Computational Modeling of Capsule-specific Antibody Transport and Binding to the *C. neoformans* capsule

Vineet Rakesh[1], Andrew D. Schweitzer[2], Ashim K. Datta[1], Arturo Casadevall[4], Oscar Zaragoza[3], Ekaterina Dadachova[2]

[1]Dept. of Biol. and Envt. Eng., Cornell University, Ithaca, NY; [2]Department of Nuc. Med., Albert Einstein Col. of Med., NY; [3]National Center for Microbio. Instituto de Salud Carlos III. Madrid, Spain; [4]Microbio. and Immunology and Med., Albert Einstein Col of Med, NY

Cryptococcus neoformans

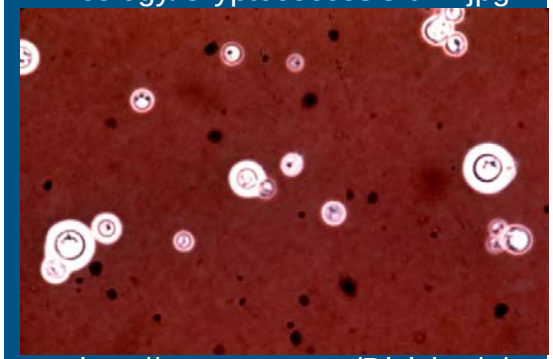
- Yeast-like fungus that causes cryptococcosis, a life-threatening illness affecting the nervous system and lungs
- Possesses capsules made of polysaccharides (mainly GXM) which makes it resistant to body's immune defenses
- The polysaccharide capsule is the main virulence factor

- Casadevall, A.; Steenbergen, J. N.; Nosanchuk, J. D. *Curr Opin Microbiol* **2003**, *6*, 332-337.

