# Spatial statistical analysis of viruses and hosts in geographic and genetic space

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Smögen 2006

Disease Ecology: What do we want to do?

Raccoon Rabies: What have we done so far?

- Example 1: Raccoon rabies in CT
- Cellular automata model
- Monte Carlo assessments of fit

Genetic structure: What we are doing now?

- Landscape genetics
- Example 2: FIV in cougars

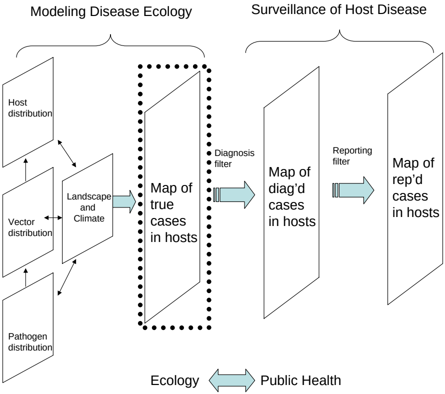
Conclusions

- Spatial landscape genetics

# Disease Ecology

- Interactions between virus, host, landscape.
- Landscape ecology (Manel et al. 2003), landscape genetics (host and virus) (Biek et al. 2006)
- People, animals, ecology, environment!
- Epidemiology, epizoology, environment interactions.
- Spatio-temporal data, mathematical models, genetic sequences, missing data, GIS!
- Fun, fun, fun!

# The “big picture”



# Raccoon rabies

# What is rabies?

- Virus in family of Lyssa virus.
- Reportable disease.
- Various strains associated with primary host (bat, dog, coyote, fox, skunk, and raccoon).
- Host cross-over, typically transmitted via bite/scratch.

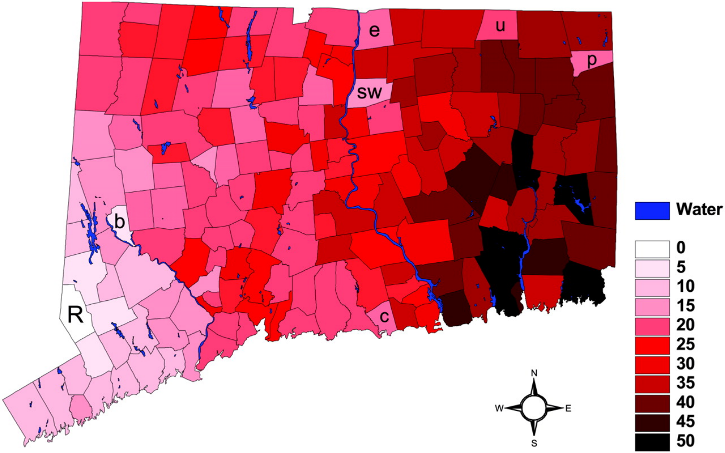
# Raccoon rabies

- Endemic in Florida and South Georgia.
- Translocation of rabid animal(s) to VA/WV border circa 1977.
- Wave-like spread since.
- Connecticut first appearance 1991-1996.
- Ohio 2005.

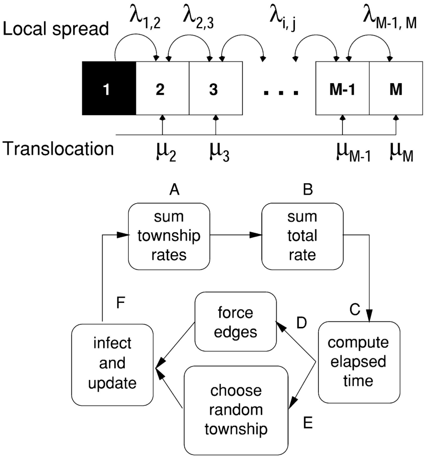
# Raccoon rabies in CT

- First appeared in western townships in 1991.
- Irregular wave roughly west-to-east.
- Crossed state in $\approx$ 5 years.
- Features of interest:
  - River effect?
  - Long distance transmittal?
  - Would a *cordon sanitaire* built from vaccinated baits work?

