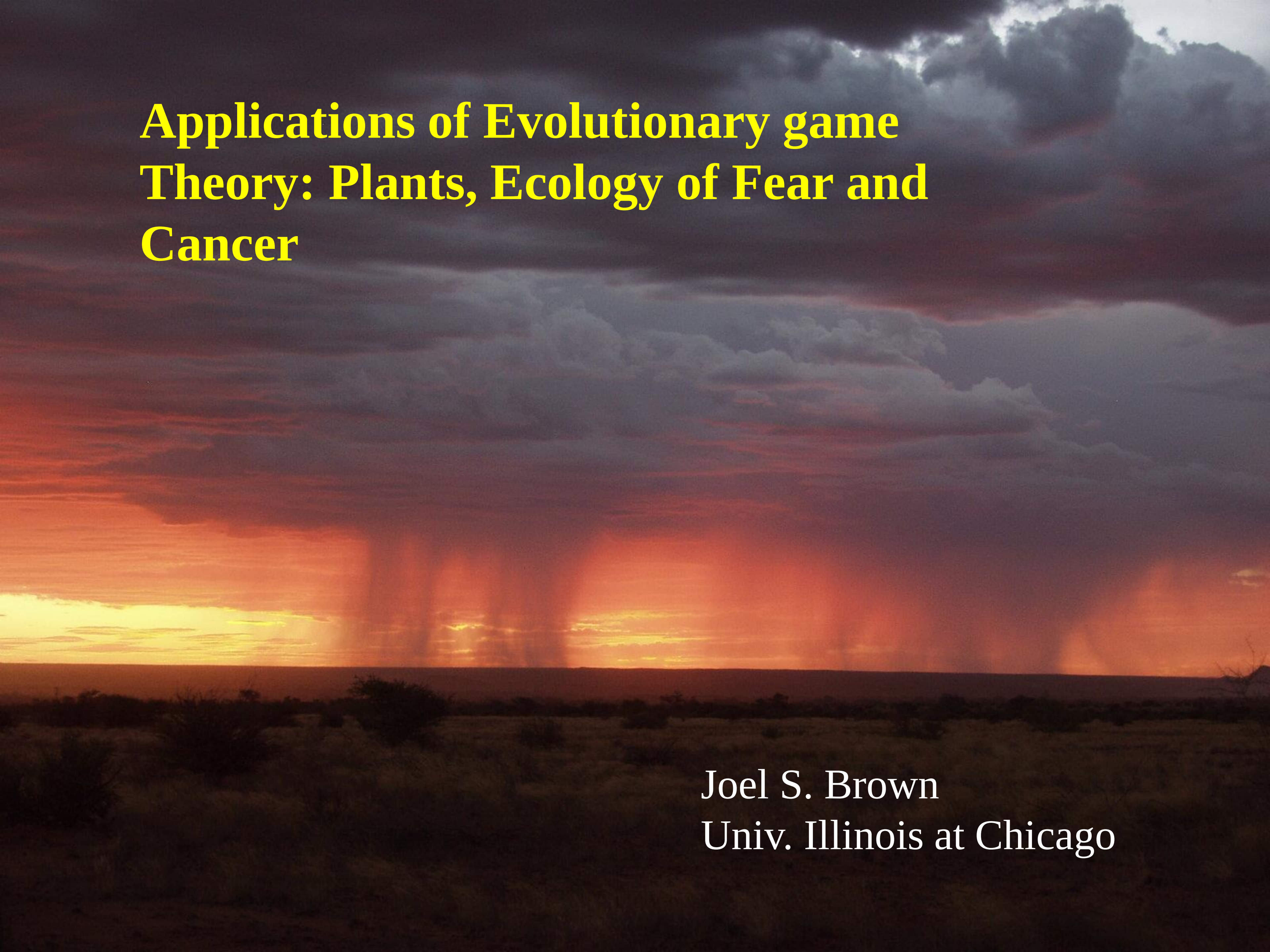


Applications of Evolutionary game Theory: Plants, Ecology of Fear and Cancer

Joel S. Brown
Univ. Illinois at Chicago

Goals (part III)

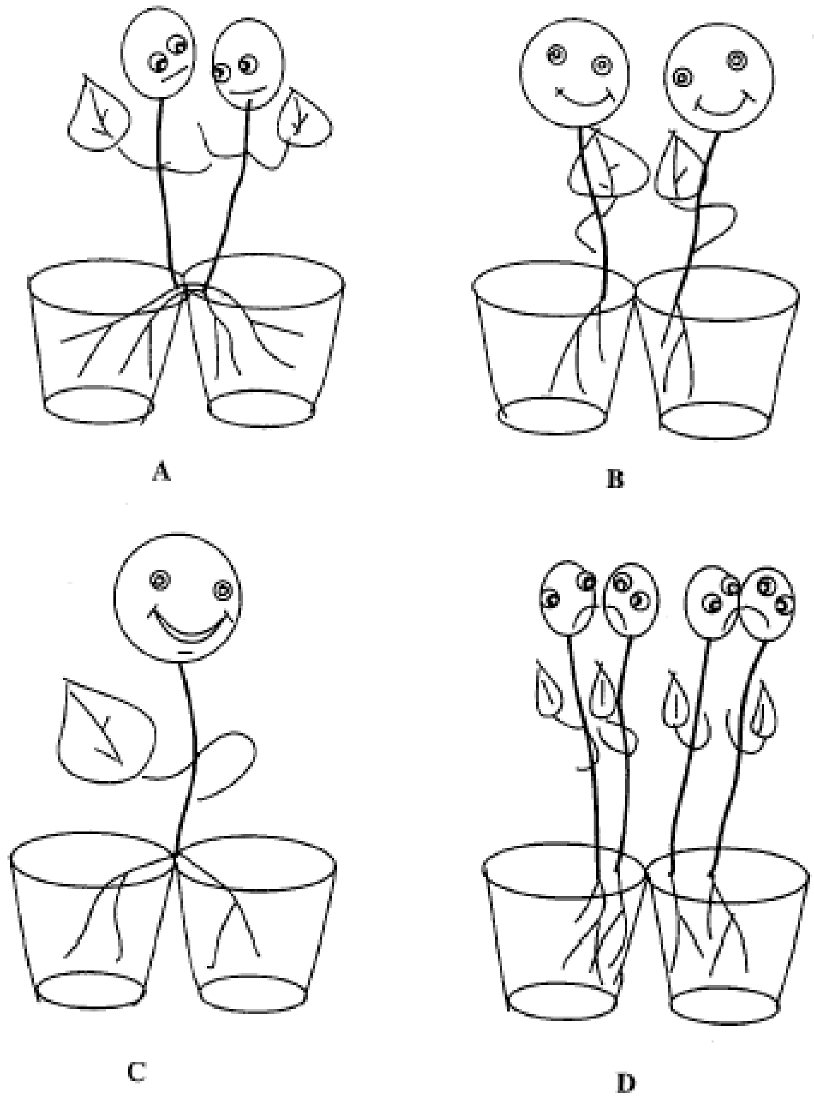
- Plants Playing Footsie
- A Night out with Gerbils
- In the Shadow of the Snow Leopard
- Cancer as an Evolutionary Game

Roots Proliferation

Models explain root proliferation and nutrient foraging of a single plant

Few good models of root proliferation and nutrient foraging of multiple plants

Inter- versus Intra-plant Competition



Why a Tragedy of the Commons?

- Each additional unit of root proliferation both increases total nutrient uptake and "steals" uptake from other roots
- Better to "steal" from ones neighbor than from oneself
- Requires a whole plant response to assessing the costs and benefits of local root production

Competition for Sunlight

- Height in plants can be thought of as a light foraging game in plants
- Additional height sacrifices nutrients to prevent shading from others
- The adaptive height may not maximize collective yield as plants "steal" light from each other
- Green Revolution resulted in part from breeding shorter cultivars -- docility in plants

A Bit of Math ....

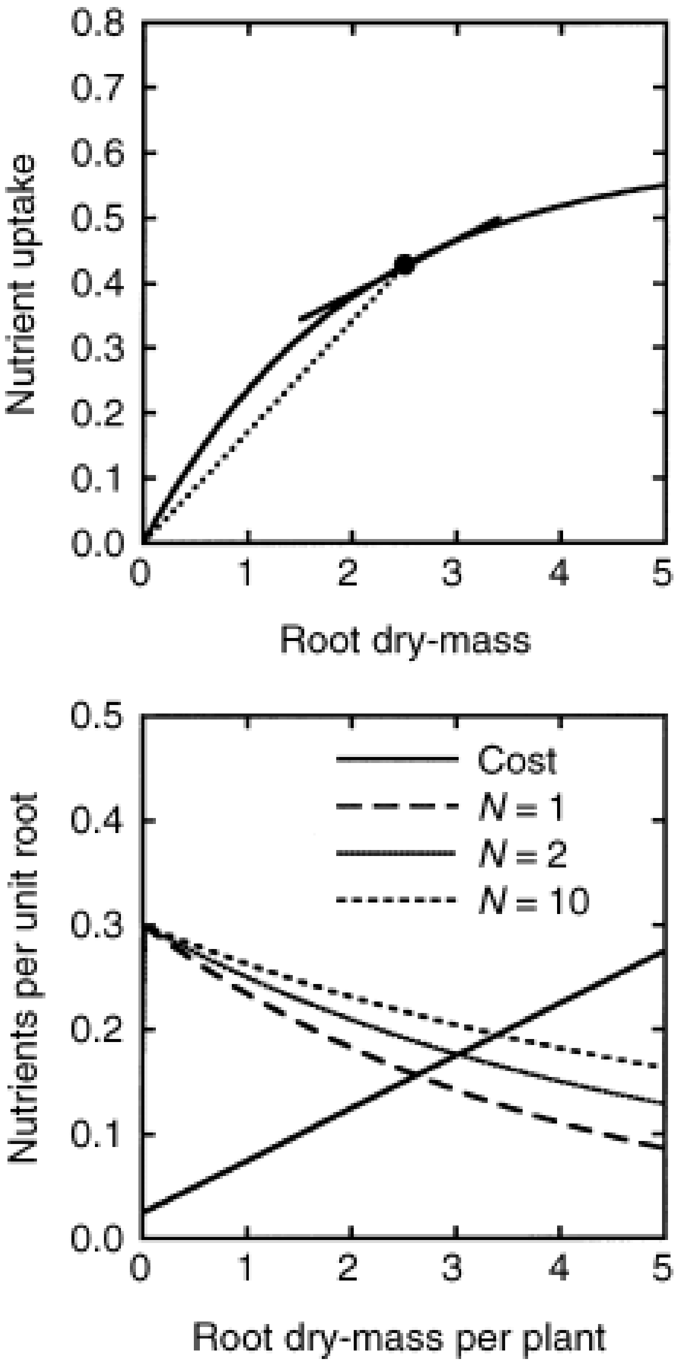
$$G(v,\underline{u},x) = (v/r)H(r) - C(v)$$

$$\partial G/\partial v = H(r)[r - v]/r^2 + (v/r)\partial H/\partial r - \partial C/\partial v$$

$$\frac{(x-1)}{x} \cdot \frac{H(r)}{r} + \frac{1}{x} \cdot \frac{\partial H}{\partial r} = \frac{\partial C}{\partial v}$$

Average uptake always greater than the Marginal uptake

Optimal Root production with differing numbers of plants and .... space per plant is equal



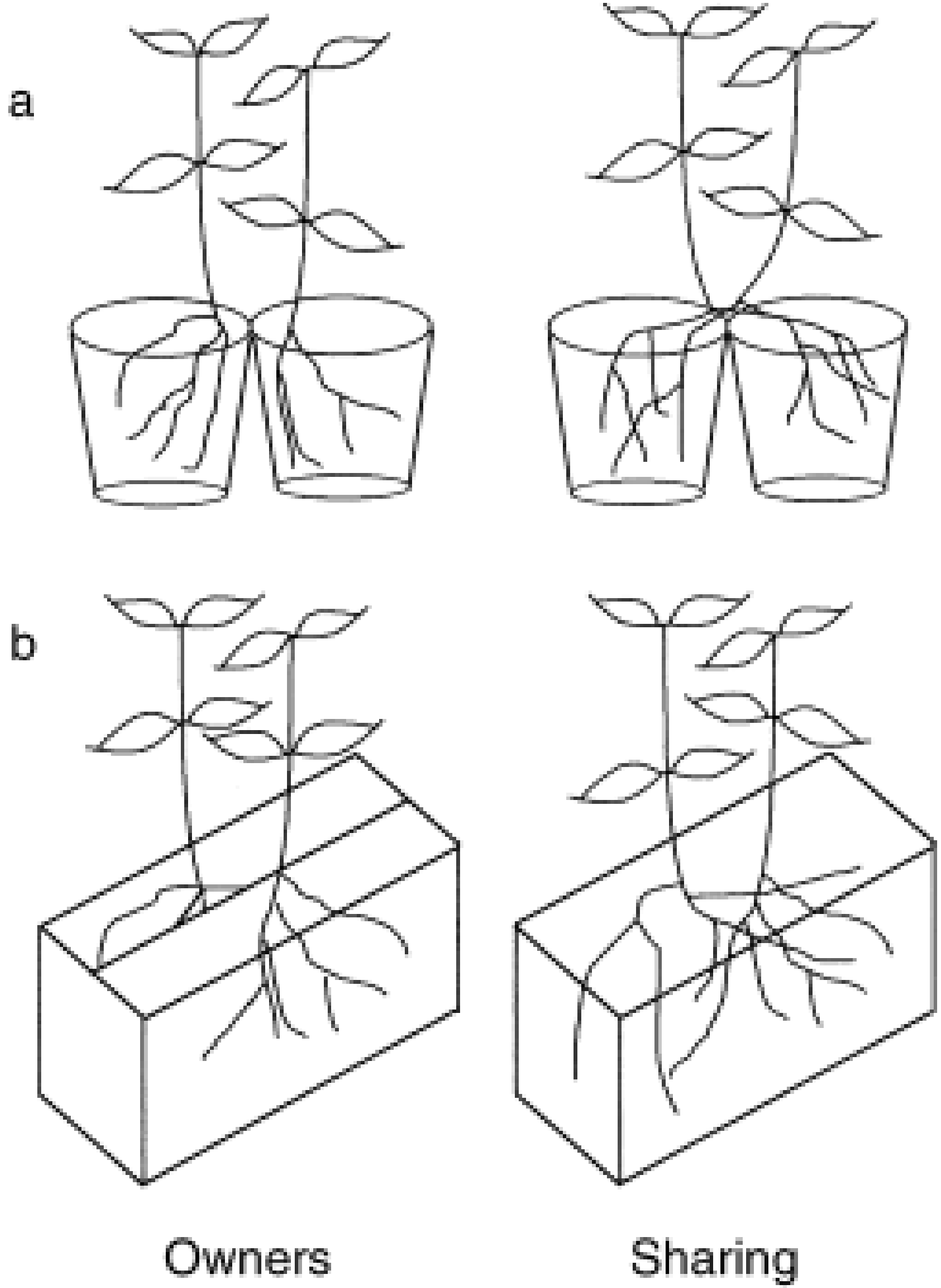
Perspectives on Root Competition

Intra-plant Avoidance (Tragedy of the Commons)

