Coast

Complex Automata Simulation Technique

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On behalf of the Coast consortium,

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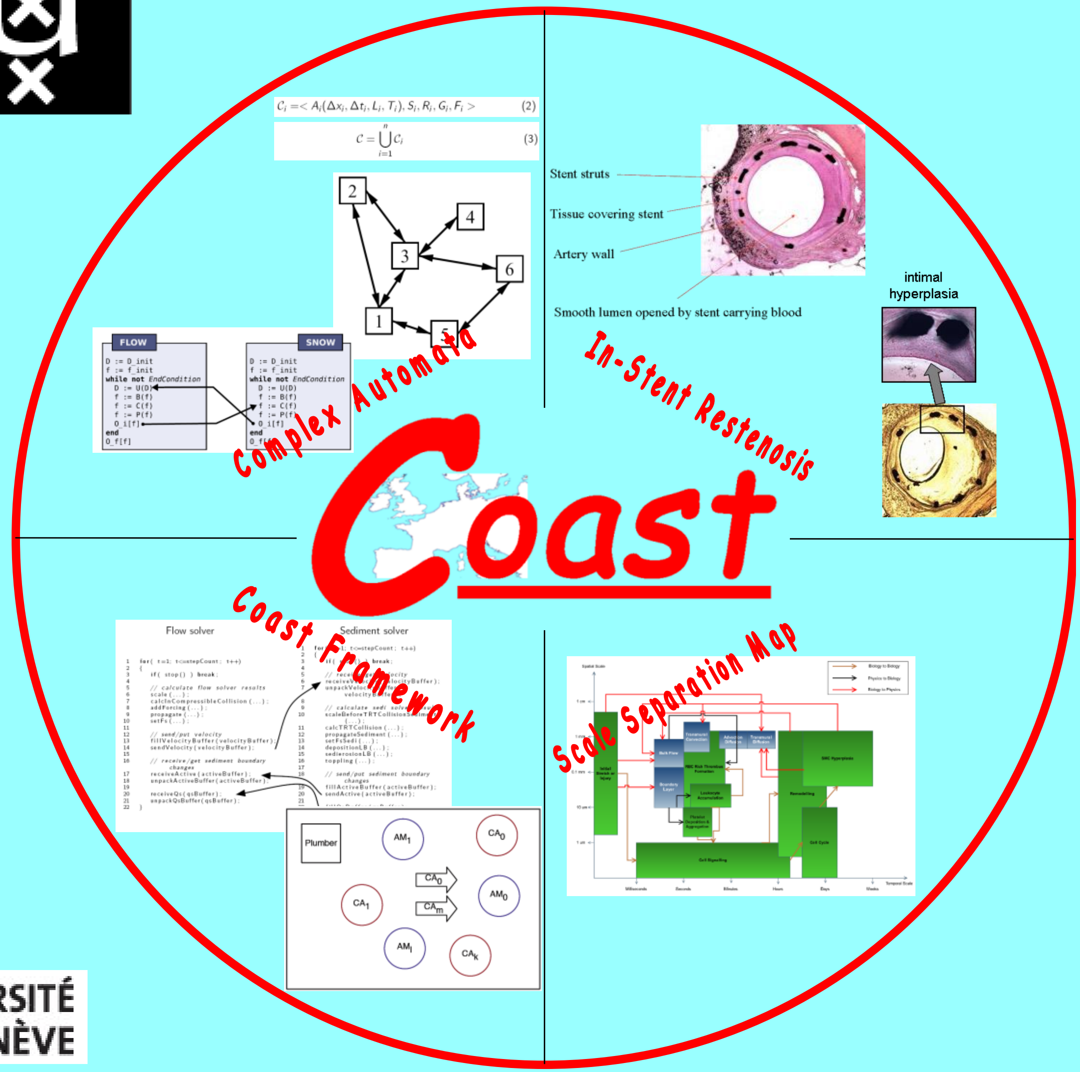


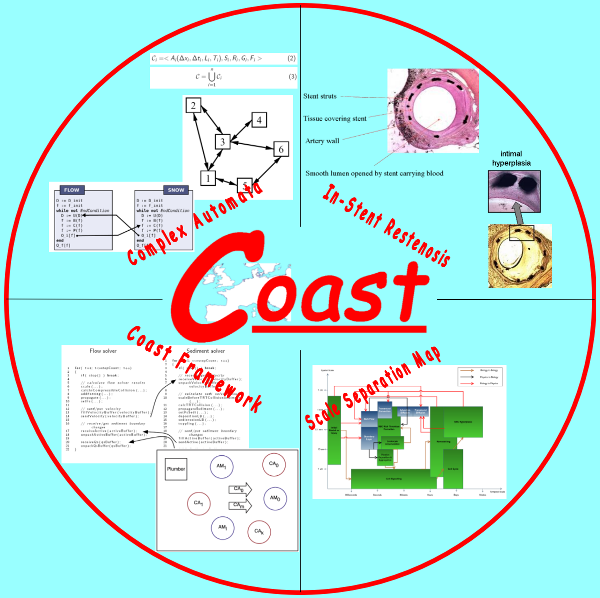
The Coast Vision

- To model and simulate **multi-scale**, **multi-science** complex systems,
- based on a **hierarchical aggregation** of **coupled Cellular Automata** (CA) and **Agent Based Models (ABM)**,
- where each CA or ABM is a single scale model,
- and coupling between the scales is facilitated by multi-scale **coupling paradigms**.

- We call this ***Complex Automata*** (CxA).

