Computational Tools for Vascular Biology

- **Computational Solid Mechanics Models of Wall Stress in Abdominal Aortic Aneurysms**
- **Biochemistry Kinetic Models Involved in Abdominal Aortic Aneurysm Development**

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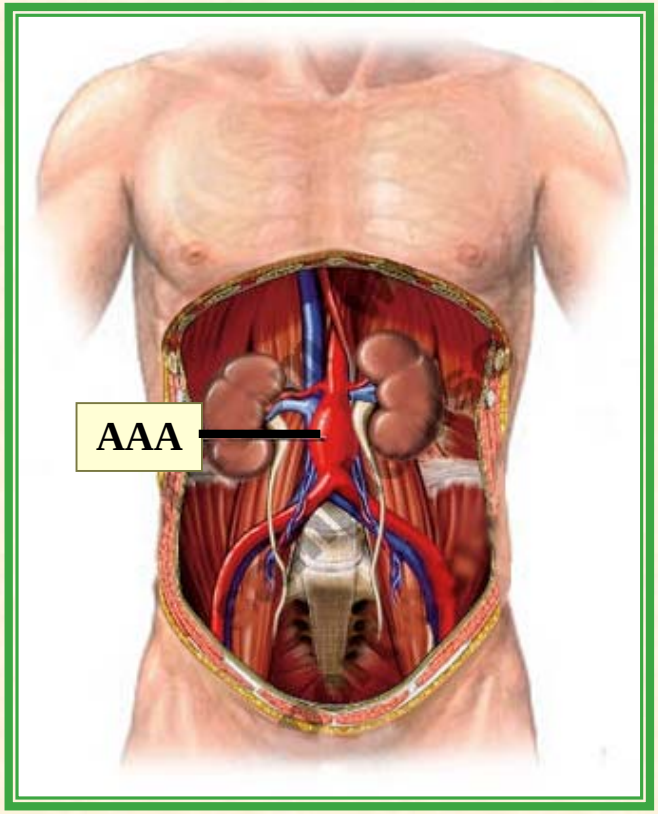
Computational Sciences & Engineering

Abdominal Aortic Aneurysm

- **An abdominal aortic aneurysm (AAA) is a disease where the abdominal aorta loses its structural integrity and dilates in a balloon-like manner.**



Occurrence & Risk

- **Currently, there are an estimated 1.5-2 million people suffering from AAA.**
- **Without medical intervention, AAAs often continue to dilate and eventually rupture.**
- **AAA rupture causes severe internal bleeding, with recorded rupture rates approaching 90%.**
- **Because of rupture and complications from surgery, AAA is the 13th leading cause of death in the USA (~15,000 deaths annually)**

AAA rupture: mechanical failure

- **Biomechanically speaking, AAAs rupture when the stress in the aneurysmal wall exceeds the strength of the wall tissue.**
- **The strength of aneurysmal wall tissue has been reported as 65 N/cm².**
- **Clinically, diagnosing those AAAs approaching a wall stress of 65 N/cm² is not yet feasible.**

- **Surgical intervention usually considered necessary with a maximum diameter (as determined from CT) above 5 cm.**

Endovascular Repair of AAA

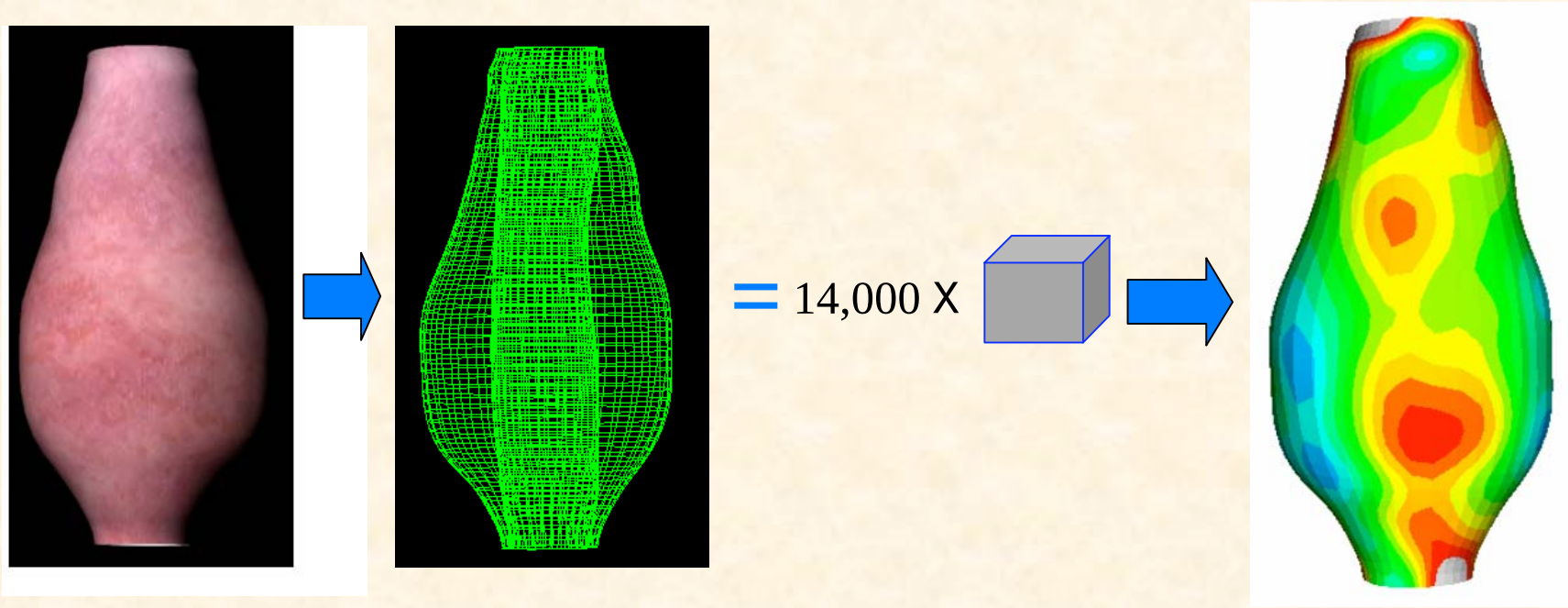
- **AAAs are most often treated with minimally invasive surgery to prevent rupture**
- **A stented vascular graft is implanted at the location of the aneurysm via catheterization from the femoral arteries**
- **Purpose is to exclude the aneurysm from circulation, which reduces the pressure load on the aneurysm wall**
- **Reducing the pressure load reduces the mechanical stress in the wall**
- **If successful, rupture risk is greatly reduced as the wall stress is prevented from exceeding the strength of the wall tissue**

