A null model for the erosion of naive T cell repertoire diversity during aging

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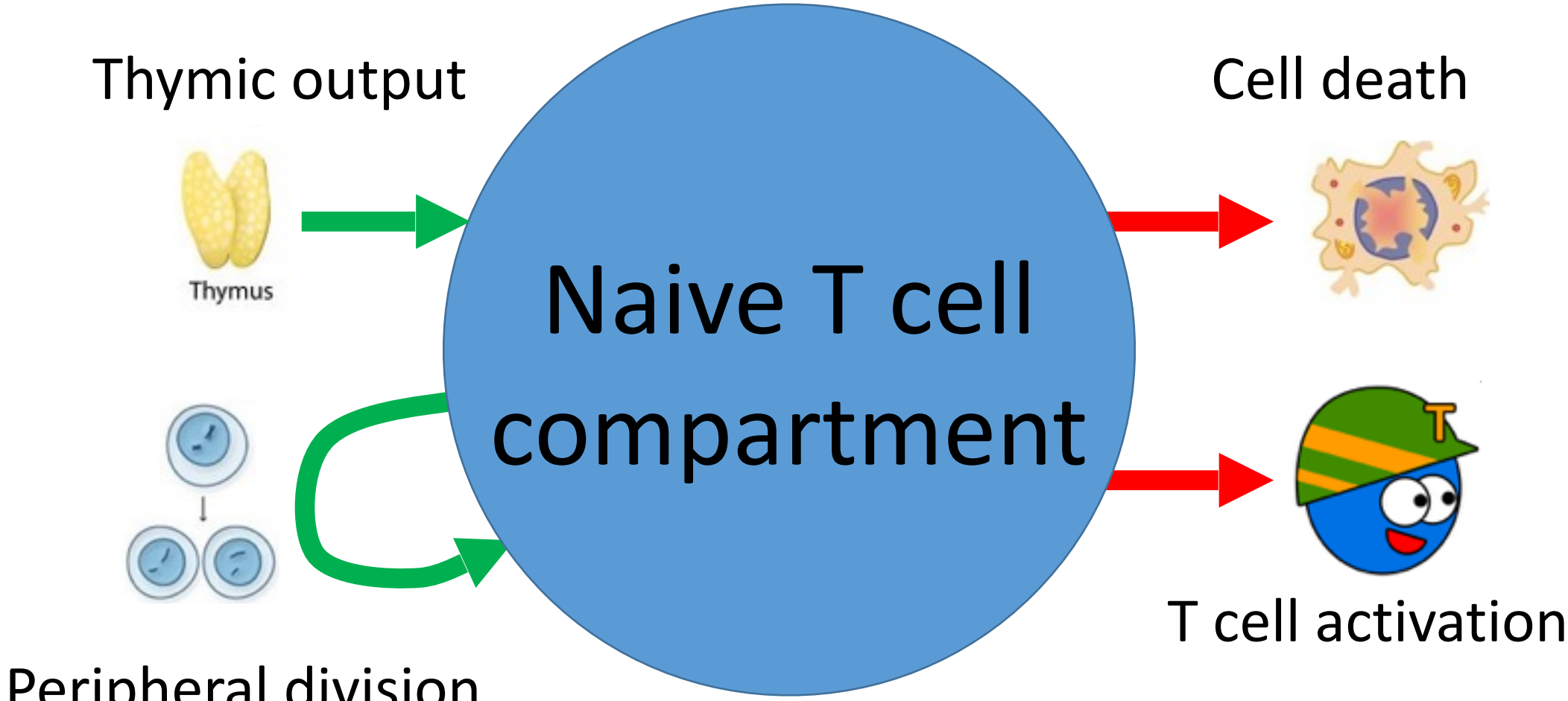
Introduction: Dynamics of naive T cells



wisegeek.org, bioninja.com.au, daviddarling.info, Immunology insight

Healthy aging of T cells

Elderly people respond poorly to vaccination

Old mice miss some of the CD8 responses to influenza epitopes (holes in the repertoire)

Number of naive T cells typically declines (in presence of CMV)

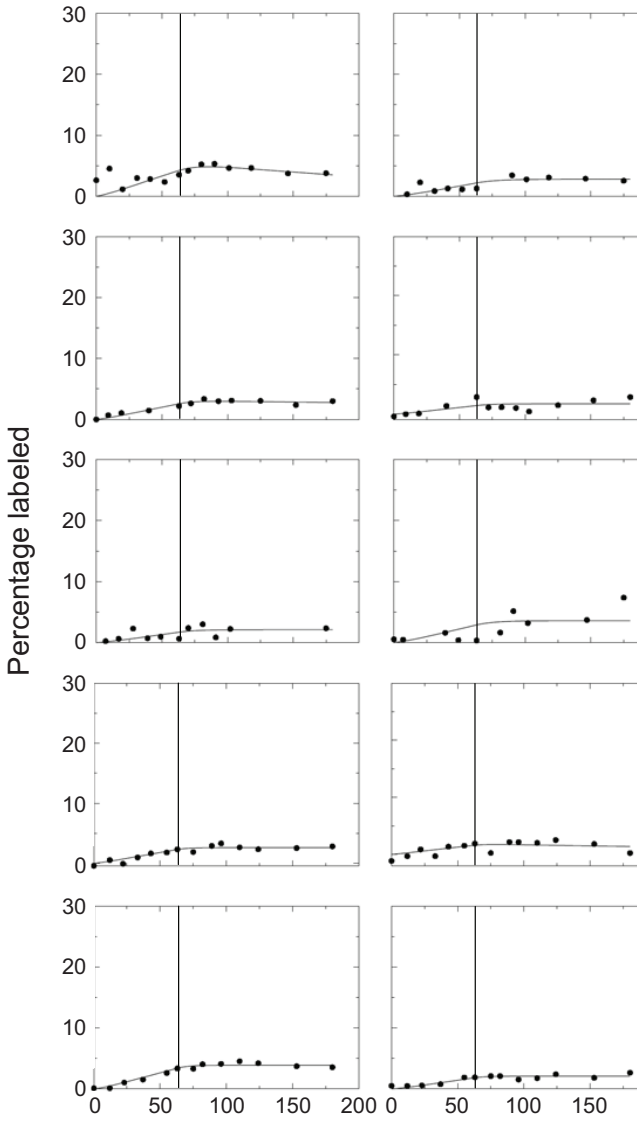
Some evidence that repertoire becomes skewed (Simpson diversity)

Effect on richness (number of clones) unclear

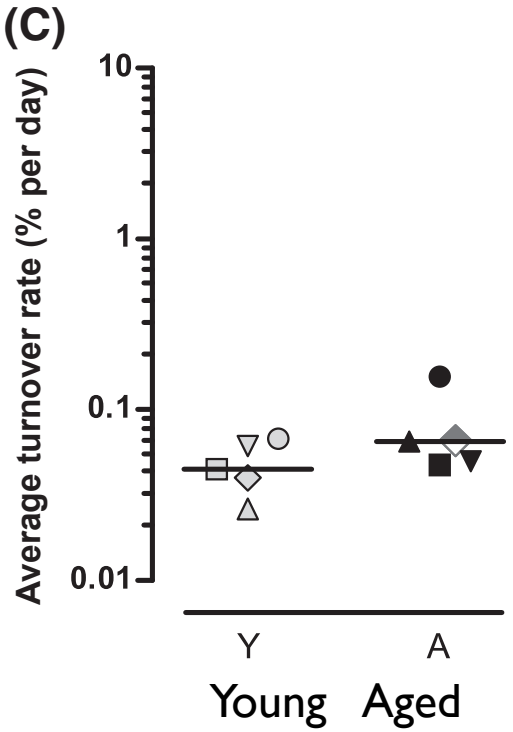
Thymus output declines 5% per y in humans and 50% per y in mice

Human naive T cells live 5-10 y (and divide)
Mouse naive T cells 1-3 mo (and hardly divide)

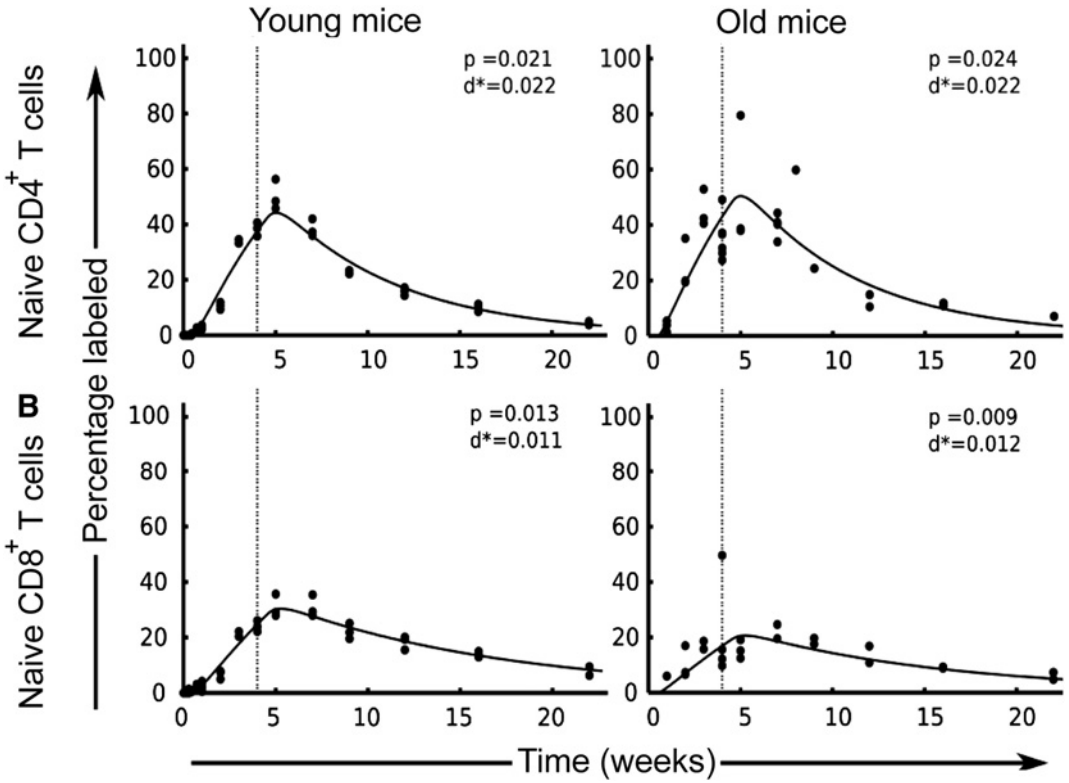
Vrisekoop et al PNAS 2006



Time in days



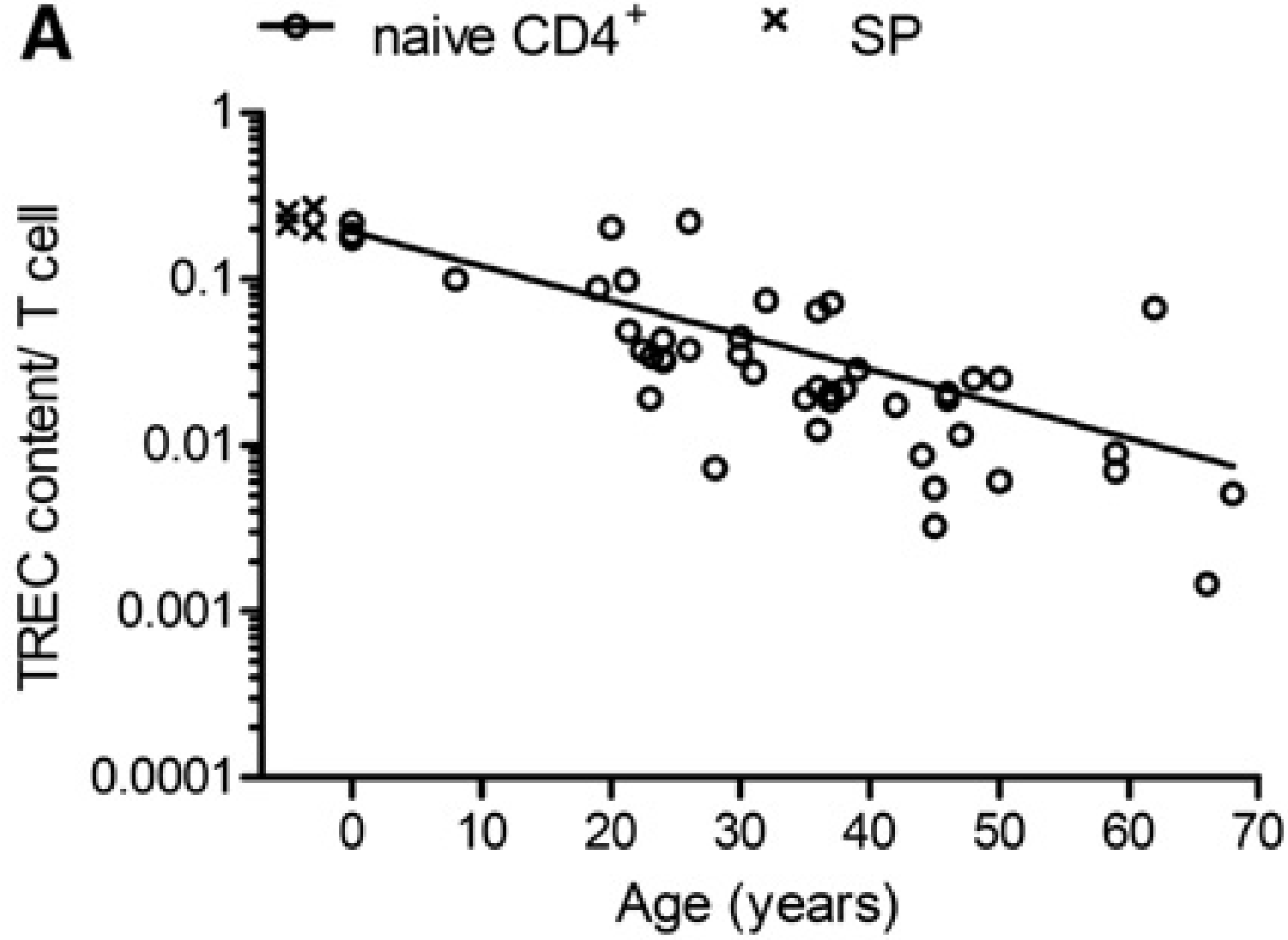
Westera et al Aging Cell 2015



Den Braber et al Immunity 2012

Thymus accounts for 20% of the production of naive T cells in young humans adults and for 2% in healthy elderly

Westera et al Immunity 2012



TREC is a DNA circle produced when the α-chain of the TCR re-arranges.