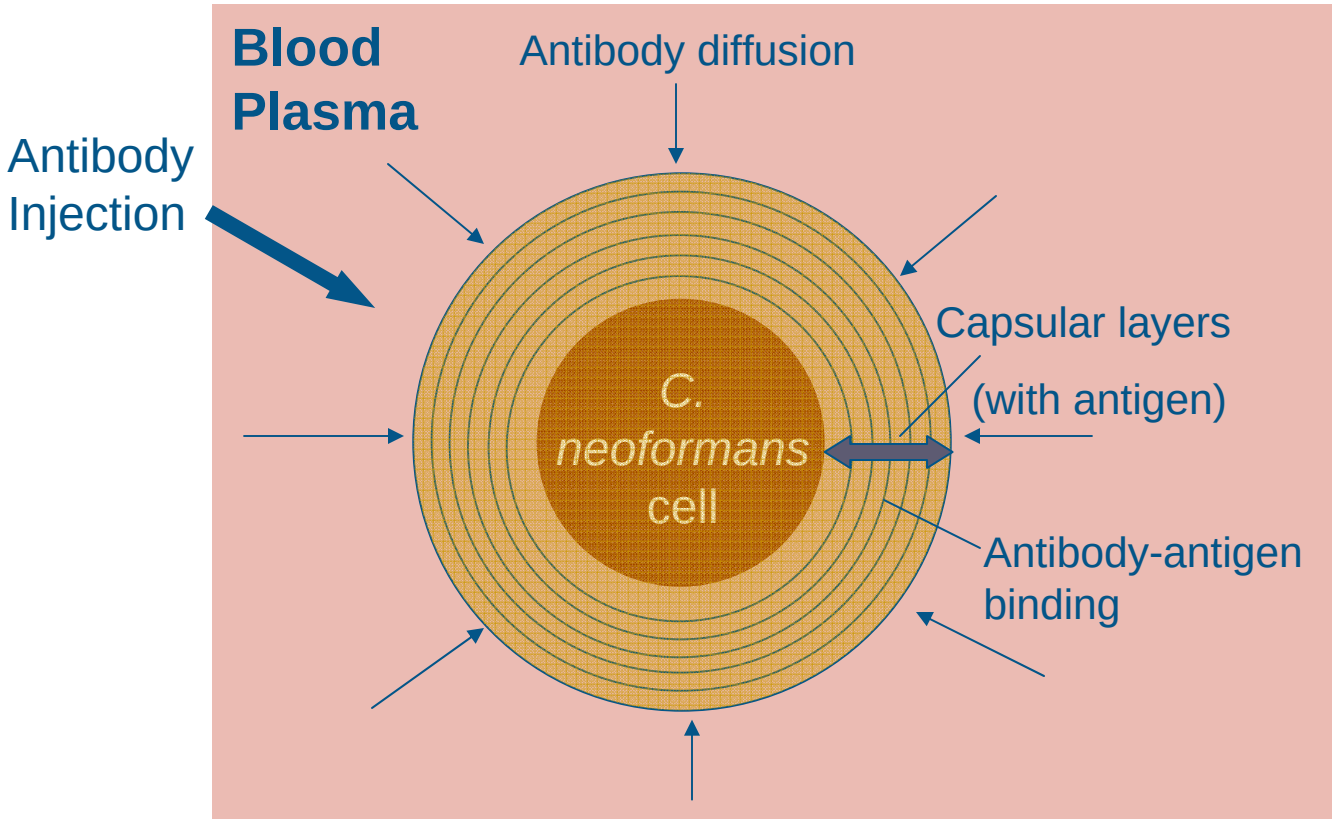
Antibody-based Therapy

- Injection of polysaccharide (antigen) specific antibody and binding with the antigen
- This increases the susceptibility of *C. neoformans* to ingestion by phagocytes (opsonization)

- http://pathmicro.med.sc.edu/mycology/Cryptococcosis-dk1.jpg



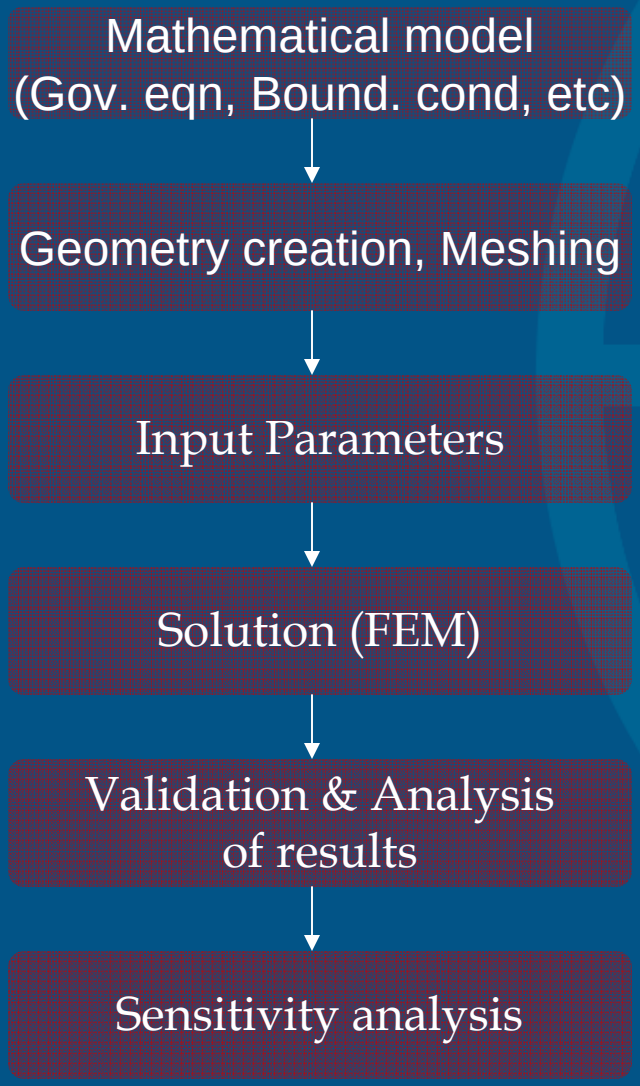
- http://www.asm.org/Division/c/photo/cneofrm1.JPG



Need for the computational model

- Currently in clinical development
- Quantification of the process
  - Determine the amount of complex formed
  - Identify the factors that limit the performance
- Capsule is structurally complex
  - Determine effectiveness in different capsular regions
- To develop better antibody-based therapies for *C. neoformans* infection

Modeling approach



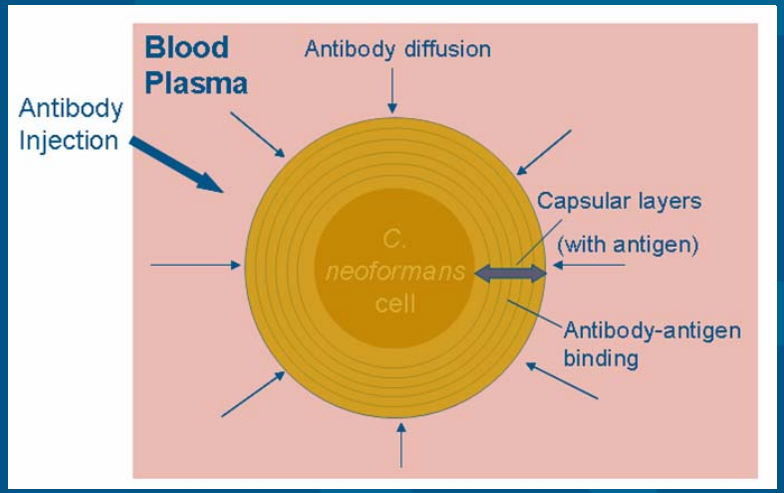
Mathematical Description

- Antibody

$$\frac{\partial c_{Ab}}{\partial t} = \underbrace{D_{cap}\frac{1}{r^2}\frac{\partial}{\partial r}\left(r^2\frac{\partial c_{Ab}}{\partial r}\right)}_{\text{diffusion}} - \underbrace{k^f c_{Ab} c_{Ag}}_{\text{complex formation}} + \underbrace{k^b c_{Ab-Ag}}_{\text{dissociation}}$$

