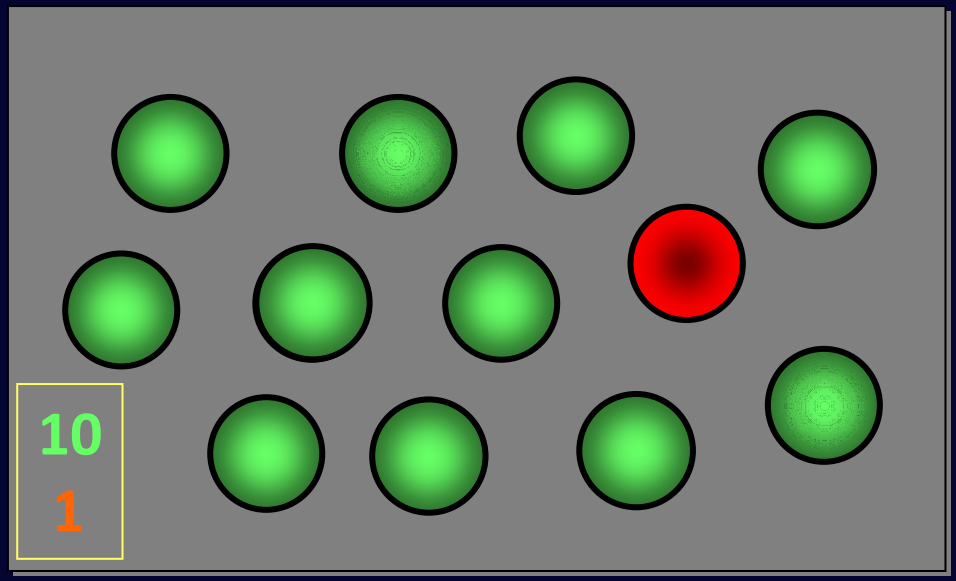
after N events, one time step has elapsed

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

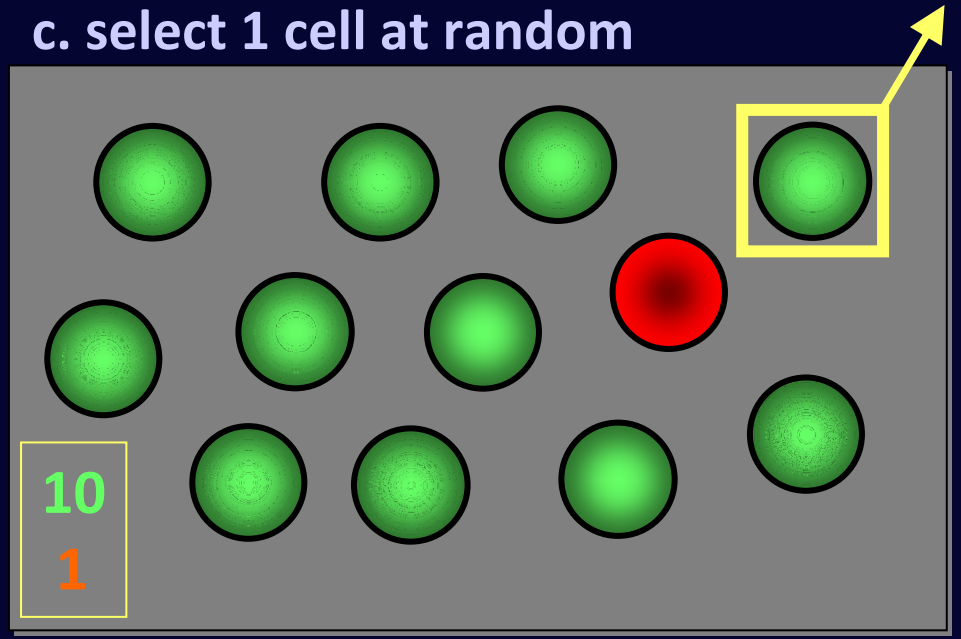
a. select 1 cell proportional to fitness



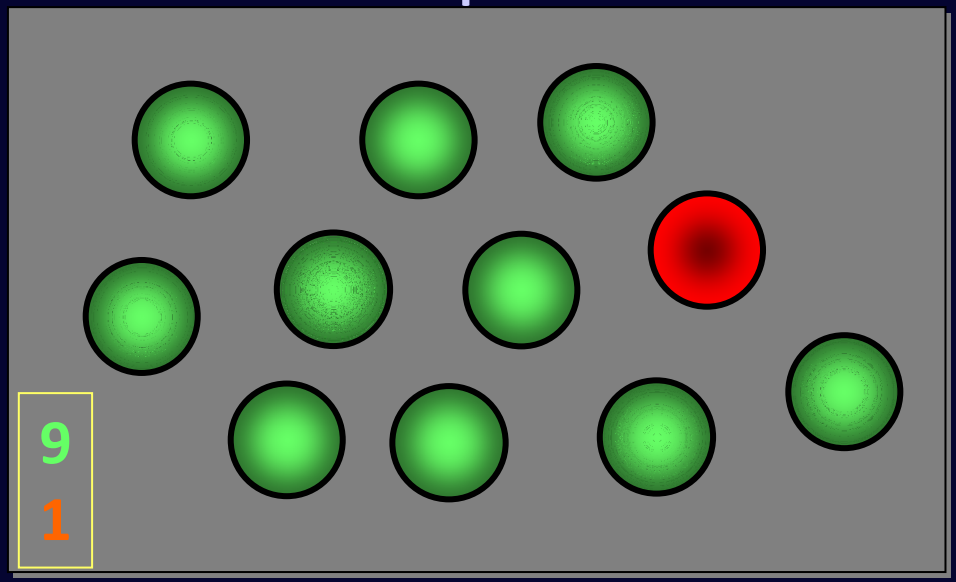
b. chosen cell replicates



c. select 1 cell at random

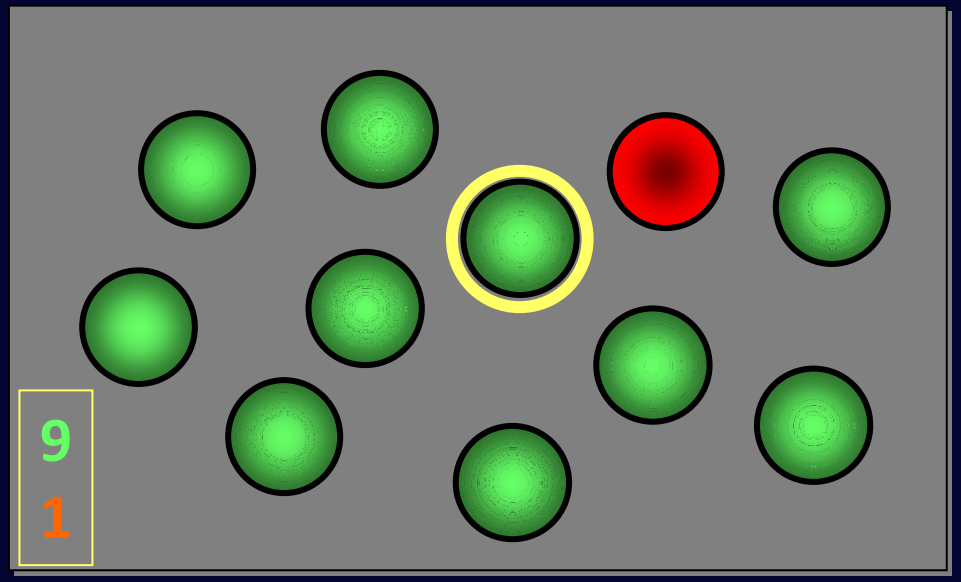


d. chosen cell is exported

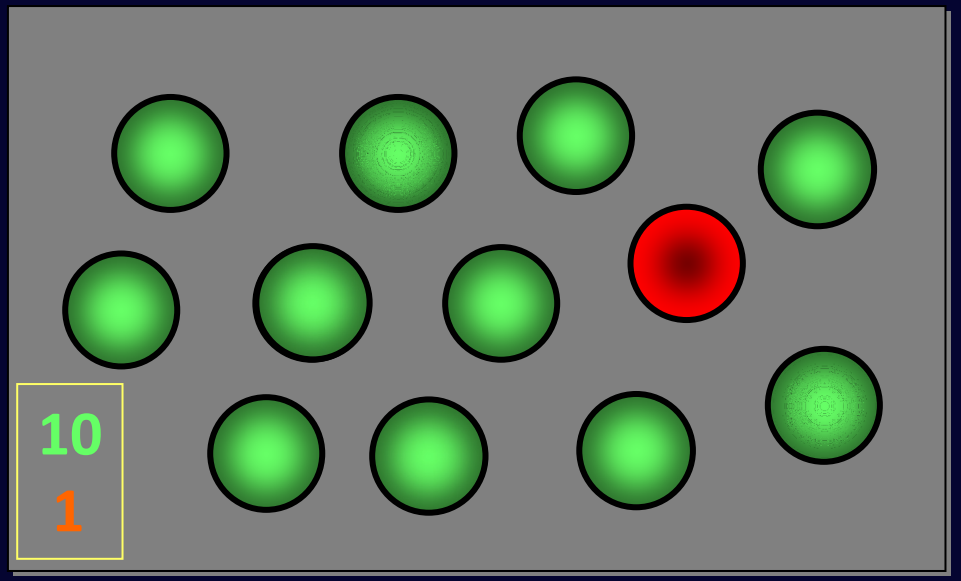


example 2: 1 CSC is exported & CSC-lineage gets extinct

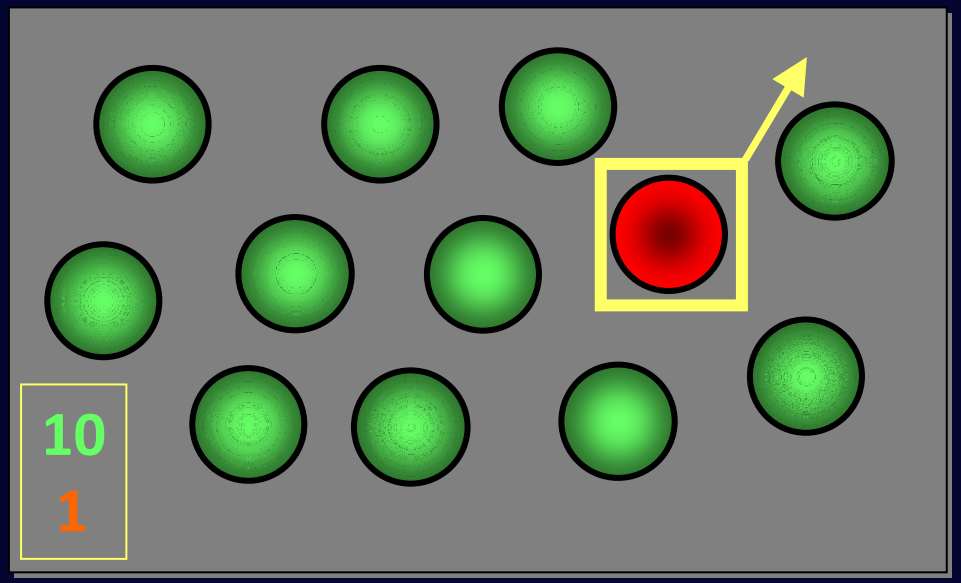
a. select 1 cell proportional to fitness