TRECs not duplicated upon division.

Basically a birthmark of cells produced in the thymus.

(after normalization)

Simple mathematical model

Naive T cells, N, and total TREC numbers, T:

$$\frac{\mathrm{d}N}{\mathrm{d}t} = s + (p - d)N \qquad \frac{\mathrm{d}T}{\mathrm{d}t} = cs - dT$$

Now define the average TREC content: $A = T/N$

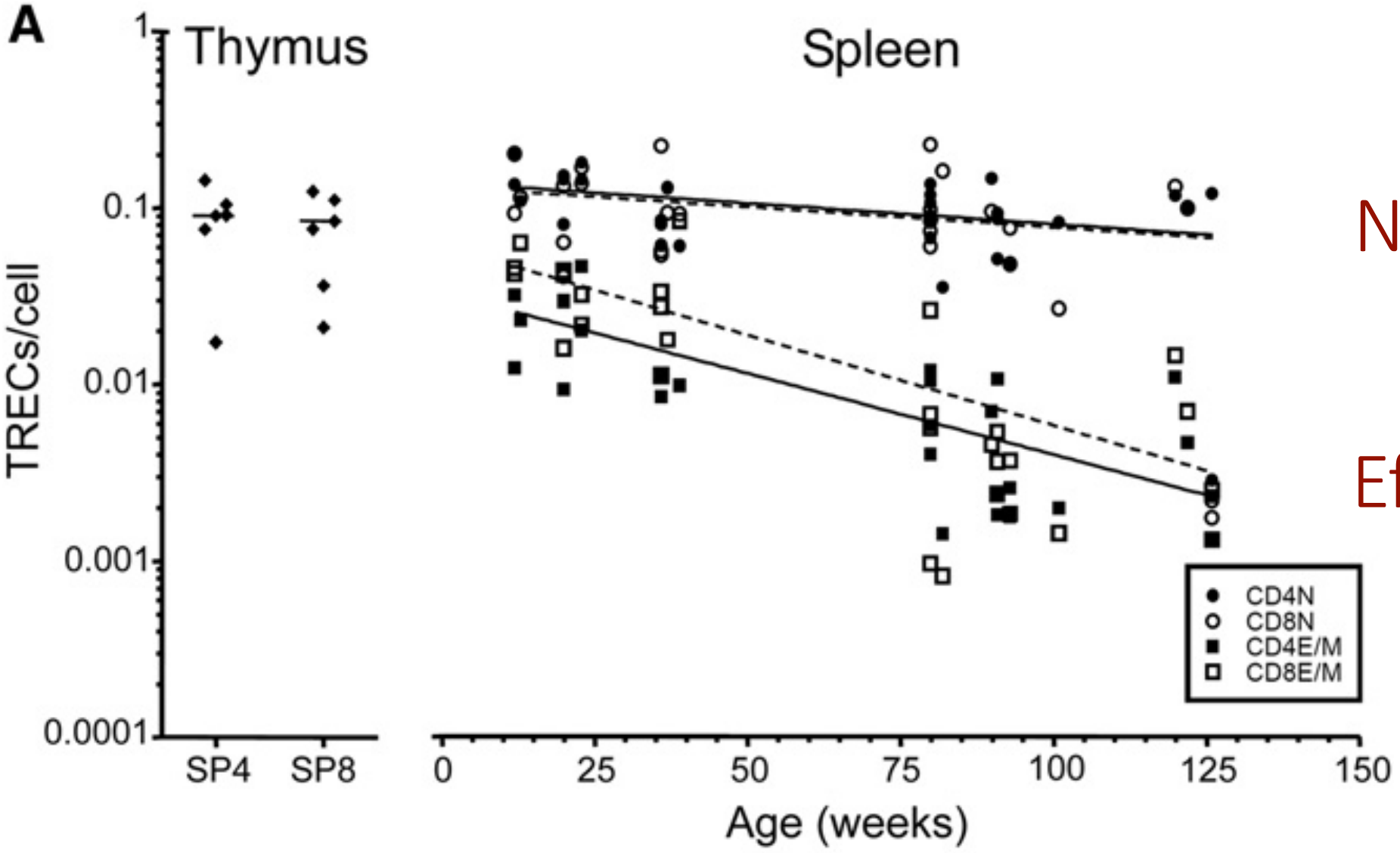
Assume quasi steady state: $\frac{\mathrm{d}A}{\mathrm{d}t} = 0$ $\qquad \frac{A}{c} = \frac{s}{s + pN}$

Fraction of TREC$^+$ cells reflects fraction produced in thymus

Hazenberg et al. Nat. Med. 2000

In mice TRECs in naives hardly decline: most naive cells produced by thymus

Westera et al Immunity 2012



Naive

Eff/Mem

Quantitative immunology: a few more numbers

At least 10^{16} possible T cell receptors
(Robins et al., 2009; Woodsworth et al., 2013; Qi et al., 2014)

Human naive T cell pool: order of magnitude 10^{11} cells
(Hansen et al., 2009; Dirksen et al., 2015; Westera et al., 2015)

Enumerating all responding cells to any novel antigen suggests that most naive T cells are unique
(Mark Jenkins (mice), Paul Thomas (mice), Su et al., 2013 (human)

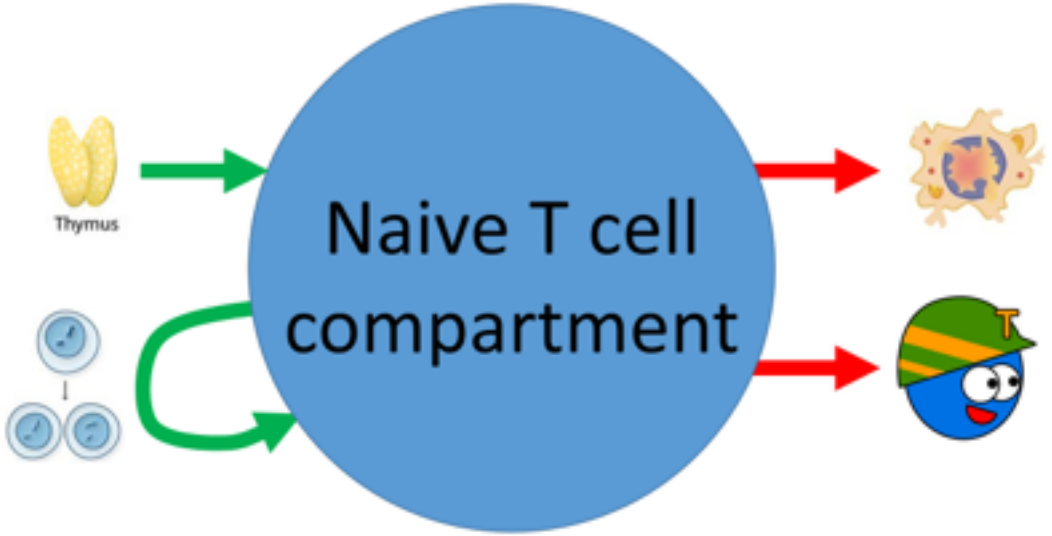
NGS of 10^6 naive T cells gives almost 10^6 sequences
(Britanova et al., JI 2014, Qi et al., PNAS, 2014)

Study effect of aging on diversity (richness)

Aging affects thymic output
(10-fold decrease at age 75)

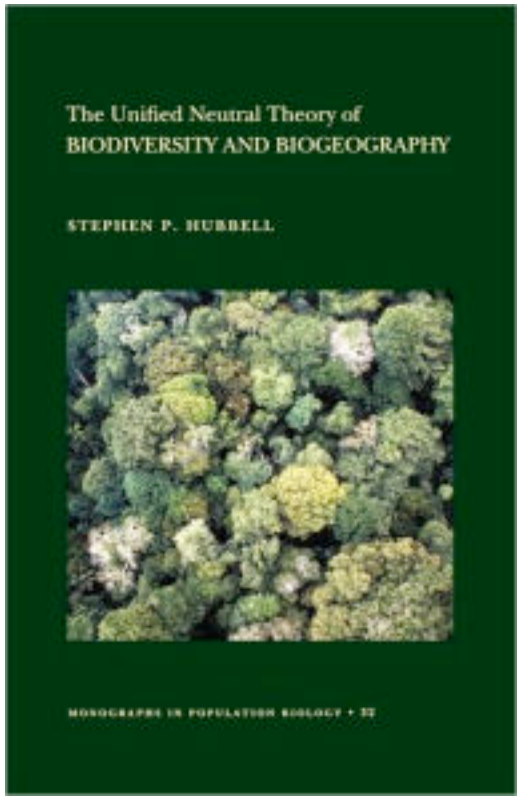
Total number of naive T cells stays relatively stable

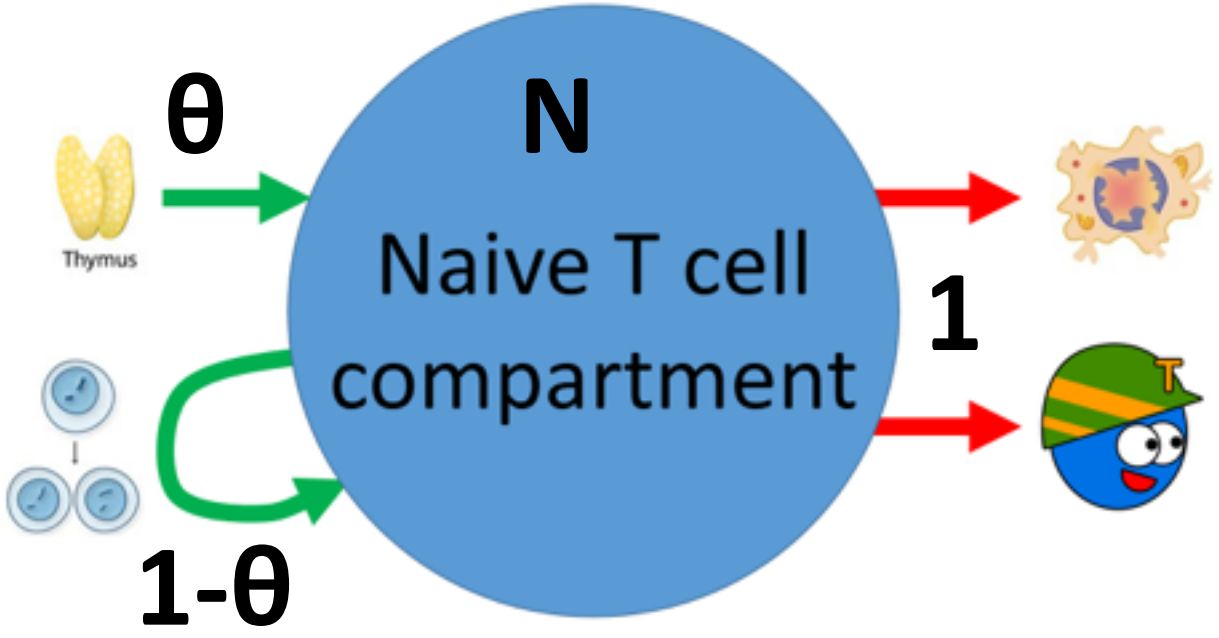
Naive cells are long-lived and divide
(extinction time of a clone >> 10y)



What to expect for repertoire diversity in the elderly?

New null model similar to Hubbell's neutral model





Fix the number of naive T cells at a large constant (N)

No fitness differences: randomly remove a single cell and replace this with another cell coming either from the thymus (θ) or cell division (1-θ)

Every thymic emigrant is a unique singleton

Similar previous work

How many TCR clonotypes does a body maintain?

JTB 2016

Grant Lythe [a,*], Robin E. Callard [b,c], Rollo L. Hoare [b,c], Carmen Molina-París [a]

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Fluctuating fitness shapes the clone-size distribution of immune repertoires

