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GSAC talk
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# Multiple Metastatic Tumors

# OUTLINE

- biological invasions
- cancer metastasis
  - ⋆ derive a model
  - ⋆ show some results

# BIOLOGICAL INVASIONS

- In nature, all organisms expand their ranges to some extent

- Many well documented examples

⋆ Muskrat through Europe, 1909-1927
⋆ California sea otter along the West Coast, 1914-present
⋆ cheatgrass in western North America, 1890-1930

- Three aspects of range expansion

⋆ random movement
⋆ reproduction
⋆ long distance dispersal

- Consider random movement and reproduction only

$\star$ random movement $\rightarrow$ diffusion
$\star$ reproduction $\rightarrow$ growth term

**Skellam Equation**: exponential growth

$$\frac{\partial}{\partial t}n = D\frac{\partial^2}{\partial x^2}n + rn$$

**Fisher Equation**: logistic growth

$$\frac{\partial}{\partial t}n = D\frac{\partial^2}{\partial x^2}n + r\left(1 - \frac{n}{k}\right)n$$

$n(x,t) =$ population density at time $t$ and location $x$

$D =$ diffusion coefficient

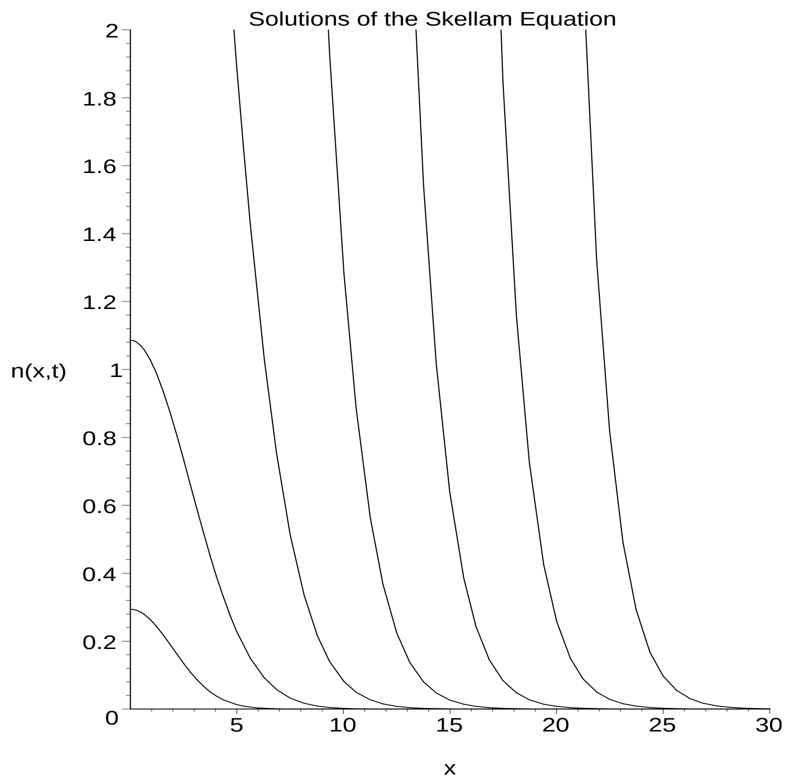
$r =$ intrinsic growth rate

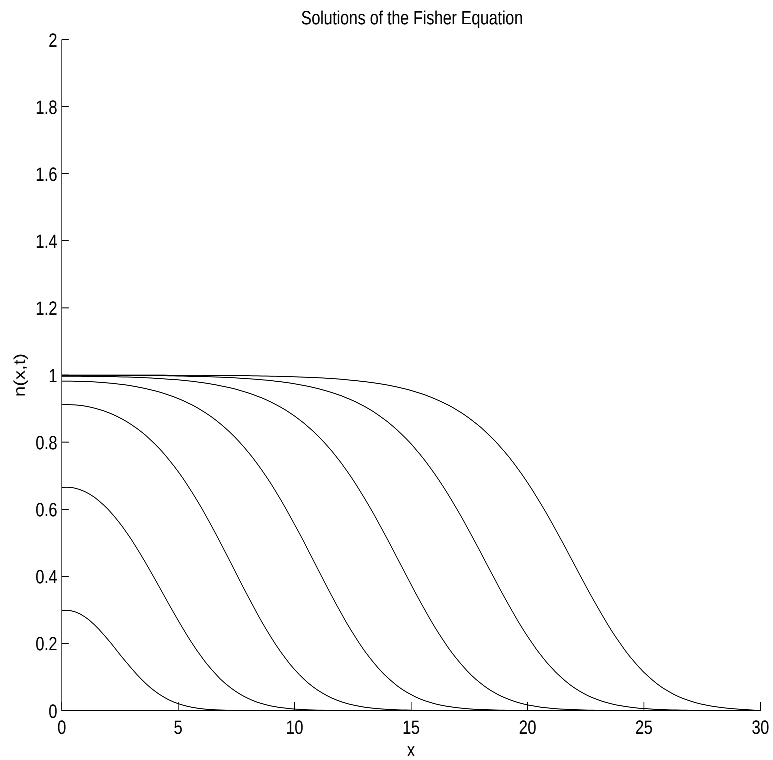
$k =$ carrying capacity