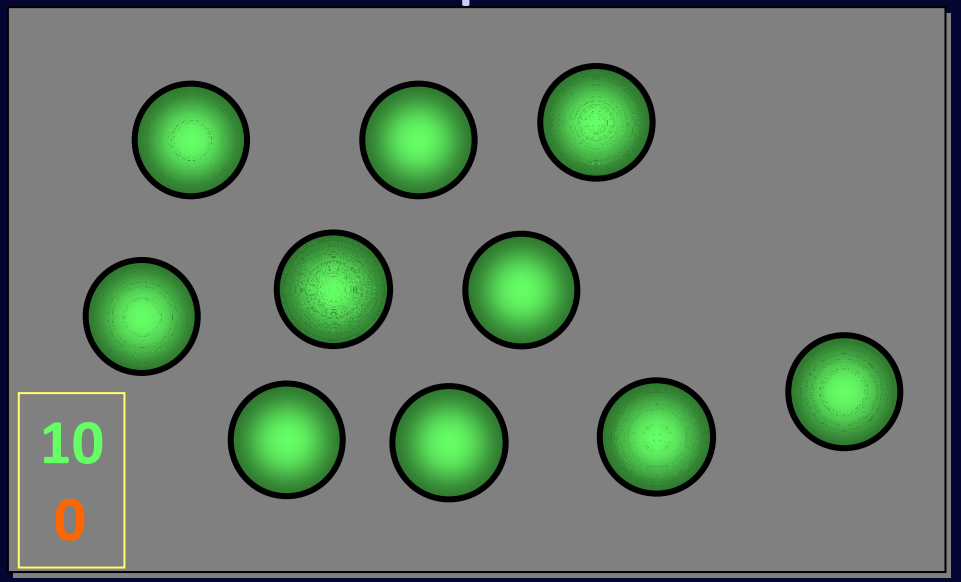
b. chosen cell replicates



c. select 1 cell at random

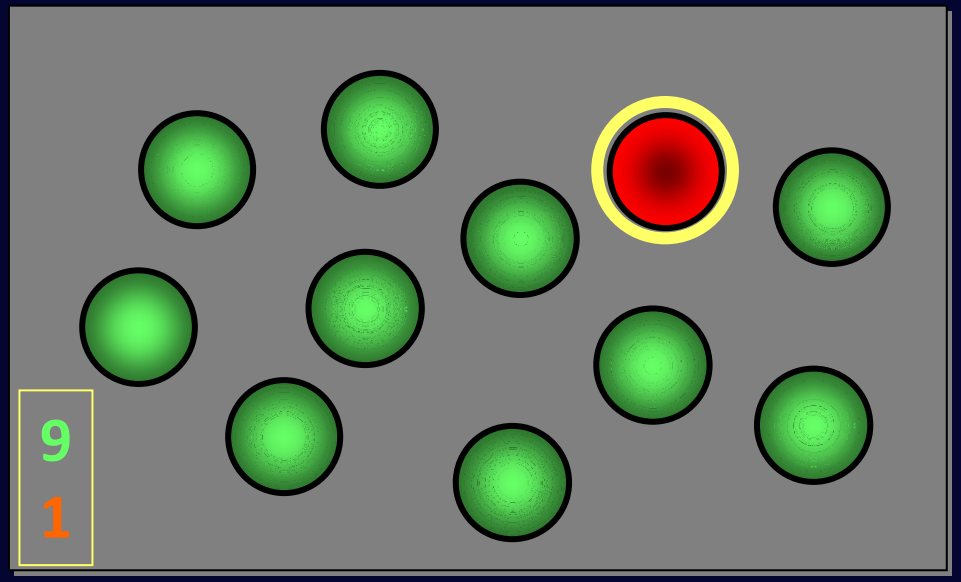


d. chosen cell is exported

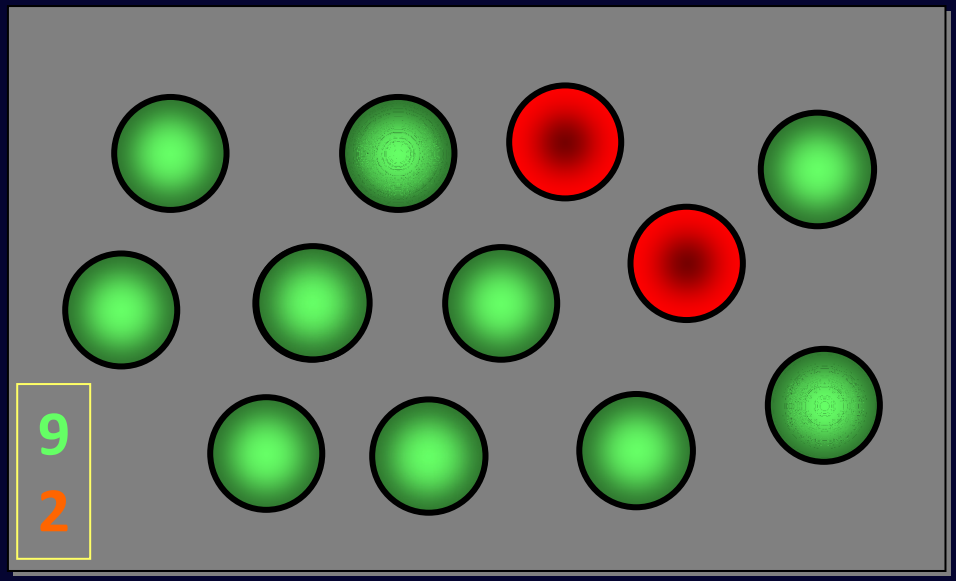


example 3: 1 HSC is exported & CSC number increases by 1

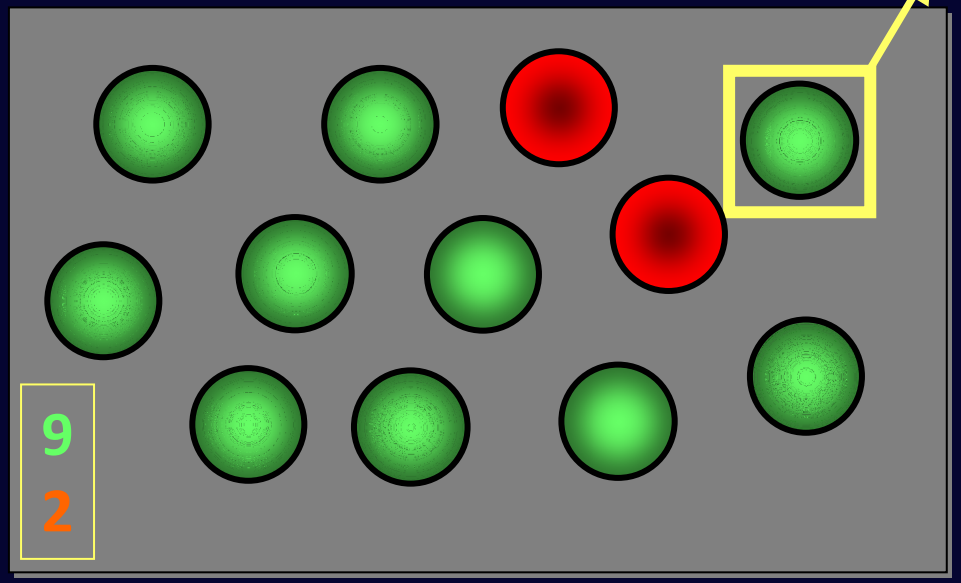
a. select 1 cell proportional to fitness



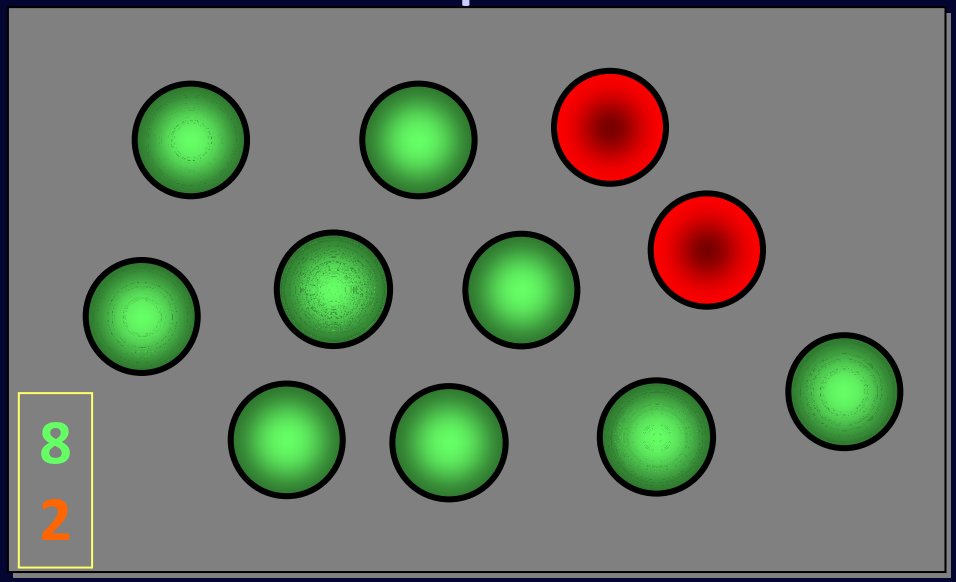
b. chosen cell replicates



c. select 1 cell at random

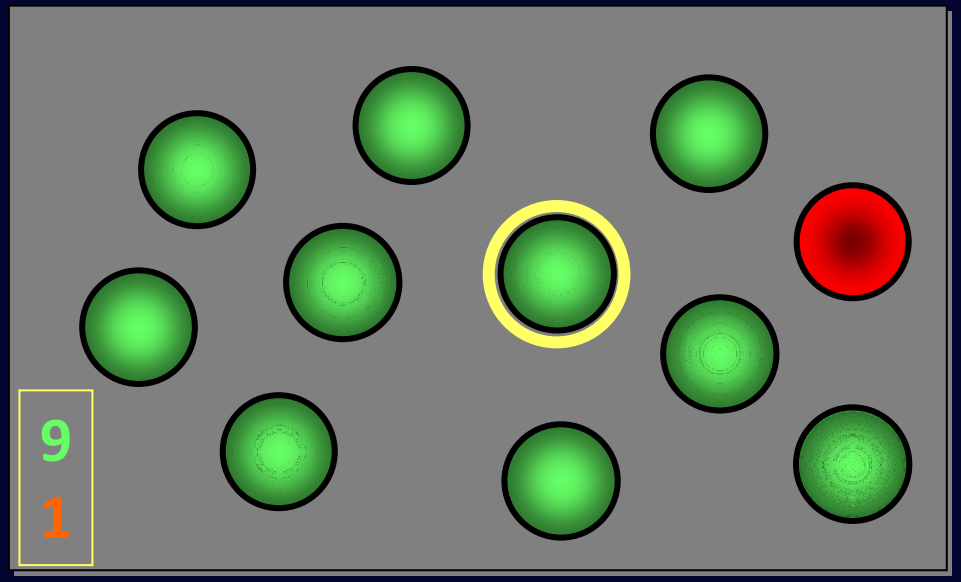


d. chosen cell is exported

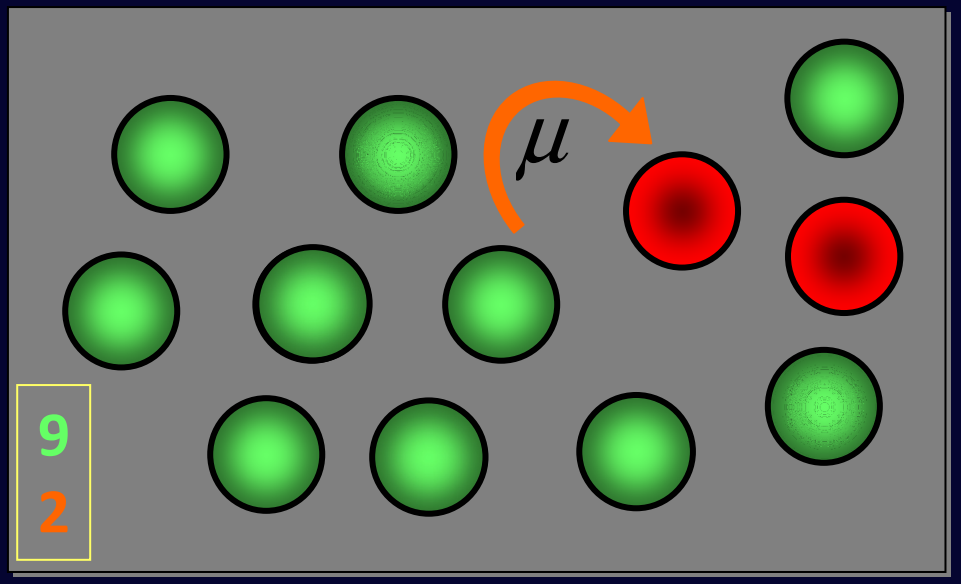


example 4: HSC mutations enter scene to make things worse

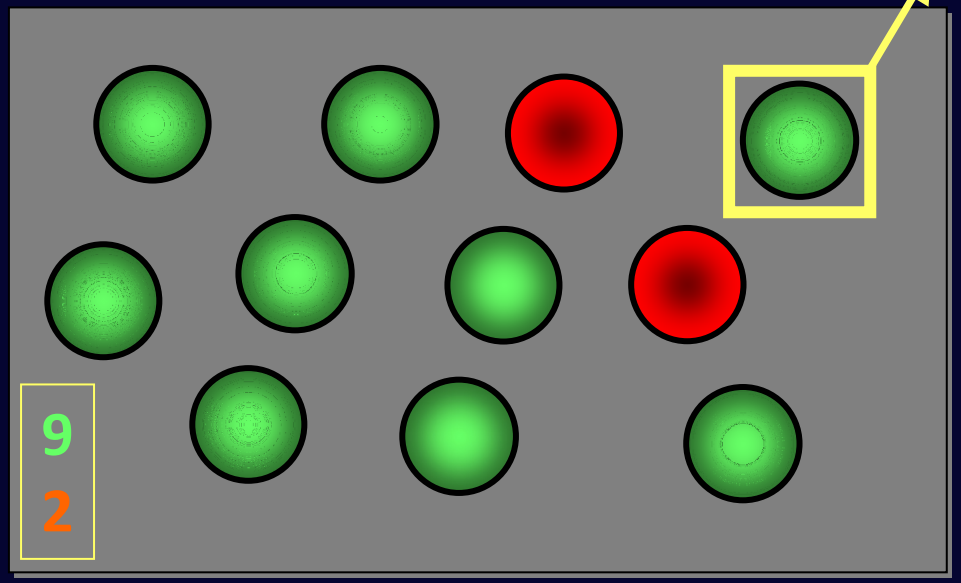
a. select 1 cell proportional to fitness