PNAS 2016

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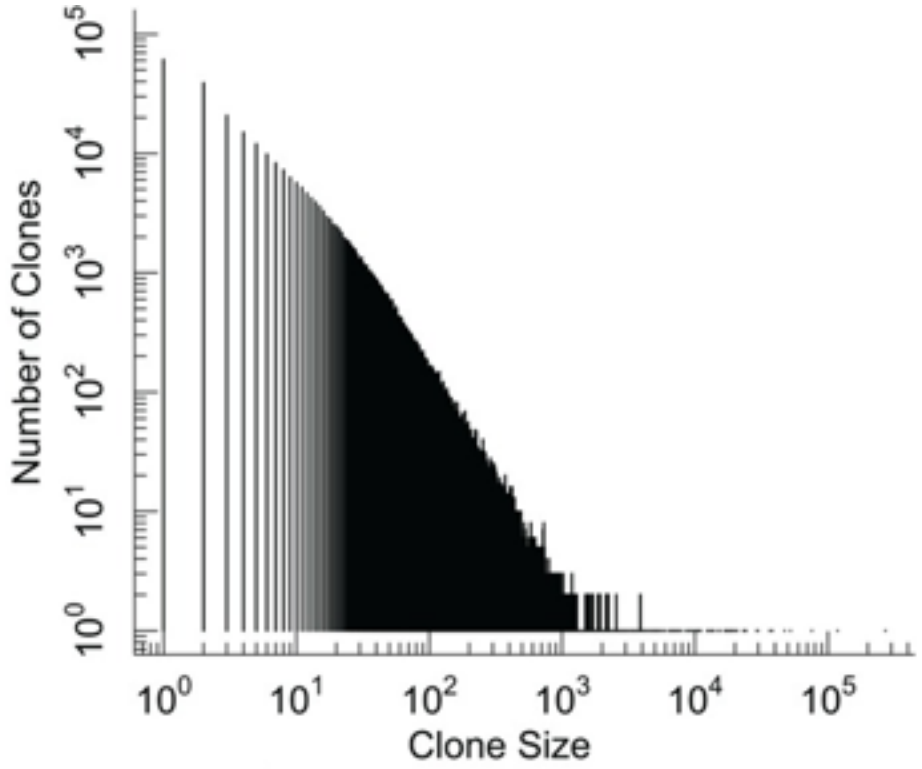
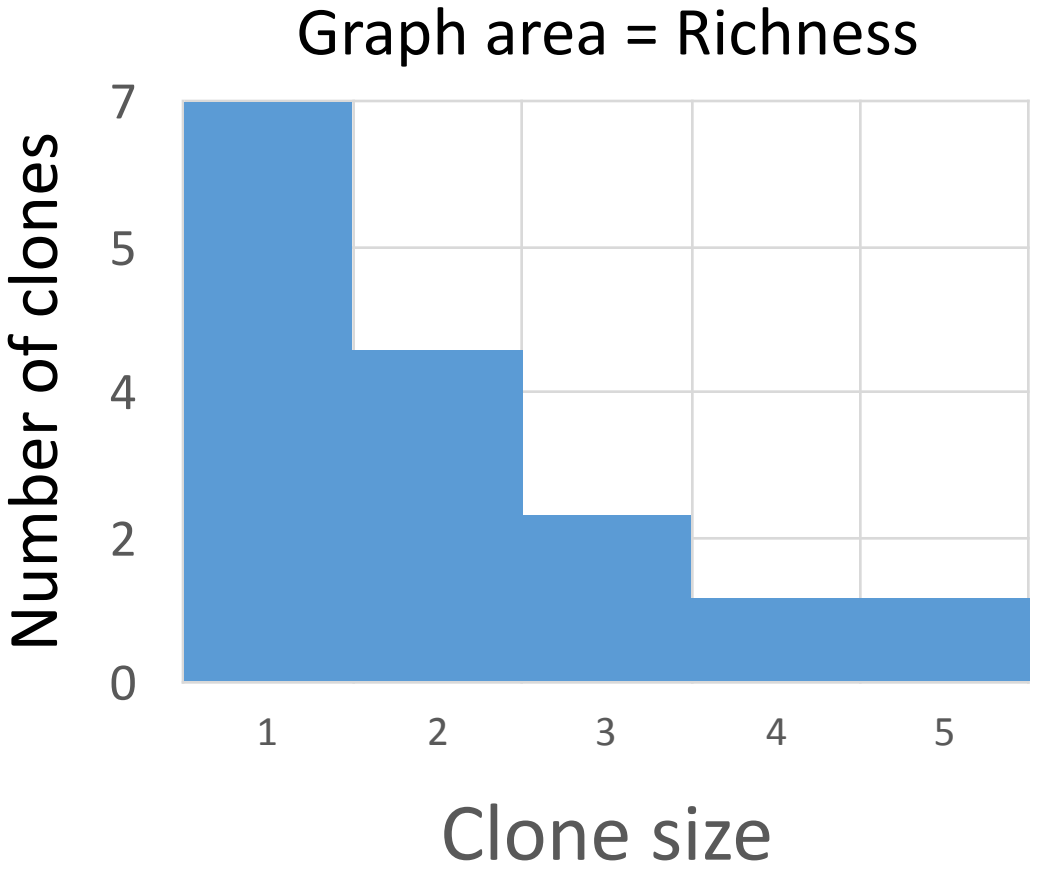
Edited by José N. Onuchic, Rice University, Houston, TX, and approved November 11, 2015 (received for review July 2, 2015)

Studying the dynamics: clone size distribution

Just store clone size distribution: number of clones of a particular size

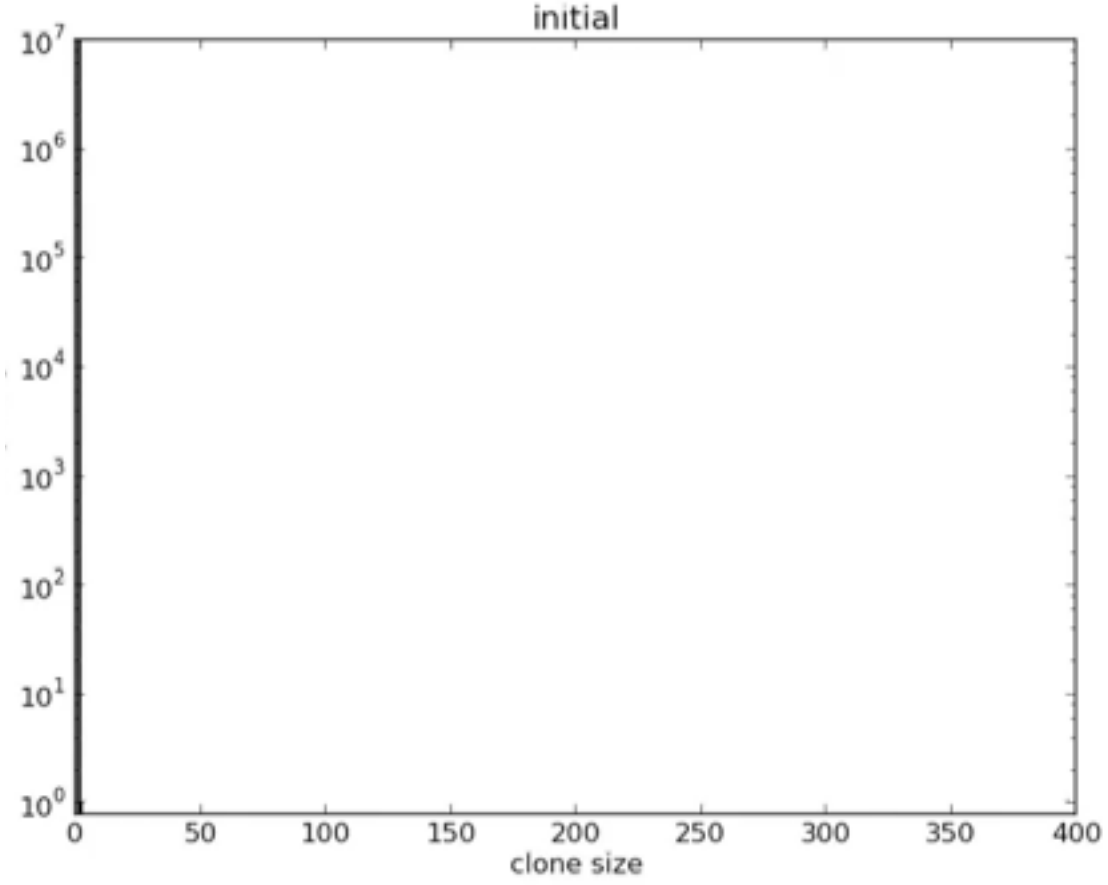


Zarnitsyna *et al.* (2013)

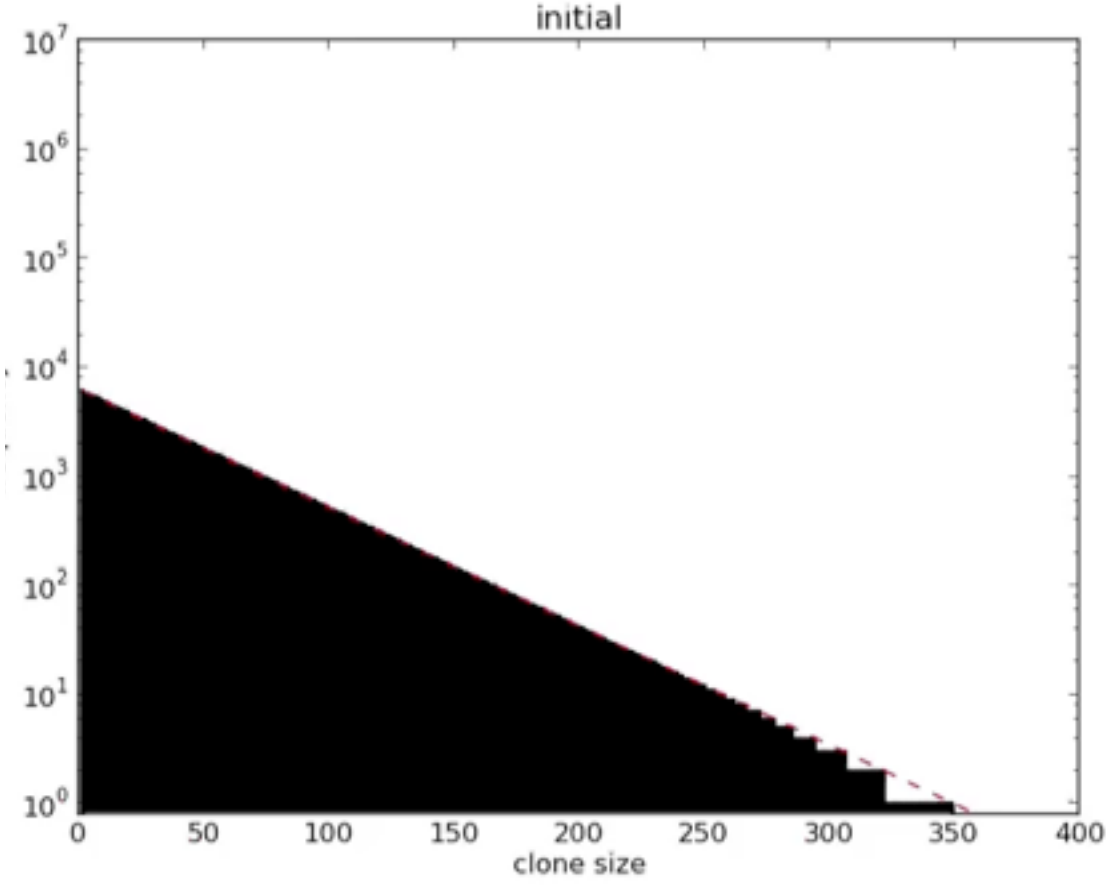


Simulate a whole mouse 10^7 naive T cells: Clone size distribution approaches steady state

Initial condition:all cells of clone size one

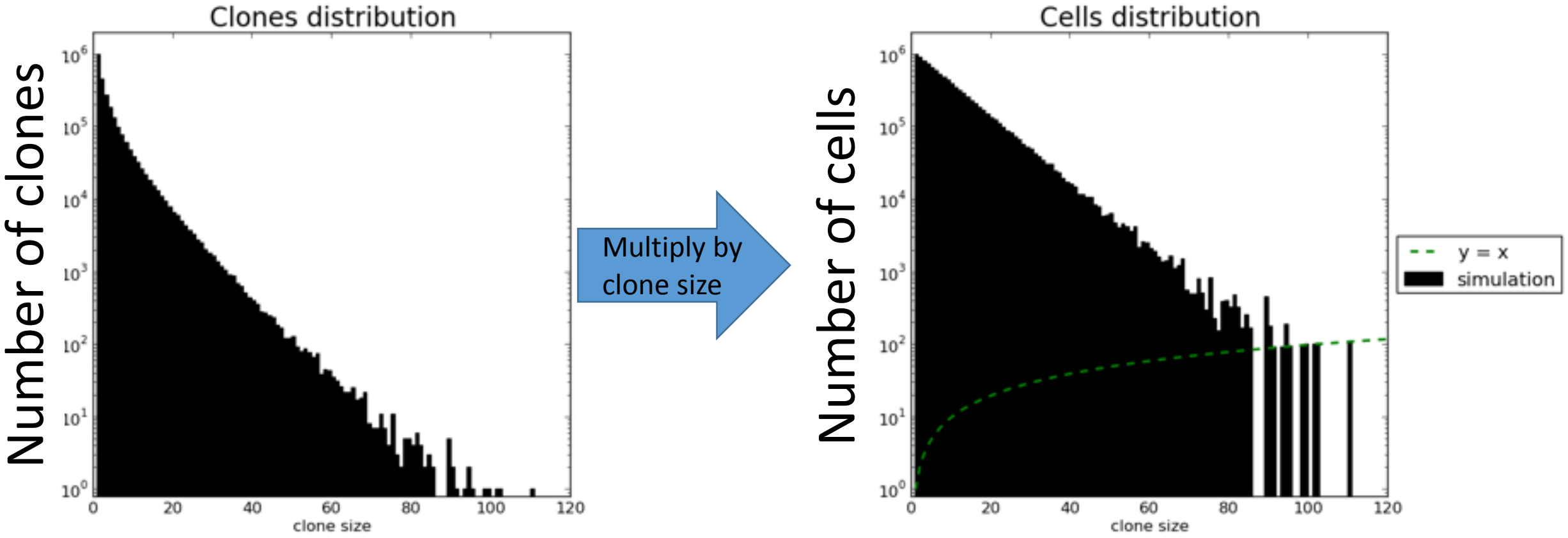


Initial condition: exponential distribution



N = 10^7 cells; θ = 0.1; 10^9 events (θ is a humanized choice here)

Clone distribution implies cell distribution



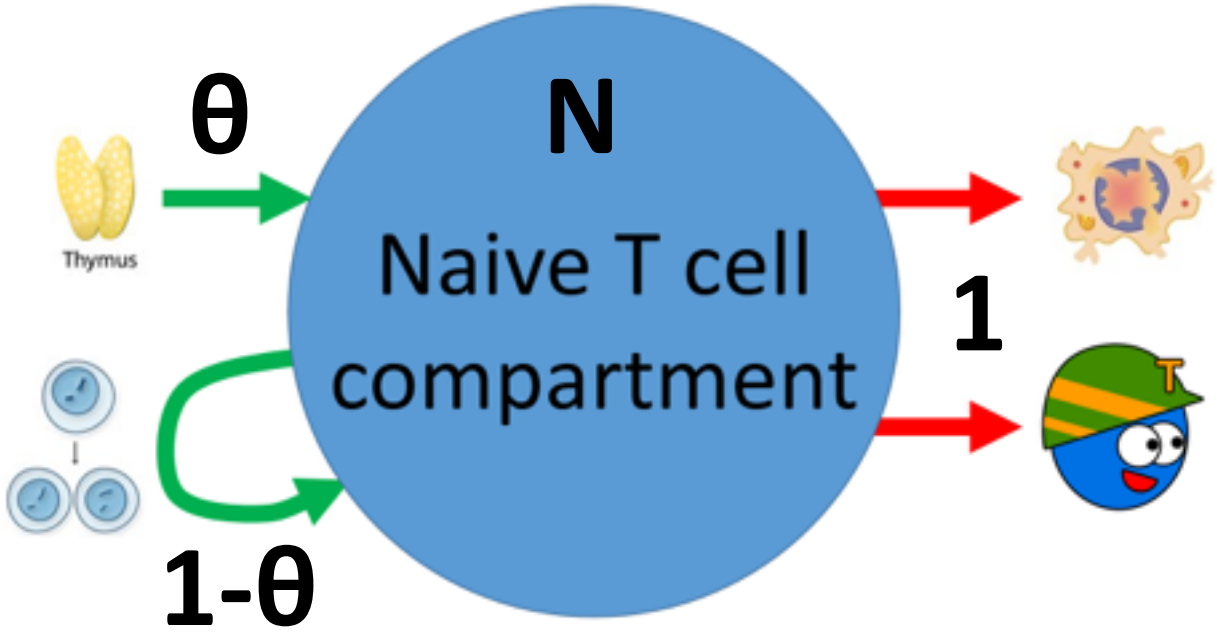
N = 10^7 cells; θ = 0.1; 10^9 events (θ is a humanized choice here)

