the evolutionary dynamics of hematopoiesis
(in health & disease)

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http://dl.dropbox.com/u/6053055/SP2016-2-of-5.pdf

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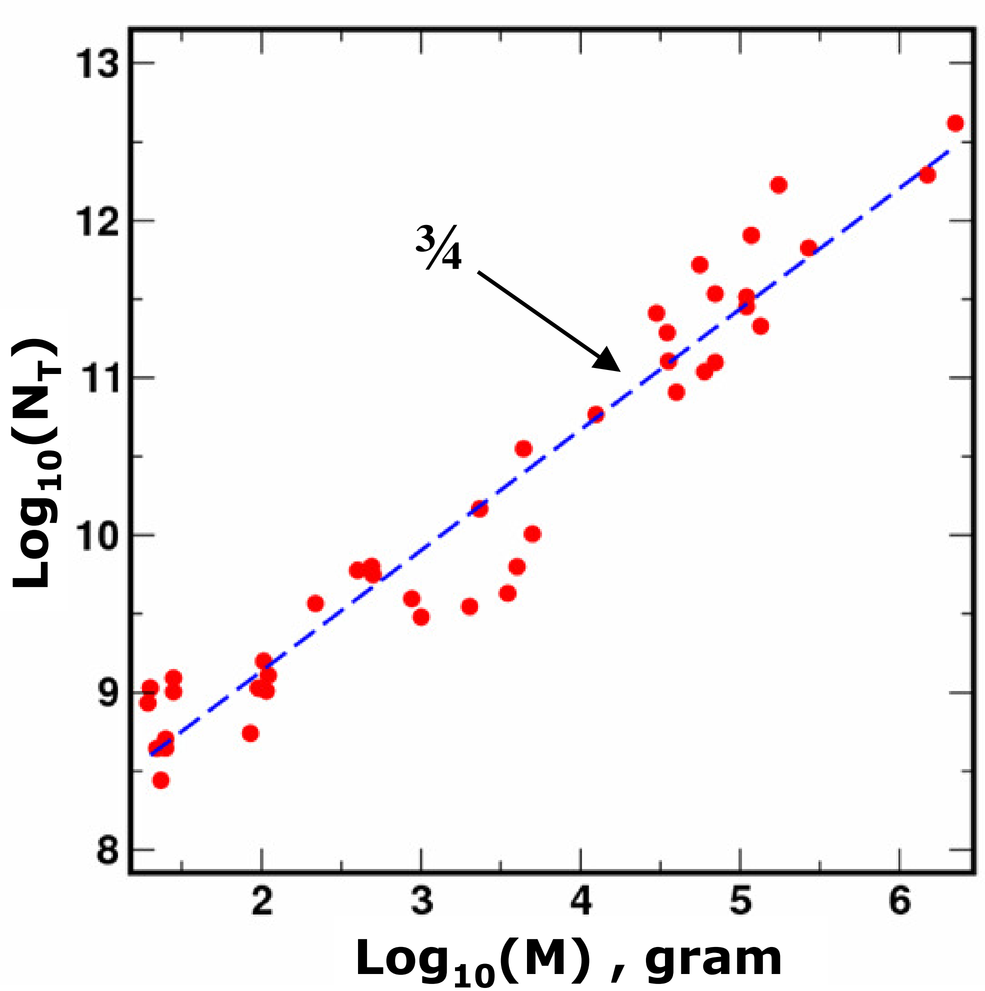
layout

tuesday – 11:15 – 12:30

- human ontogeny & hematopoiesis
- allometric scaling of metabolic rate during ontogeny
- energy allocation during ontogeny
- HSC scaling during ontogeny
- the mouse as a model of human hematopoiesis ?