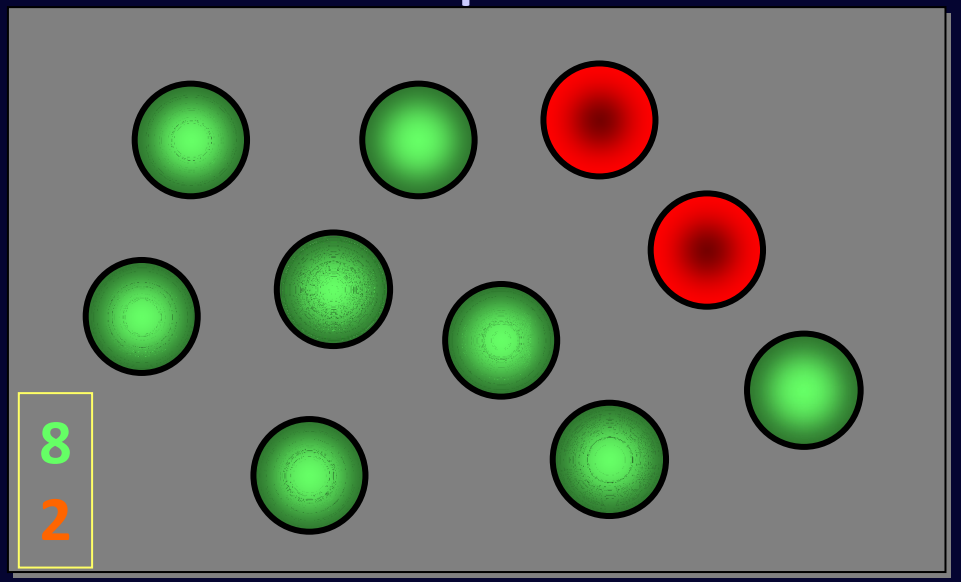
b. chosen cell replicates & mutates



c. select 1 cell at random

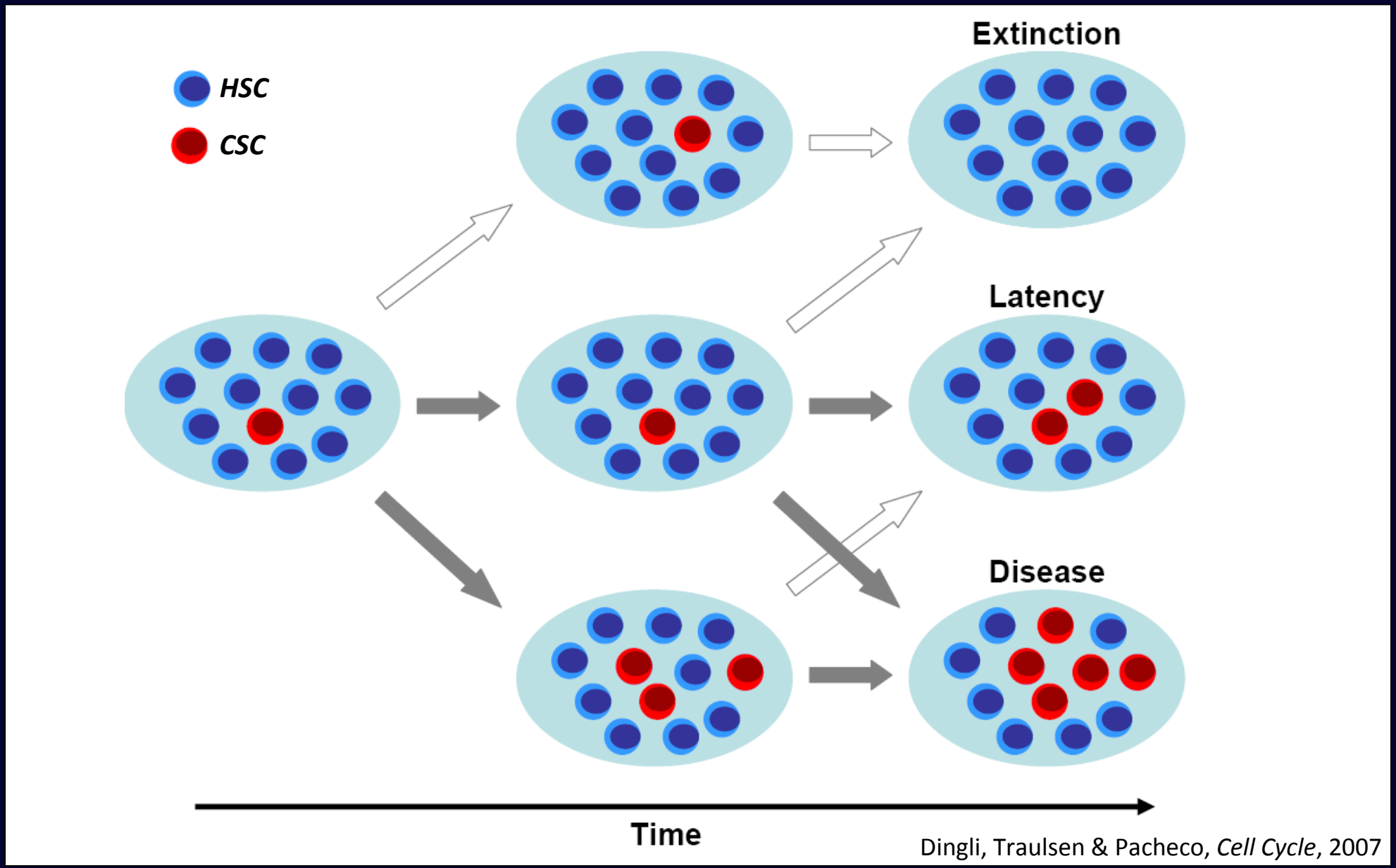


d. chosen cell is exported



stochastic dynamics of *HSC*

several possible scenarios :



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

stochastic dynamics of *HSC*

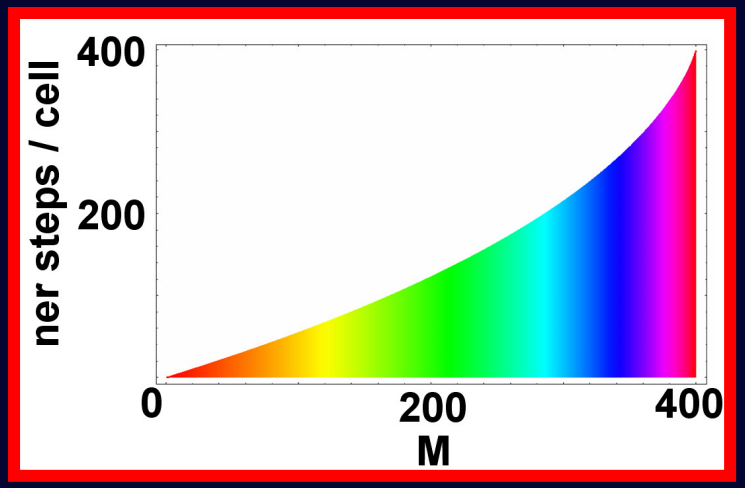
this model has been well-studied & results have been worked-out:

fixation probability

$$\phi_j^{N_k} = \frac{1 - r^{-j}}{1 - r^{-N_k}} \xrightarrow[\text{(neutral)}]{r \to 1} \frac{j}{N_k}$$

average fixation times (neutral drift)

$$t_1^M = \frac{N_0}{M} \sum_{i=1}^{M-1} \frac{M - i}{N_0 - i}$$



***important detail** : animals have a finite lifespan . . .*

stochastic dynamics of *HSC*

. . . which means there may be no time for thresholds to be reached

the previous formulas provided ***average values***

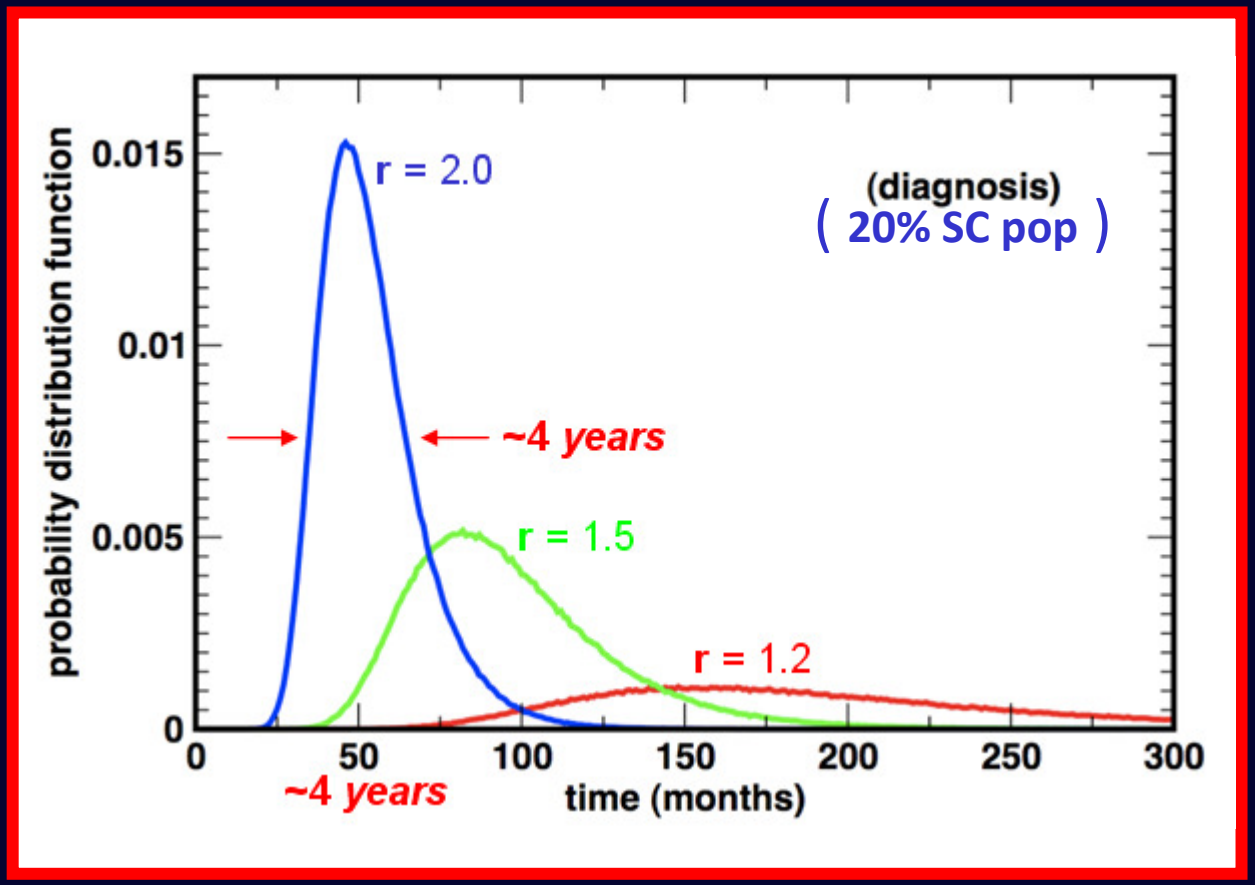
stochastic dynamics → time distributions

disease diagnosis :

20% "blasts" in AML
(acute myeloid leukemia)

10% of plasma cells in MM
(multiple myeloma)

how much time is required for a mutation to develop and give rise to diagnosis of a hematopoietic disorder ?