Parameters for human simulations

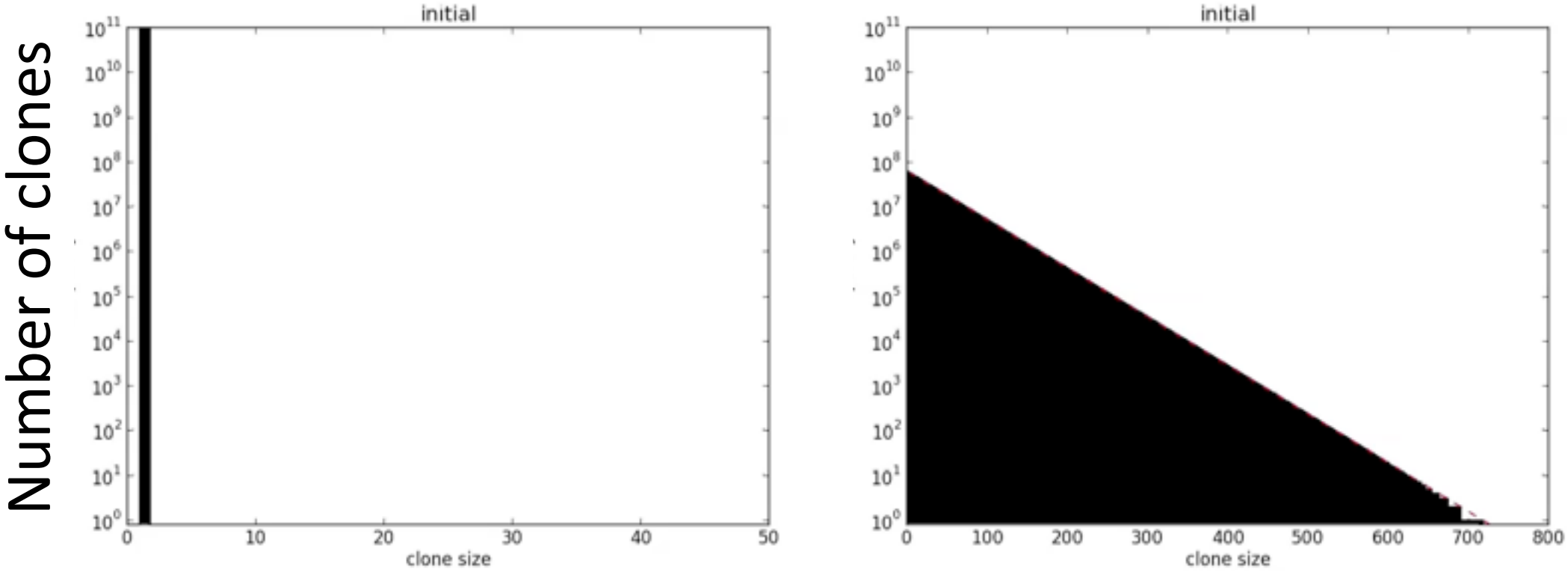
Simulate dynamics in humans between age 25 and 75

Number of cells $N = 10^{11}$ cells

Thymic output $0.01 < \theta < 0.2$



Simulating a whole person takes too long

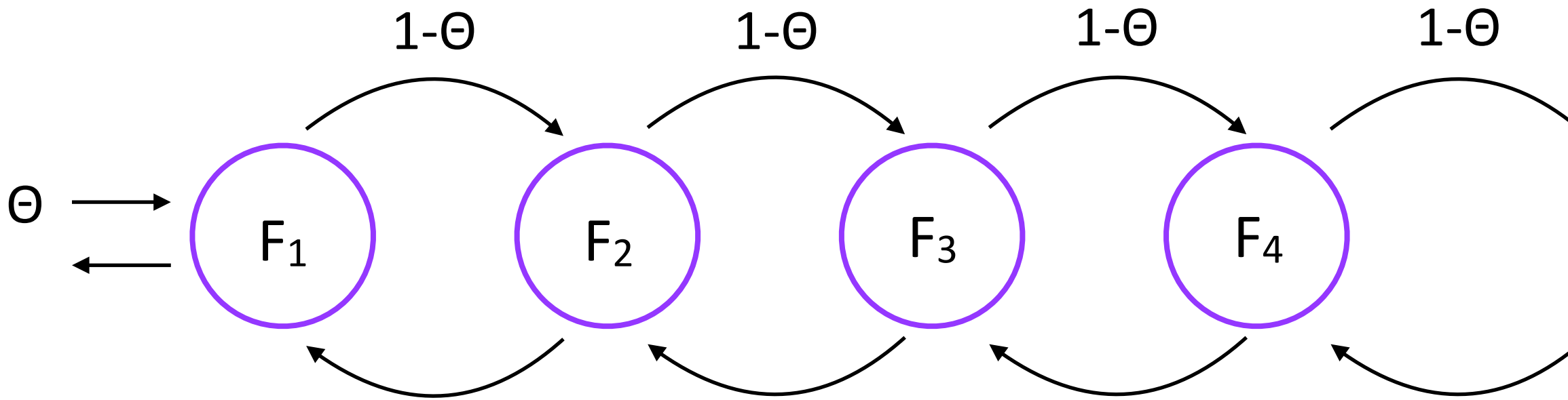


Distribution after one day computer time still determined by initial distribution

→ ≈ 6 weeks dynamics

N = 10^{11} cells; θ = 0.1; 3x10^{9} events; θ is a realistic choice here

To study humans we need a mathematical solution

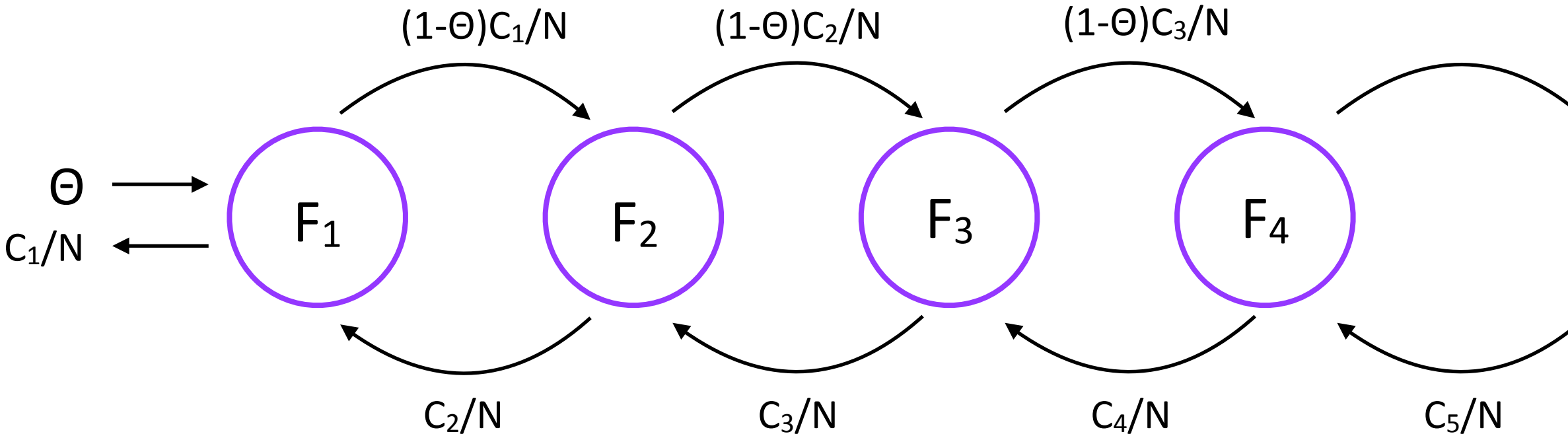


Number of clones comprised of one cell

Number of clones comprised of four cells

birth death process

To study humans we need a mathematical solution

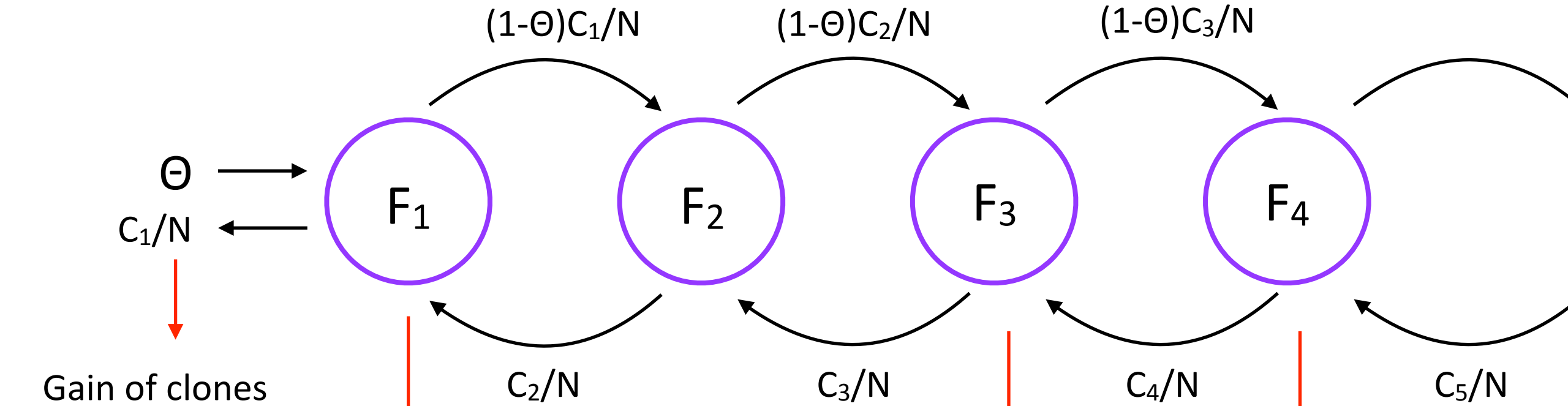


Let C_i be the number of cells in bin i: $C_i = iF_i$

Leftward arrows: Probability a cell dies in bin i: $iF_i/N = C_i/N$

Rightward arrows: Probability a cell divides from bin i: $(1-\Theta)C_i/N$

To study humans we need a mathematical solution



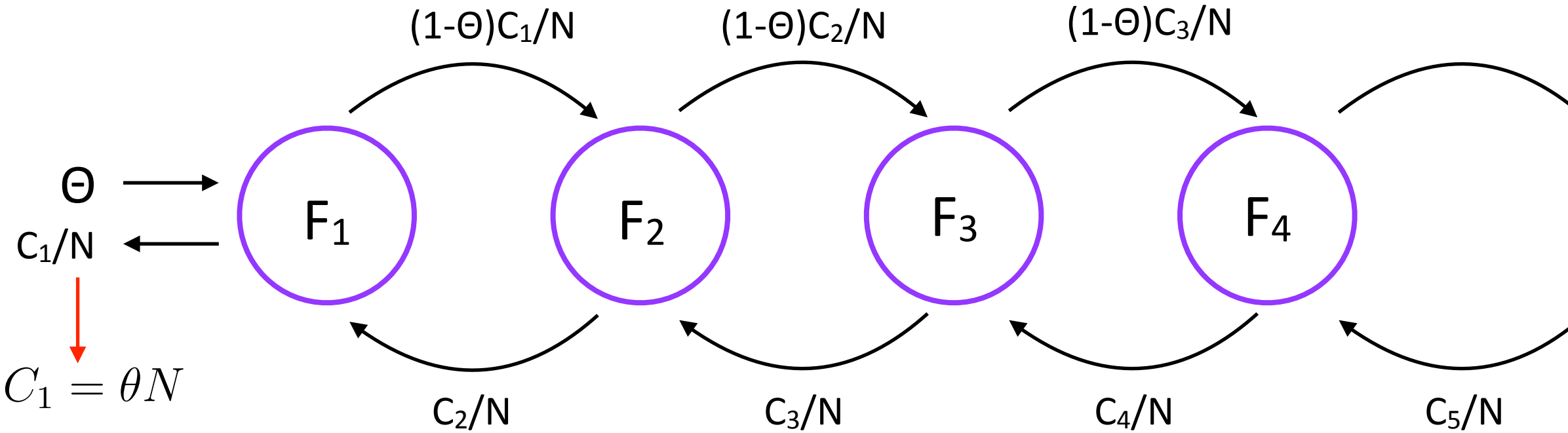
Gain of clones balances their loss

$$C_1 = \theta N$$

$$\frac{C_1}{N} + \frac{(1-\theta)C_1}{N} = \theta + \frac{C_2}{N}$$

$$\frac{C_i}{N} + \frac{(1-\theta)C_i}{N} = \frac{(1-\theta)C_{i-1}}{N} + \frac{C_{i+1}}{N} \quad \text{for } i = 2, 3, \ldots, \infty \ ,$$

To study humans we need a mathematical solution

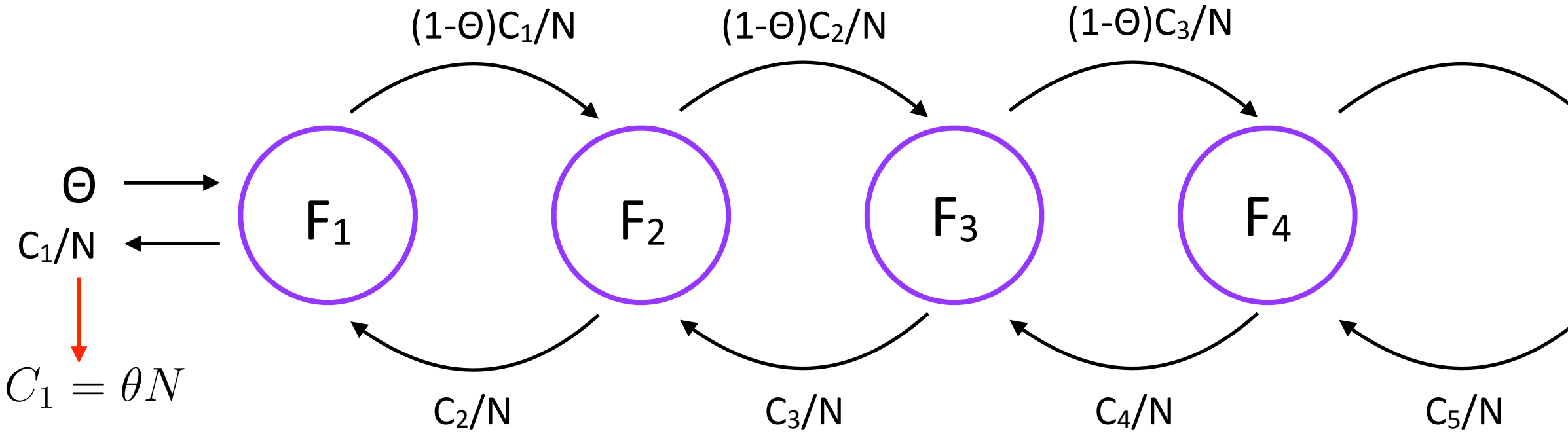


$C_1 = \theta N$

$$C_i = (1-\theta)C_{i-1} = (1-\theta)^{i-1}\theta N \quad \text{and} \quad F_i = C_i/i \ , \quad \text{for } i = 1, 2, \ldots, \infty$$

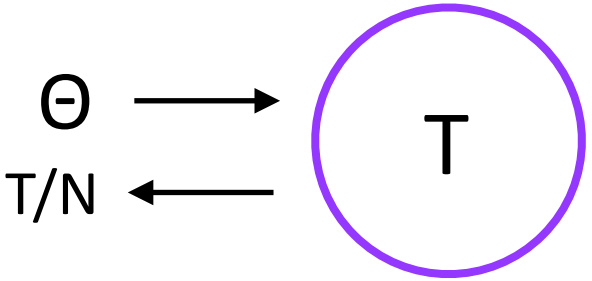
One parameter model!