Roots: Fence-Sitters > Owners

Seed Yield: Fence-sitters < Owners

Two-ways of creating "Fence-sitters"
versus "Owners"
while
keeping space and nutrients per plant equal



Soybeans were first germinated and then planted as seedlings. At maturity dry-mass of seeds, roots and shoots were measured

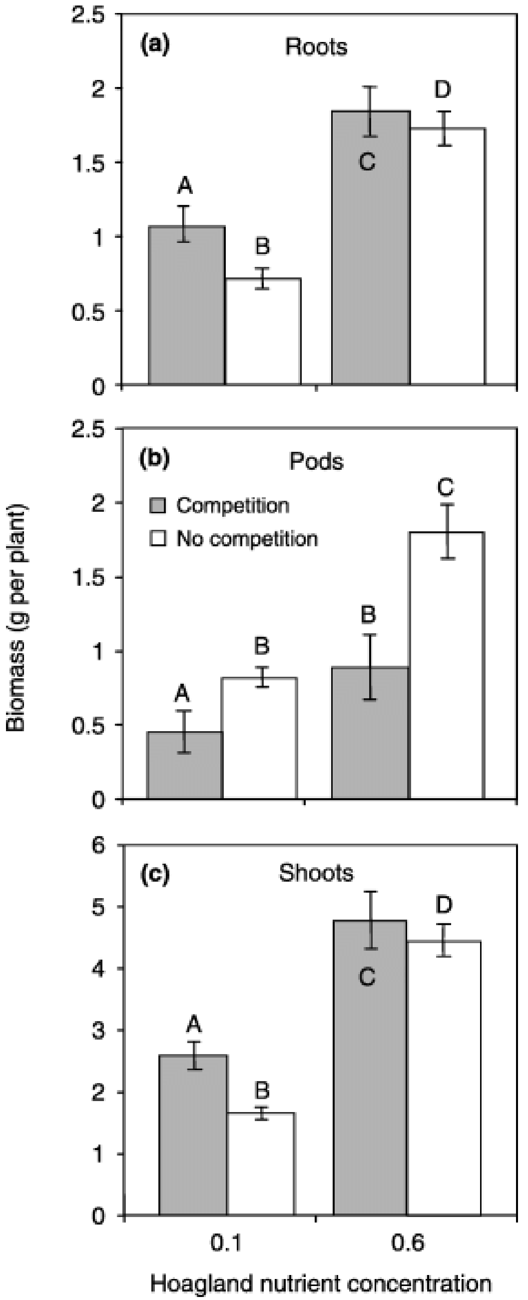

GA. TANK
DUTY


Home Guide
A24
Old-world charm and upscale ideas

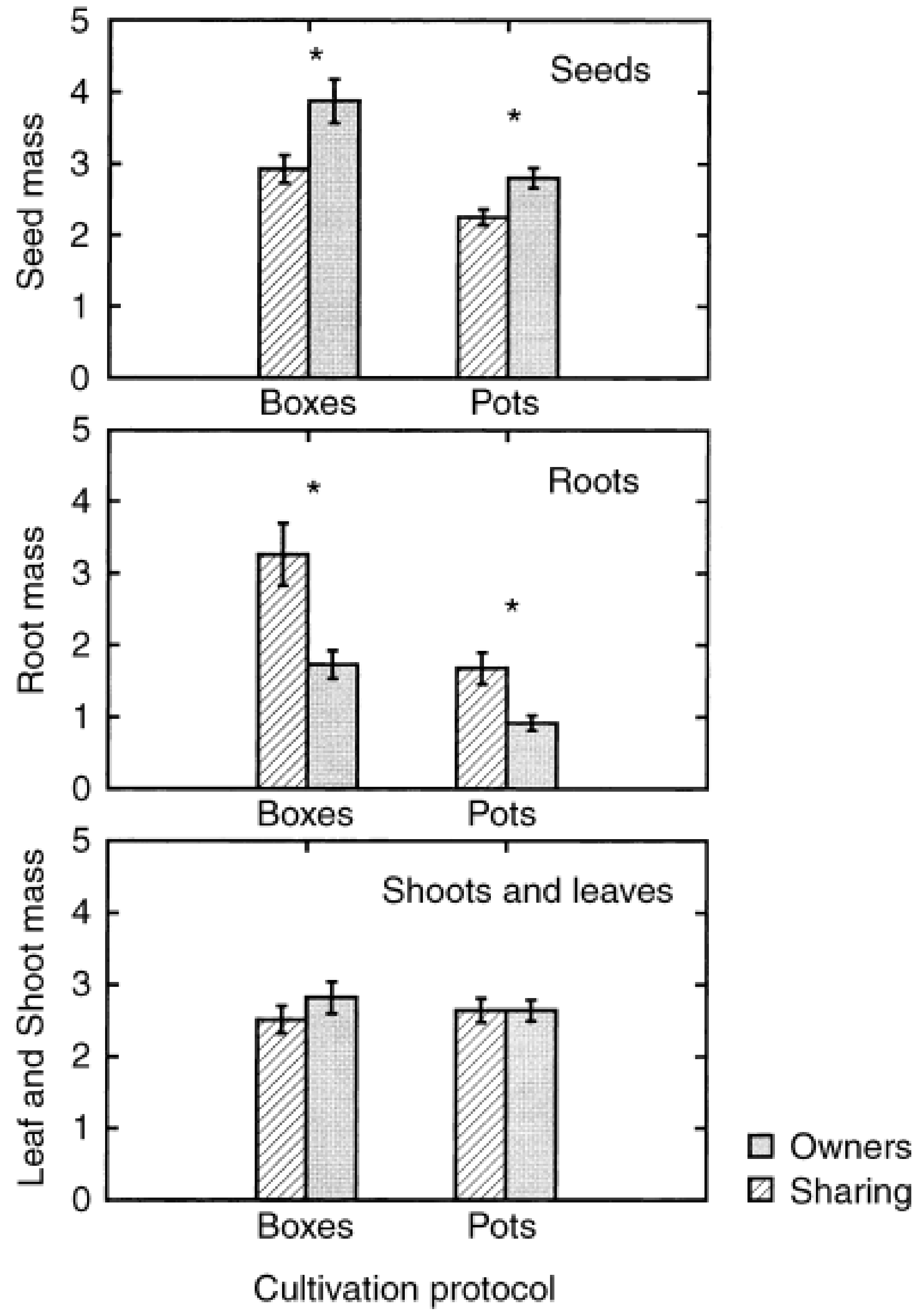
Roots: Fence-sitters > Owners

Seeds: Owners > Fence-sitters

Shoots: Fence-sitters > Owners



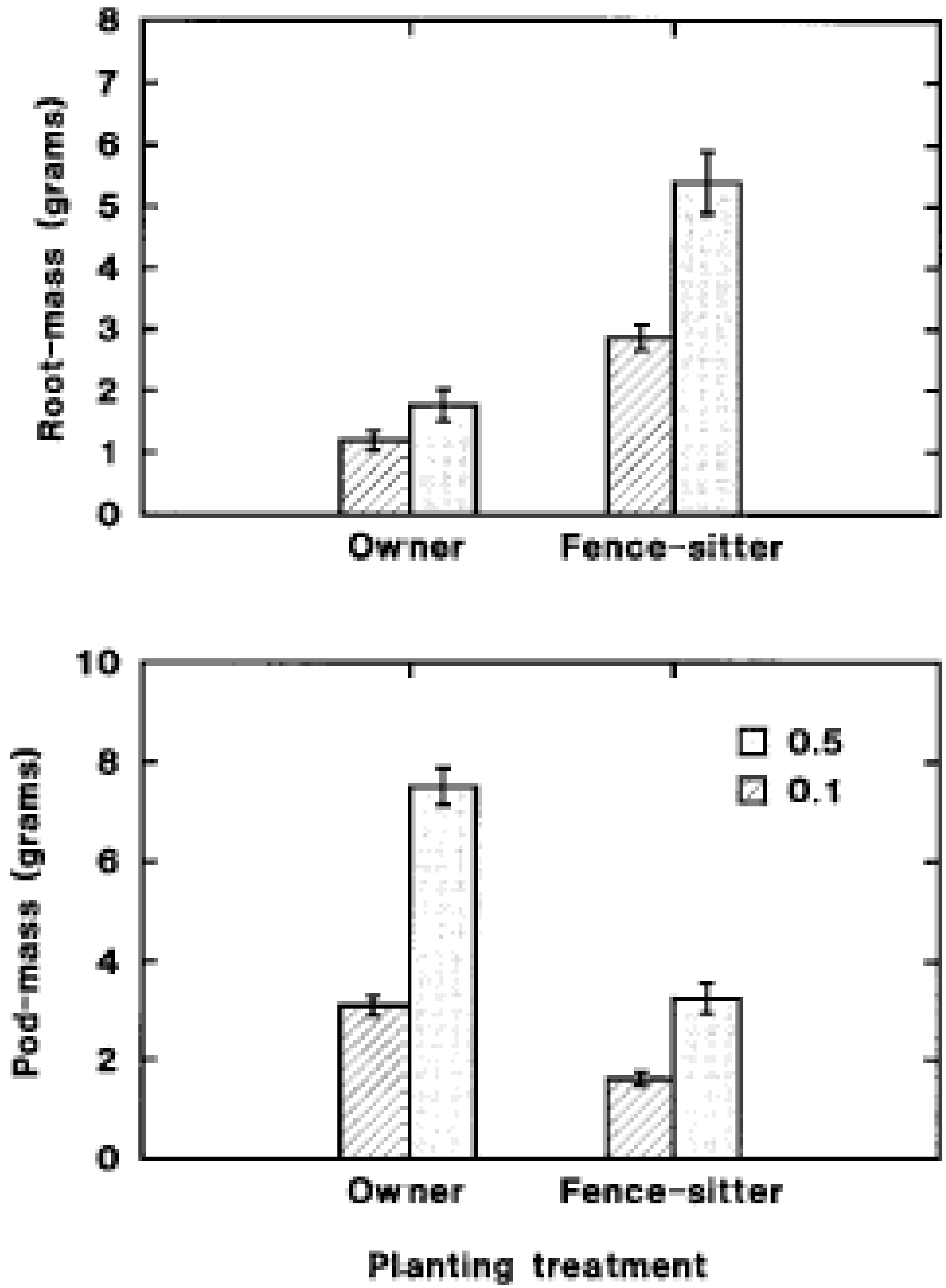
Cultivation technique did not influence the presence of the Tragedy of the Commons



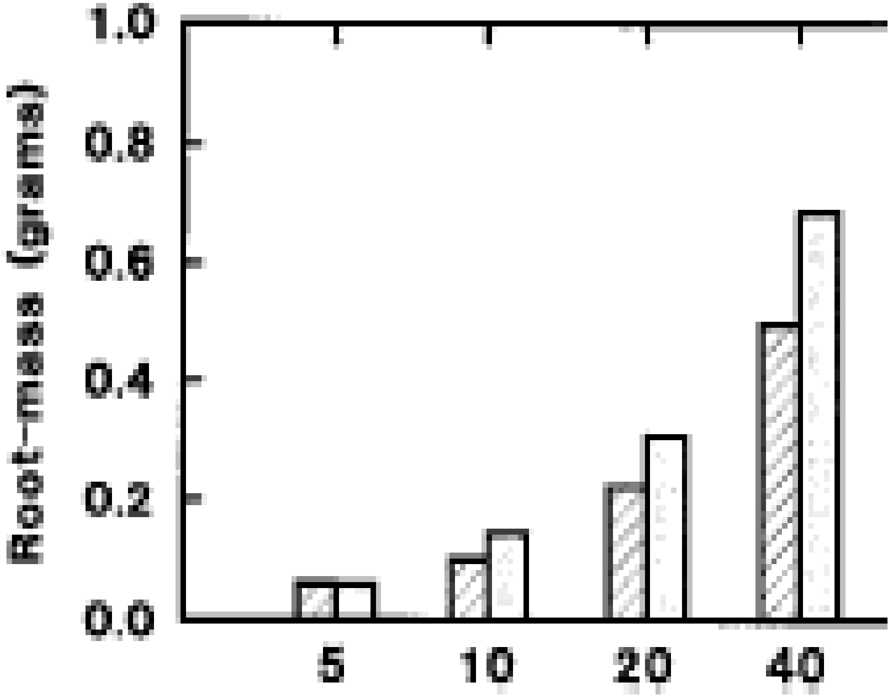
Experiments with Beans

Roots:
Fence-sitters > Owners

Seed Yield:
Owners > Fence-sitters

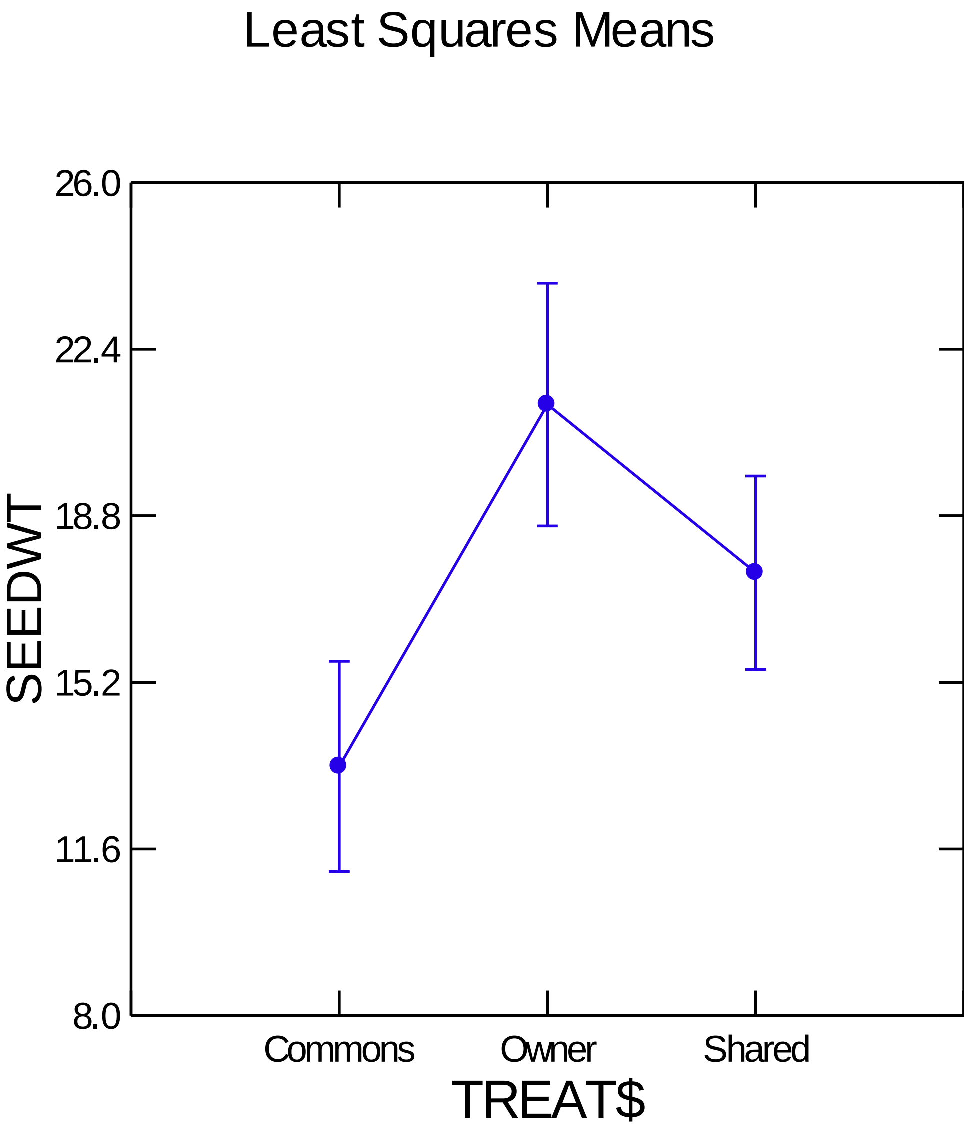


The greater root mass
of fence-sitters appears
within 10 days of planting
the seedlings



Root Mass Versus Time (days)

Is there a green revolution underground?