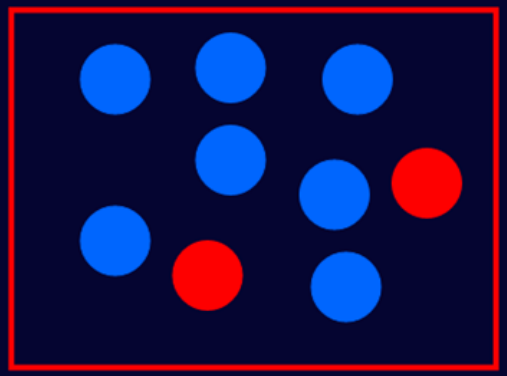


Dingli, Traulsen & Pacheco, *Cell Cycle*, 2007

stochastic protection

THE MOST ROBUST MAMMAL

protection : the *best* of mammals



N cells

CSC
cancer stem cells

HSC
normal stem cells

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

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

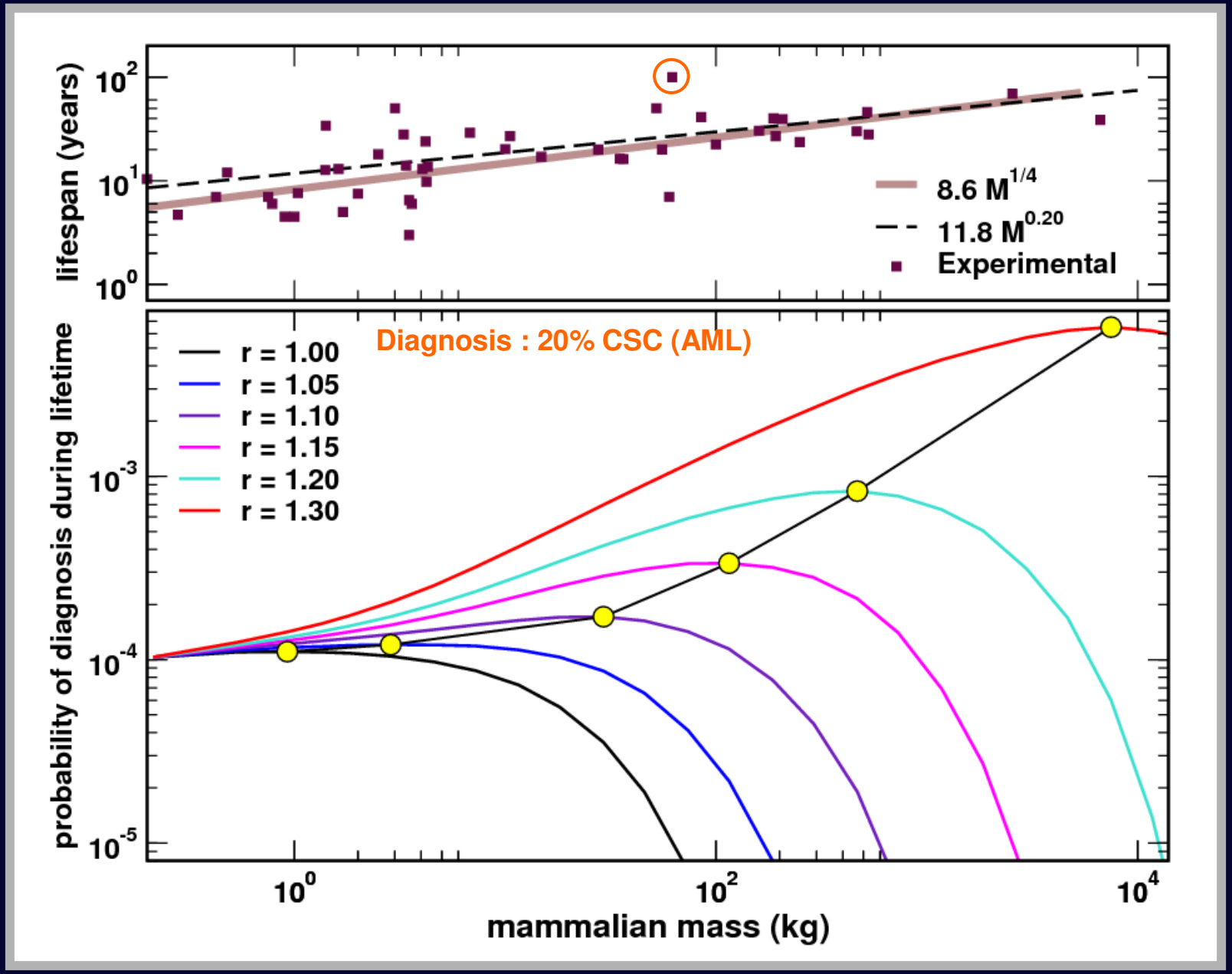
mass specific metabolic rate : $B_c \sim M^{-1/4}$

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



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

protection : the *best* of mammals

- ***r** is very difficult to determine experimentally; unfortunately, practitioners believe that **r** should be 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).*

neutral evolution

PAROXYSMAL NOCTURNAL HEMOGLOBINURIA

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

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

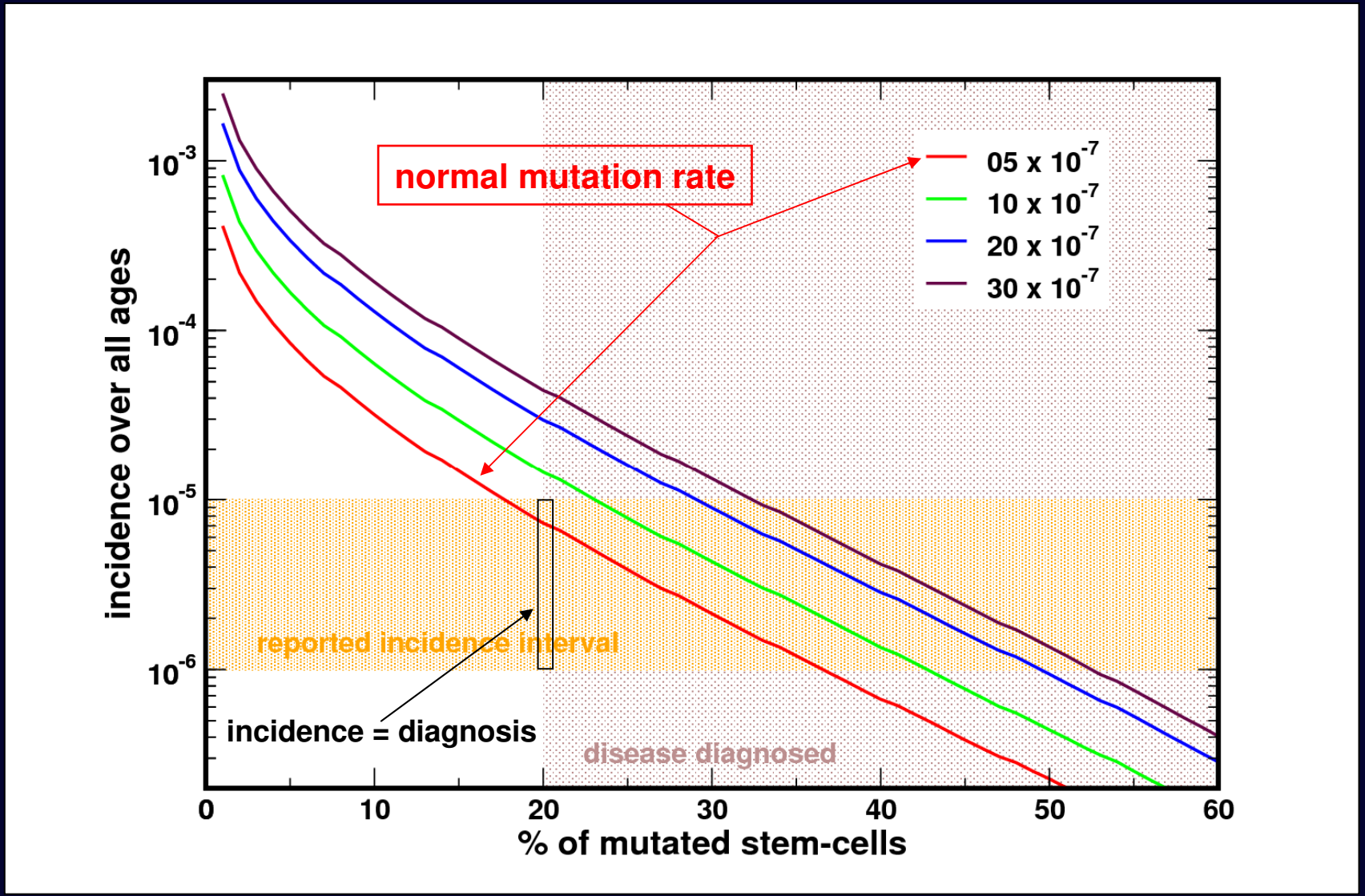
- *relative fitness advantage* of PNH cells due to an imunne attack to normal HSC → disease expansion

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

scaling across mammals

in

CYCLIC NEUTROPENIA

Dingli, Antal, Traulsen & Pacheco, Cell Proliferation 42 (2009) 330-338
Pacheco, Traulsen, Antal & Dingli, American Journal of Hematology, 83 (2008) 920

cyclic neutropenia

Dingli, Antal, Traulsen & Pacheco, Cell Proliferation 42 (2009) 330-338
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*

cyclic neutropenia

there is a study on mice which claims there is no CN

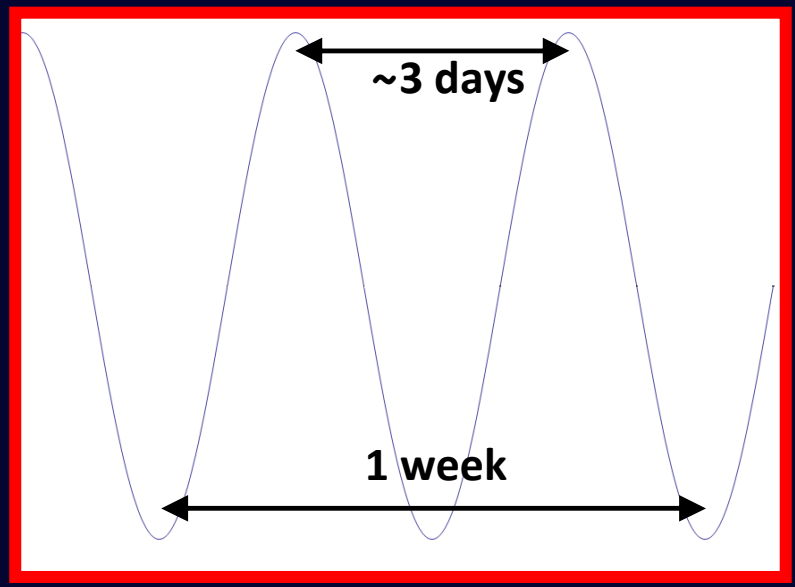
- *is that true ?*
- *what did they do ?*
- *they measured neutrophil count every week . . .*

cyclic neutropenia

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 never observe oscillations*



progenitor driven
CHRONIC MYELOID LEUKEMIA

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

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* & *nilotinib* (*abl-kinase inhibitors*)**
- **several data sets available**
  - Michor *et al, Nature*, 2005
  - Roeder *et al, Nature Medicine*, 2006
  - other data recently available for ***nilotinib*** **(GIMEMA study)**
- **data fitting**

model features

disease development

- use model of *tree - architecture*
- 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*

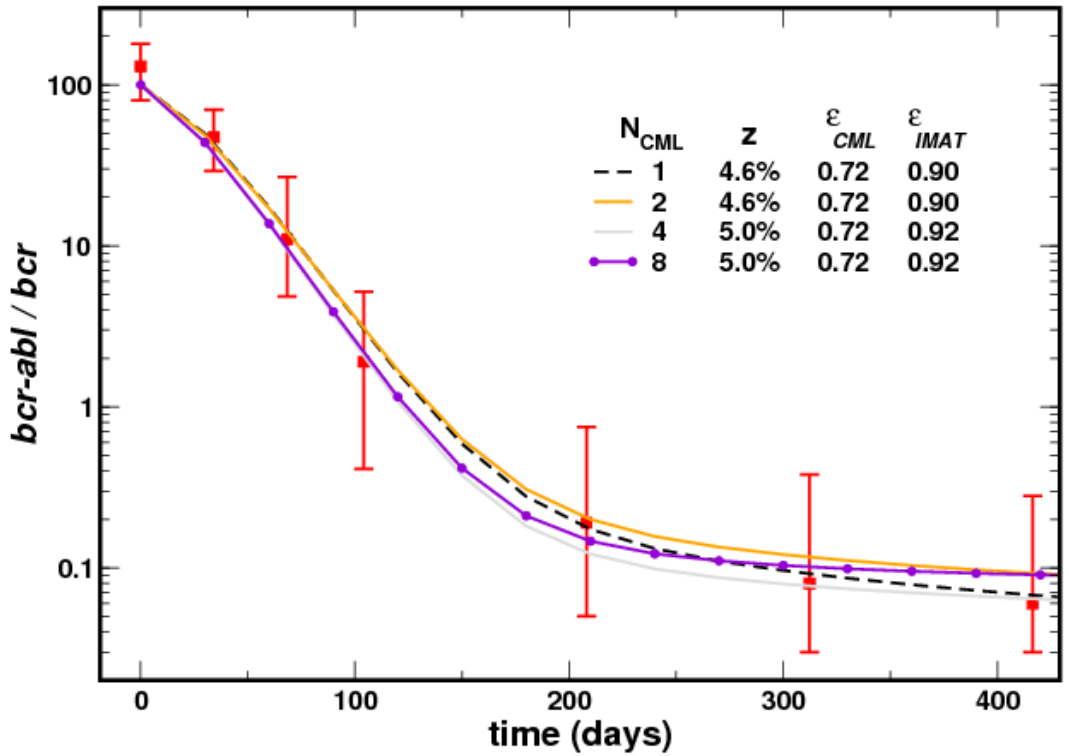
CML dynamics under *imatinib*

we define (deterministic model . . .)