Coast

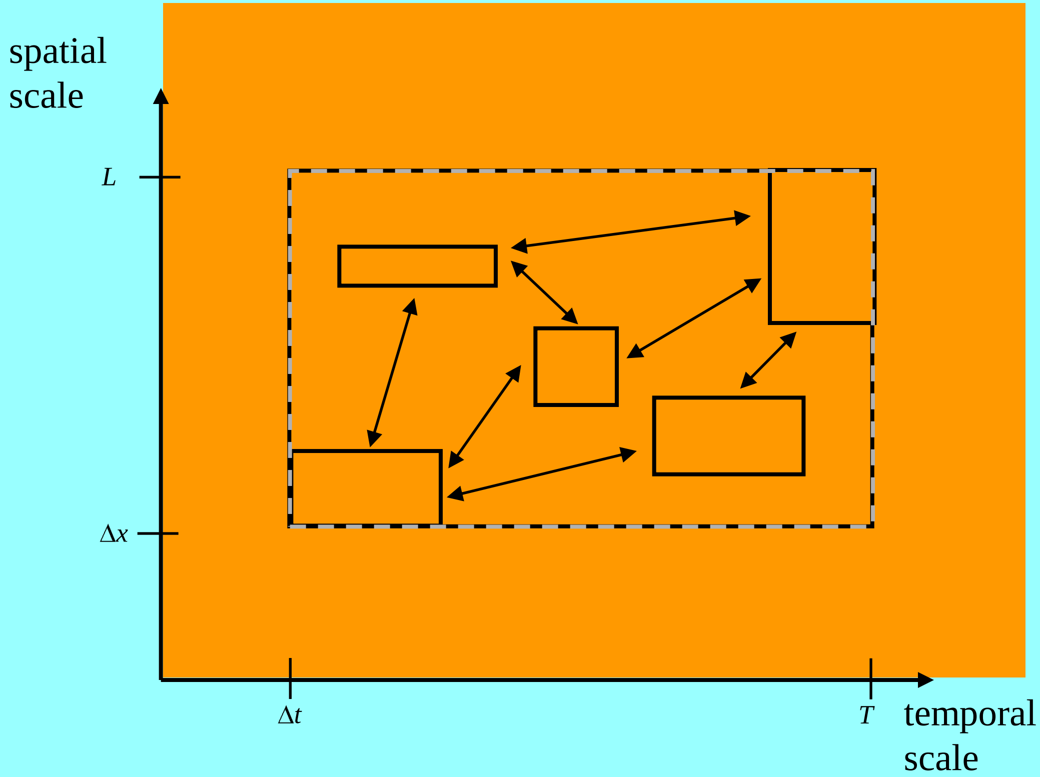
4 pieces of the pie



- Complex Automata theory
- COAST framework
- Single Scale models and their mutual coupling
- In-Stent Restenosis

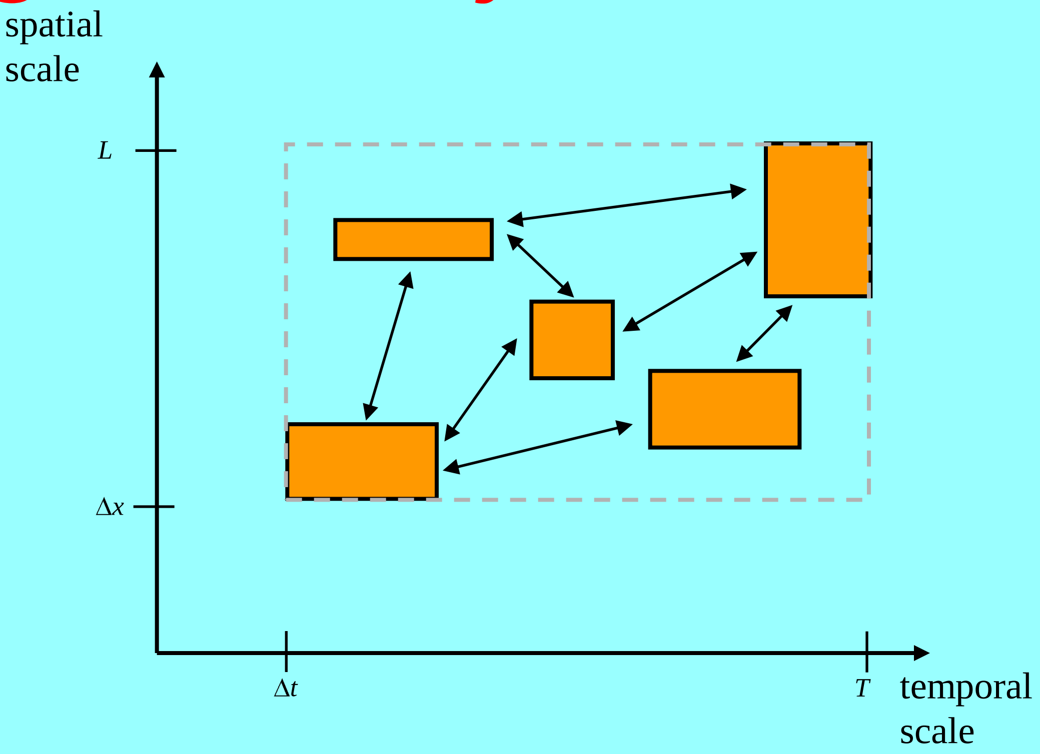
Multi-Scale modeling

- Mathematical models
- Multi-scale
- Simulate on computers
- Intractable when having to simulate on the finest spatial and temporal scales
- Need to find Multi-Scale models,
- and Multi-Scale simulation environments



