Models of Polyclonal Tumor Initiation in the Mouse Intestine

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Dec. 7th

Fall 2007 Shapiro Fellowship

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Tumor origin: Monoclonal vs Polyclonal

- Monoclonal

  - Single initiation event

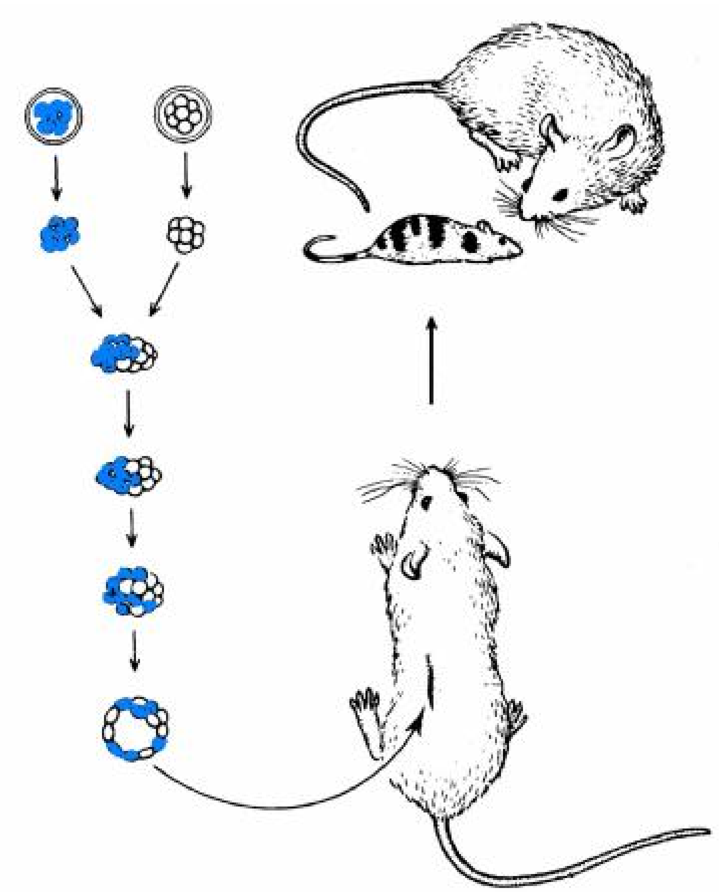
  - Normal cell converts to a cancer state

  - All cells in tumor are descendents of this progenitor.