a scaling model of HSCs



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

Dingli & Pacheco, *PLoS ONE*, 2006

a scaling model of HSCs

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

HSC scaling during ontogeny

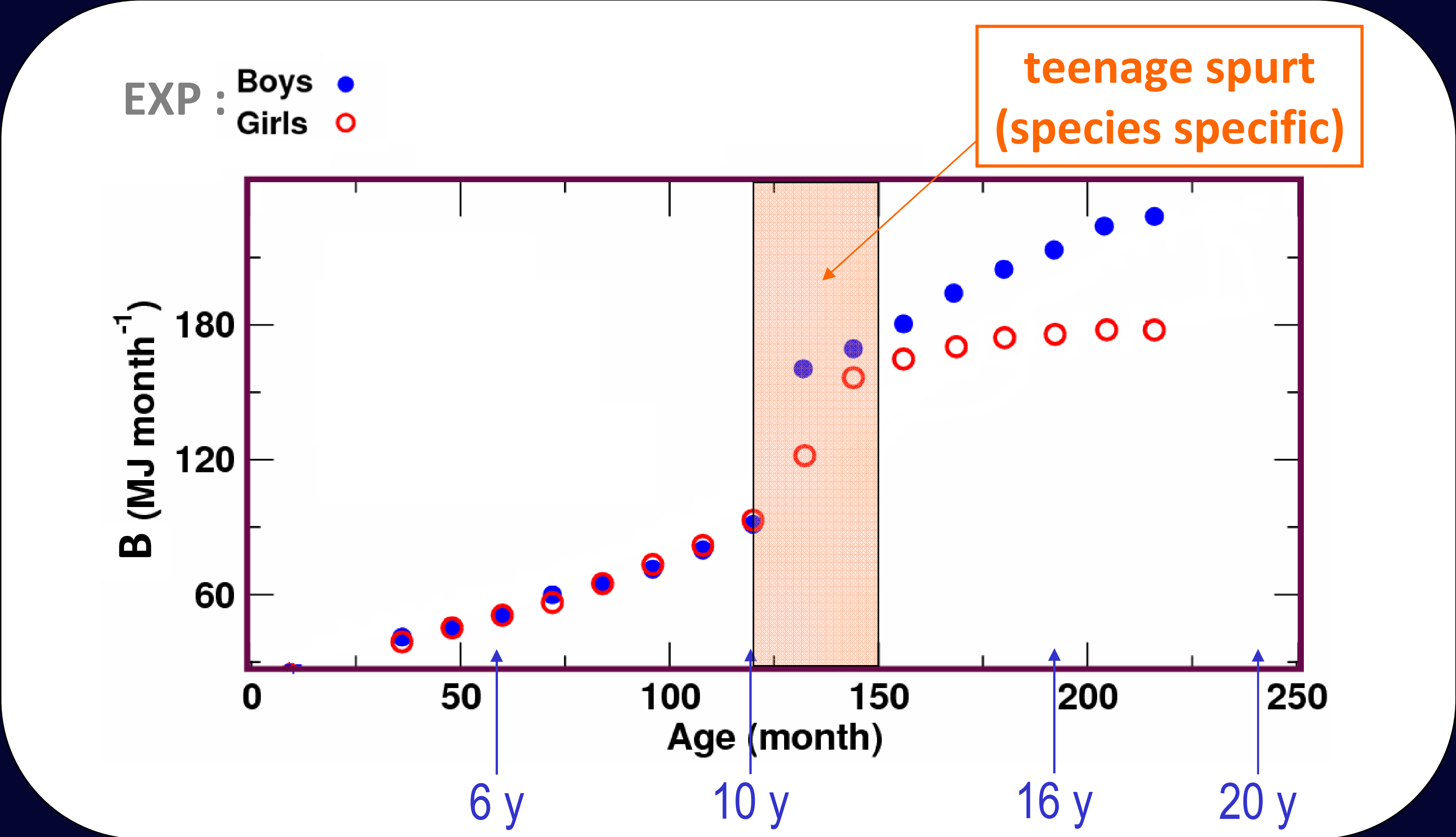
Dingli & Pacheco, *PRS* ***B****274 (2007) 2479*

scaling during human ontogeny

- *previous relations were valid for adult mammals (inter-species)*
- ***what happens during human growth ?***
- *does a **newborn baby** with **4kg** have the same number of* **HSC** *than an **adult cat** with **4kg** ?*
- ***allometric scaling also during ontogeny ? How does energy consumption scale with mass during ontogeny ?*** *(intra-species)*

energy allocation during ontogeny

***EXPerimentally**, the rate of energy expenditure in humans is*



Brody, S. 1964 Bioenergetics and growth. Darien, CT: Hafner Press.

energy allocation during ontogeny

$B(t)$: *rate of energy consumption of a growing organism at time t*

Theoretically, $B(t)$ *receives contributions from 2 terms*

$$B(t) = \sum_{c = cell\ types} \left[\text{maintenance} + \text{growth} \right]$$

G. West et al., *Nature* 413 (2001) 628

energy allocation during ontogeny

$B(t)$: *rate of energy consumption of a growing organism at time t*

cells of given type

metab. rate of cells at time *t*

$$B(t) = \sum_{c\,=\,cell\ types} \left[N_c(t) B_c(t) + \qquad \right]$$

maintenance

growth

energy allocation during ontogeny

$B(t)$: *rate of energy consumption of a growing organism at time t*

energy cost of producing a new cell

rate of cell growth

$$B(t) = \sum_{c = cell\ types} \left[N_c(t) B_c(t) + E_c \frac{dN_c(t)}{dt} \right]$$

maintenance

growth

energy allocation during ontogeny

rewriting in terms of mass **:**

$$B(t) = \frac{B_c}{m_c} m(t) + \frac{E_c}{m_c} \frac{dm(t)}{dt}$$

maintenance **growth**

energy allocation during ontogeny

rewriting in terms of mass **:**

$$B(t) = \frac{B_c}{m_c} m(t) + \frac{E_c}{m_c} \frac{\mathrm{d}m(t)}{\mathrm{d}t}$$

