# the evolutionary dynamics of hematopoiesis
## (in health & disease)

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atpgroup

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

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South American Institute for Fundamental Research

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UNIVERSIDADE ESTADUAL PAULISTA
"JÚLIO DE MESQUITA FILHO"

# layout

**friday – 11:15 – 12:30**

- hints for future refinements of the *standard model* (SM)

  telomere length & age

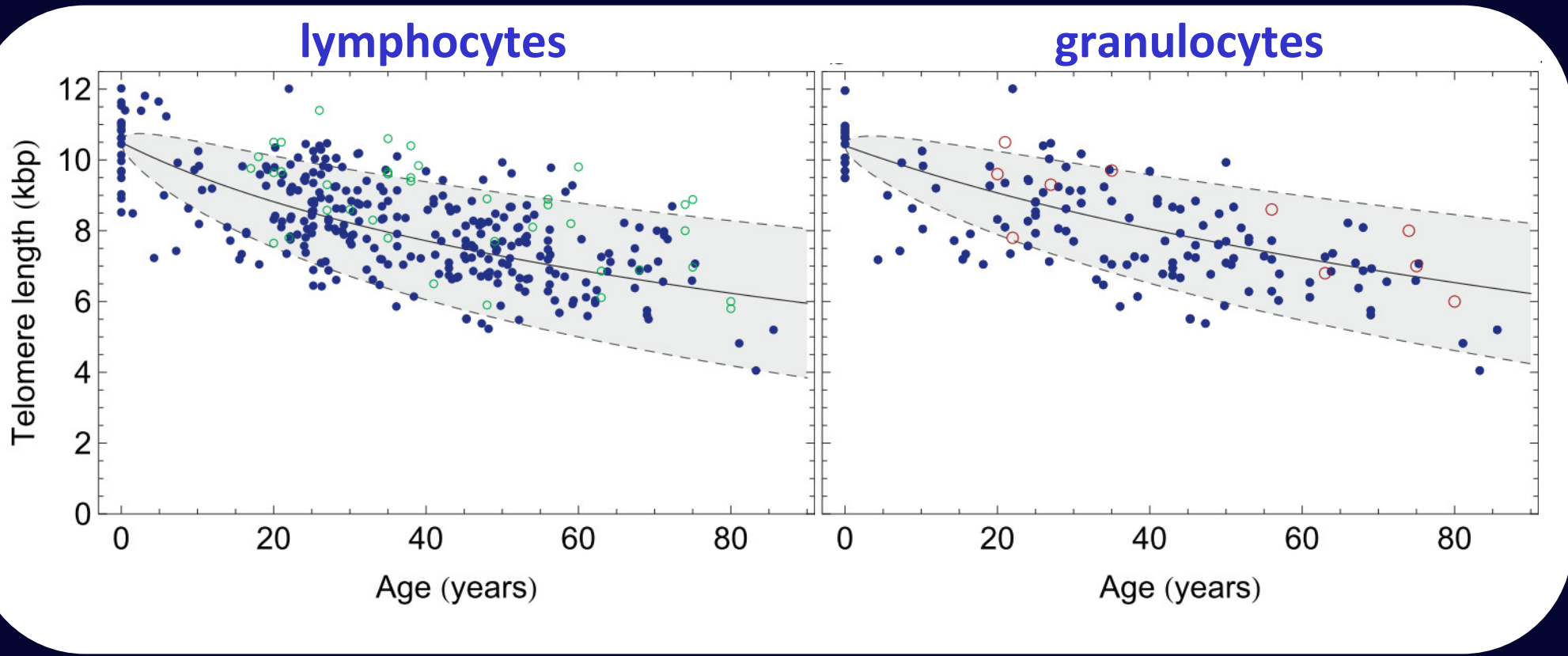
  ontogeny, symmetric and asymmetric cell division

- the ecology of cancer from an Evolutionary Game Theory perspective – a concrete application to yet another hematopoetic disease

# possible refinements of the SM

## telomere length & age

follow-up of telomere length with age in a cohort of 385 patients




same **log during growth** and **linear/log during adulthood** dependence with age is confirmed by an independent follow-up of a 2nd cohort with of 875 healthy humans;

Werner et al, eLife 2015 / 10.7554/eLife.08687

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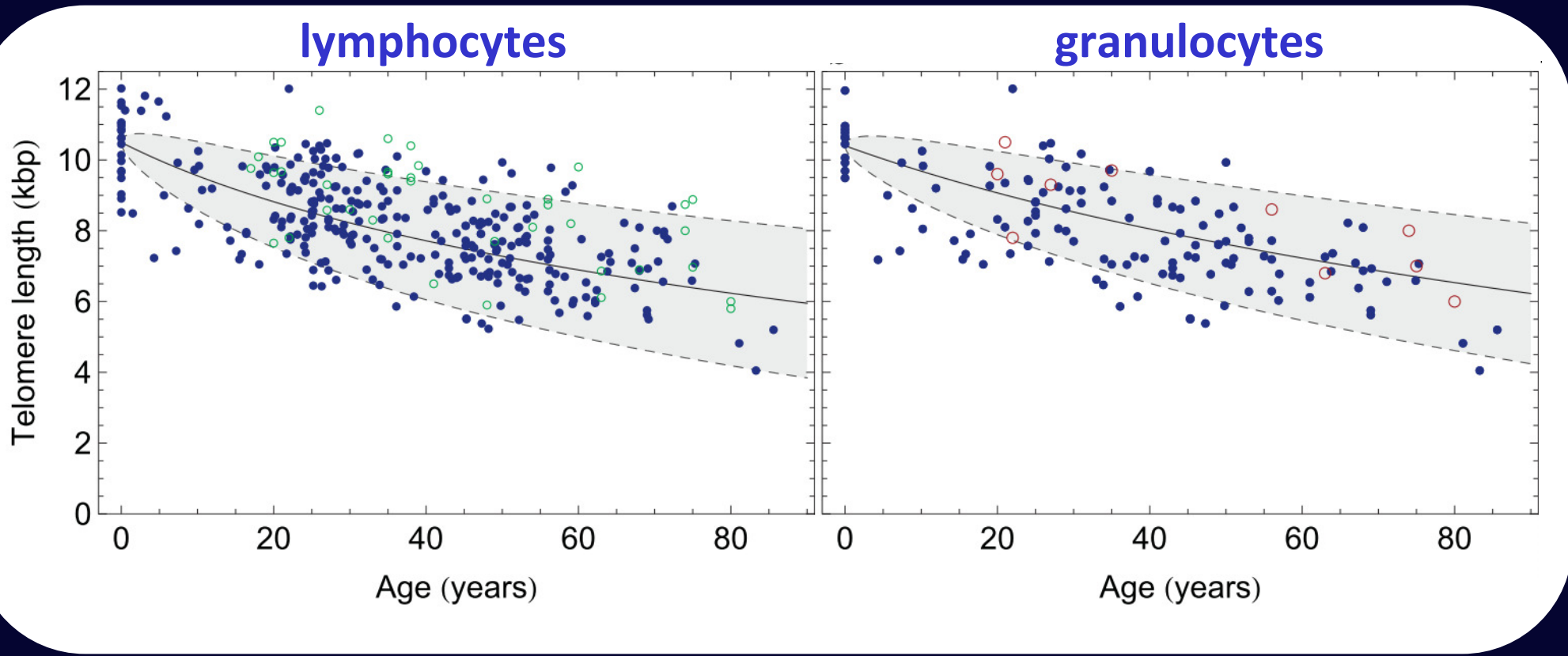


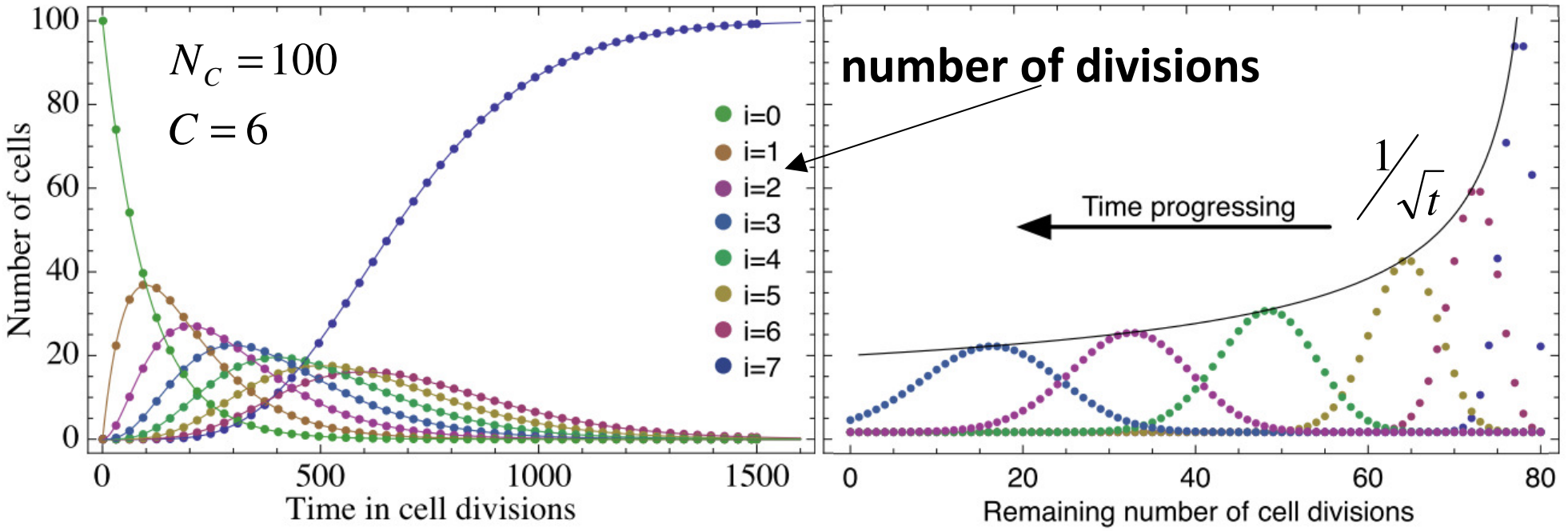

during ontogeny, cell replication rates may change in time & symmetric self-renewal as well as asymmetric cell division are more likely (log) than in adulthood (lin).

Werner et al, eLife 2015 / 10.7554/eLife.08687

# possible refinements of the SM

## telomere length & age

## math model investigates patterns of HSC replication in time




## the telomere length distribution is a traveling wave (in time) that widens and shifts towards shorter length values; maximum scales like 1/√t

Werner et al, eLife 2015 / 10.7554/eLife.08687

## possible refinements of the SM

### telomere length & age

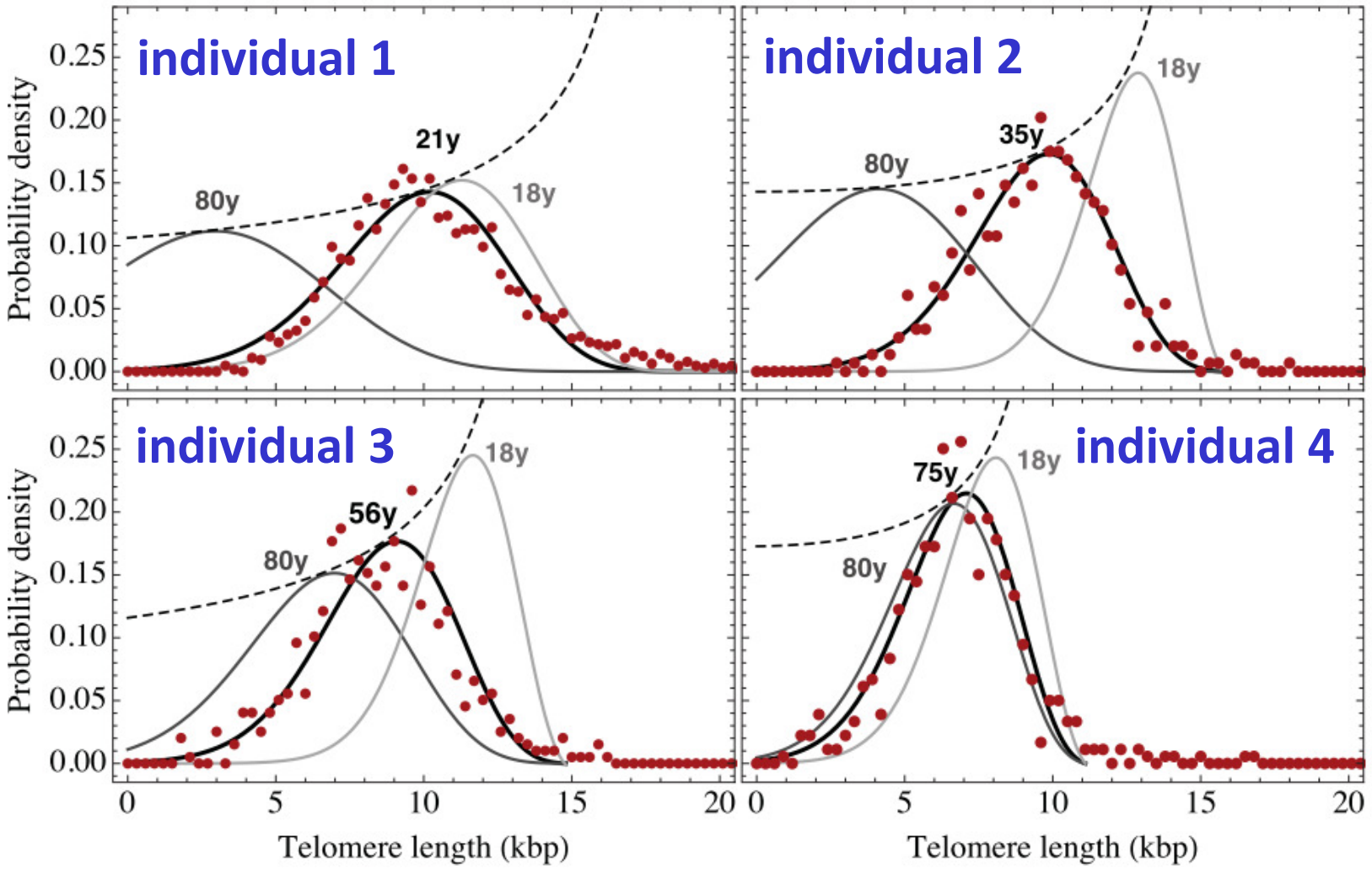
**further analysis of 47 cord blood and 28 bone marrow samples reveals:**

- **an increasing stem cell pool during childhood adolescence &**
- **an approximately maintained stem cell population in adults**