• with the initial condition: $n(x,0) = n_0 \delta(x)$

and... $n_0 = 1$ $r = 1$ $D = 1$

• the results... for $t = 2, 4, 6, 8, 10, 12, 14$




**Skellam:** exact solution $\rightarrow n(x,t) = \frac{n_0}{4\pi Dt} exp\left(rt - \frac{x^2}{4Dt}\right)$

**Fisher:** numerical solution $\rightarrow$ forward Euler finite difference scheme

- Consider long distance dispersal in addition

## <u>Scattered Colony Model</u>

⋆ consider an initial colony of size $x$

... could be radius, or some other measure of size

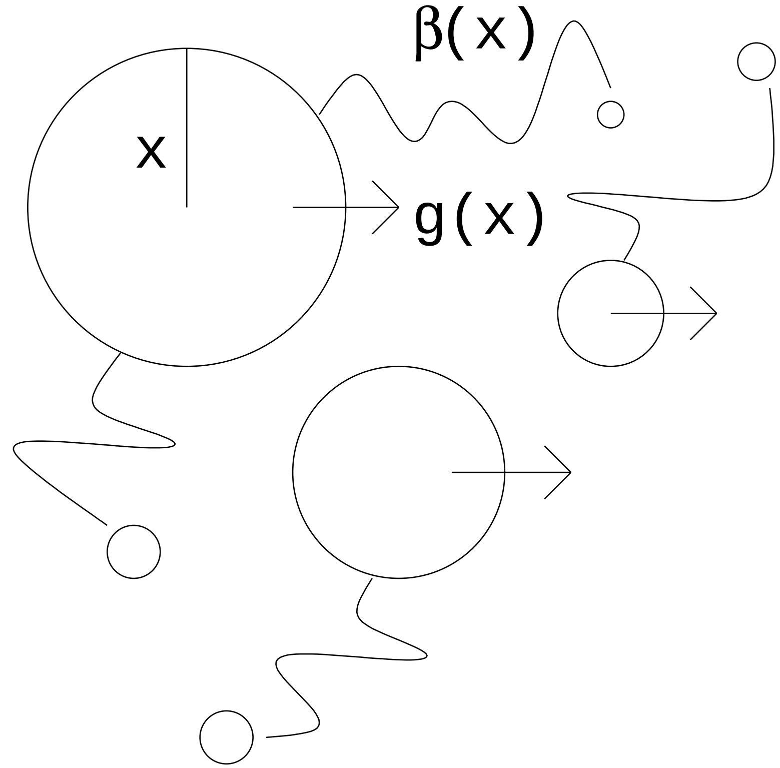
⋆ assume the species expands its colony size at rate $g(x)$

... calculated from an equation like Skellam or Fisher

⋆ the colony produces long distance migrants at some rate $\beta(x)$

⋆ the migrants start new colonies, and so on...

⋆ keep track of the density of colonies of size $x$ at time $t$



# CANCER

- **Primary Tumor:** original location

- **Angiogenesis:** infiltration of blood vessels

- **Metastasis:** spread of cancer to another part of the body

$\star$ colon $\longrightarrow$ liver
$\star$ lung $\longrightarrow$ brain
$\star$ thyroid $\longrightarrow$ bone

- **Problem:** no way of telling how many other tumors exist

$\star$ a mathematical model is needed!