- Antigen

$$\frac{\partial c_{Ag}}{\partial t} = n\left(- \underbrace{k^f c_{Ab} c_{Ag}}_{\text{complex formation}} + \underbrace{k^b c_{Ab-Ag}}_{\text{dissociation}}\right)$$

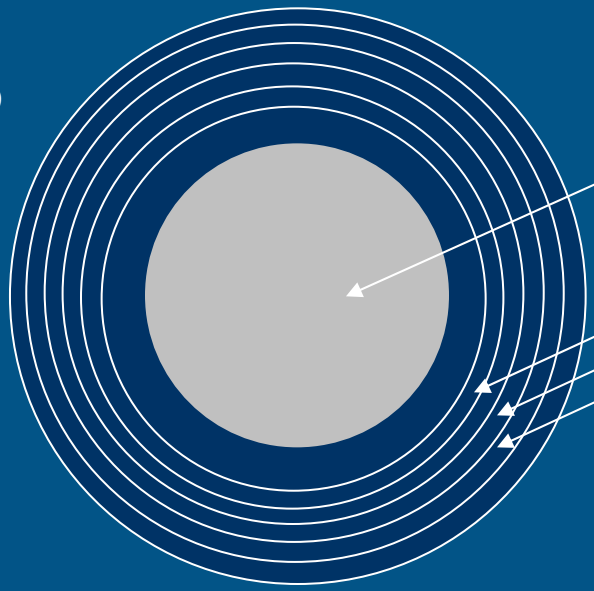


- Complex

$$\frac{\partial c_{Ab-Ag}}{\partial t} = \underbrace{k^f c_{Ab} c_{Ag}}_{\text{complex formation}} - \underbrace{k^b c_{Ab-Ag}}_{\text{dissociation}}$$

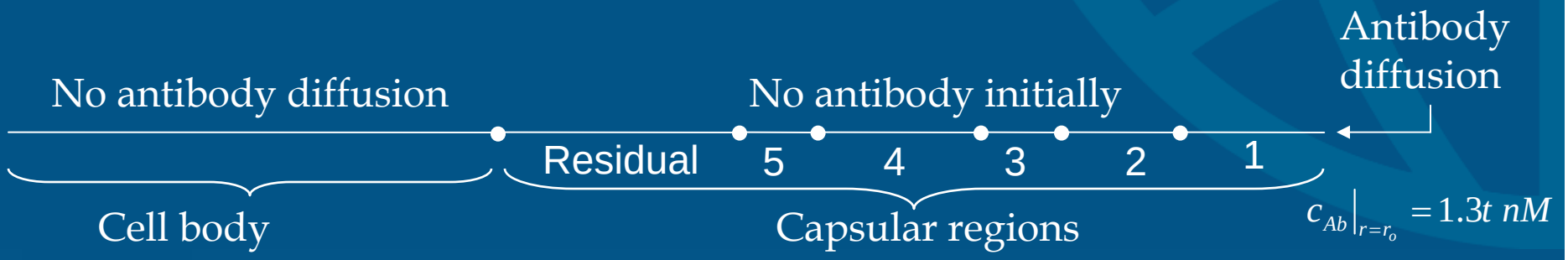
Schematic

Spherical 3D Geometry



- In the different capsular regions:
  - Different initial antigen concentrations
  - Different antibody diffusivity
  - Different reaction rates