Werner et al, eLife 2015 / 10.7554/eLife.08687

# possible refinements of the SM

## telomere length & age

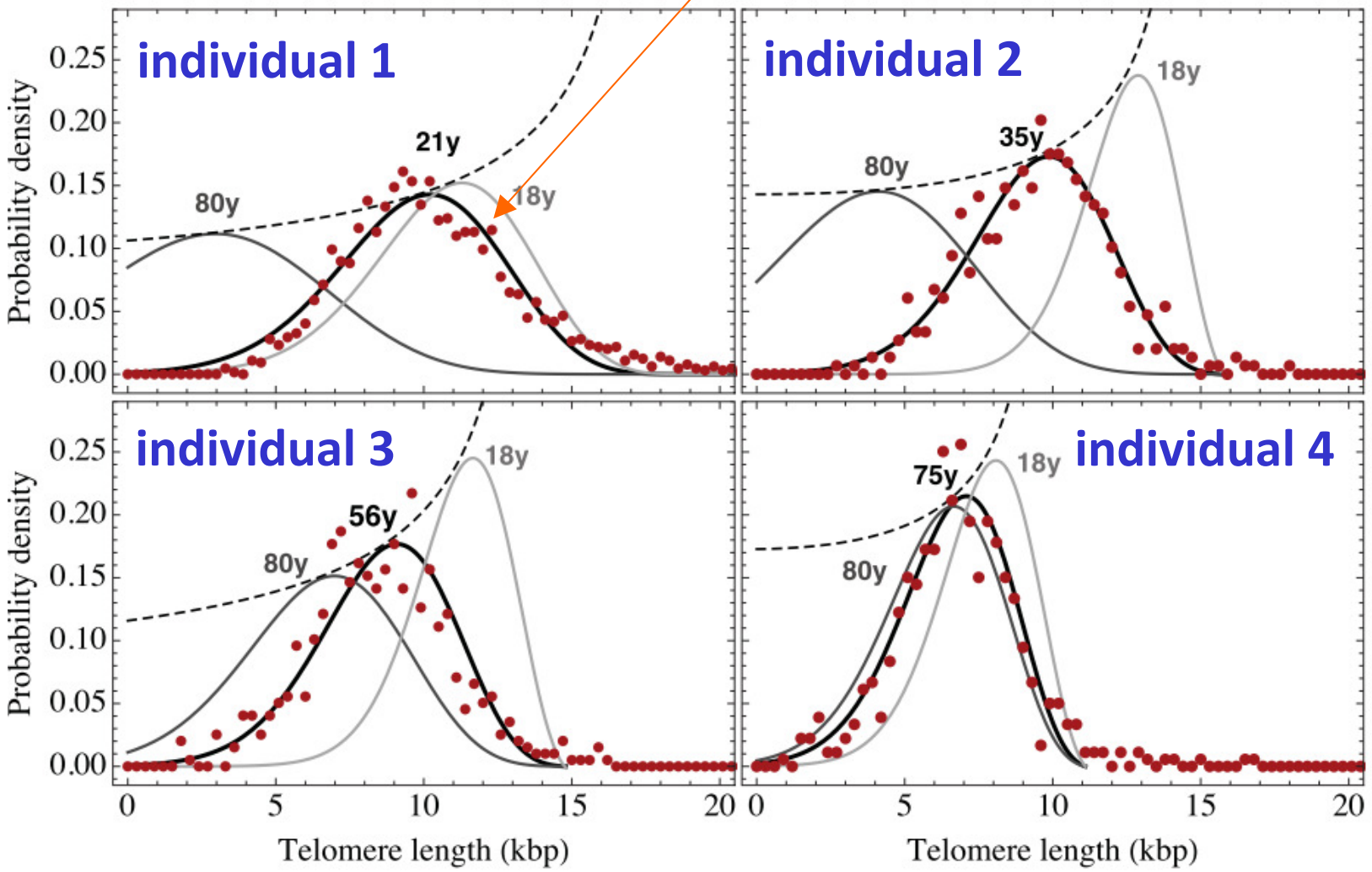



Werner et al, eLife 2015 / 10.7554/eLife.08687

# possible refinements of the SM

telomere length & age

single measurement of telomere length

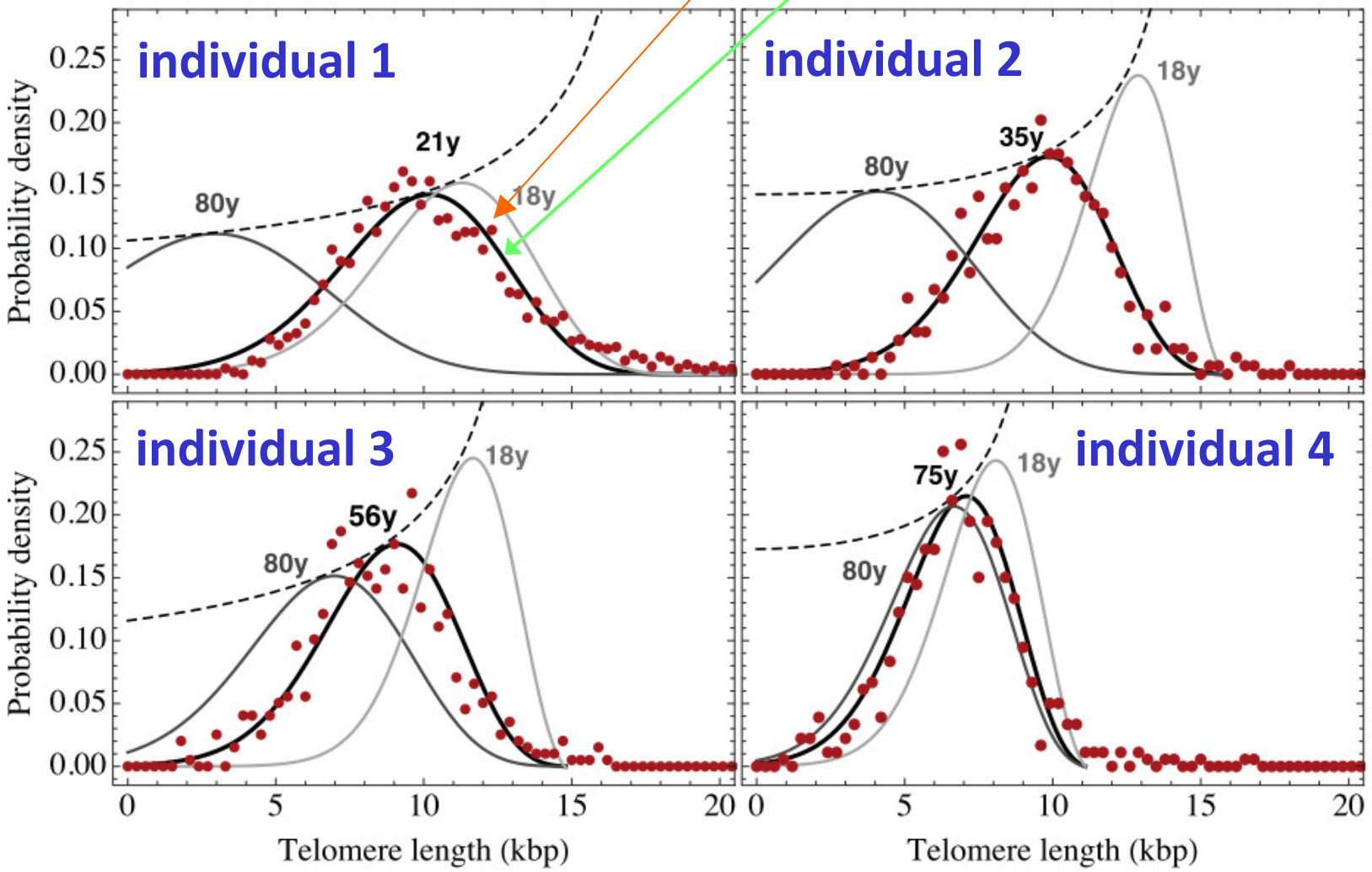



Werner et al, eLife 2015 / 10.7554/eLife.08687

# possible refinements of the SM

telomere length & age

single measurement of telomere length
model fit to same age

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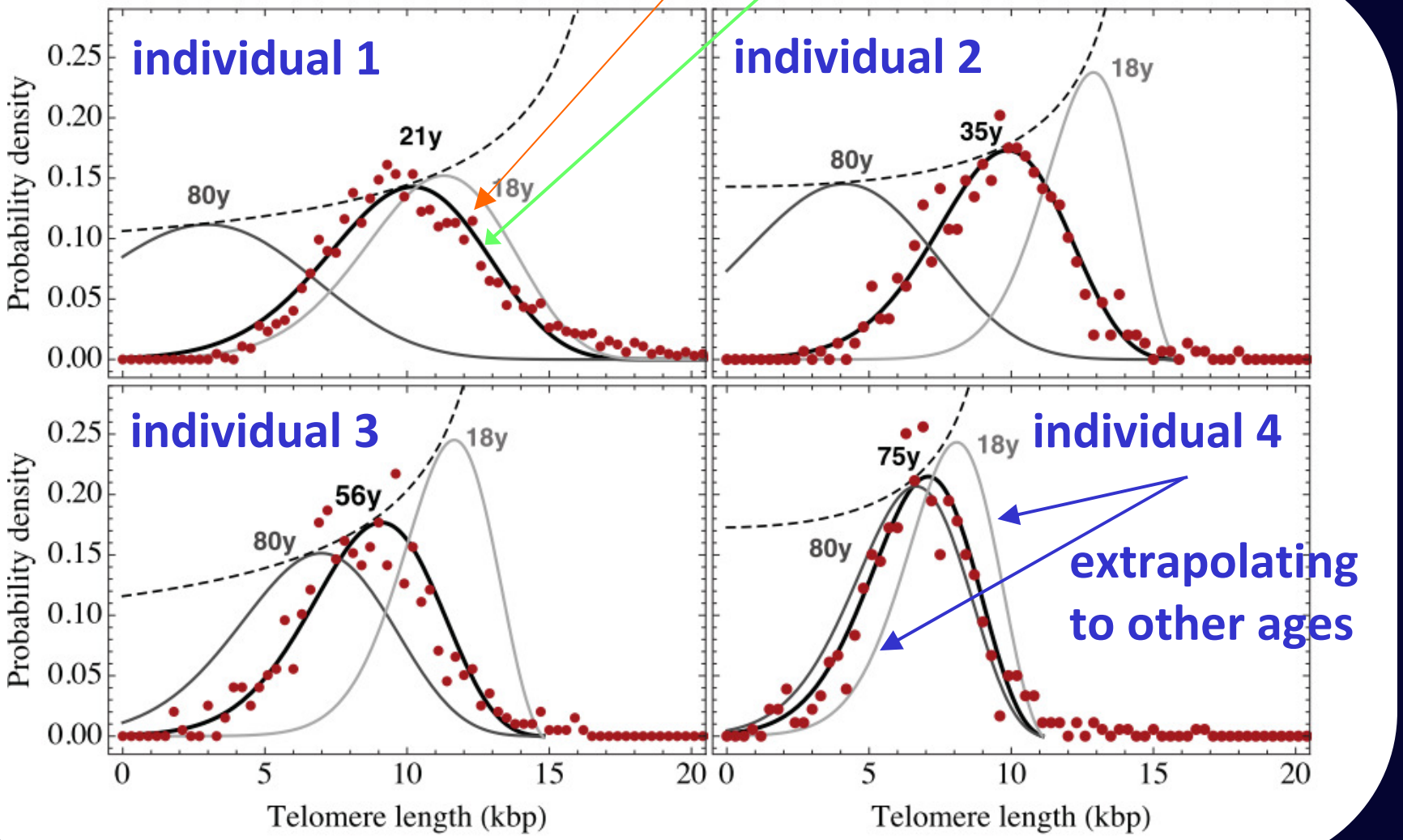
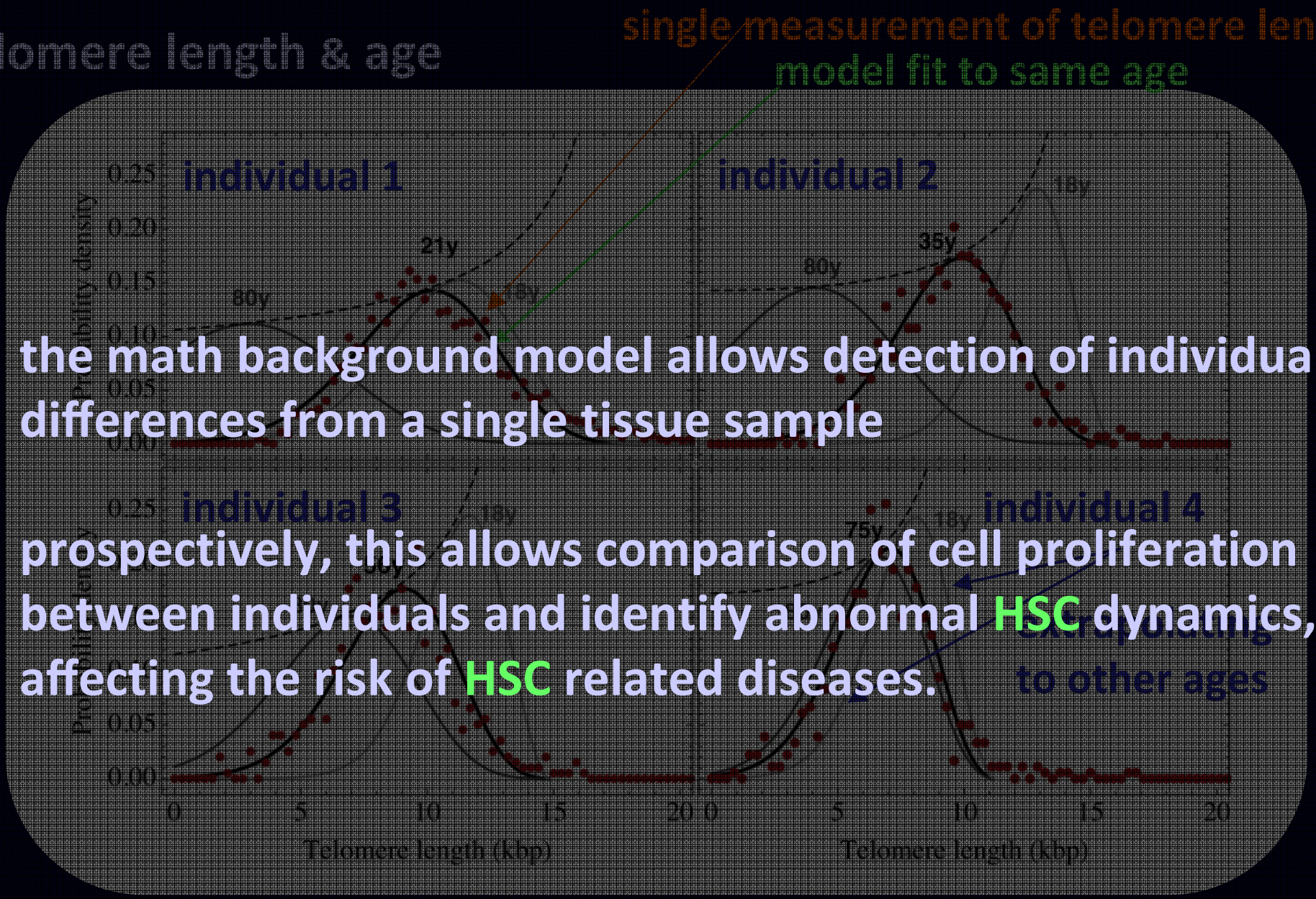



Werner et al, eLife 2015 / 10.7554/eLife.08687

# possible refinements of the SM



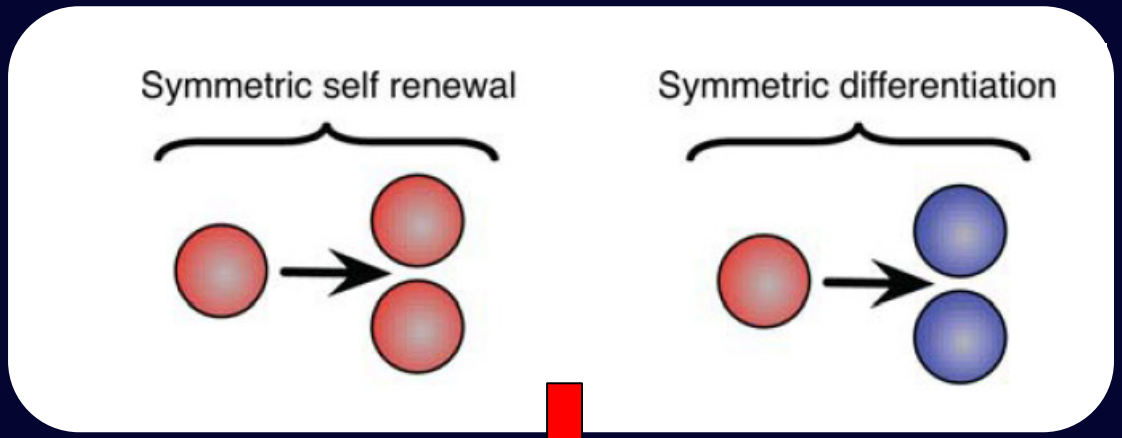

the math background model allows detection of individual differences from a single tissue sample

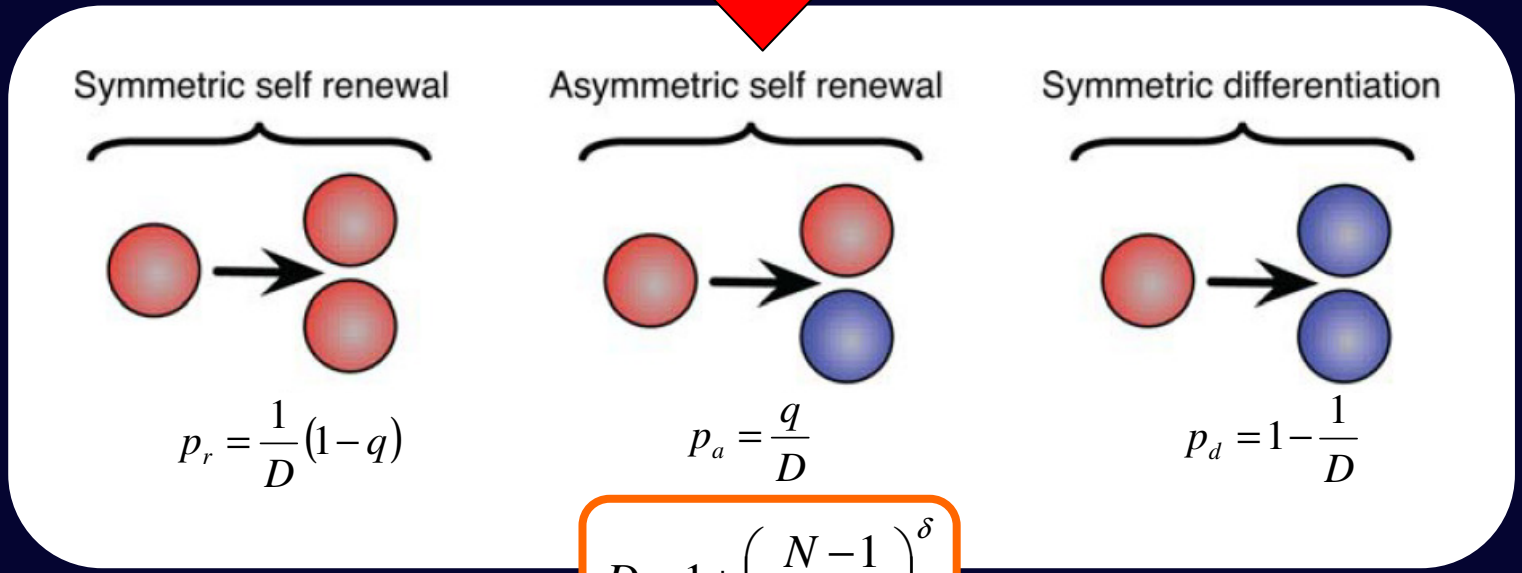
prospectively, this allows comparison of cell proliferation between individuals and identify abnormal HSC dynamics, affecting the risk of HSC related diseases.

Werner et al, eLife 2015 / 10.7554/eLife.08687

# possible refinements of the SM

**the possibility that, during ontogeny, HSC cell replication rates may change in time allows the following generalization**



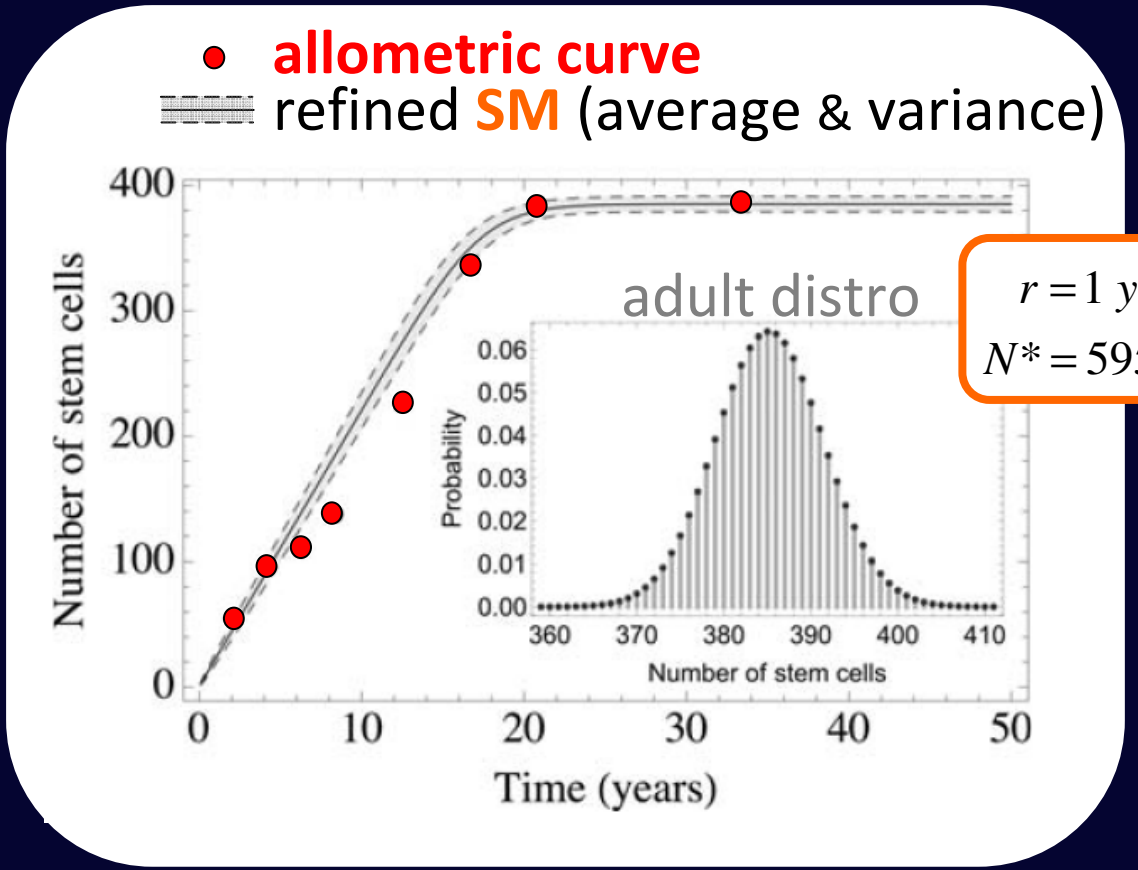




$$D = 1 + \left(\frac{N-1}{N^*-1}\right)^{\delta}$$

Werner et al, Stem Cells (2016, in press)

# possible refinements of the SM

## ontogenic growth of active HSC pool in humans

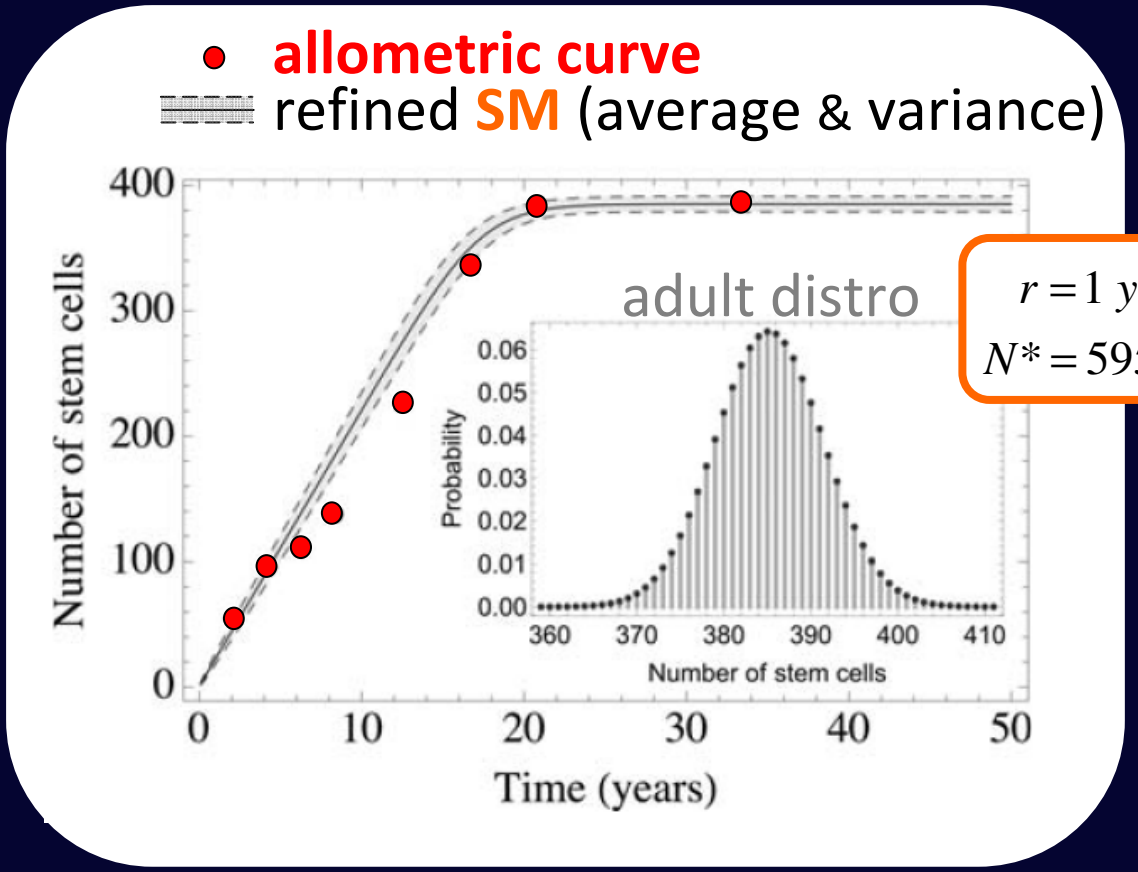



**refined SM leads to a context dependent cell replication dynamics that allows an understanding of some previously unexplained diseases :**