To study humans we need a mathematical solution



$C_1 = \theta N$

Finally TRECs:



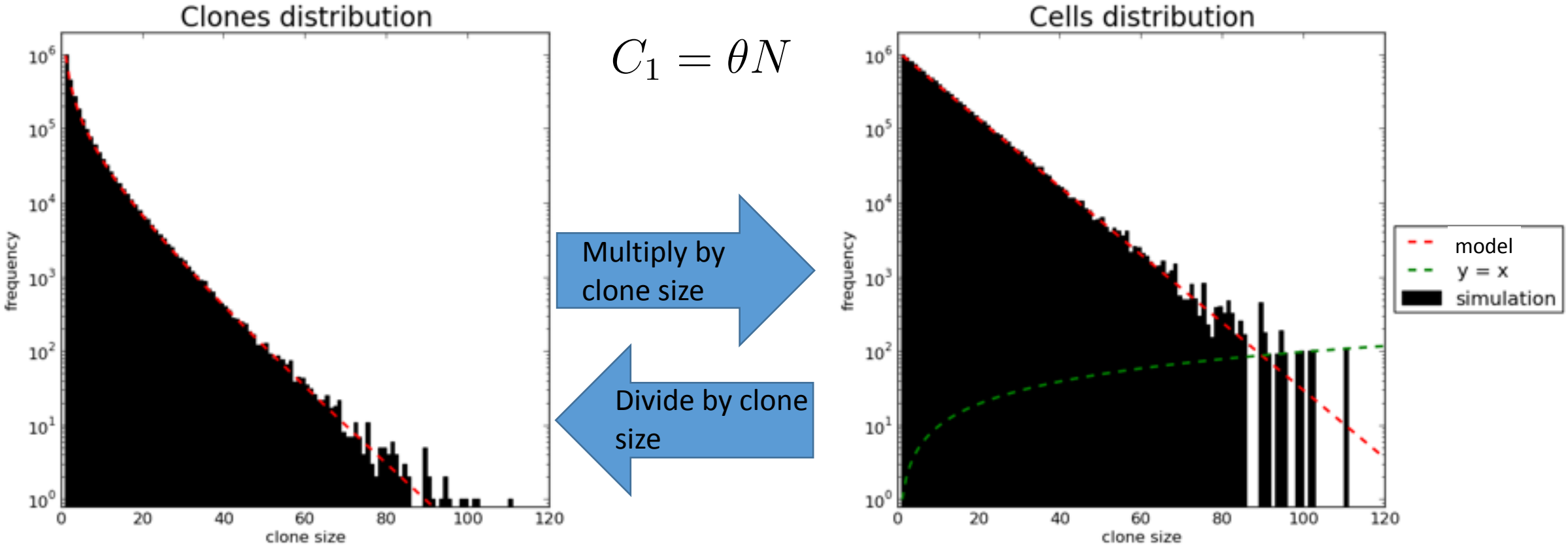
Θ = T/N (at steady state)

Model & simulation: noise at large clone sizes

$$F_i = C_i/i$$

$$C_i = (1-\theta)C_{i-1} = (1-\theta)^{i-1}\theta N$$

$$C_1 = \theta N$$



N = 10^7 cells; θ = 0.1; 10^9 events (θ is a humanized choice here)

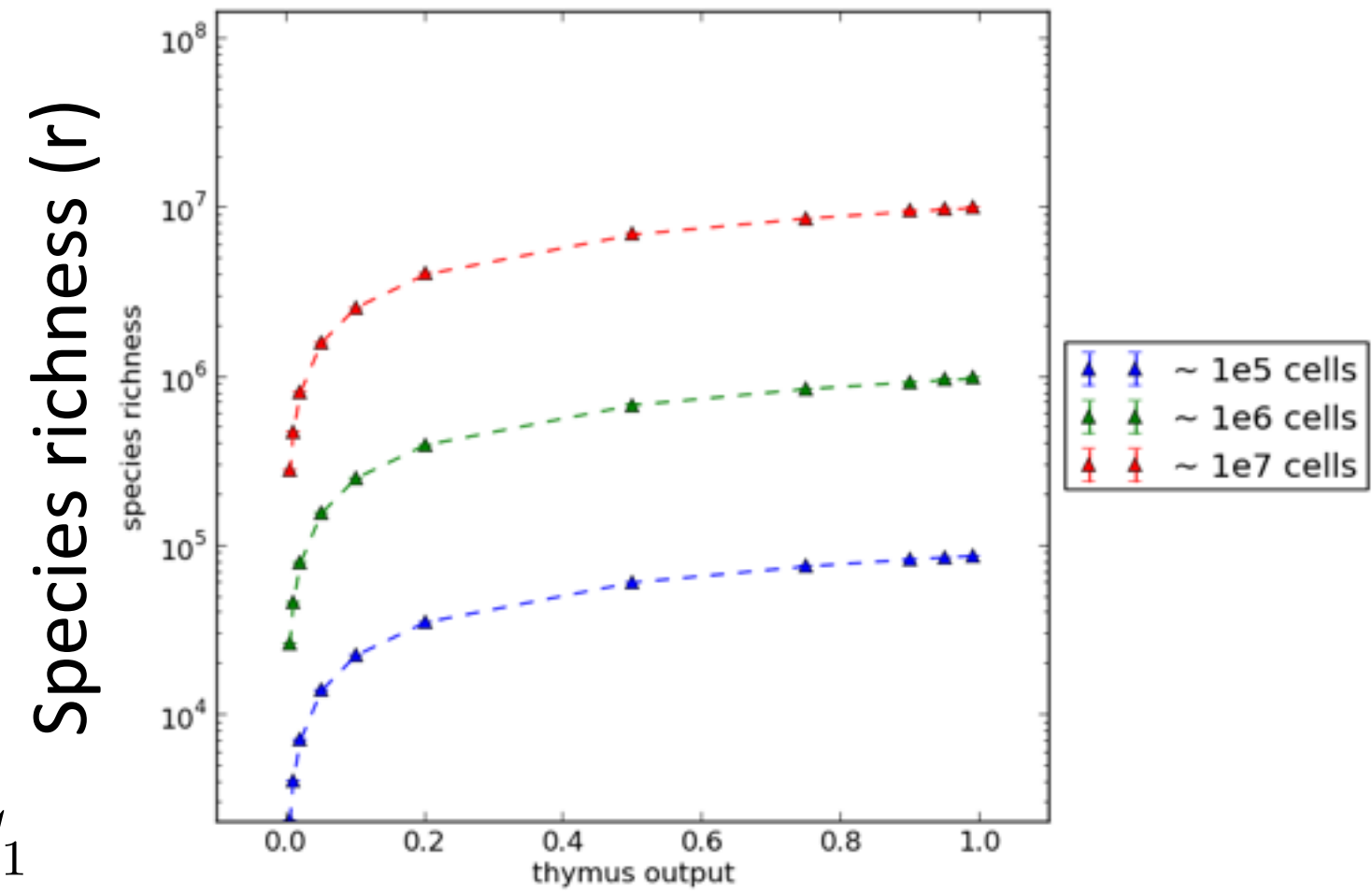
Use model to estimate richness (number of clones)

$$r = \sum_{i=1}^{\infty} F_i = \frac{\theta N \ln \theta}{\theta - 1}$$

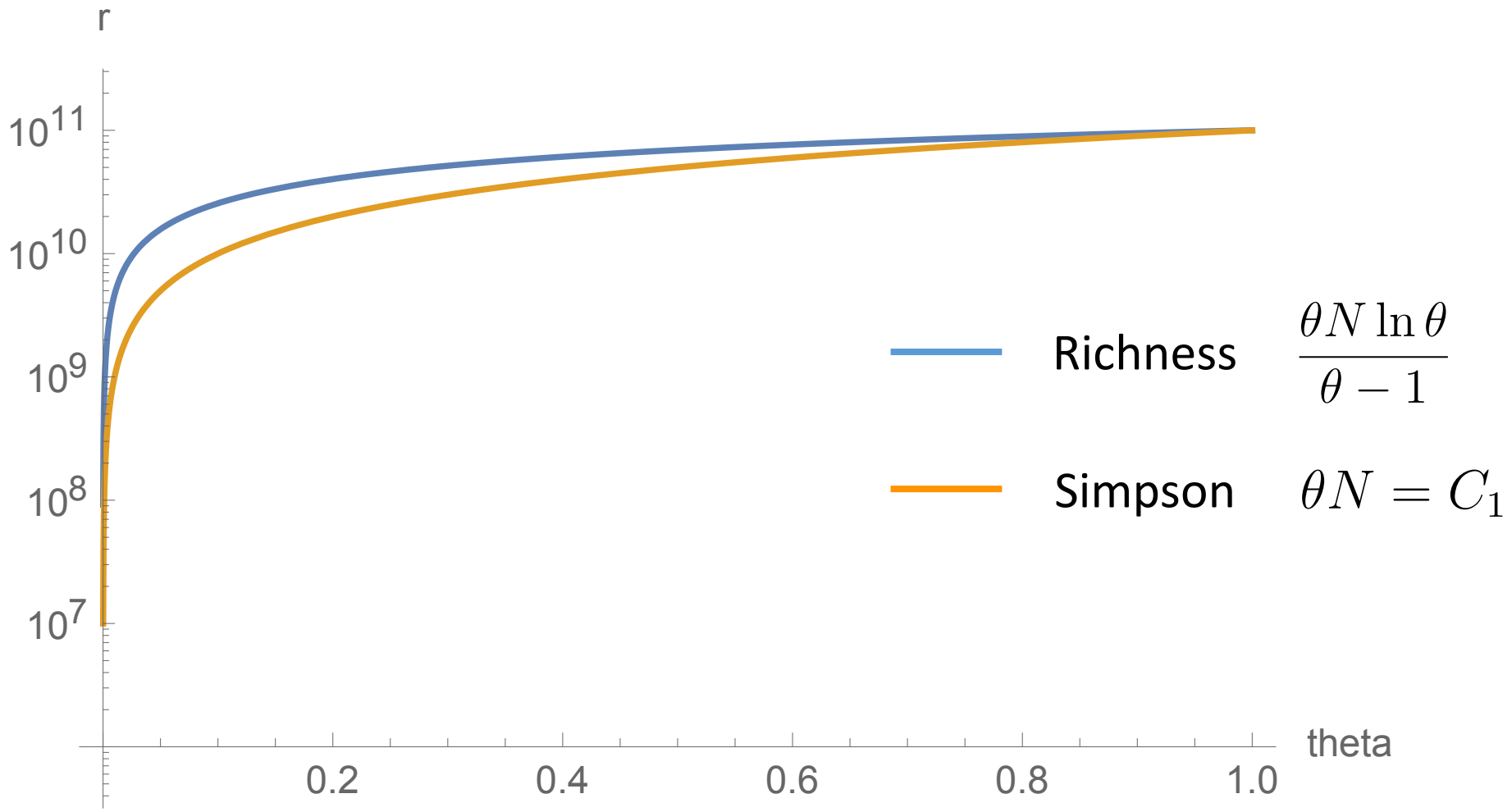
Simpson diversity

$$1/\sum_{j}^{\infty}(n_j/N)^2$$

$$s = 1/\sum_{i=1}^{\infty} F_i \left(\frac{i}{N}\right)^2 = \theta N = C_1$$



Extrapolation to the human naive T cell pool



old young adult very young

Extrapolation to human T cell pool ($N=10^{11}$)

$$\frac{\theta N \ln \theta}{\theta - 1} \qquad \theta N = C_1$$

Age	Thymic output	Richness	Simpson's diversity
25 year	θ ≈ 0.2	4×10^{10}	2×10^{10}
75 year	θ ≈ 0.02	8×10^{9}	2×10^{9}
	10 fold decrease	5 fold decrease	10 fold increase