Lethal Effects of Predators:

Predators kill their prey

Non-Lethal Effects:

Predators frighten their prey

Ecology of Fear

The population, community and evolutionary consequences of the behavioral responses of prey and predators to each other

Cost of Predation or penalty of risk taking

$$\frac{(\textit{Risk of Predation})*(\textit{Survivor's Fitness})}{(\textit{Marginal Value of Energy})}$$




Predator Facilitation

Evolutionary Double Bind


Depletable Food Patches

Giving-up Density (GUD)

- The amount of food left behind in a depletable food patch by a forager
- Should increase with:
- Food abundance
- State of animal
- Risk

State-Dependencies

- Animal’s in a high state (high F) or with little need for energy (low dF/de) should have higher GUDs and take fewer risks
- Do the gerbils know this? Do the owls know this?
- Do the gerbils know when the owls are hungry and vice-versa?

Gerbils and Owls

- Daily renewal of seed resources
- Nightly depletion of seed abundance, y(t)
- Gerbils select $u_1(t)$, probability of being active
- Owls select $u_2(t)$, probability of being active

Resource Depletion

$$\dot{y} = -a_1 x_1 u_1(t) y$$

$$y(t) = y_0 e^{-a_1 x_1 \int u_1(t) dt}$$

a_1 = encounter probability of a gerbil on a seed
x_1 = number of gerbils

The nightly Seed harvest by a Gerbil

$$E_1 = a_1 \int y(t) u_1(t) dt - c_1 \int u_1(t) dt + k_1 \int [1 - u_1(t)] \, dt$$

c_1 = metabolic cost of activity

k_1= metabolic cost of resting

Where $c_1 > k_1$

As a Gerbil Sees the Game

Seed Harvest

$$E_1(v_1) = a_1 \int y(t) v_1(t) dt - c_1 \int v_1(t) dt + k_1 \int (1 - v_1(t)) dt$$

Surviving Owls

$$p_1 = e^{-a_2 x_2 \int u_1(t) u_2(t) dt}$$

Fitness

$$G_1(v_1(t), u_1(t), u_2(t), x_1, x_2) = p_1(v_1)[1 + b_1 E_1(v_1)]$$

As an Owl Sees the Game

Gerbil Harvest

$$E_2\left(v_2\right) = a_2 x_1 \int v_2(t)dt - c_2 \int v_2(t)dt + k_2 \int (1 - v_2(t))dt$$

Surviving Injury

$$p_2\left(v_2\right) = e^{-\gamma \int v_2(t)dt}$$

Fitness

$$G_2(v_2(t), u_1(t), x_1) = p_2[1 + b_2 E_2(u_2)]$$

Behavioral Thresholds

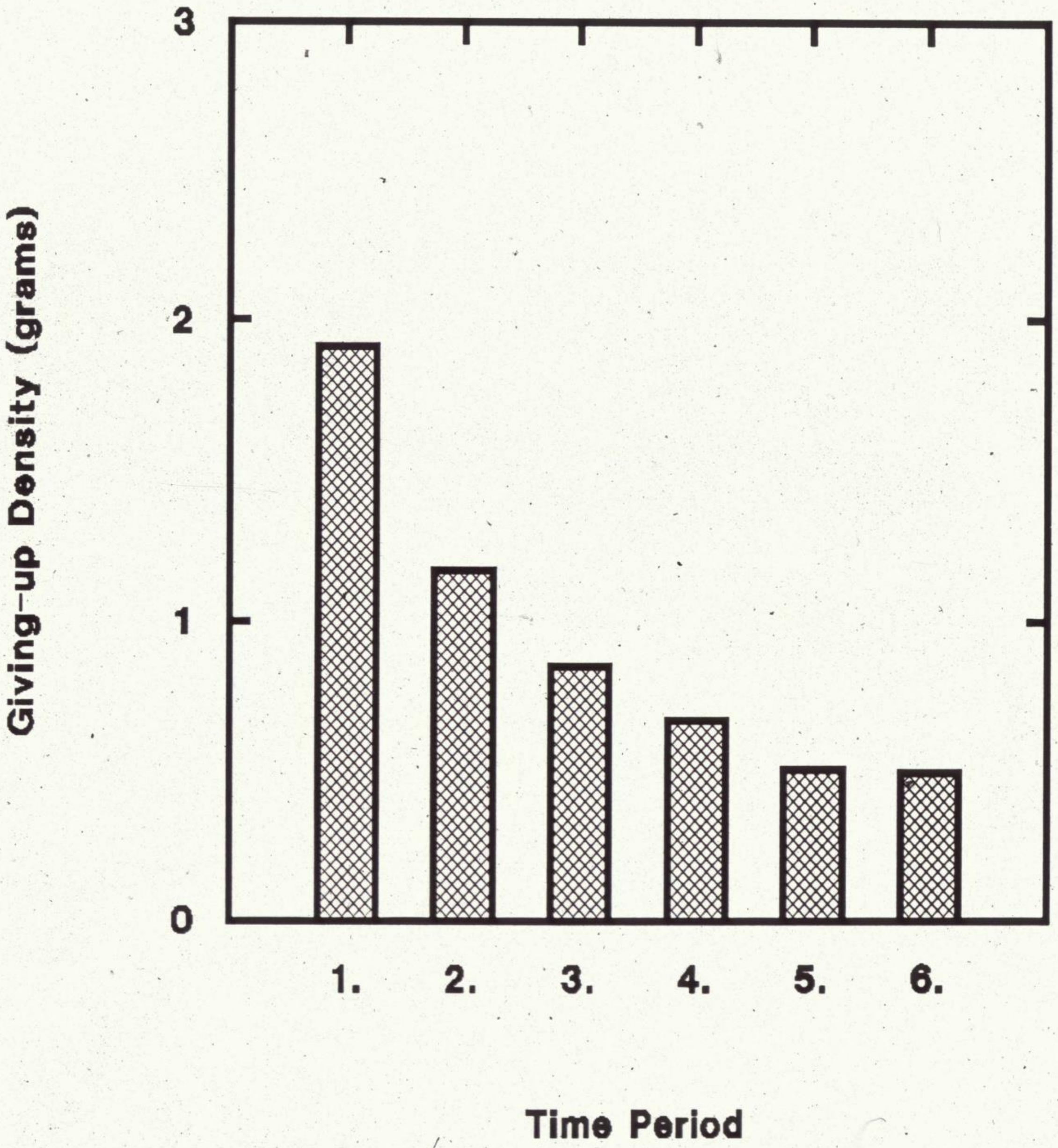
$$f_1 = a_1 y(t) \geq (c_1 - k_1) + a_2 x_2 u_2(t) \frac{1 + E_1}{b_1}$$

$$f_2 = a_2 u_1(t) x_1 \geq (c_2 - k_2) + \frac{\gamma(1 + E_2)}{b_2}$$

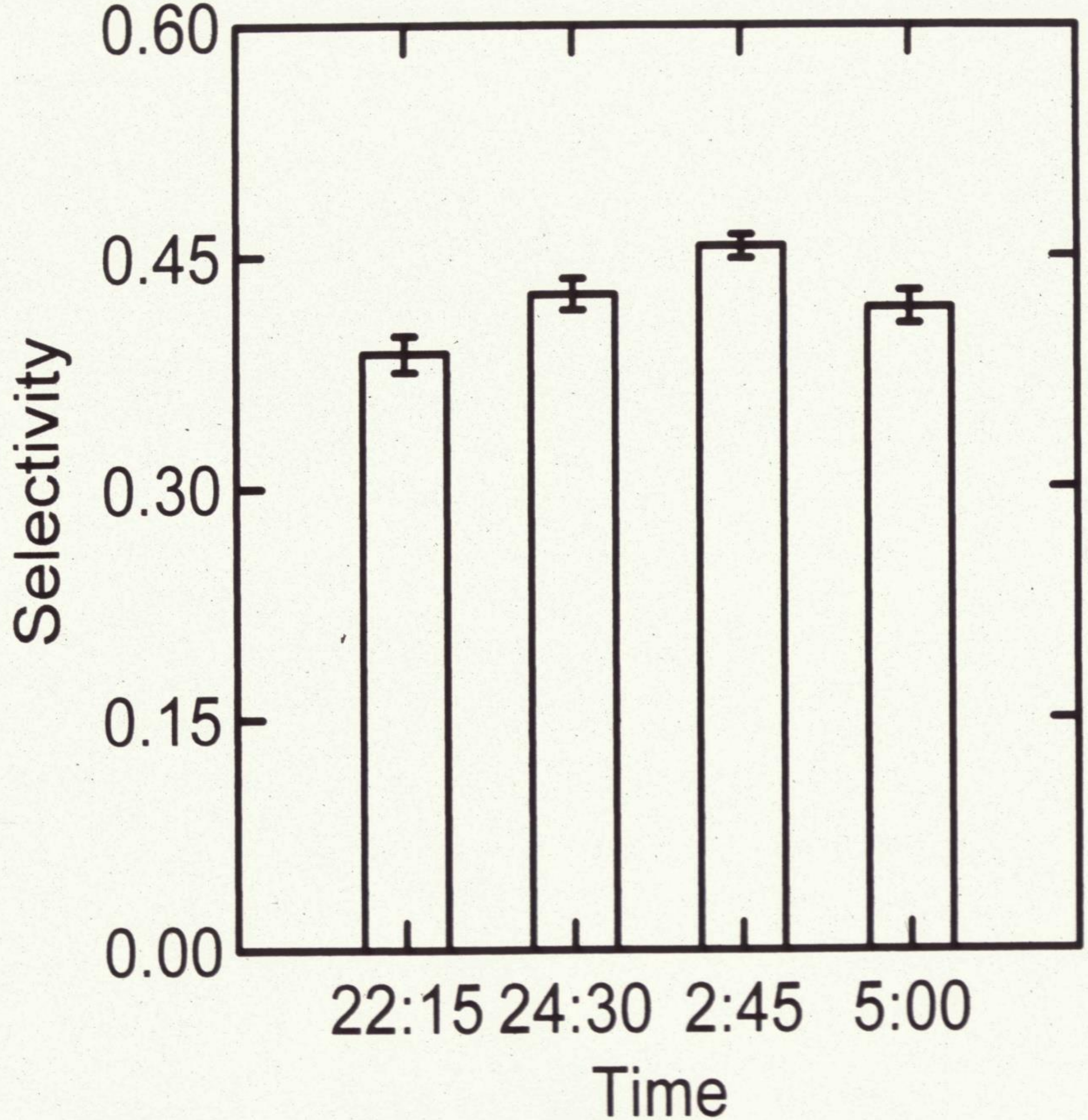
Evolutionarily Stable Strategy (ESS) has two phases:

All gerbils and all owls active

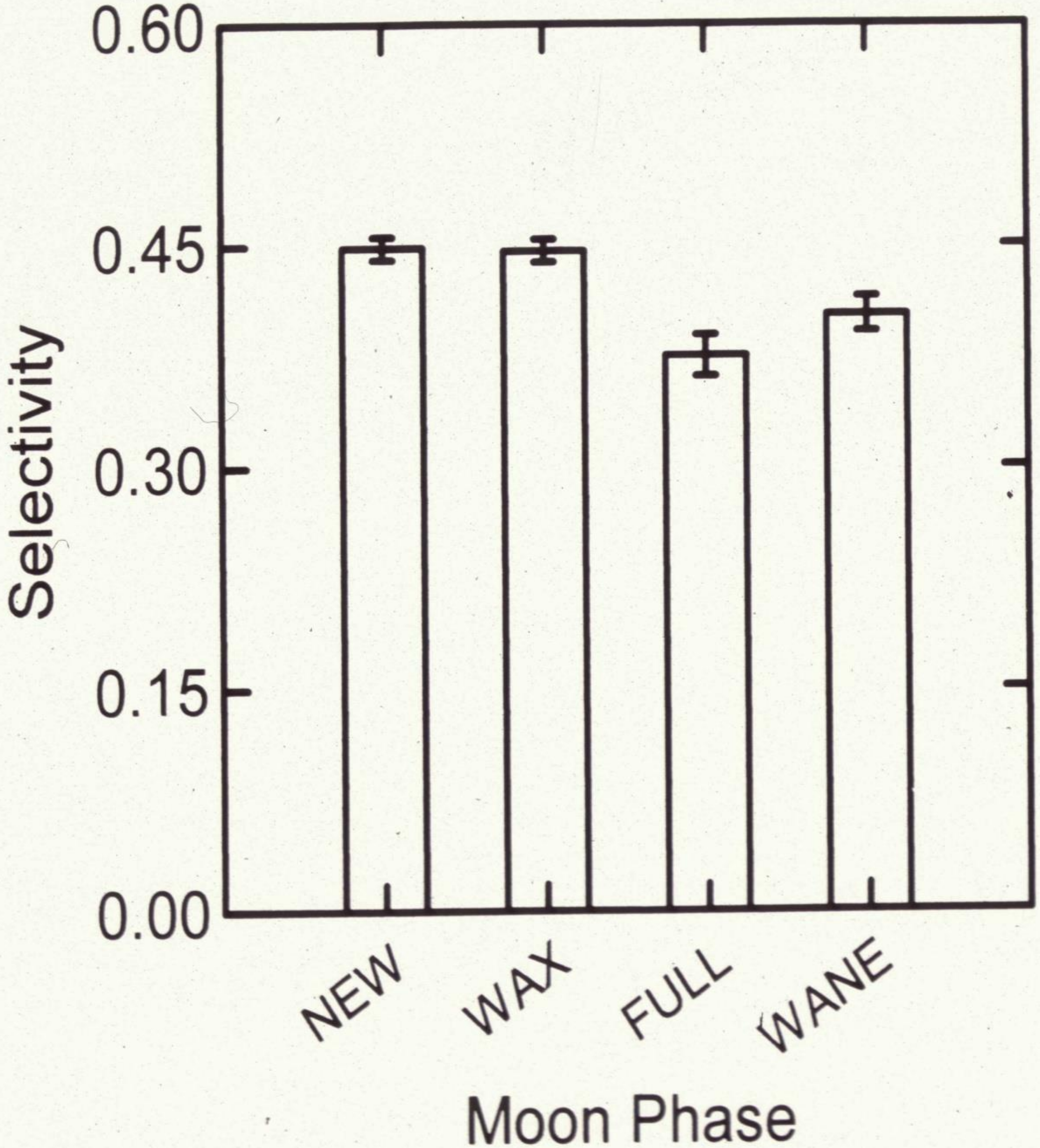
Some gerbils and some owls active



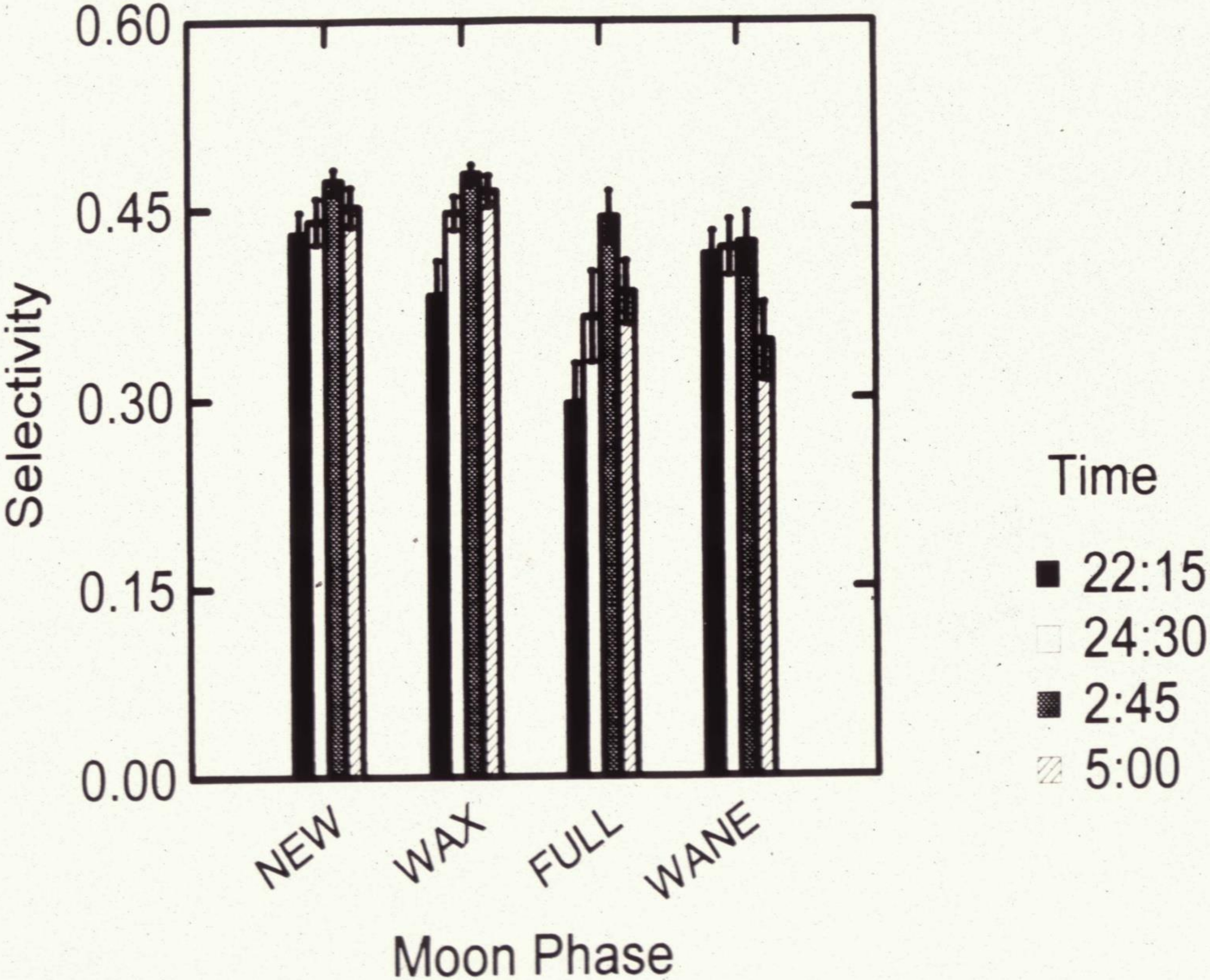
Giving-up Density (grams)
3
2
1
0
1.
2.
3.
4.
5.
6.
Time Period



0.60
0.45
0.30
0.15
0.00
Selectivity
22:15
24:30
2:45
5:00
Time



0.60
0.45
0.30
0.15
0.00
Selectivity
NEW
WAX
FULL
WANE
Moon Phase



0.60
0.45
0.30
0.15
0.00
Selectivity
NEW
WAX
FULL
WANE
Moon Phase
Time
22:15
24:30
2:45
5:00


TOYOTA

The Deer's Side of the Game

Fitness

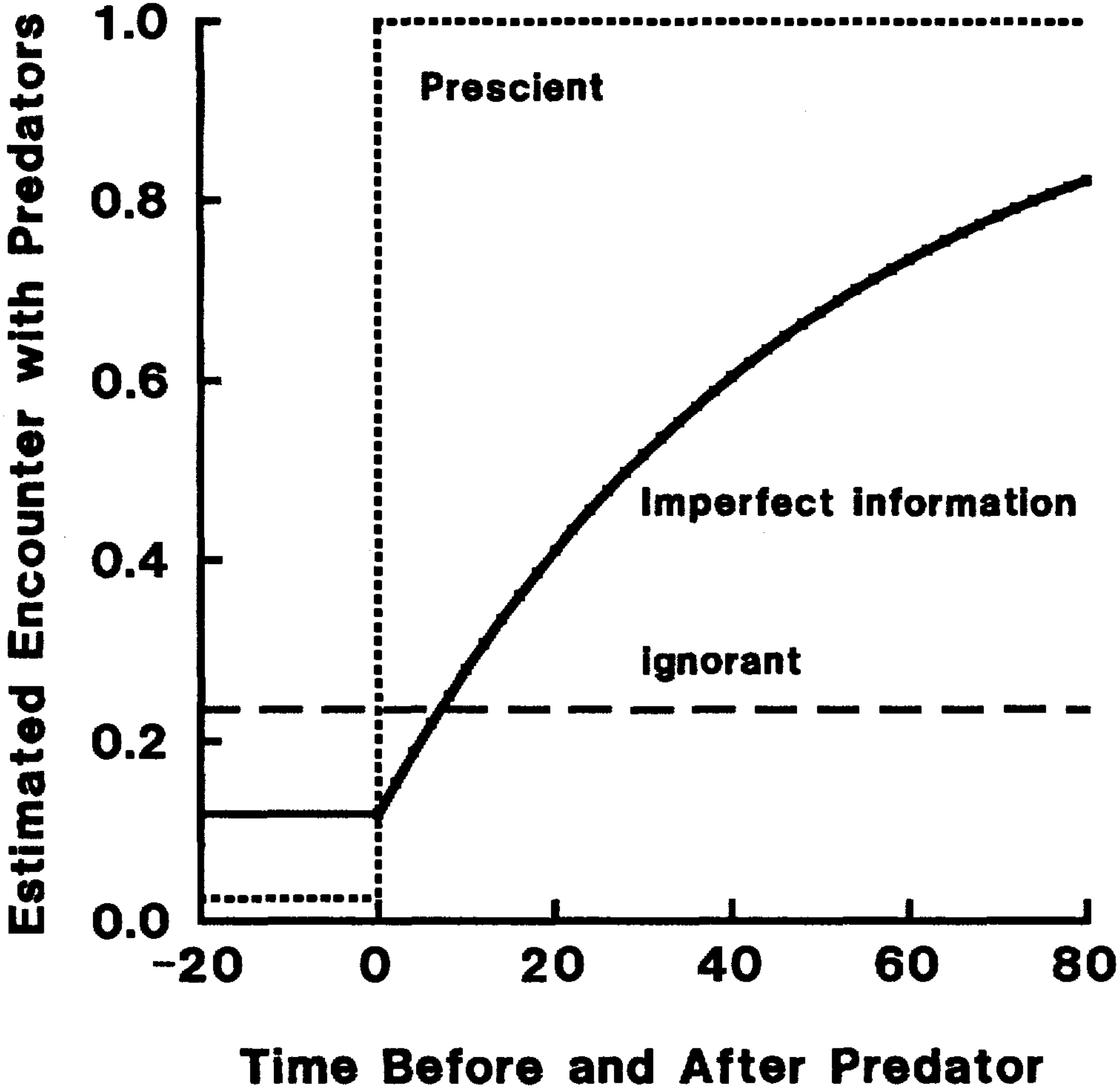
$$\dot{x}_1 = r\left[\frac{(1-w)K}{x_1+\chi} - c\right] - \mu x_2$$

Predation risk

$$\mu = \frac{m}{k+bw}$$

Optimal vigilance

$$w^* = \sqrt{\frac{mr(x_1+c)}{bR}} - \frac{k}{b}$$


Estimated Encounter with Predators
1.0
0.8
0.6
0.4
0.2
0.0
Prescient
Imperfect information
Ignorant
-20
0
20
40
60
80
Time Before and After Predator

Vigilance and Risk

The Learning Curve

$$m(t) = u_1 + (M - u_1)(1 - e^{-at)})$$

Average Risk

$$\bar{\mu} = p \int_0^{u_2} \frac{M}{k + b w^*_{pr}(t)} dt$$

Average Vigilance

$$\bar{w} = (1-p) w^*_{ab} + p \int_0^{u_2} w^*_{pr}(t) dt$$

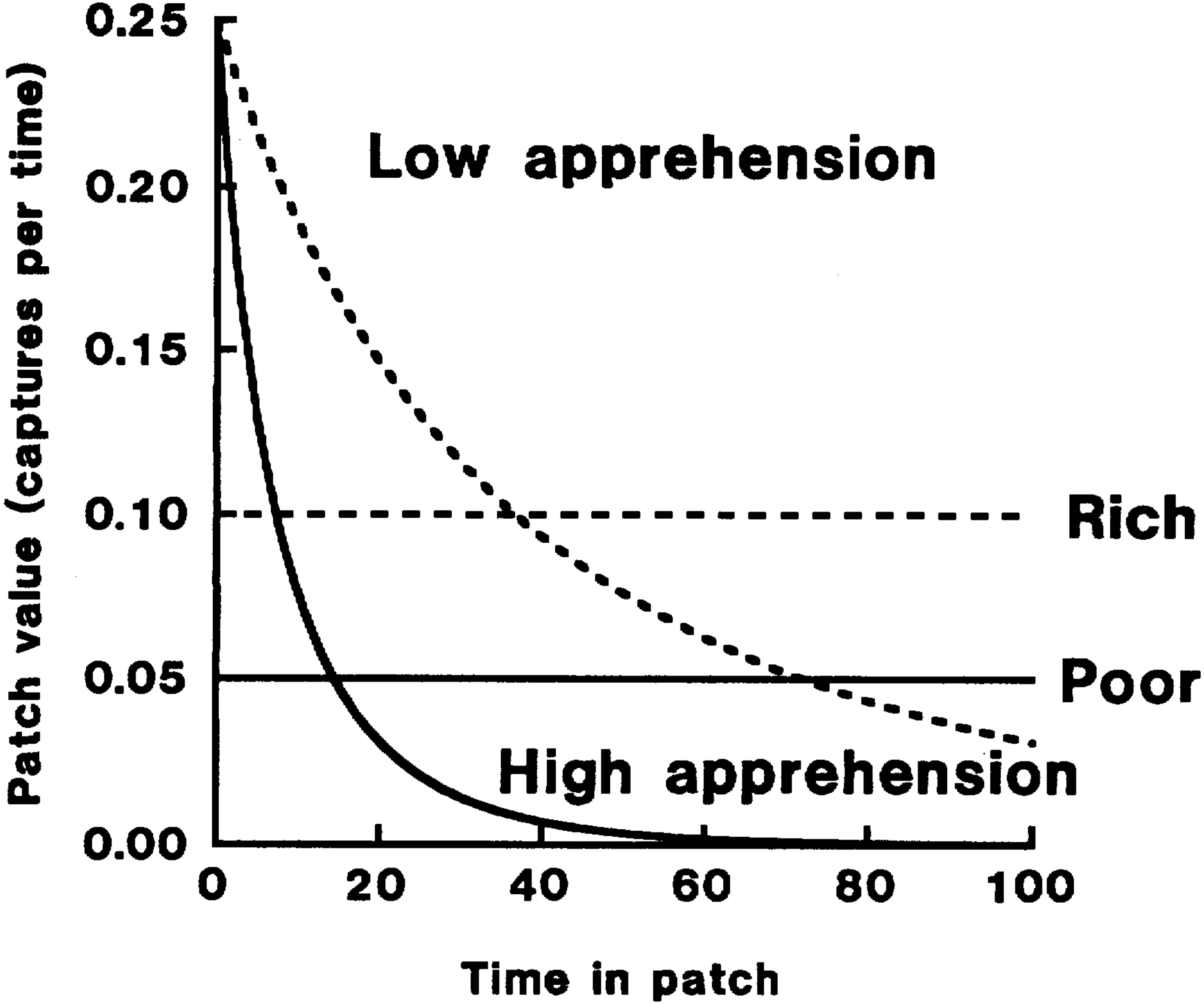
Mountain Lion's Perspective

Harvest of deer

$$H(u_2) = \frac{1 - e^{\left(\int_0^{u_2} \mu(t)dt\right)}}{T + u_2}$$

Leaving Rule

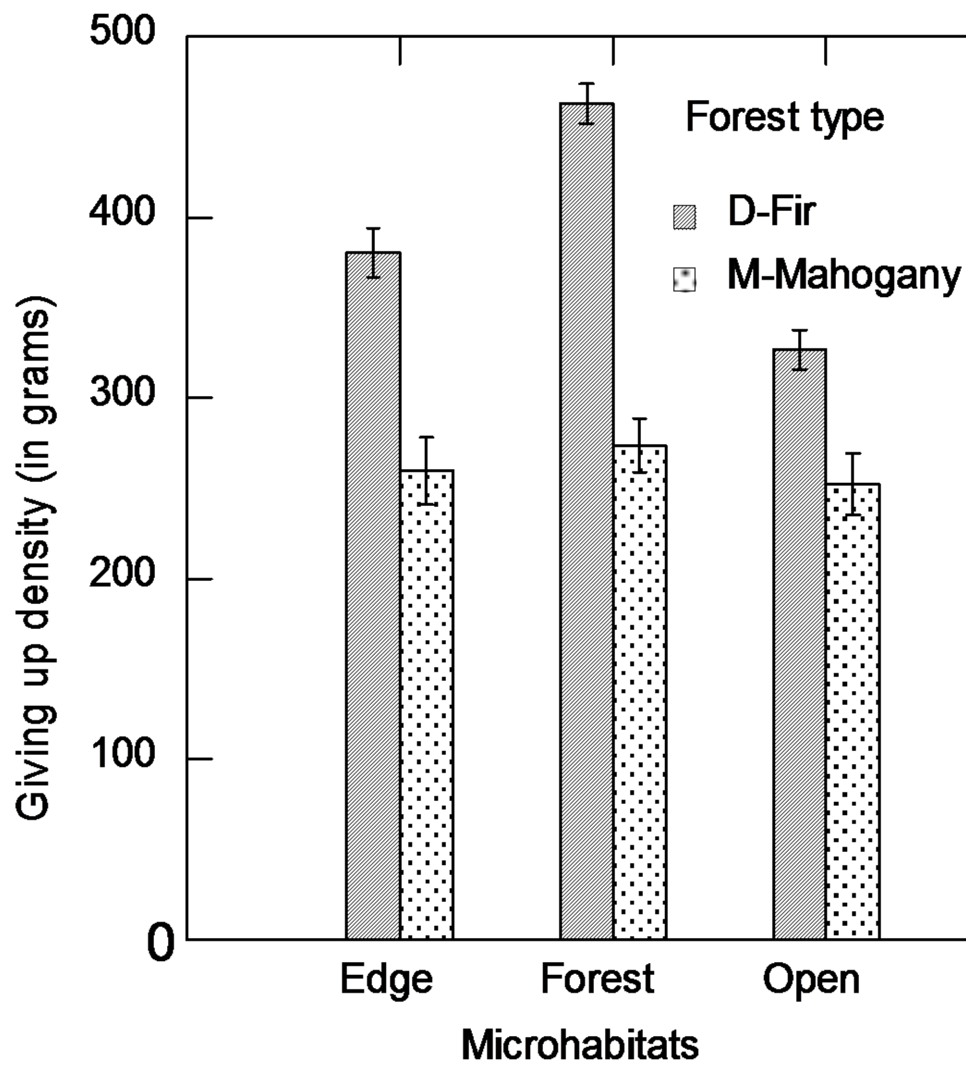
$$\mu(u_2) = H(u_2)$$


0.25
0.20
0.15
0.10
0.05
0.00
Patch value (captures per time)
Low apprehension
Rich
Poor
High apprehension
0
20
40
60
80
100
Time in patch