Considerations

- **Surgery, both traditional and endovascular, are expensive**
- **Patient risks (complications, convalescence, etc.)**
- **Especially with endovascular repair, success is not guaranteed (endotension, endoleak, continued expansion)**
- **Is a 5 cm diameter an accurate surgical indicator?**
  - **AAA diameter (cm): <4, 4-5, 5-7, 7-10**
  - **Frequency of rupture: 8%, 25%, 50%, 64%**
  - **Some with smaller diameter rupture**
  - **Some with larger diameter don't rupture, and the risks of surgery are avoidable**
  - **Finite element analysis (FEA) is currently the leading potential alternative**

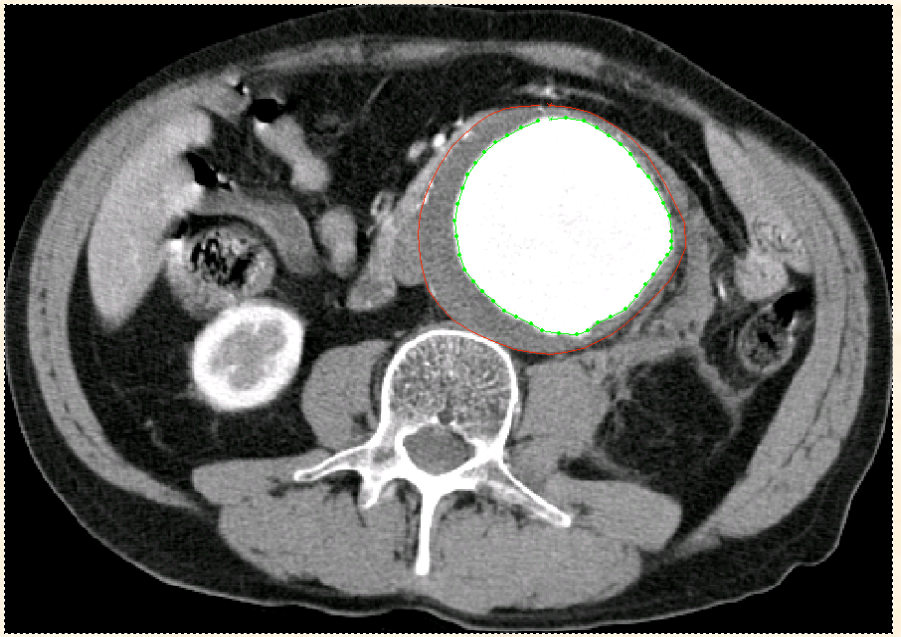
Finite Elements, an overview

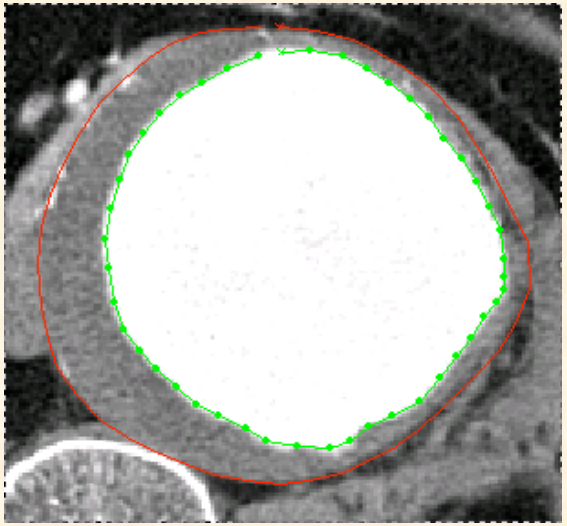
- **Conducting stress analyses of simple, regular objects is relatively simple**
- **Once geometries become irregular, analyzing stress by traditional methods becomes unpractical**



