Cancer in mice and men: a comparison

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- <u>Scientific Journalist :</u>

  Dr. Folkman, will the new experimental findings in angiogenesis have an impact on cancer therapy?
- <u>Dr. Folkman :</u>

  If you are a mouse under treatment for cancer, I think I can cure you.

Animal models (mostly mice) have contributed to the understanding and treatments of human cancers

Problem

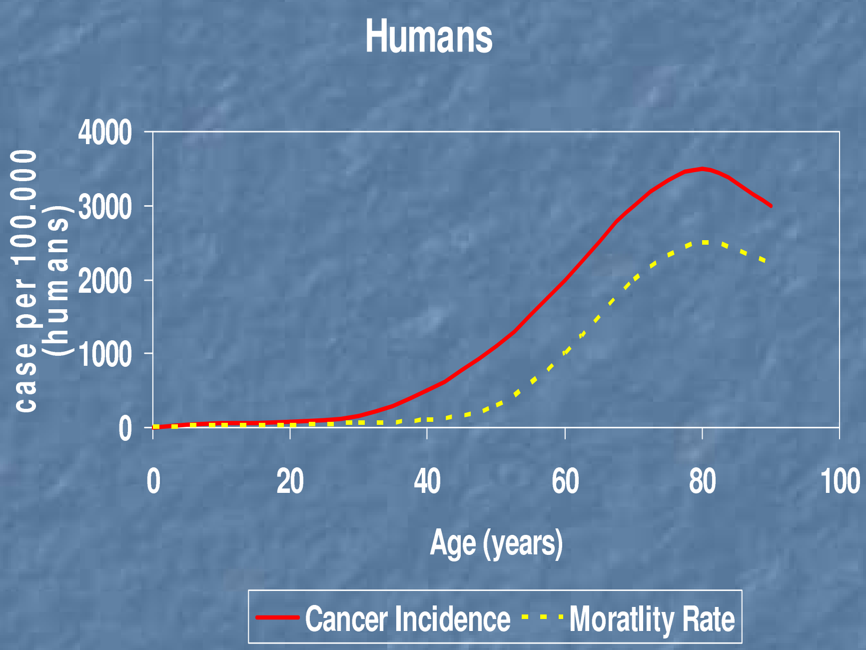
1. What are the limitations to the use of mice models in studies of human cancer?
2. To what extent can these limitations be resolved?

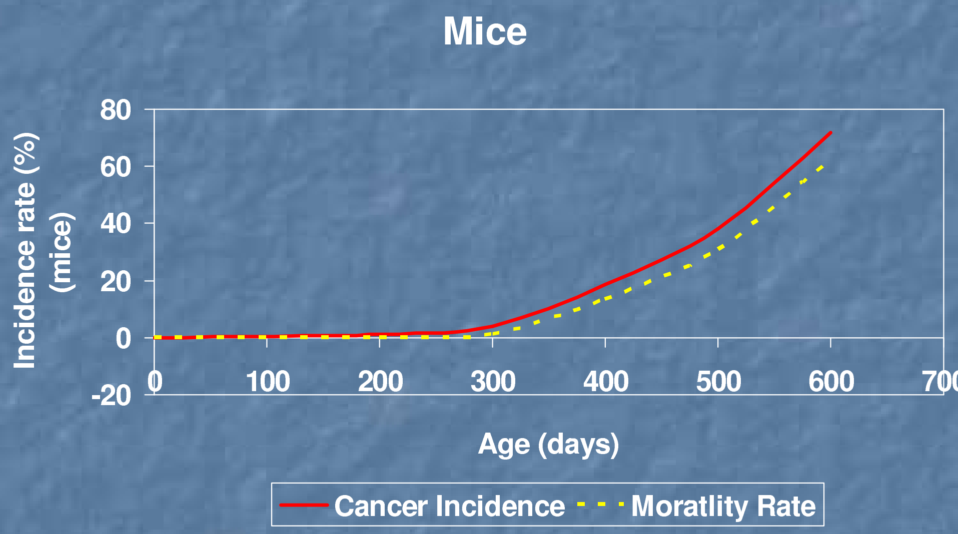
Incidence of spontaneous cancers in mice and humans