Clone size at 25y 2.5 cells/clone and at 75y 12.5 cells/clone

Richness declines less than proportional with thymic output

Simpson's diversity declines proportional with thymic output

Thymic output decreases faster than convergence to steady state

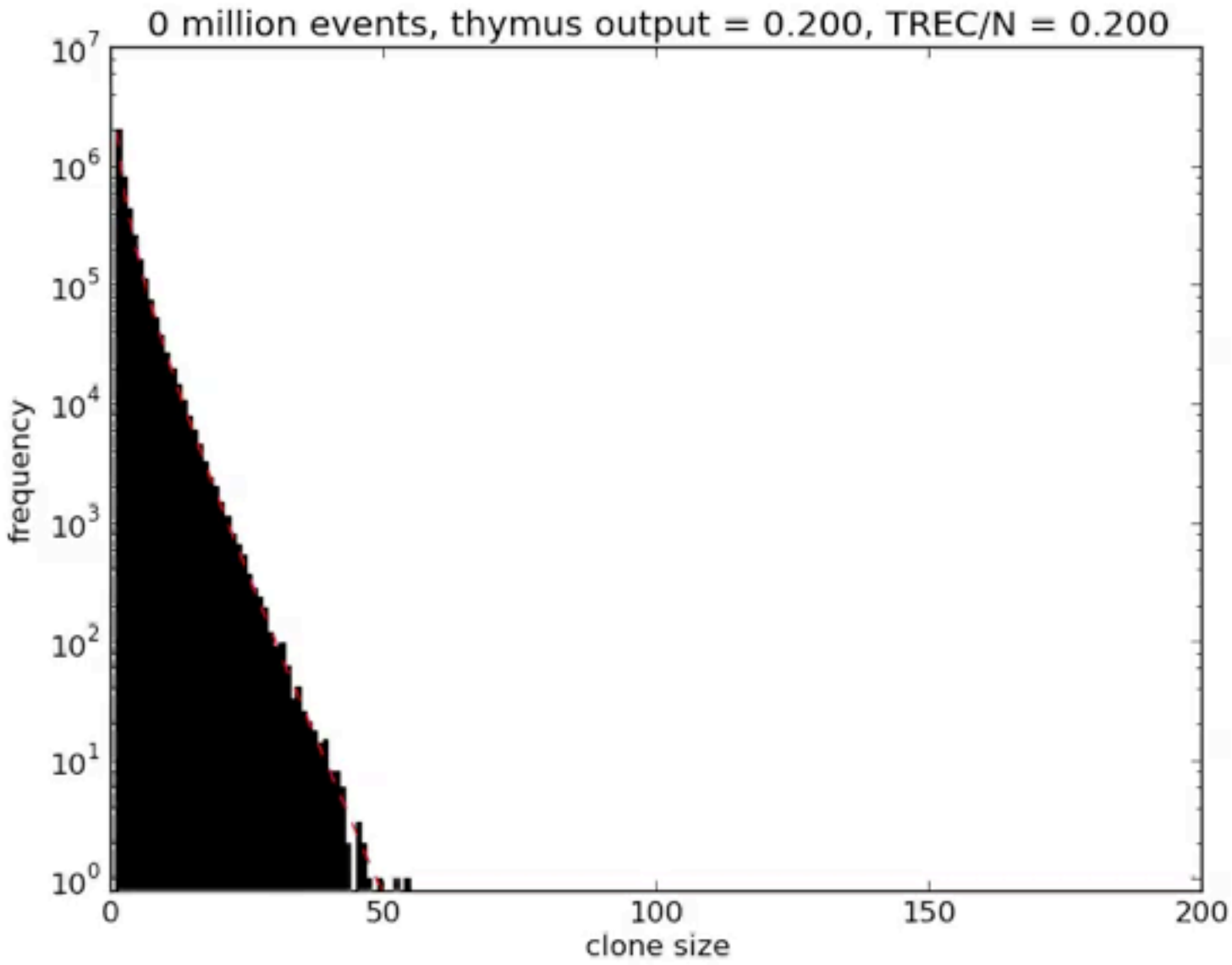
N = 10^7 cells: Human dynamics downsized to mouse numbers.

Thymic output θ initially 0.2

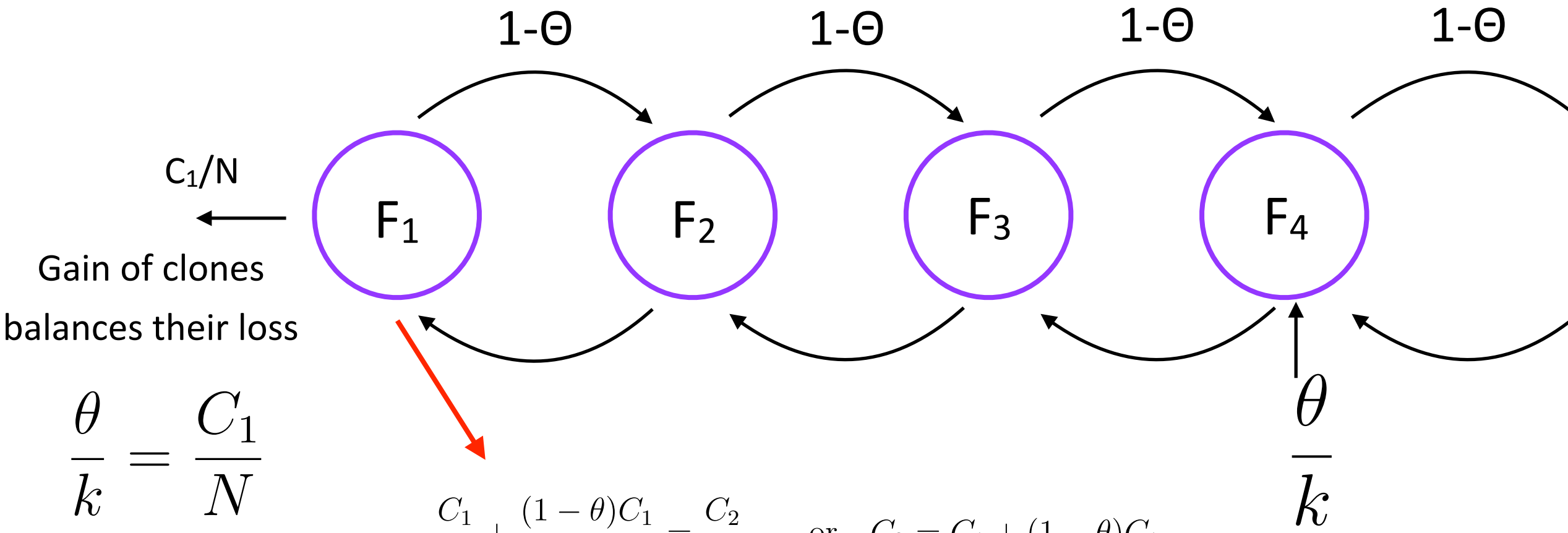
Dashed line: solution

5% decrease thymic output/year

cells live 10y: a year is 10^6 events



What if clones have expanded in thymus? k=4



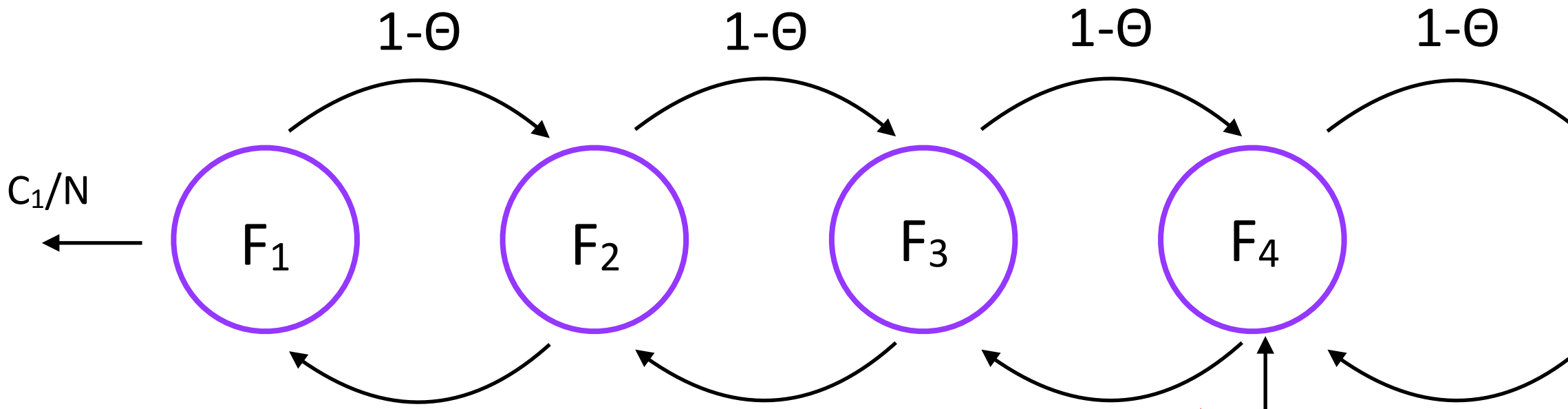
$$\frac{\theta}{k} = \frac{C_1}{N}$$

$$C_1 = \frac{\theta N}{k}$$

$$\frac{C_1}{N} + \frac{(1-\theta)C_1}{N} = \frac{C_2}{N} \quad \text{or} \quad C_2 = C_1 + (1-\theta)C_1$$

$$C_i = C_1 + (1-\theta)C_{i-1} \quad \text{and} \quad F_i = C_i/i\ , \quad \text{for } i = 1, 2, \ldots, k\ .$$

What if clones have expanded in thymus? k=4



$$\frac{C_k}{N} + \frac{(1-\theta)C_k}{N} = \frac{(1-\theta)C_{k-1}}{N} + \frac{C_{k+1}}{N} + \frac{\theta}{k}$$

$$C_{k+1} = (1-\theta)C_k \quad \text{or generally} \quad C_{k+j} = (1-\theta)^j C_k$$

Summarizing: two parameter model θ and *k*

$$C_1 = \frac{\theta N}{k}$$

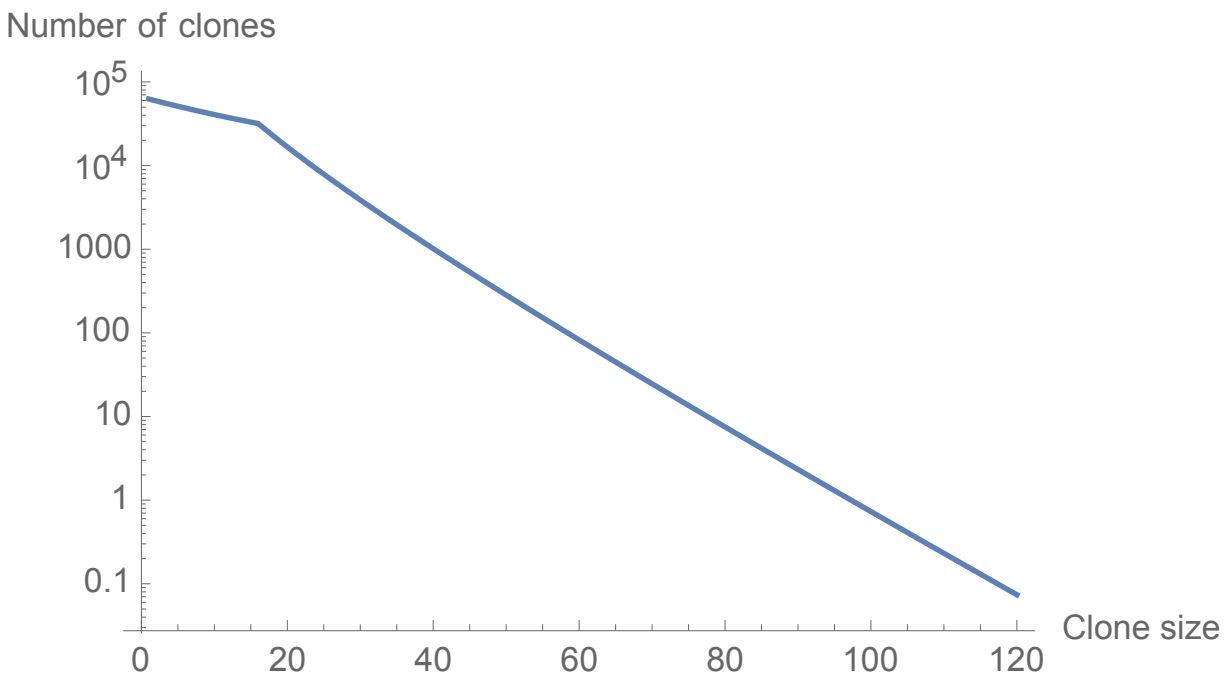
$$C_i = C_1 + (1-\theta)C_{i-1} \quad \text{and} \quad F_i = C_i/i \ , \quad \text{for } i = 1, 2, \ldots, k$$

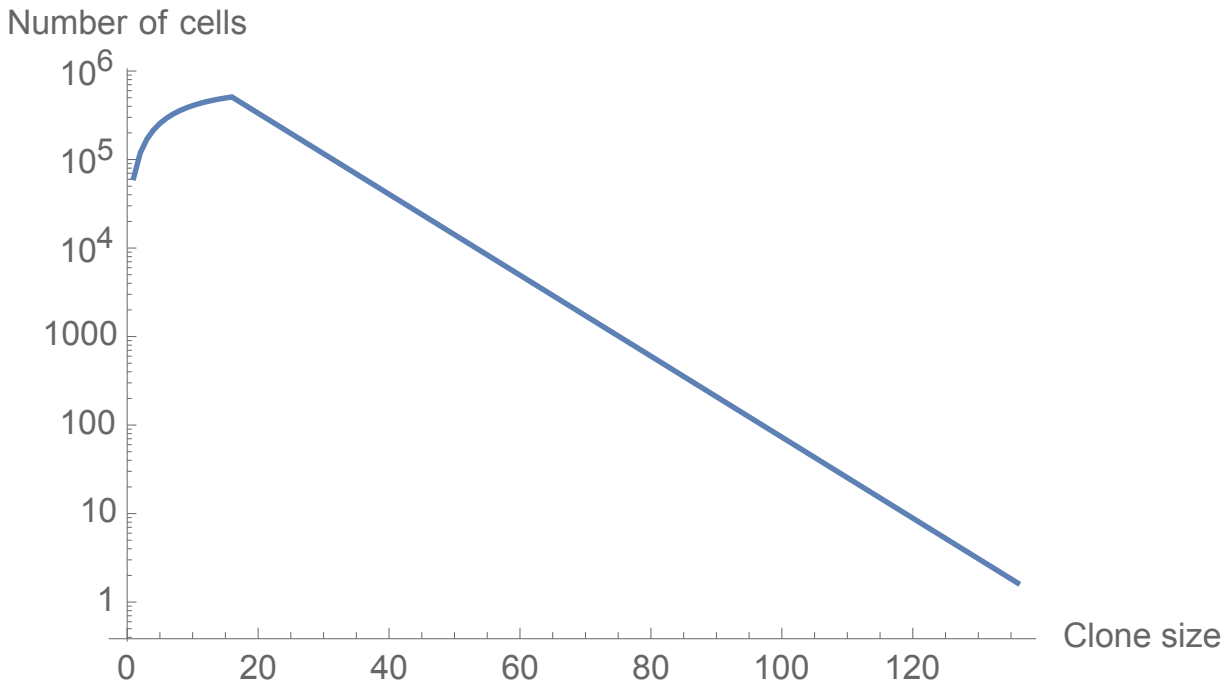
$$C_{k+j} = (1-\theta)^j C_k \ , \quad \text{and} \quad F_{k+j} = \frac{C_{k+j}}{k+j} \ , \quad \text{for } j = 1, 2, \ldots, \infty$$