# Data: Months to first appearance



# Cellular automata stochastic model



# Does the model fit the data?

- Smith et al. (2002, *PNAS*), Waller et al. (2003, *Eco Mod*)
- For today: two models of interest:
  1. *Null:* Homogeneous spread ($\lambda_{ij} = \lambda$) + translocation.
  2. *River:* Probability of spread lower across river boundaries (two values for $\lambda_{ij}$) + translocation.

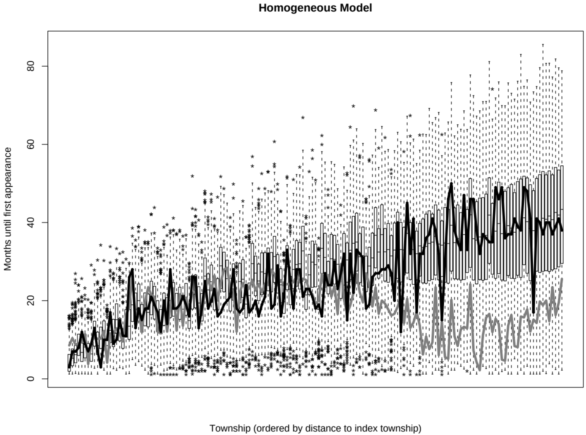
# What do we have?

- We have 5,000 independent realizations under the fitted model.
- We have one data realization from the "true" process.
- If we use the data to define a likelihood, we could see if the model seems consistent with the data.
- *OR* we could use the 5,000 realizations and ask "Do the data seem consistent with the model?"
- Do the data look like they could have been a realization of the model?

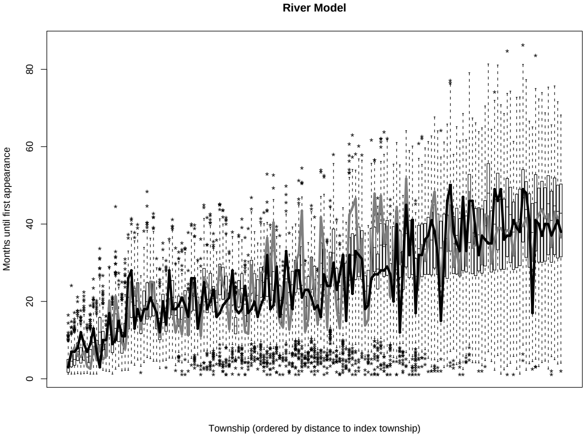
# Monte Carlo testing

- Barnard (1963) discussion of Bartlett (1963).
- For a test statistic $T$, we want the distribution of $T$ under $H_0$.
- Observe value $t^*$ from the data set.
- $p$-value $= \Pr[T > t^* | H_0 \text{ true}]$.
- We have 5,000 data sets under $H_0$ : model is true, calculate $T$ for each of these.
- Histogram of these values approximates distribution of $T$ under $H_0$.
- Proportion of simulated $T$'s $> t^*$ approximates $p$-value.

# Model realizations: Homogeneous model



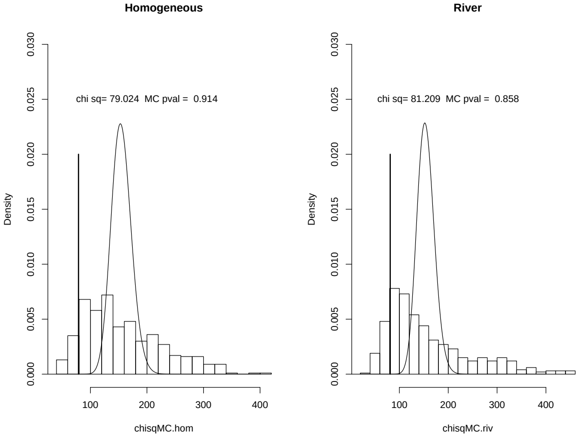
# Model realizations: River model



# Measuring fit

- Consider $Y^2 = \sum_{i=1}^{n}[(O_i - E_i)^2/V_i]$.
- Sum of squared, standardized residuals.
- Null distribution of $Y^2$?
- Cross validation approach: Calculate $Y^2$ for each simulated data set as $O_i$ and other 4,999 defining $E_i$ and $V_i$.