Werner et al, Stem Cells (2016, in press)

# possible refinements of the SM

## ontogenic growth of active HSC pool in humans




**more specifically : changes in population size**

**→ mutant *fitness* becomes age dependent ;**

**→ HSC mutation effects may vary with age;**

**what are possible consequences of such effects ?**

# Transient Amplifying Leukemia

Werner et al, Stem Cells (2016, in press)

## Transient Amplifying Leukemia (TL)

**what is known :**

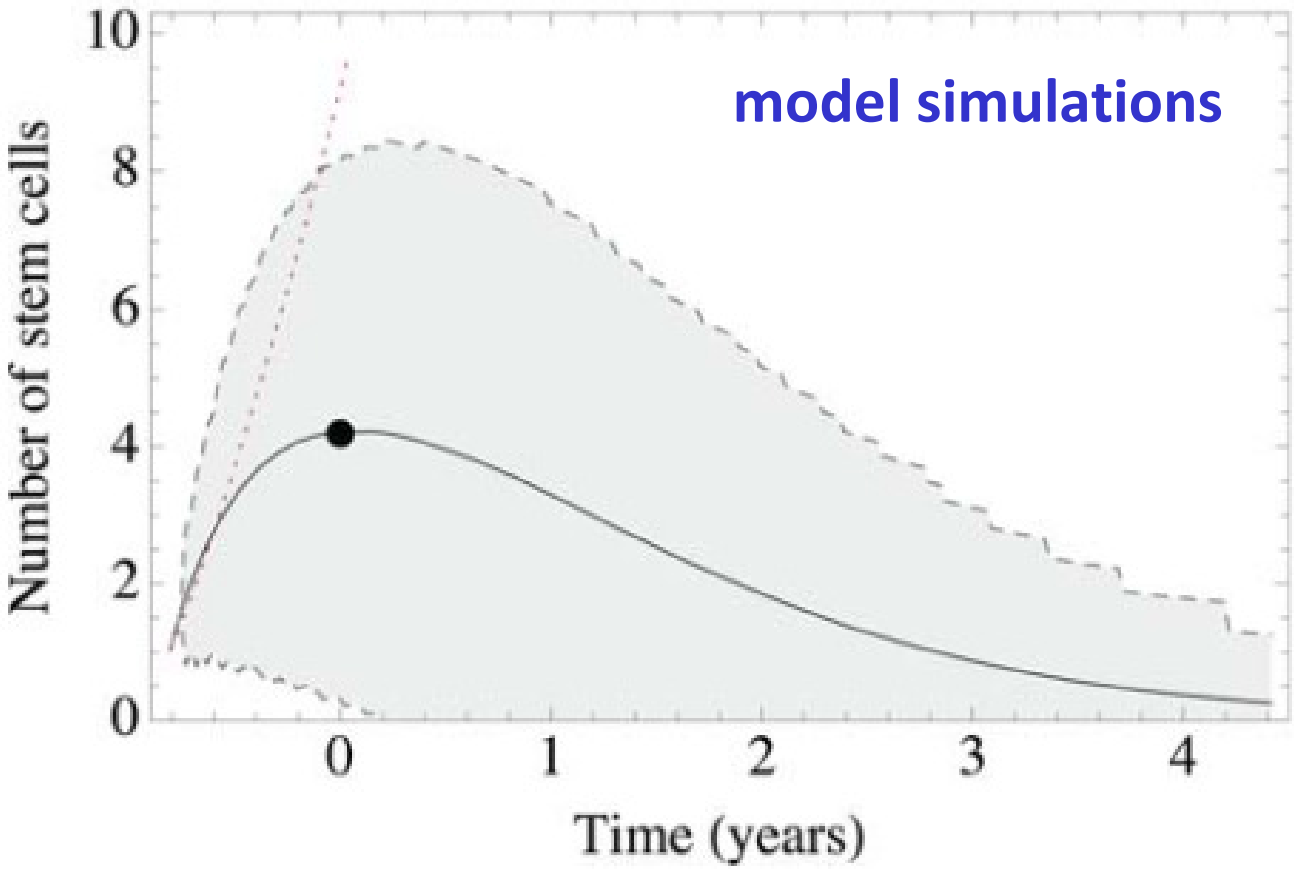
- arises in utero
- occurs in ~30% of infants with Down syndrome (also known as trisomy 21)
- mutation in exon 2 of the gene coding for the transcription factor GATA1 is involved
- additional (unknown) factors on chromosome 21 cooperate with GATA1 leading to disease
- can be fatal (so that effective incidence may be higher)

## Transient Amplifying Leukemia (TL)

**what is known :**

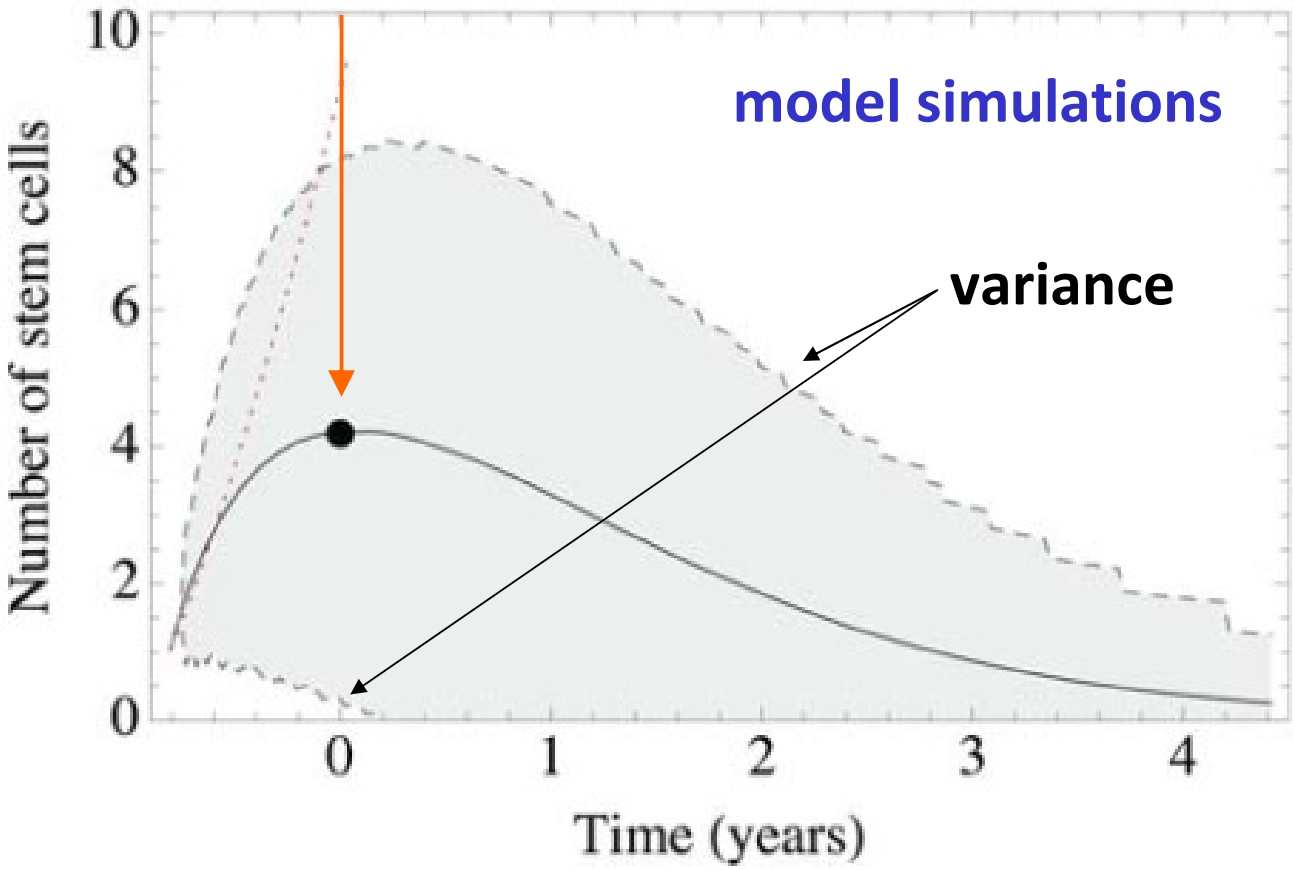
- in most cases, **TL** resolves without specific therapy
- in a few cases, it progresses into acute megakaryoblastic leukemia (**AMKL**)
- this may happen years after the **TL** clone had become undetectable.

## Transient Amplifying Leukemia (TL)



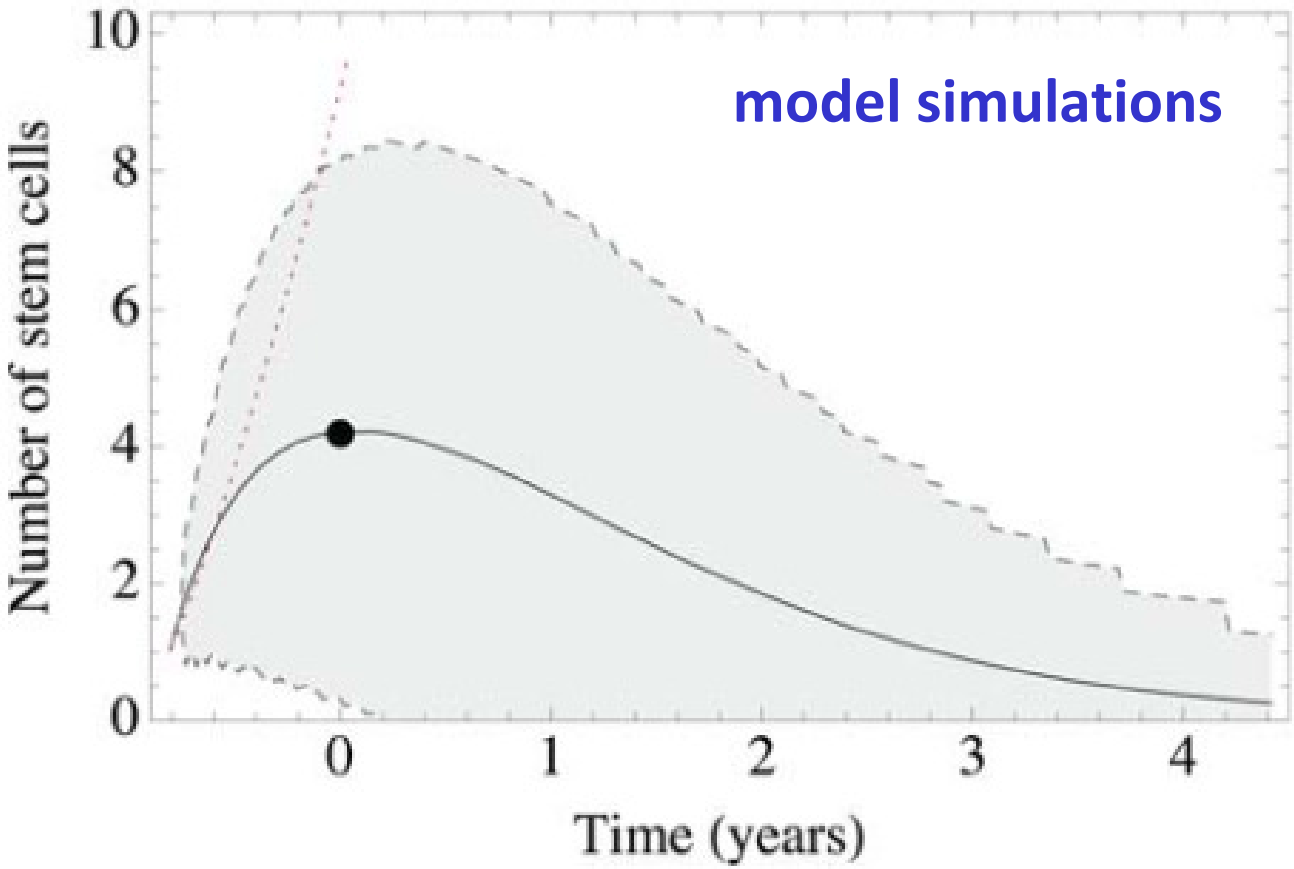

mutational hit occurs early in embryonic development

## Transient Amplifying Leukemia (TL)



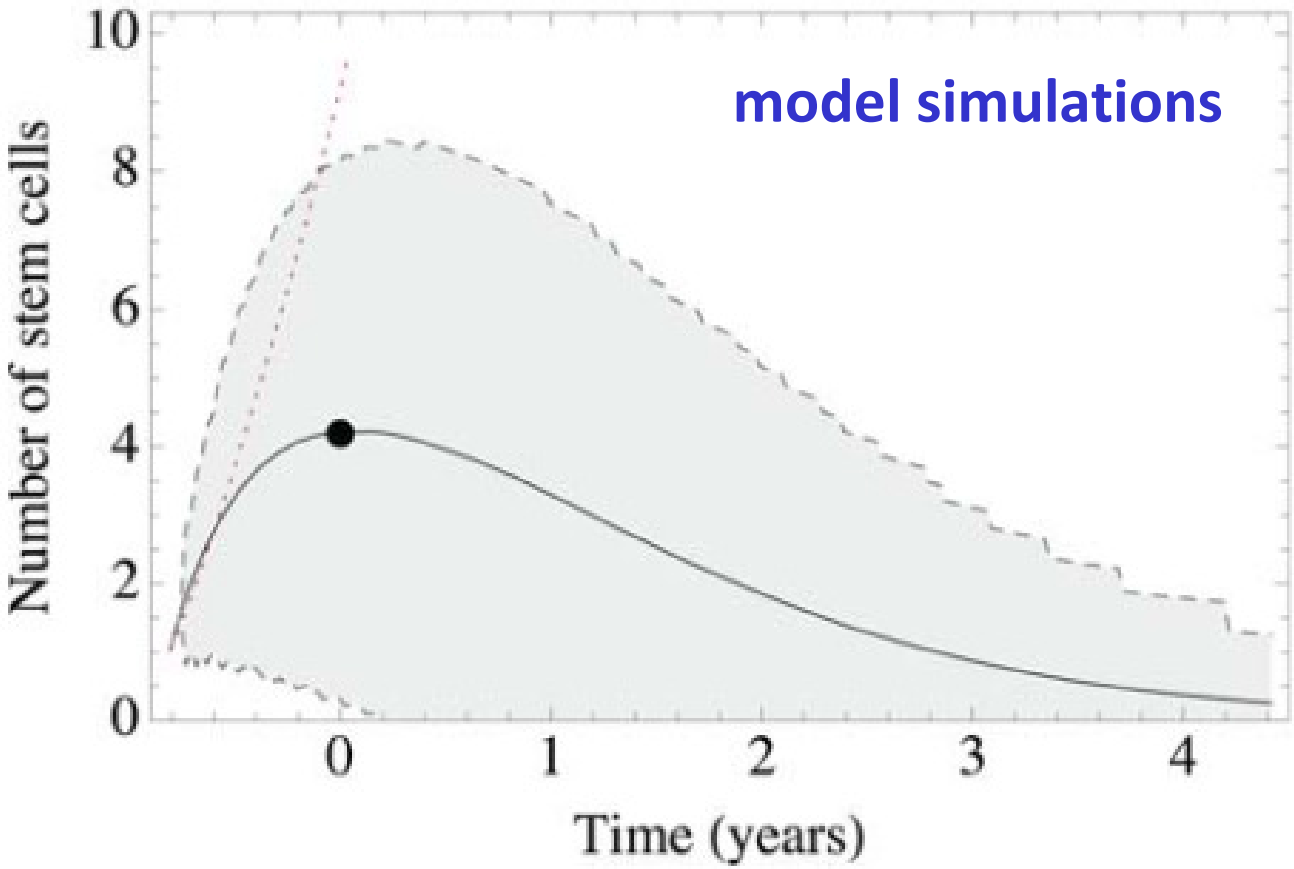

clonal load (black line) reaches its peak on average shortly after birth (black dot)