maintenance **growth**

we use **:**

G. West et al.,
Nature 413 (2001) 628

$B_c = B_0 M^{-1/4}$ = (*humans*) = 9.77×10^{-6} J .month^{-1}

$E_c = 2.1 \times 10^{-5}$ J

$m_c = 3 \times 10^{-12}$ kg

energy allocation during ontogeny

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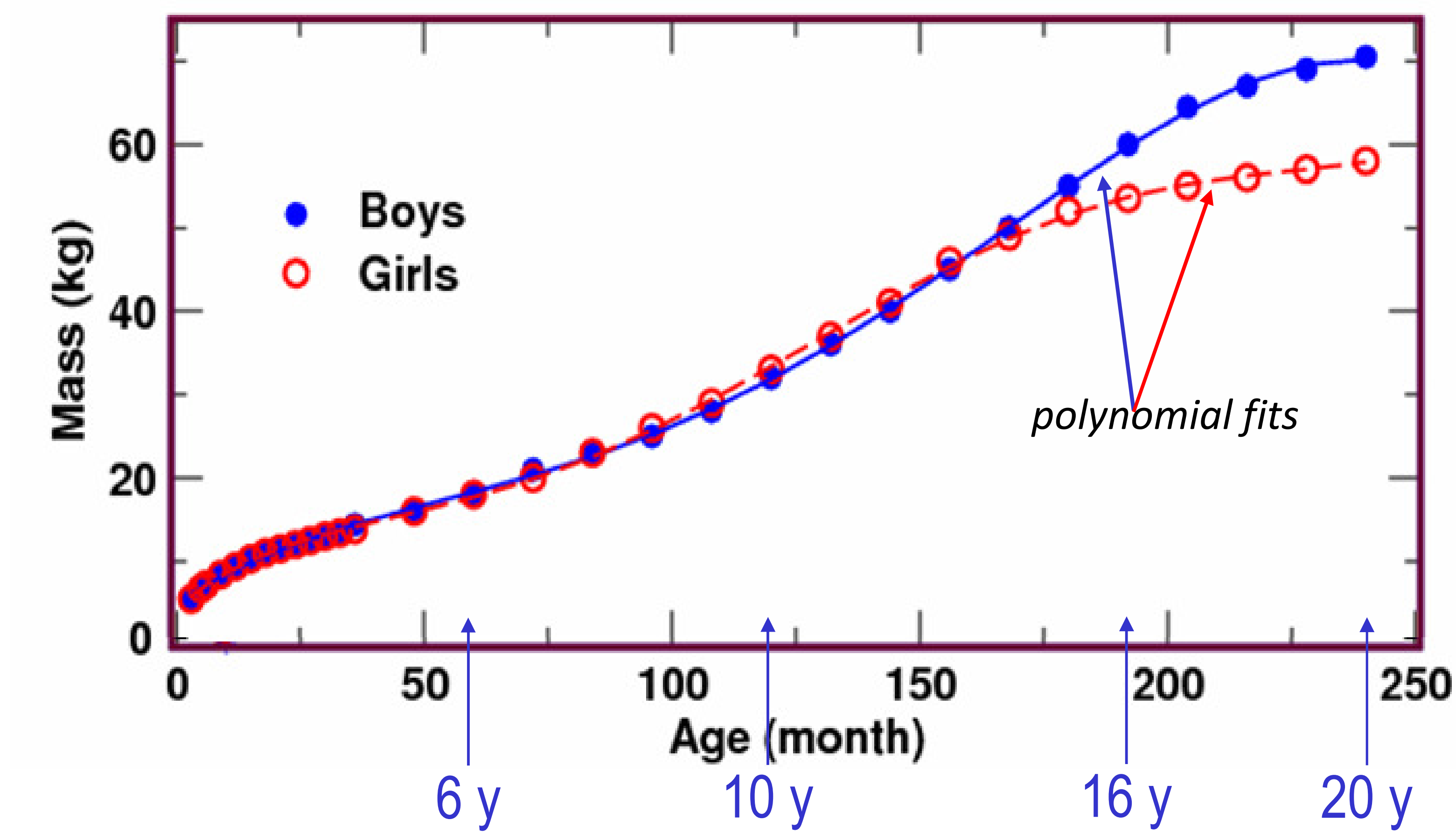
& **what about $m(t)$?**