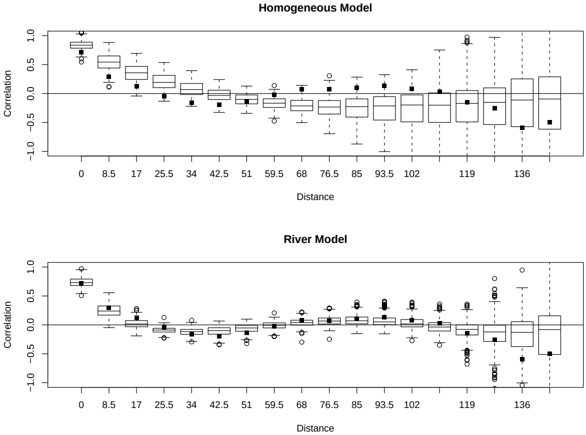
# Adjusted Pearson results



# But there's more!

- What about the joint (spatial) fit?
- Models defined by local interactions, induce joint (global) associations.
- Do the models generate spatial patterns similar to the observed pattern?
- Calculate the correlogram (correlation as function of distance) for data and for each realization.

# Correlograms



# Other measures of fit?

- Mayer and Butler (1993, *Eco Mod*) propose *modelling efficiency*, an $R^2$ type measure of fit.

  $$EF = 1 - \frac{\sum_{i=1}^{n}(O_i - E_i)^2}{\sum_{i=1}^{n}(O_i - \bar{O})^2}$$

  where $\bar{O}$ is the sample mean observed value.
- What fraction of variation around overall mean is captured by variation around model expectations?
- Note: $\bar{O}$ is worst-case regression, not same thing here.

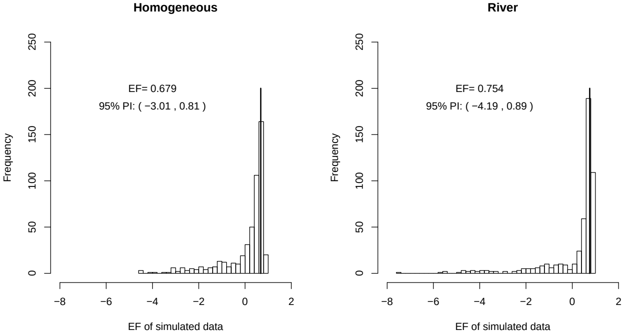
# Modelling efficiency

- EF(Homogeneous) = 67.9%, EF(River) = 75.9%
- Variability under $H_0$, cross-validate again!
- For $r$th simulation, calculate

$$EF = 1 - \frac{\sum_{i=1}^{n}(O_{r,i} - E_{-r,i})^2}{\sum_{i=1}^{n}(O_{r,i} - \bar{O}_{-r})^2}$$

where subscript $r$ denotes within $r$th simulation, $-r$ excluding $r$th simulation.

# Modelling efficiency



# What we have so far

- Mathematical model of spatio-temporal dynamics of spread on landscape scale.
- Monte Carlo assessments of fit to data.
- Raccoon rabies moved into Ohio in last year.
- Why is it moving faster in Northeast than it did in Southeast?
- Susceptible hosts? Molecular evolution of virus?
- Tissue samples of hosts and viruses at CDC.
- Sequencing genes from hosts and viruses.

# Landscape genetics

- Two key steps:
  - Detection and location of genetic discontinuities.
  - Correlation (association) of discontinuities with landscape features
- Landscape ecology: Manel et al. (2003, *Trends Ecol Evol*)
- Spatial epidemiology: Ostfeld et al. (2005, *Trends Ecol Evol*)
- Conservation medicine: Aguirre et al. (2002, Oxford Univ. Press)

# Spatial landscape genetics

- Guillot et al. (2005, *Genetics*)
- Hierarchical Bayes spatial model to determine:
  - How many population subgroups (phylogenies).
  - Where subgroups are.
  - Posterior probability of belonging to subgroups.
- Endgame: Link to environmental features.