Cancer	Mice	Humans
Breast	+	+
Lung	-	+
Prostate	-	+
Colon	-	+
Stomach	-	+
Liver	-	+
Endometrial carcinoma	-	+
Leukemia Lymphoma	+	+
Bladder	-	+

+ := common spontaneous cancer   - := uncommon spontaneous cancer

Age – Pattern of incidence and mortality rates





Cancer development

Condition	Mice	Human
Tumour origin	Mesodermal sarcomas	Epithelial carcinomas
Spontaneous regression of tumours	Common in adult mice	Rare in adult humans
Induction of malignant transformation: number of genetic events	few	several

Claim

- The observed differencies in

1. **Tissue susceptibility**
2. **Mortality rate**
3. **Cancer development**

have an evolutionary rationale

Hypothesis

Species-Specific Differencies

1. Tissue susceptibility
2. Mortality rate
3. Tumour development

are the consequence of

Species-Specific Differencies in

I. Life-History properties
   1. Age of sexual maturity
   2. Life span
   3. Litter size

II. Physiological Properties
   1. Metabolic rate
   2. Metabolic stability

These life history and physiological properties have an evolutionary rationale.

Differences in life history and physiological properties

Species	Age of sexual maturity	Litter size	Age at which reproduction ceases	Life span
Mice	35-50 days	4-8	3 years	4 years
Humans	13 years	1	50 years	122 years

Claim

Species-Specific variation in

a. Tissue susceptibility
b. Mortality rate
c. Tumour development

Can be explained in terms of the following two concepts

1. Demographic entropy : A measure of the diversity of pathways of energy flow in a population of replicating organisms

2. Metabolic entropy : A measure of the diversity of the pathways of energy flow in a regulatory or metabolic network

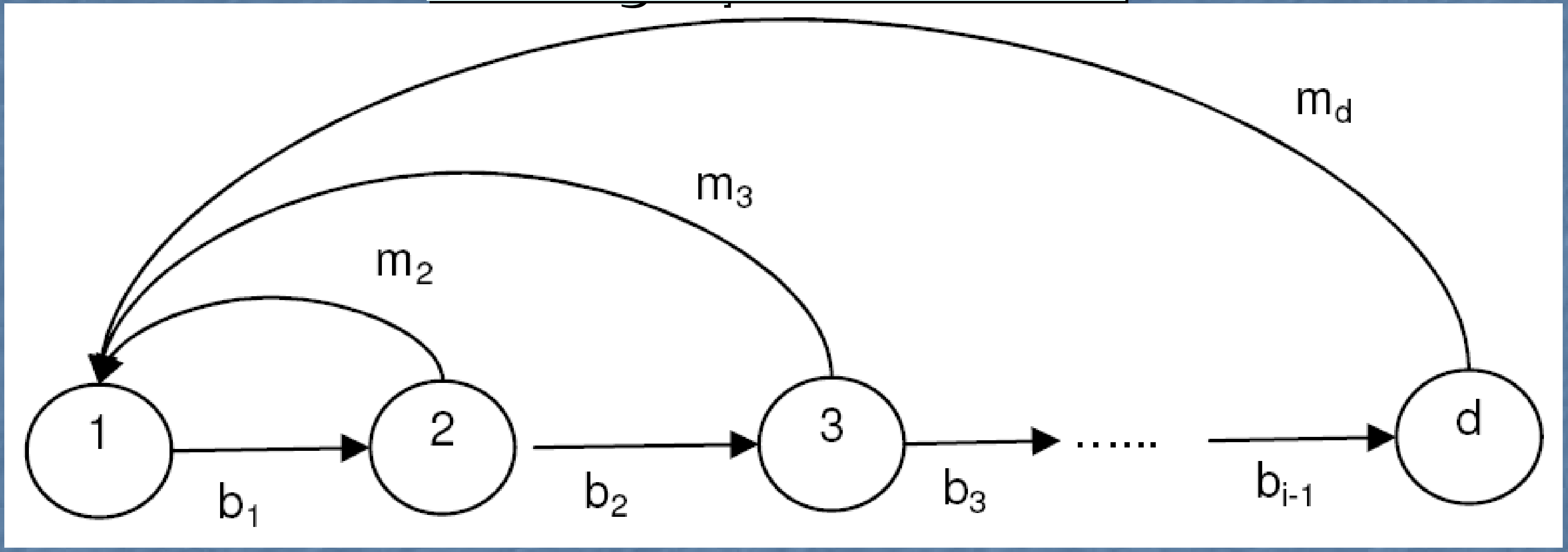
Demographic entropy

Measure of Darwinian Fitness in evolutionary theory: This concept explains interspecific variation in life-history features: Maximal life span, metabolic rate.