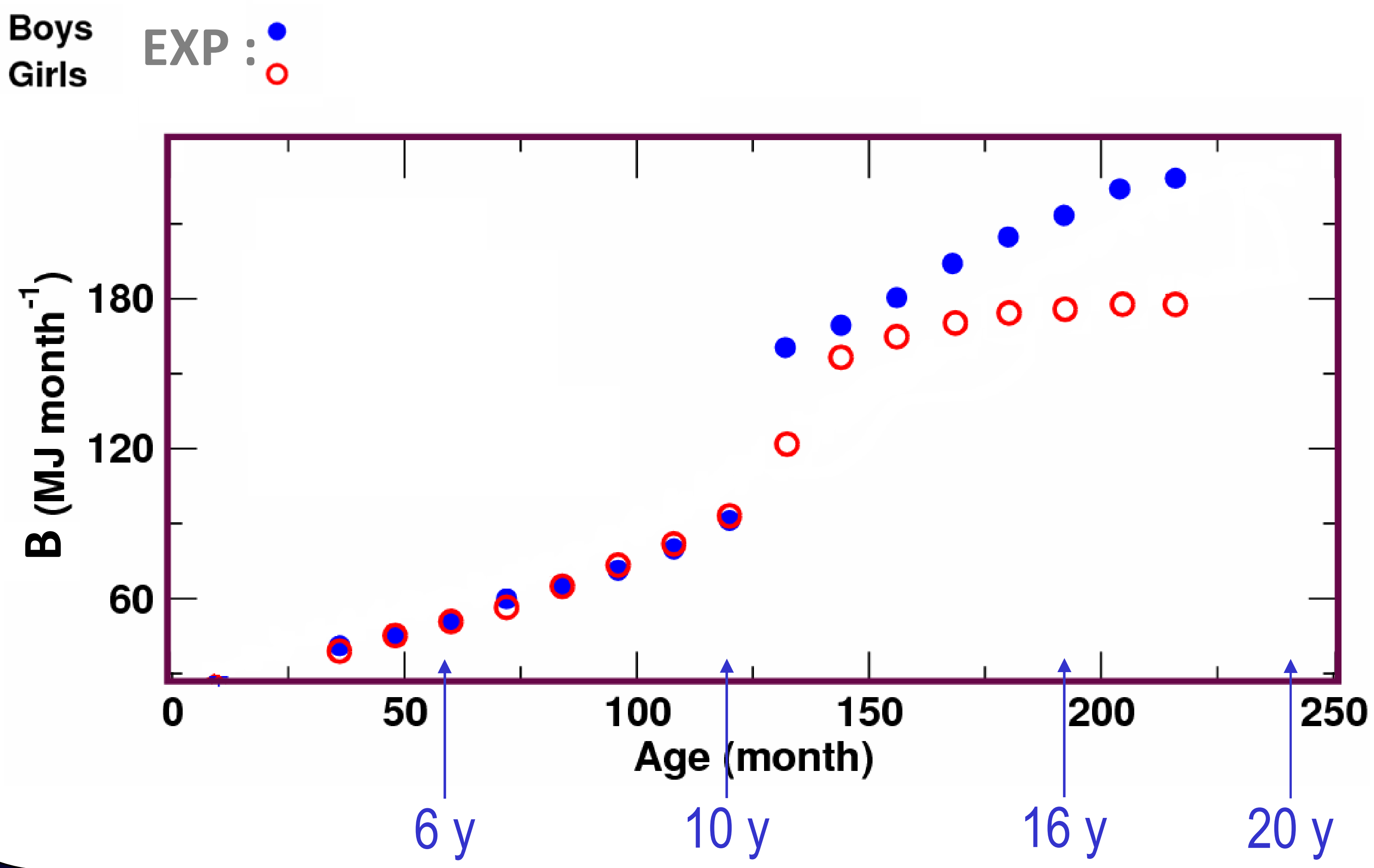
energy allocation during ontogeny

using Experimental values for $m(t)$



energy allocation during ontogeny

we get



energy allocation during ontogeny

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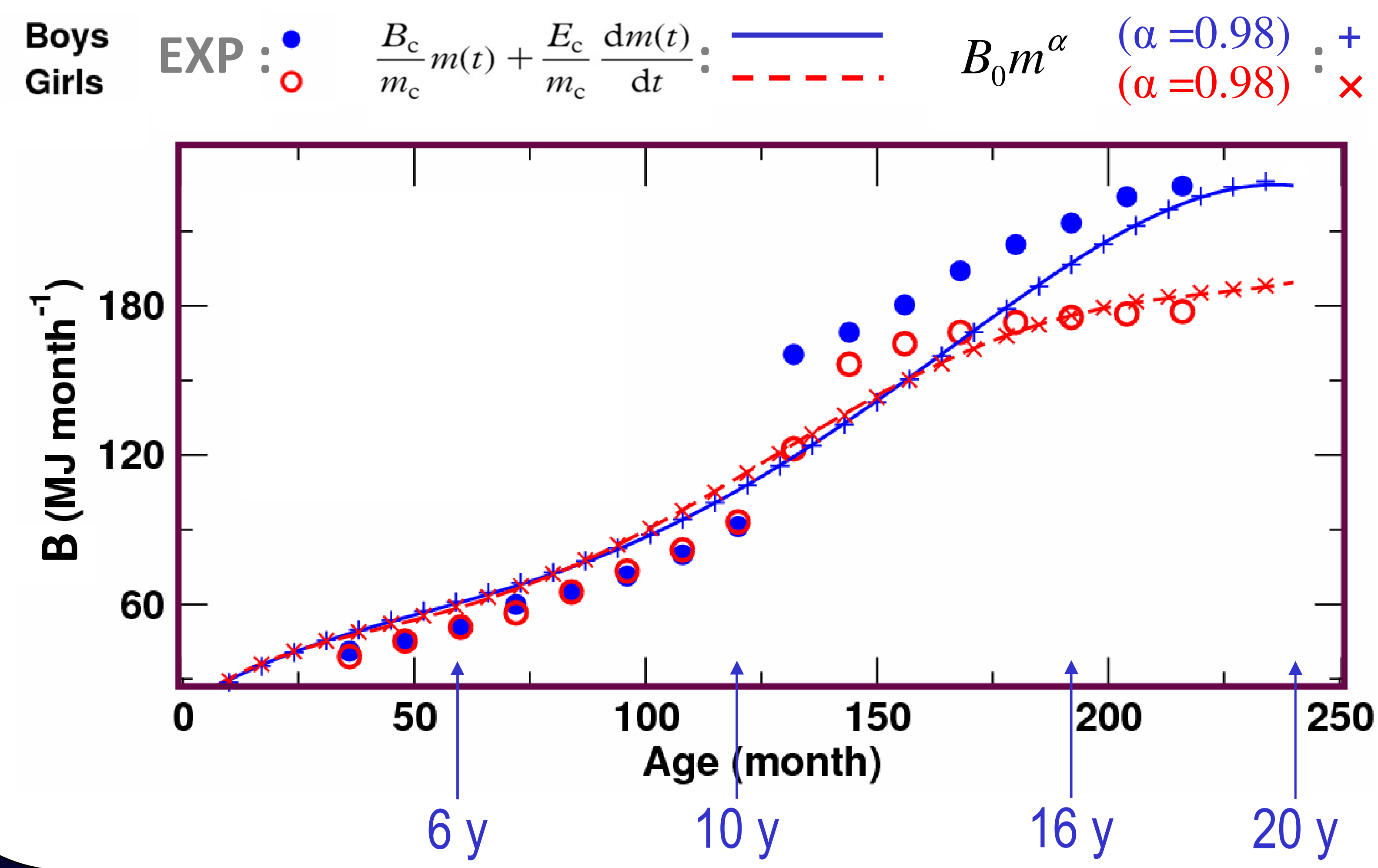


energy allocation during ontogeny

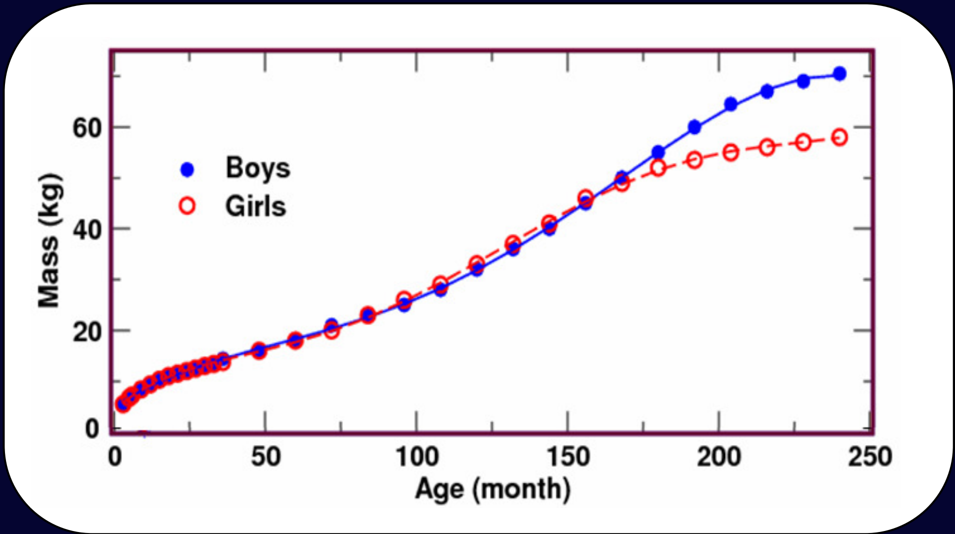
- *since $0.98 \approx 1$, energy allocation leads essencially to a linear scaling of the energy consumption rate with mass during ontogeny*

- *this is different from the $M^{3/4}$ scaling found in adult mammals*

- *thus, one may expect that HSC scaling with m during ontogeny to be different as well.*

scaling of mean reticulocyte count

- *we know empirically how mass **m** changes with **time** during ontogeny:*



- *if we assume that the structure of the hematopoietic tree remains unchanged during ontogeny,*