- Polyclonal

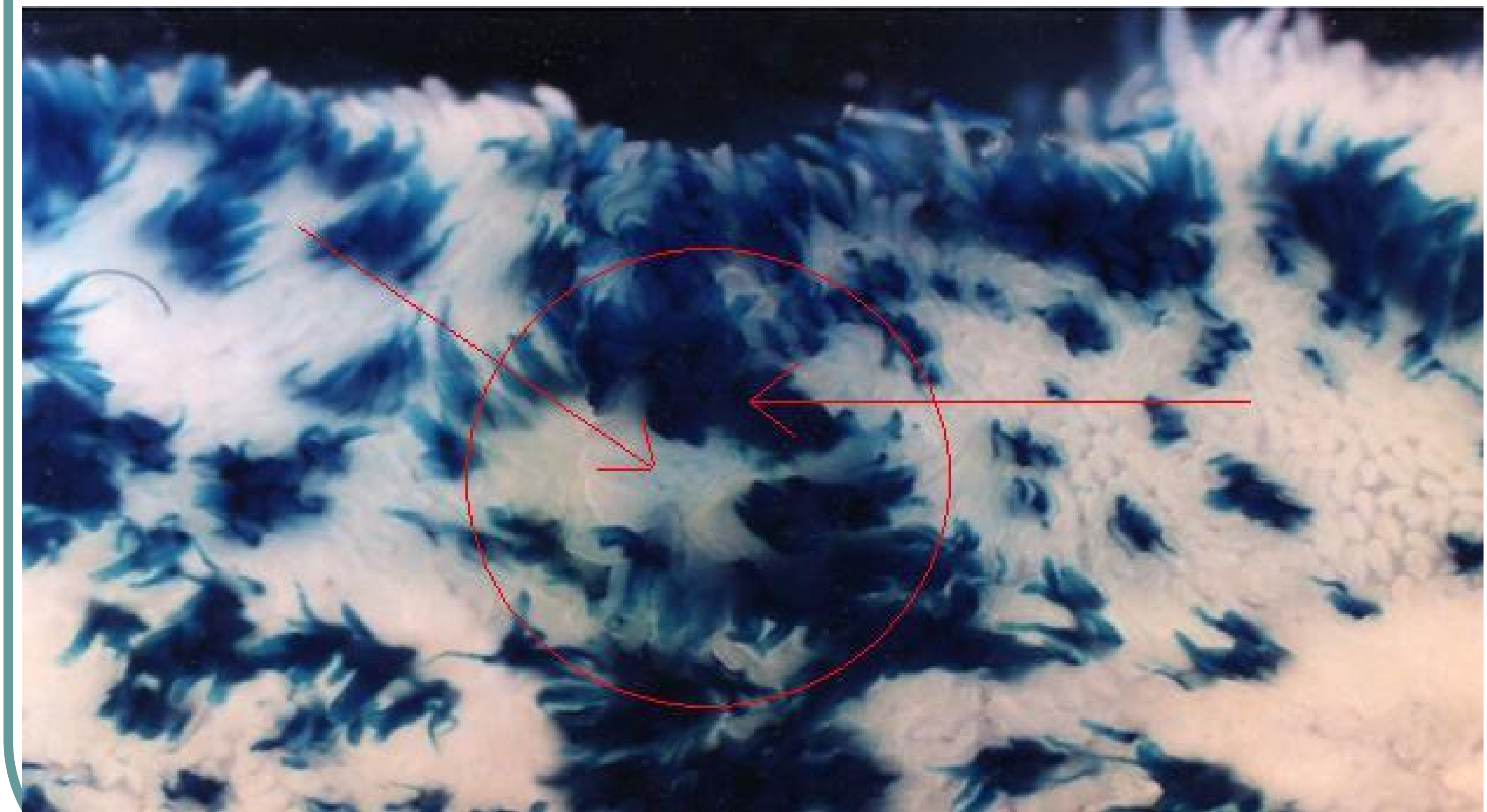
  - Multiple initiation events contributing to the tumor

Chimera [Thliveris et al 2005]



Heterotypic Tumor

Heterotypic Tumor



My Project

- Develop statistical models for the probability of heterotypic or pure tumors.
- Frequencies of heterotypic (H), blue (B), or white (W) tumors are observable.
- Using such multinomial data, we could compare different models for P(H), P(B), P(W).