Metabolic entropy

Measure of Darwinian Fitness in a theory of organismic development: This concept explains intraspecific variation in developmental properties: Cell Proliferation and cell differentiation, metabolic stability.

Evolutinary model
Demographic network



b_i := proporsion of individuals that survive from age class (i) to (i+1)

m_i := mean number of offspring produced by individuals in age class (i)

$l_j := b_1 \ldots b_{j-1}$ = survivorship to age class (j)

$V_j = l_j m_j$ = Net-reproduction at age class (j)

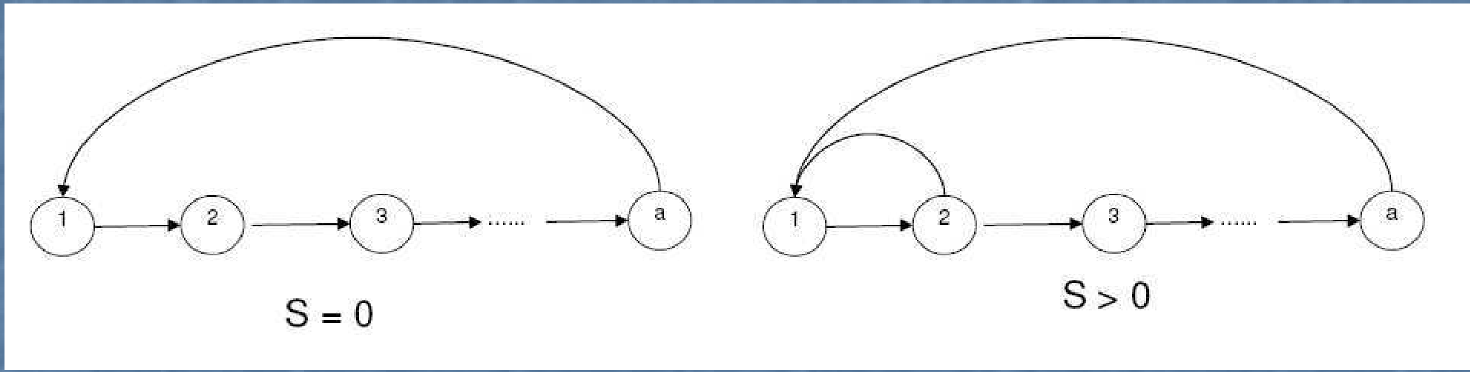
$R = \sum V_j$ = Total net-reproduction

Demographic entropy

$$S = -\sum_{j=1}^{d} p_j \log p_j \quad ; \quad p_j = \frac{V_j}{R}$$

Properties

1. Diversity of pathways of energy flow



2. Demographic Stability / Robustness

Rate at which the population returns to the steady state condition after a perturbation

Demographic entropy
as
Darwinian fitness

$$p_j = \frac{V_j}{R} \quad ; \quad R = \sum V_j$$

$$E = \sum p_j \log V_j \quad ; \quad S = -\sum p_j \log p_j$$

$$\boxed{\log_e R = S + E}$$

Incumbent population = V_j

Mutant type = V_j^*

V_j^*:= a perturbation of V_j

Competition between variants and incumbent

1. E < 0 : If S* > S : Mutants displaces the incumbent
2. E > 0 : If S* < S : Mutant displaces the incumbent

Evolutionary changes in demographic entropy

- Equilibrium species: Populations which spend the greater part of their evolutionary history in the stationary growth phase – (human)

  ($E < 0$)
- Opportunistic species: Populations which undergo episodes of rapid population growth followed by decline – (mice)

  ($E > 0$)