- *then knowledge of mean reticulocyte count N_R as a function of **time** will allow us to **find how N_R scales with m***

scaling of mean reticulocyte count

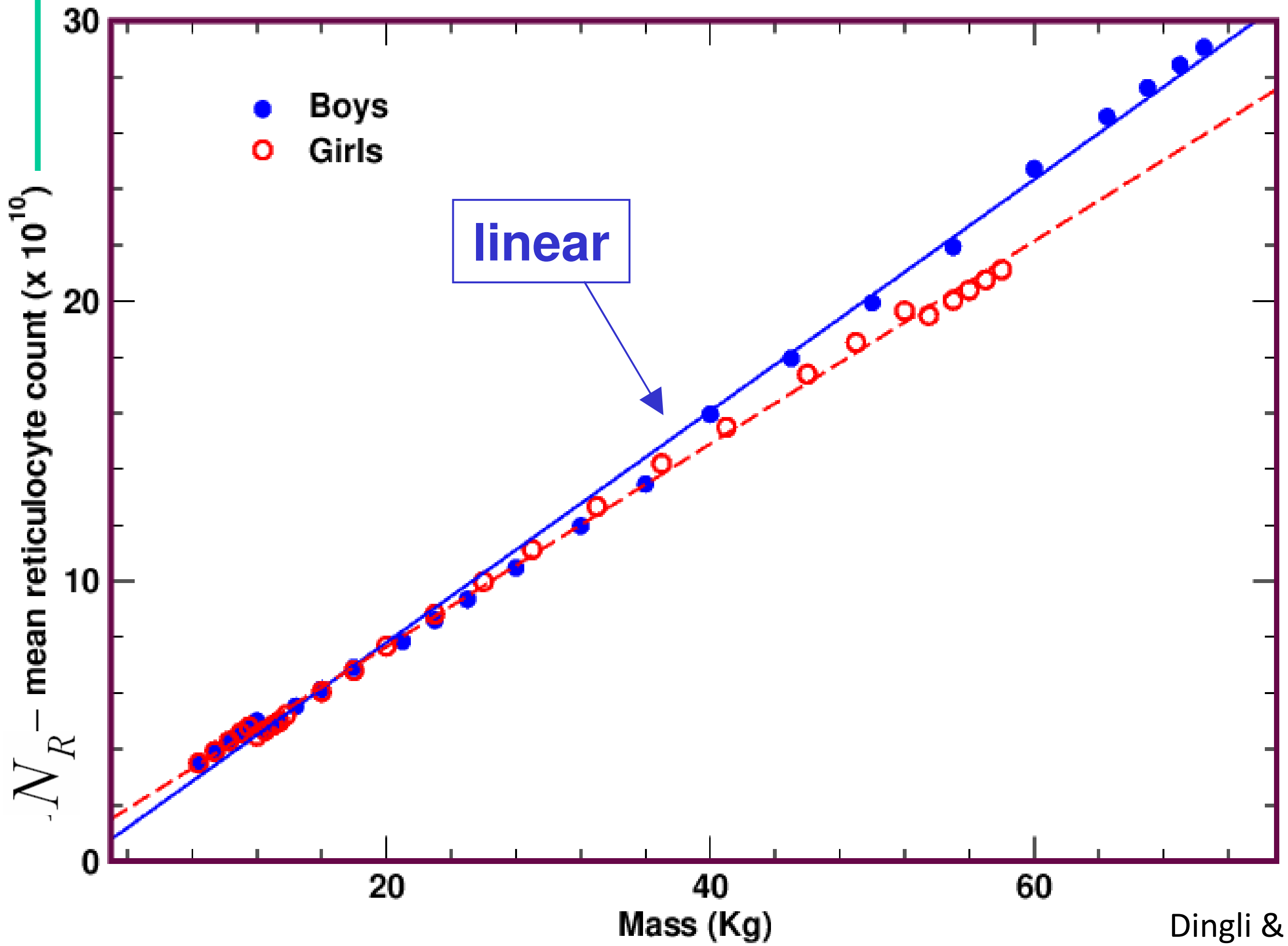
red blood cells / liter

blood volume

retics percentage

$$N_R = RBC \times BV \times RT$$

(age specific)



$$\left.\begin{array}{l} N_R(t) \\ M(t) \end{array}\right\} N_R(M)$$

Dingli & Pacheco, *PRS B274 (2007) 2479*

Goldston, E., Reynolds, A. (2005) *in Current Pediatric Diagnosis and Treatment*, pp 66-101 (Hay, W.W., Levin, M.J., Sondheimer, J.M., Deterding, R.R., Edts.)

