RAMS as a Gateway for Computational Modeling with Application to Medicine

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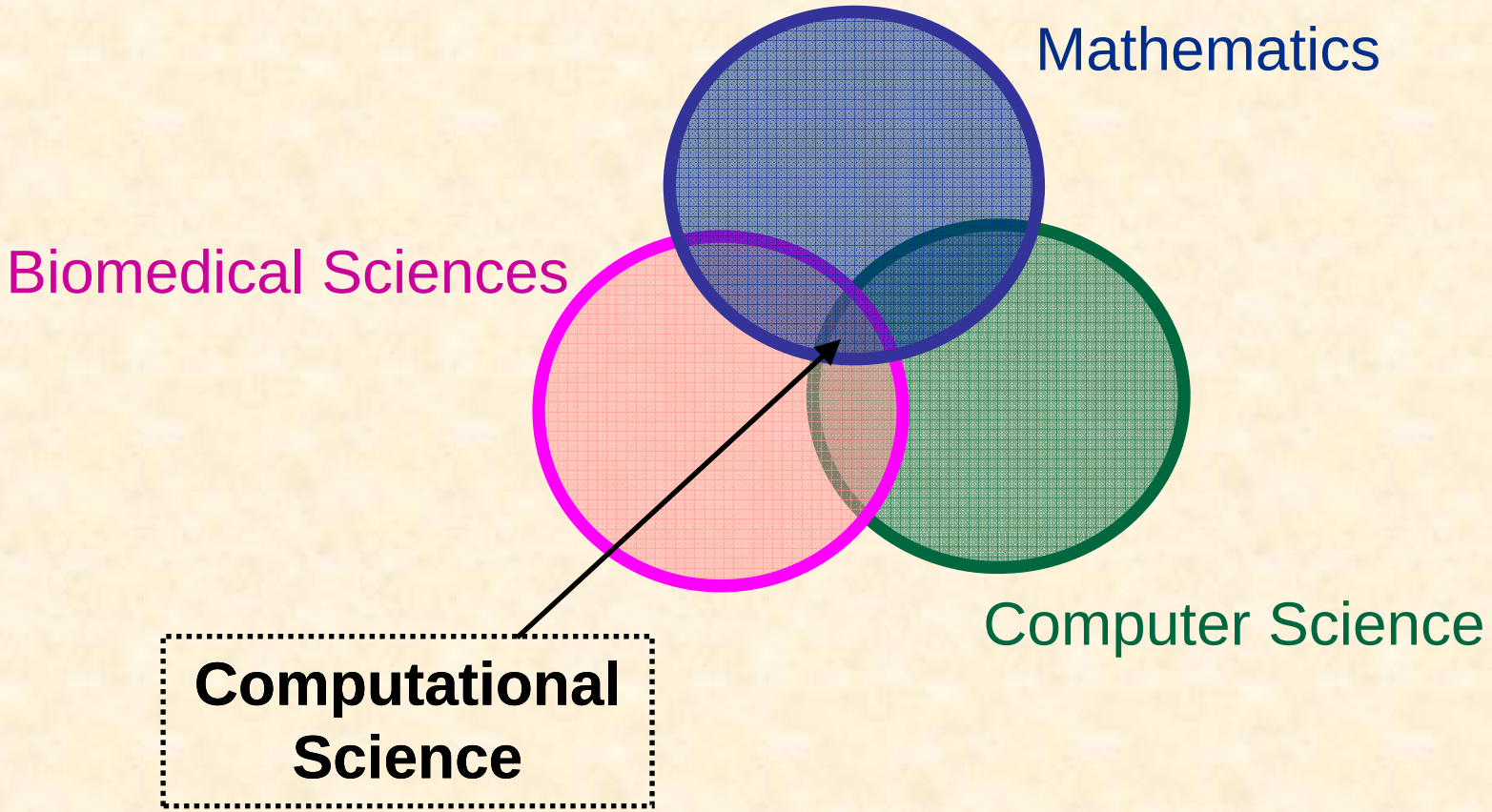
Presented to
Review Committee
Research Alliance in Math and Science

Oak Ridge, Tennessee
December 3, 2008

Interdisciplinary Research



3 Levels of Enzyme Regulation

1. **Gene Transcription**
   - **Marfan's Syndrome**
   - **Kawasaki Disease**

   - Symptoms appear at early ages

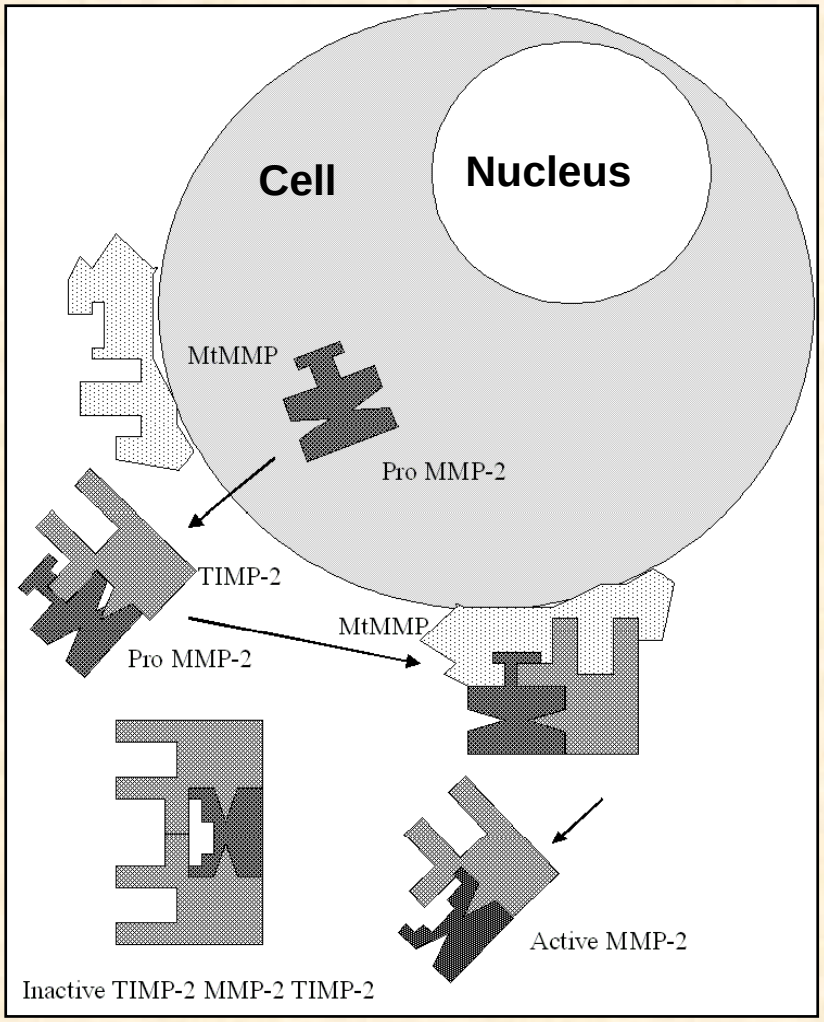
2. **Activation of latent form of enzyme** (pro-MMP/zymogen)

3. **Inactivation by specific endogenous inhibitors** (tissue inhibitor MMP (TIMP))