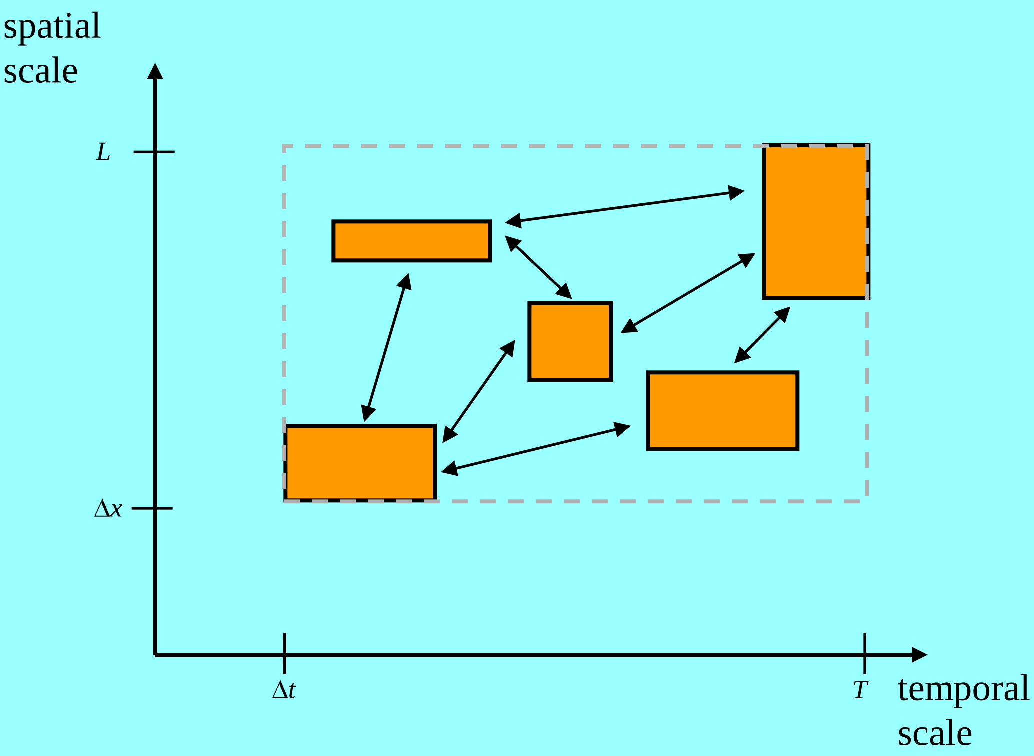
From Multi-Scale System to many Single-Scale Systems

- Identify the relevant scales
- Design a specific models which solve each scale
- Couple the subsystems using a coupling method



Single Scale Models

- Cellular Automata (CA) or Agent Based Models (ABM)
  - powerful approaches to describe complex systems
  - CA and ABM can be decribed in a generic way (see below)
  - With less, do more : Complex Automata (CxA)



Coast Complex Automata Modeling

- CxA as a collection of CA's
- Define a CA as

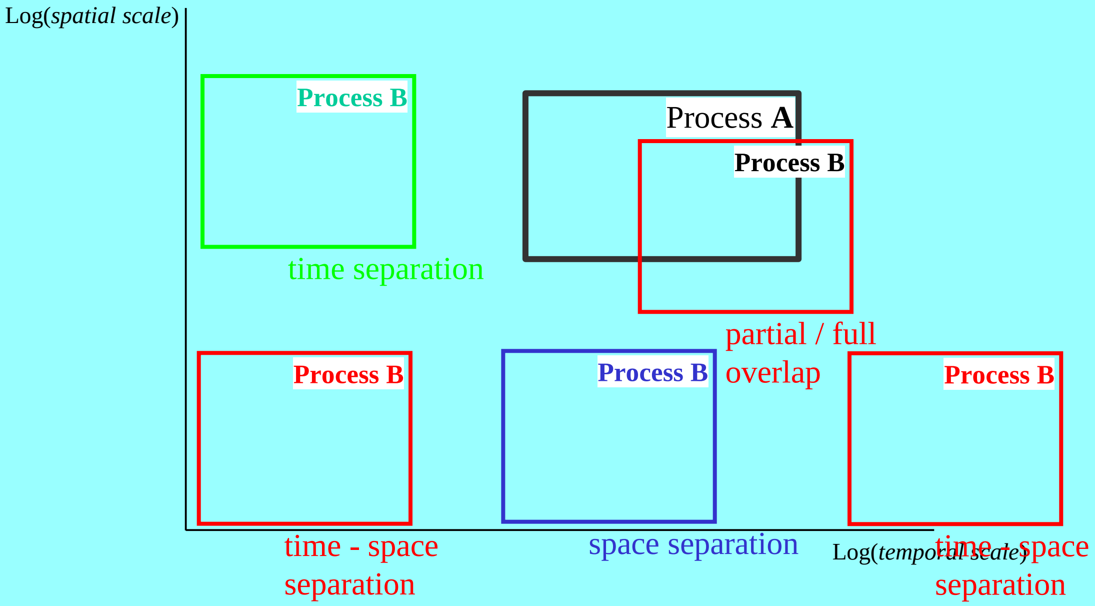
$$C = \langle A(\Delta x, \Delta t, L, T), S, R, G, F \rangle$$

- $A(\Delta x, \Delta t, L, T)$: Spatio-temporal domain of CA
- S: Set of possible states
- R: Evolution Rule
- G: Neighborhood
- F: Information exchange with environment

- A CxA is now a graph χ with vertices V and edges E
- Each vertex is a CA $V_i = \langle A_i(\Delta x_i, \Delta t_i, L_i, T_i), S_i, R_i, G_i, F_i \rangle$
- Each edge E_{ij} is a multi-scale coupling between V_i and V_j.