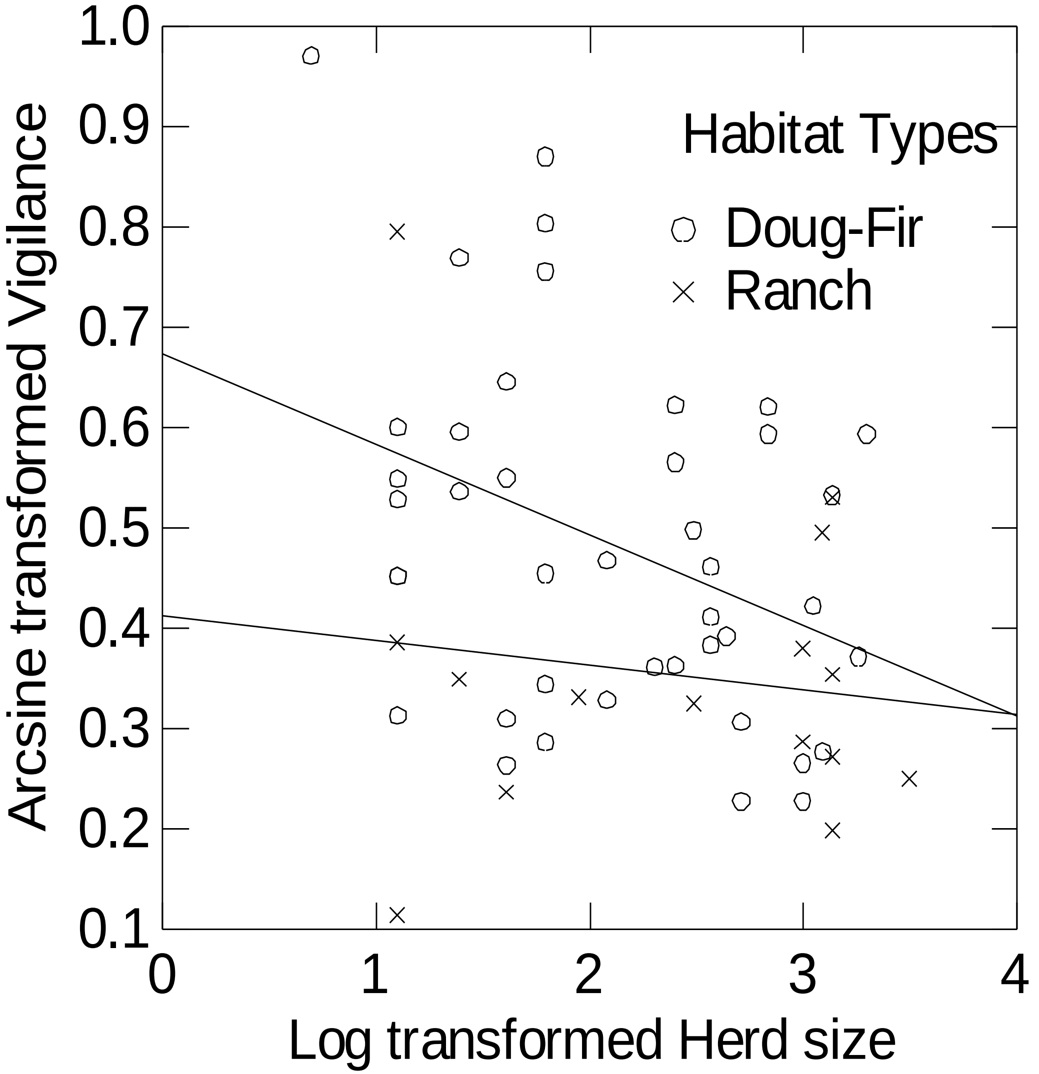
Mule Deer and Mountain Lion Game

$$G_1(v, u_2, x_1, x_2) = r\left[\frac{(1-\bar{w})K}{x_1+\chi} - c\right] - \bar{\mu}x_2$$

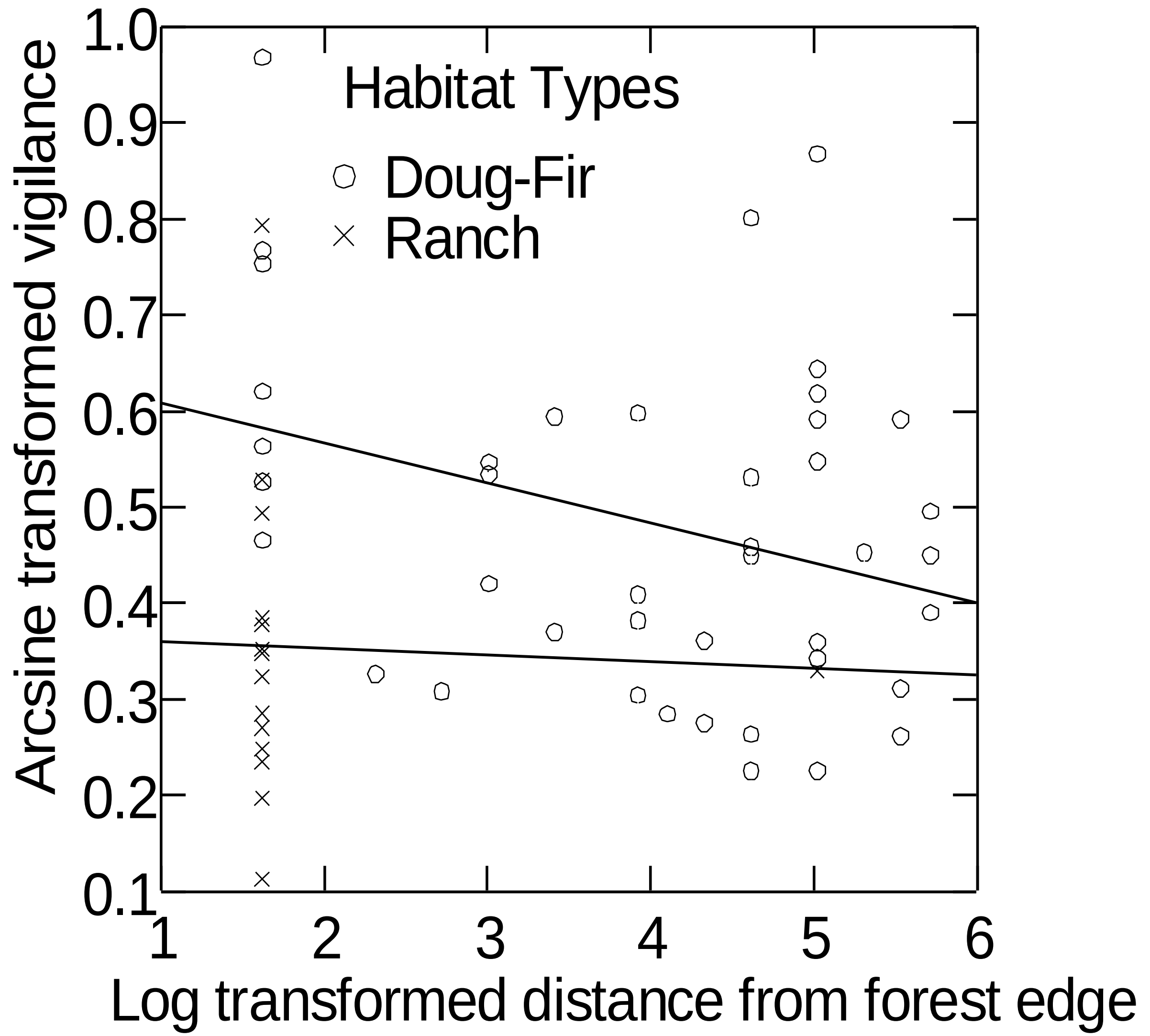
$$G_2(v, u_1, u_2, x_1, x_2) = r_P H - d$$



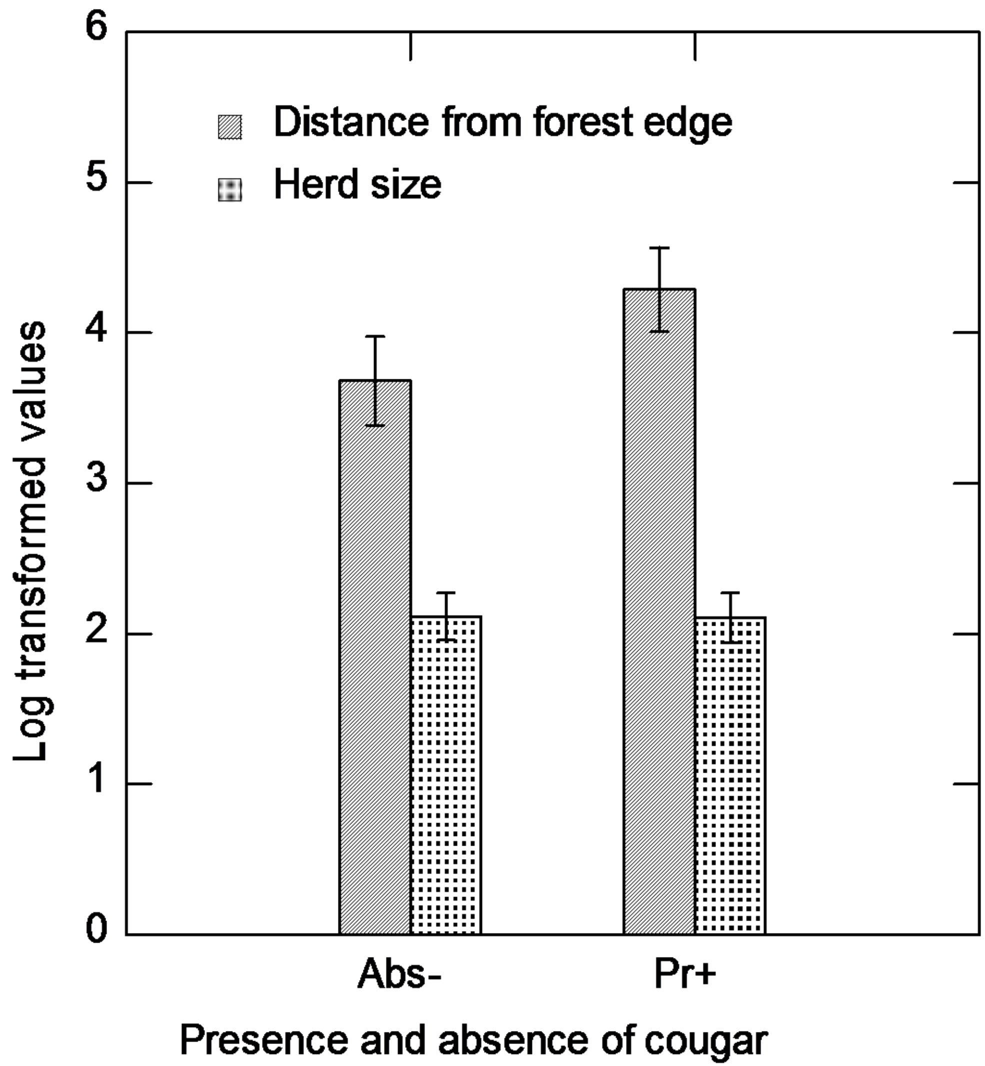
Forest type
D-Fir
M-Mahogany
500
400
300
200
100
0
Giving up density (in grams)
Edge
Forest
Open
Microhabitats



Arcsine transformed Vigilance
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
1
2
3
4
Log transformed Herd size
Habitat Types
Doug-Fir
Ranch



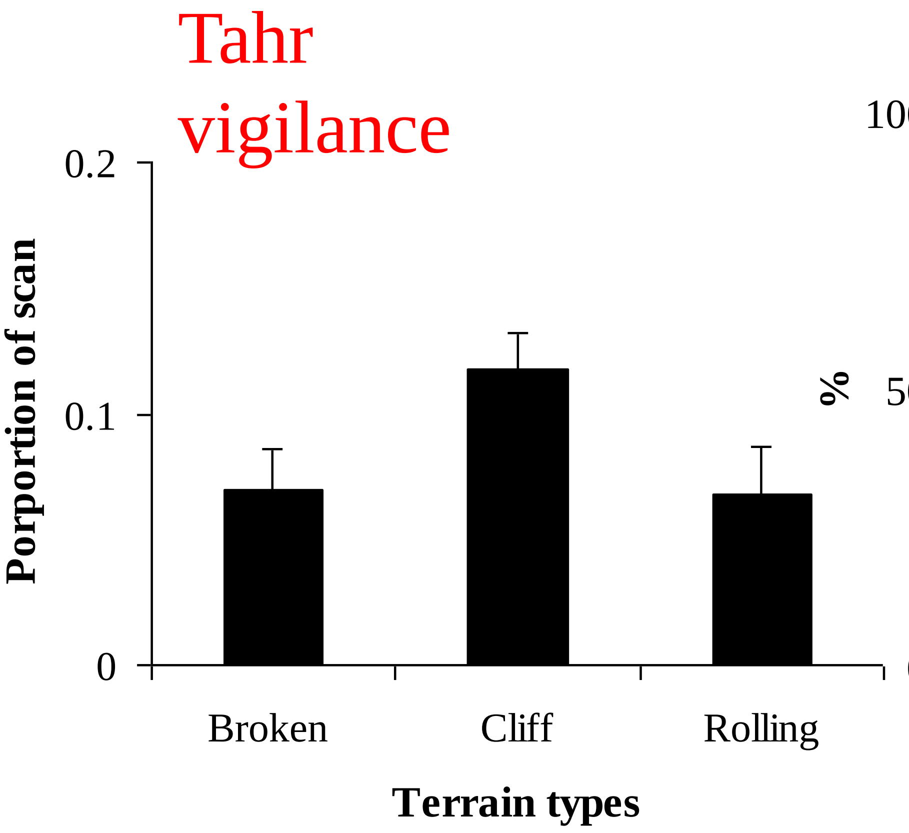
Habitat Types
Doug-Fir
Ranch
Arcsine transformed vigilance
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
1
2
3
4
5
6
Log transformed distance from forest edge