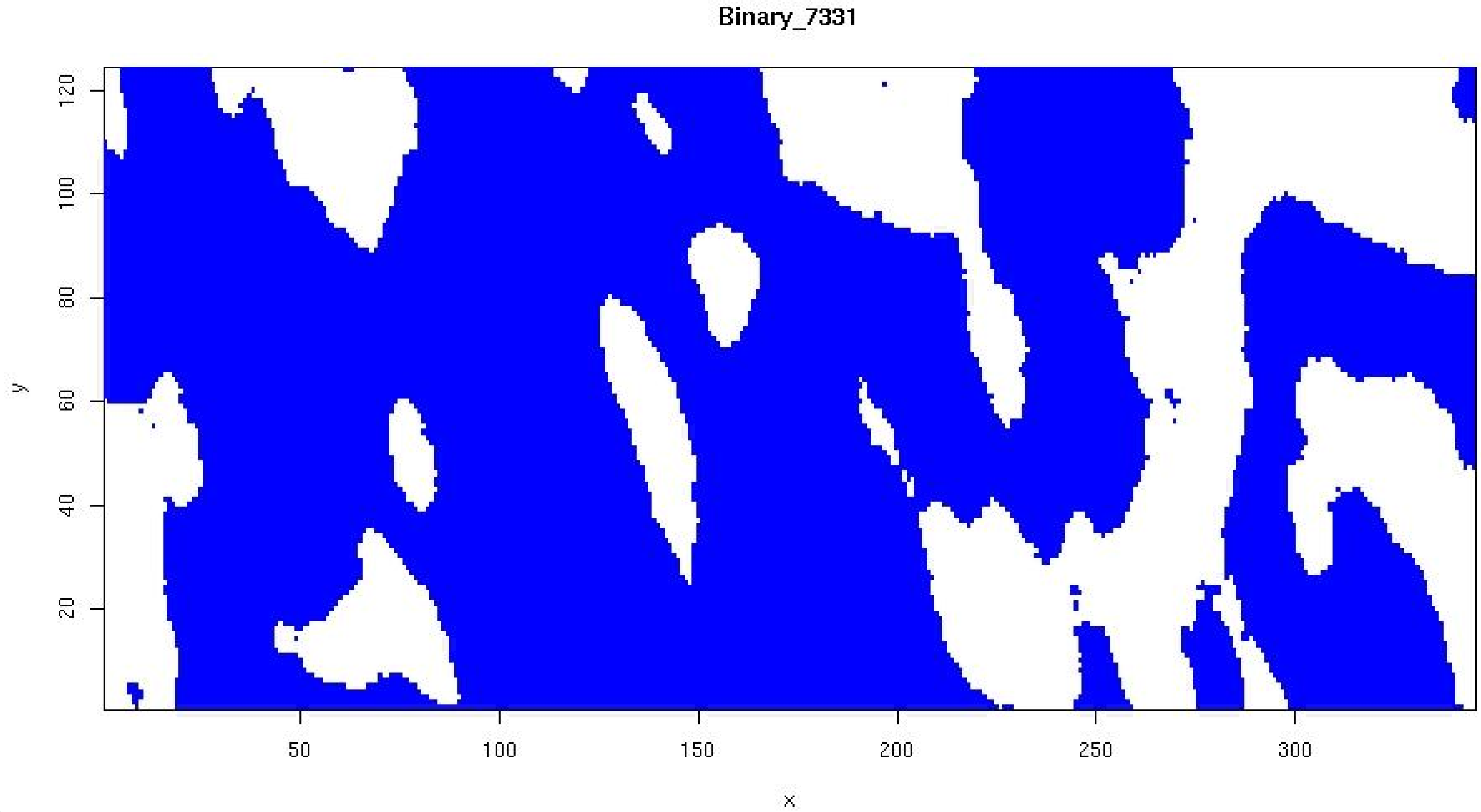
Formation of Polyclonal Tumor

- Two models:
  - Recruitment
  - Selection

- Data: images showing the chimeric patchwork in mouse intestine.

Example binary image

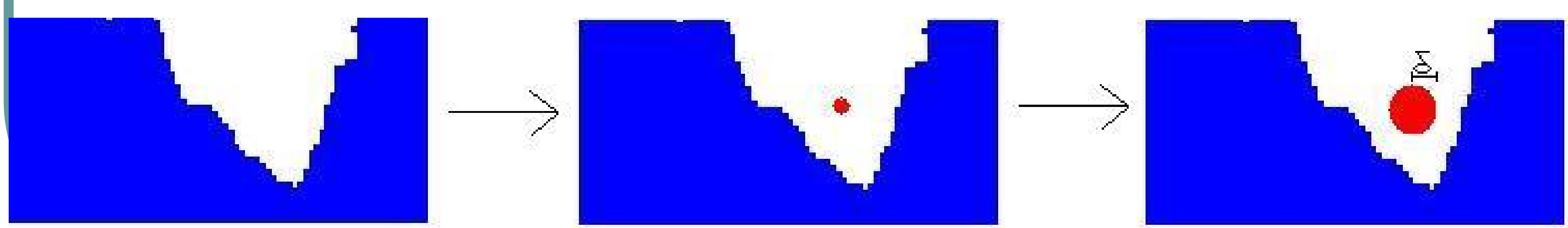
- Represents a small section in intestine:

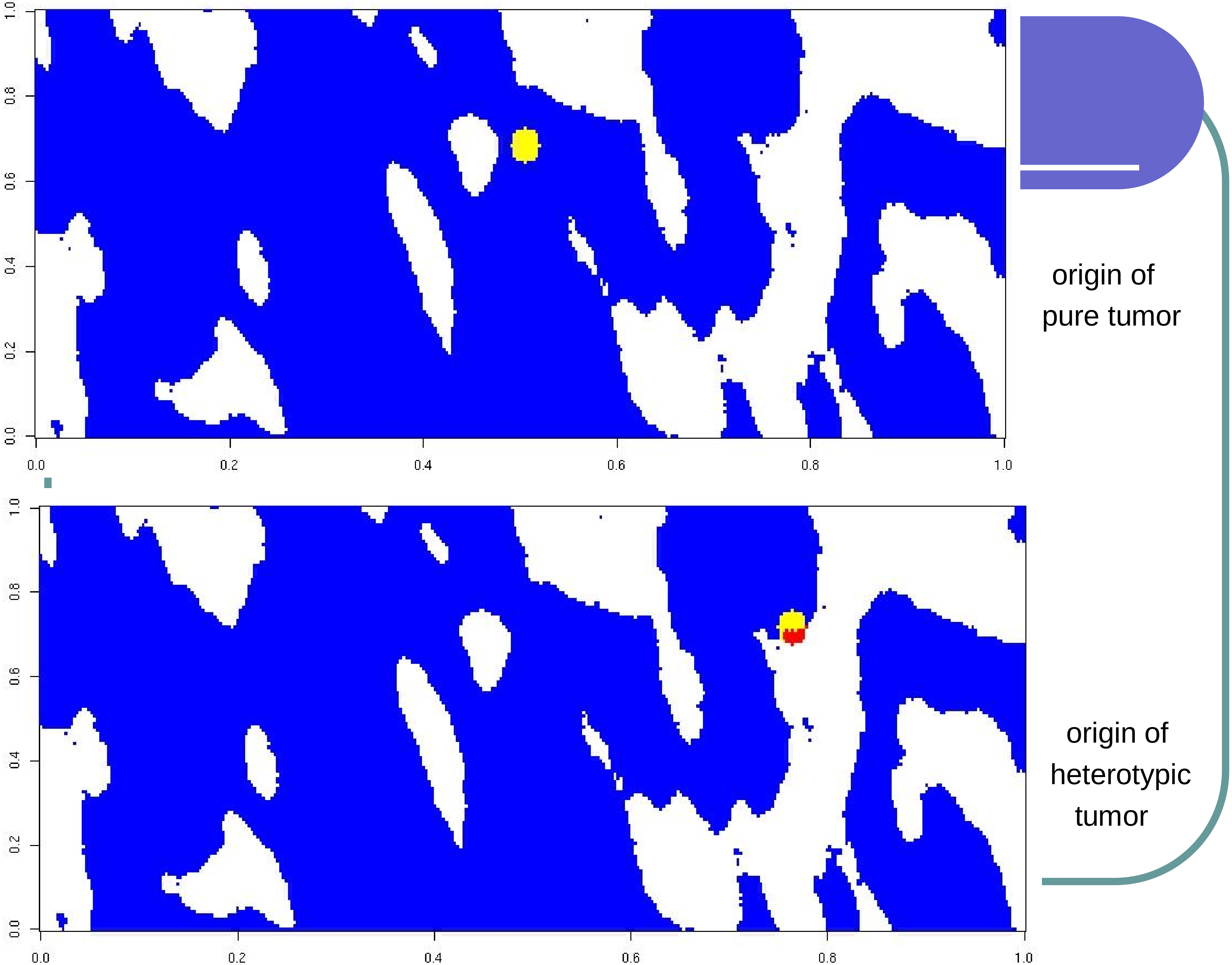


Recruitment

- Single initiation event at position X
- X may be nonuniformly distributed ~ f
- Recruitment distance δ
- Model: all cells in $disc_d(x) = \{y : \|y - x\| \le d\}$ are converted to tumor.