For *k*=1 we retrieve the original model, TREC model stays the same θ = T/N

Simpson: $$s = 1/\sum_{i=1}^{\infty} F_i \left(\frac{i}{N}\right)^2 = \frac{2\theta N}{2 + (k-1)\theta}$$

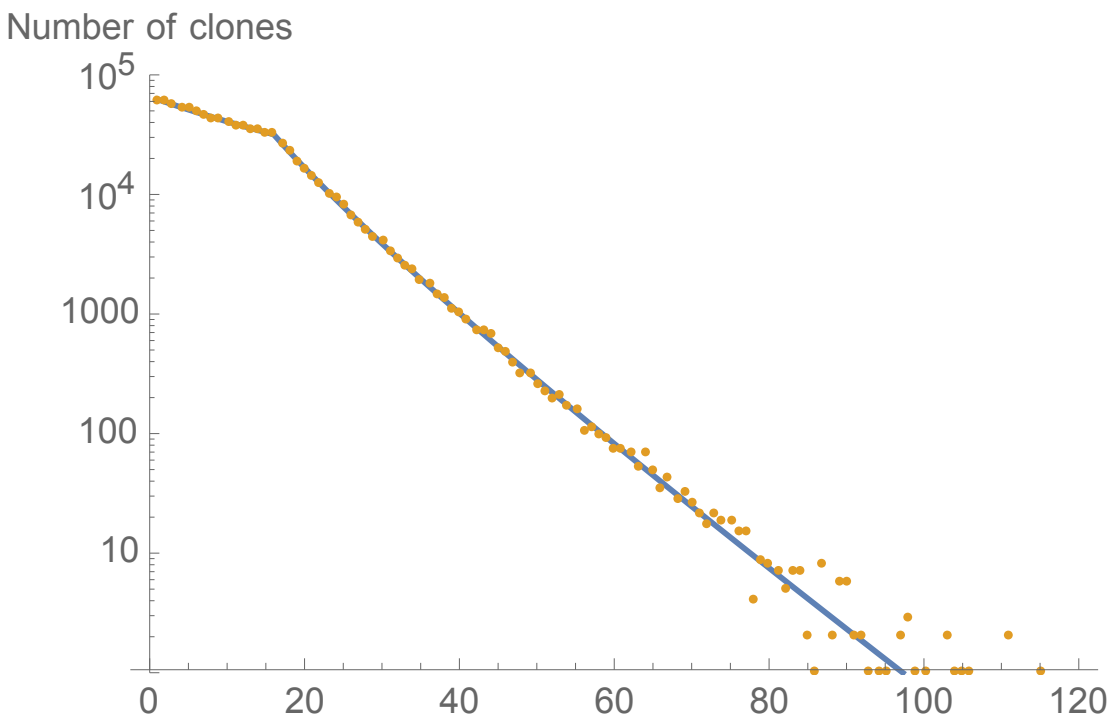
Distributions for k=16

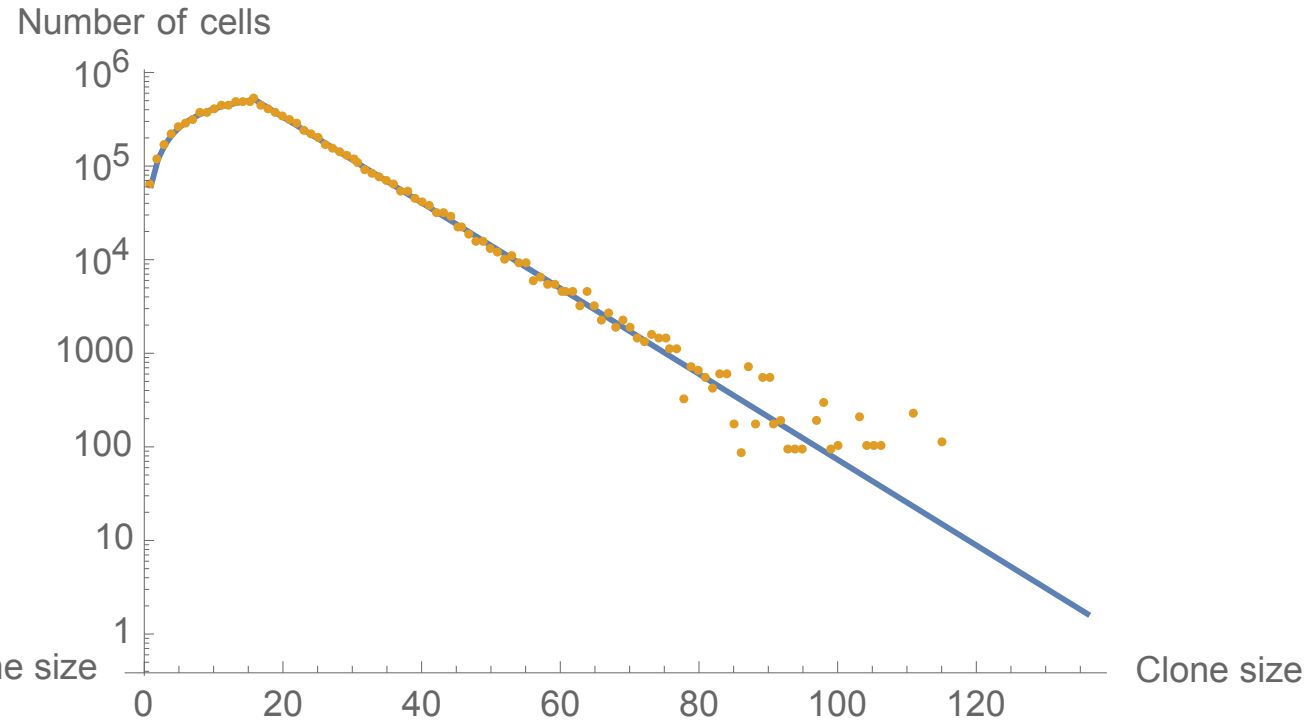




$N = 10^7$ cells; $\theta = 0.1$ (θ is a humanized choice here)

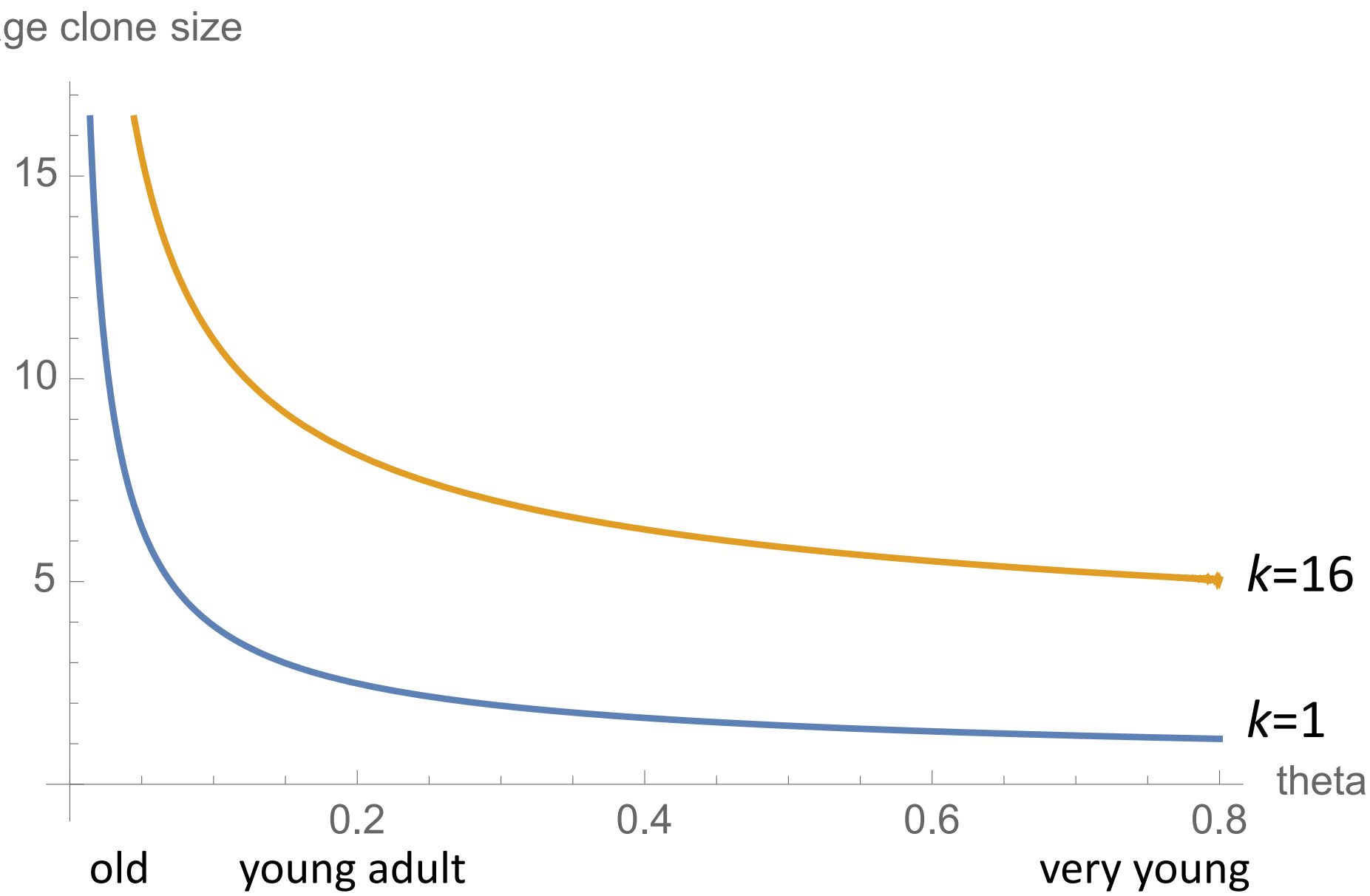
Distributions for k=16: with simulation



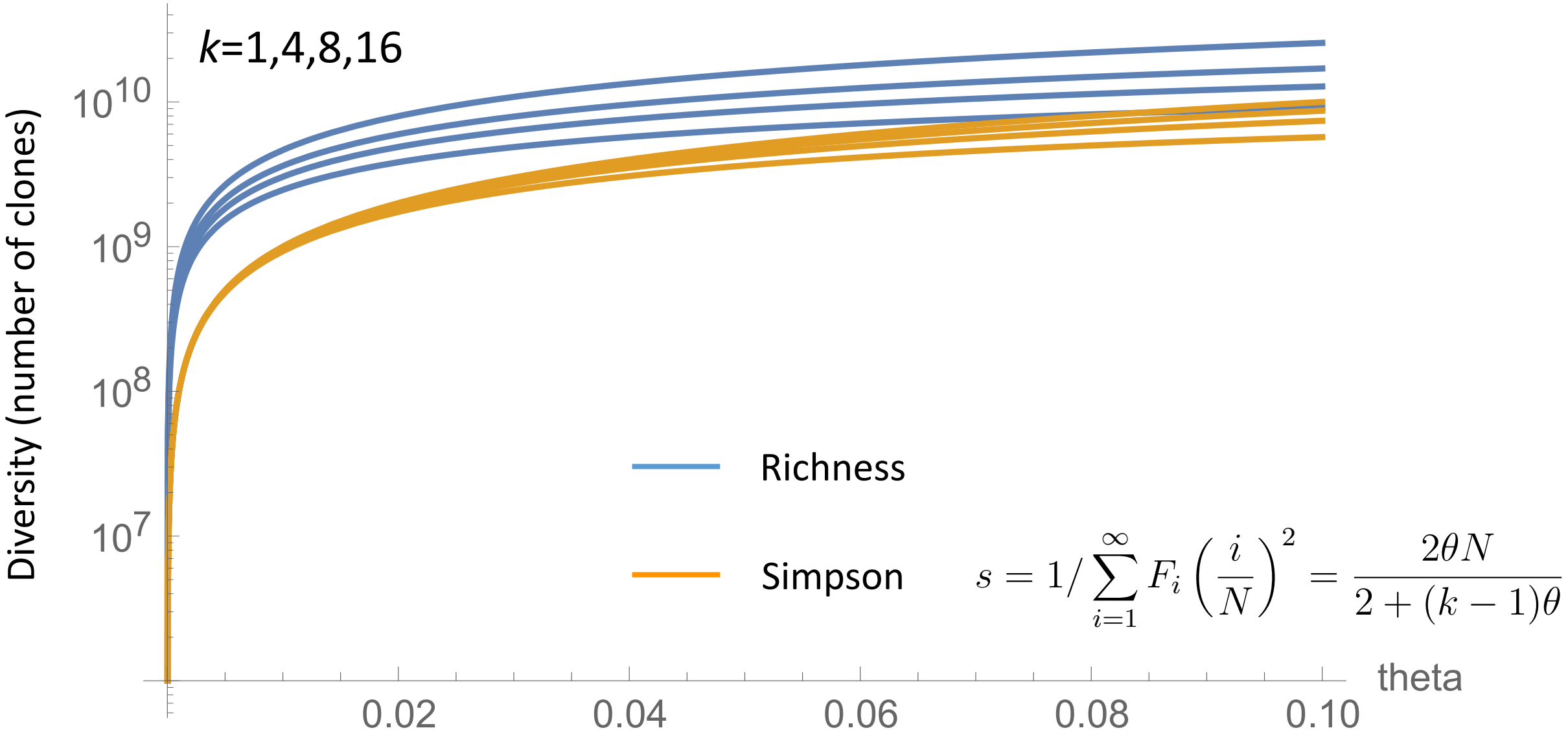


N = 10^7 cells; θ = 0.1; 10^9 events (θ is a humanized choice here)

Average clone size for k=1, 16 (human: $N=10^{11}$)



Aging: diversity for different k (human: $N=10^{11}$)