# A Dynamic Model for the Growth and Size Distribution of Multiple Metastatic Tumors

paper by

K. Iwata, K. Kawasaki, and N. Shigesada

*Journal of Theoretical Biology*, 2000

$\rightarrow$ apply the scattered colony model to the spread of cancer

- **Growth of Tumors:**

  $\star$ cancer cells live in colonies called tumors

  $\star$ $x(t) =$ the number of cells in a tumor at time $t$

  $\star$ describe the growth of a tumor by, $\frac{dx}{dt} = g(x)$

  $\star$ assume all tumors start out with one cell, $x(0) = 1$

  $\star$ denote the primary tumor $x_p(t)$

  ... we really care about keeping track of metastatic tumors

- **Metastatic Tumors:**

  ⋆ $\rho(x,t) =$ density of metastatic tumors with $x$ cells at time $t$

  … density with respect to size rather than space

  … dimensions of $\rho(x,t)$ are "# / unit size"

  … $\rho(x,t)\Delta x =$ number of tumors in size range $x$ to $x + \Delta x$

  … $\int_x^\infty \rho(x,t)dx =$ total number of tumors with $x$ or more cells

  ⋆ we want to keep track of $\rho(x,t)$

- **Conservation Equation:**

  ⋆ it says the tumors are each growing at rate $g(x)$

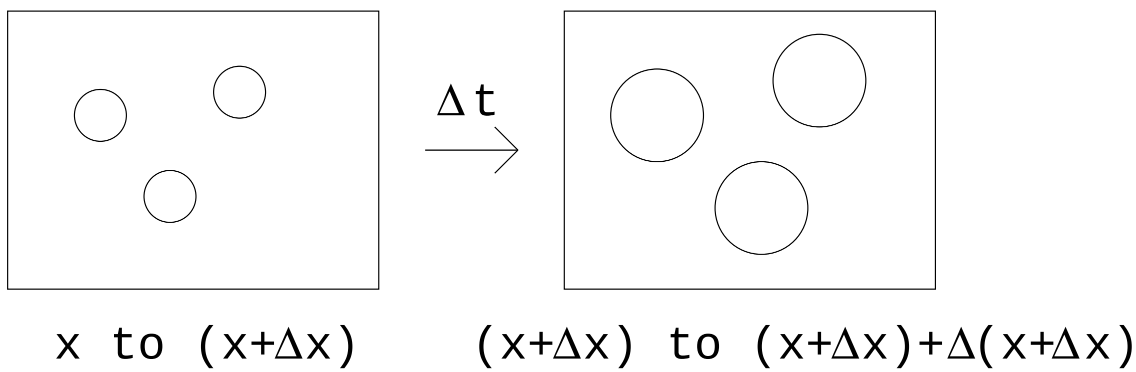
$$\frac{\partial}{\partial t}\rho(x,t) + \frac{\partial}{\partial x}(g(x)\rho(x,t)) = 0$$

... the way I derived it

  ⋆ suppose there are $n$ tumors in the class size $x$ to $x + \Delta x$

$$n = \rho(x,t)\Delta x$$

  ⋆ they all moving into the next class together...




  ⋆ which means after a time $\Delta t$,

$$n = \rho(x + \Delta x, t + \Delta t)(\Delta(x + \Delta x))$$

$\star$ which means that,

$$\rho(x,t)\Delta x = \rho(x+\Delta x, t+\Delta t)(\Delta(x+\Delta x))$$

$\star$ we also know, $\frac{dx}{dt} = g(x) \longrightarrow \frac{\Delta x}{\Delta t} = g(x)$

$$\rho(x,t)\Delta x = \rho(x+g(x)\Delta t, t+\Delta t)(g(x+\Delta x)\Delta t)$$

$\star$ expand with respect to $\Delta x$ and $\Delta t$

$\star$ divide both sides by $\Delta x$ and $\Delta t$

$\star$ then, in the limit that $\Delta x \rightarrow 0$ and $\Delta t \rightarrow 0$,

$$\boxed{\frac{\partial}{\partial t}\rho(x,t) + \frac{\partial}{\partial x}(g(x)\rho(x,t)) = 0}$$