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

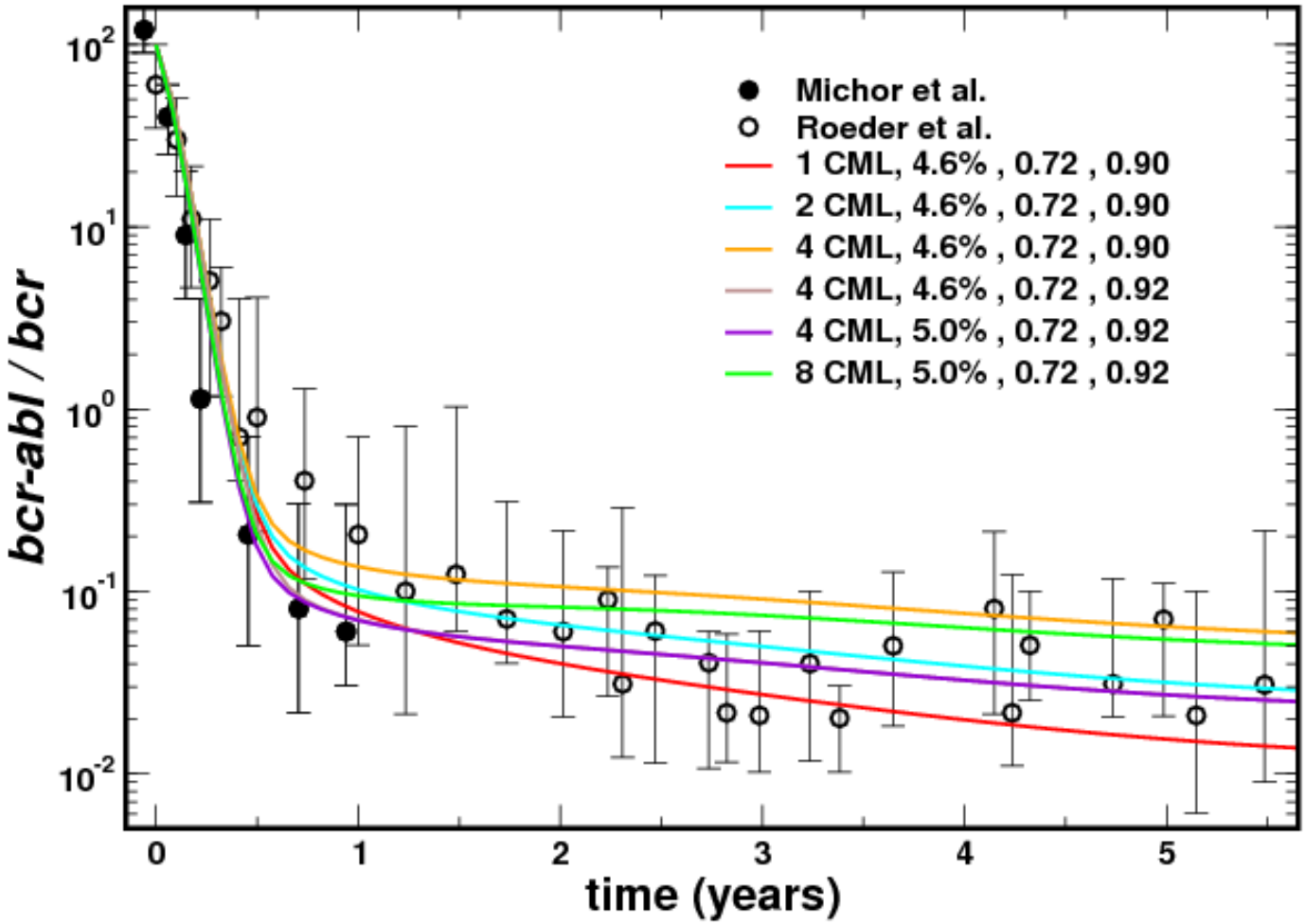
input rate from compartment "i-1" $b_{i-1} = 2 \cdot \varepsilon \cdot r_{i-1}$

$$\frac{dN_i^{CML}}{dt} = -(1-z) \cdot d_i^{CML} \cdot N_i^{CML} - z \cdot d_i^{IMAT} \cdot N_i^{CML} + (1-z) \cdot b_{i-1}^{CML} N_{i-1}^{CML} + z \cdot b_{i-1}^{IMAT} N_{i-1}^{CML}$$



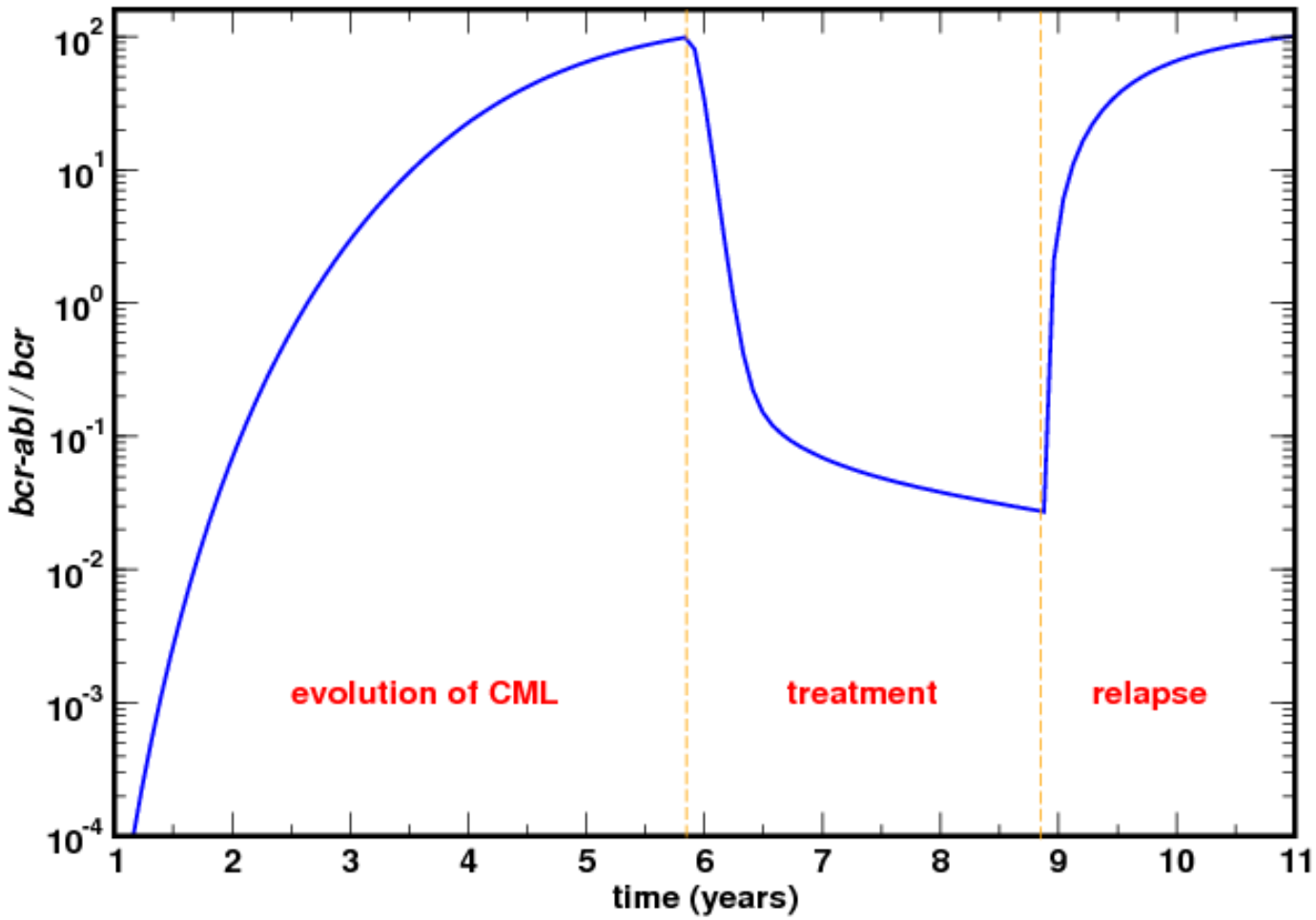
fit to Michor *et al.* data

results



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

features



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

features of CML

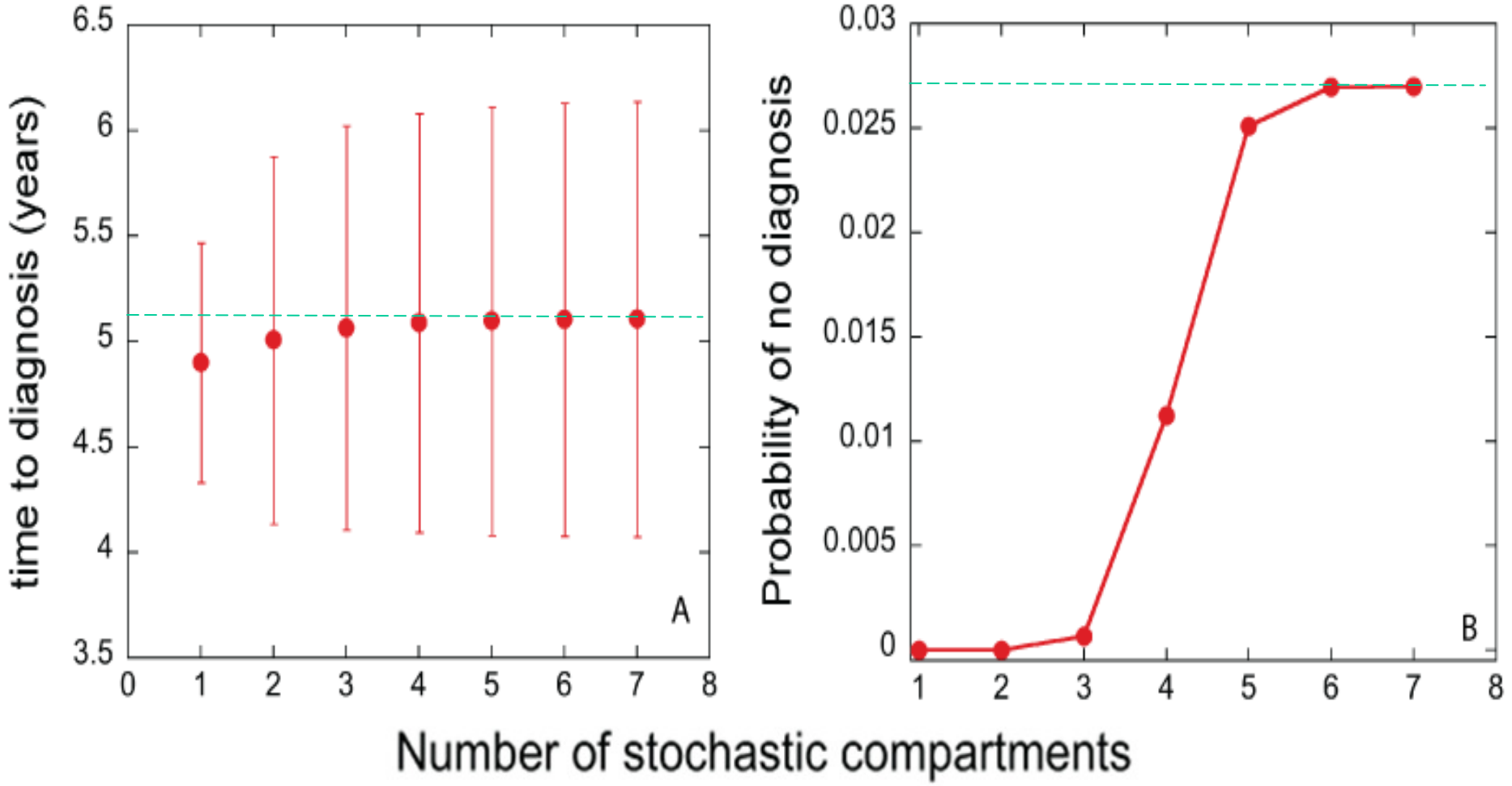
- CML is driven by a small number of neoplastic stem cells
- *imatinib* reduces the fitness of the neoplastic cells
- many CML progenitors persist
- only a fraction of CML cells are responding to therapy at any time
- relapse is driven by CML progenitors not just HSC