  Directionality principipes
- Equilibirum species: Evolution results in a unidirectional increase in entropy
- Opportunistic species: Evolution results in unidirectional decrease in entropy

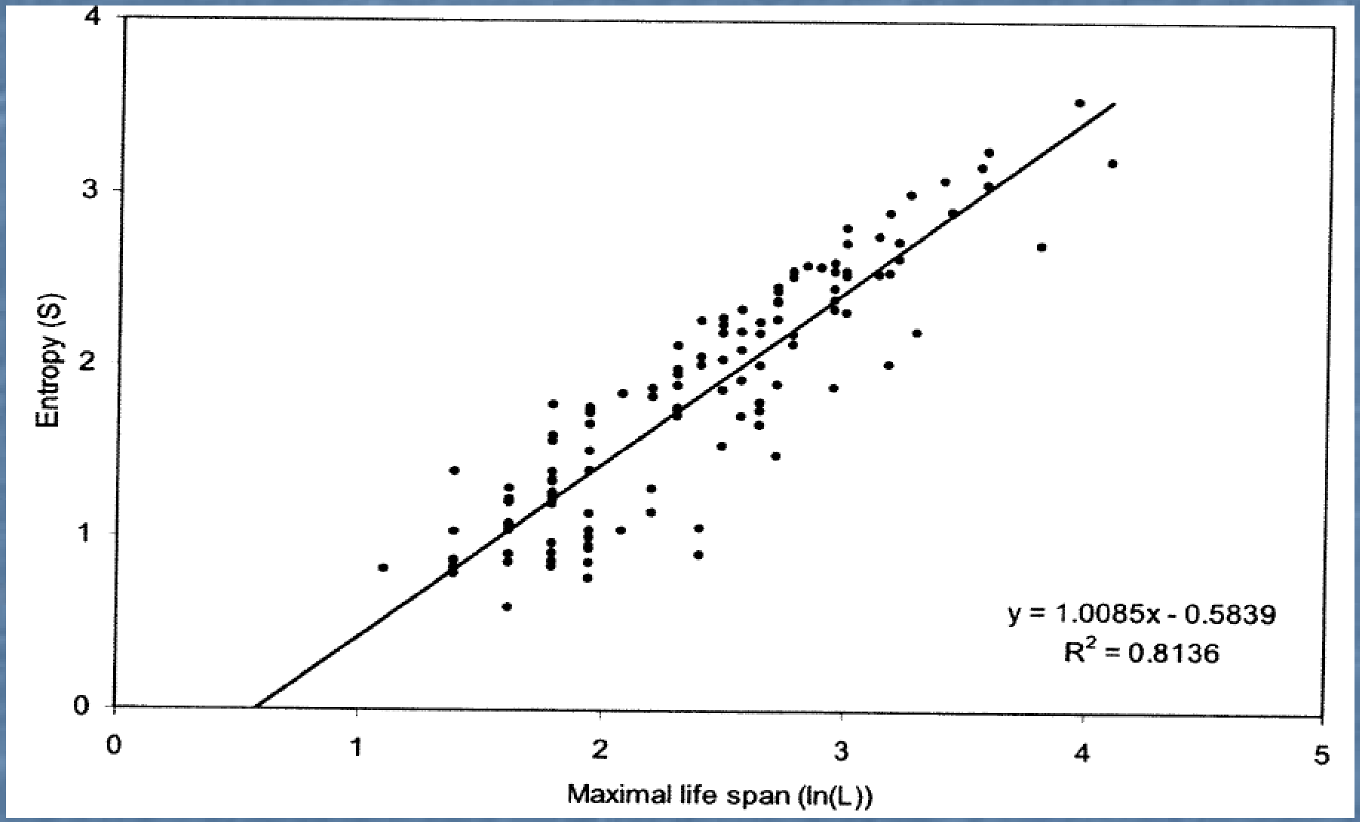
Analytic relation between entropy and Life span, metabolic rate, body size

1. $S = a_1 + b \log L$; $\text{L} \equiv \text{Life Span}$

2. $S = a_2 + \dfrac{1-b}{b} \log P$; $\text{P} \equiv \text{Metabolic rate}$

3. $S = a_3 + (1-b) \log W$; $\text{W} \equiv \text{Body size}$

Relation between entropy and life span (Empirial study) (Mammals)