# Guillot's model

- Data:
    - Locations: $\mathbf{t} = (t_1, \ldots, t_n)$
    - Genotypes: $\mathbf{z} = (\mathbf{z}_1, \ldots, \mathbf{z}_n)$ where $\mathbf{z}_i$ = vector of $L$ allele pairs for each of $L$ loci.
- Assume $K$ subpopulations in subdomains $\Delta_1, \ldots, \Delta_K$ partitioning overall study area.
- Throw down a bunch of points (nuclei) across study area, define Voronoi tessellation.
- Classify nuclei in groups $1, \ldots, K$, *with spatial correlation*.
- Aggregate Voronoi cells to identify subpopulation areas.

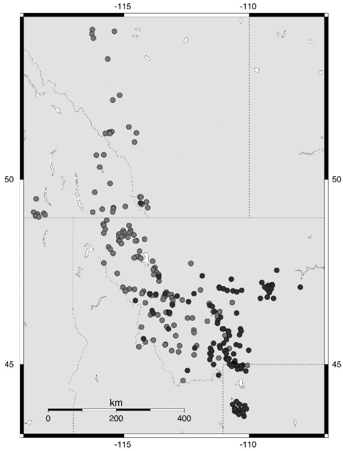
# Guillot's model (continued)

- Number of subpopulations.
- Number, location, and "color" of nuclei. (Marked Poisson Process).
- Spatial prior on "color".
- Ancestral allele frequencies.
- Present allele frequencies given ancestral frequencies.
- Likelihood from $\mathbf{z}|\mathbf{t}$.
- R library Geneland.

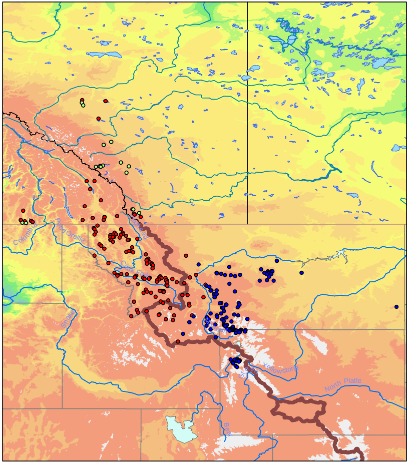
# FIV in cougars

- Sequencing ongoing for raccoons and virus, especially in Ohio samples.
- To illustrate methods, consider FIV data in cougars.
- Poss et al. (2002, *Conservation Medicine*), Biek et al. (2006, *Science*).
- Cougar samples from hunters in western U.S. and Canada.
- Biek et al. (2006) use `Structure` to categorize host samples into two subgroups (7 groups for virus).
- We apply Guillot's `R` library `Geneland` to same data.

# Non-spatial assignment (Structure)



# Population assignment, 3 populations



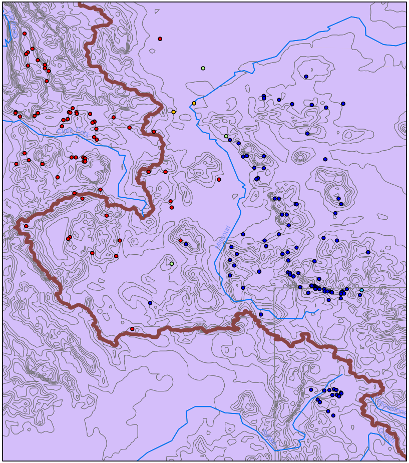
**Legend**

**3 population posterior**

- ● 1.00000
- ● 1.00001 - 2.00000
- ● 2.00001 - 3.00000

μ

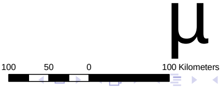
# Closer look with elevation



**Legend**

**3 population posterior values**

- ● 0.00000 - 0.20000
- ● 0.20001 - 0.40000
- ● 0.40001 - 0.60000
- ● 0.60001 - 0.80000
- ● 0.80001 - 1.00000



# Overall Conclusions

- Much to be done to link mathematical models to statistical ideas.
- Disease ecology offers a myriad of interesting statistical problems.
- Models of transmission, models of interaction, models of data collection.
- Mathematical models can inform statistics, statistics can inform models.
- Room to move past “ad-hockery”.