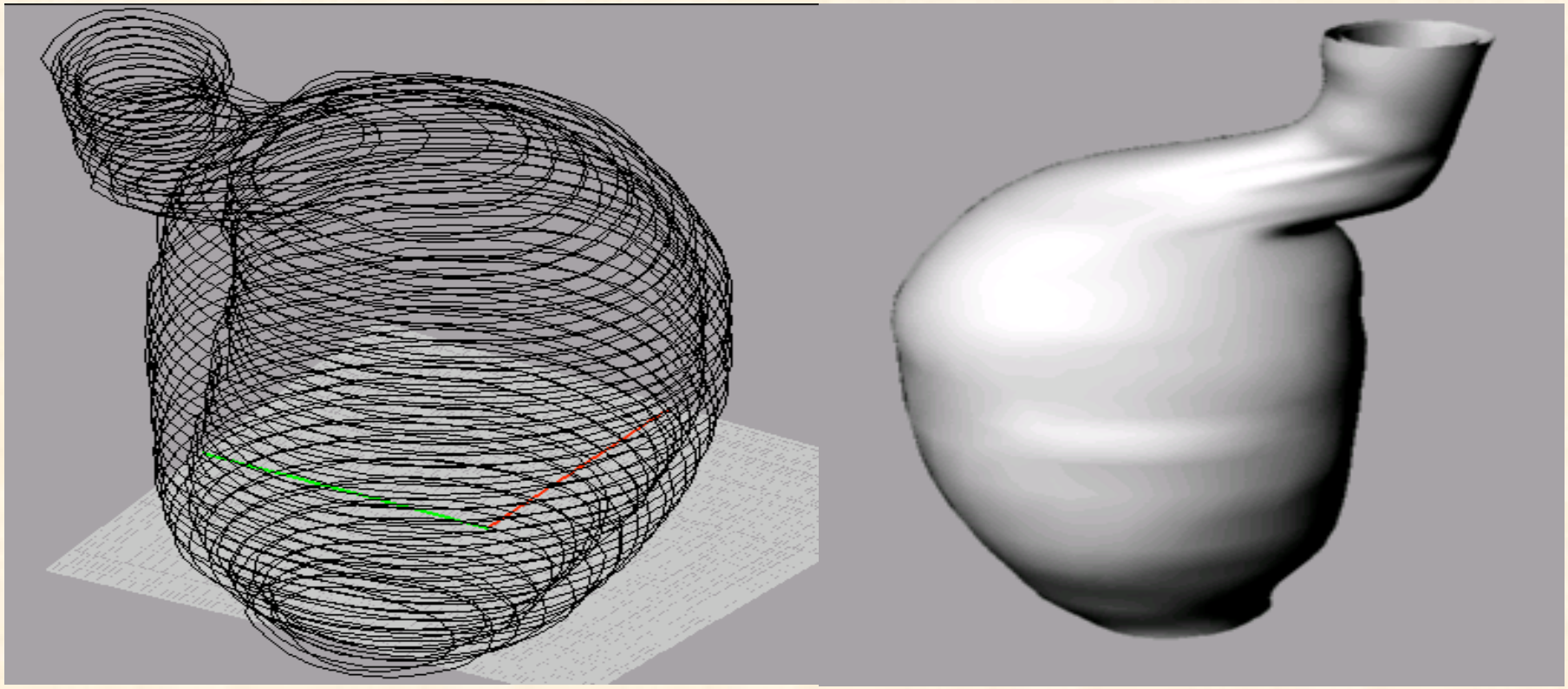
Create contours from CT scans

- **CT slices at 3 mm increments segmented**
- **AAA consists of 3 primary sections: wall, thrombus, and lumen**
- **Model consisted of two contours per slice: an outer wall and an inner luminal wall**



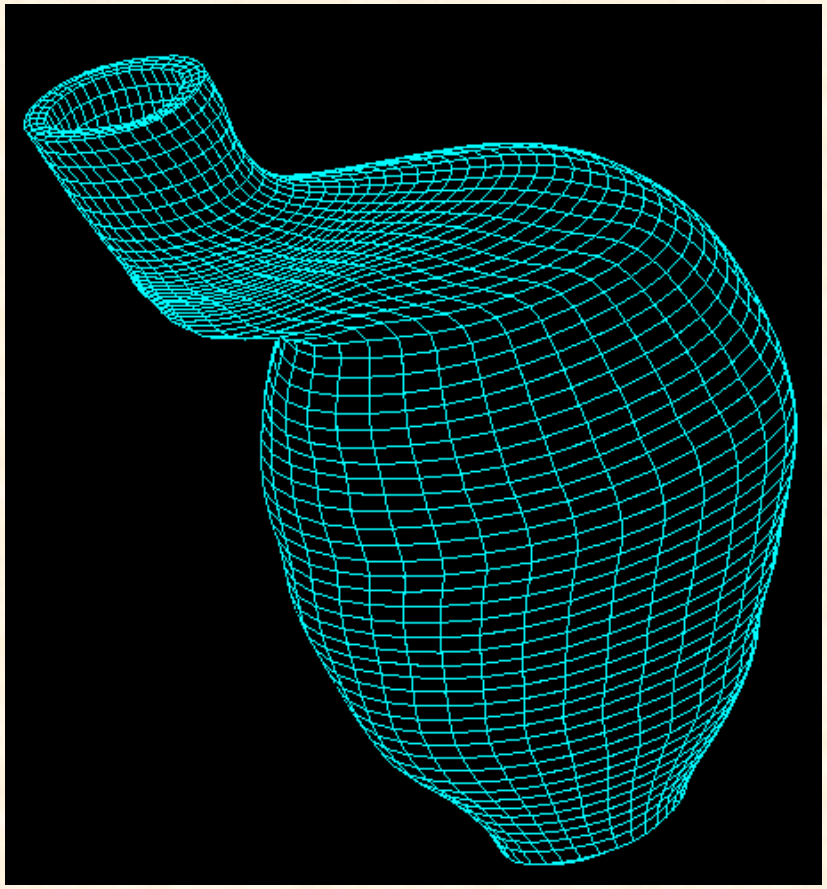


Surface the contours



- **Surfaces generated, creating the lumen and AAA wall**
- **Smoothing functions performed on both curves and surface**