## Transient Amplifying Leukemia (TL)



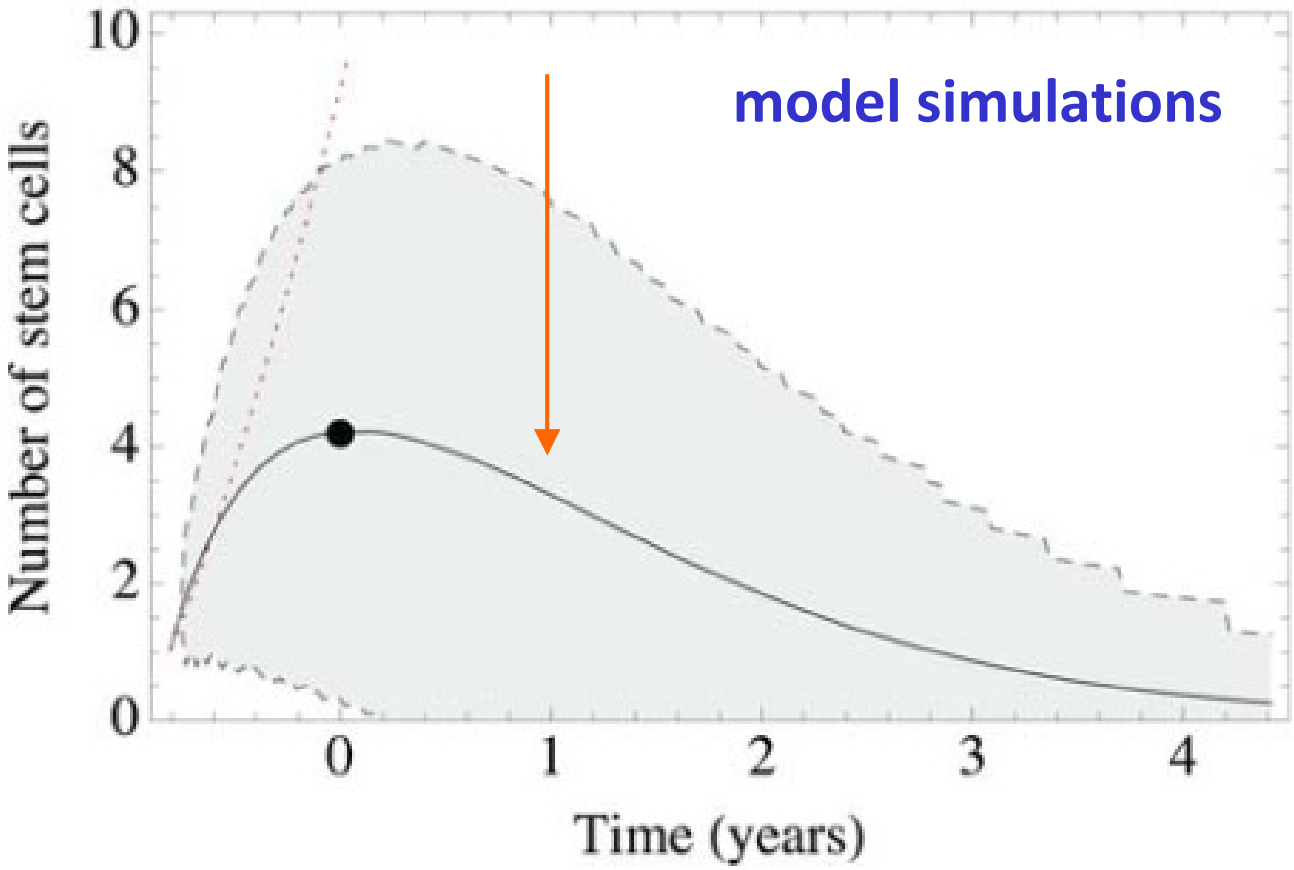

as the clone proliferates, also total stem cell number increases

## Transient Amplifying Leukemia (TL)



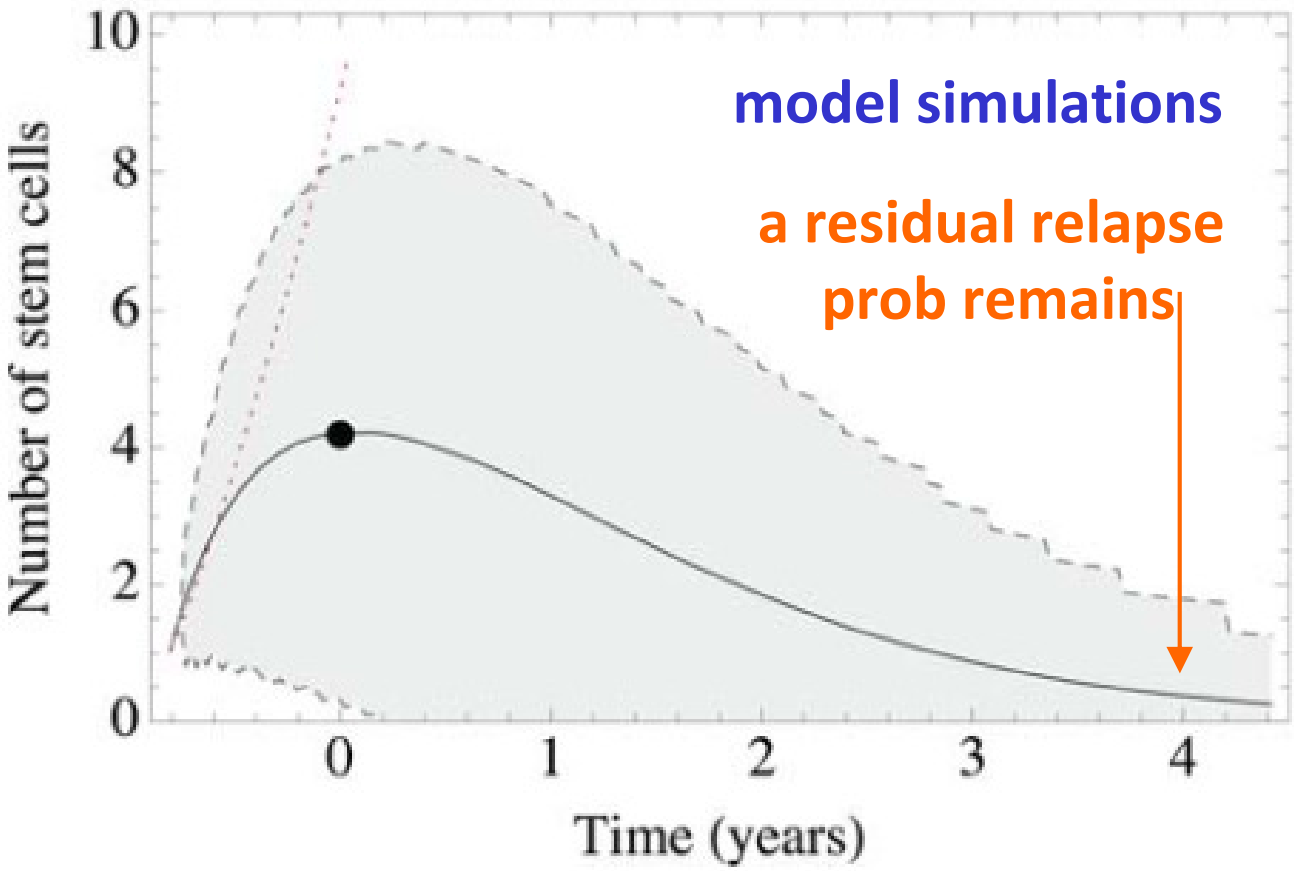

thus downregulating clonal expansion which is outcompeted once the size of the healthy stem cell population is high enough

## Transient Amplifying Leukemia (TL)




contribution of the clone becomes negligible after approximately 1 year

## Transient Amplifying Leukemia (TL)




however, total extinction of the clone requires about 4 years

# the ecology of cancer
# from an
# Evolutionary Game Theory perspective

British Journal of Cancer (2009), 1 – 7

www.bjcancer.com

**Full Paper**

# Cancer phenotype as the outcome of an evolutionary game between normal and malignant cells

**D Dingli*[,1], FACC Chalub[2], FC Santos[3], S Van Segbroeck[4] and JM Pacheco[5]**

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Molecular Systems Biology 8; Article number 621; doi:10.1038/msb.2012.54
**Citation: *Molecular Systems Biology* 8:621**

www.molecularsystemsbiology.com

molecular systems biology

# Competition between species can stabilize public-goods cooperation within a species

**Hasan Celiker[1] and Jeff Gore[2,*]**

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Received 5.6.12; accepted 26.9.12

British Journal of Cancer (2009), 1 – 7

www.bjcancer.com

**Full Paper**

Cancer phenotype as the outcome of an evolutionary game between normal and malignant cells

**spatial populations of cells & other micro-organisms often show coexistence behavior in nature (coined recently as *negative frequency dependence* )**

*Nature Reviews Cancer* | AOP, published online 17 April 2014; doi:10.1038/nrc3712

PERSPECTIVES

OPINION

# Turning ecology and evolution against cancer

*Kirill S. Korolev, Joao B. Xavier and Jeff Gore*

of endangered and extinct species that were not able to adapt to the changing environment. So, in this Opinion article, we turn to conservation biology, ecology and evolution to identify the common mechanisms that cause extinction or that inhibit adaptation.

Despite the broad appreciation of cancer as an evolutionary process, much less work has gone into characterizing the ecological aspects

**this being the case,**

- **what is the nature of the cell-cell interaction ?**
- **what is the "game" cells play ?**

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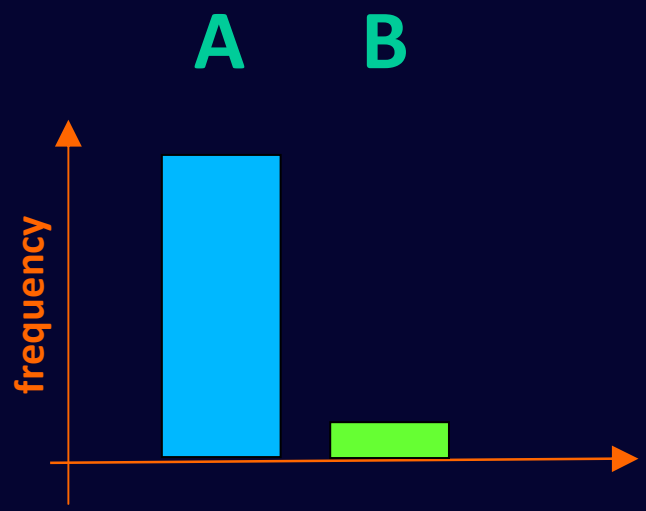
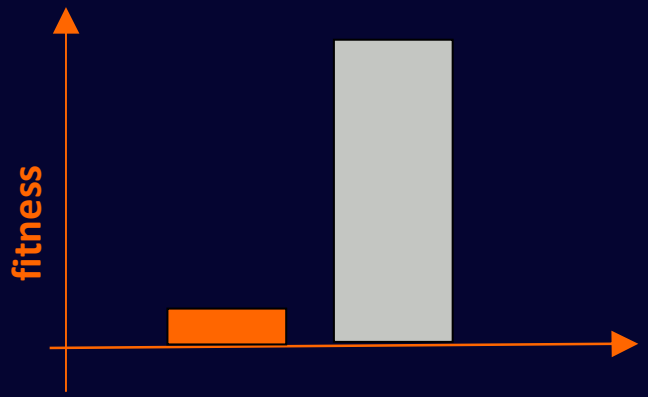
- what is the nature of the cell-cell interaction ?
- what is the "**game**" cells play ?




$$\dot{x} = x(1-x)(f_a - f_b)$$

$$f_a < f_b \rightarrow x \searrow$$



**this being the case,**

- what is the nature of the cell-cell interaction ?
- what is the "**game**" cells play ?

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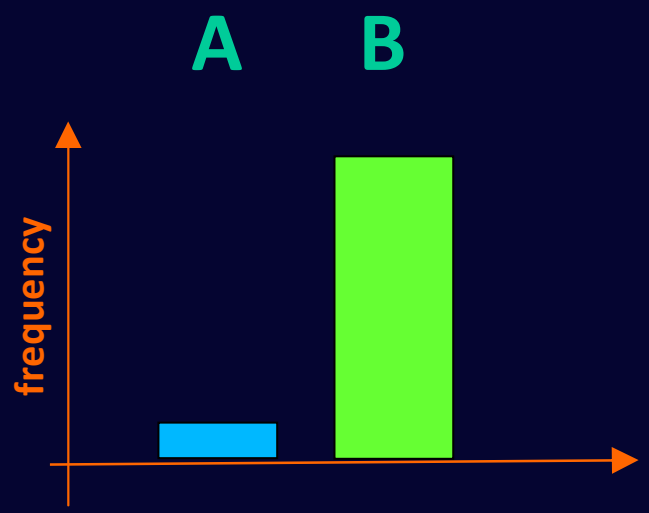
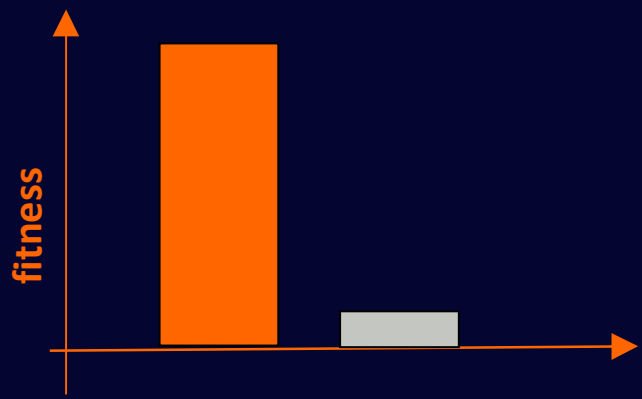
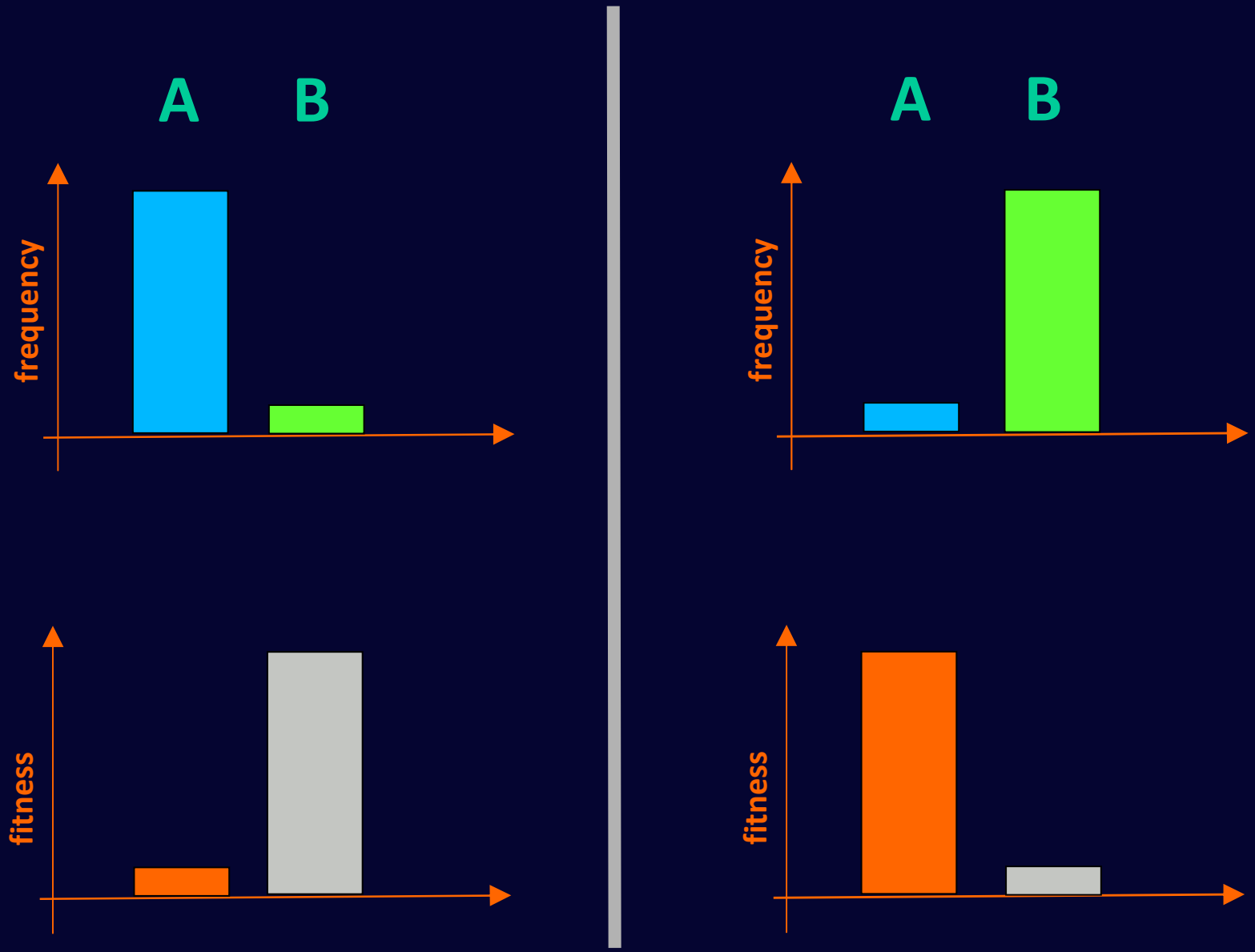
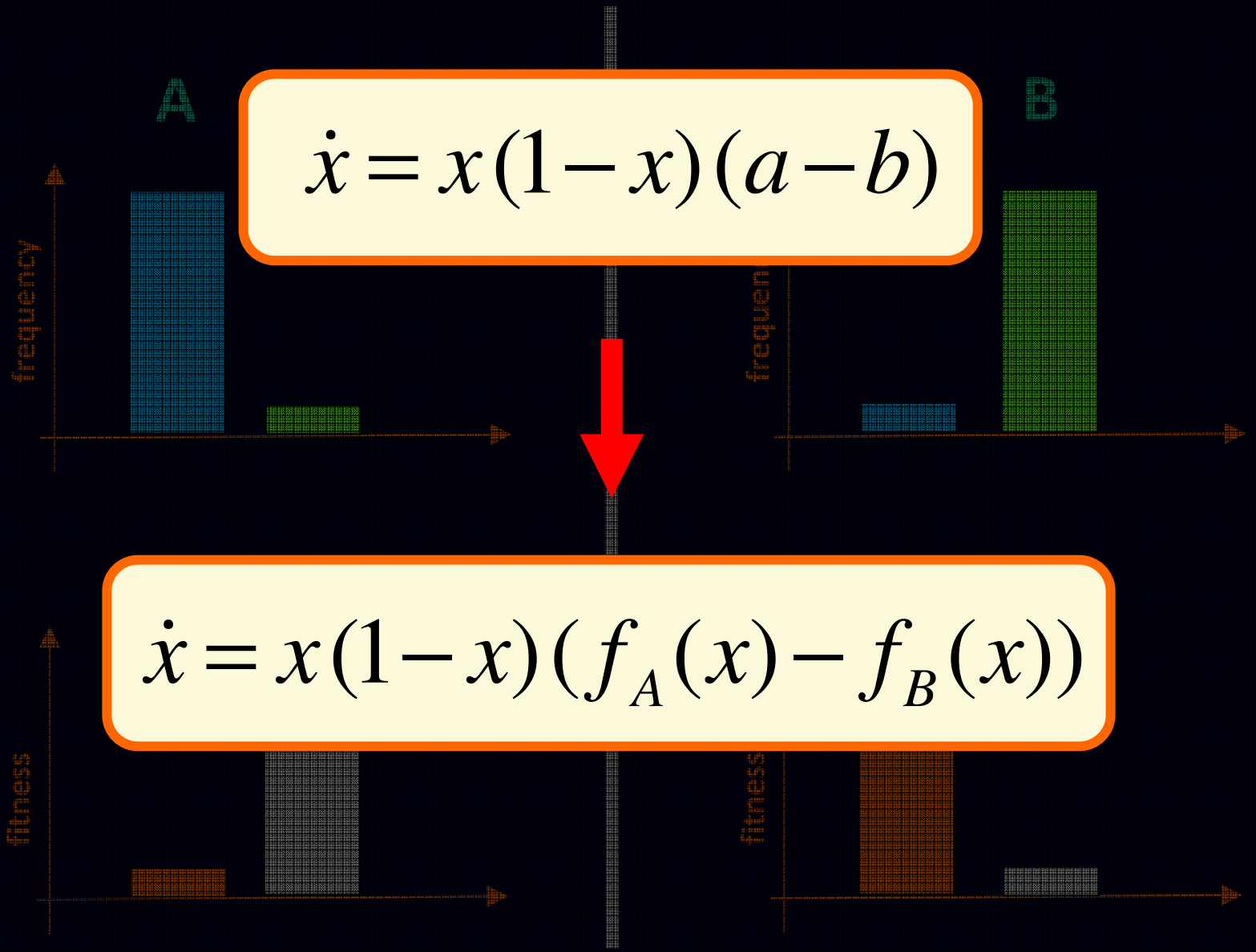


this means $f_a$ and $f_b$ in the replicator equation are ***frequency dependent***



this means $a$ and $b$ in the replicator equation are *frequency dependent*



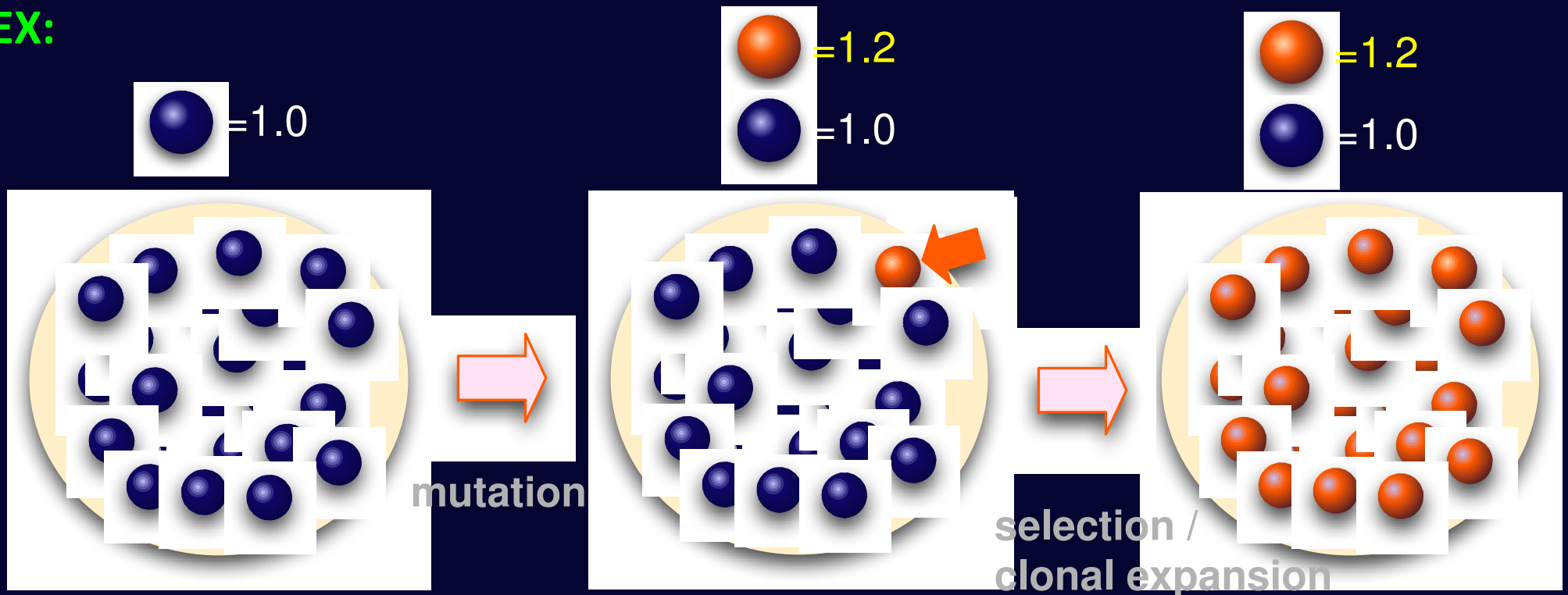
# frequency independent selection (2 cell lineages)

$$\begin{array}{c} \\ 1 \\ 2 \end{array}\begin{array}{c} \begin{array}{cc} 1 & 2 \end{array} \\ \begin{bmatrix} a & a \\ b & b \end{bmatrix} \end{array}$$

$$f_1(x) = x\times a + (1-x)\times a = a$$
$$f_2(x) = x\times b + (1-x)\times b = b$$
$$\Rightarrow \quad \dot{x} = x(1-x)(a-b)$$