Focus primarily on #'s 2 & 3

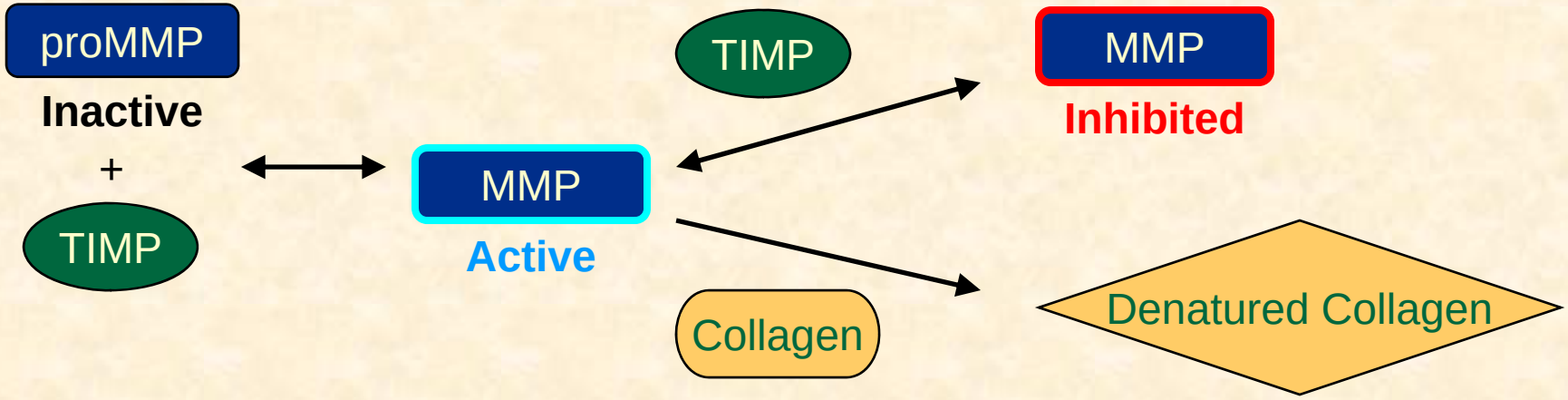
All affected by environmental factors

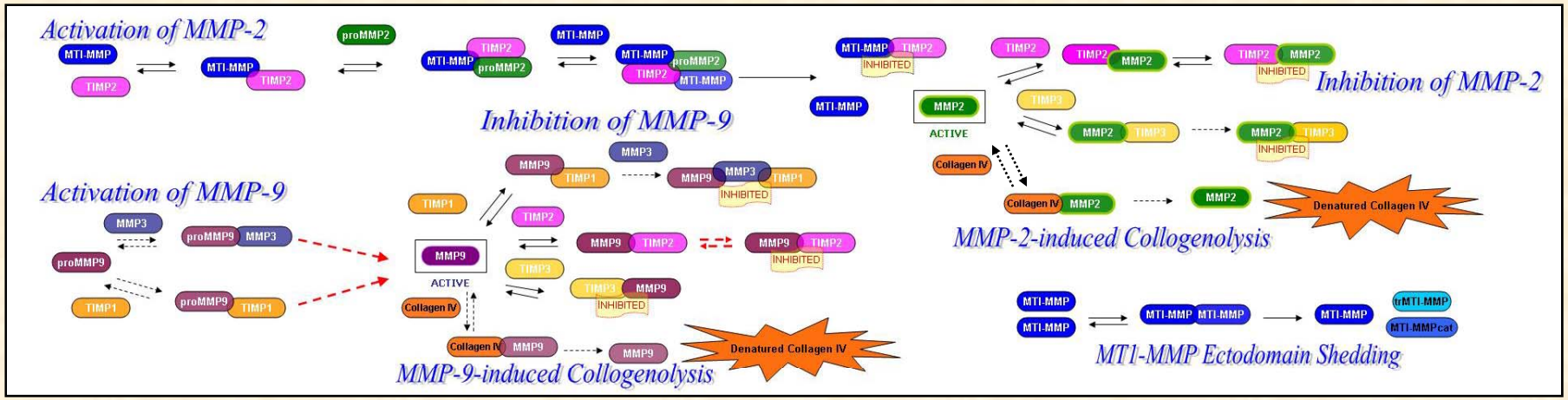
- **Smoking**
- **Diet**



http://herkules.oulu.fi/issn03553221/

Matrix Metalloproteinase Pathways





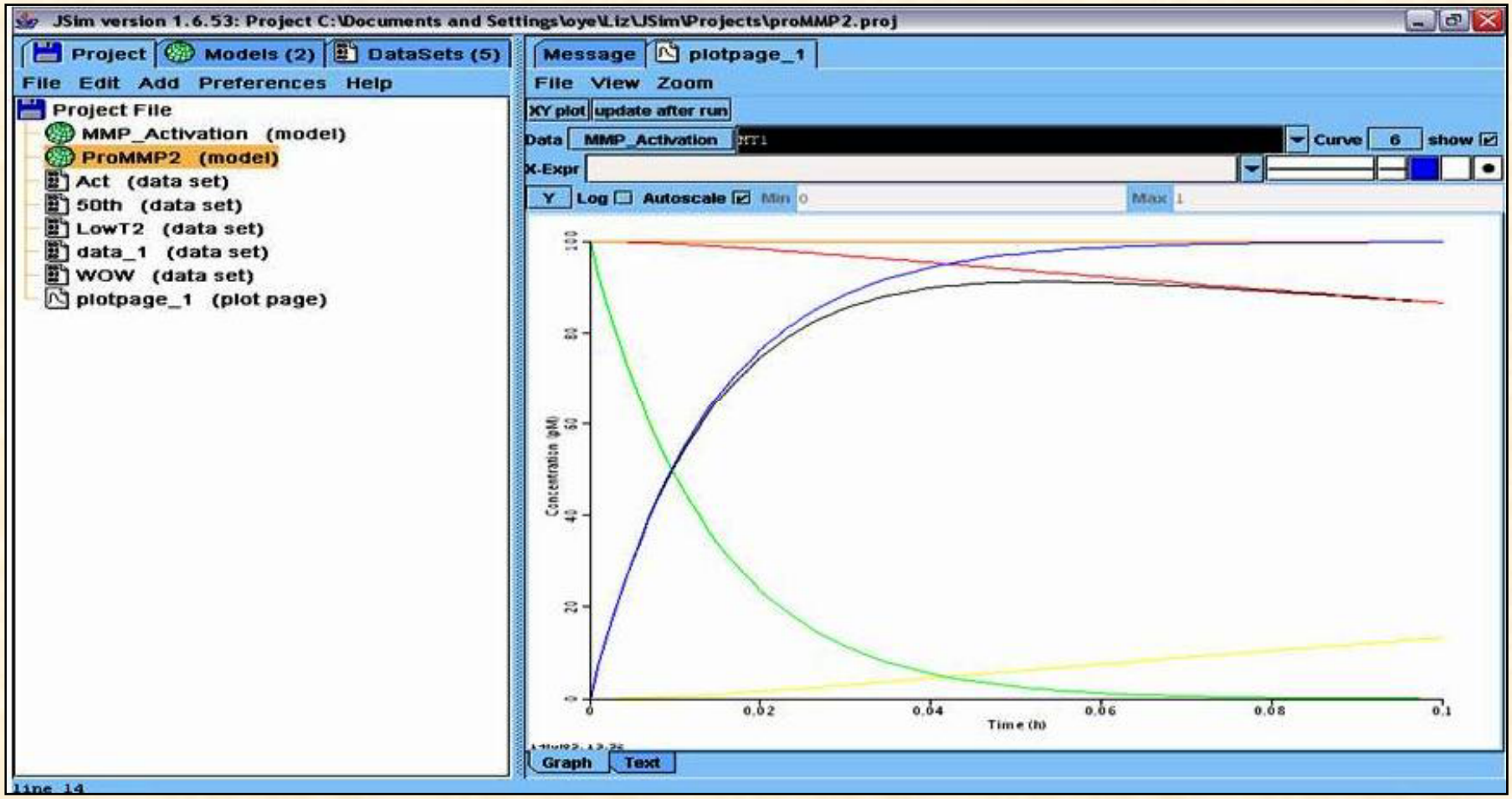
Model Implementation

$$\mathrm{E} + \mathrm{S} \underset{k_2}{\overset{k_1}{\rightleftharpoons}} \mathrm{ES} \underset{k4}{\overset{k3}{\rightleftharpoons}} \mathrm{E} + \mathrm{P}$$

Model Assumptions

1. Reaction occurs in a well mixed system
2. Temperature is constant
3. Volume of the system is constant
   - allows use of concentrations in rate laws

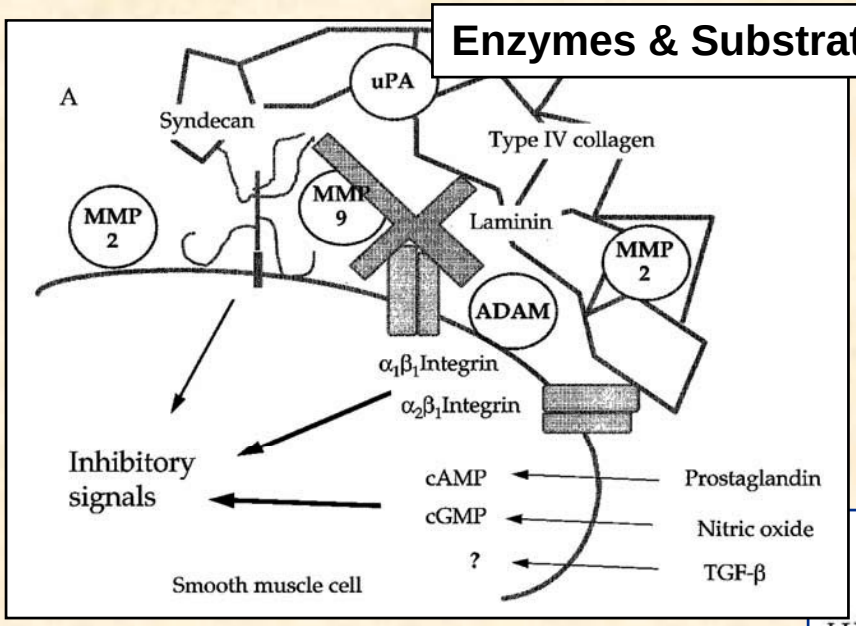
JSim



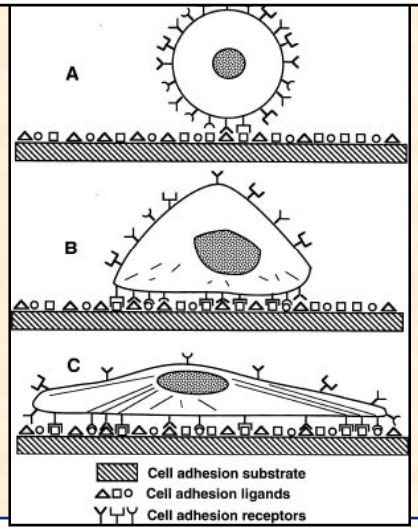
"JSim is a software environment for scientific modeling that provides tools for development of models, for their run-time control, and for analysis of their behavior."
(*National Simulation Resource, Univ. of Washington*)