***BUT* :**

- **hematopoiesis is stochastic in nature**

what is the impact of stochastic effects on CML dynamics ?

stochasticity in CML

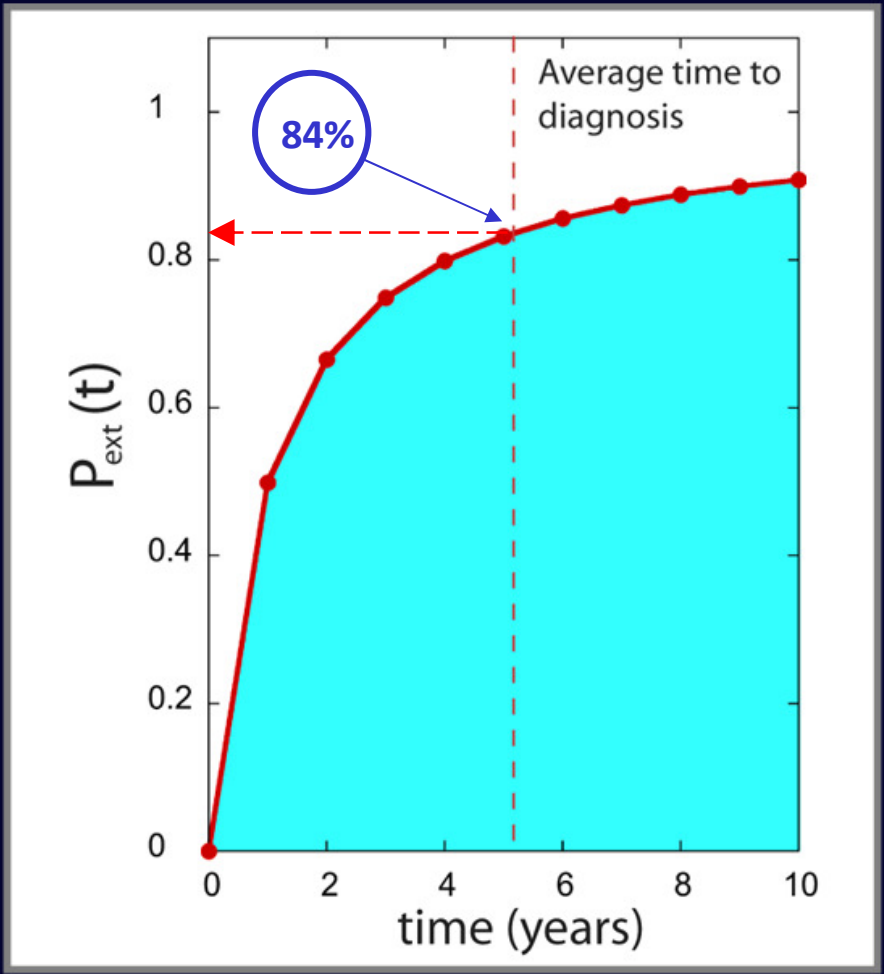


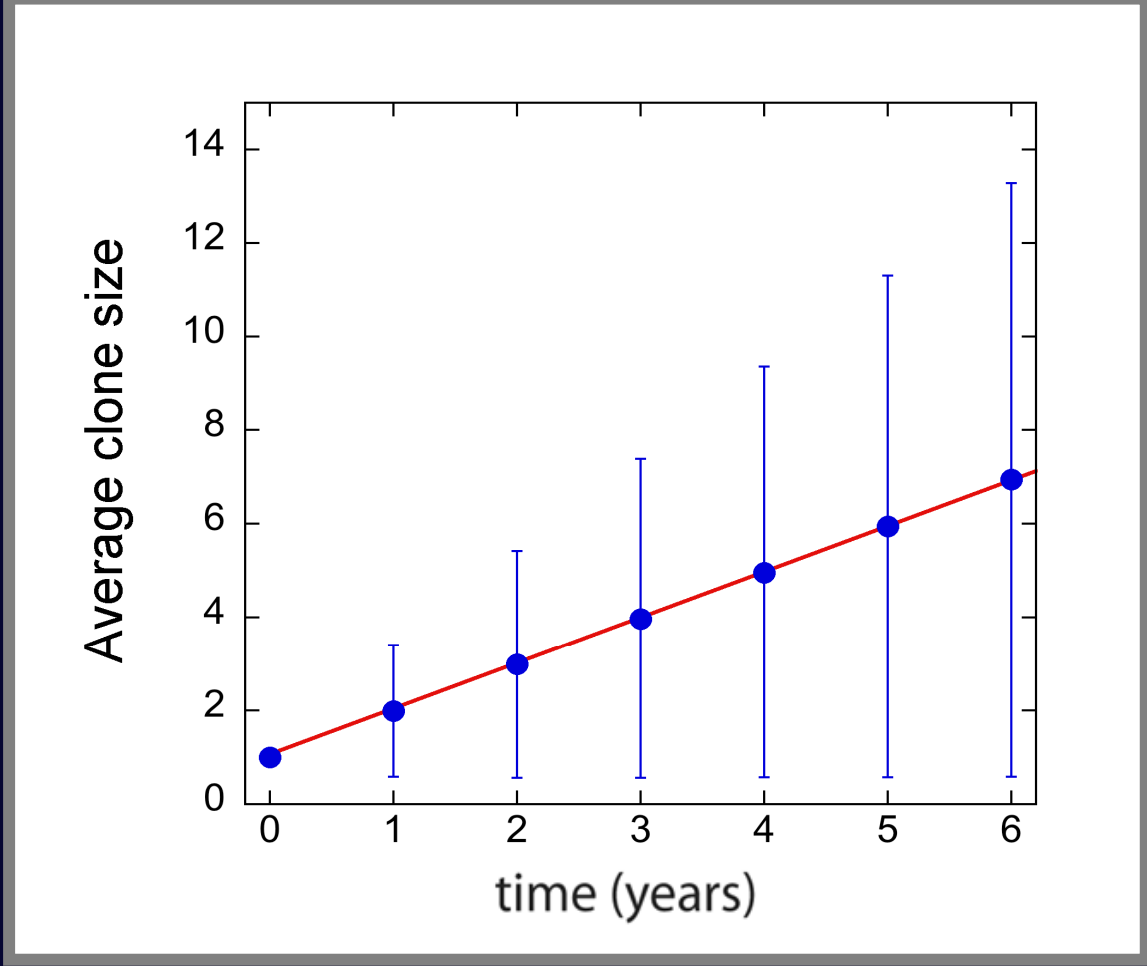
Tom Lenaerts et al., Haematologica 95 (2010) 900-907

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

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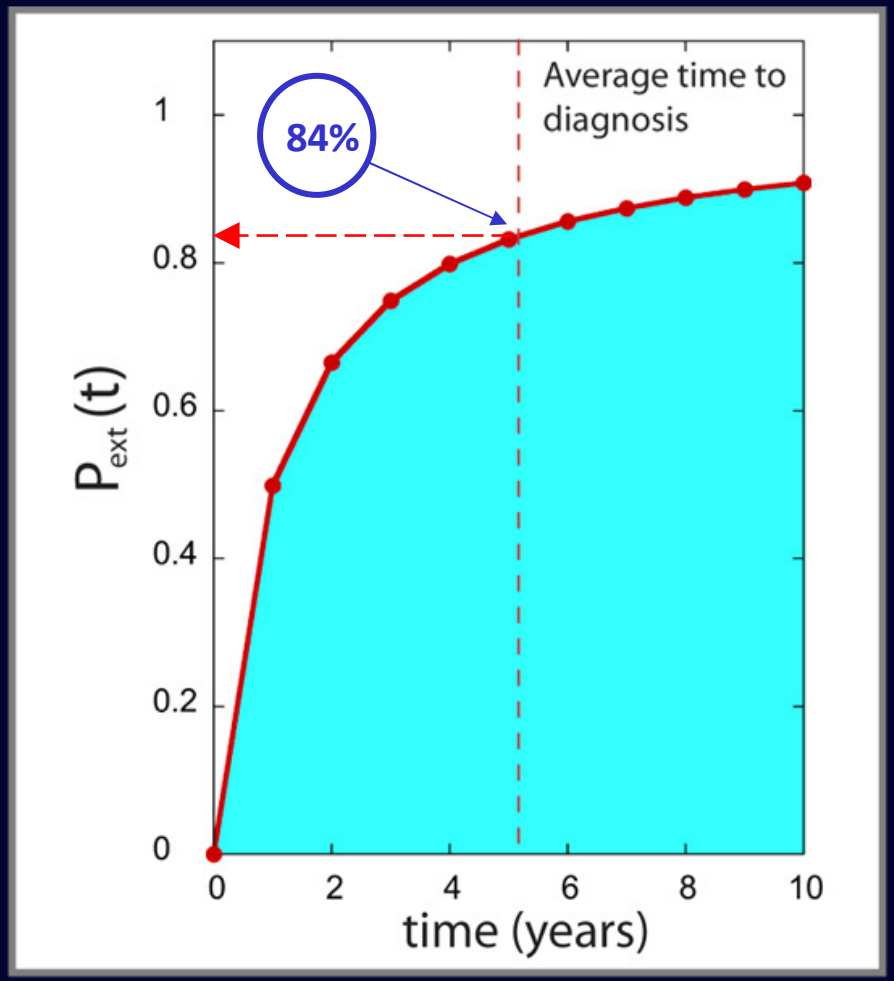
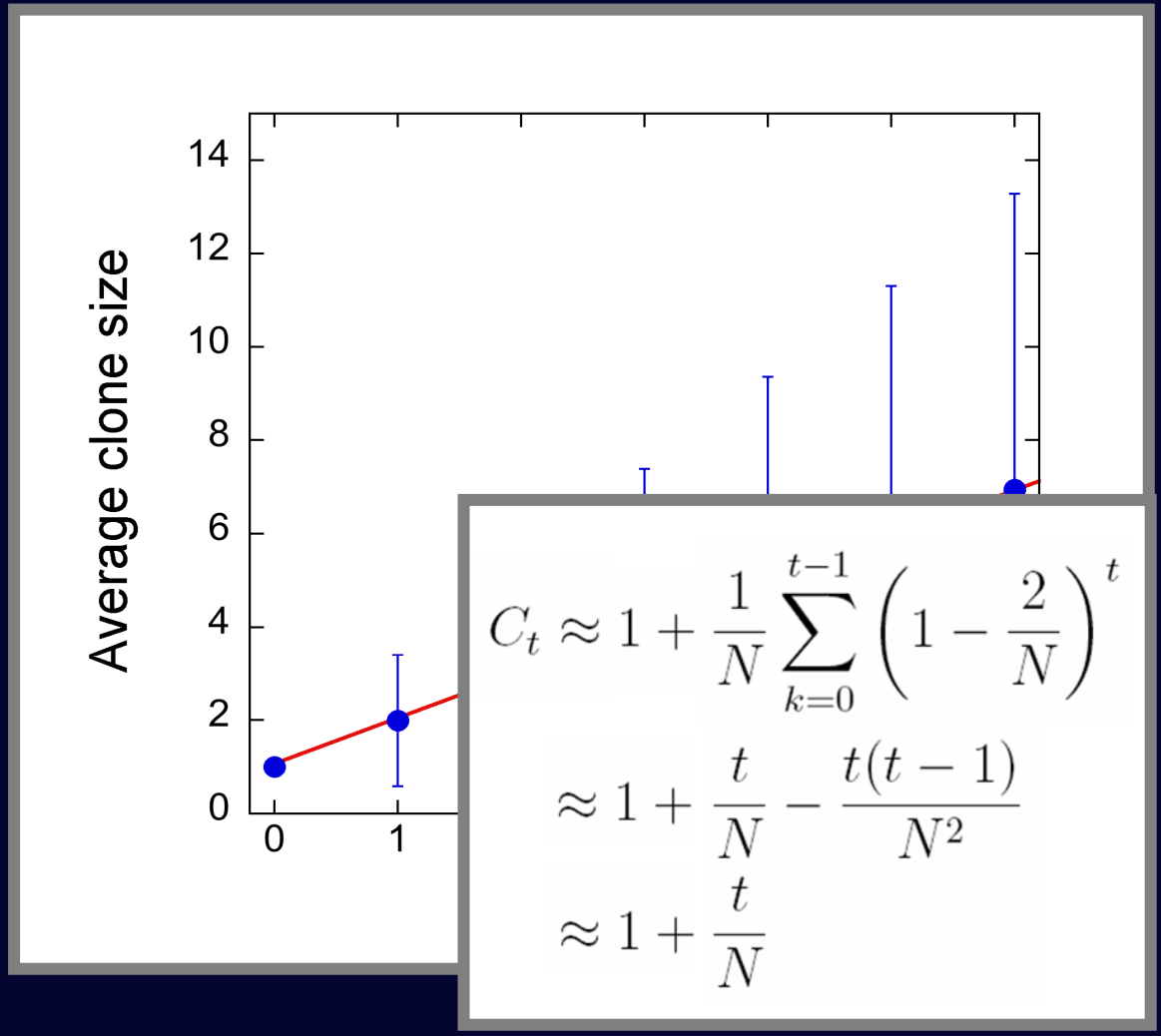