The relation of logarithm of maximal life span (L) to demographic entropy (S) with the linear fit for the whole mammals data set

Predictions of directionality principies for evolutionary entropy

1. Equilibrium species: (humans)

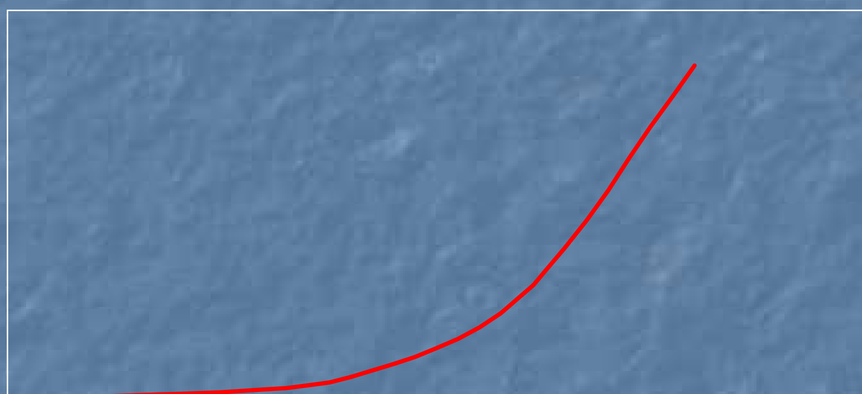
   Mortality rase will increase exponentially with age and abate with age at advanced age

2. Opportunistic species: (mice)

   Mortaility rate will increase exponentially with age

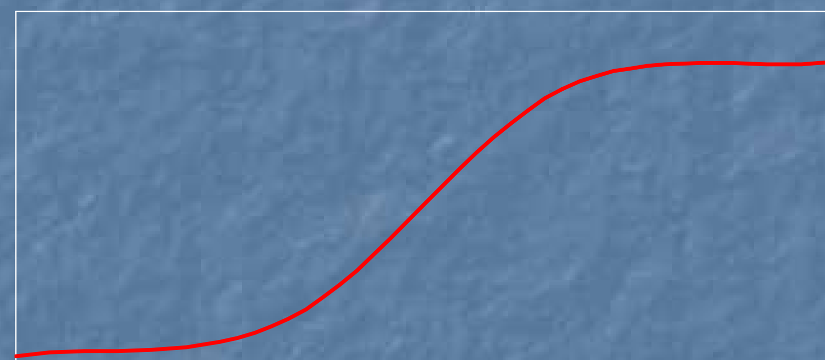
Differences in mortality rates in mice and humans have an evolutionary rationale

mice



age

human



age

Humans: Equilibrium species : Evolution acts to increase demographic entropy

Mice: Opportunistic species: Evolution acts to decrease entropy

Claim

Differencies in tissue susceptibility and tumor development in mice and humans can be explained in terms of metabolic entropy