Problem Definition

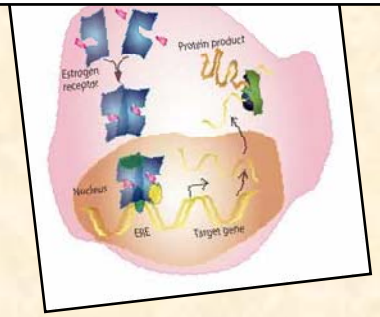
Enzymes & Substrates

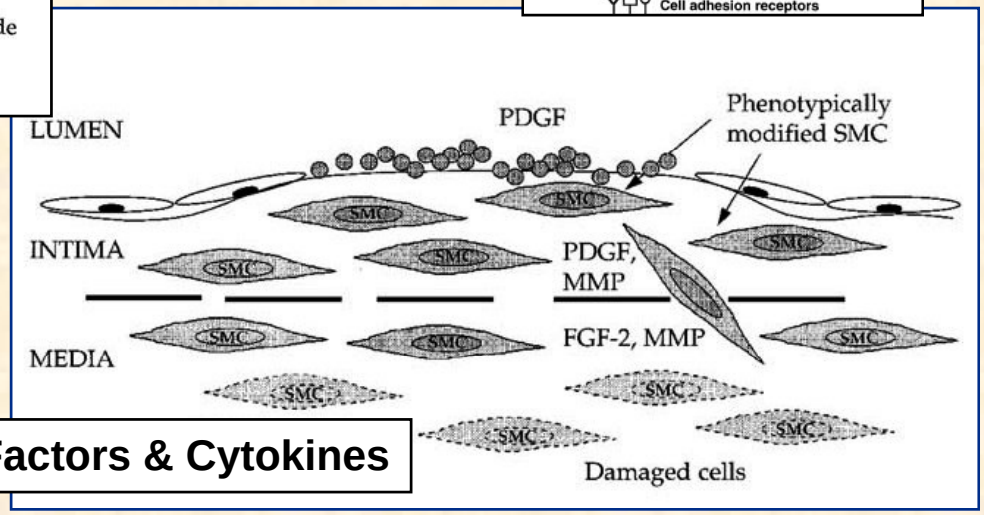


Receptors & Cell Adhesion Molecules



Estrogen & Progesterone



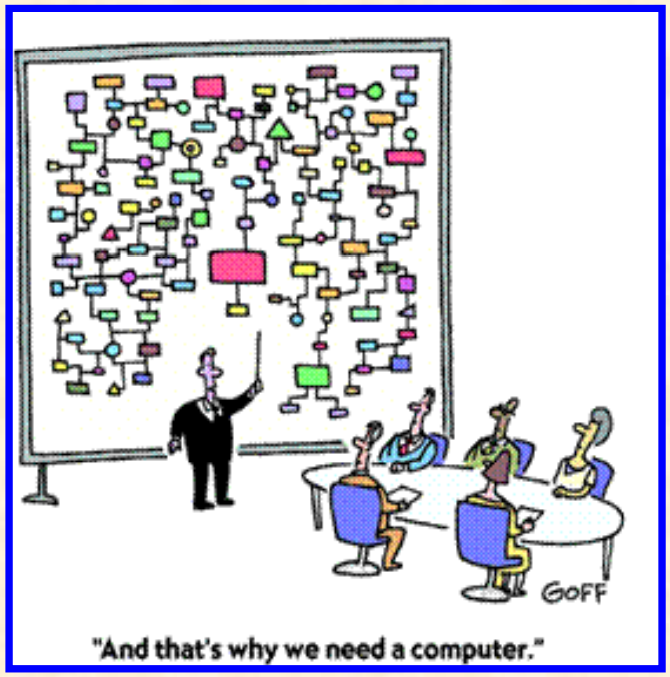


Growth Factors & Cytokines

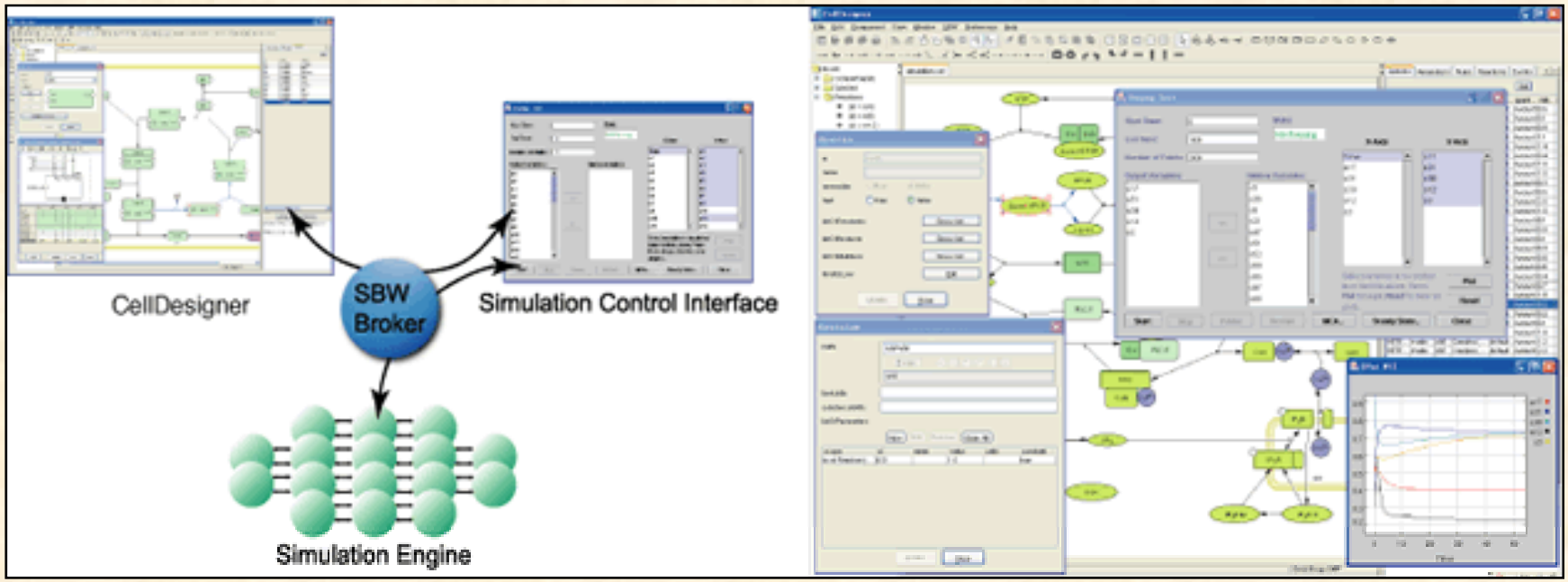
" Intimal hyperplasia, the obstacle in bypass grafts"

Abstraction of Disease Mechanism

- **Obtain information from published literature on what disease processes responsible**
- **Layout what pathways and experimentation fit within the defined reactive system**
- **Document relationships of each component for future reference by implementing pathways with software**