- **1** gets $a$ from interacting with **1** and $a$ from interacting with **2**
- **2** gets $b$ from interacting with **1** and $b$ from interacting with **2**

**EX:**




fitness is independent of the relative abundance of each cell lineage

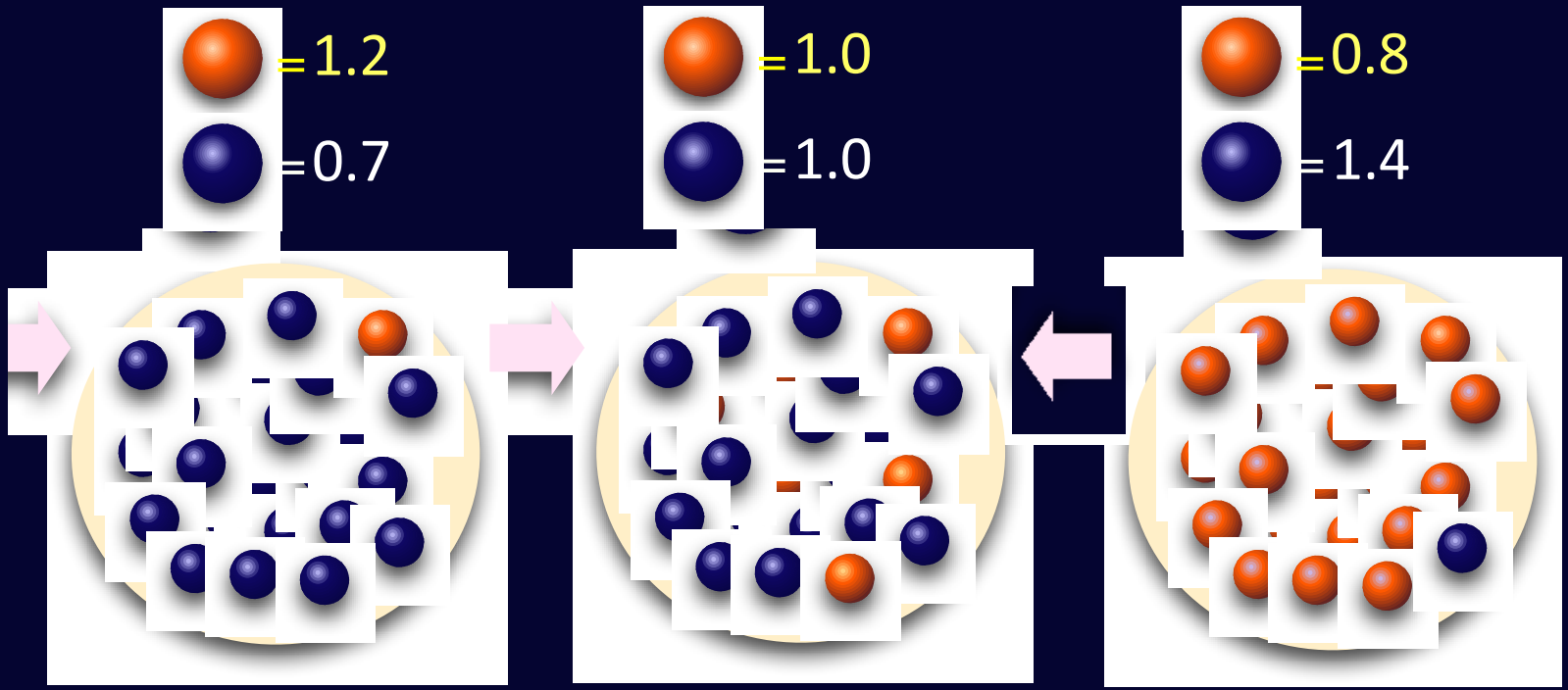
# frequency dependent selection (2 cell lineages)

$$\begin{array}{c} \\ 1 \\ 2 \end{array}\begin{array}{c} \begin{array}{cc} 1 & 2 \end{array} \\ \begin{bmatrix} a & c \\ d & b \end{bmatrix} \end{array}$$

$$f_1(x) = x\times a + (1-x)\times c \neq a$$
$$f_2(x) = x\times d + (1-x)\times b \neq b$$
$$\Rightarrow \quad \dot{x} = x(1-x)(f_1(x) - f_2(x))$$

- **1** gets $a$ from interacting with **1** and $c$ from interacting with **2**
- **2** gets $d$ from interacting with **1** and $b$ from interacting with **2**

**EX:**

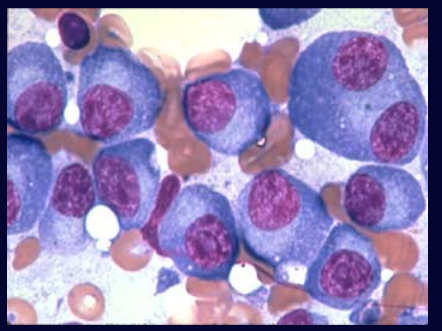



fitness now **depends** on the relative abundance of each cell lineage

# Multiple Myeloma

[Dingli et al, Brit J Cancer (2009]

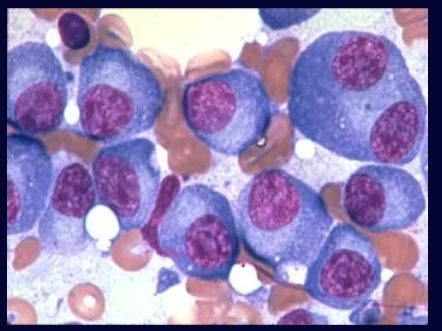
## a case study: Multiple Myeloma Bone Disease (MM)



- **Multiple Myeloma is a cancer** of the plasma cells, a type of **blood cell** present in the bone marrow
- **MM** affects about **750,000 people worldwide**, & although quite a few treatments are available, it remains incurable.
- average rate of survival ~3 years

[ Berenson, *Curr Treat Options Onc*, 2001 ]
[ Kyle and Rajkumar, *N Eng J Med* 2004]
[ Harper and Weber, *Endoc Metab Clin North Am* 1998]

## a case study: Multiple Myeloma Bone Disease (MM)

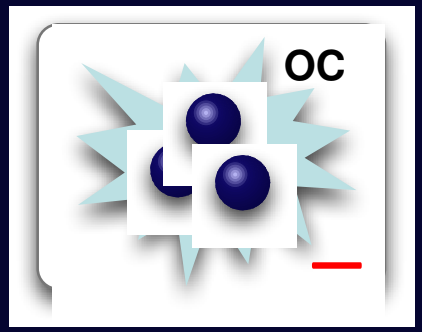


- Health problems caused by multiple myeloma cells (**MM** cells) can **affect our bones**, immune system, kidney and red blood cells.
- associated effects: **pain, bone loss & fractures (focal lesions & osteoporosis)** and neurologic deficits.

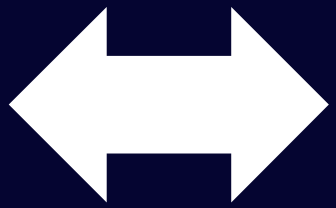
[ Berenson, *Curr Treat Options Onc*, 2001 ]
[ Kyle and Rajkumar, *N Eng J Med* 2004]
[ Harper and Weber, *Endoc Metab Clin North Am* 1998]

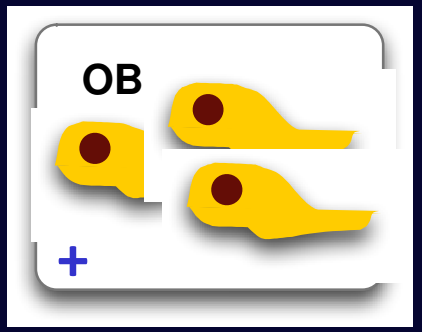
## a case study: Multiple Myeloma Bone Disease (MM)

**normal bone remodeling is a consequence of the dynamic balance between:**



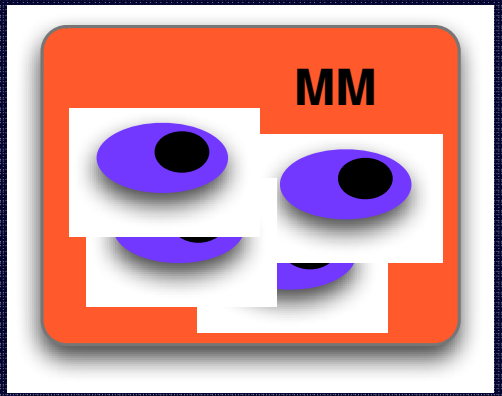

***Osteoclasts (OC)***
***Mediate bone resorption***






***Osteoblasts (OB)***
***Mediate bone formation***

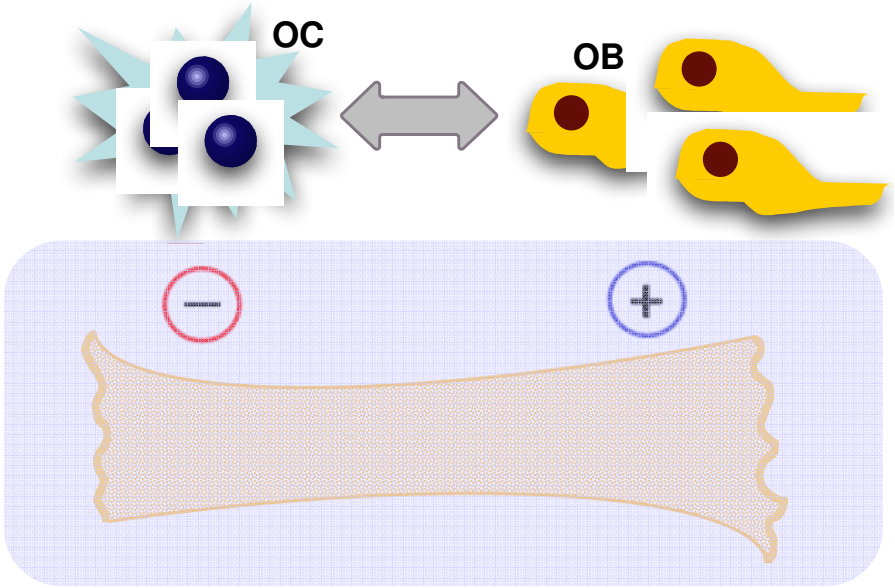
[Roodman, *Blood Cells Mol Dis* 2004]
[Terpos et al, *Blood* 2007]




***Myeloma cells (MM)***
***MM cells disrupt this dynamical equilibrium between OC and OB cells, favouring OC cells***

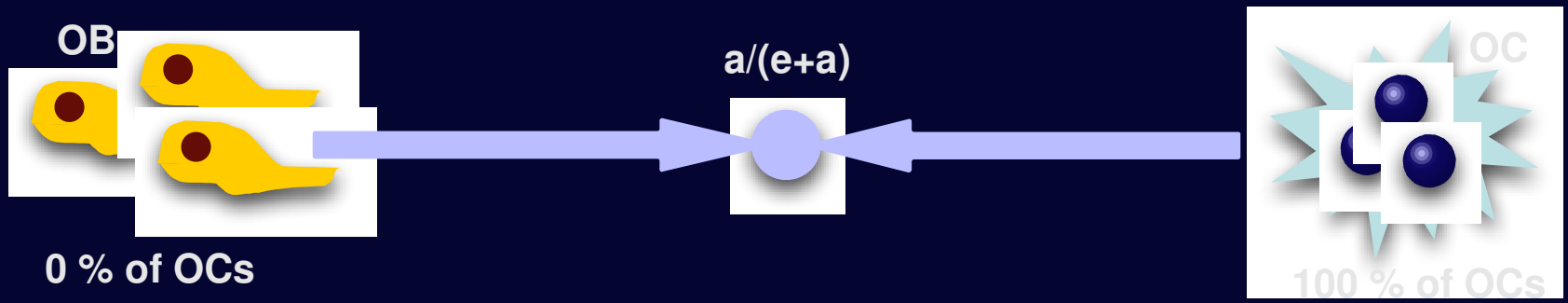
# normal bone remodeling

$$\begin{array}{c} \\ OC \\ OB \end{array} \begin{array}{c} \begin{array}{cc} OC & OB \end{array} \\ \begin{bmatrix} 0 & a \\ e & 0 \end{bmatrix} \end{array}$$




$$\begin{cases} \dot{x}_{OC} = x_{OC}(f_{OC}(\vec{x}) - \phi) \\ \dot{x}_{OB} = x_{OB}(f_{OB}(\vec{x}) - \phi) \end{cases}$$

$$\phi = x_{OC} f_{OC} + x_{OB} f_{OB}$$
$$f_{OC}(\vec{x}) = x_{OC}.0 + x_{OB}.a$$
$$f_{OB}(\vec{x}) = x_{OC}.e + x_{OB}.0$$

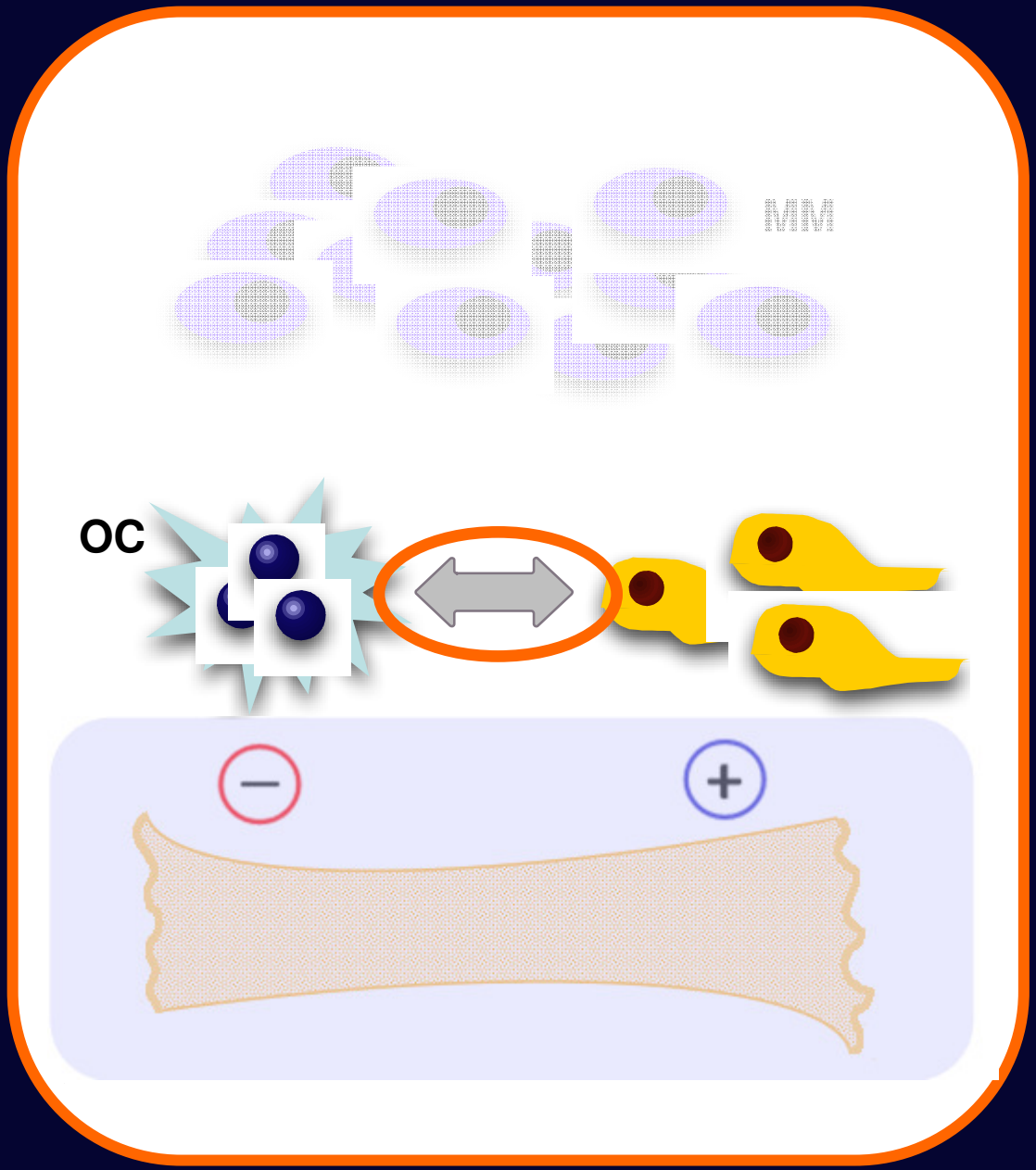



frequency of OCs

# bone turnover under pathological conditions

**without** the effects of MM-cells

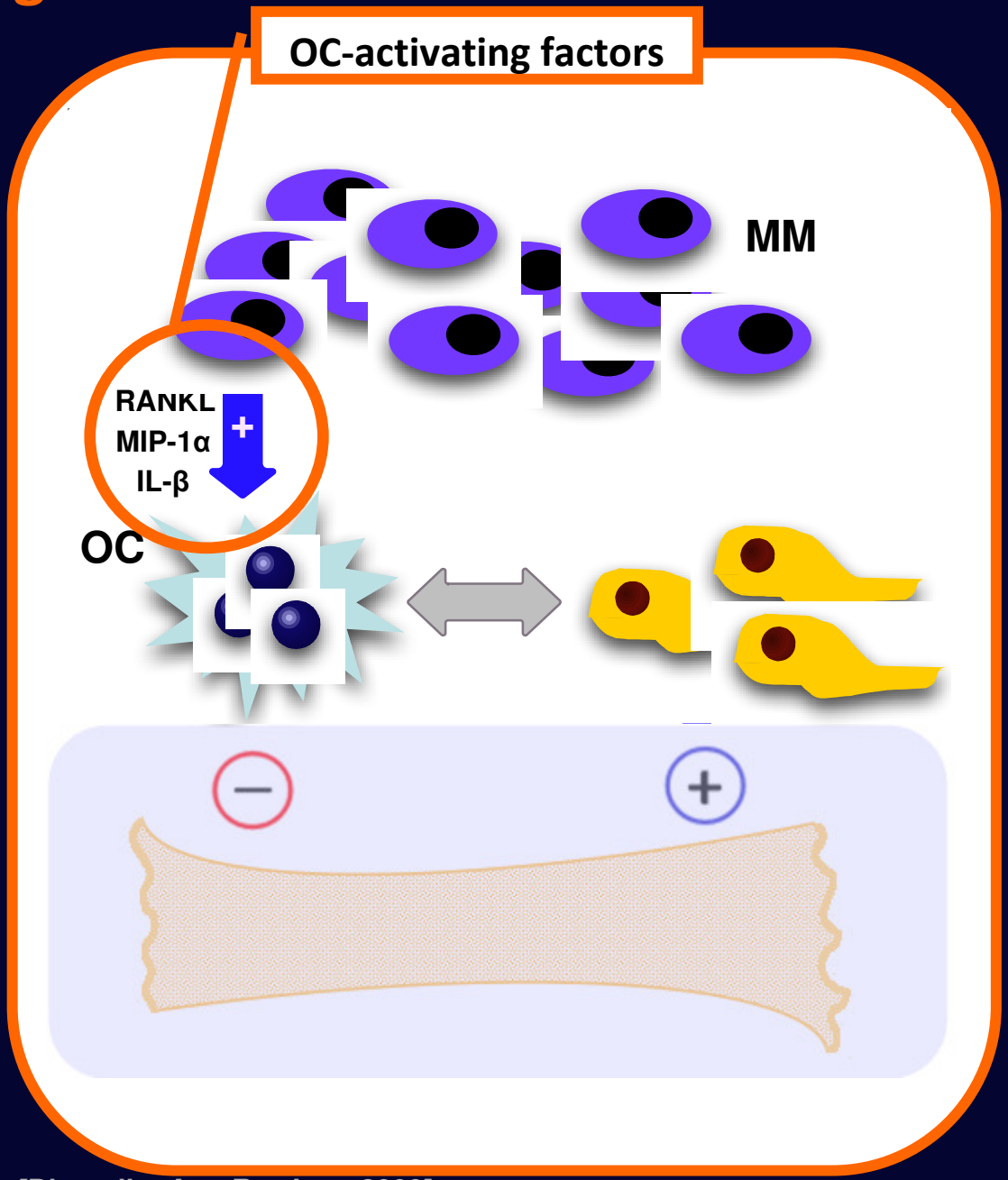
$$f_{OC}(\vec{x}) = x_{OC}.0 + x_{OB}.a + x_{MM}.0$$
$$f_{OB}(\vec{x}) = x_{OC}.e + x_{OB}.0 + x_{MM}.0$$
$$f_{MM}(\vec{x}) = x_{OC}.0 + x_{OB}.0 + x_{MM}.0$$