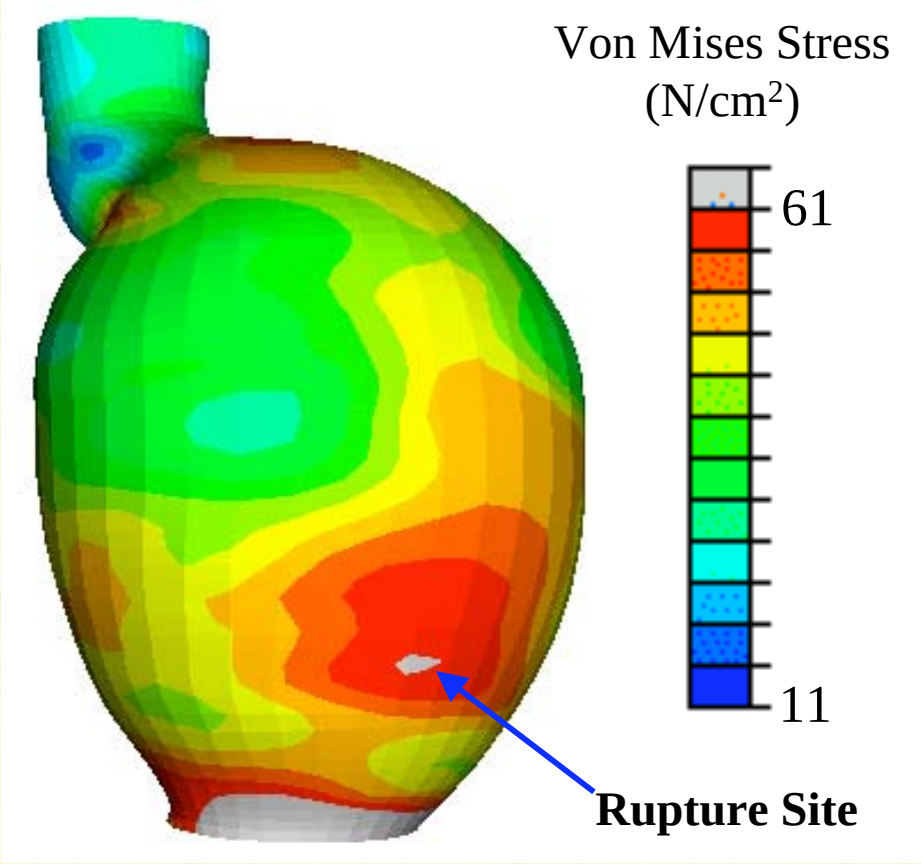
Mesh the geometry



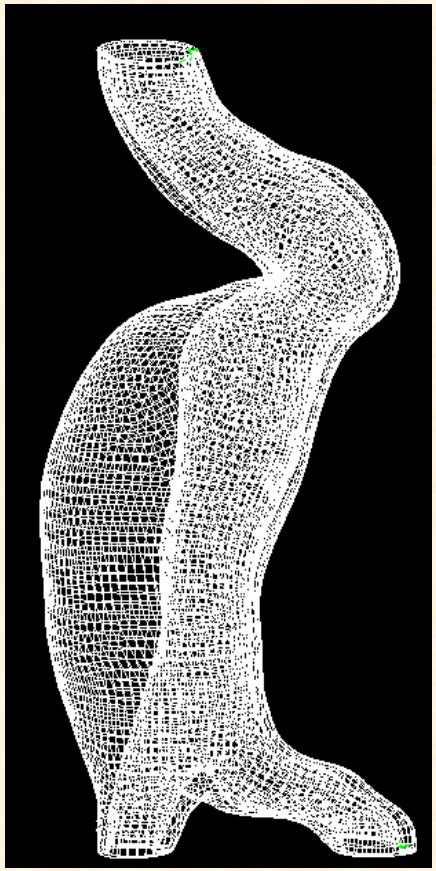
- **AAA geometry model meshed with finite elements**

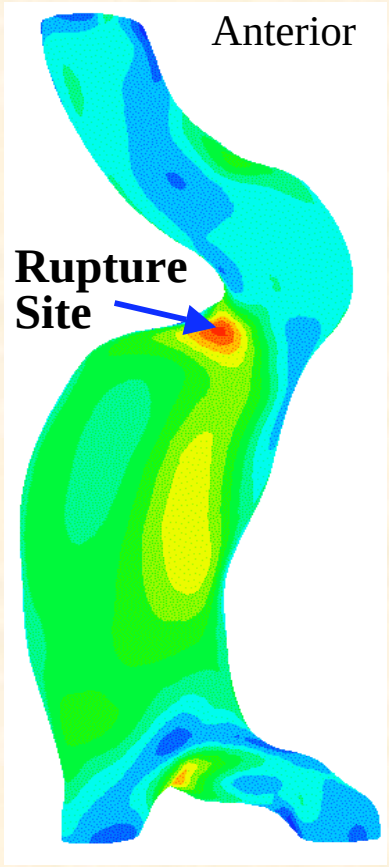
AAA Rupture Site Predicted

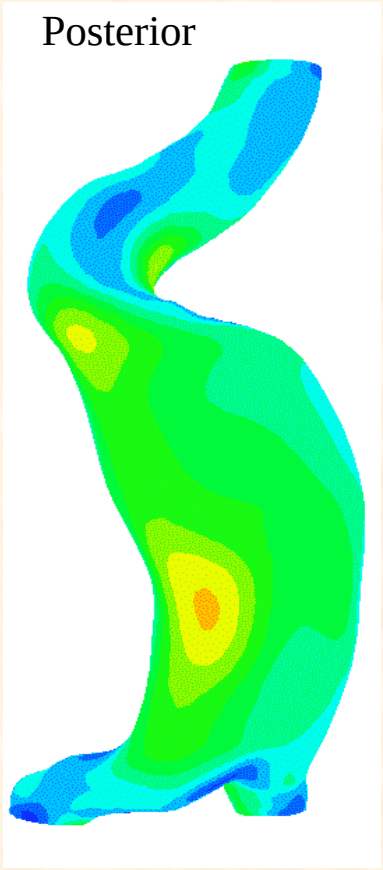
- **Numerical simulations give wall mechanical stress distribution**
- **Computational stress analysis correctly predicted rupture site**