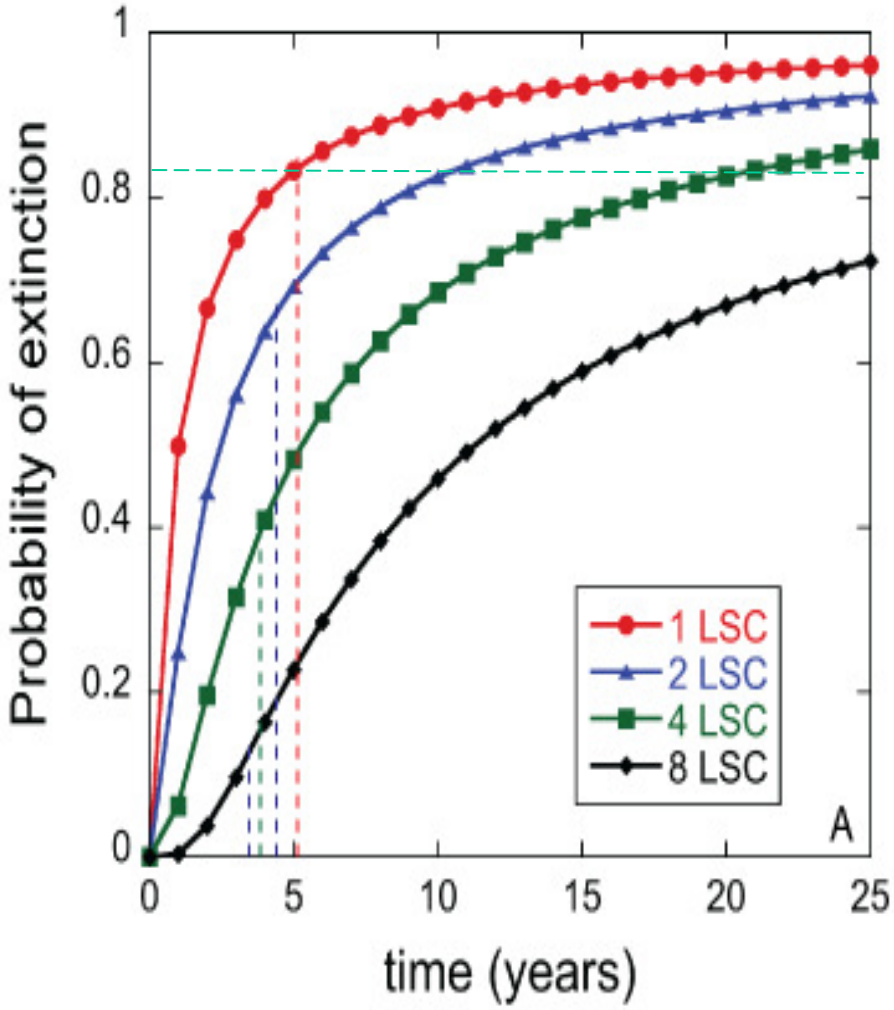
$$C_t \approx 1 + \frac{1}{N}\sum_{k=0}^{t-1}\left(1-\frac{2}{N}\right)^t$$

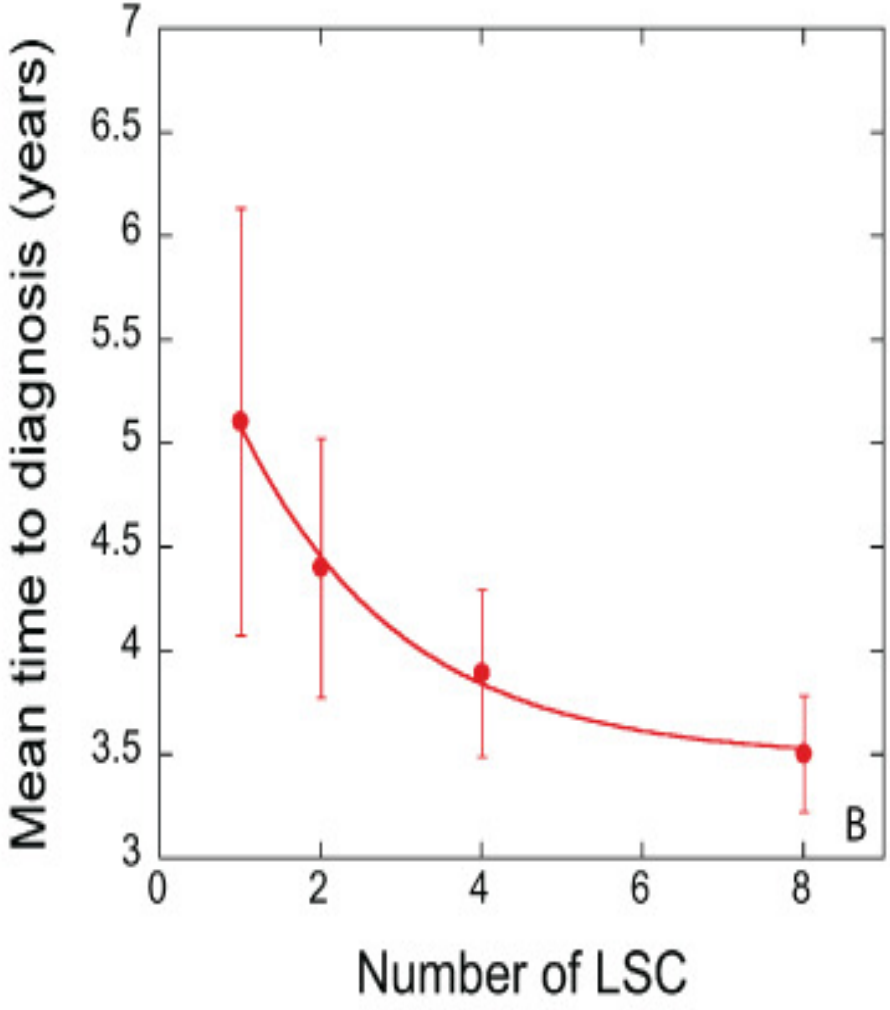
$$\approx 1 + \frac{t}{N} - \frac{t(t-1)}{N^2}$$