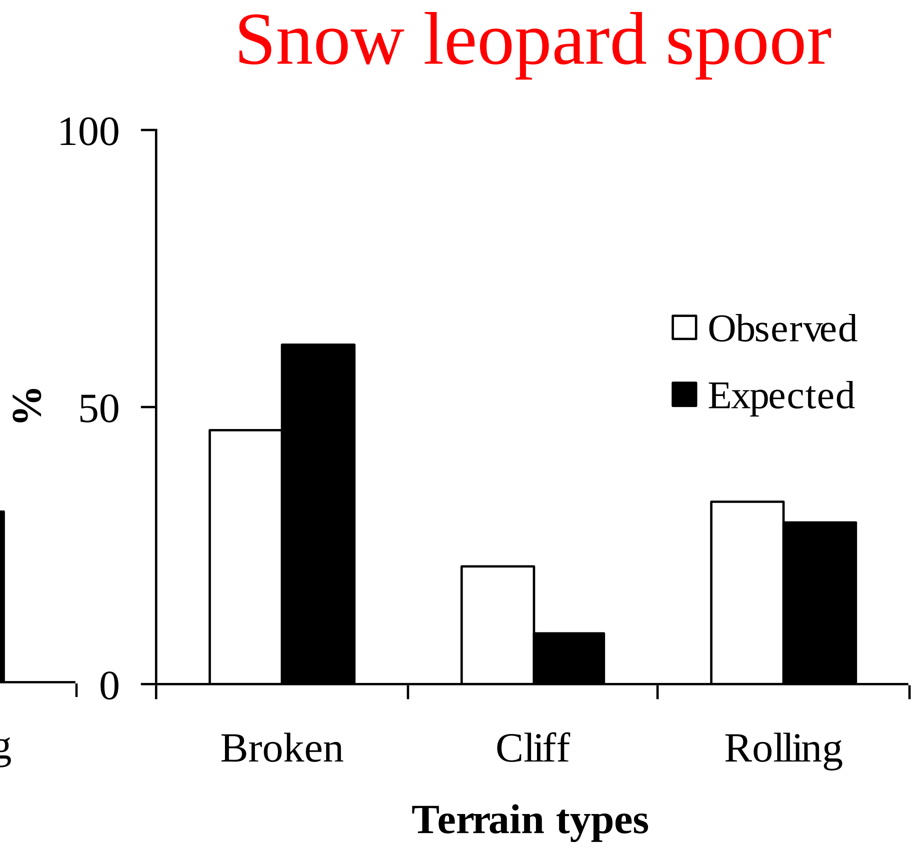


Distance from forest edge
Herd size
6
5
4
3
2
1
0
Log transformed values
Abs-
Pr+
Presence and absence of cougar


adidas

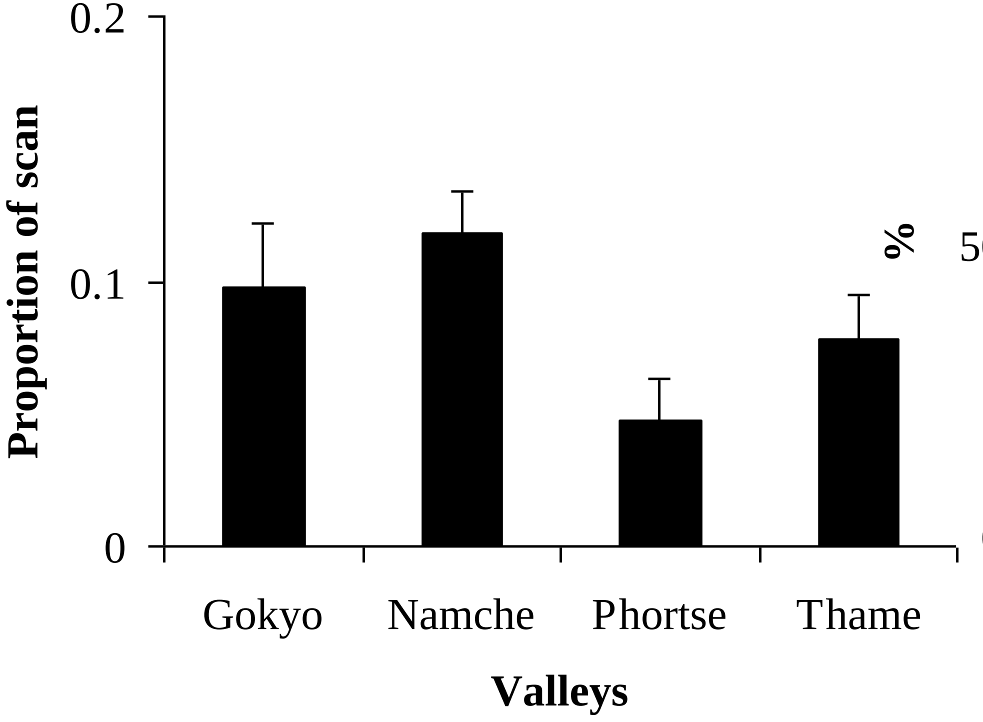
Tahr are more vigilant in habitats with more snow leopard spoor



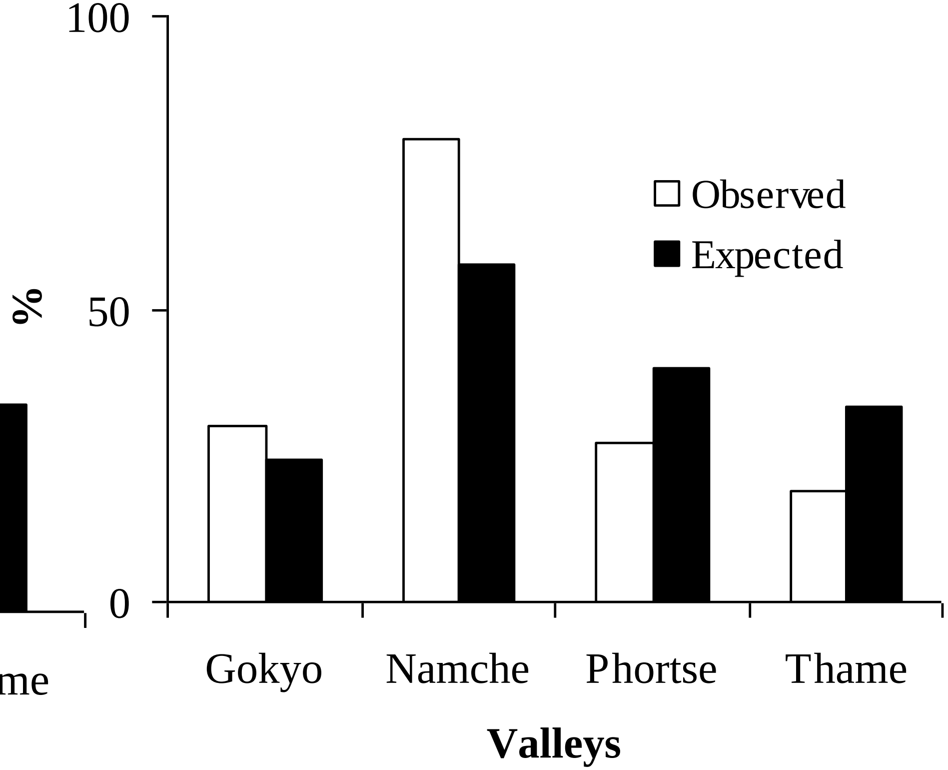


Tahr are more vigilant in areas with more snow leopard spoor

Tahr vigilance

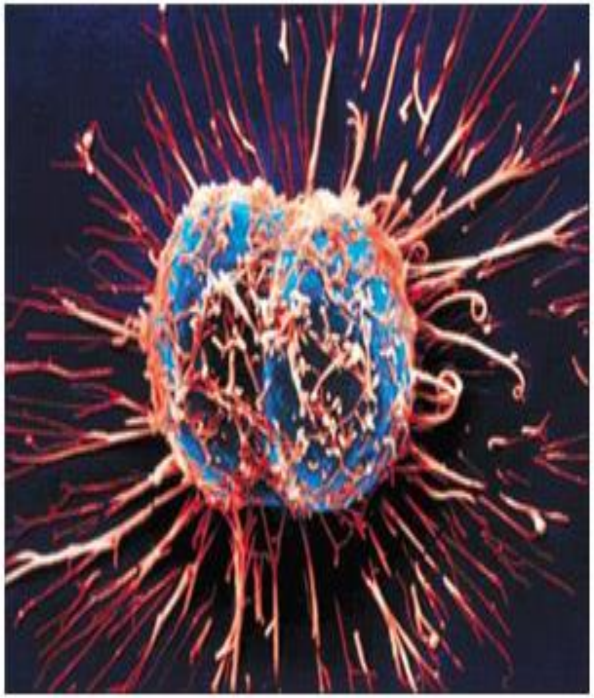


Snow leopard spoor



Like Nature, Cancer is a

- A complex dynamical system
- Hierarchical – from molecules to ecosystems
- Product of natural selection



(Cancererous cells splitting apart)

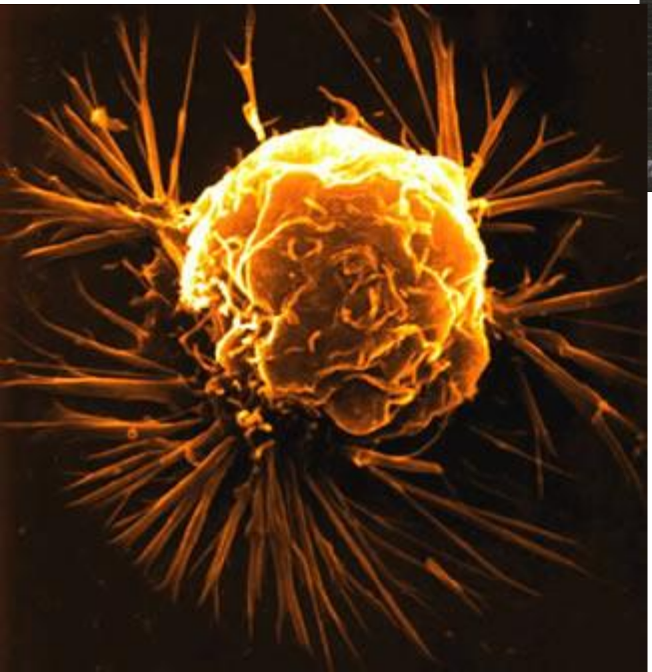
Like Nature, Cancer can be studied

- Through the recipe of inheritance: Genetics
- As a historical process: Phylogenetics
- Fit of Form and Function: Adaptations

Fit of Form and Function

- Cancer cells evolve **adaptations** for their environment
- Phenotypic plasticity permit tumor cells to **acclimate** to environmental circumstances
- Cancer cells can be expected to first **acclimate** and then **adapt** to their conditions

Cancer is an ecological and evolutionary process running rampant in your body

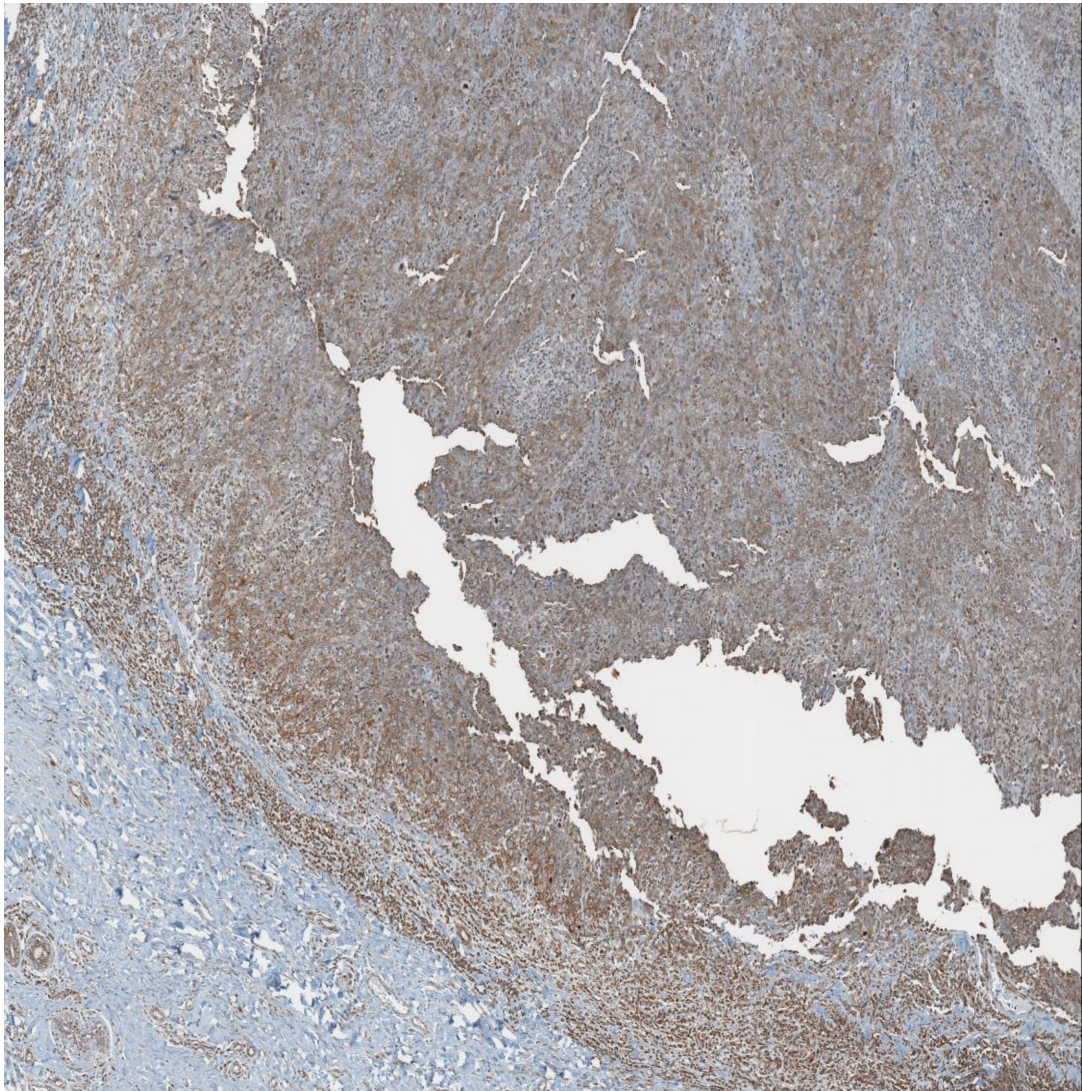


This opossum is an ecological and evolutionary process running rampant in the city