Predicting AAA Rupture 2 Days After CT Scan

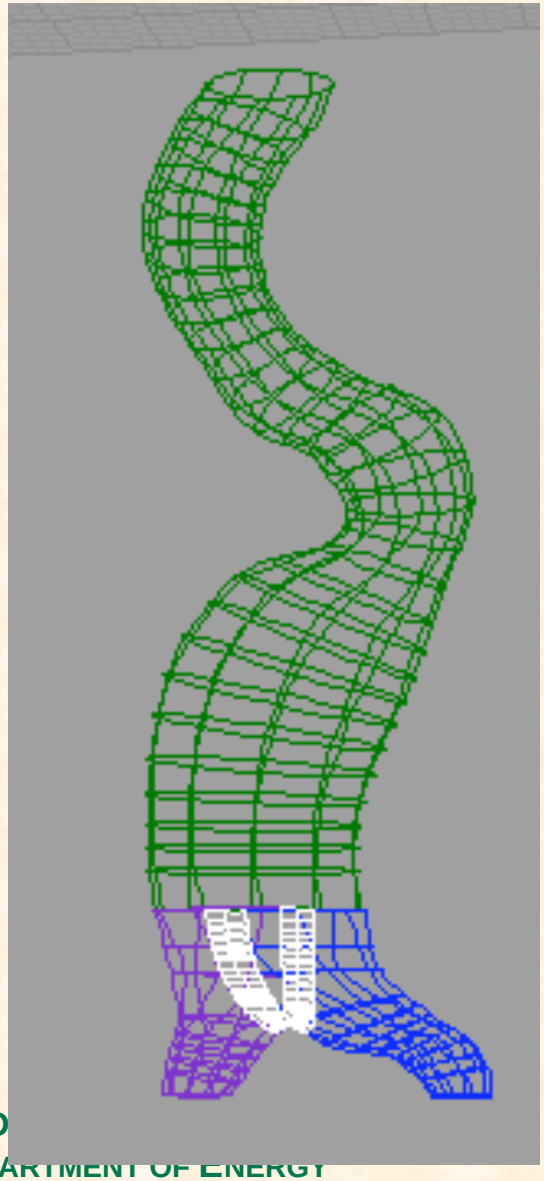


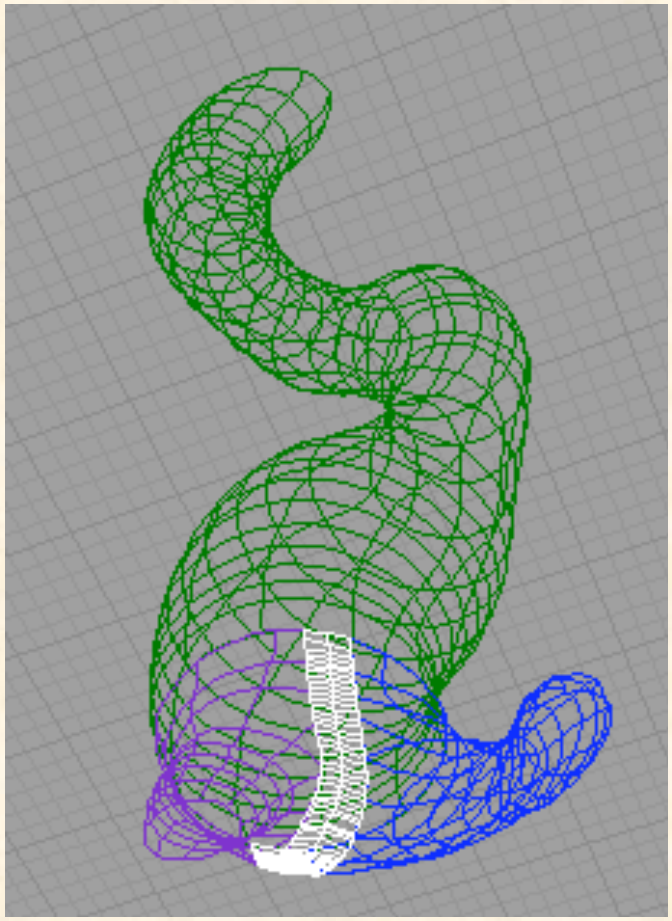




- **CT scan obtained 48 hours prior to AAA rupture**
- **Computational stress analysis correctly predicted rupture site**