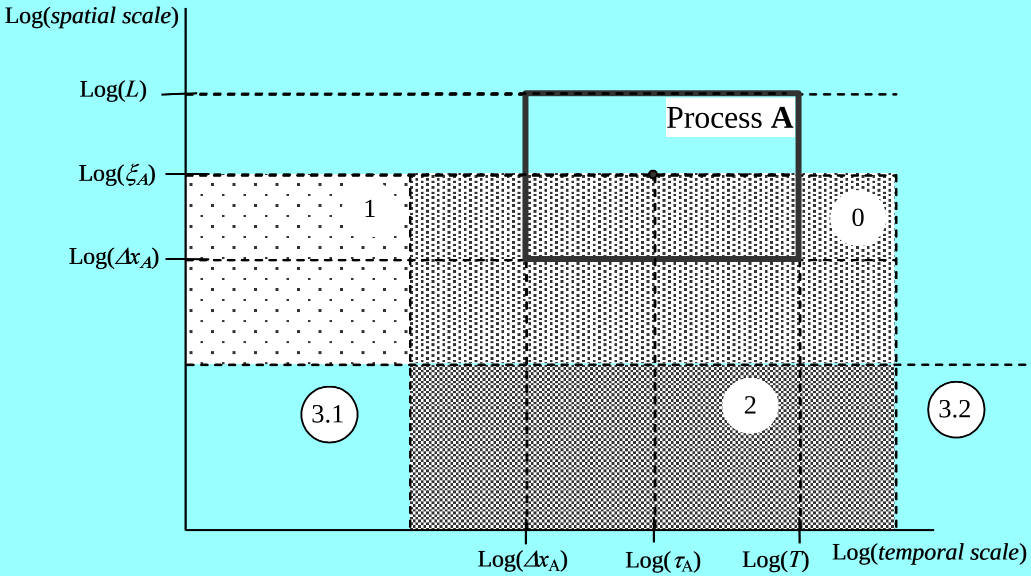
The Scale Separation Map

- A powerful methodological way to identify sub-models
- Classify the sub-model interactions as full or partial overlap of scales.



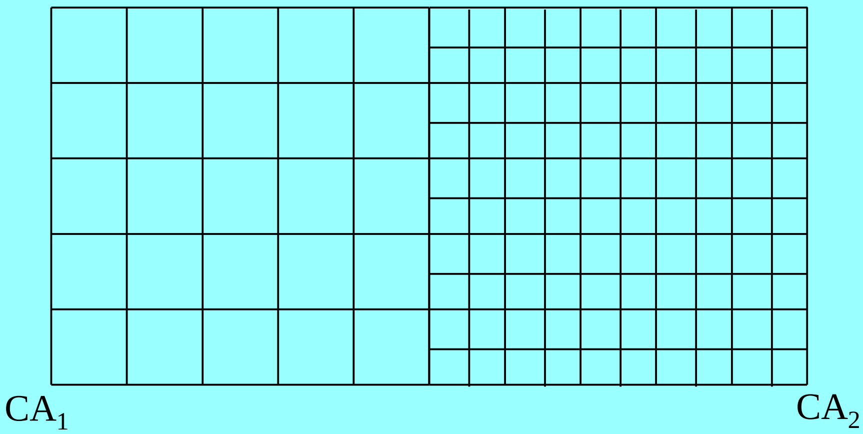
The Scale Separation Map

- A powerful methodological way to identify sub-models
- Classify the sub-model interactions as full or partial overlap of scales.
- Specify the relation between the sub models in five interaction regions.



Relation between computational domains

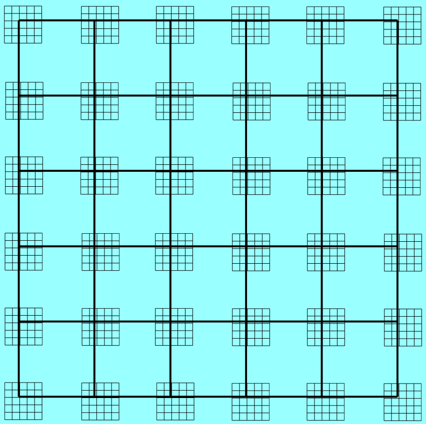
Multi Domain



(scale overlap)

The computational domain is split into
a coarse and a fine sub domain

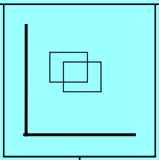
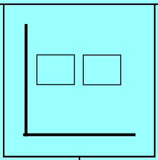
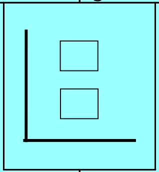
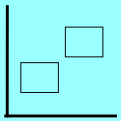
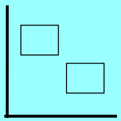
Single Domain



(micro-macro separation)

Classification of systems

- single-Domain (sM) or multi-Domain (mD)
- Relation on the Scale Separation Map

	Time Overlap			Time Separation		
Space overlap	**Single Domain** Coupling through collision operator *Snow transport, diffusion/advection*		**Multi-Domain** Coupling through boundary condition *Fluid Structure, grid refinement*	**Single Domain** Coupling through collision operator *Forest-Savannah-Fire interactions*		**Multi-Domain** Coupling through boundary, initial conditions *Coral growth*
Space separation	**Single Domain** Coupling through collision operator *Algae-Water ecological model*		**Multi-Domain**		**Hierarchical Coupling** Coupling through collision operator and initialisation *Suspension, Fluid*	
					**Physics Biology Coupling** Coupling through boundary conditions and initialisation *Oscillating blood flow and endothelial cells*	