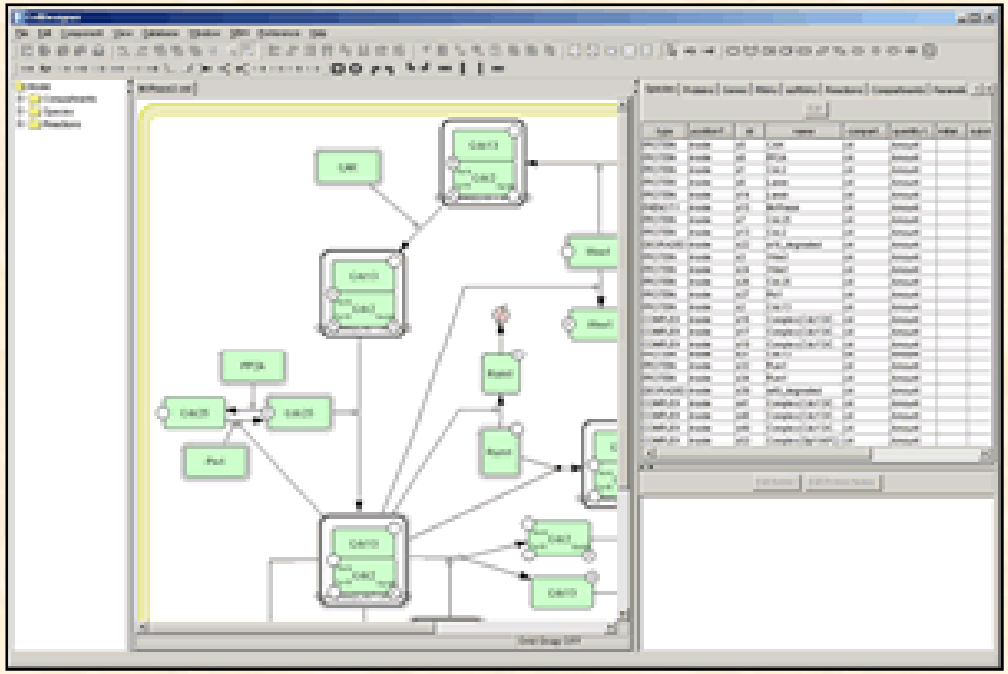


CellDesigner



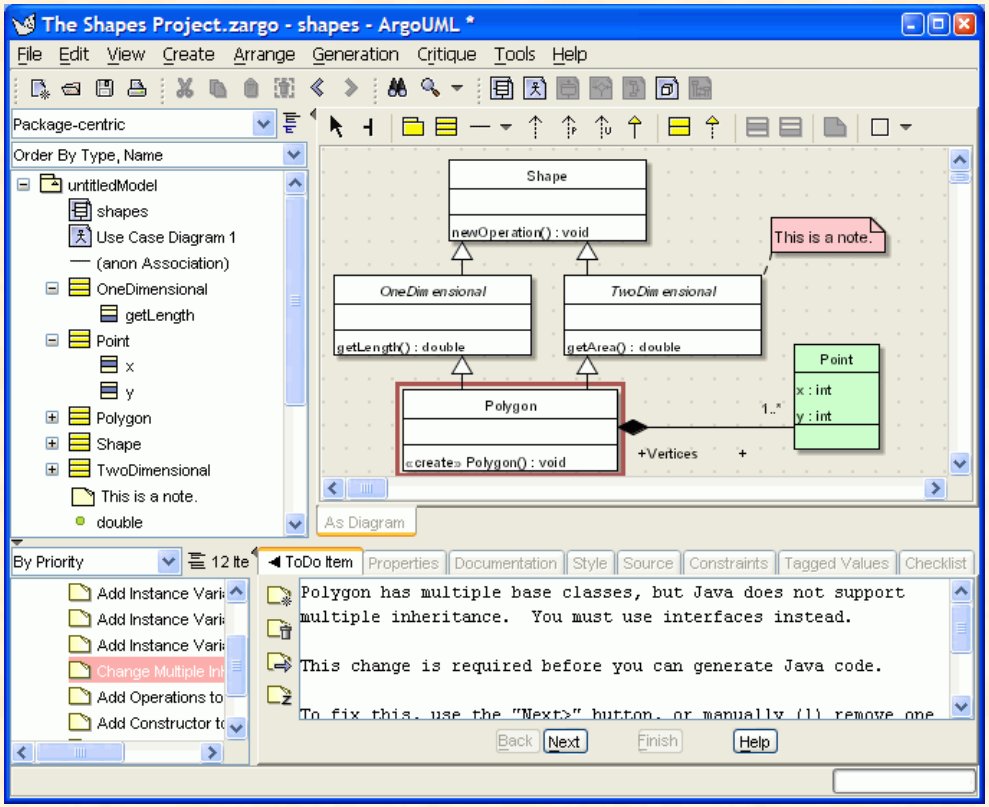
- **Tool used to model biochemical and gene-regulatory pathways involved in IH reactive system**
- **Pathways represented with standard graphical notation**

CellDesigner



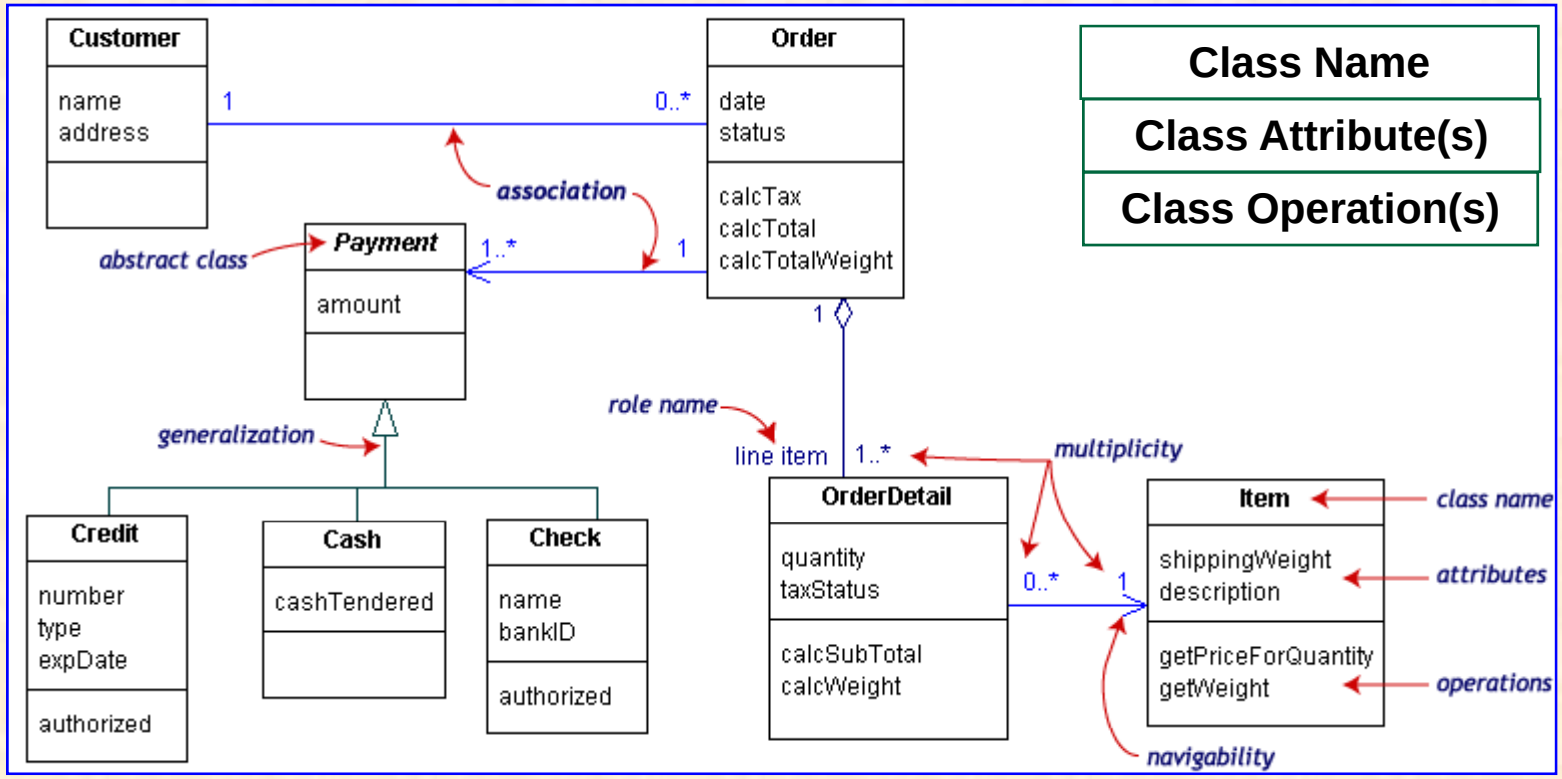
- **Developed by the Systems Biology Institute, Japan**
- **Open source software package**
- **Stores pathway information in Systems Biology Markup Language (SBML) – XML-like**
- **Compliant with Systems Biology Workbench (SBW)**

ArgoUML



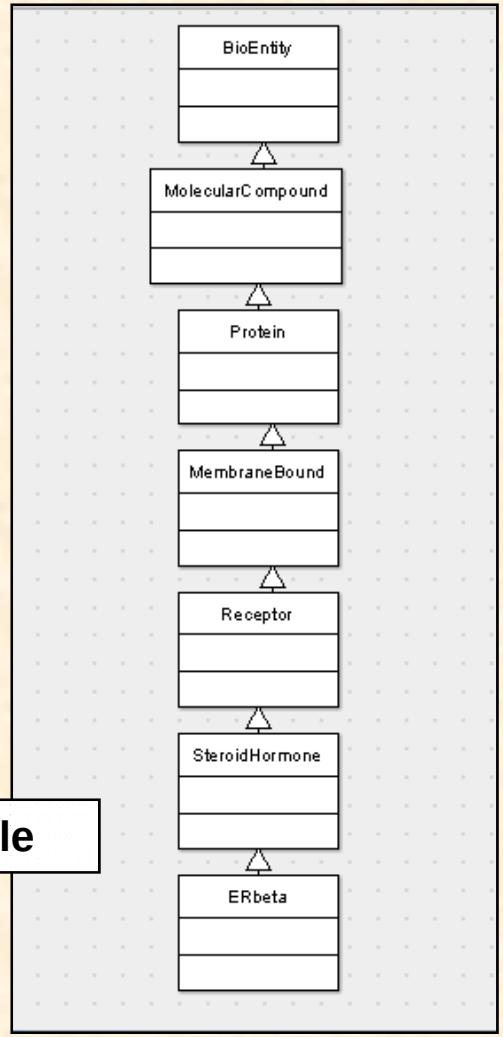
- **Developed as an open source project**
- **Java-based Universal Modeling Language (UML) tool**
- **Tool used to diagrammatically model object-oriented system design with agent-based formalisms**