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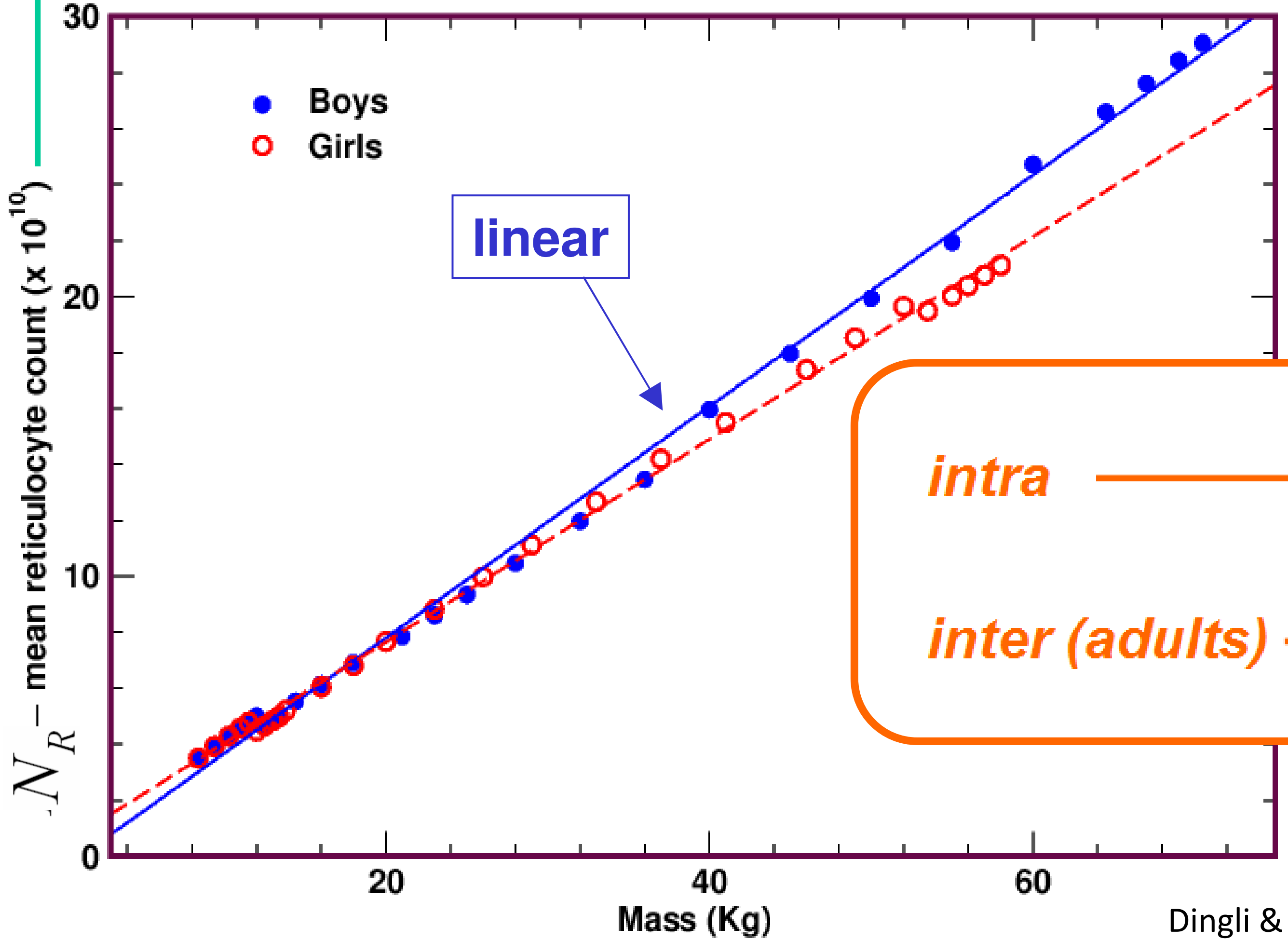