- **Initial Condition:**

  $\star$ no metastatic tumors exist at $t = 0$

$$\boxed{\rho(x,0) = 0}$$

- **Boundary Condition:**

  $\star$ metastatic single cells are being created

$$\boxed{g(1)\rho(1,t) = \int_1^\infty \beta(x)\rho(x,t)dx + \beta(x_p(t))}$$

LHS: rate at which tumors with 1 cell are entering the system

$\star$ $g(1)\rho(1,t)$ has dimensions “size/time · #/size” = “#/time”

RHS: rate at which existing tumors are producing metastases

$\star$ sum of the rates at which all of the metastatic tumors are producing new metastatic tumors plus the rate at which the primary tumor is producing new metastatic tumors

- **Rate of Metastasis:**

⋆ production of metastases is proportional to degree of angiogenesis

$$\beta(x) = mx^{\alpha}$$

$m$ = colonization coefficient (size · time)$^{-1}$

$\alpha$ = fractal dimension of blood vessels entering the tumor

... assume blood vessels are distributed on the surface of a tumor

$\Rightarrow$ $\alpha$ =2/3 because surface area of a tumor is proportional to $x^{2/3}$

- **Full Model:**

[1] $\frac{\partial}{\partial t}\rho(x,t) + \frac{\partial}{\partial x}(g(x)\rho(x,t)) = 0$

[2] $\rho(x,0) = 0$

[3] $g(1)\rho(1,t) = \int_1^\infty \beta(x)\rho(x,t)dx + \beta(x_p(t))$

where,

$\frac{dx_p}{dt} = g(x_p)$ with $x_p(0) = 1$

$\beta(x) = mx^\alpha$

- **Tumor Growth Rate:**

I. Exponential: $g(x) = ax$
II. Gompertzian: $g(x) = axlog(\frac{b}{x})$

$a$ = growth rate constant $(\text{time})^{-1}$
$b$ = tumor size at saturated level (size)

- **Solve using Laplace Transforms:**

I. Exponential: $g(x) = ax$

⋆ primary tumor $\rightarrow$ $x_p(t) = e^{at}$

⋆ Laplace Transform the PDE to get an ODE in $x$,

$$\tfrac{s+a}{ax}\widehat{\rho}(x,s) + \tfrac{d}{dx}\widehat{\rho}(x,s) = 0$$

solve...

$$\rightarrow \widehat{\rho}(x,s) = c(s)x^{-s/a-1}$$

⋆ Laplace Transform the BC to get

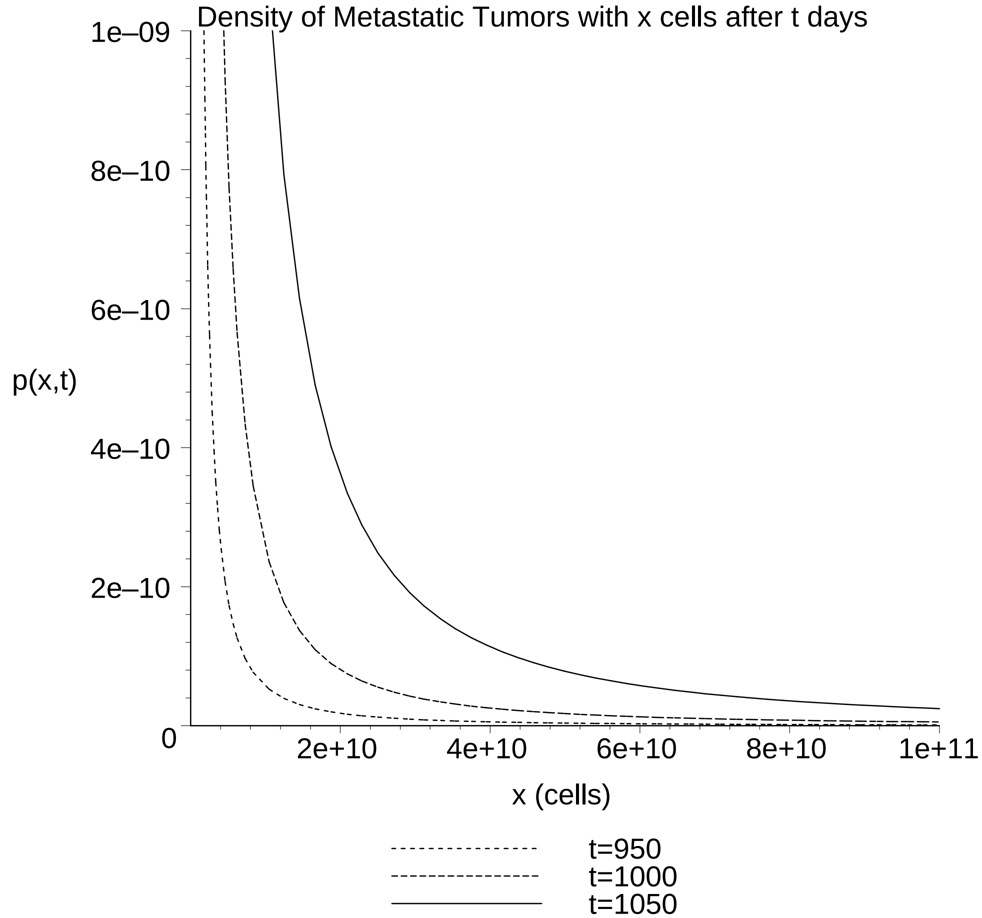
$$g(1)\widehat{\rho}(1,s) = \int_1^\infty \beta(x)\widehat{\rho}(x,s)dx + \int_0^\infty \beta(x_p(t))e^{-st}dt$$