Classic Class Diagram for Order



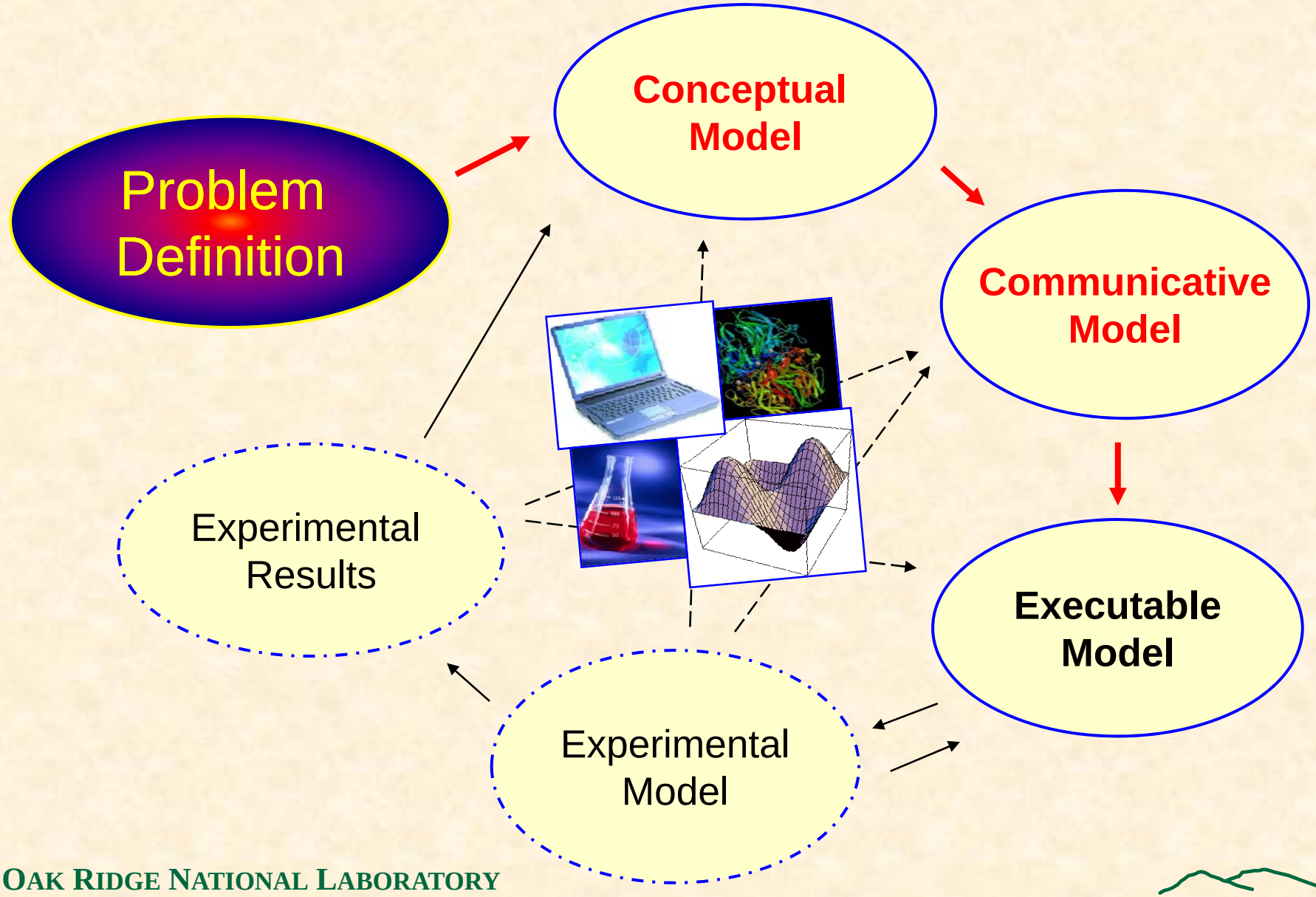
Class Diagram Example: ERbeta

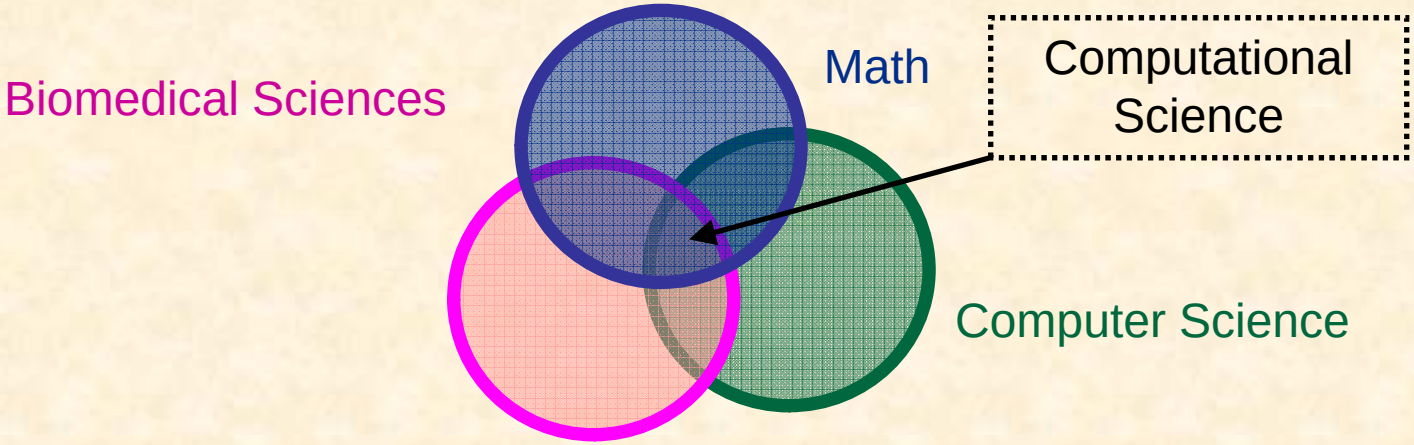
- **Utilized to ontologically define the biological entities, interactions, and processes significant in cellular remodeling**
- **Object-oriented classification**



General Example

Model Development

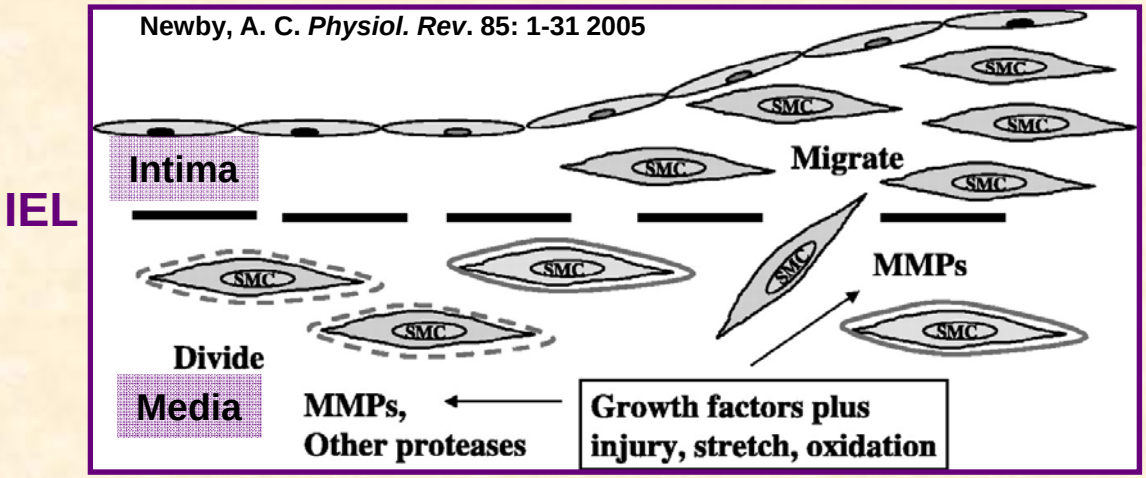


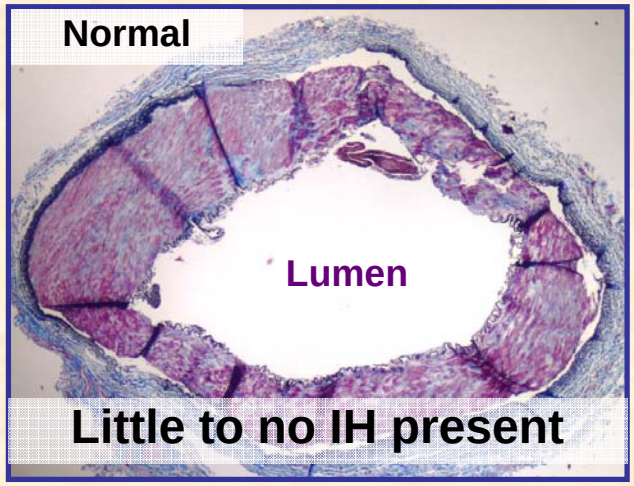

Biomedical Sciences
Math
Computational Science
Computer Science

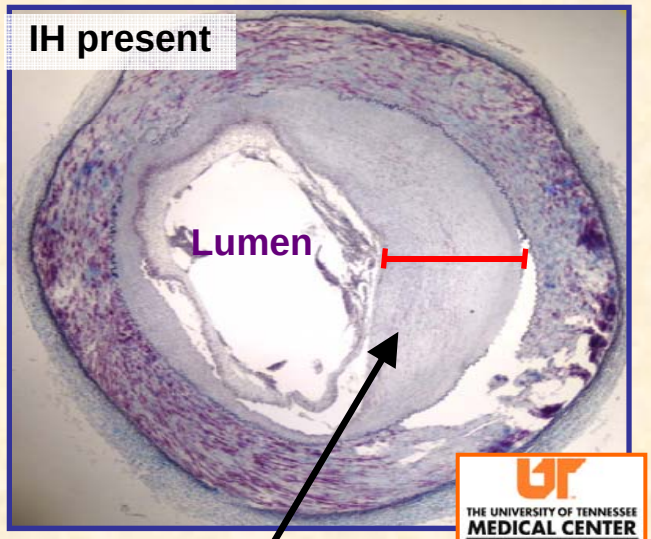
Questions?