Regulatory Network

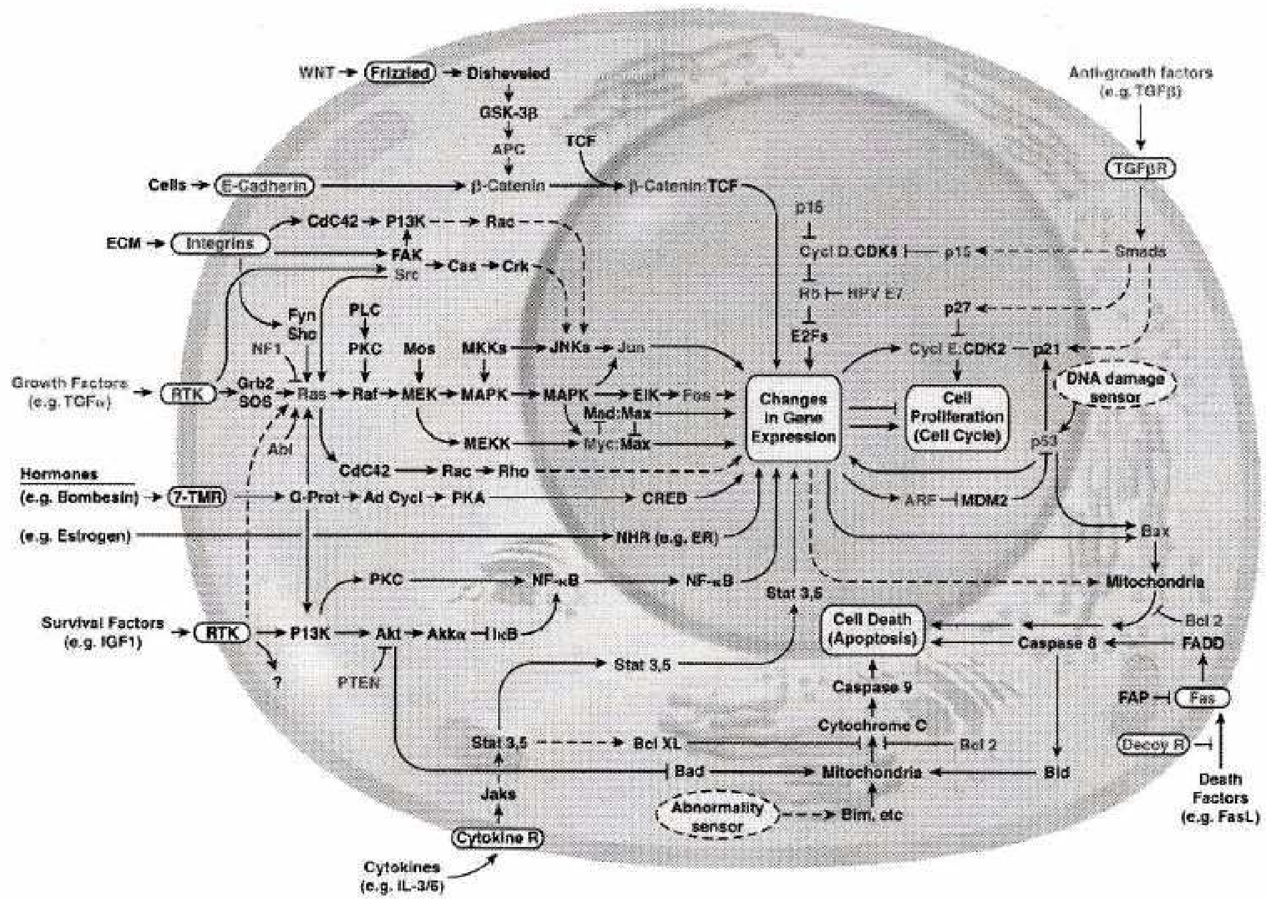
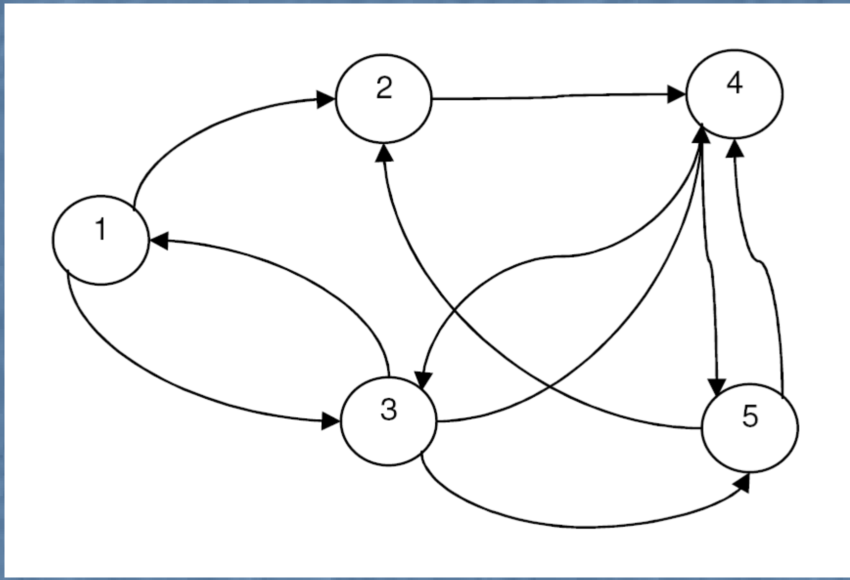