⋆ plug in the expressions for $\widehat{\rho}(x,s)$ and $x_p(t)$, solve for $c(s)$

$$\rightarrow \widehat{\rho}(x,s) = \tfrac{-m}{a(a\alpha-s+m)}x^{-s/a-1}$$

⋆ take the inverse Laplace Transform to get...

$$\rho(x,t) = \frac{m}{a} e^{(a\alpha+m)t} x^{-\alpha-m/a-1}$$




$a = 0.00286 \text{ (day)}^{-1}$

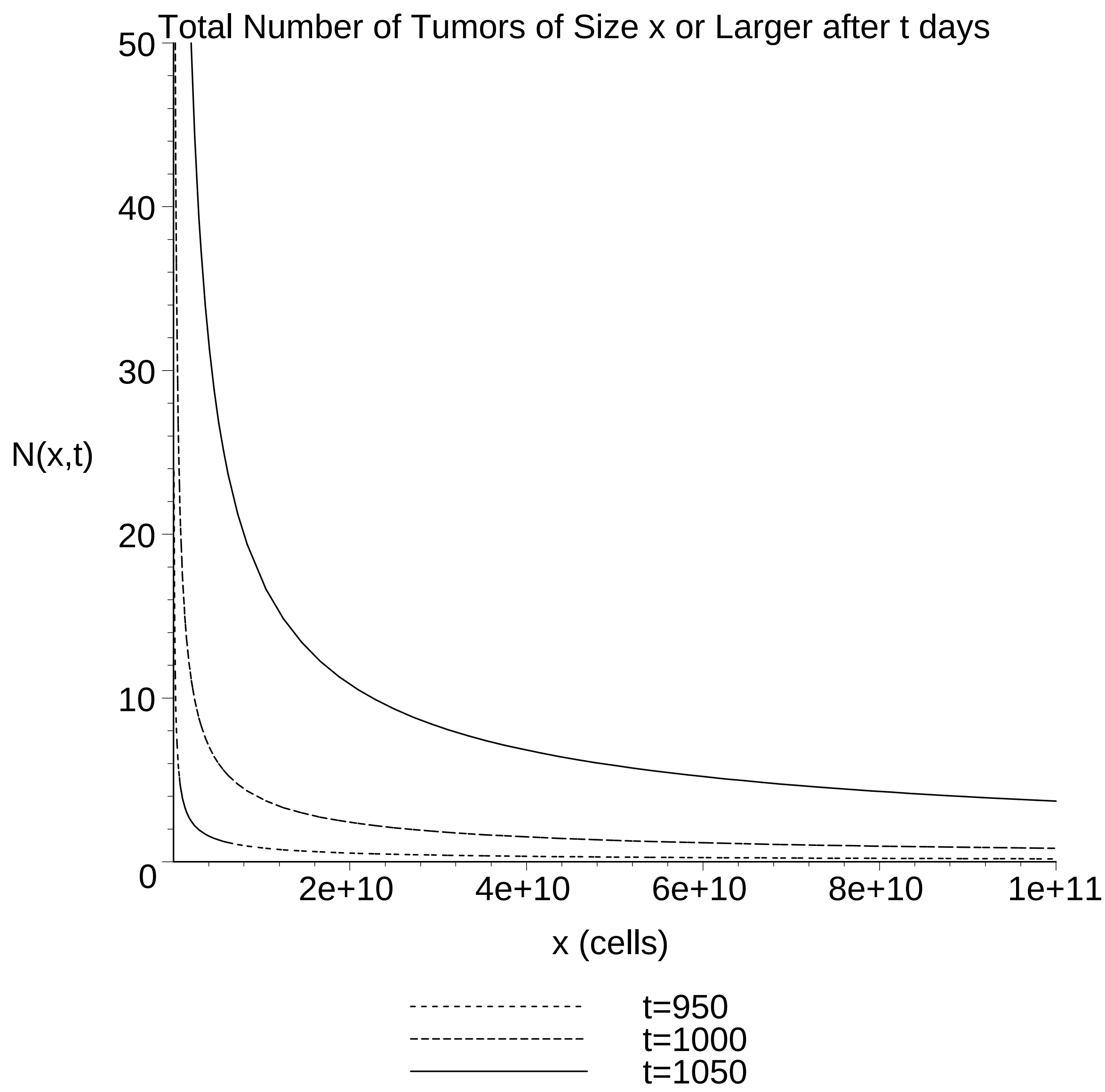
$m = 5.3 \cdot 10^{-8} \text{ (cells} \cdot \text{day)}^{-1}$