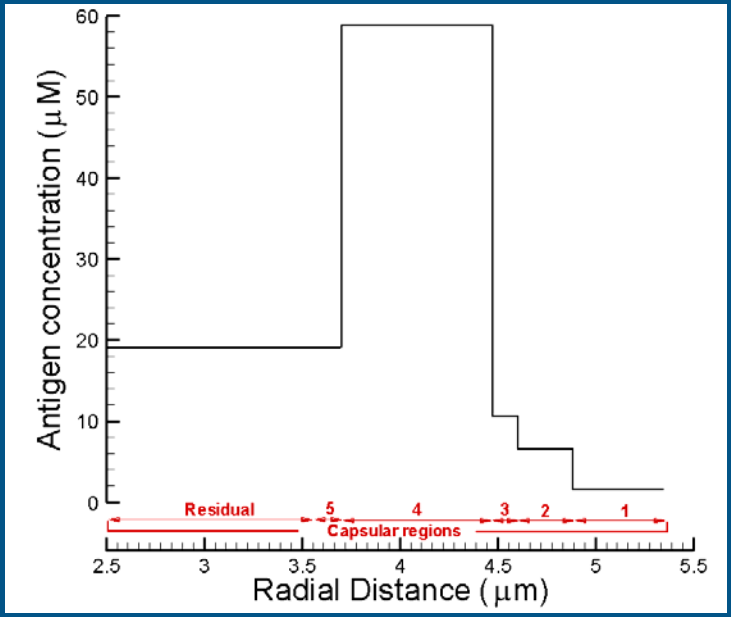
1D Geometry to reduce computations

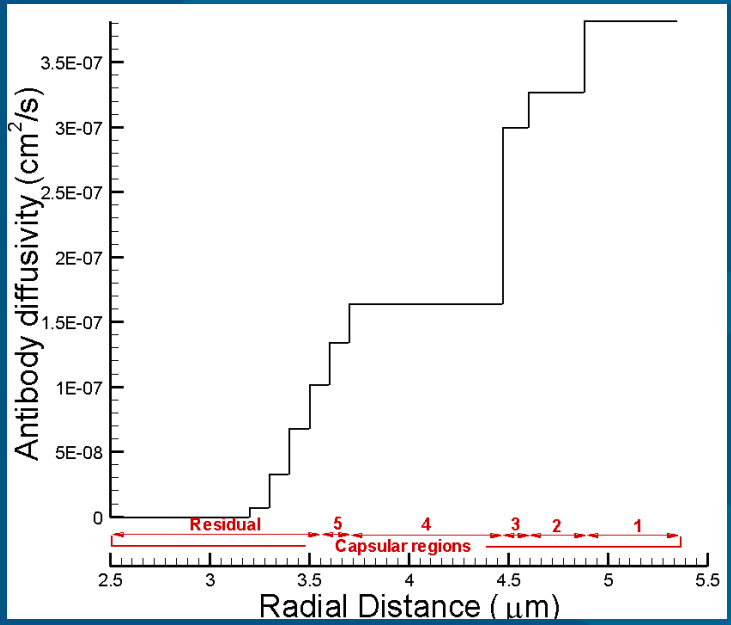


Important input parameters

- Capsule radii, antigen concentrations, reaction constants- determined using experiments[1]
- Antibody diffusivities in the capsular regions[2]

$$\frac{D_{ig}}{D_{iw}} = \left(1 - \frac{2R_S}{D_p}\right)^2 \left[1 - 2.104\left(\frac{2R_S}{D_p}\right) + 2.09\left(\frac{2R_S}{D_p}\right)^3 - 0.95\left(\frac{2R_S}{D_p}\right)^5\right]$$