Coast Submodel Execution Loop

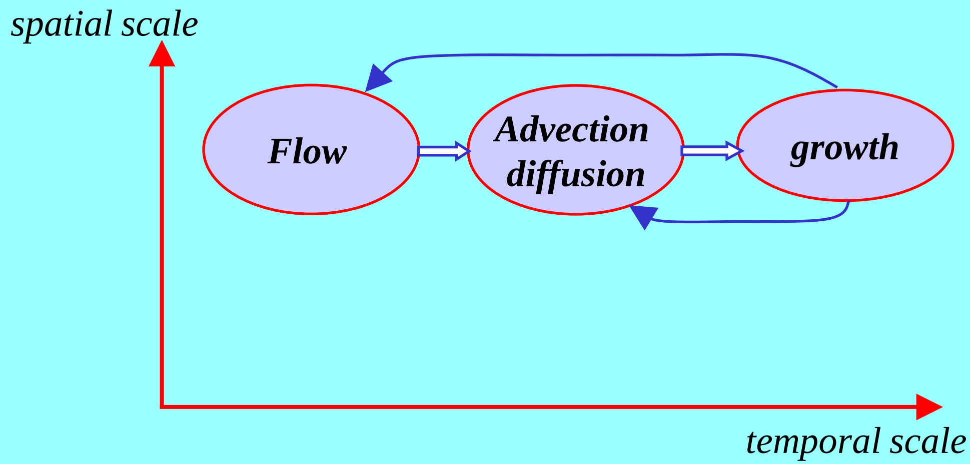
```
D := Dinit                /* initialization of the domain */
f := finit                /* initialization of state variables */
t := 0                    /* initialization of time */
   While Not EC
          t += Dt        /* increase time with one timestep Dt */
          D := U(D)      /* update the domain */
          f := B(f)      /* apply boundary conditions */
          f := C(f)      /* collision, update state of cells */
          f := P(f)      /* propagation, sent information to neighbors */
          Oi(f)          /* compute observables from new state */
   End
Of(f)                     /* compute observables from final state */
```

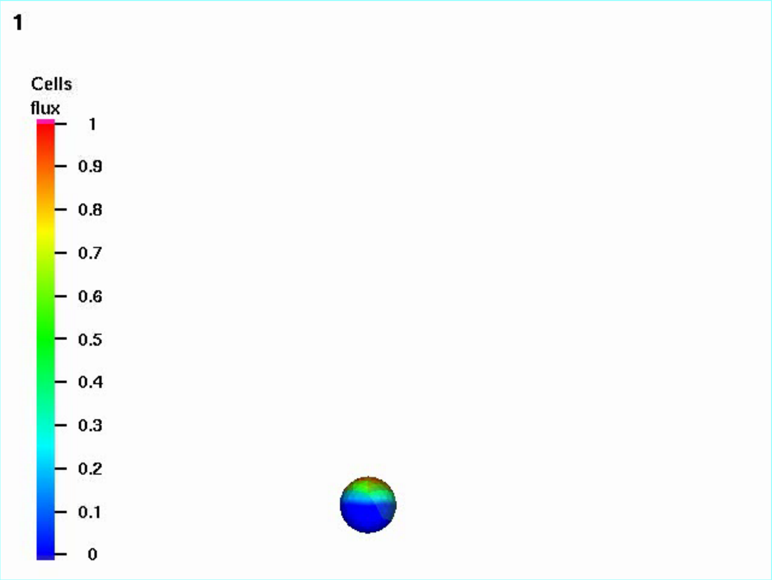
Coupling through SEL operators

The Submodel-Execution-Loop (SEL) gives a generic way of implementing the different couplings.