$\alpha = 2/3$

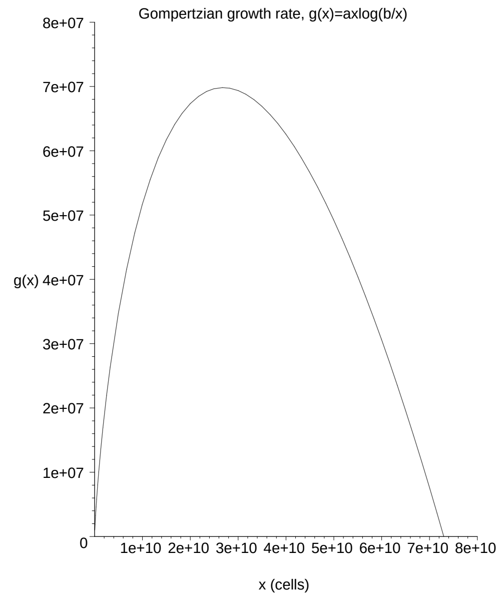
⋆ the total number of tumors can be found by integrating,

$$\rightarrow N(x,t) = \int_x^\infty \rho(x,t)dx = \# \text{ of tumors size } x \text{ or larger at time } t$$

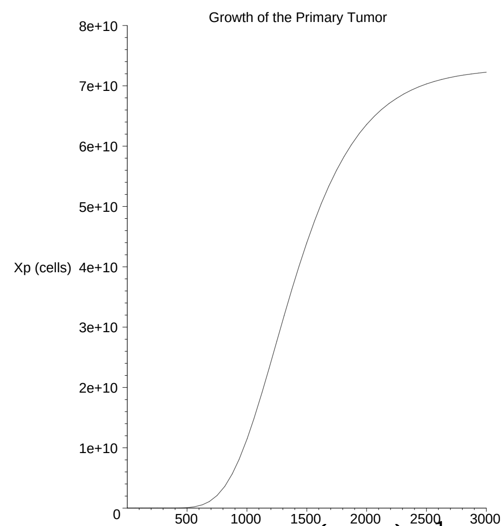
$$\boxed{N(x,t) = \frac{m}{a\alpha+m} e^{(a\alpha+m)t} x^{-\alpha-m/a}}$$



II. Gompertzian: $g(x) = axlog(\frac{b}{x})$




$\star$ primary tumor $\rightarrow x_p(t) = b^{1-e^{-at}}$




$a = 0.00286$ (day)$^{-1}$

$b = 7.3 \cdot 10^{10}$ cells

...using LT in this case is not quite as easy...