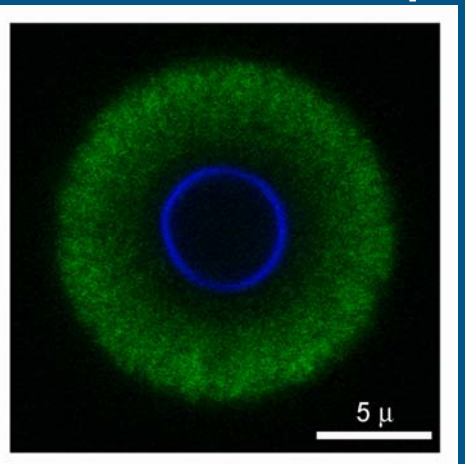


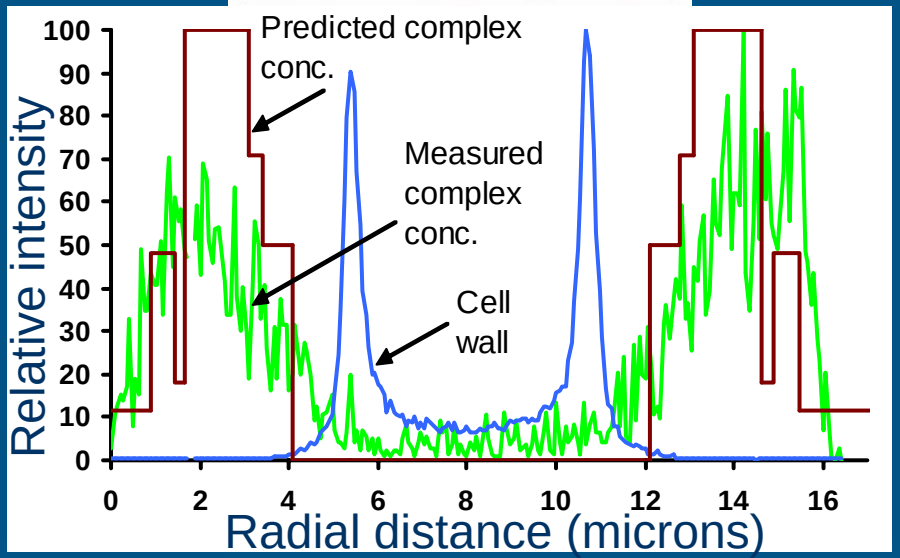


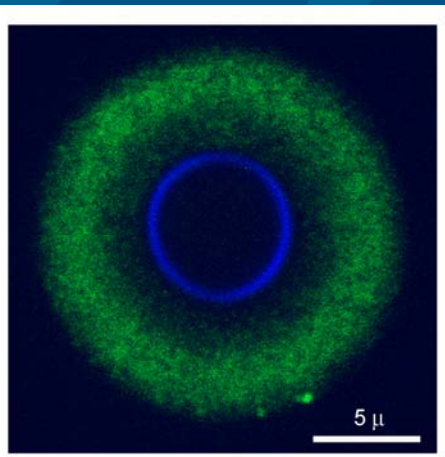
- Maxson, M. E.; Cook, E.; Casadevall, A.; Zaragoza, O. *Fungal Genet Biol* **2007**, *44*, 180-186.
- Renkin, E. M. *J Gen Physiol* **1954**, *38*, 225-243.