(Normal) **à** (Initiation) **à** (Recruitment)





0.0
0.2
0.4
0.6
0.8
1.0
origin of
pure tumor
origin of
heterotypic
tumor

Recruitment

Events:

B=[Tumor is pure blue]

W=[Tumor is pure white]

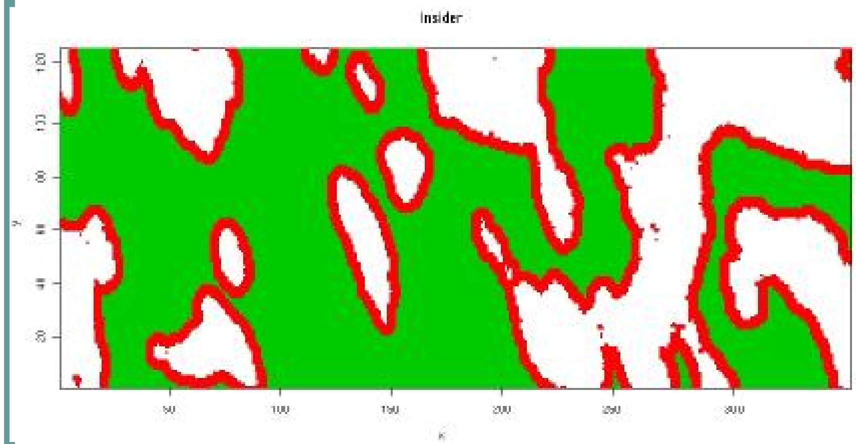
$H=(B \cup W)^c$

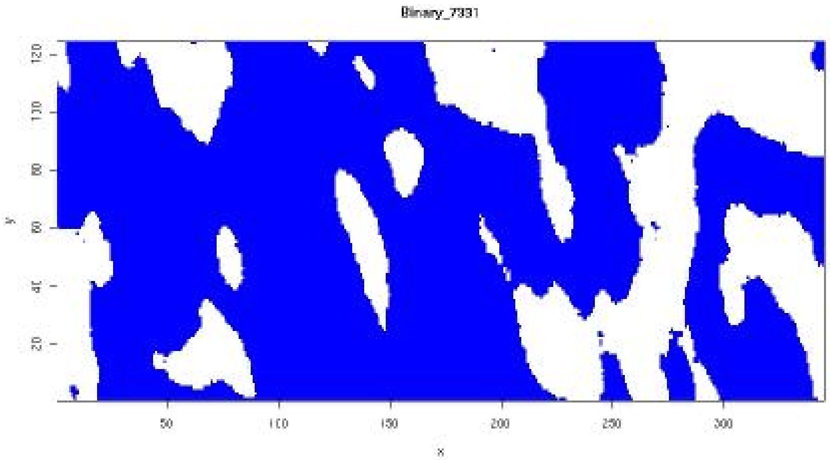
Problem: Compute P(B), P(W) and P(H).

Recruitment

- Define $d_B(d) = \{x : \text{cells in disc}_d(x) \text{ are pure blue}\}$

The green part below is $d_B(d)$:





Obviously, $d_B(0)$ is the part of blue.

Similarly, we can define:

$$d_W(d) = \{x : \text{cells in disc}_d(x) \text{ are pure white}\}$$

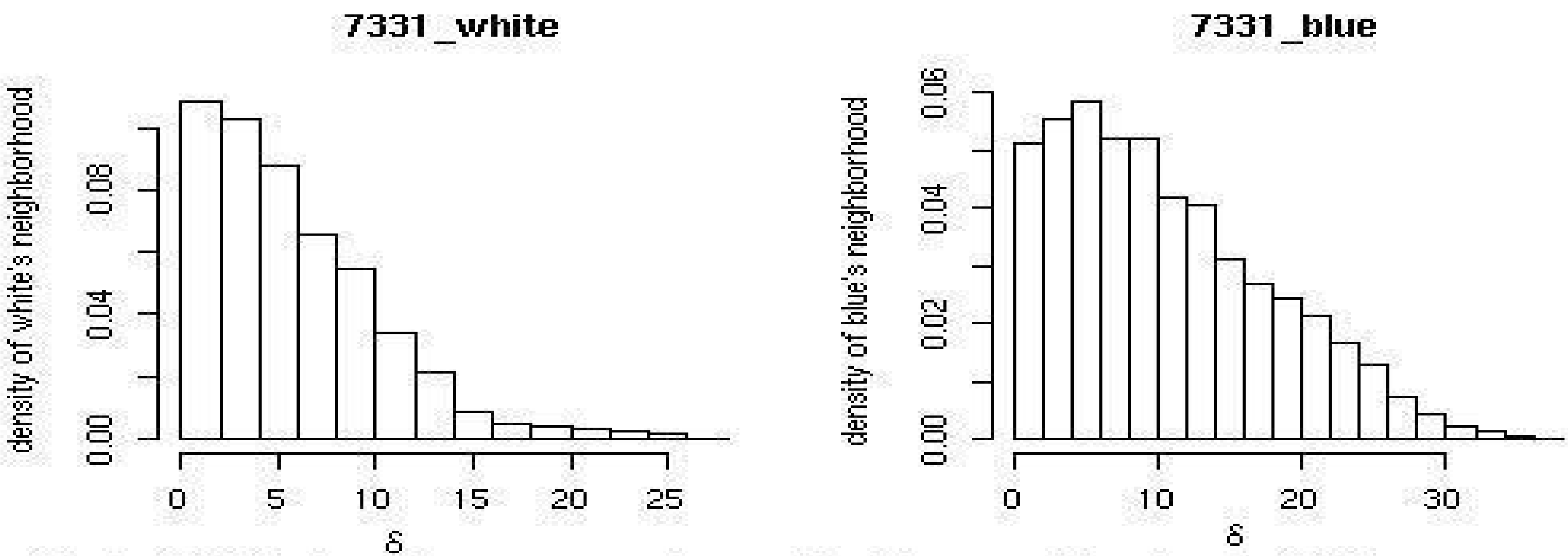
Computation

- Set $c(x) = 1\{x \, is \, blue\}$
- The position X has pdf: $f(x) = \begin{cases} a & c(x) = 0 \\ b & c(x) = 1 \end{cases}$
- To be a pdf, it requires: $a \cdot Area(d_W(0)) + b \cdot Area(d_B(0)) = 1$
- Then

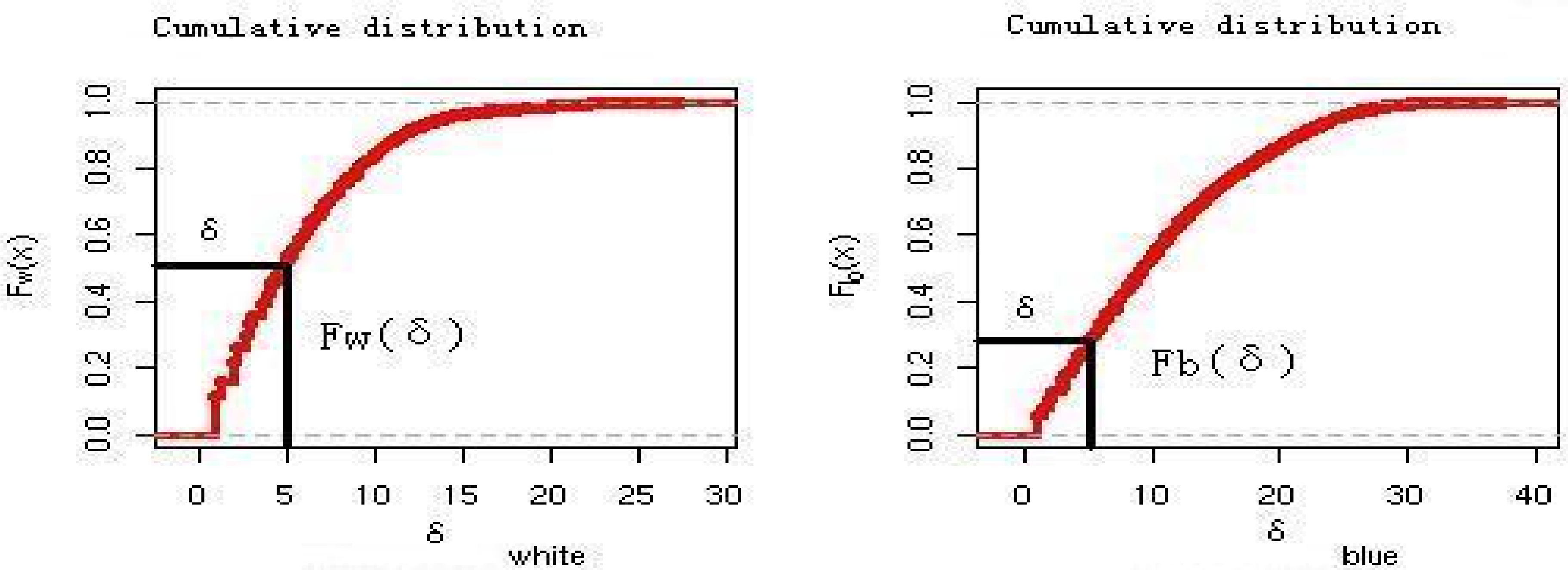
$$P(B) = \int f(x) 1\{x \in d_B(d)\} dx = b \cdot Area(d_B(d))$$