Figure 2. The Emergent Integrated Circuit of the Cell

Schematic represantation of a regulatury network



$A = (a_{ij}) \geq 0$: adjacency matrix

$$A = \begin{bmatrix} 0 & 1 & 1 & 0 & 0 \\ 0 & 0 & 0 & 1 & 0 \\ 1 & 0 & 0 & 1 & 1 \\ 0 & 0 & 1 & 0 & 1 \\ 0 & 1 & 0 & 1 & 0 \end{bmatrix}$$

Characterisation of metabolic entropie

$$Au = \lambda u$$

$$\lambda \equiv \text{dominant eigenvalue}$$

$$\mathrm{P} = (p_{ij}) \geq 0$$

$$p_{ij} = \frac{a_{ij} u_j}{\lambda u_i}$$

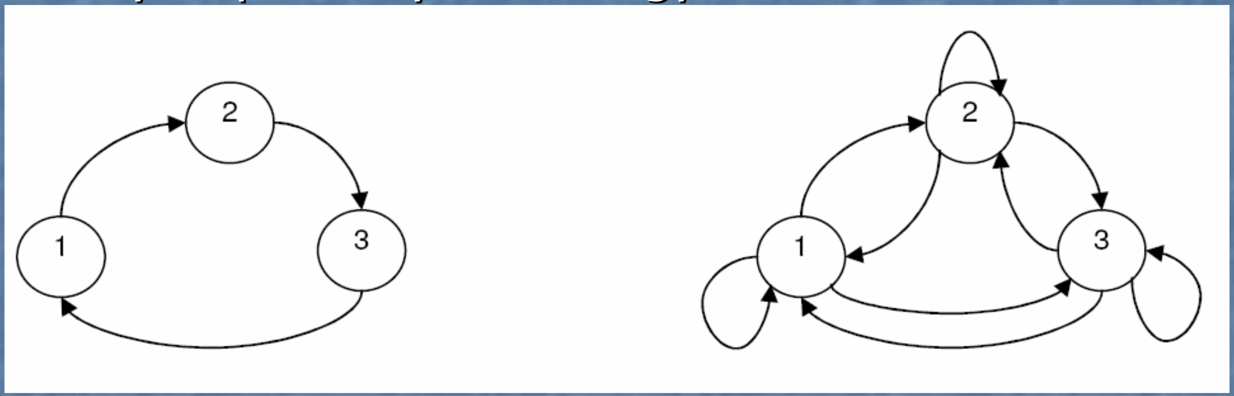
$$\pi = (\pi_{\mathrm{i}}) \equiv \text{stationary distribution of P.}$$

$$\underline{\text{Metabolic entropy } H}$$

$$H = -\sum_i \sum_j \pi_i p_{ij} \log p_i$$

Properties of metabolic entropy

1. Diversity of pathways of energy flow in the network



H=0

H = log3

2. Measure of metabolic stability = rate at which a metabolic flux parameters returns to the steady state condition after a random perturbation in the enzymatic reaction rates
3. Metabolic entropy measures the efficency with which a cell or tissue transforms external resources into metabolic energy

Metabolic entropy as Darwinian Fitness

Metabolic entropy predicts the outcome of competition between cells utilizing the same resources

$$\Phi = \sum_{i,j} \pi_i p_{ij} \log a_{ij}$$

$$\log \lambda = H + \Phi$$

Incumbent network: $A=(a_{ij})$

Mutant network: $A^*=(a_{ij})^*$

A* = Pertubation of A

Predictions

$$\Phi < 0 \,;\, \mathrm{H}^* > \mathrm{H} : \text{Mutants displaces incumbent}$$

$$\Phi > 0 \,;\, \mathrm{H}^* < \mathrm{H} : \text{Mutants displaces incumbent}$$

Predictions of metabolic entropy

1. Individual life span
2. Metabolic stability of tissues
3. Number of genetic events necessary for induce malignant transformation

Mice and Humans

- **Mice:** Low entropic species
  - (a) Early age of sexual maturity
  - (b) Short life span
  - (c) High mass specific metabolic rate