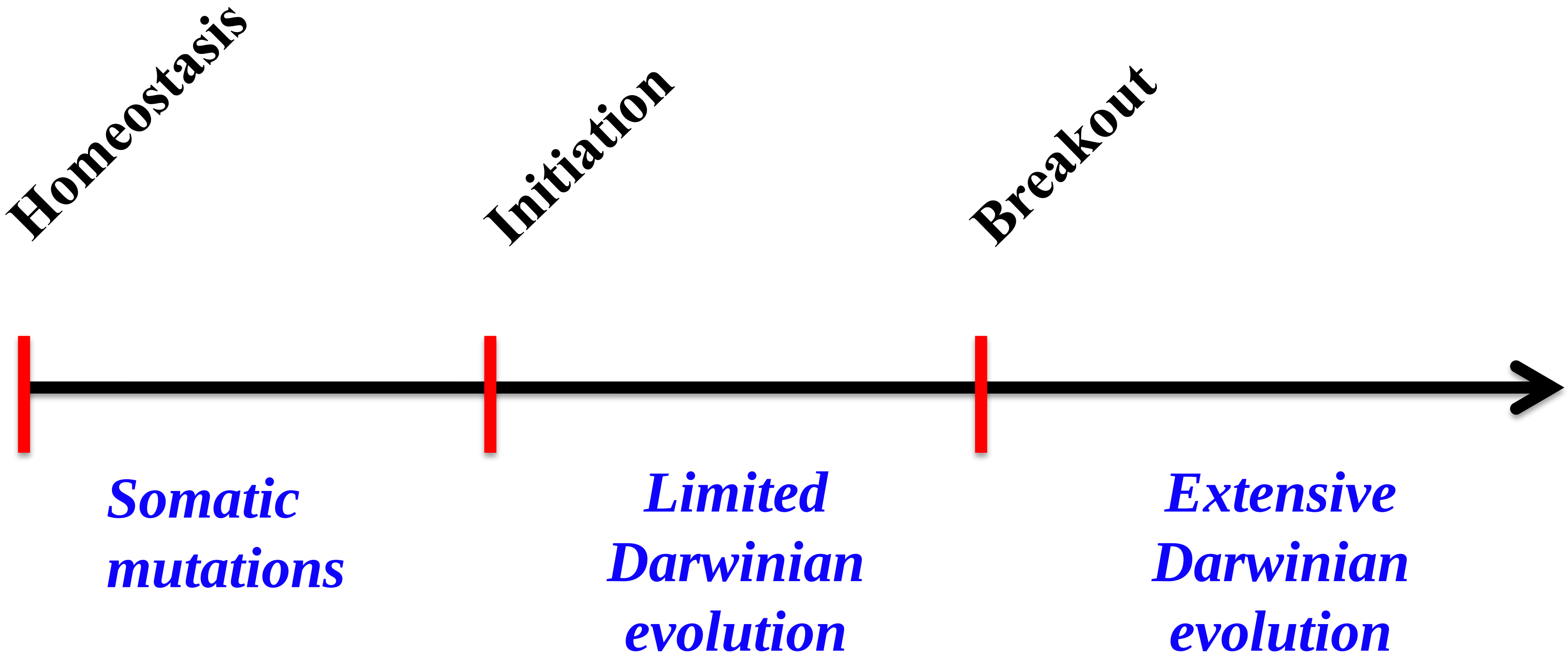
**The human body is not
a host in the traditional sense.
It is a novel, uninhabited
Planet where ecology and
evolution begins anew**

Cancer as a Game

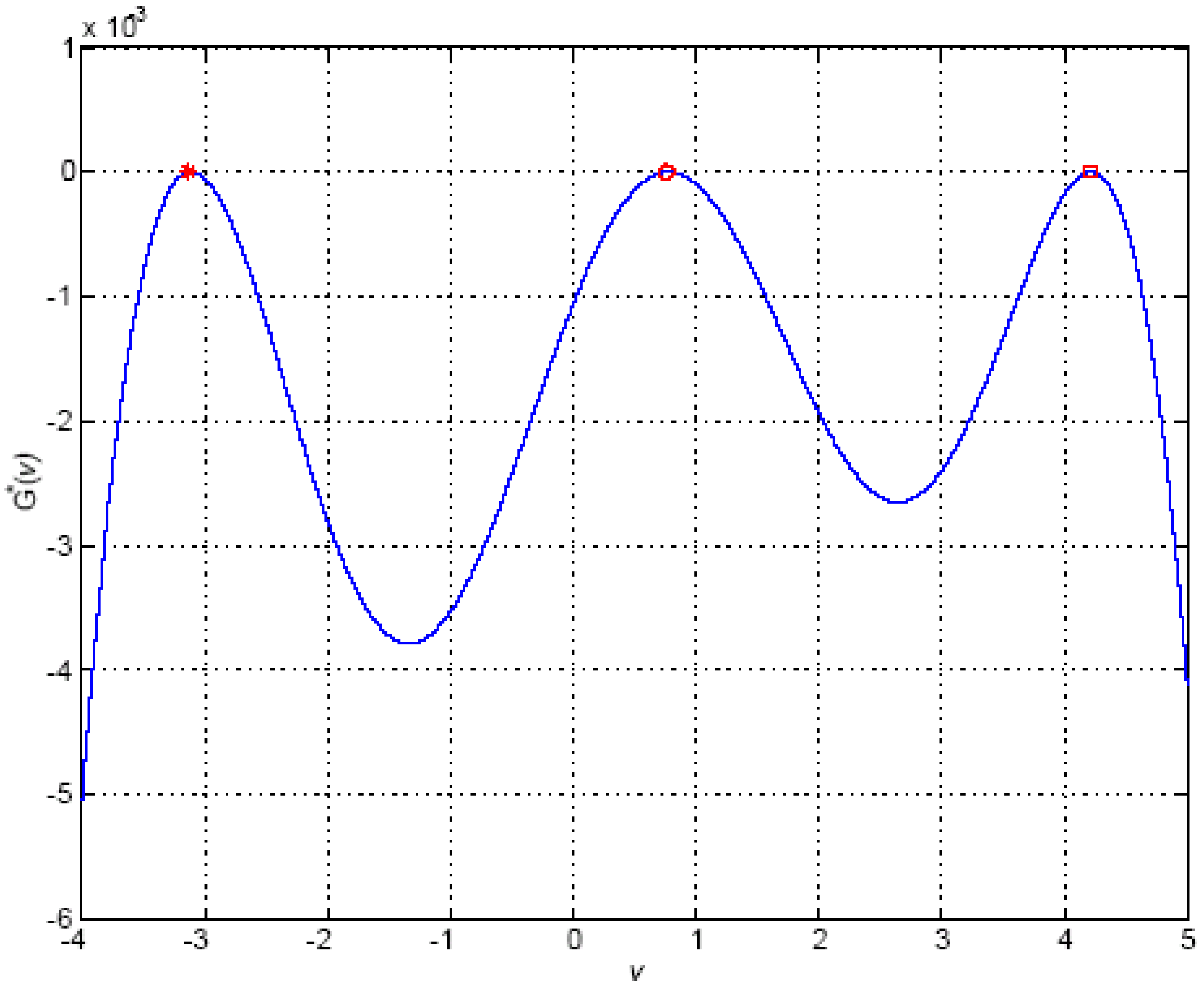
- Individual tumor cells are the players
- Heritable traits are their strategies
- The game is between the tumor cells
- Per capita growth rates are the payoffs
- The tissue and tumor environment sets the rules
- Treatment strategies become part of the game



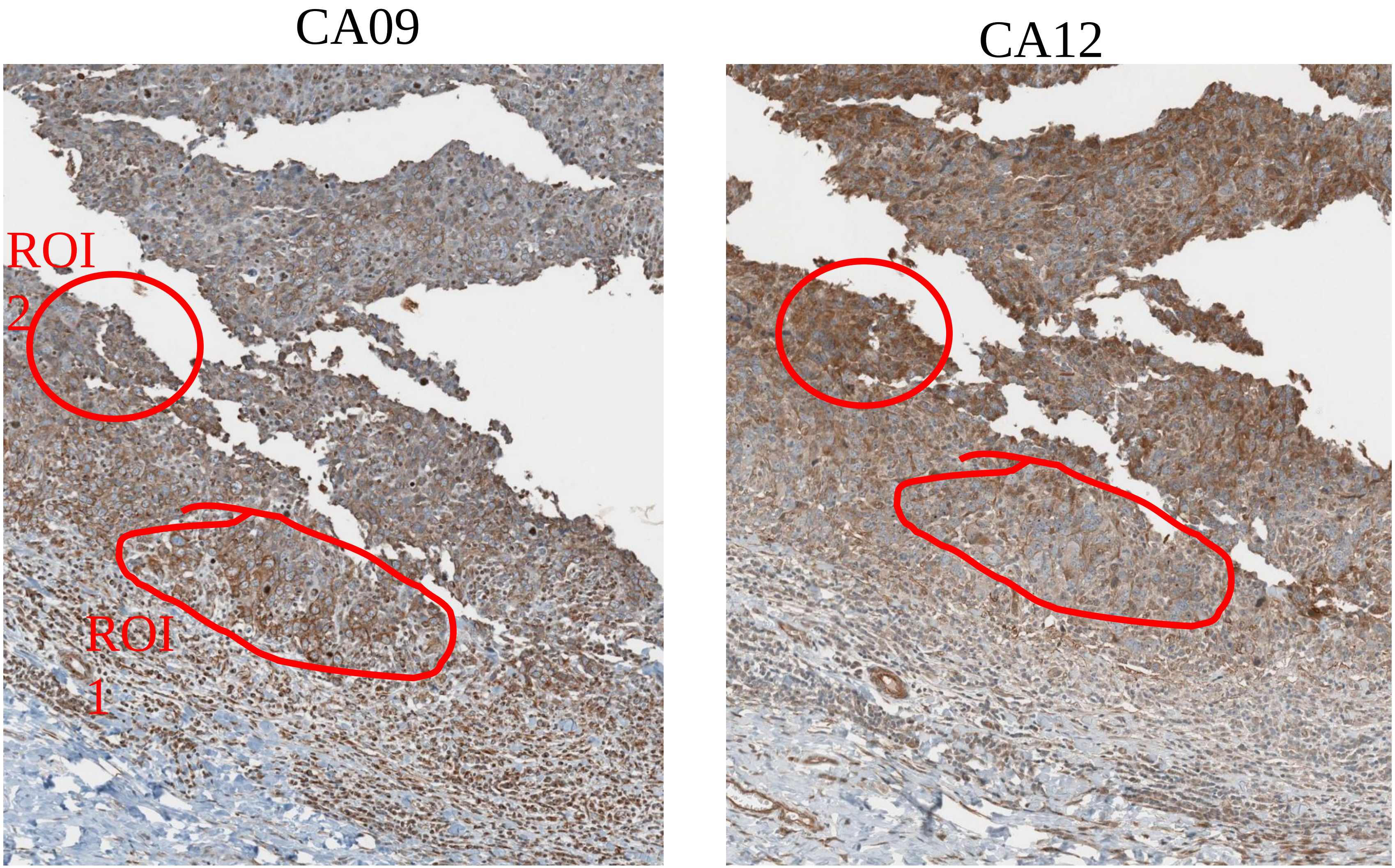
Metastatic cancer is the evolution of a new single-celled, asexual Protist



Cancer progresses from a disease of the genes to a disease of natural selection



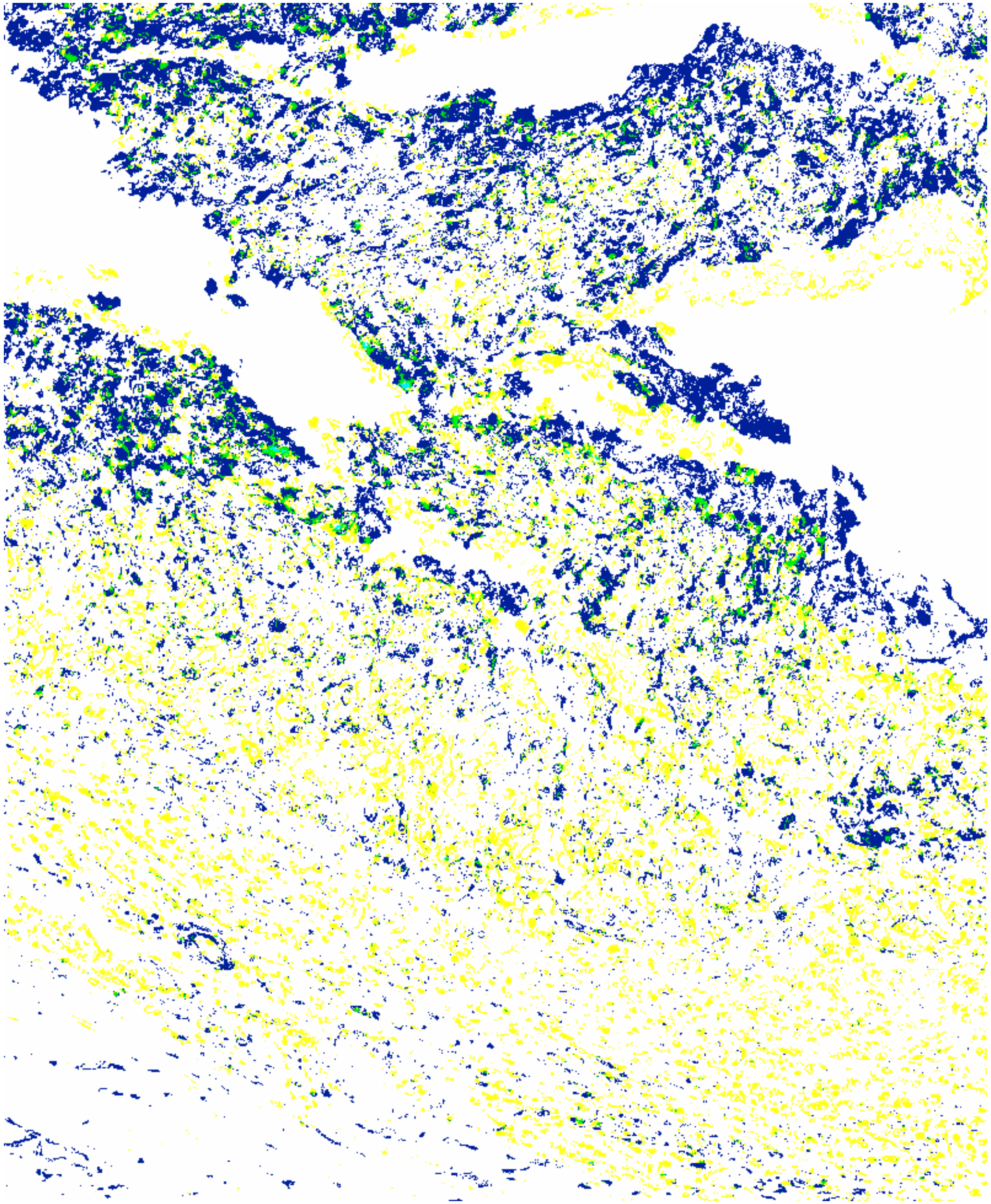
Speciation and Niche Coevolution may promote predictable and distinct niches within a cancer



Invasive grade III Breast Cancer: ROI1 with higher CAIX intensity; and ROI2 with higher CAXII expression. (Mark Lloyd et al., Moffitt Cancer Center)

Distinct Habitat segregation between lower density, “edge” species (CAIX in yellow) and higher density, “interior” species (CAXII in blue).