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

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

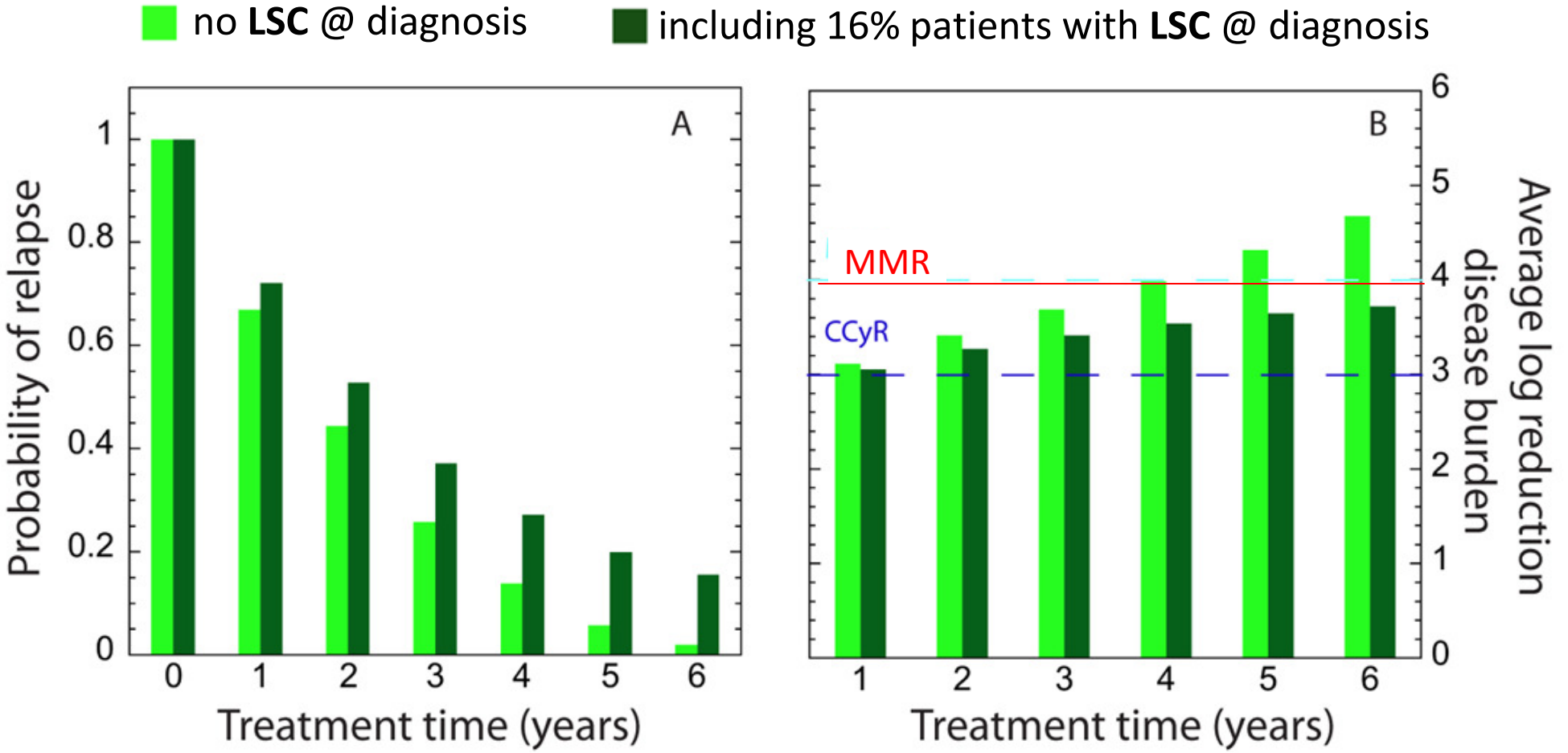
stochasticity in CML





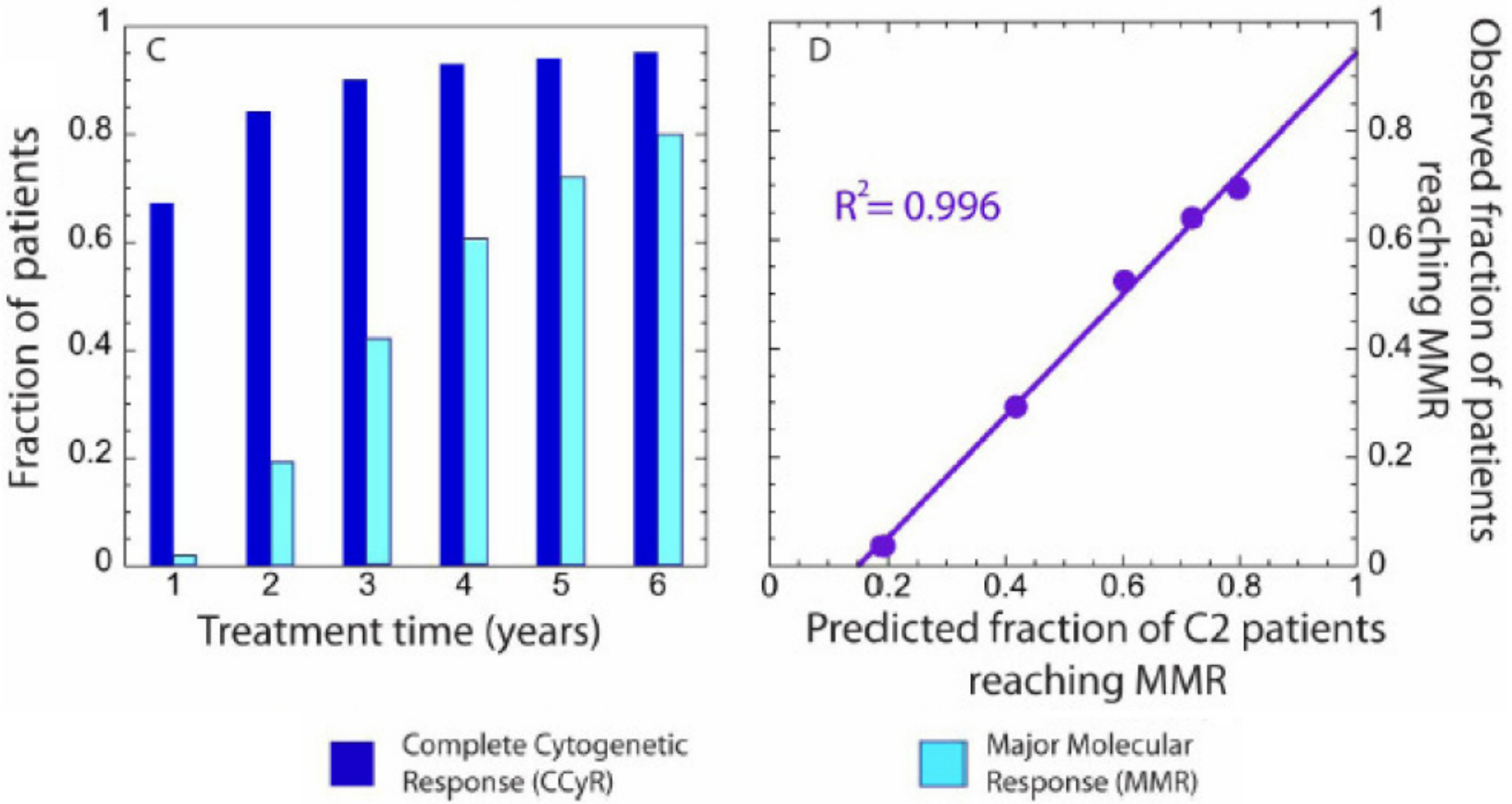
Tom Lenaerts et al., Haematologica 95 (2010) 900-907

stochasticity in CML

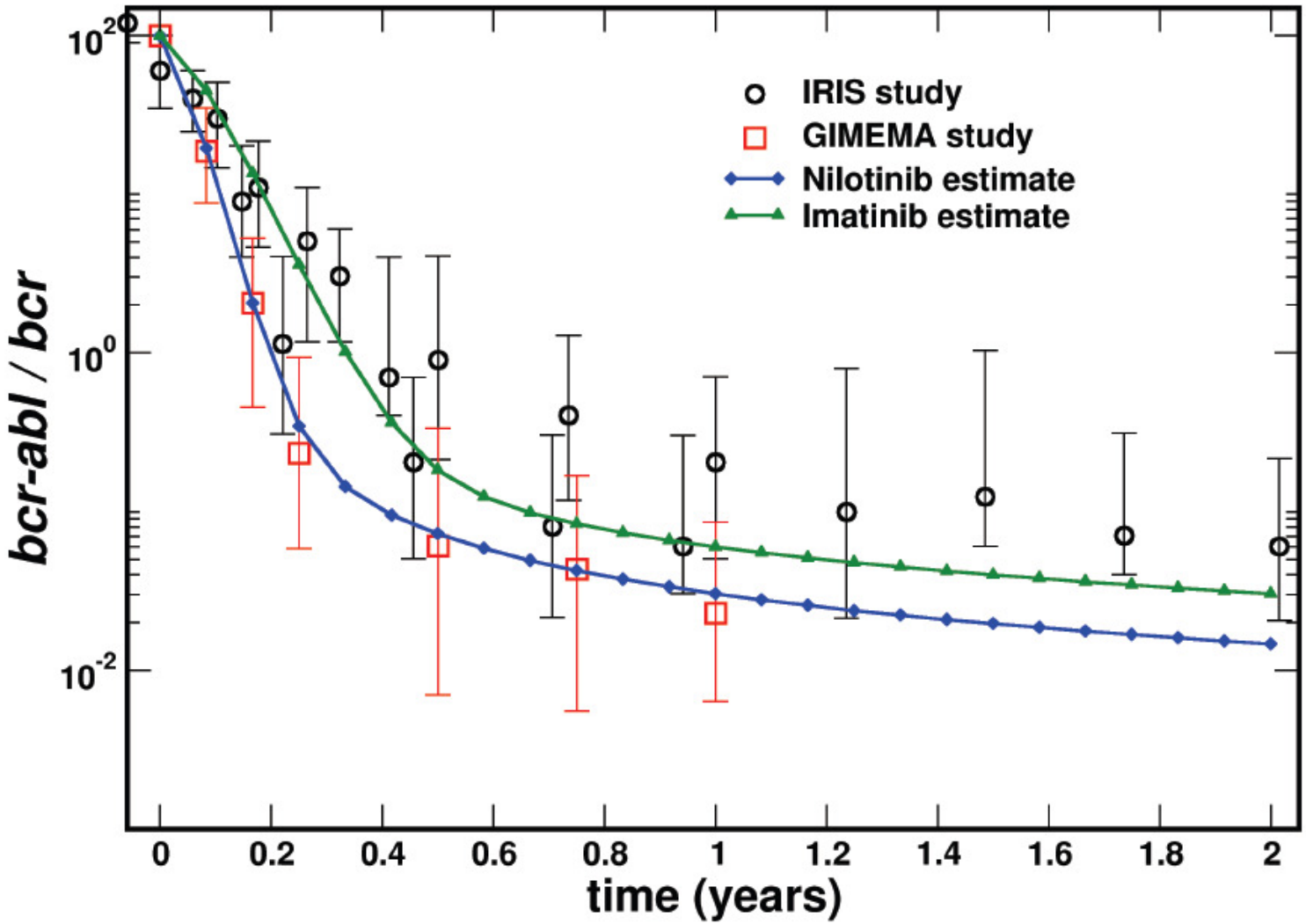


despite *NOT* affecting directly CSC,
***imatinib* + natural selection can cure the majority of CML patients**
missing: development of resistance . . .

stochasticity in CML



imatinib ⊗ nilotinib



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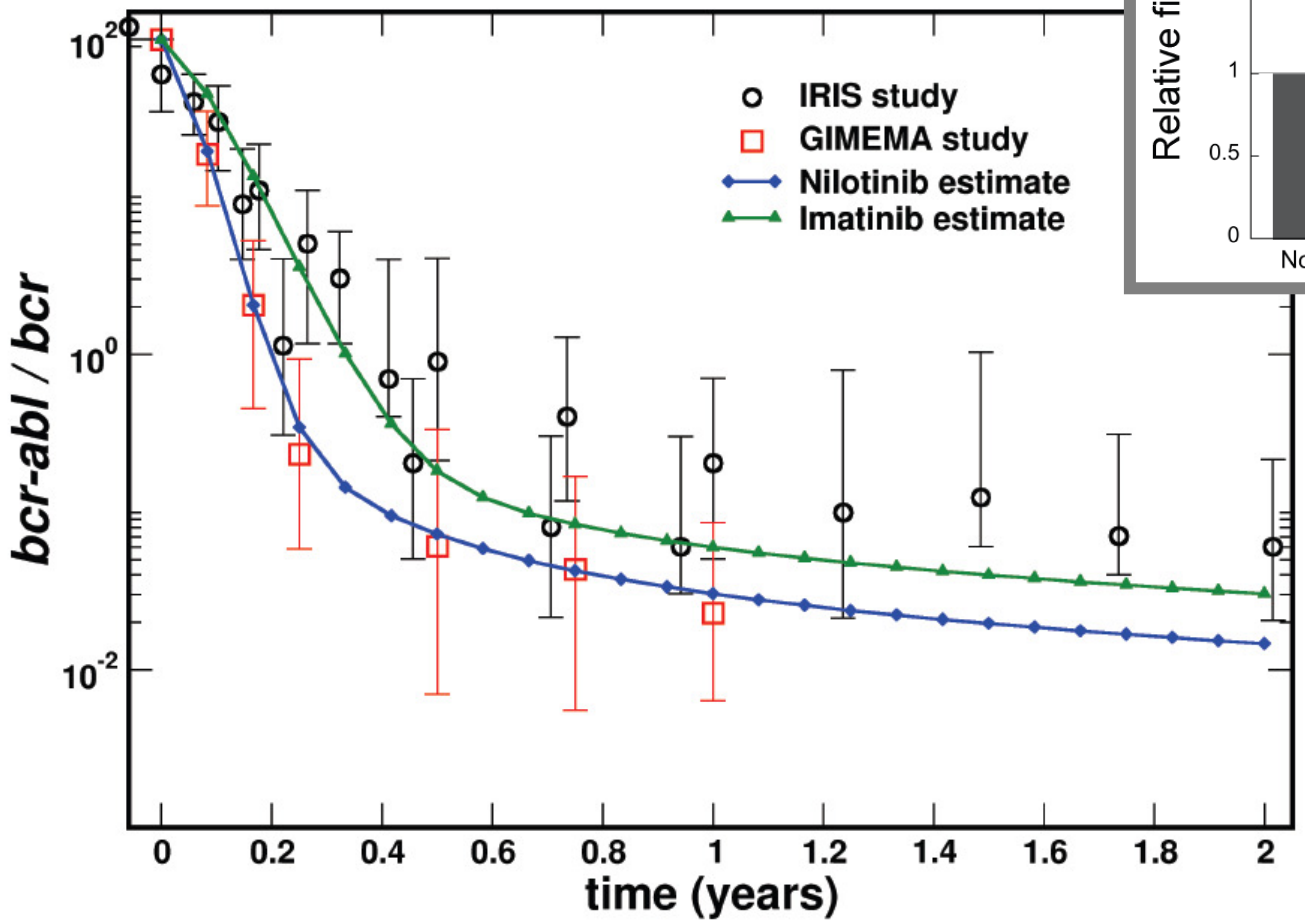

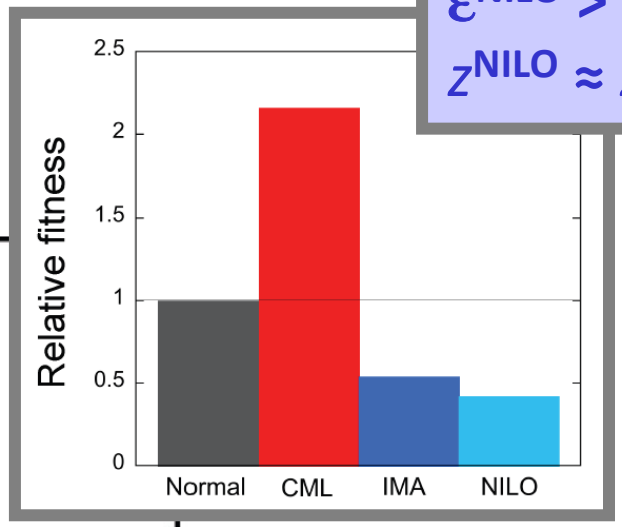

$\varepsilon^{NILO} > \varepsilon^{IMAT}$

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

imatinib ⊗ nilotinib

in vitro **: *no* differences**

in vivo **: *important* differences**

(ecology of cancer cells is important)

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

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