  CANCER DYNAMICS

  Induction: Few genetic events

  Spontaneous regression: Common

- **Humans:** High entropic species
  - (a) Late age of sexual maturity
  - (b) Long life span
  - (c) Low mass specific metabolic rate

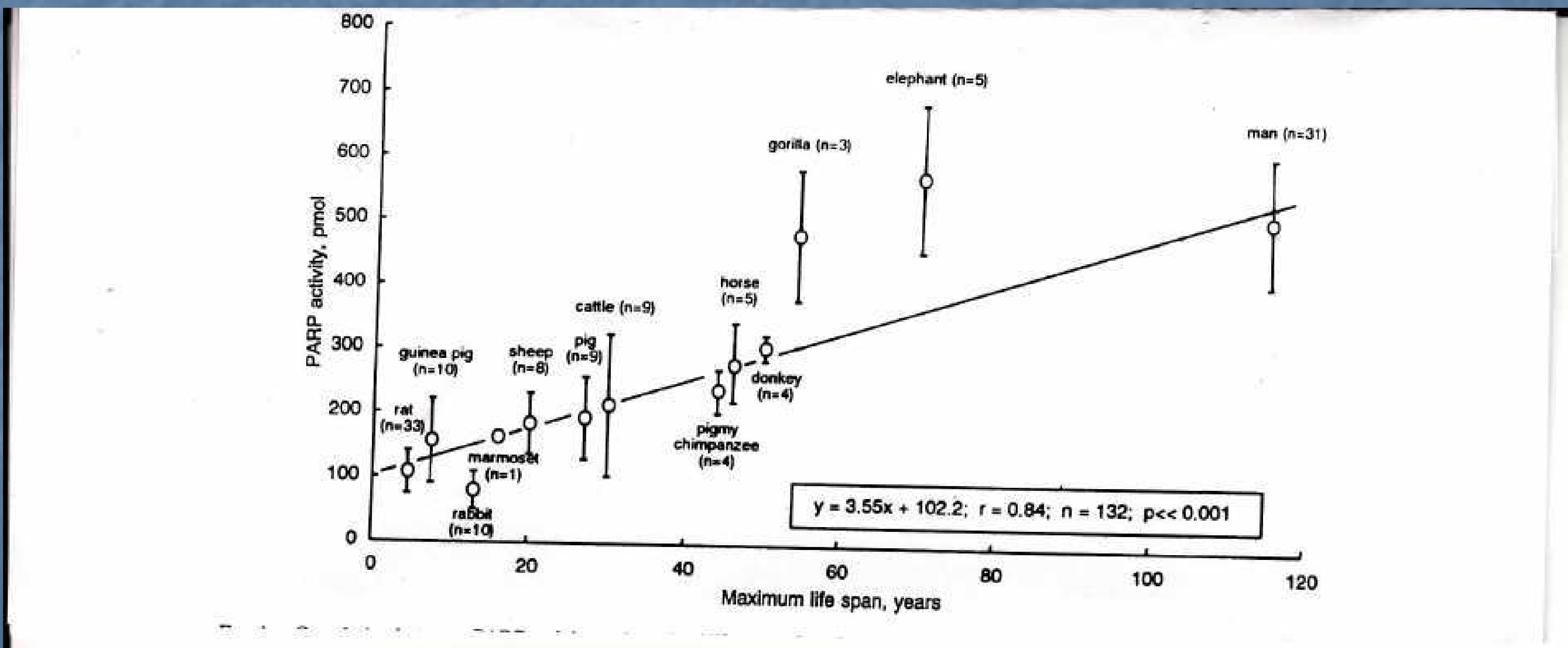
  CANCER DYNAMICS

  Induction: Several genetic events

  Spontaneous regression: Rare

Empirical considerations

Realtion between metabolic entropy and life span



Summary

1. Cancer is an age-related disease due to the instability of genetic and metabolic networks.
2. Metabolic stability is correlated with demographic entropy and metabolic entropy, parameters, which differ between mice and humans.
3. Extrapolating experimental results from mice to humans must consider these differencies in metabolic and demographic stability.