Biological Problem

Intimal Hyperplasia (IH) - Thickening of intima which restricts blood flow in an artery





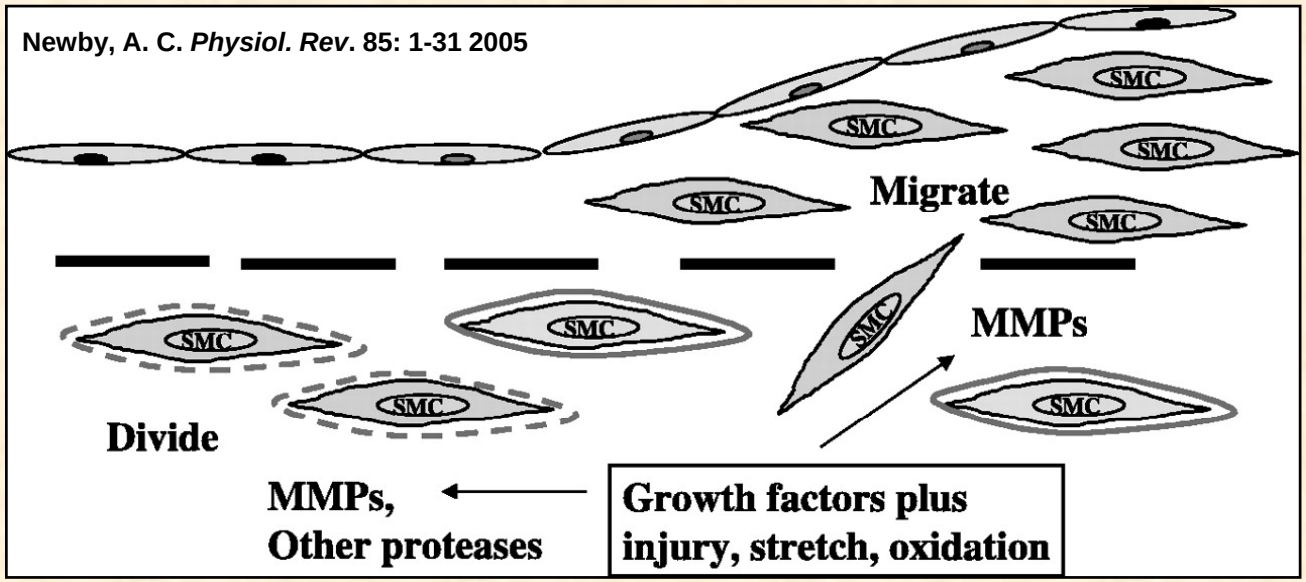


- Injury to EC causes release of matrix metalloproteinases (MMPs) which degrade collagen
- Results in abnormal proliferation & migration of vascular smooth muscle cells (SMC)
- SMCs move through the IEL and invade intima attracted by chemoattractants such as growth factors
- Lumen is narrowed as SMCs accumulate

Region of proliferation of SMCs resulting in intimal hyperplasia

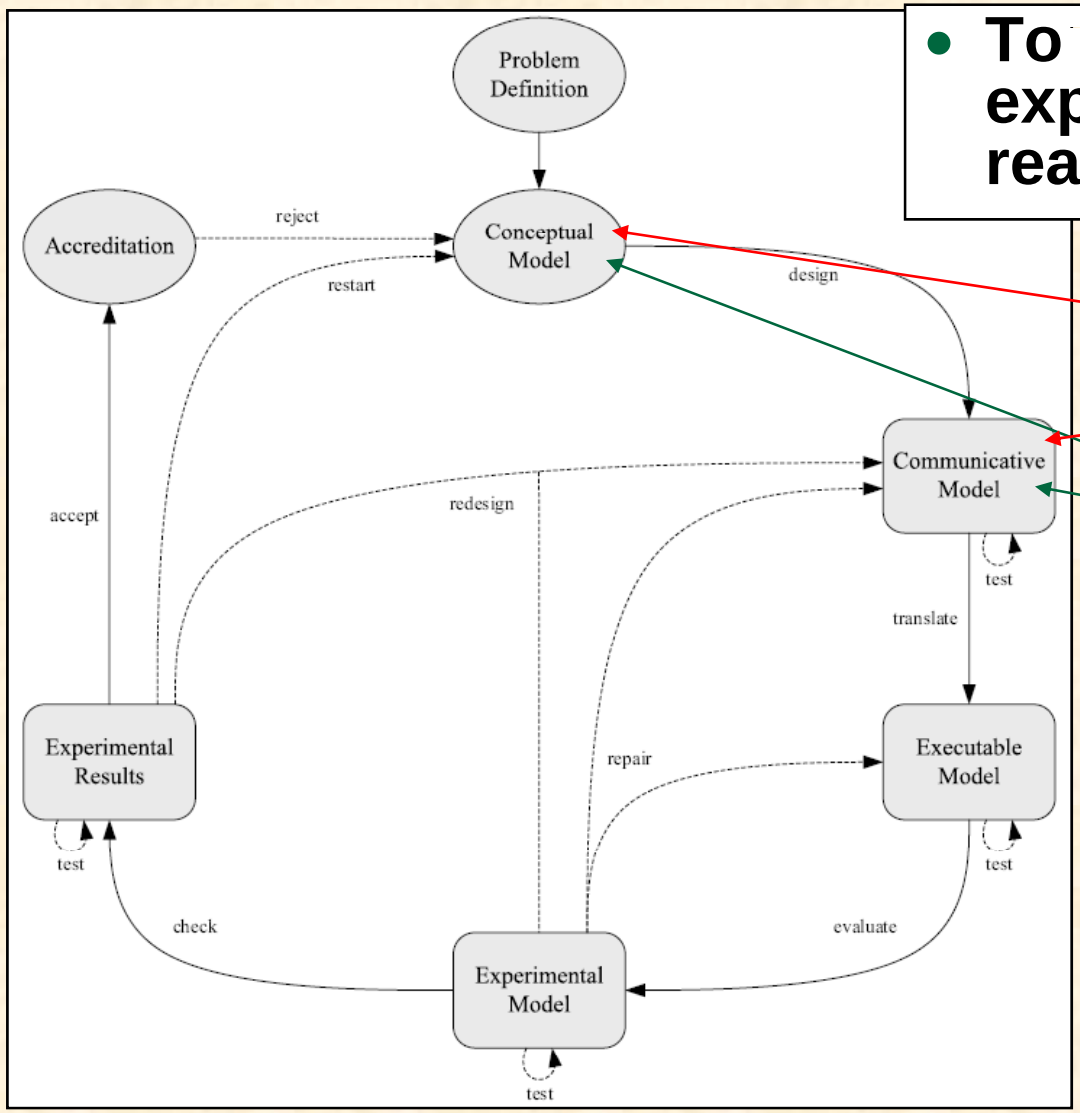
Intimal Hyperplasia - Thickening of intima which restricts blood flow in an artery

- Universal response of vessels to injury
  - Balloon angioplasty
  - Arterial bypass grafts
  - Atherosclerosis
- Abnormal growth of vascular smooth muscle cells (SMC)



❖ Summary of the effects of MMPs on vascular SMC basement membranes, migration, and proliferation

Model Implementation – Abstraction

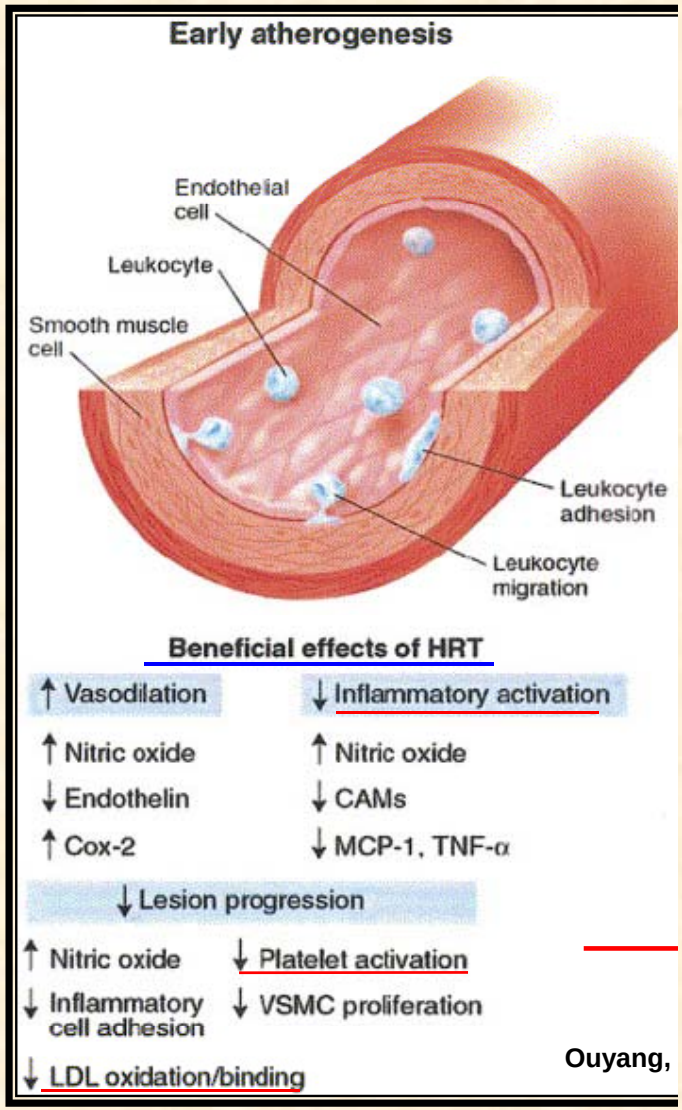


- **To test the hypotheses explaining the biochemical reaction network**

ArgoUML

CellDesigner

Atherosclerosis and Hormone Replacement Therapy (HRT)