Example, Coral Growth

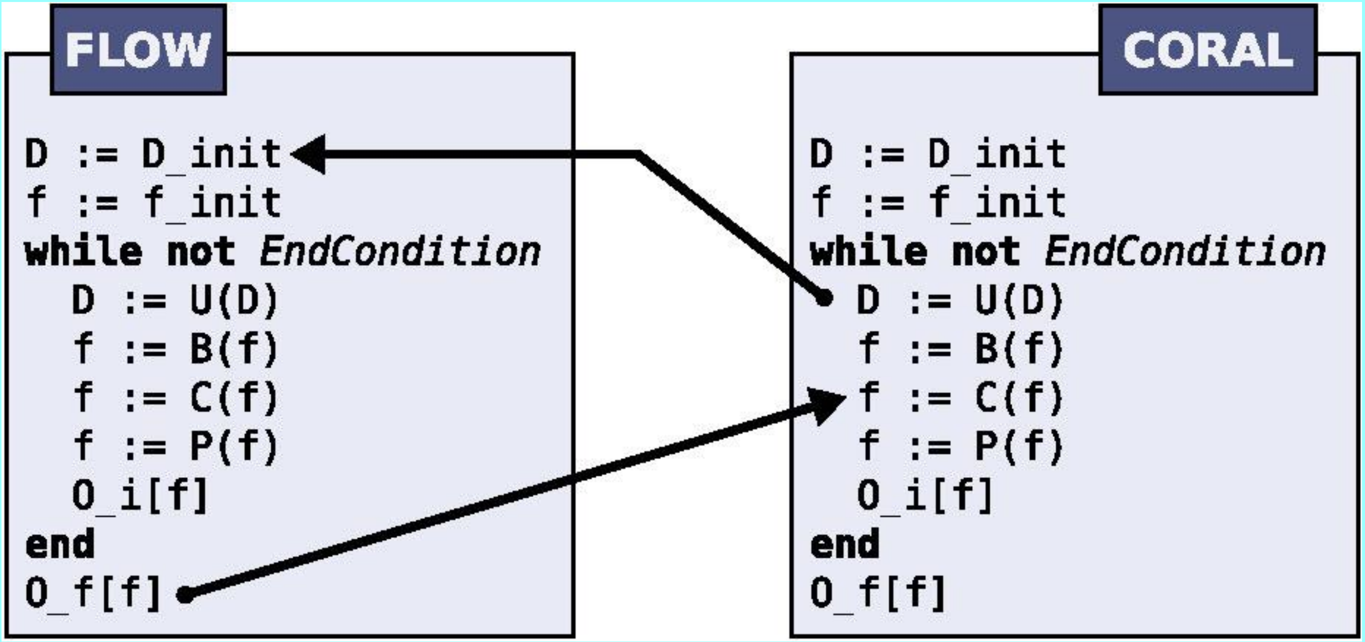
- Simulated Coral Growth
  - Growth dictated by influx of nutrients at coral surface
  - Nutrients are transported by water flow around the coral
- Three subsystems
  - All operating on the same length scale of the coral
  - Flow around the coral
    - Fast process, O(s)
  - Advection-diffusion of nutrients
    - Diffusion time scale O(10 s) to O(1 min)
  - Growth of coral
    - Accretive growth or aggregation
    - Slow process, ~20 mm/year





Kaandorp et al., see e.g.
Merks, Hoekstra, Kaandorp, Sloot, J. Theoret. Biol. **224**, 153-166, 2003
Merks, Hoekstra, Kaandorp, Sloot, Int. J. Mod. Phys. C **14**, 1171-1182, 2003
Merks, Hoekstra, Kaandorp, Sloot, J. Theoret. Biol. **228**, 559-576, 2004

Example, Coral Growth



CxA Simulation Software

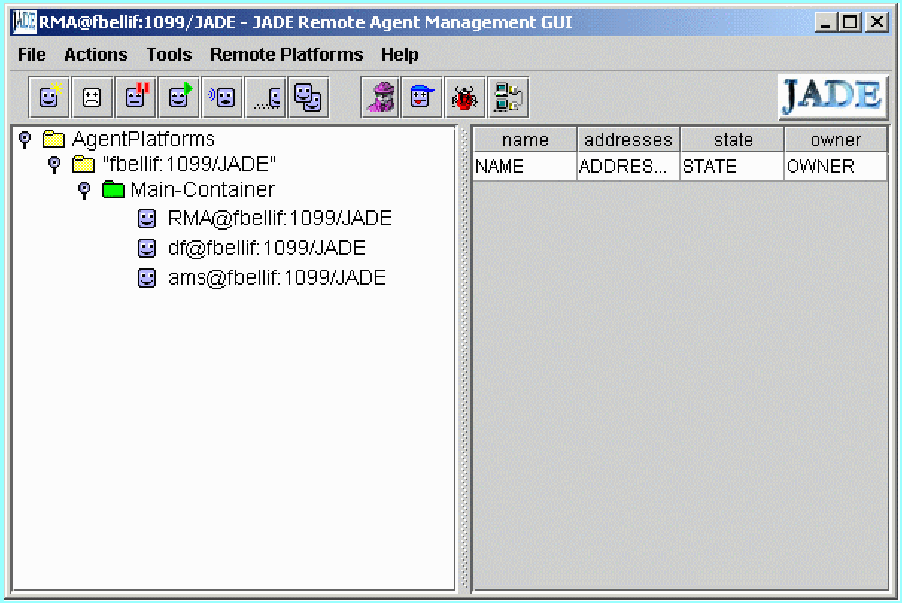
- A ***generic software environment*** for Complex Automata,…
- based on an existing ***agent-based*** computational environment,…
- allowing a high-level and straightforward implementation of ***multi-scale coupling templates***.

Software Requirements

- Supporting multitude of communication patterns
- Hierarchical control structures
- Supporting flexible and distributed (not necessary parallel) coupling/communications
- Flexible coupling platform
- Heterogeneous hardware
- Agent-based models
- Wrap approaches different CA (which may operate on different scales in time and space)
- Open source compliant

JADE

- Multi-agent system
- Agent Framework
- Public domain
  - http://jade.tilab.com/
- Java
- GUI