- taking the inverse LT we get

$$\rho(x,t) = \frac{1}{alog(b)x}\left(1 - \frac{log(x)}{log(b)}\right)^{-1} \sum_{k=1}^{n} Res[f(z), z_k]$$

  - ⋆ where $f(z) = \frac{\frac{m}{z}}{1-\frac{m}{z}F} \cdot e^{\frac{z}{a}log\left(1-\frac{log(x)}{log(b)}\right)+zt}$

  - ⋆ and $z_k$ are the roots of $1 - \frac{m}{s}F = 0$

  - ⋆ YIKES!!!

... **Solve it Numerically**

- Upwind type of scheme

  $\star$ forward difference in $t$ to approximate $\frac{\partial}{\partial t}$

  $\star$ backward difference in $x$ to approximate $\frac{\partial}{\partial x}$

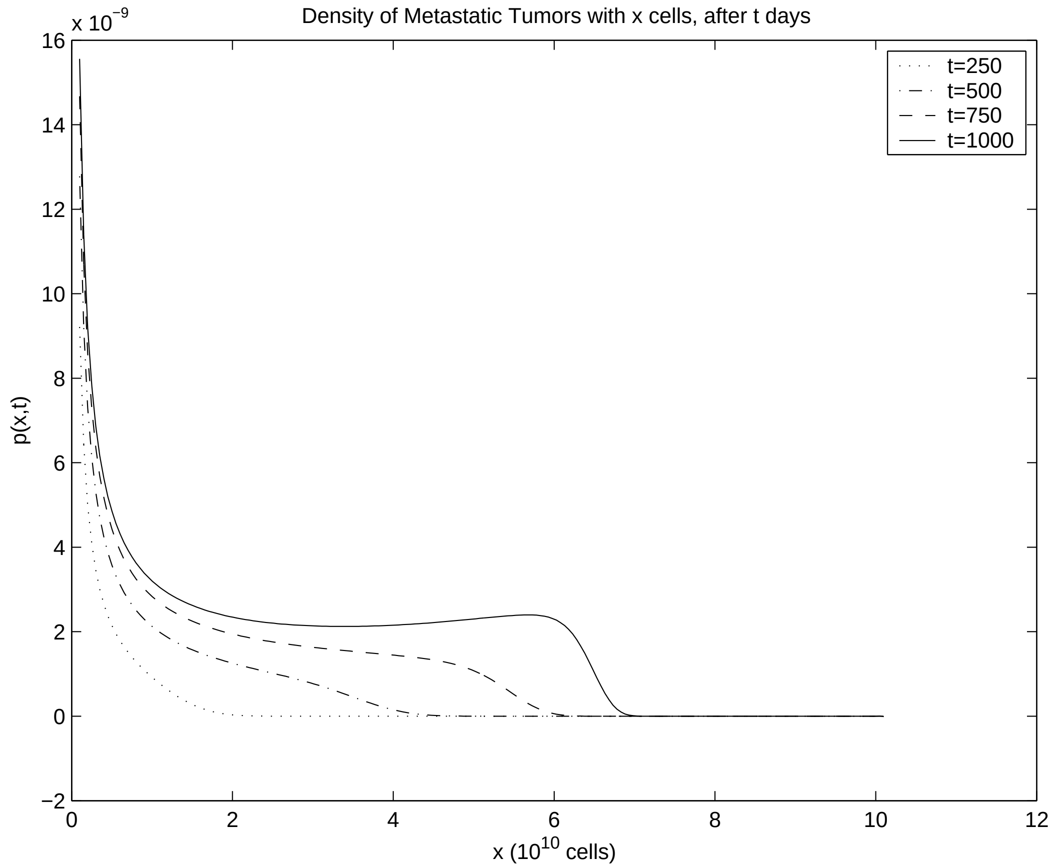
$$\text{PDE} \rightarrow U_j^{n+1} = (1 - \tfrac{\Delta t}{\Delta x} g(j))U_j^n + \tfrac{\Delta t}{\Delta x} g(j-1)U_{j-1}^n$$

$$\text{BC} \rightarrow U_1^{n+1} = \frac{1}{g(1)}\left[\sum_{j=1}^{J} \beta(j)U_j^n \Delta x + \beta(x_p(n))\right]$$