Ouyang,

Software as tools

Areas of Research

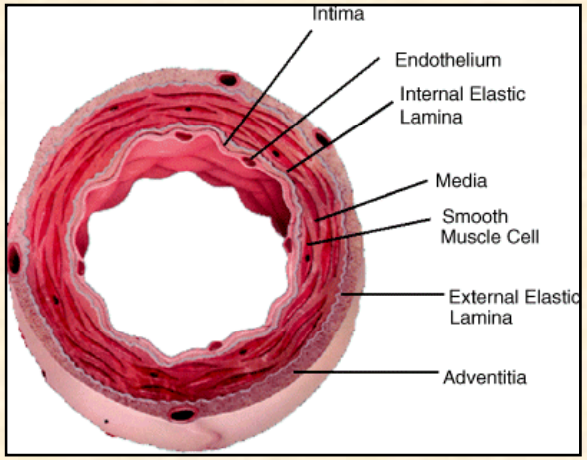
- **Lower level enzyme regulation**
- **Higher level molecular and cellular interactions and relationships**

Other RAMS THings

- **Workshops**
- **Seminars**
- **Poster Presentations**
- **Oral Presentations**
- **SC|05**

Restenosis

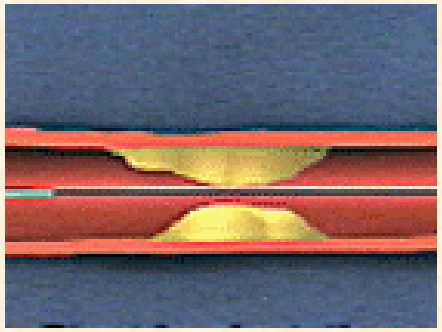
Davis, C. et al. Thrombosis and Haemostasis 1: 1699-1709 2003

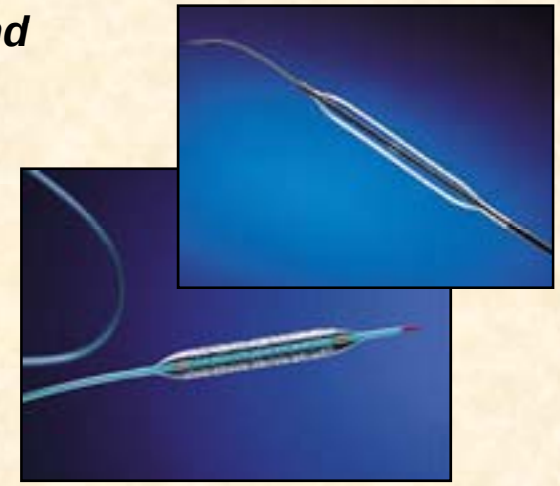


- **Restenosis – the reoccurrence of stenosis**
  - Hardening of an artery
  - One of biggest limitations in angioplasty and causes need for repeating procedure
  - Provoked by injury, inflammation, and stress
- **Occurs pathologically in:**
  - pulmonary hypertension, atherosclerosis, after angioplasty, in transplanted organs, and in vein grafts
- **A better understanding for better treatment**
  - ***"There are probably several mechanisms that lead to restenosis. An important one is the inflammatory response, which induces tissue proliferation around an angioplasty site." - Wikipedia***

Current treatments

- **Angioplasty**
  - Balloon
  - Stent (medicated)





Experimental Percautions

- **Quantitative techniques**

Intimal Hyperplasia (IH) Modeling

- **Model development**
- **Disease mechanisms**
- **Model implementation**
  - **CellDesigner: Diagram**
  - **ArgoUML: Class model**
- **Future research**

Future Research and Applications

What Next?

Created reactive system models of molecular and cellular interactions will be integrated into a mathematical model of vascular remodeling currently under development at ORNL

Why?

Kinetic modeling of biochemical and cellular interactions is an approach for understanding complex reactive systems which describe a disease's mechanism quantitatively

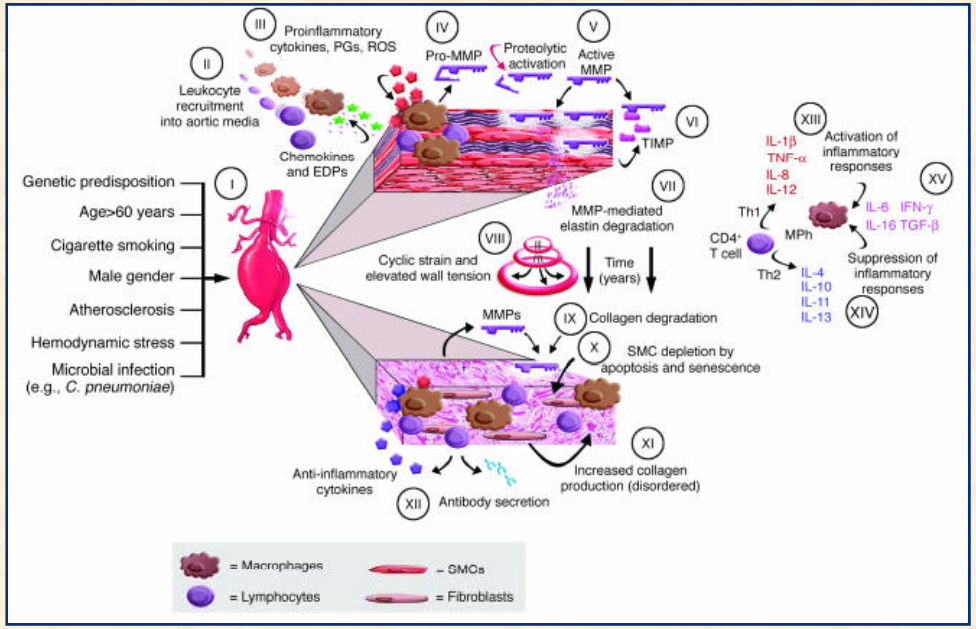
Applicable to Other Disease Mechanisms…

Expand model to study involvement in:

- ***Hormone replacement therapy*** promotes vascular health ← Current work!
- ***Arteriosclerosis***
- ***Aneurysm formation***
- Effects of ***smoking*** on collagen degradation
- ***Nitrous oxide*** – a vasodilator

Other applications:

- **Angiogenesis** in tumor formation
- Orthopedic diseases



J Clin Invest. 2004 July 15; 114(2): 168–171

Collaborations

ORNL

Kara Kruse, M.S.E., Richard Ward, Ph.D., and James Nutaro, Ph.D.

Computational Sciences and Engineering Division

Debbie McCoy and Sara Peak

Research Alliance in Math and Science Program

Clinical Vascular Research Laboratory

University of Tennessee Graduate School of Medicine, Knoxville:

Oscar Grandas, M.D., Michael Freeman, M.D., Mitchell Goldman, M.D.

Diedra Mountian, Ph.D., Stacy Kirkpatrick, M.S., Wendy Packan, Eva Bukovska

Acknowledgments

The Research Alliance in Math and Science program is sponsored by the Mathematical, Information, and Computational Sciences Division, Office of Advanced Scientific Computing Research, U.S. Department of Energy.

The work was performed at the Oak Ridge National Laboratory, which is managed by UT-Battelle, LLC under Contract No. De-AC05-00OR22725. This work has been authored by a contractor of the U.S. Government, accordingly, the U.S. Government retains a non-exclusive, royalty-free license to publish or reproduce the published form of this contribution, or allow others to do so, for U.S Government purposes.

Algorithms for Generic Model

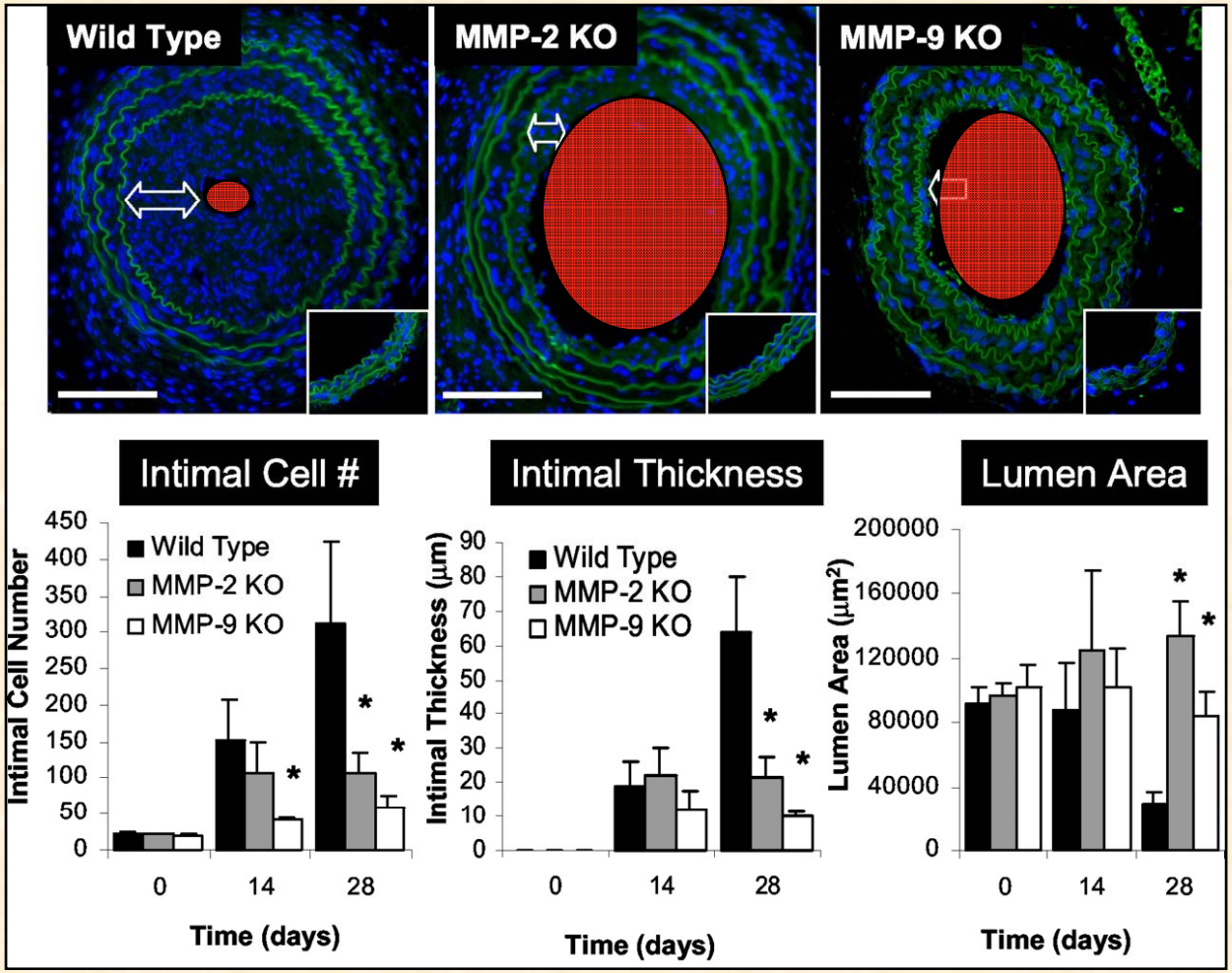
- **Example algorithms for actions of BioEntities defined in ArgoUML model**