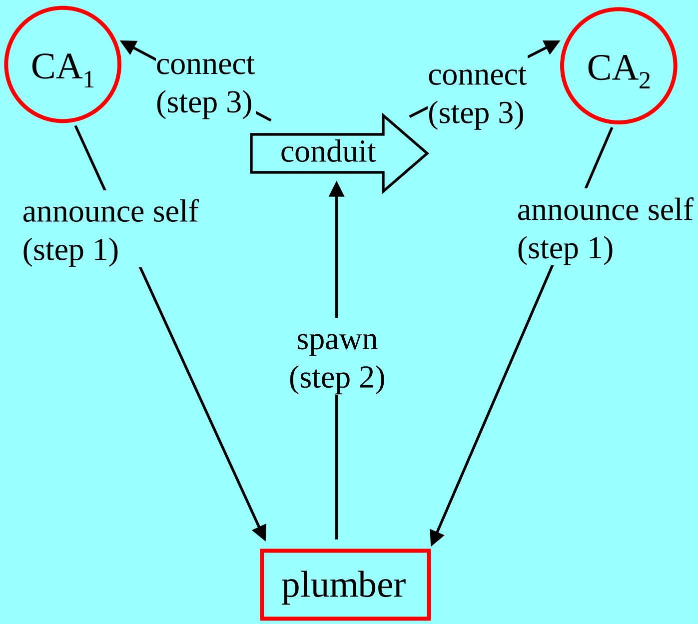


Coast Running the COAST framework

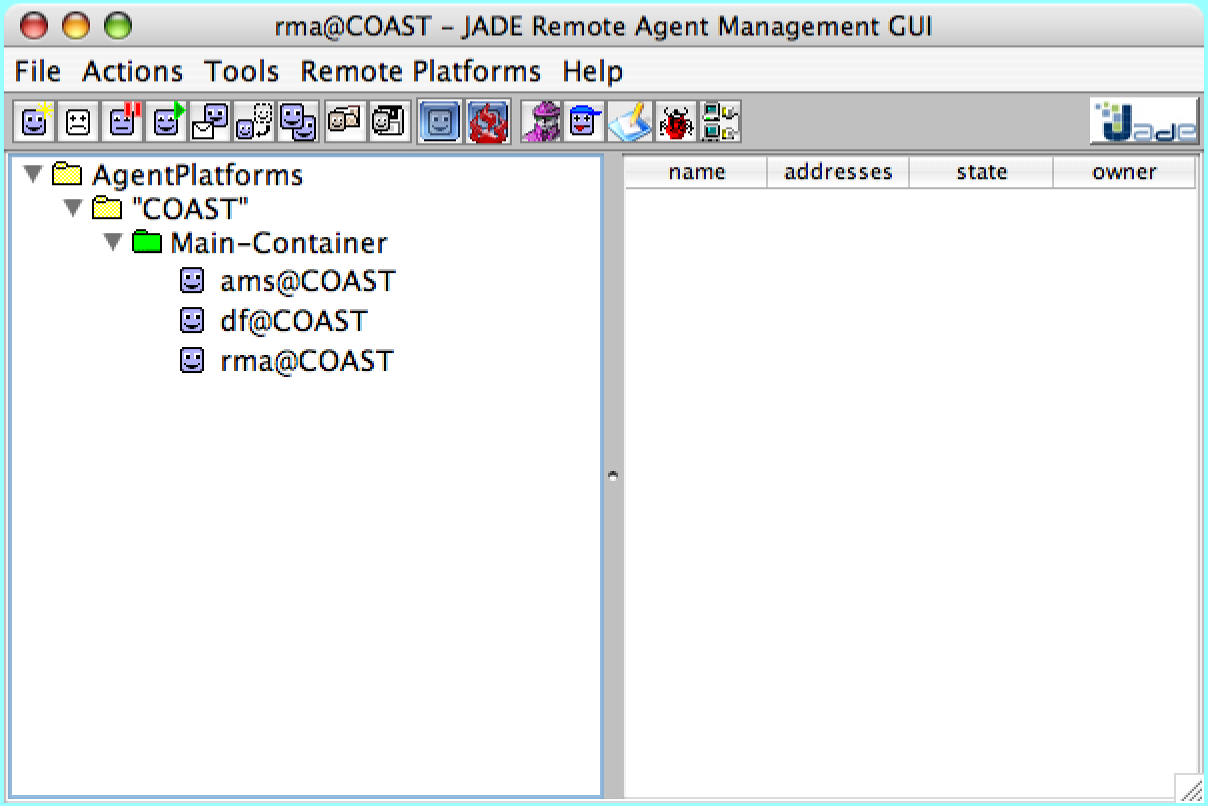
- Transfer of data during the simulation is done via so called **conduits**.
  - Point-to-point communication with embedded processing (like active messages)
  - Within the conduit, data can be modified to match a specific output format.
  - A filter mechanism allows the configuration of common conduit functionality like interpolation (e. g. coarse to fine space scale or coarse to fine time scale) or scaling of data-sets.
- A CxA XML configuration file is used to introduce allowed connections between the different single scale models.
- This description is parsed by the *plumber* agent who spawns the required conduits at runtime.

Coast Running the COAST framework

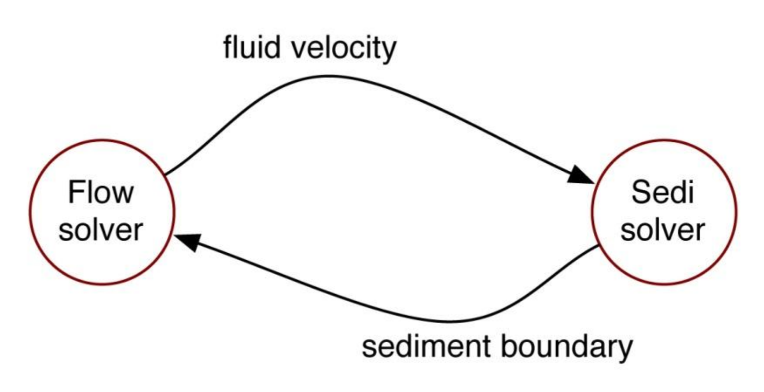
1. Plumber is started
2. Required single scale models are launched
3. New single scale models contact the plumber
4. The Plumber spawns designated conduit
5. Conduit and the sink and source CAs form a peer to peer channel