Bifurcated AAA



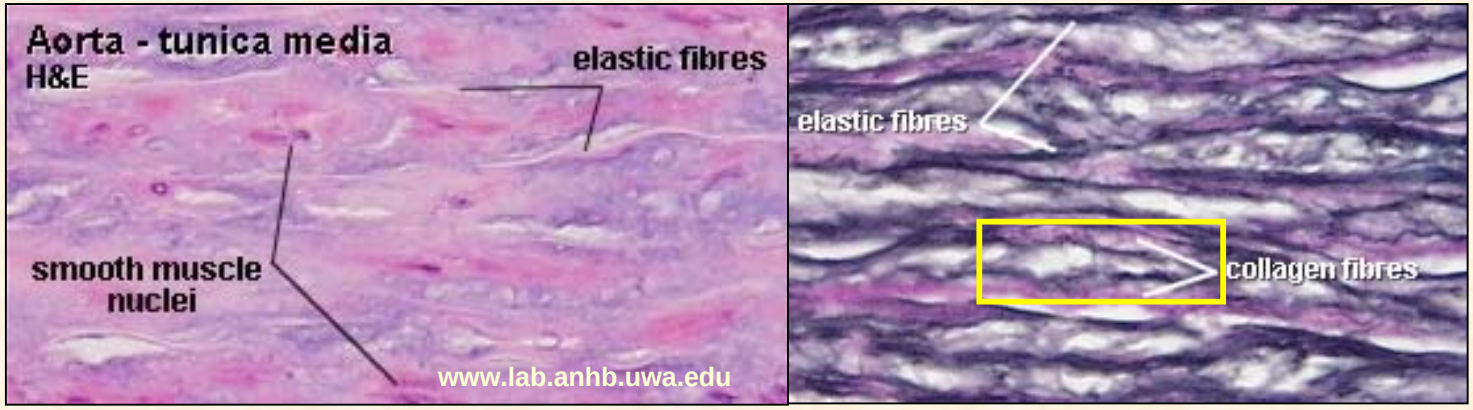


- **Bifurcated AAA model is very difficult to build**

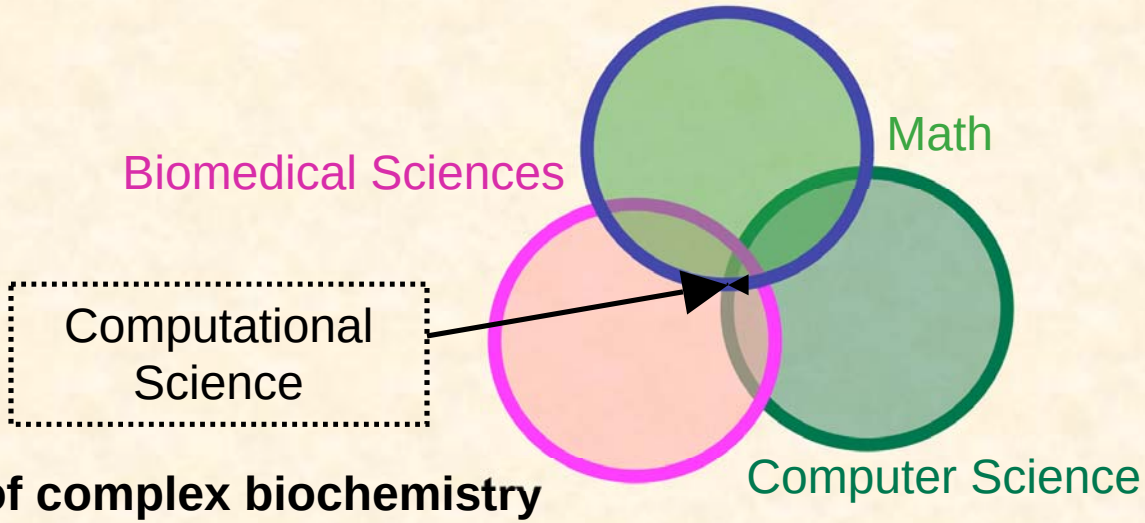
Aneurysm Development

- **Arterial walls composed of proteins**
  - Elastin for elasticity
  - Collagen for strength
- **Matrix metalloproteinases breakdown collagen & elastin**
  - Complex interactions involving up to **25 MMPs**
  - **MMP-2** & **MMP-9** most important
- **Inhibitors block proteinases**
  - **TIMP** – Tissue Inhibitor Metalloproteinase
- **Imbalance between proteinases & inhibitors**
  - Elastin degradation – artery balloons
  - Collagen degradation – artery ruptures
- **How is this balance regulated?**

Aorta Histology

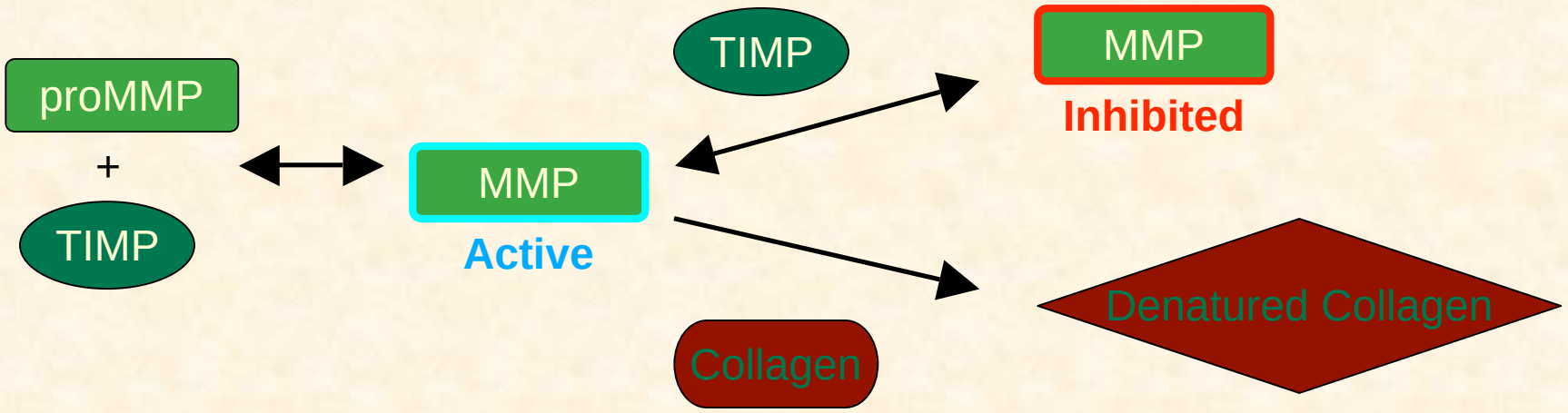


Approach



- **Develop math model of complex biochemistry**
  - Collagen type IV proteolysis
  - MMP-2 & MMP-9 kinetics
  - Reaction rates from:
    - Literature
    - Experiments (**UTMCK**)
- **Model developed by:**
  - Separate studies of individual reactions
  - In vitro controlled conditions
- **Validate model**
  - Simulate integrated system behavior
  - Design experimental procedures
  - Compare experimental results to math model predictions
- **Update model**