Example algorithm entered here!

Disease Mechanism Hypotheses

- **Layout hypotheses…**
- **More components added then those involved in these hypotheses**

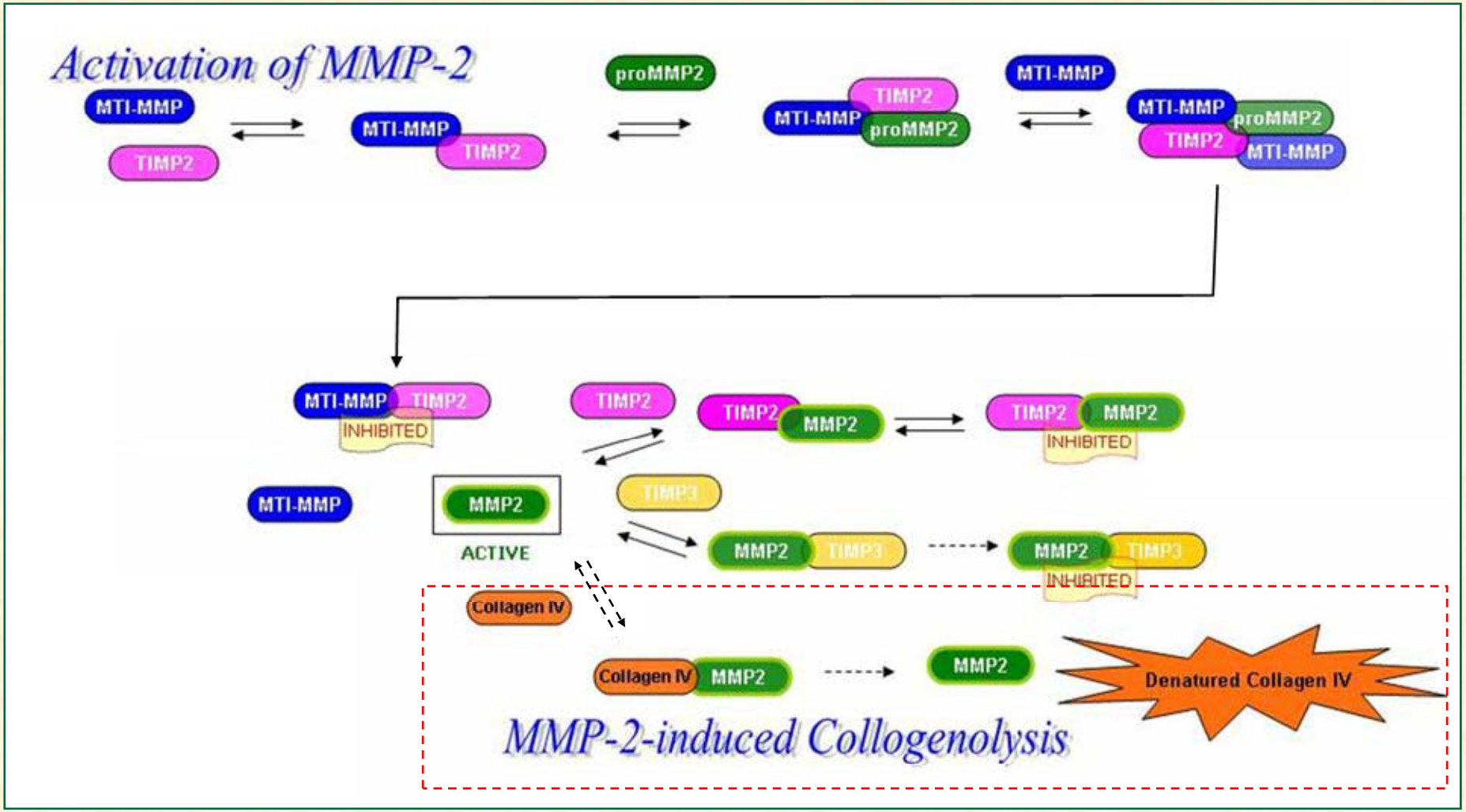
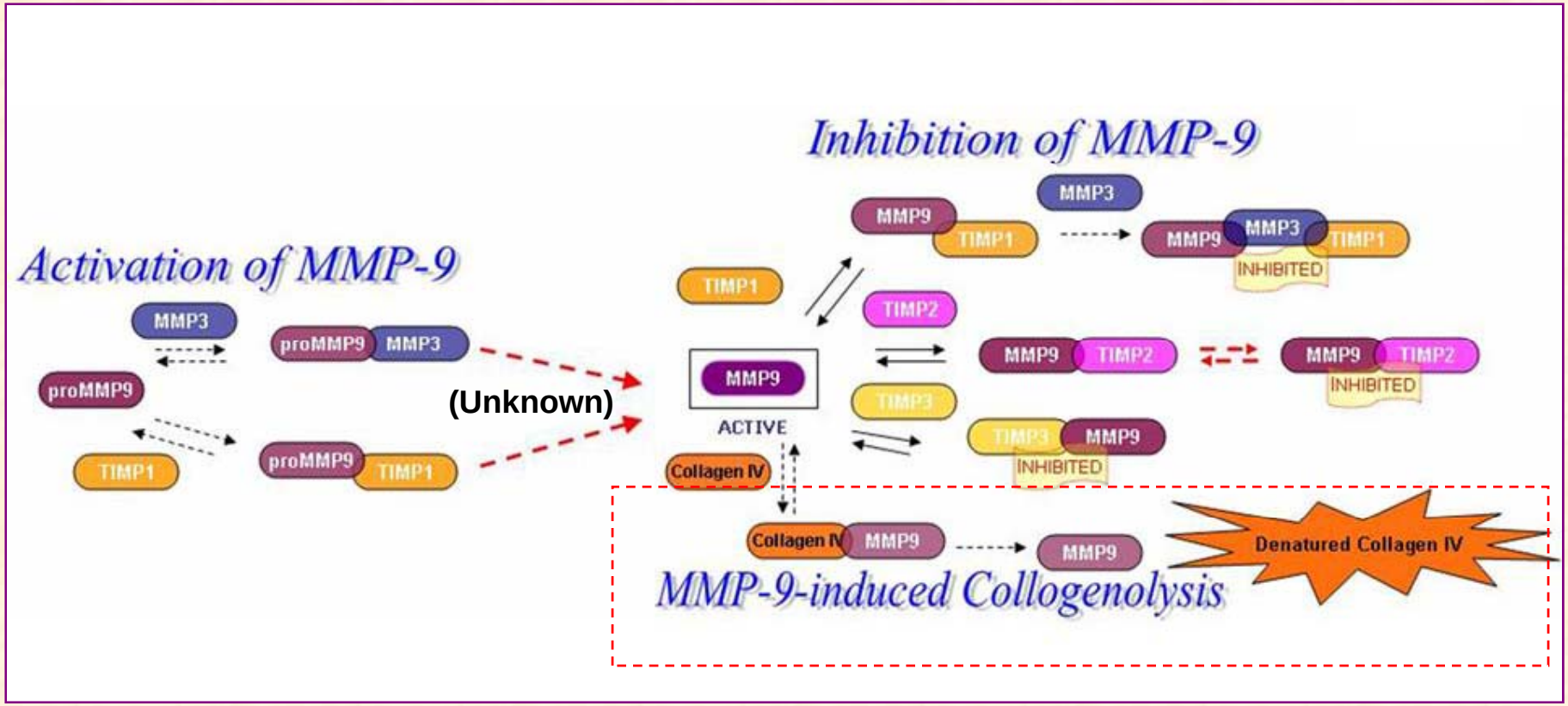
Intimal Hyperplasia - Thickening of intima which restricts blood flow in an artery



- MMP-2 or MMP-9 genetic deficiency impairs neointimal hyperplasia of mouse carotid artery

Johnson, C. et al. *Arterioscler Thromb Vasc Biol* 2004;24:54-60

MMP-2 Pathways



MMP-9 Pathways