# bone turnover under pathological conditions

***Myeloma cells (MM)***
***produce a variety of "cytokines", summarized as "osteoclast activating factors", which stimulate the growth of OC cells***

$$f_{OC}(\vec{x}) = x_{OC}.0 + x_{OB}.a + x_{MM}.b$$
$$f_{OB}(\vec{x}) = x_{OC}.e + x_{OB}.0 + x_{MM}.0$$
$$f_{MM}(\vec{x}) = x_{OC}.0 + x_{OB}.0 + x_{MM}.0$$



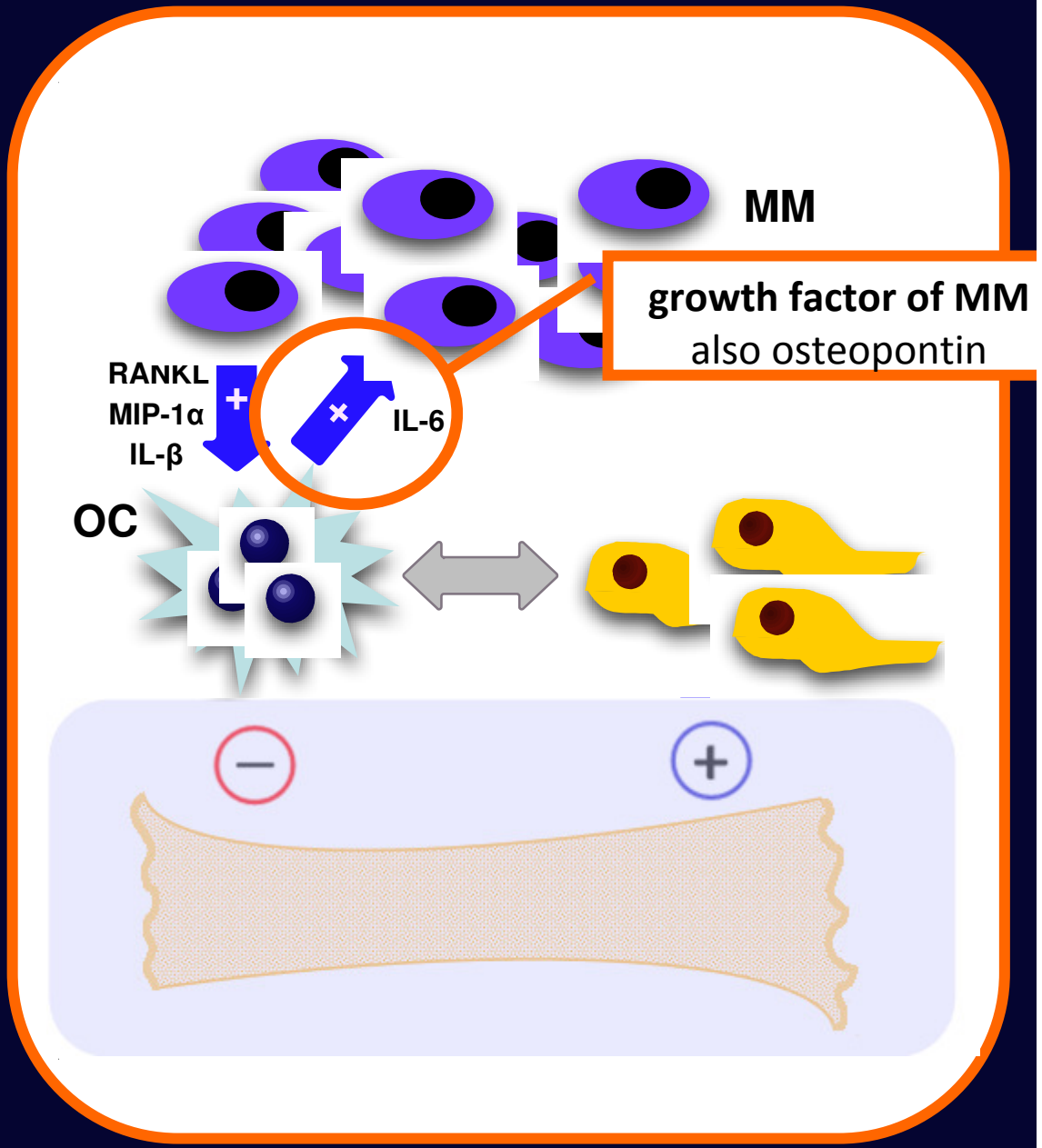

[Roodman, *Blood Cells Mol Dis* 2004]
[Roux & Mariette, *Leuk Lymphoma* 2004]

[Dinarello, Ann Rev Imm 2009]
[Croucher et al *Blood* 2001]
[Choi et al J Clin Invest 2001]

# bone turnover under pathological conditions

*Osteoclast cells (OC)*
*produce growth factors (IL-6)*
*which*
*stimulate the growth of MM cells*

$$f_{OC}(\vec{x}) = x_{OC}.0 + x_{OB}.a + x_{MM}.b$$
$$f_{OB}(\vec{x}) = x_{OC}.e + x_{OB}.0 + x_{MM}.0$$
$$f_{MM}(\vec{x}) = x_{OC}.c + x_{OB}.0 + x_{MM}.0$$



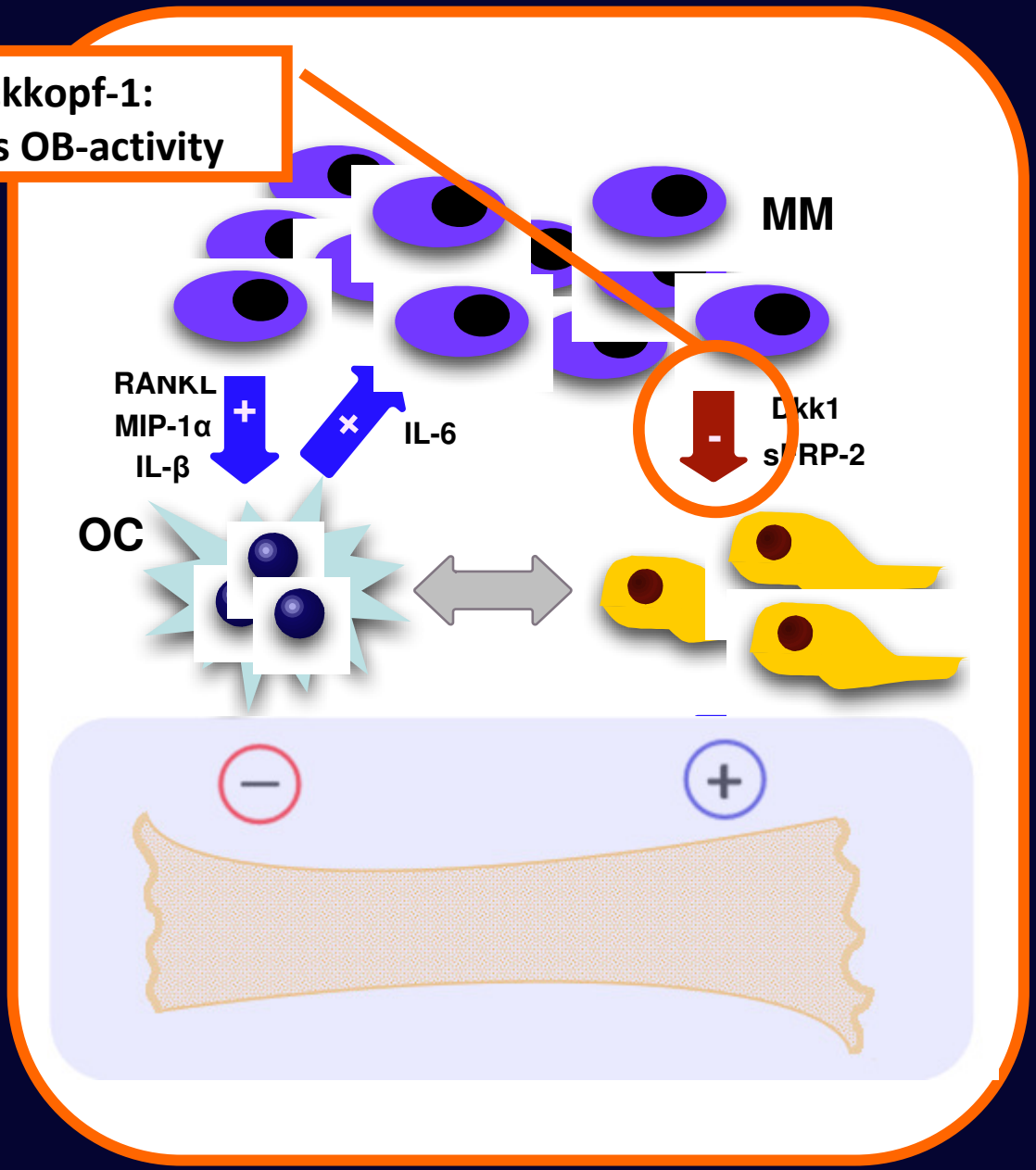

[Terpos et al, *Blood* 2007]
[Roux & Mariette, *Leuk Lymphoma* 2004]

# bone turnover under pathological conditions

*Myeloma cells (MM)*
*inhibit the differentiation of*
*Osteoblasts (OBs)*
*(Dkk1, sFRP-2, etc.)*

$$f_{OC}(\vec{x}) = x_{OC}.0 + x_{OB}.a + x_{MM}.b$$
$$f_{OB}(\vec{x}) = x_{OC}.e + x_{OB}.0 + x_{MM}.(-d)$$
$$f_{MM}(\vec{x}) = x_{OC}.c + x_{OB}.0 + x_{MM}.0$$

[Terpos et al, *Blood* 2007]
[Roux & Mariette, *Leuk Lymphoma* 2004]

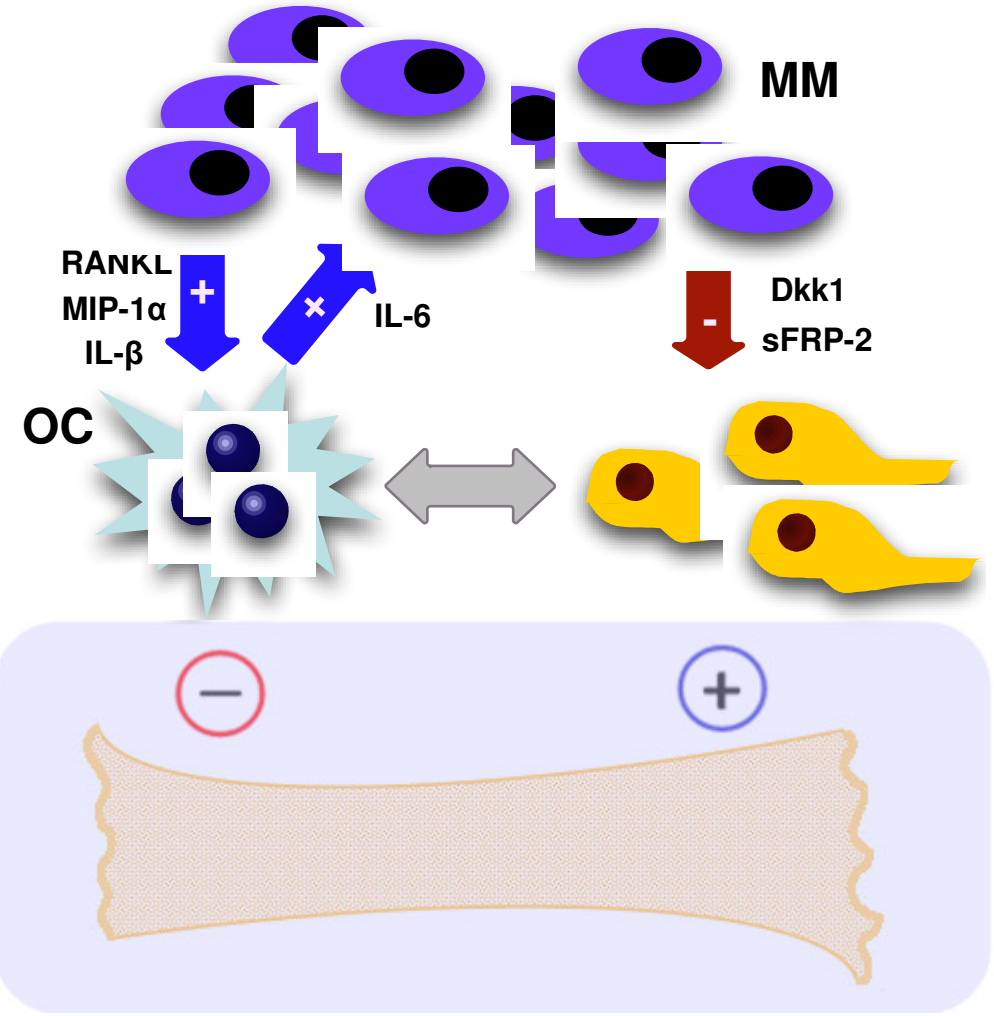



[Qiang et al. *Bone* 2008]
[Qiang et al. *Blood* 2008]

# bone turnover under pathological conditions

$$A_{ij} = \begin{array}{c} \\ OC \\ OB \\ MM \end{array} \begin{array}{c} \begin{array}{ccc} OC & OB & MM \end{array} \\ \begin{bmatrix} 0 & a & b \\ e & 0 & -d \\ c & 0 & 0 \end{bmatrix} \end{array}$$

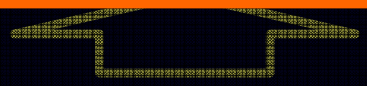
$$f_{OC}(\vec{x}) = x_{OC}.0 + x_{OB}.a + x_{MM}.b$$
$$f_{OB}(\vec{x}) = x_{OC}.e + x_{OB}.0 + x_{MM}.(-d)$$
$$f_{MM}(\vec{x}) = x_{OC}.c + x_{OB}.0 + x_{MM}.0$$




[Dingli et al, Brit J Cancer (2009]

# bone turnover under pathological conditions

$$\begin{array}{c} \\ OC \\ OB \\ MM \end{array} \begin{array}{c} \begin{array}{ccc} OC & OB & MM \end{array} \\ \begin{bmatrix} 0 & a & b \\ e & 0 & -d \\ c & 0 & 0 \end{bmatrix} \end{array}$$



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$$f_{OB}(\vec{x}) = x_{OC}.e + x_{OB}.0 + x_{MM}.(-d)$$
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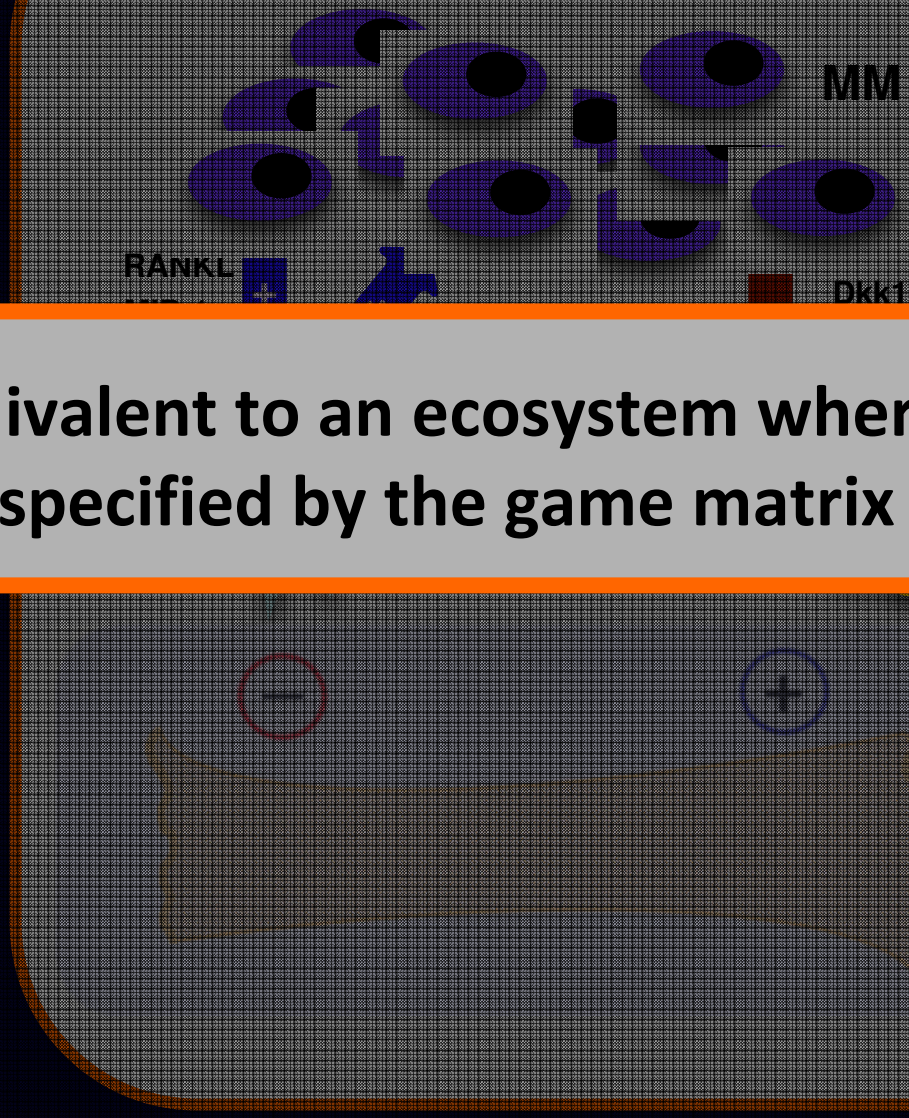


**this is mathematically equivalent to an ecosystem where species interactions are specified by the game matrix**

[Dingli et al, Brit J Cancer (2009)]

## disease evolution (math)

$$A_{ij} = \begin{array}{c} \\ OC \\ OB \\ MM \end{array} \begin{array}{c} \begin{array}{ccc} OC & OB & MM \end{array} \\ \begin{bmatrix} 0 & a & b \\ e & 0 & -d \\ c & 0 & 0 \end{bmatrix} \end{array}$$

$$\dot{x}_i(t) = x_i(t)\left[f_i(x_1, x_2, x_3) - \phi\right]$$

$$f_i(x_1, x_2, x_3) = \sum_{k=1}^{3} A_{ik} x_k$$

$$\phi = \sum_{i=1}^{3} \sum_{k=1}^{3} x_i A_{ik} x_k$$

- the nature of the fixed points of the evolutionary dynamics (though not their location) remains unaffected under a projective transformation of the relative cell frequencies

[Hofbauer & Sigmund, 1998]

## disease evolution (math)

$$B_{ij} = \frac{A_{ij}}{\eta_j} \qquad \eta = (e, a, be/c)$$

$$A_{ij} = \begin{array}{c} \\ OC \\ OB \\ MM \end{array} \begin{array}{c} \begin{array}{ccc} OC & OB & MM \end{array} \\ \begin{bmatrix} 0 & a & b \\ e & 0 & -d \\ c & 0 & 0 \end{bmatrix} \end{array}$$

$$B_{ij} = \begin{array}{c} \\ OC \\ OB \\ MM \end{array} \begin{array}{c} \begin{array}{ccc} OC & OB & MM \end{array} \\ \begin{bmatrix} 0 & 1 & c/e \\ 1 & 0 & -dc/be \\ c/e & 0 & 0 \end{bmatrix} \end{array}$$

◎ the nature of the fixed points of the evolutionary dynamics (though not their location) remains unaffected under a projective transformation of the relative cell frequencies

[Hofbauer & Sigmund, 1998]