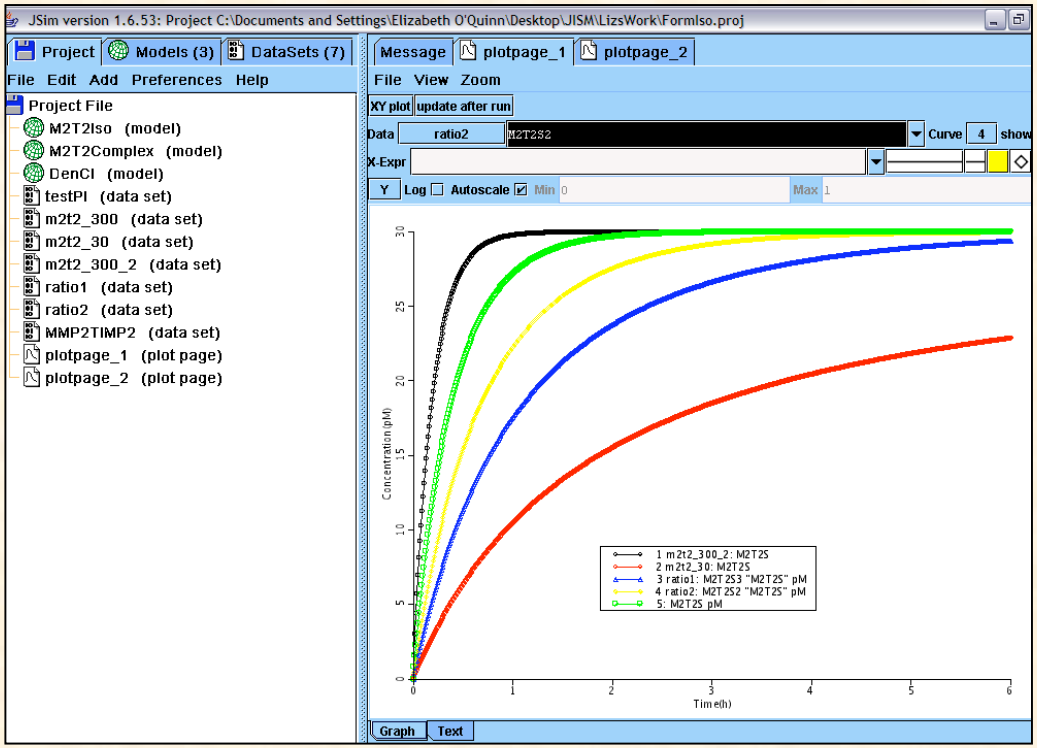
Matrix Metalloproteinase Pathways



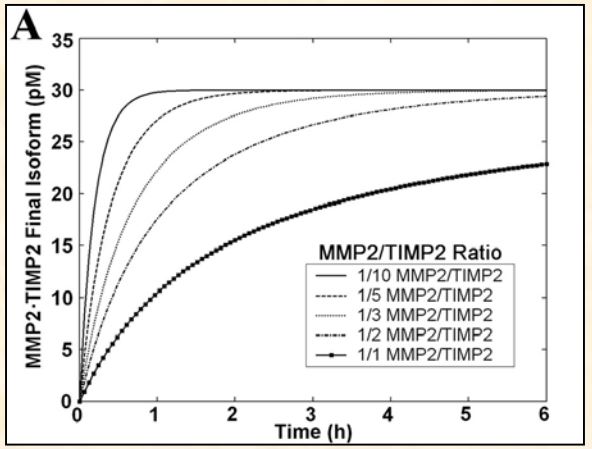
Verification of JSim Implementation

Behavior of MMP2/TIMP2 Isoforms

- Initial concentration of MMP2 while the TIMP2 concentration varies
- With ratios 1/10, 1/5,1/3, 1/2, 1/1 of MMP-2/TIMP-2