These may represent “pioneer” and “ecological engineering species, respectively



Evolutionarily Enlightened Management Strategies

Appreciating, Modeling and/or Anticipating
the ecological and evolutionary consequences
of management, conservation or **therapy** efforts

Brown and Parmen 1993, Ashley et al. 2003

Games against Cancer: Teleology versus Teleonomy

- Wittingly or unwittingly the cancer therapists engage in an evolutionary game with the cancer cells
- Cancer cells can only evolve to what has or is happening – they are "teleonomic" in that they cannot anticipate
- Therapies can be "teleologic" and anticipate the ecological and evolutionary responses of the cancer cells

Model of Tumor Treatment

$$\frac{\partial x}{\partial t} = rx\left(\frac{K - x}{K}\right) - \mu x$$

x = cancer cell density
K = cell carrying capacity
μ = mortality rate from treatment

Treatement Effectiveness

$$\mu = \frac{m}{k + bv}$$

m = encounter rate of treatment with cancer cells
k = lethality of treatment in absence of resistance
b = effectiveness of resistence at reducing lethality
v = degree of resistence by cancer cell

Penalty of Resistence

$$K = K_{\max} \exp\left(\frac{-v^2}{2\sigma_K^2}\right)$$

The cell, by increasing resistance reduces treatment effectiveness but also reduces its carrying capacity

Cancer Cells' Fitness function as an Evolutionary Game

$$G(v,u,x) = r\left(\frac{K(v)-x}{K(v)}\right) - \mu(v)$$

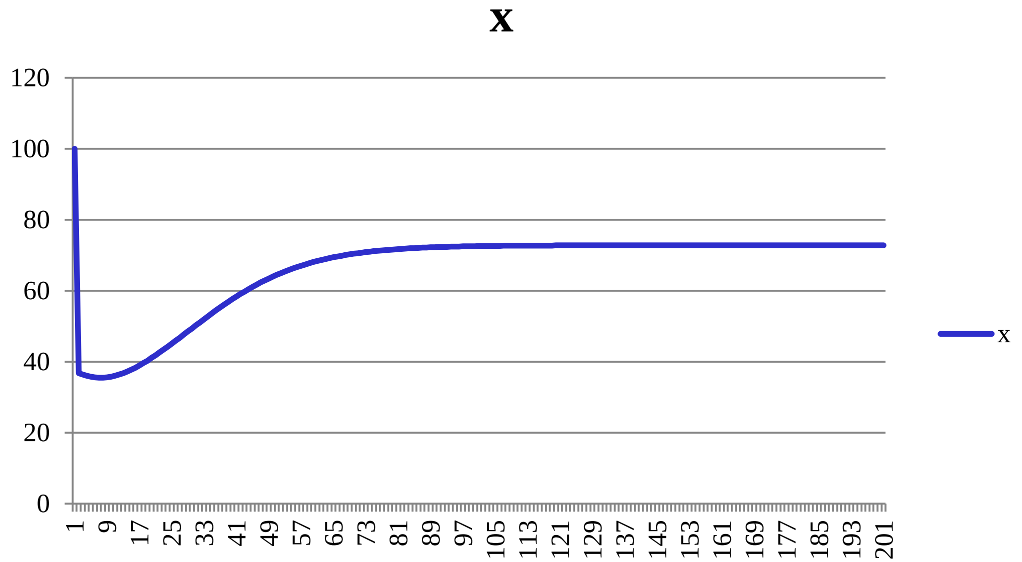
Ecological Dynamics: $\partial x_i/\partial t = x_i G$

Strategy Dynamics: $\partial u_i/\partial t = k(\partial G/\partial v)$

evaluated at $v = u_i$

Single Treatment, Single Resistance Response

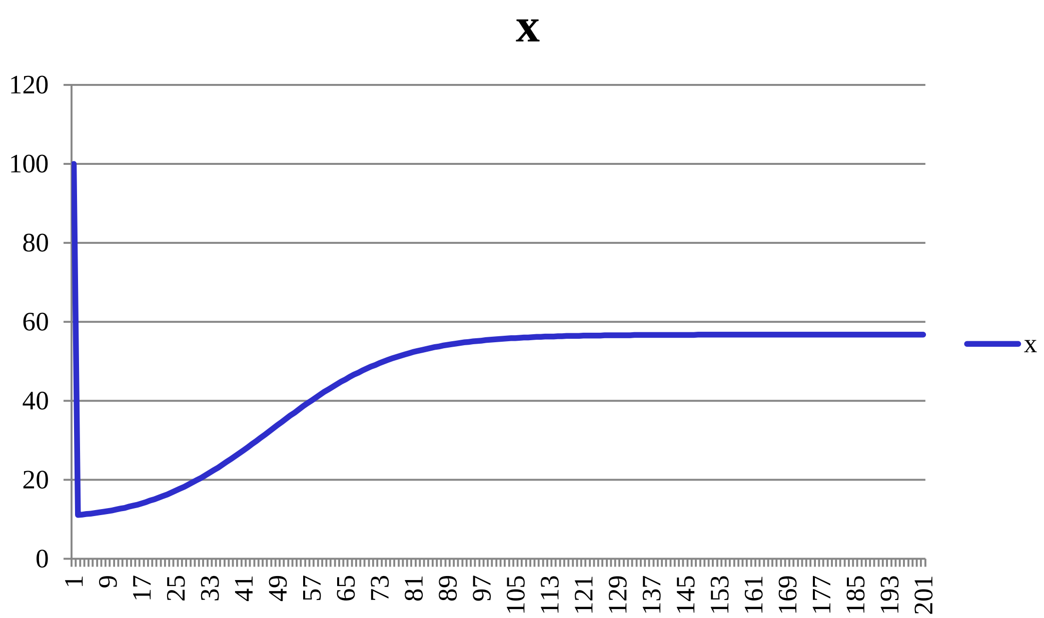
$$G(v,u,x) = r\left(\frac{K(v)-x}{K(v)}\right) - \frac{m}{k+bv}$$



Two treatments eliciting
One resistance response

Two Treatments Requiring one resistence response

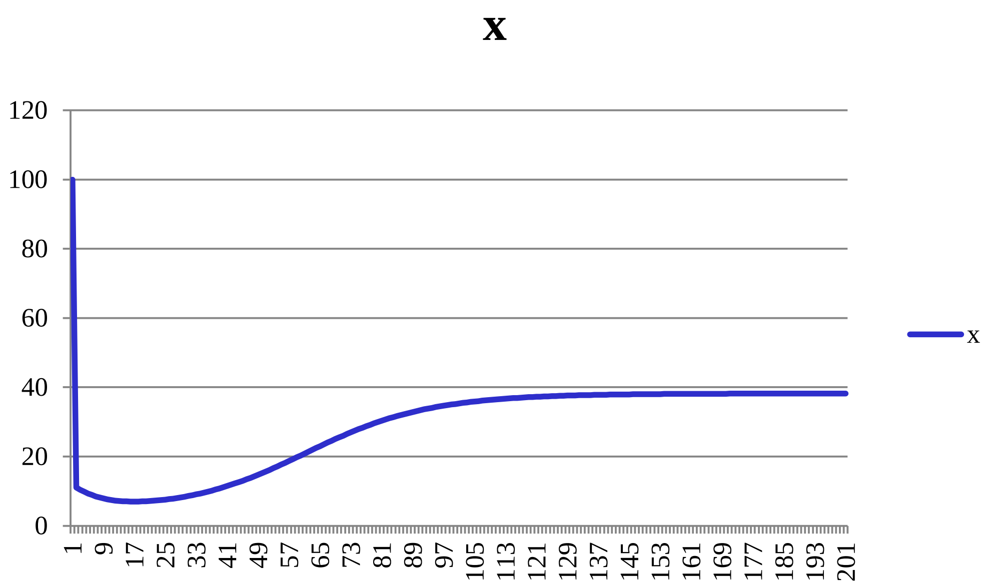
$$G(v,u,x) = r\left(\frac{K(v)-x}{K(v)}\right) - \frac{m_1}{k_1+b_1 v} - \frac{m_2}{k_2+b_2 v}$$



Two treatments
Requiring separate
And independent
Resistance responses

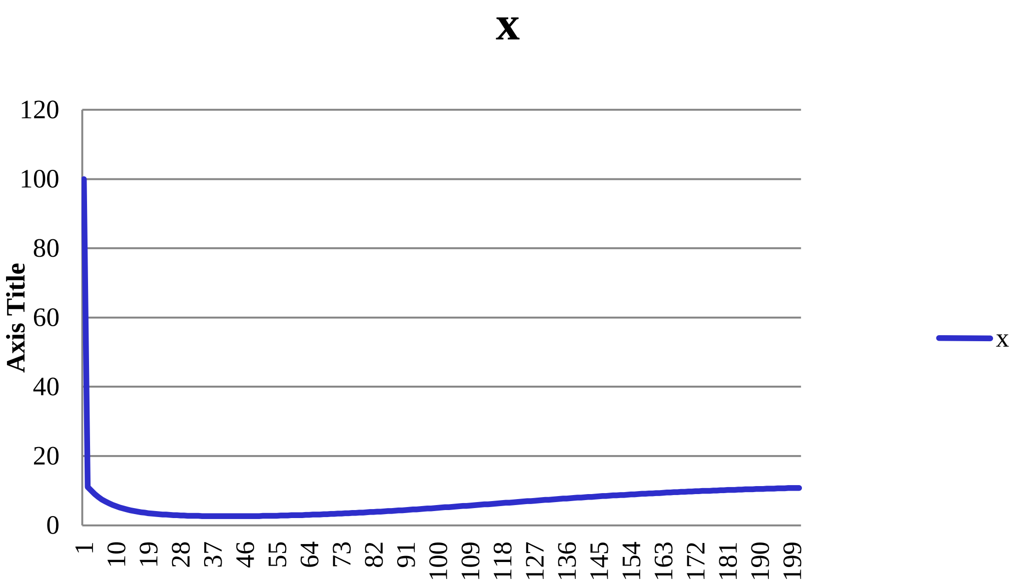
Two Treatments requiring two resistance responses

$$G(\mathbf{v}, \mathbf{u}, x) = r\left(\frac{K(\mathbf{v}) - x}{K(\mathbf{v})}\right) - \frac{m_1}{k_1 + b_1 v_1} - \frac{m_2}{k_2 + b_2 v_2}$$



Strong Evolutionary Double Bind

$$G(\mathbf{v}, \mathbf{u}, x) = r\left(\frac{K(\mathbf{v}) - x}{K(\mathbf{v})}\right) - \frac{(1+v_2)m_1}{k_1 + b_1 v_1} - \frac{(1+v_1)m_2}{k_2 + b_2 v_2}$$



Antonia et al: 2nd and 3rd line therapy in small cell lung cancer with vaccine against mutant p53. Results: strong immune response elicited but only one partial clinical response in 29 subjects

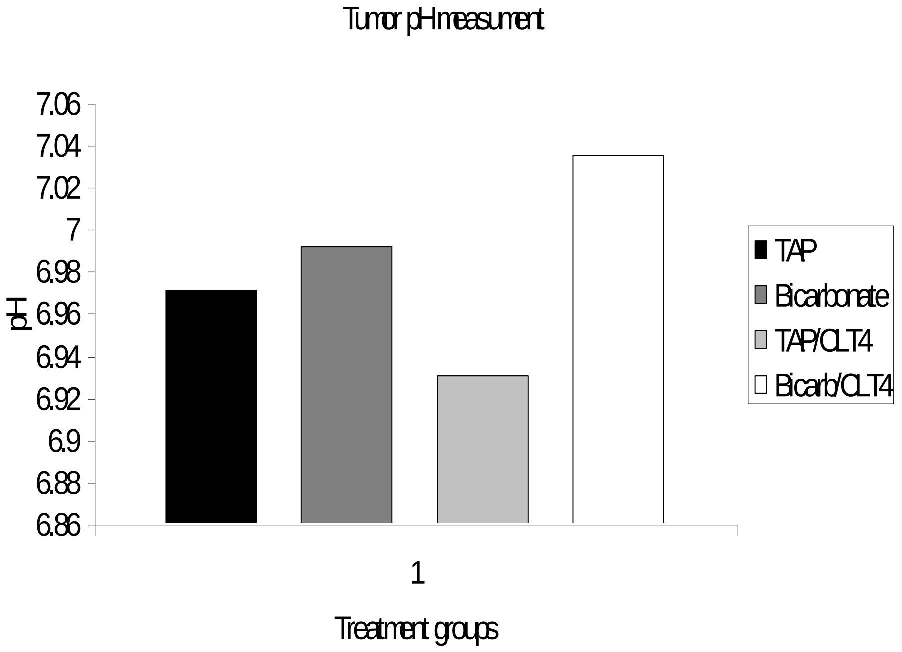
Table 3. Response to second-line chemotherapy in vaccinated patients

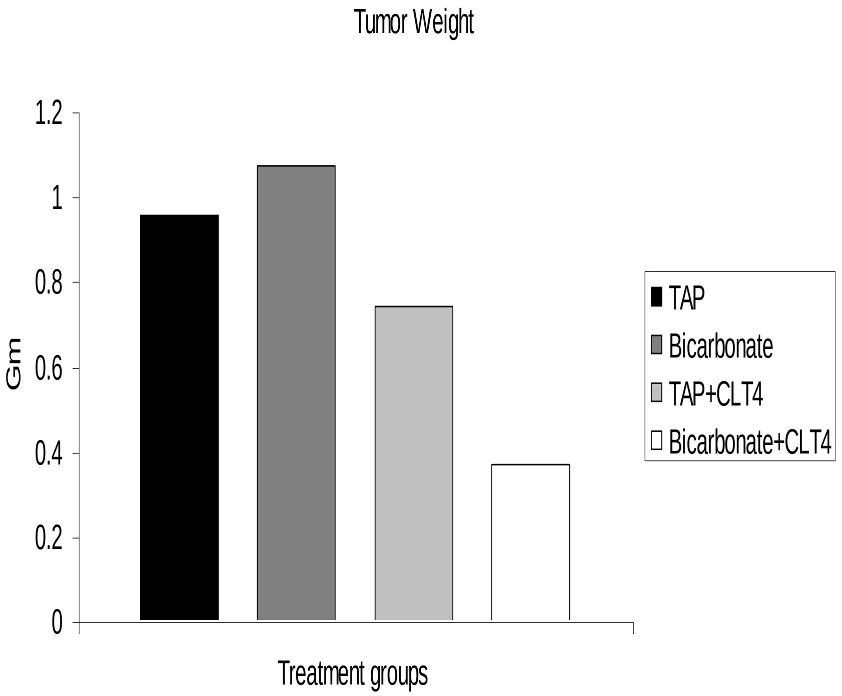
All patients who received chemotherapy after vaccine (*n* = 21)		Platinum-resistant patients who received chemotherapy after vaccine (*n* = 13)	
Response	*n* (%)	Response	*n* (%)
CR	3 (14.3)	CR	1 (8)
PR	10 (47.6)	PR	7 (54)
SD	4 (19.05)	SD	3 (23)
PD	4 (19.05)	PD	2 (15)
CR + PR	13 (61.9)	CR + PR	8 (61.5)

Abbreviations: PD, progressive disease; SD, stable disease; PR, partial response; CR, complete response (all according to Response Evaluation Criteria in Solid Tumors).

Fortuitously, the patients were followed after exiting the trial. 21 received 2nd or 3rd line chemotherapy. Historical experience predicts a response rate of <5%

Another double bind – “if the mouse hides under a bush, add a cow to eat the bush” (Robert Gatenby)





Gatenby et al., Moffitt Cancer Center