Diversity of human naive T cell pool ($N=10^{11}$)

$$\frac{\theta N \ln \theta}{\theta - 1}$$

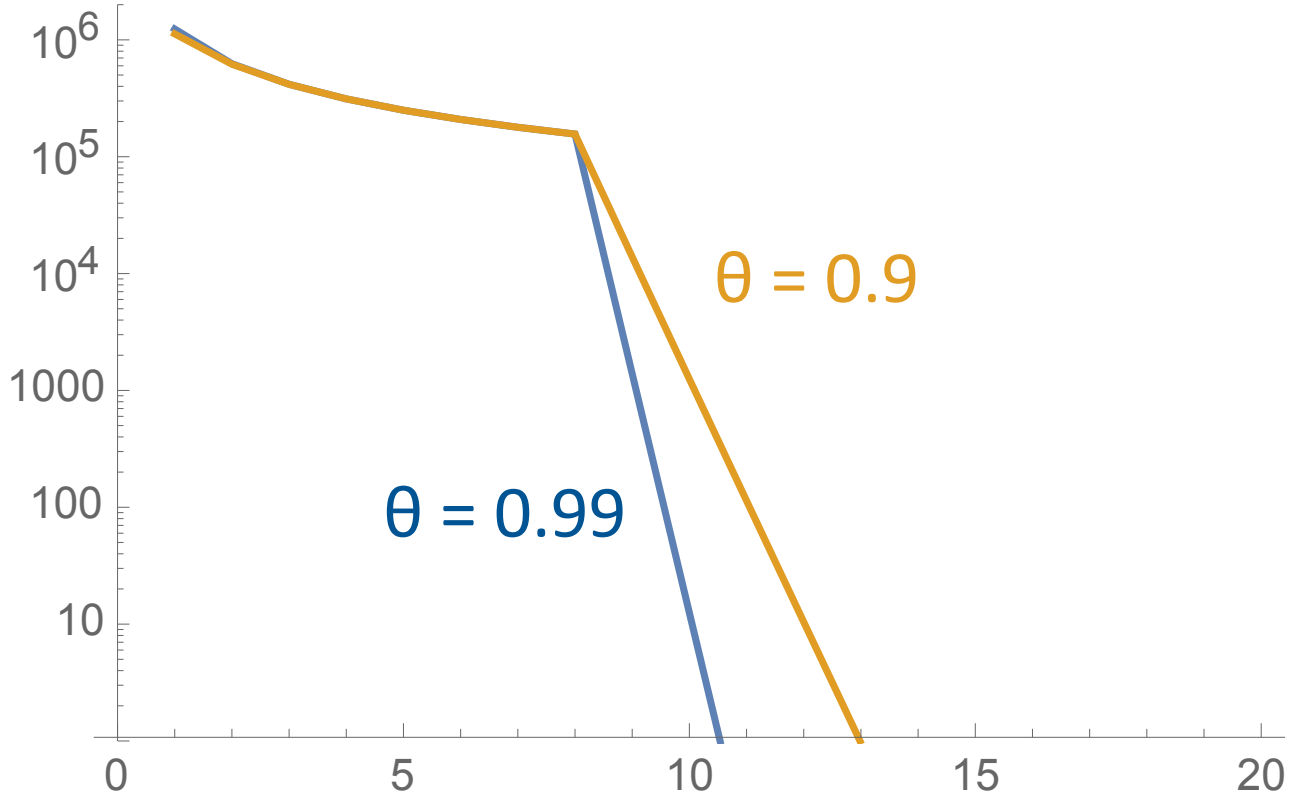
Age	Thymic output	Richness k=1	Richness k=16
25 year	θ ≈ 0.2	4×10^{10}	1.2×10^{10}
75 year	θ ≈ 0.02	8×10^{9}	3.8×10^{9}
	10 fold decrease	5 fold decrease	3.2 fold decrease

$$\theta N \qquad \frac{2\theta N}{2 + (k-1)\theta}$$

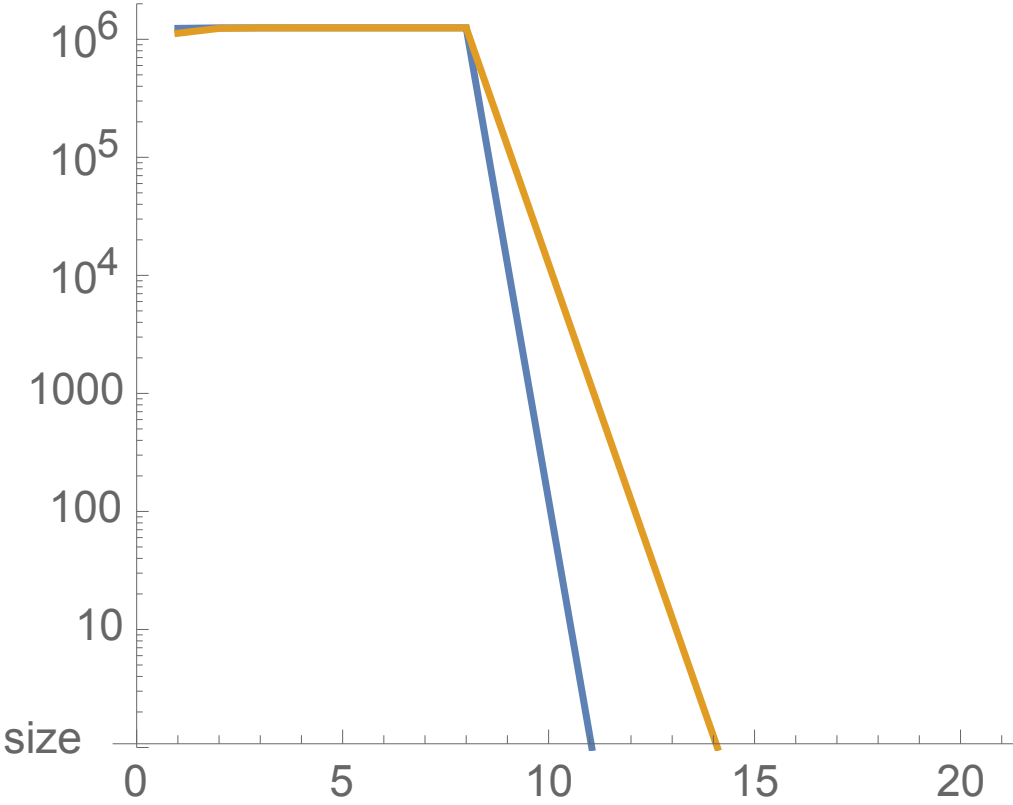
Age	Thymic output	Simpson k=1	Simpson k=16
25 year	θ ≈ 0.2	2×10^{10}	8×10^{9}
75 year	θ ≈ 0.02	2×10^{9}	1.7×10^{9}
	10 fold decrease	10 fold decrease	4.7 fold decrease

Aging in mice: from θ=0.99 to θ=0.9 (k=8)

Number of clones $F_i = C_i/i$



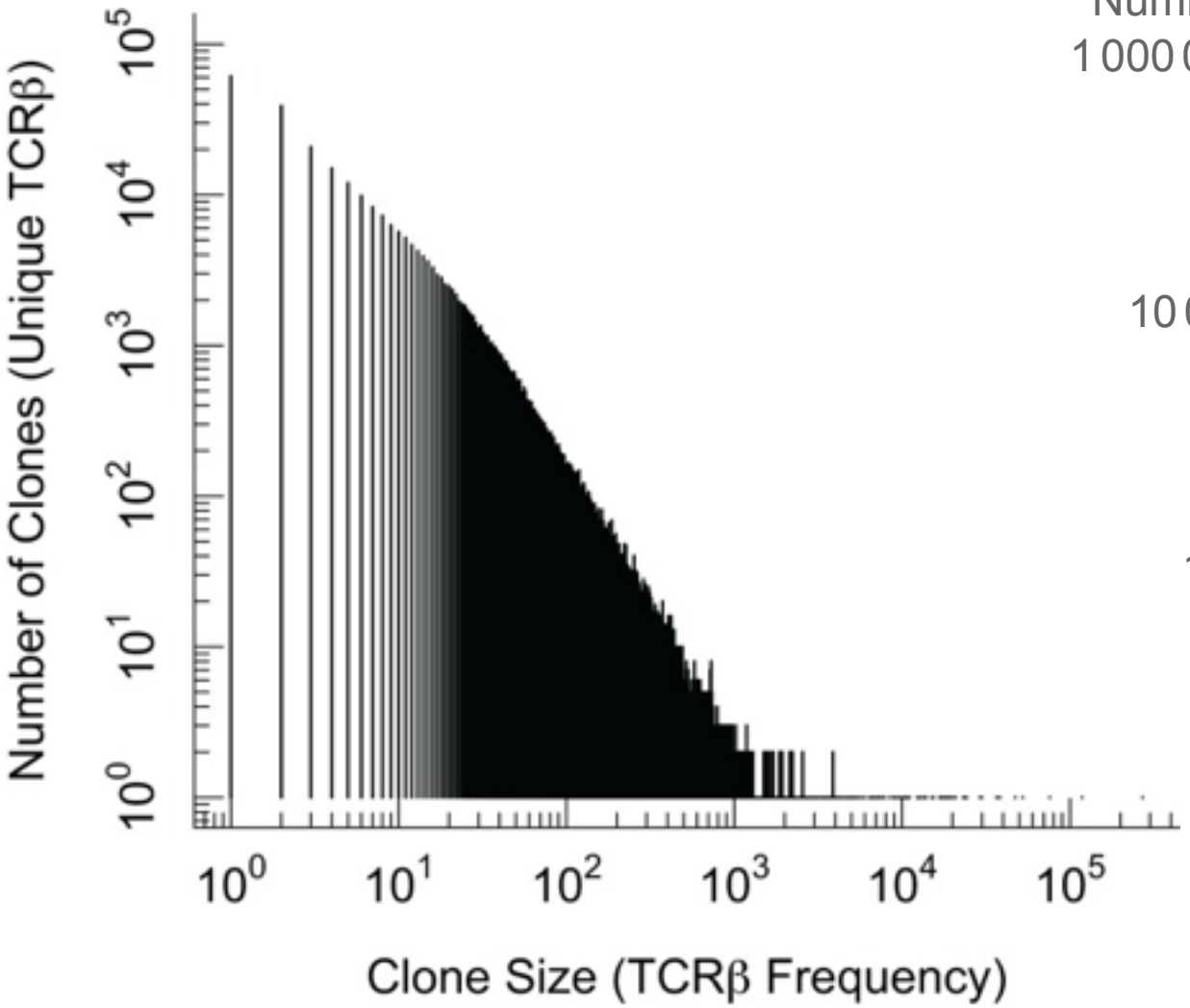
Number of cells $C_i = C_1 + (1-\theta)C_{i-1}$



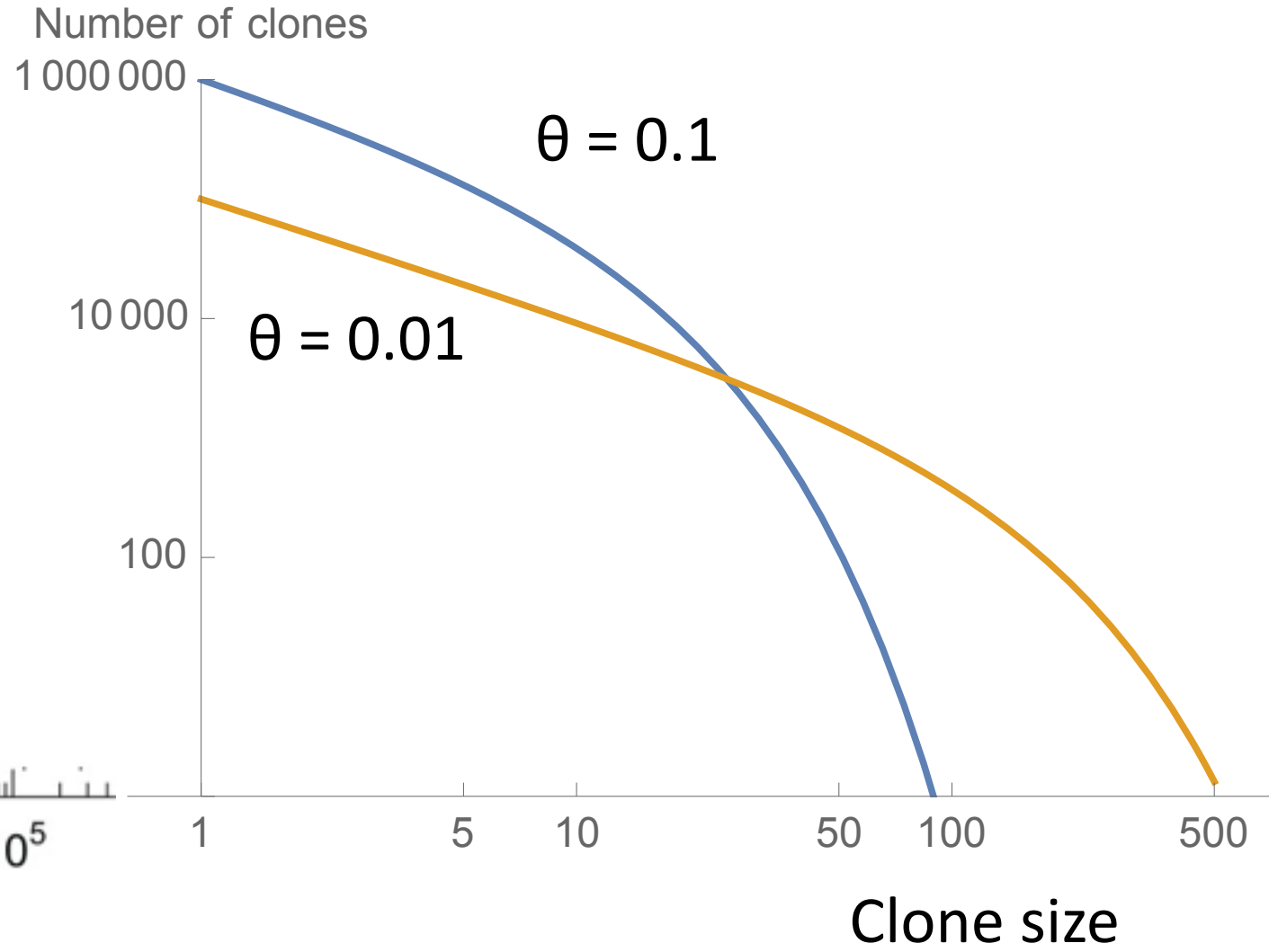
Most clones are one cell, $F_2 \sim F_1/2$, $F_i \sim F_i/i$ until i=k

LogLog Plot: power law in experimental data?

Zarnitsyna *et al.*, 2013



Mouse: N = 10^7 cells (k=1)



Conclusions

Simple birth death model describing clone size distribution

Model can simulate a whole mouse

Solution predicts human dynamics

Richness declines slower than thymic output (steady state & transient)

Simpson diversity is proportional to thymic output

Simpson diversity would overestimate effect of aging

In young adult and in old mice we expect mostly singletons