JSim Model

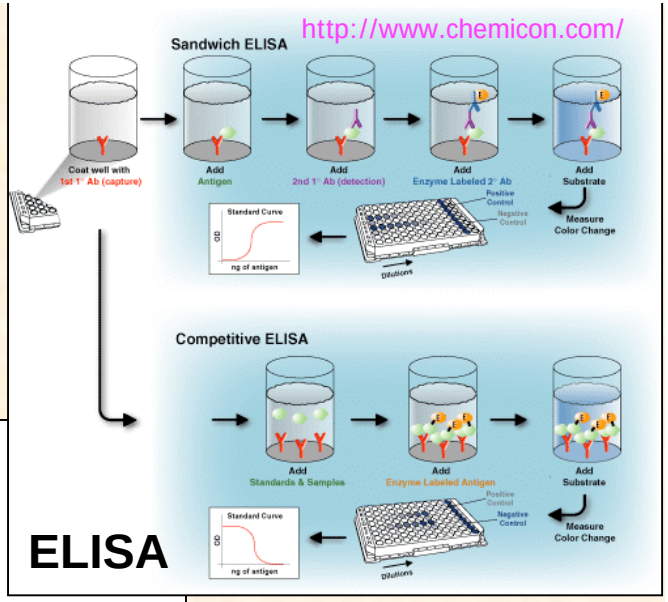


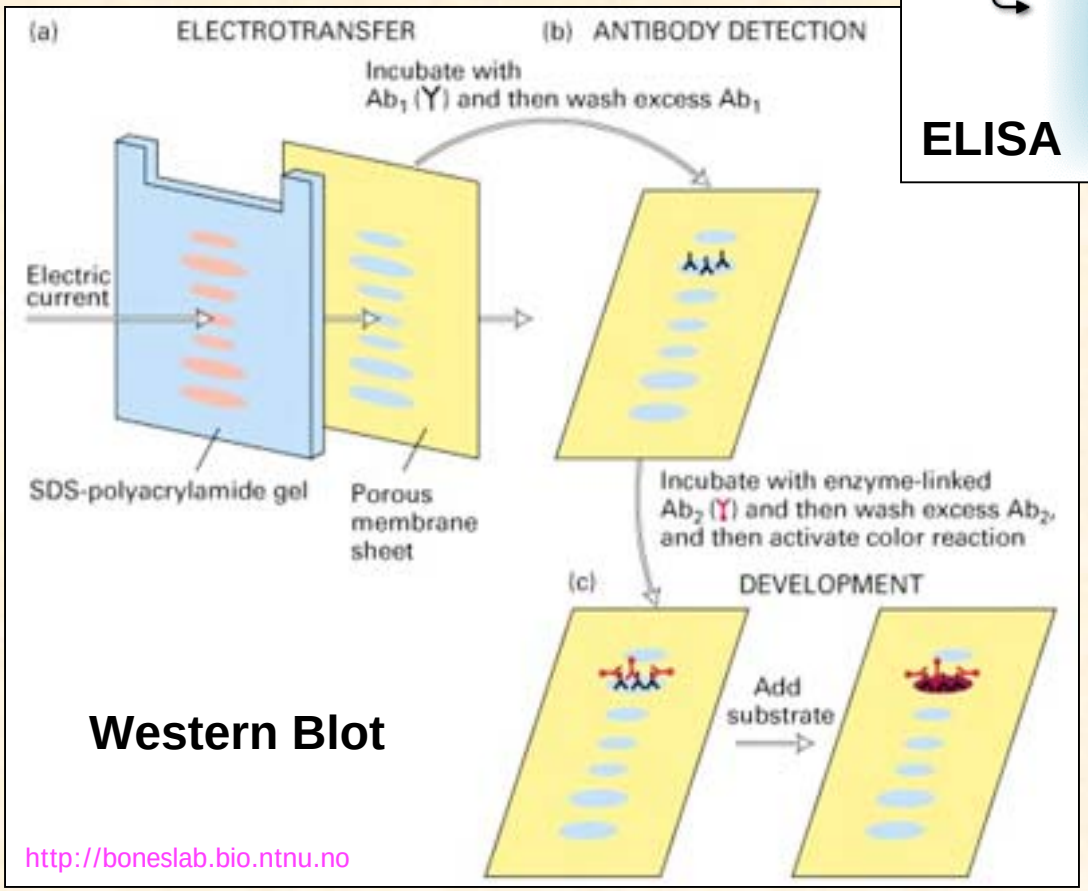
MatLab Model

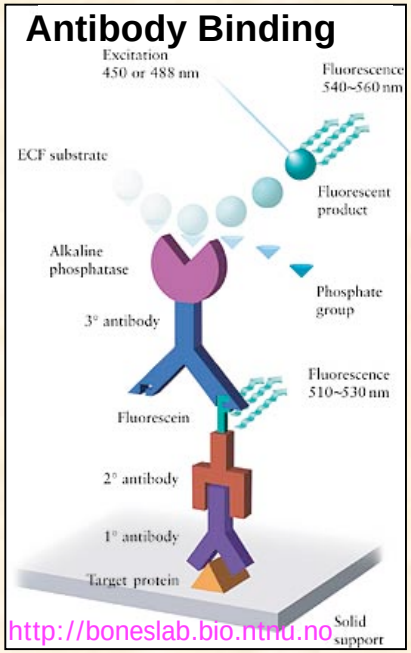
Karagiannis ED, Popel AS (2004)

Reaction Rates

- **Several Techniques**
  - ELISA, Western Blot, & HPLC
  - Rate Analysis Optimization
- **Incorporate measured rates into JSim model**







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EXPANDING THE FRONTIERS OF MEDICINE.

What do mentors look for?

- **Some only want students with best grades from best schools.**
- **Some want students from schools with less opportunities for research experiences.**

- **Student with the following qualities:**
  - **Passionate about learning & research**
  - **Can teach themselves**
  - **Can solve problems in innovative ways**

Resumes & Applications

- **Summary/Objective –**
  - **SELL YOURSELF !!!**
  - Highlight your most important relevant skill(s) and experience(s).
  - For student internships, mention future plans like attending medical or graduate school.
  - After reading the Objective and Summary sections, the reader should be left with a good impression of what type of work you want to do now and in the future and why you are the person they should hire. **All other sections just provide more data to back this up!**

- **Education**
  - List school, major, minor, graduation date.
  - List overall GPA, also GPA in sciences if significantly different.
  - List undergraduate thesis titles and short description.

Resumes & Applications

- **Experience**
  - Include all experiences that have a research, computing, or scientific development flavor including voluntary work and lab helper/assistant.
  - Include other experiences such as “Sales clerk at Home Depot” but write less about these.
  - If you learned a special skill in a non-research/scientific experience that might be applicable to research, mention that skill. For example, if you learned to do plumbing or electrical work while a sales clerk at Home Depot, this is a skill for the hands on building of things that could carry over to experimental laboratory research.

Resumes & Applications

- **Skills**
  - List computer skills (programming languages, software & hardware)
  - List experimental laboratory skills
  - List any other special skills you are especially good at (for example, writing research papers, independent problem solving).
- **Courses**
  - List all Math, Science, Computing, & Engineering courses all ready taken and that you will have taken by the time the position starts.
  - If you know a good bit about the position you are applying for, you can mention only those courses that are applicable.
  - If this is your second undergraduate degree, list courses from your first degree also.
  - A class list is less important if you have a lot of previous relevant job experiences.