- CFL condition: $\frac{\Delta x}{\Delta t} >> g(x)$

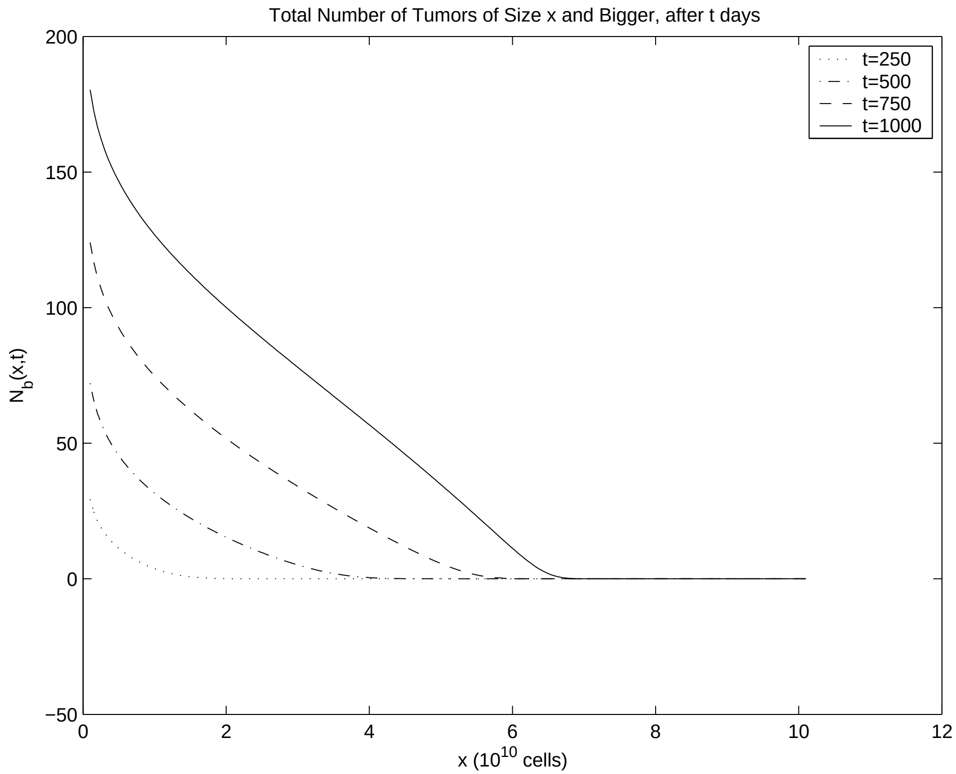
$\star$ characteristics of PDE must lie within characteristics of numerical scheme

Results...




$$a = 0.00286 \text{ (day)}^{-1}$$
$$b = 7.3 \cdot 10^{10} \text{ cells}$$
$$m = 5.3 \cdot 10^{-12} \text{ (cells} \cdot \text{day)}^{-1}$$
$$\alpha = 2/3$$

• total number of tumors of size $x$ or bigger is given by $(N_b)_j^n = \sum_{k=j}^{J} U_k^n \Delta x$

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# CONCLUSIONS

- Cancer metastasis can be thought of as a biological invasion
- Derived a model
  - ⋆ growth of individual tumors
  - ⋆ long distance dispersal
- Analyzed the model
  - ⋆ analytically
  - ⋆ numerically
- If parameter values $a$, $b$, $m$, and $\alpha$ could be quantified

  $\rightarrow$ the model could be a useful tool

# REFERENCES


- K. Kawasaki, N. Shigesada
*Biological Invasions: Theory and Practice*, Oxford Series in Ecology and Evolution, Oxford University Press (1997)

- K. Iwata, K. Kawasaki, N. Shigesada
*A Dynamical Model for the Growth and Size Distribution of Multiple Metastatic Tumors*, J. Theor. Biol., 203, pp.177-186 (2000)

- J.G. Skellam
*Random Dispersal in Theoretical Populations*, Biometrika, 38, pp.196-213 (1951)

- J.A. Lubina, S.A. Levin
*The Spread of a Reinvading Species: Range Expansion in the California Sea Otter*, American Naturalist, 131, pp. 526-543 (1988)

- R. Mack
*Invasion of Bromus Tectorum L. into Western North America: An Ecological Chronicle*, Agro-Ecosystems, 7, pp.145-165 (1981)