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$$B_{ij} = \frac{A_{ij}}{\eta_j} \qquad \eta = (e, a, be/c)$$

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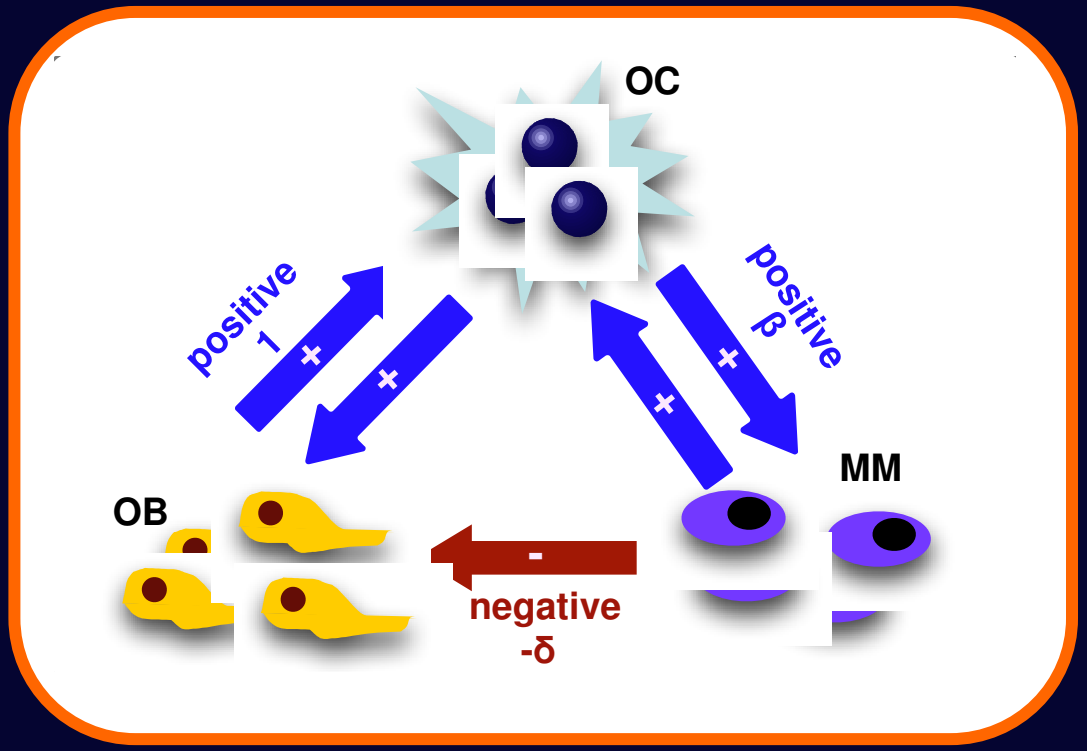
$$B_{ij} = \begin{array}{c} \\ OC \\ OB \\ MM \end{array} \begin{array}{c} \begin{array}{ccc} OC & OB & MM \end{array} \\ \begin{bmatrix} 0 & 1 & \beta \\ 1 & 0 & -\delta \\ \beta & 0 & 0 \end{bmatrix} \end{array}$$

- the nature of the fixed points of the evolutionary dynamics (though not their location) remains unaffected under a projective transformation of the relative cell frequencies

[Hofbauer & Sigmund, 1998]

# disease evolution (math & biology)




$$B_{ij} = \begin{array}{c} \\ OC \\ OB \\ MM \end{array} \begin{array}{c} \begin{array}{ccc} OC & OB & MM \end{array} \\ \begin{bmatrix} 0 & 1 & \beta \\ 1 & 0 & -\delta \\ \beta & 0 & 0 \end{bmatrix} \end{array}$$

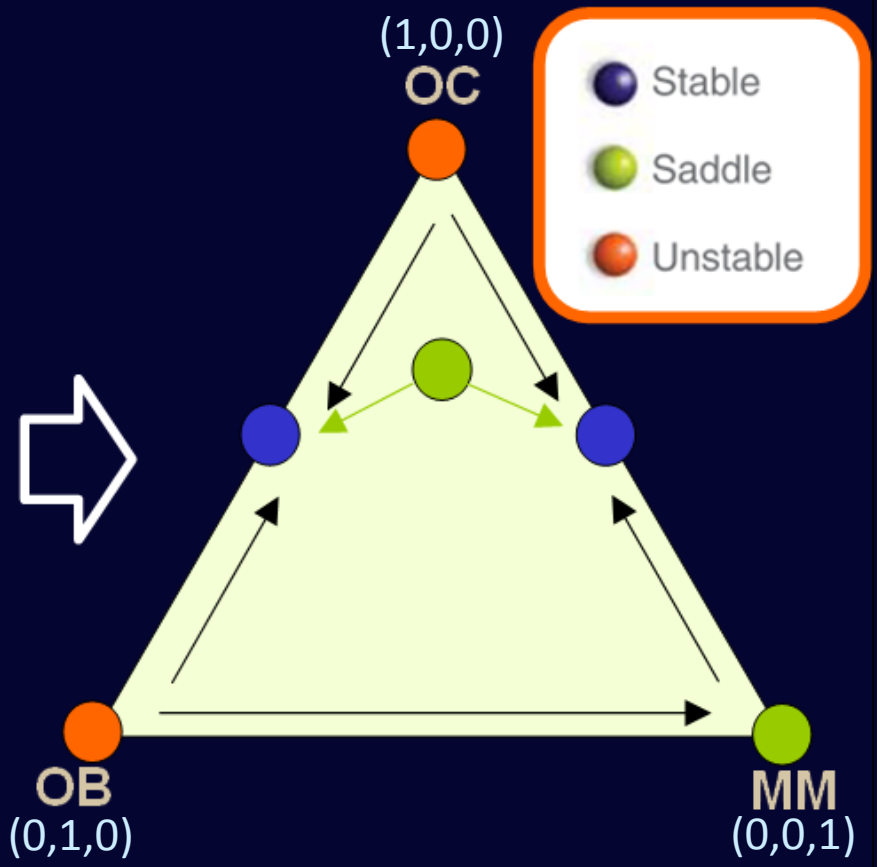
- $\delta$ measures the (net) ***negative*** impact on OB cells by MM cells
- $\beta$ measures the ***synergistic*** effect between MM and OC cells
- a **symmetric feedback** OC←→OB (=1) positions the equilibrium associated with normal physiology at $x_{OC} = x_{OB} = 0.5$

# Fixed points of the disease dynamics

fixed points ($x_{OC}^*, x_{OB}^*, x_{MM}^*$) of the evolutionary dynamics under the reduced matrix :

- (0,1,0) and (1,0,0) are *unstable* fixed points
- (½,½,0) associated with a healthy physiology is *unstable* whenever $\beta > 1$, being *stable* otherwise
- (½,0,½) is *stable* whenever $\beta > 1$ or whenever $\beta < 1$ and $\beta + \delta > 1$
- In the latter case, there is an internal saddle point located at

$$q^* = \left( \frac{\delta}{1+\delta+\beta(\delta+\beta-2)}, \frac{\beta(\delta+\beta-1)}{1+\delta+\beta(\delta+\beta-2)}, \frac{1-\beta}{1+\delta+\beta(\delta+\beta-2)} \right)$$



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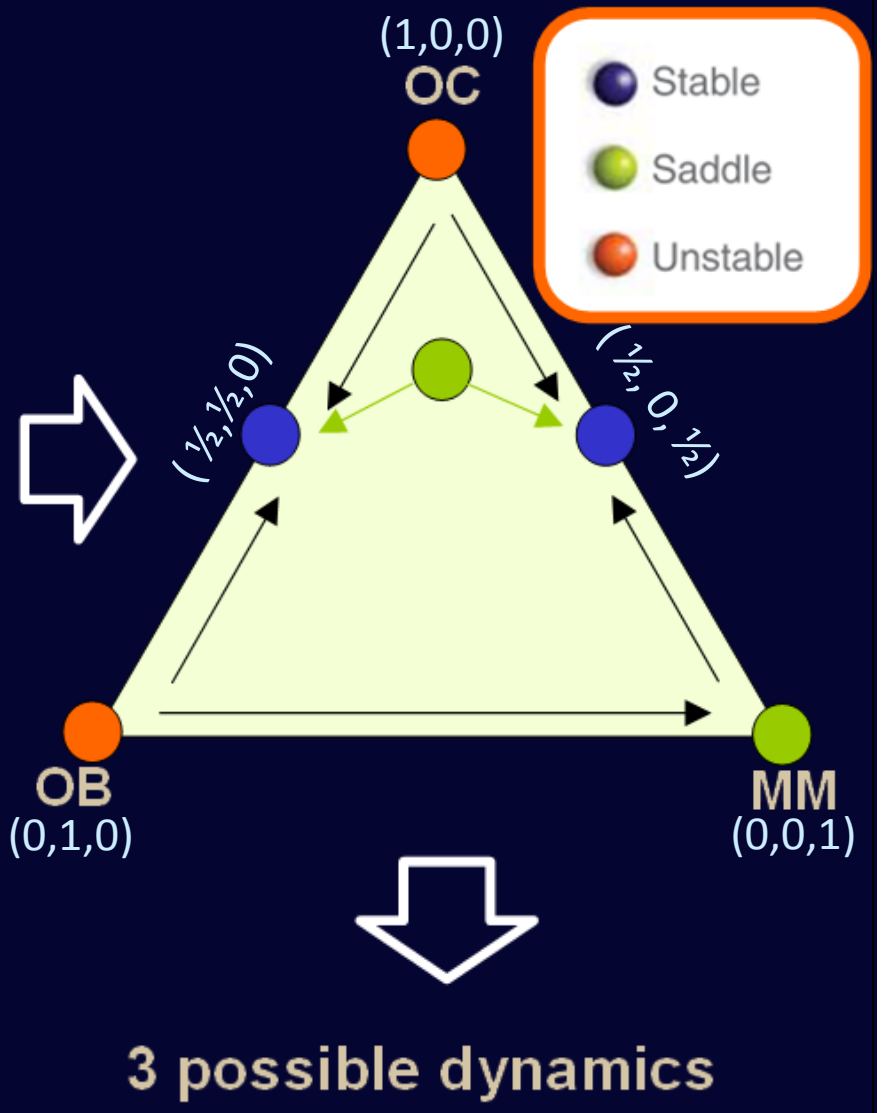
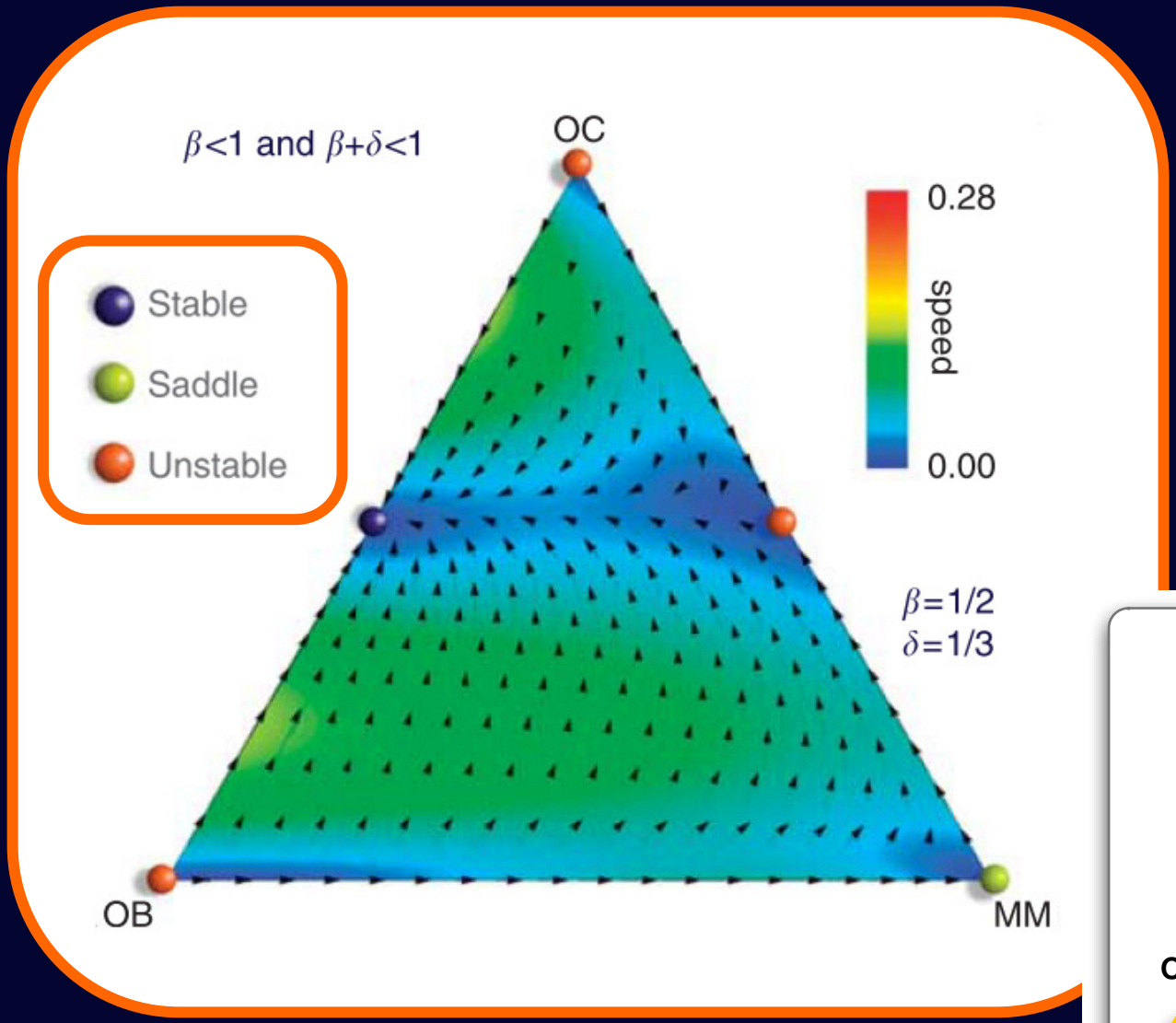
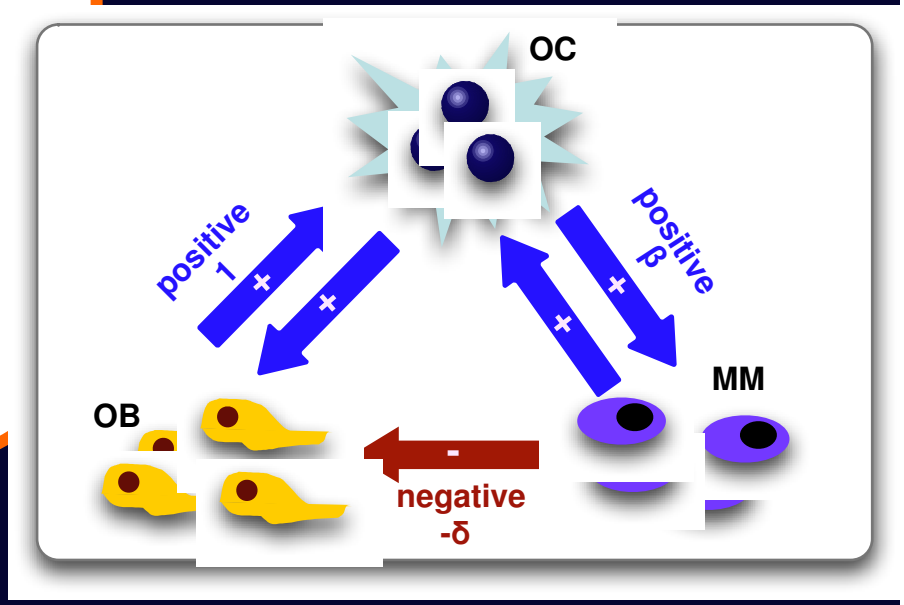


# possible dynamical scenarios under pathological conditions

case 1

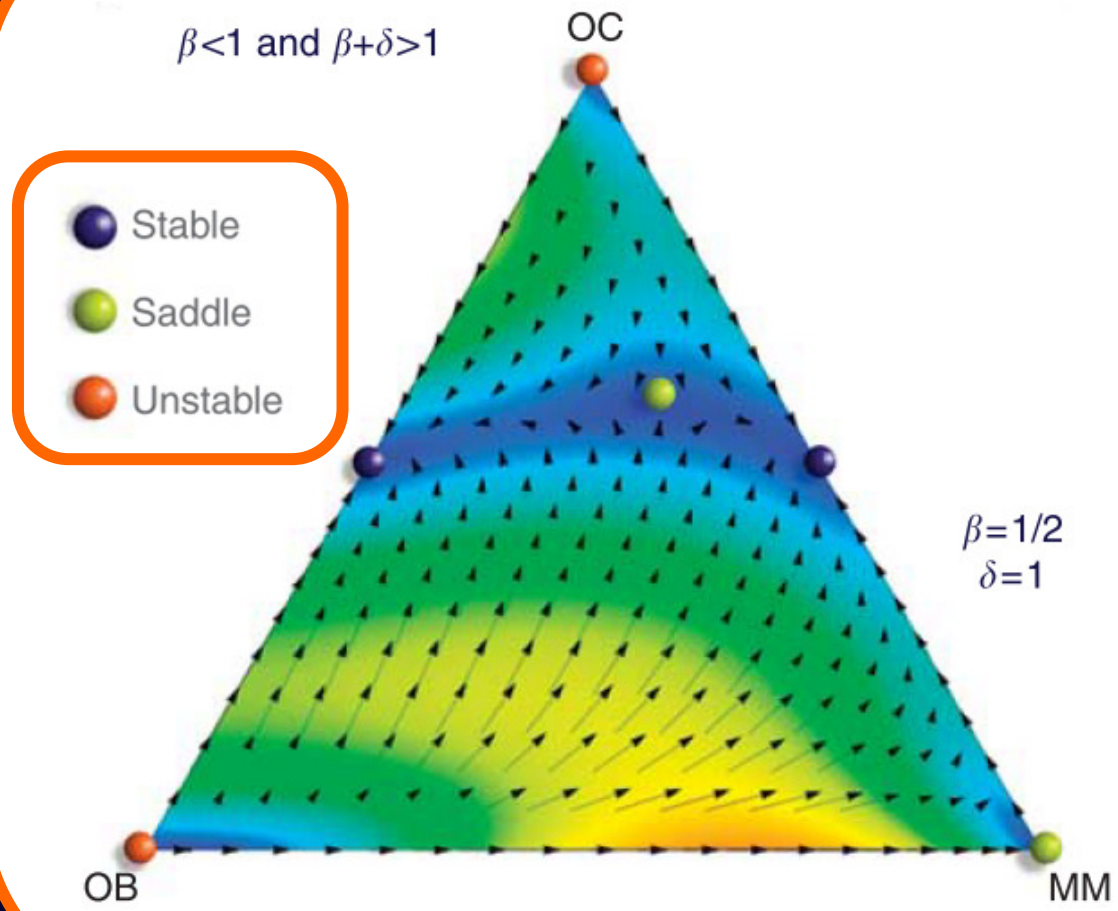
never detected, right ?