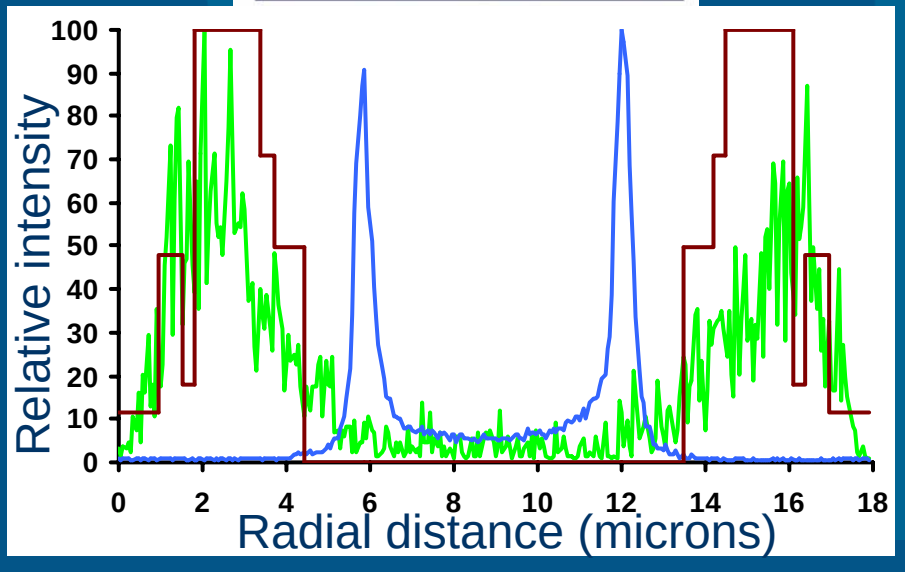
Comparison with experiments

- Capsule fluorescently-labeled to visualize spatial distribution of complex

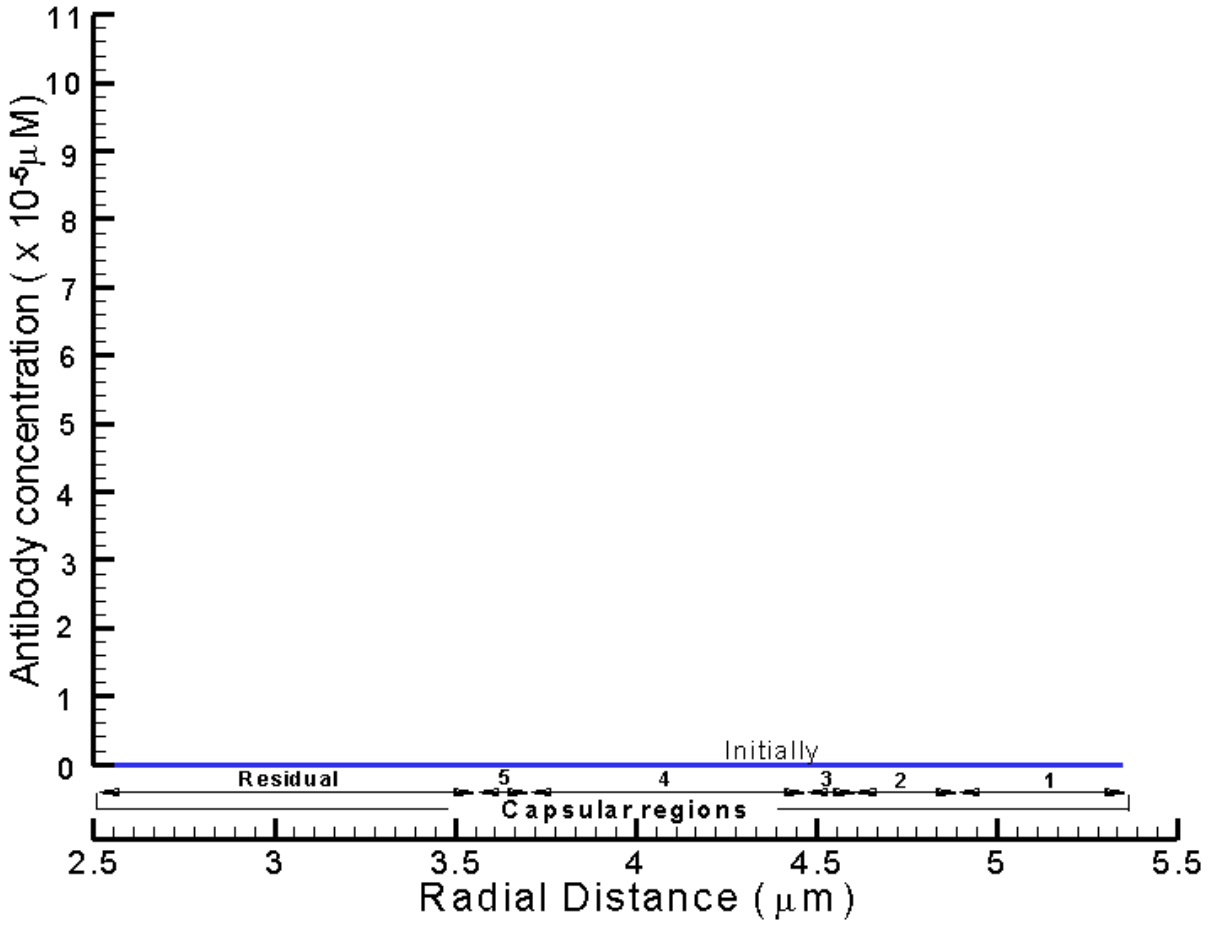




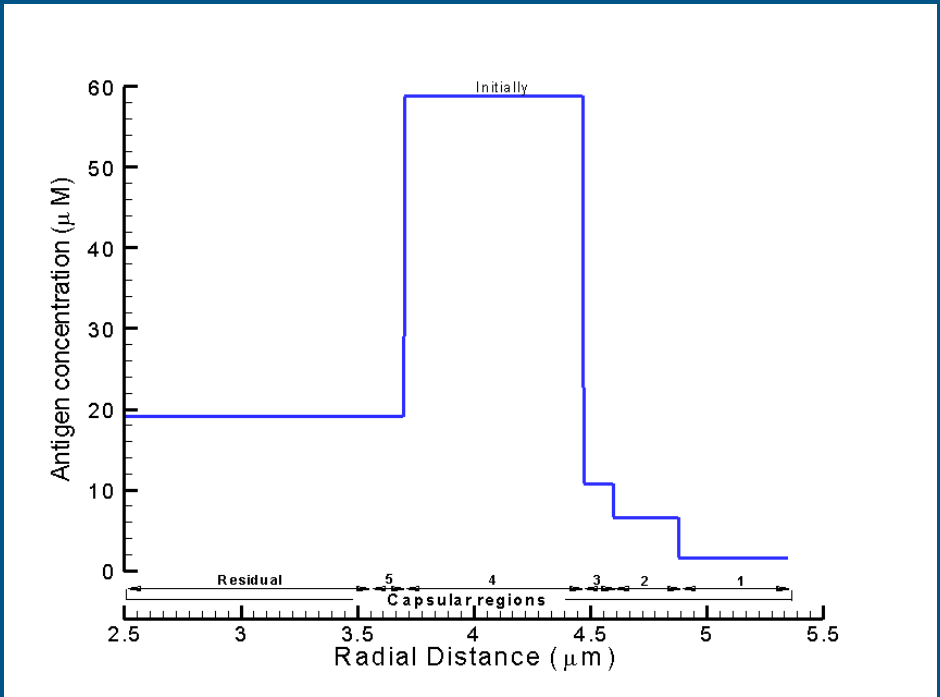


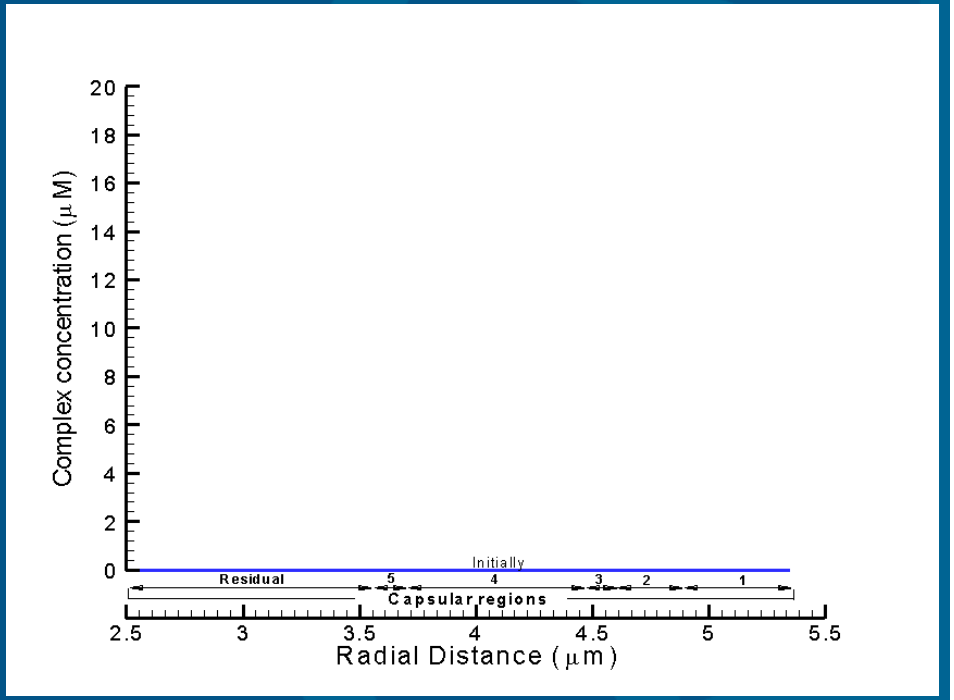


Rapid diffusion of antibody



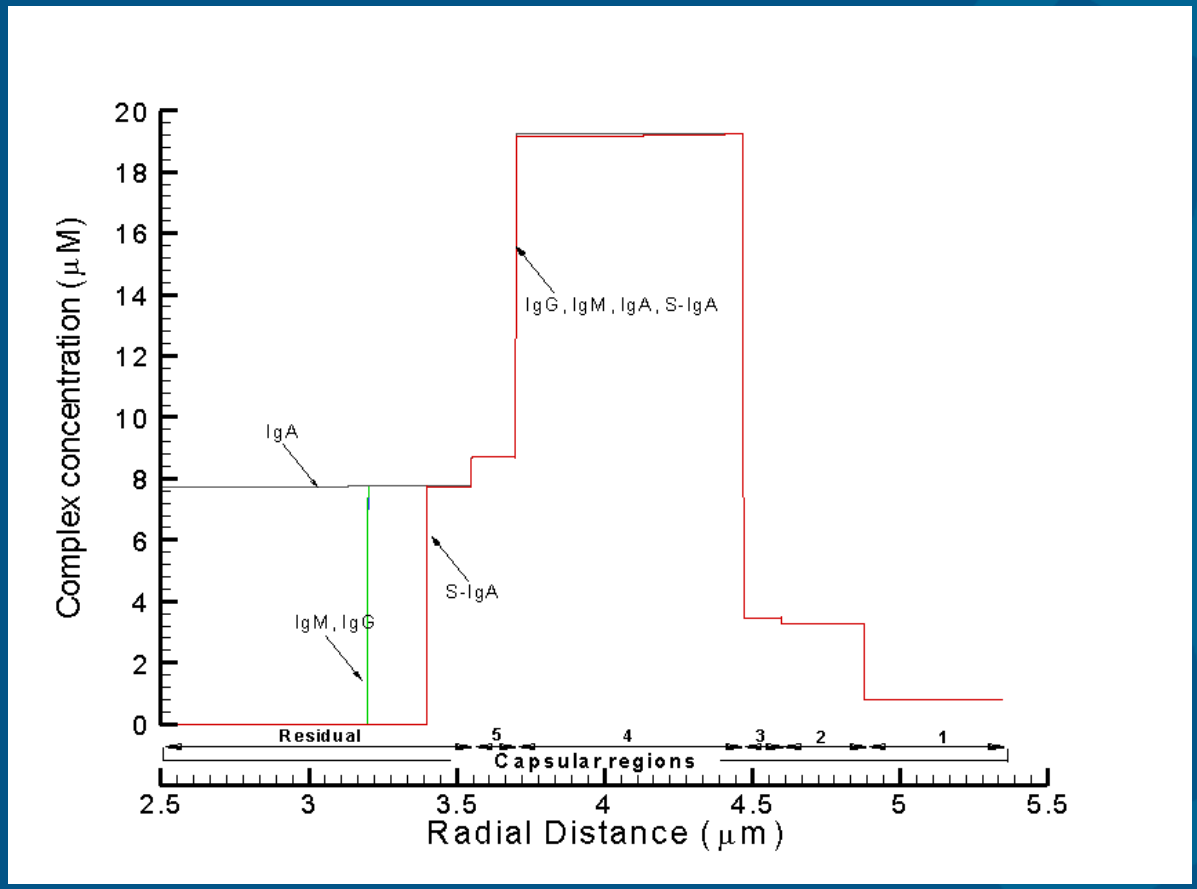
Change in antigen and complex with time