$$\left.\begin{matrix} N_R(t) \\ M(t) \end{matrix}\right\} N_R(M)$$

intra → $N_{SC} \sim m$

inter (adults) → $N_{SC} \sim M^{3/4}$

Dingli & Pacheco, *PRS B274 (2007) 2479*

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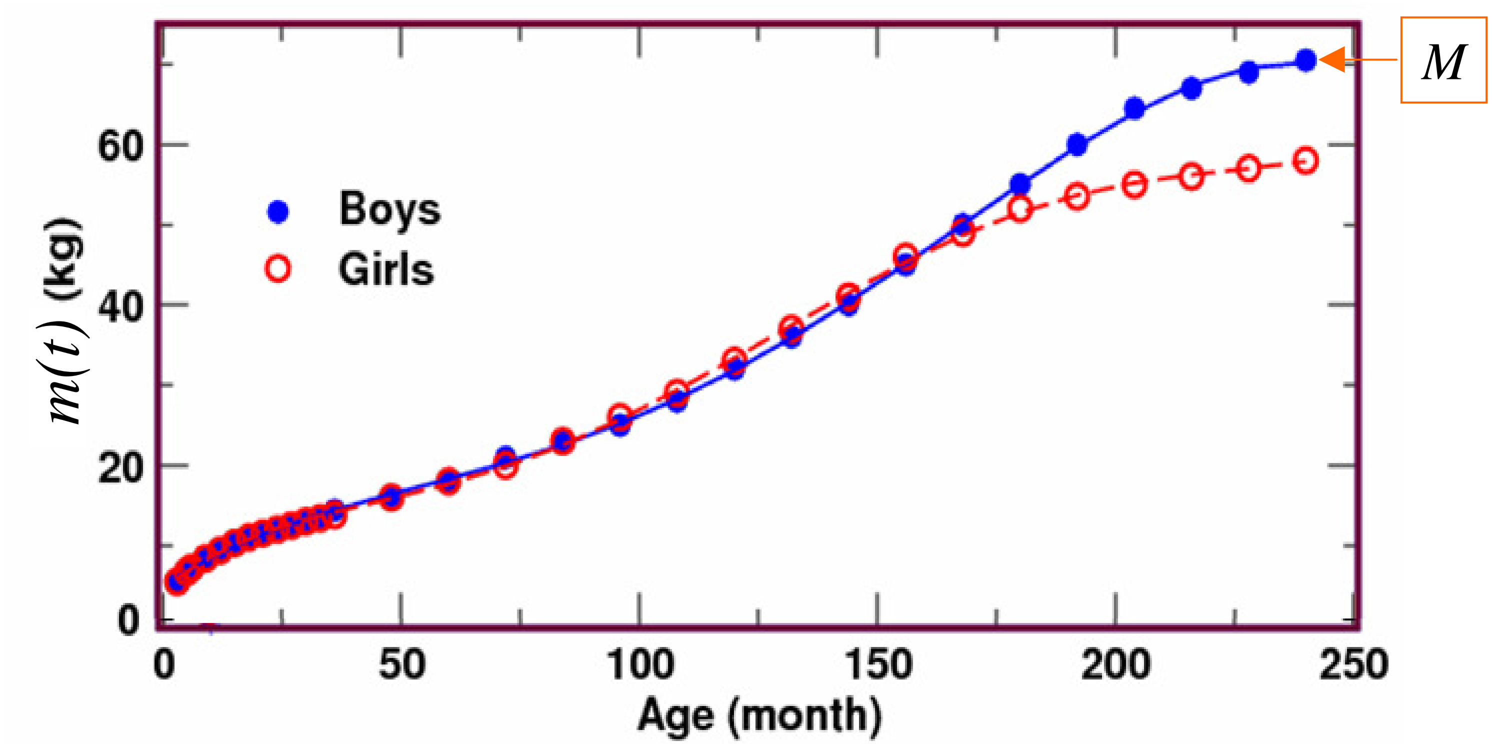
intra- & *inter*- species allometric scaling of HSC



	cats	Humans
newborn		~25
adult	~40	~400

intra → $N_{SC} \sim m$

inter (adults) → $N_{SC} \sim M^{3/4}$

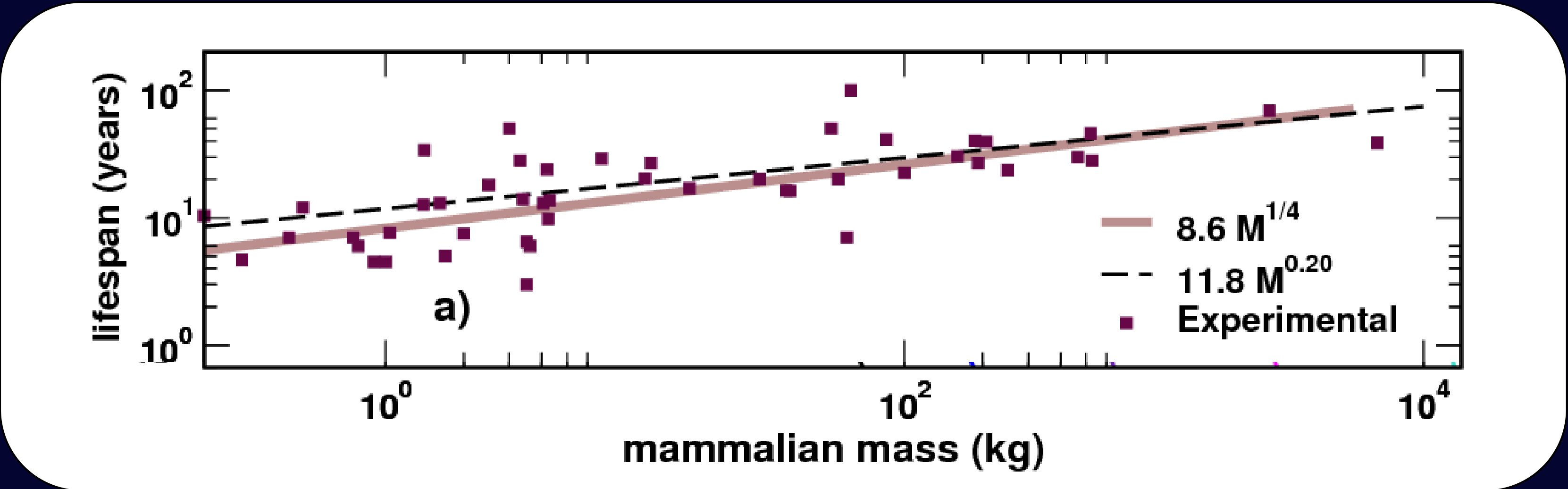
m (newborn Human) ~ M (adult cat) ~ 4 kg

Dingli & Pacheco, *PRS* ***B****274 (2007) 2479*

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 :* $$\rho_c \approx 2.9\, M^{-1/4}$$ (*year*$^{-1}$)
- *average life-span :* $$L \approx 8.6\, M^{1/4}$$ (*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 main exception, as we live much longer than the lifespan estimate.