$$P(W) = \int f(x) 1\{x \in d_W(d)\} dx = a \cdot Area(d_W(d))$$

$$P(H) = 1 - P(B) - P(W)$$



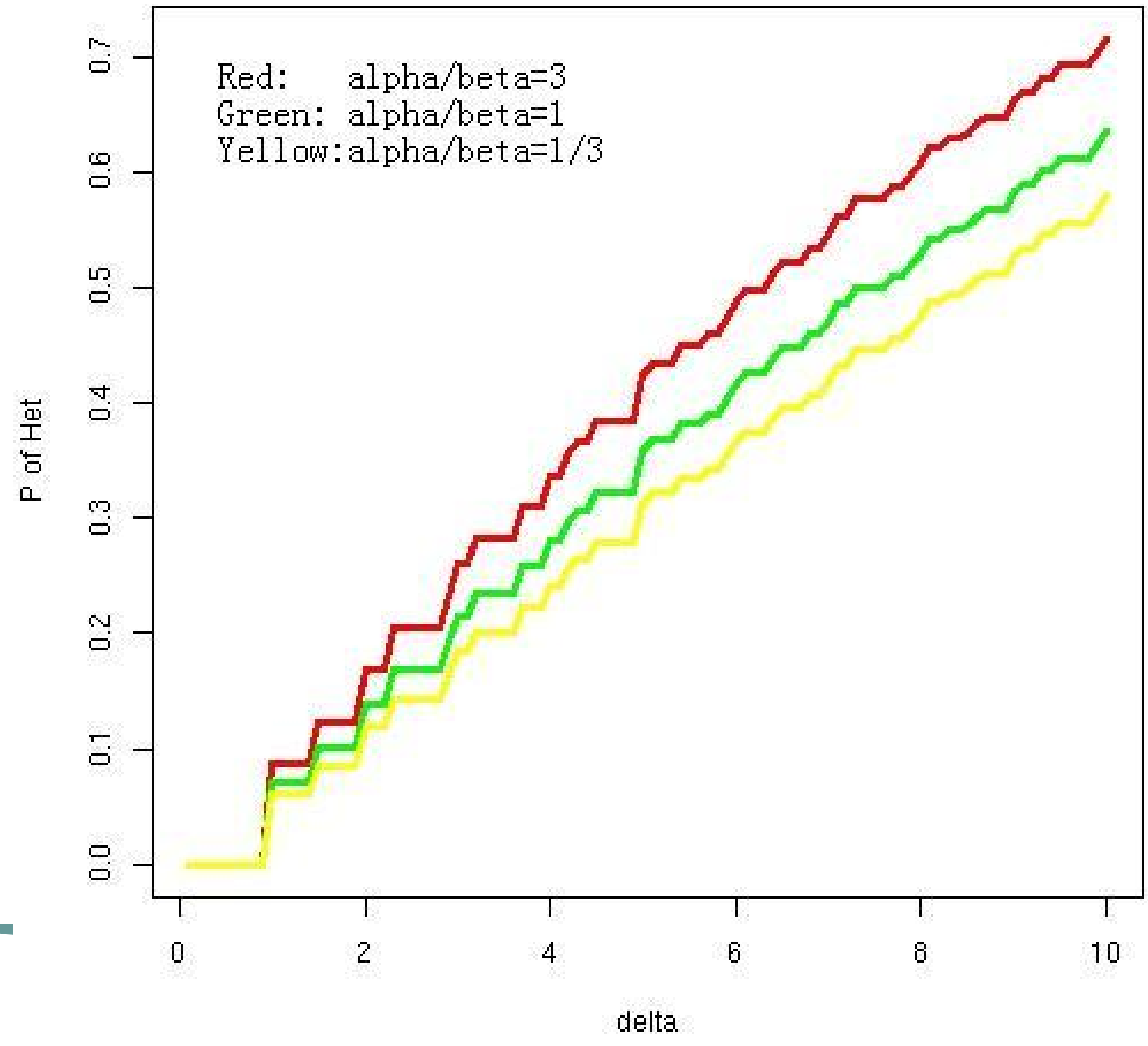
(1-Fw(δ)) is the proportion of white cells in $d_w(\delta)$.
(1-Fb(δ)) is similar