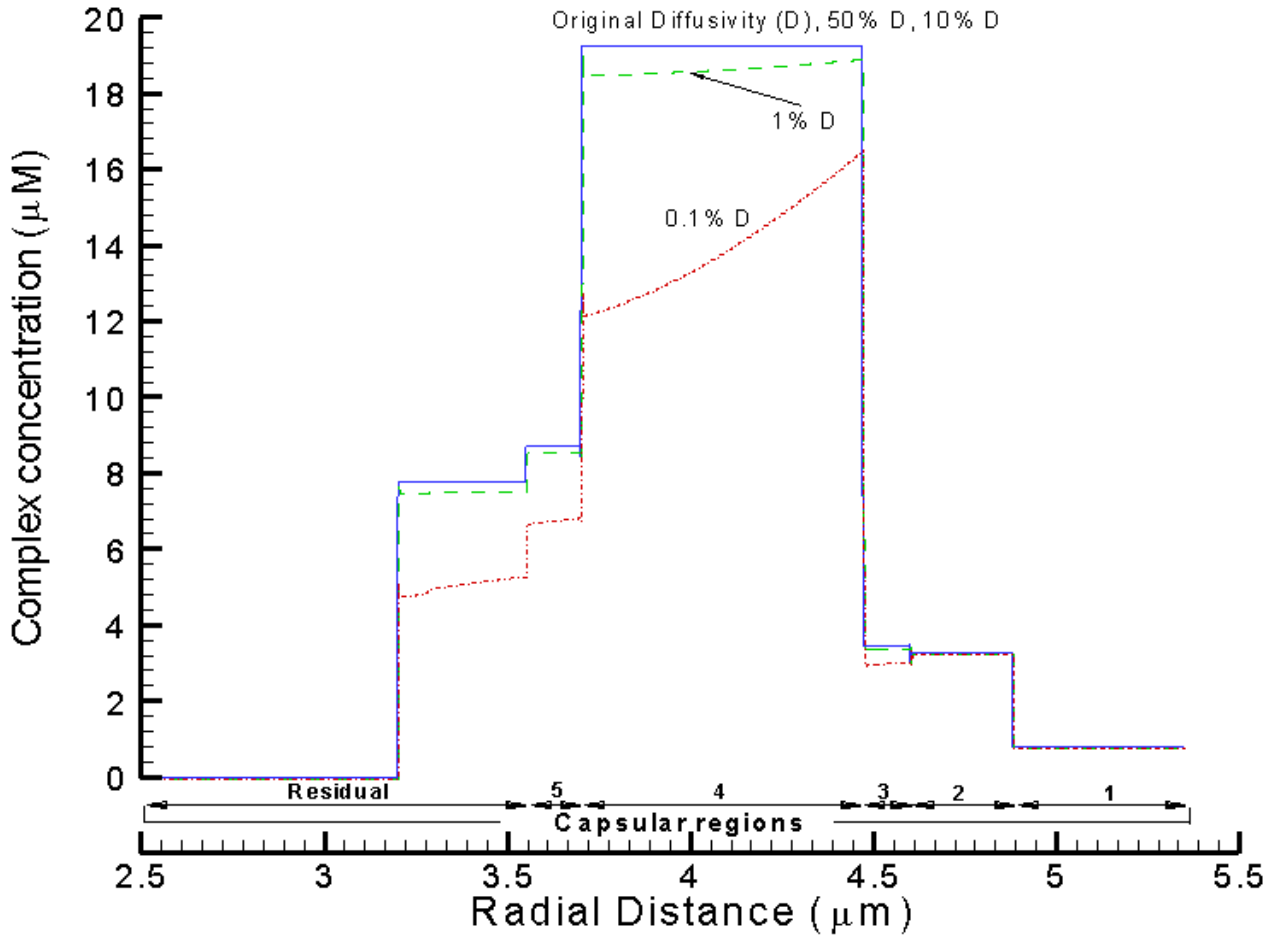
- Complex formation in each region is determined by the forward binding reaction and antigen concentration

Performance of different antibodies



- At outer capsular regions, different antibody isotypes (IgM, IgA, and S-IgA) result in similar complex formation
- At inner regions, IgA and S-IgA result in different depth of binding

Change in antibody diffusivity



Summary and Conclusions

- Simulations were used to test various scenarios in a treatment procedure
- It was used as an alternative to experiments
- The concentration profiles predicted by the model closely matched the experimental data
- Effectiveness of different antibodies to target the antigen was determined
- Results can be used for the development of more efficient antibody-based therapies

Thank You

Questions?