# Moving on...

- Sequencing virus and host for raccoon rabies in eastern US.
- Nagging questions: How to incorporate model selection into model fit.
- Guillot's spatial prior too strong?
- Incorporating geographic and genetic space in models?
- Linking landscape features in a more meaningful (inferential) way.
- Perfect opportunity for future dissertations and post-docs.

# References

- Lucey et al. (2002) Spatiotemporal analysis of epizootic raccoon rabies propagation in Connecticut, 1991-1995. *Vector Borne and Zoonotic Diseases* **2**, 77-86.
- Smith et al. (2002) Predicting the spatial dynamics of rabies epidemics on heterogeneous landscapes. *PNAS* **99**, 3668-3672.
- Russell et al. (2003) *A priori* predictino of disease invasion dynamics in a novel environment. *Proc. R. Soc. Lond. B* **271**, 21-25.
- Waller et al. (2003) Monte Carlo assessments of fit for ecological simulation models. *Ecological Modelling* **164**, 49-63.
- Real et al. (2005) Unifying the spatial population dynamics and molecular evolution of epidemic rabies virus. *PNAS* **102**,

# Guillot's model (continued)

- Likelihood: $[\mathbf{t}, \mathbf{z}|\boldsymbol{\theta}] = [\mathbf{z}|\mathbf{t}, \boldsymbol{\theta}] = \prod_{i=1}^{n} \prod_{\ell=1}^{L} [z_{i,\ell}|\boldsymbol{\theta}]$
- Parameters: $\boldsymbol{\theta} = (K, m, \mathbf{u}, \mathbf{c}, d, \mathbf{f}, \mathbf{f}_A, s)$
- $[z_{i,\ell} = (\alpha, \beta)|\boldsymbol{\theta}] = 2 f_{k\ell\alpha} f_{k\ell\beta}, (\alpha \neq \beta)$ or $f_{k\ell\alpha}^2 (\alpha = \beta)$.
- $K =$ number of subpopulations.
- $(m, \mathbf{u}) =$ number, location of nuclei. (Poisson Process).
- $\mathbf{c} =$ "color" (marks).
- $\mathbf{f} =$ present allele frequencies given ancestral frequencies.
- $\mathbf{f}_A =$ ancestral allele frequencies (Falush et al. (2003)).
- $d =$ genetic drift parameter (linearly related to $F_{ST}$).
- $t_i = s_i + \epsilon_i$ (location noise).

# Guillot's model (priors)

- Likelihood: $[\mathbf{t},\mathbf{z}|\boldsymbol{\theta}] = [\mathbf{z}|\mathbf{t},\boldsymbol{\theta}] = \prod_{i=1}^{n}\prod_{\ell=1}^{L}[z_{i,\ell}|\boldsymbol{\theta}]$
- Parameters: $\boldsymbol{\theta} = (K, m, \mathbf{u}, \mathbf{c}, d, \mathbf{f}, \mathbf{f}_A, s)$
- $K \sim \text{Unif}(K_{min}, K_{max})$
- $(m, \mathbf{u}) = \text{Poisson Process}(\lambda), \lambda \sim \text{Unif}(0, \lambda_{max})$
- $\mathbf{c} : Pr[c_{u_1} = c_{u_2}] \downarrow$ as $d_{1,2} \uparrow$
- $\mathbf{f} \sim \text{Dirichlet}\left(f_{A\ell 1}\left(\frac{1-d_k}{d_k}\right), \ldots, f_{A\ell J_\ell}\left(\frac{1-d_k}{d_k}\right)\right)$
- $\mathbf{f}_A \sim \text{Dirichlet}(1, \ldots, 1)$
- $d \sim \text{Beta}(2, 20)$
- $t_i = s_i + \epsilon_i$