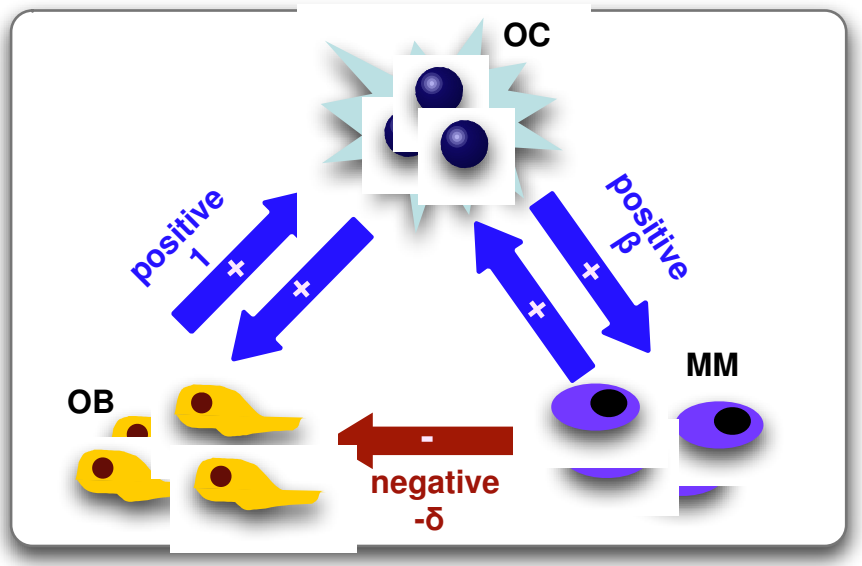


# possible dynamical scenarios under pathological conditions

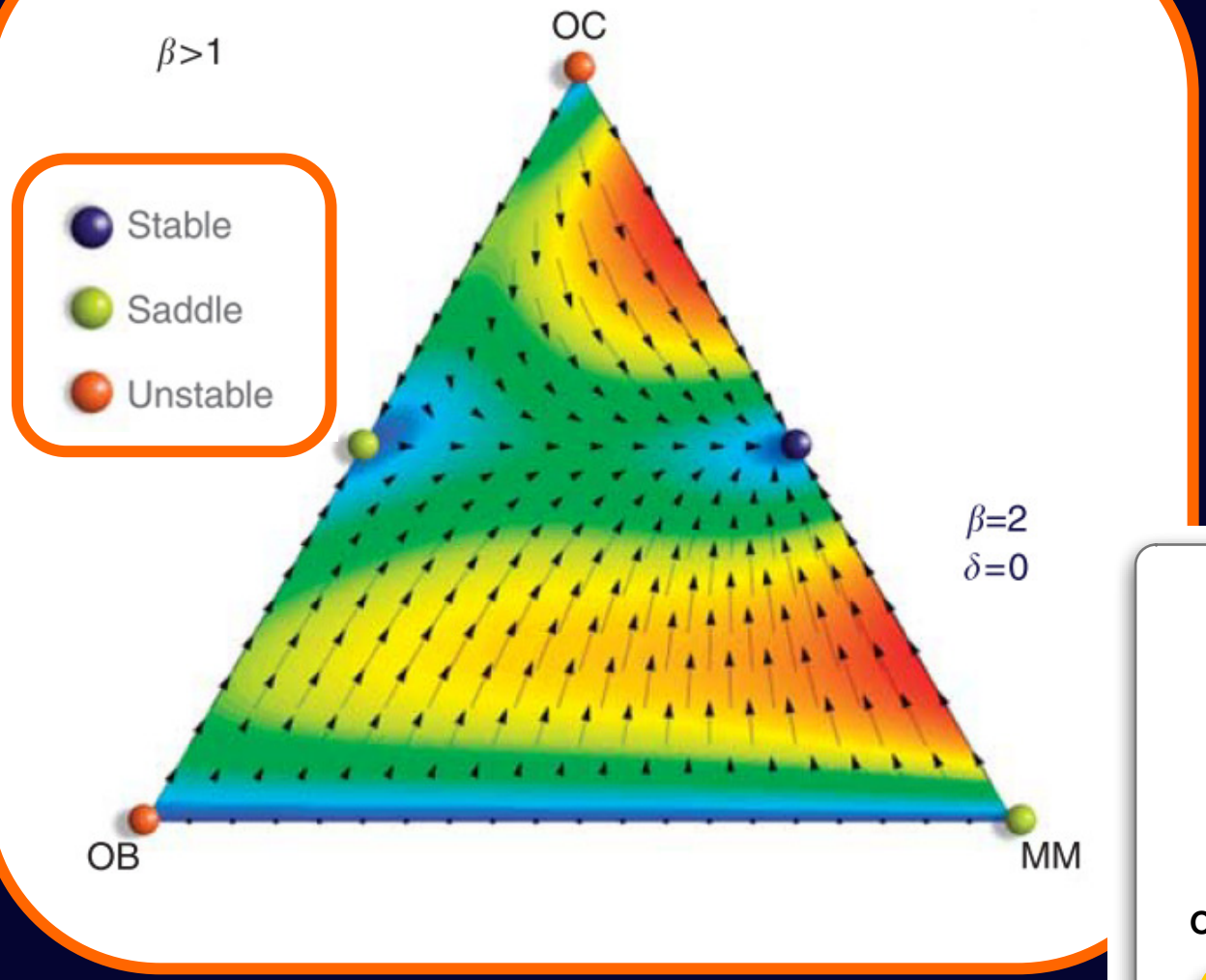
case 2

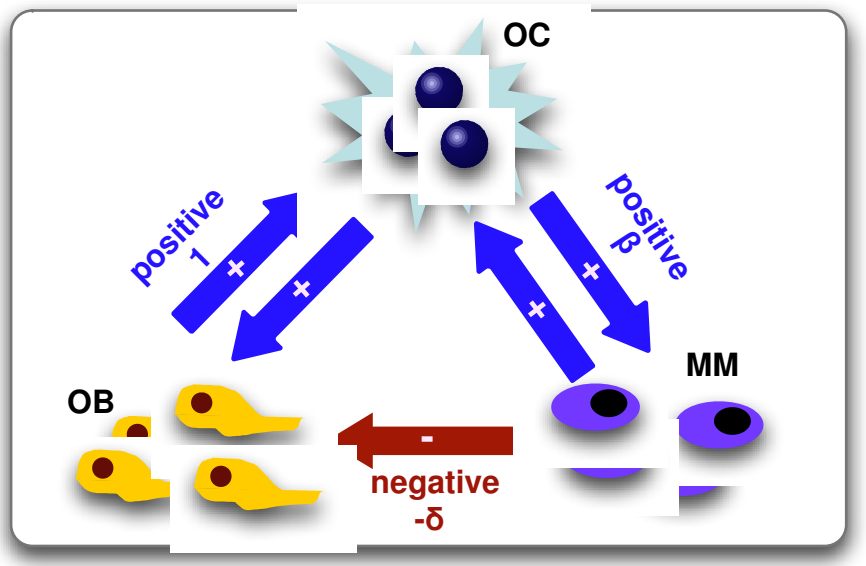


# possible dynamical scenarios under pathological conditions

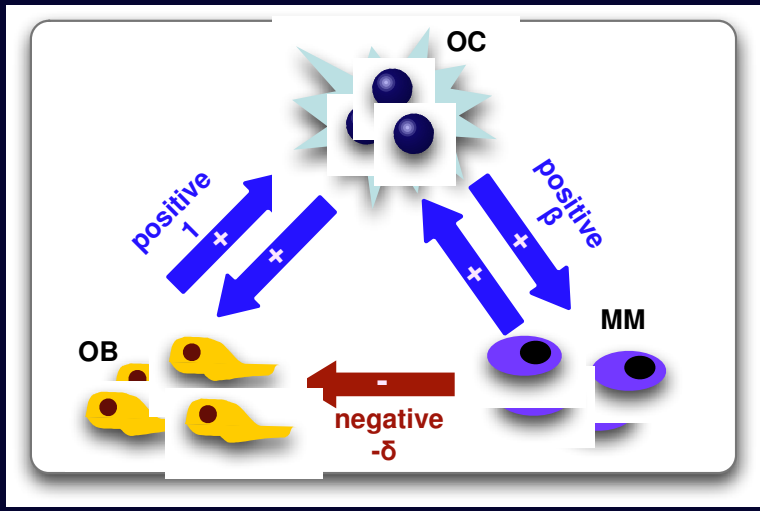
case 3



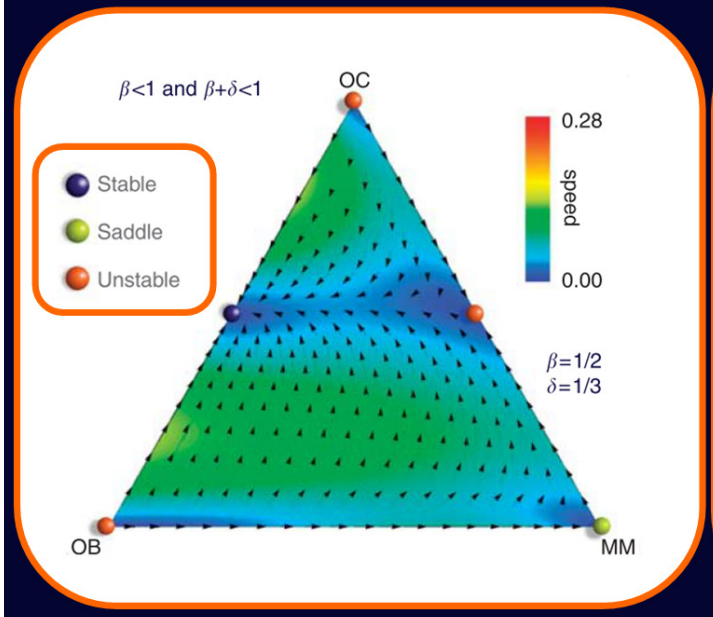



# possible dynamical scenarios under pathological conditions

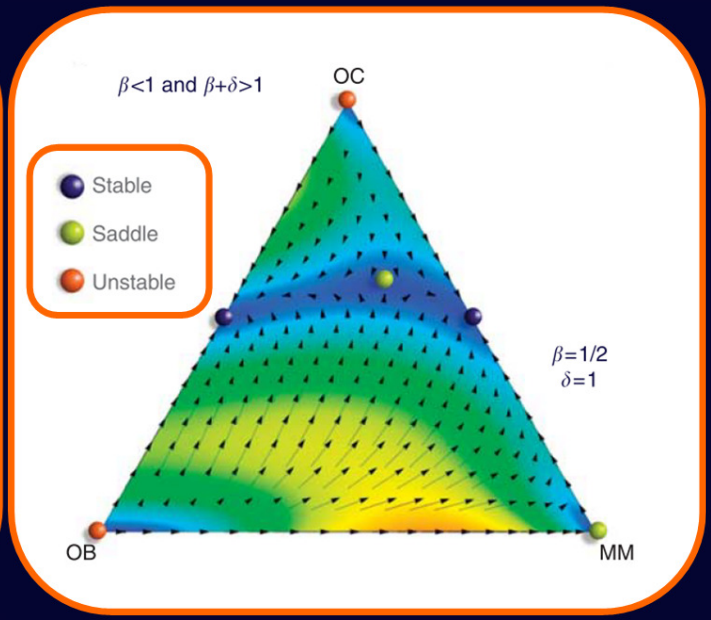
- agents that alter $\beta$ (ex: bisphosphonates, MIP-$\alpha$, IL-6) can lead the dynamics to a healthy state.
- even when $\beta<1$, changing $\delta$ (ex: Dkk1) may modify the position of the saddle point



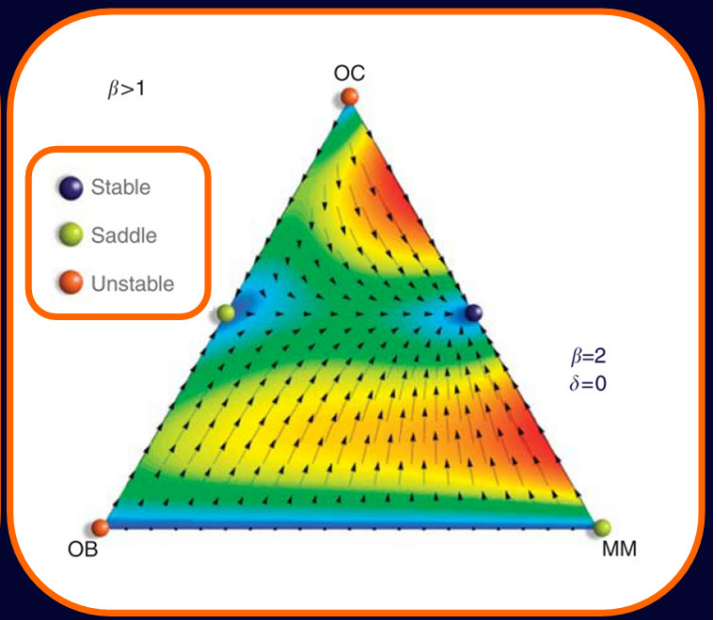

Case 1




Case 2

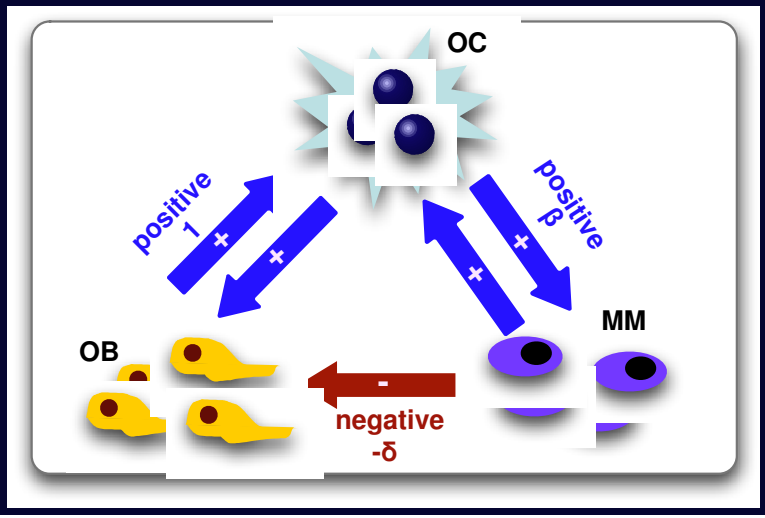


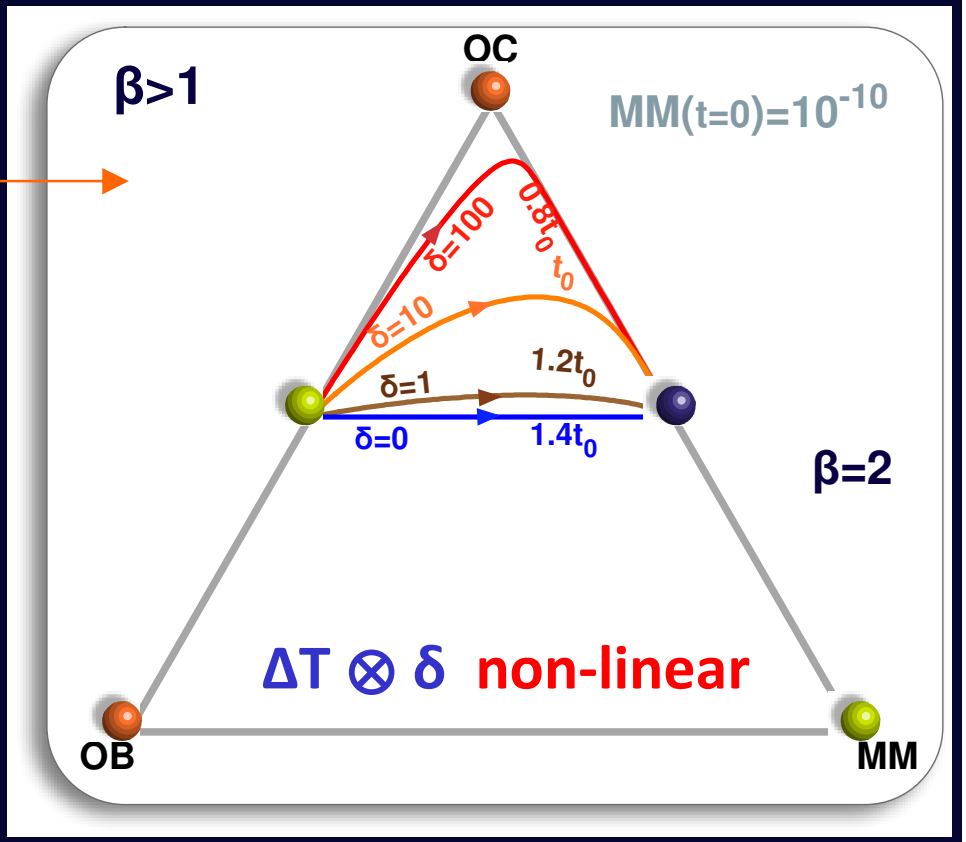

Case 3



# $\beta > 1$

- various studies suggest that $\beta < 1$ is the exception rather than the norm [Roodman, 2002] & [Epstein, 2003]
- $\delta$ has an impact on the time associated with disease progression
- therapies aiming at reducing $\delta$ (ex: Dkk1, sFRP-2) may change disease paths & progression time.
- large $\delta$ mimics common myeloma-induced osteoporosis without large MM cell burden



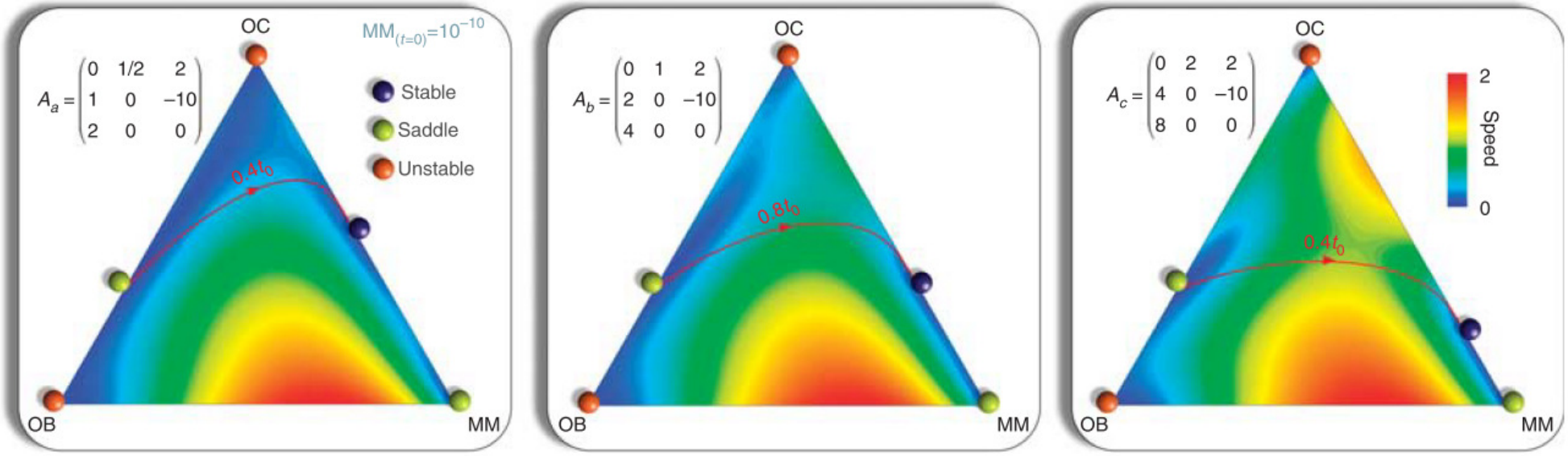



## the era of individualized medicine

$$\begin{array}{c} \\ OC \\ OB \\ MM \end{array} \begin{array}{c} \begin{array}{ccc} OC & OB & MM \end{array} \\ \begin{bmatrix} 0 & a & b \\ e & 0 & -d \\ c & 0 & 0 \end{bmatrix} \end{array}$$

- genetic differences in myeloma cells
- normal physiology varies from patient to patient

⇨ characterizing host-specific disease progression




$\beta$ =2.0 $\delta$ =10.0

## conclusions

- employing the principles of EGT we managed to describe the core features of MM using 2 parameters.

- therapies that kill MM cells can slow down the disease progression and improve bone structure (via chemo-
- therapy and stem cell transplantation).
  yet, the disease invariably relapses.

- agents that alter $\beta$ (ex: bisphosphonates) can change the disease dynamics by "*altering the game*", leading to a "*stable*" & "*healthy*" dynamics.

[ Dingli, Chalub, Santos, Segbroeck, Pacheco,
*British Journal of Cancer* 101 1130-1136 (2009)]

## conclusions

- **this has been tested: therapy against MIP-α (an agent that contributes to β) blocked bone destruction in a mouse MM** (Choi et al, *J Clin Invest* 2001)**.**

- **in humans,** Lust et al, *Mayo Clin Proc* 2009 **showed that therapies which reduce one of the factors included in β (IL-1 β) slows down the progression of the disease.**

- **similarly, therapies that reduce δ may attenuate morbidity by slowing the speed of bone loss. This has also been tested by means of therapies against Dkk-1 (an agent that contributes to δ)** (Yaccoby et al, *Blood* 2007)

**[ Dingli, Chalub, Santos, Segbroeck, Pacheco,**
***British Journal of Cancer* 101 1130-1136 (2009)]**

**a common take-home message**
**regarding the**
**war on cancer**

***instead of trying to kill***
***every cancer cell . . .***

**a common take-home message regarding the war on cancer**

***instead of trying to kill every cancer cell . . .***

+

***therapies should aim at reducing the fitness of malignant cells, allowing natural selection to eradicate cancer cells***


end