Computation

$$
\begin{aligned}
P(H) &= 1 - P(B) - P(W) \\
&= 1 - a\,(1 - F_b(d))\,Area(d_B(0)) \\
&\quad - b\,(1 - F_w(d))\,Area(d_W(0)) \\
&= 1 - a\,Area(d_B(0)) - b\,Area(d_W(0)) \\
&\quad + a\,Area(d_B(0))F_b(d) + b\,Area(d_W(0))F_W(d) \\
&= a \cdot Area(d_B(0)) \cdot F_b(d) + b \cdot Area(d_W(0)) \cdot F_W(d)
\end{aligned}
$$

Result



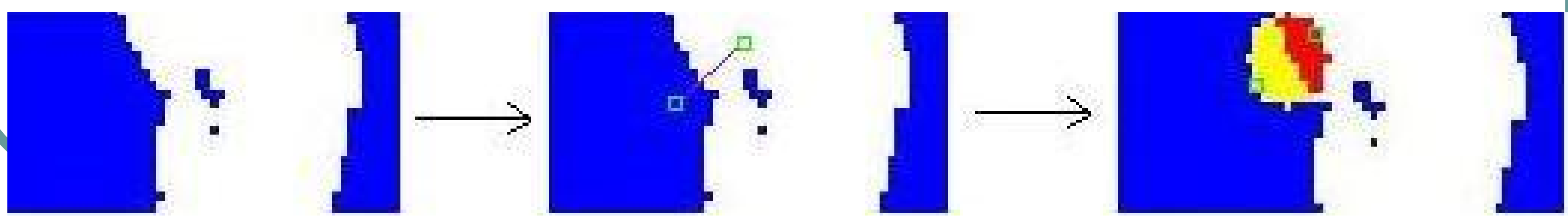
Red: alpha/beta=3
Green: alpha/beta=1
Yellow:alpha/beta=1/3
P of Het
0.0
0.1
0.2
0.3
0.4
0.5
0.6
0.7
0
2
4
6
8
10
delta

Selection

- Multiple initiation events
- e.g. n=2, at position X,Y ~ f
- Conditional on $E = \{ \|Y - X\| = d \}$
- Model: all cells in $disc_{d/2}((X+Y)/2)$

  are converted to tumor.

(Normal) à (Initiation) à (Selection)



Discussion – Future work

- Combine information of different images.
- Develop models further.
- Compare the prediction of these 2 models in multiple biological context.
- What does the calculation tell us about biology.

Reference

[1] Andrew T. Thliveris, Richard B.Halberg, Linda Clipson, William F. Dove, Ruth Sullivan, Mary Kay Washington, Stephen Stanhope, and Michael A. Newton. Polyclonality of familial murine adenomas: Analyses of mouse chimeras with low tumor multiplicity suggest short-range interactions. PNAS May10, 2005. vol.102, no.19

[2] Michael A. Newton. On estimating the polyclonal fraction in lineage-marker studies of tumor origin. Biostatistics(2006), 7,4, pp. 503-514

[3] Michael A. Newton, Linda Clipson, Andrew T. Thliveris, and Richard B. Halberg, A Statistical Test of the Hypothesis that Polyclonal Intestinal Tumors Arise by Random Collision of Initiated Clones. Biometrics.