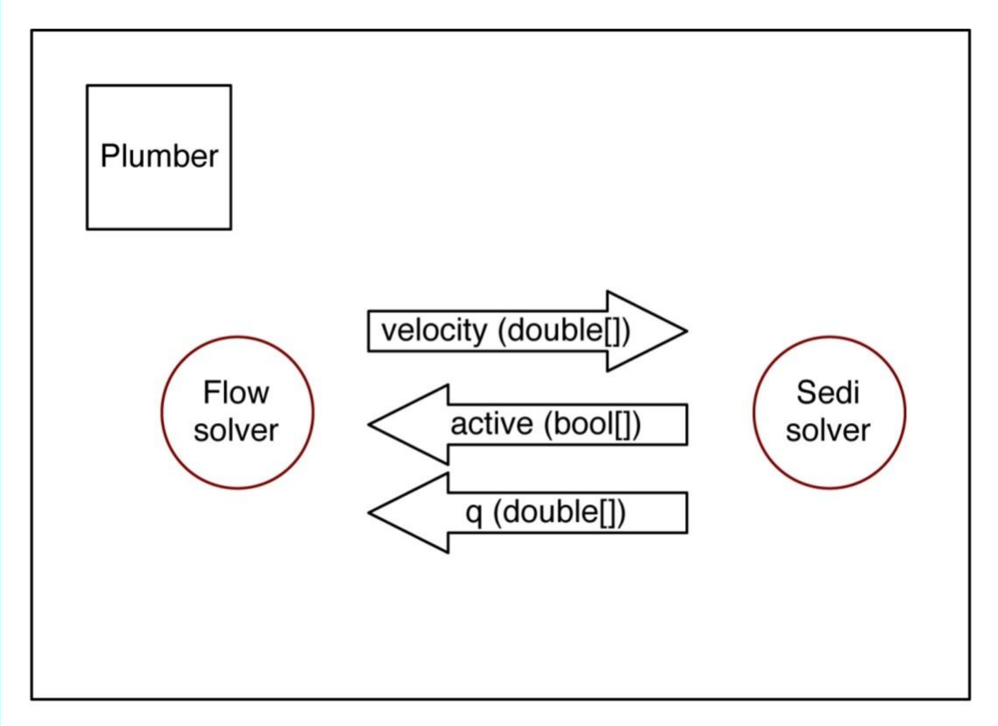


Empty Platform

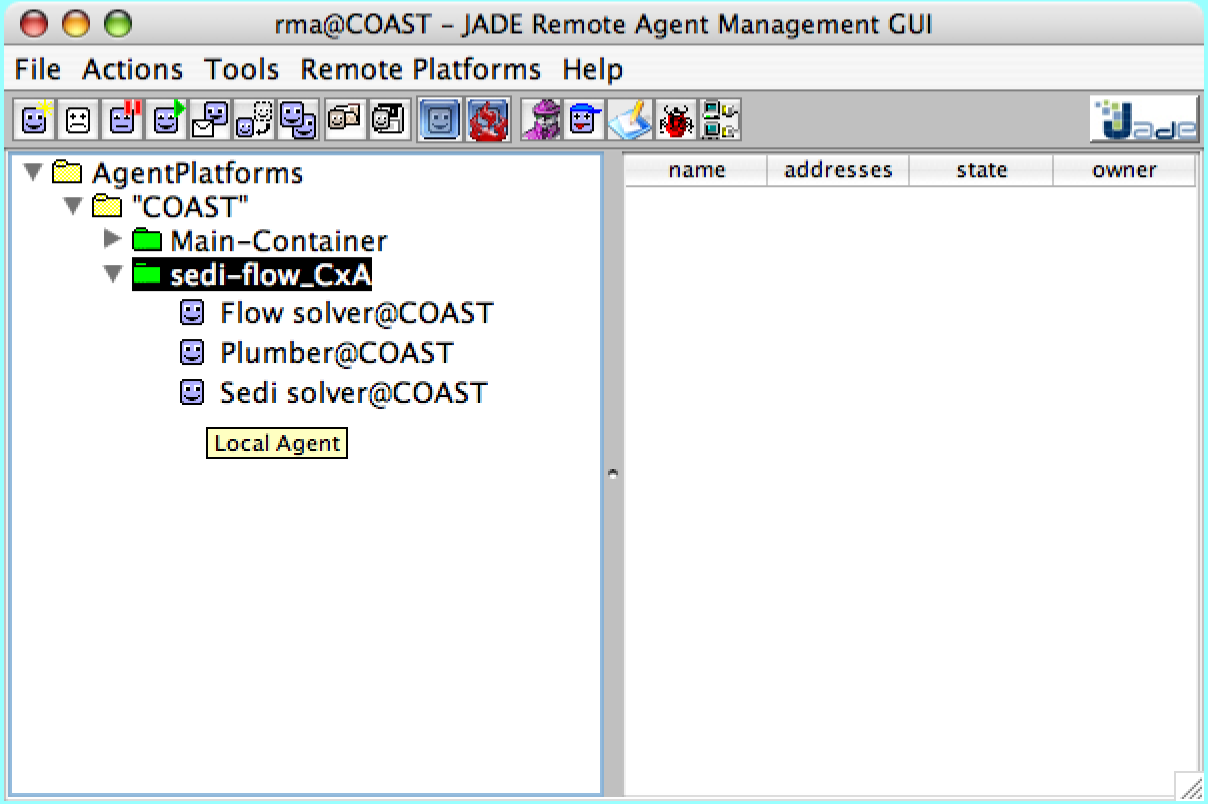


Example: sedimentation/erosion/flow

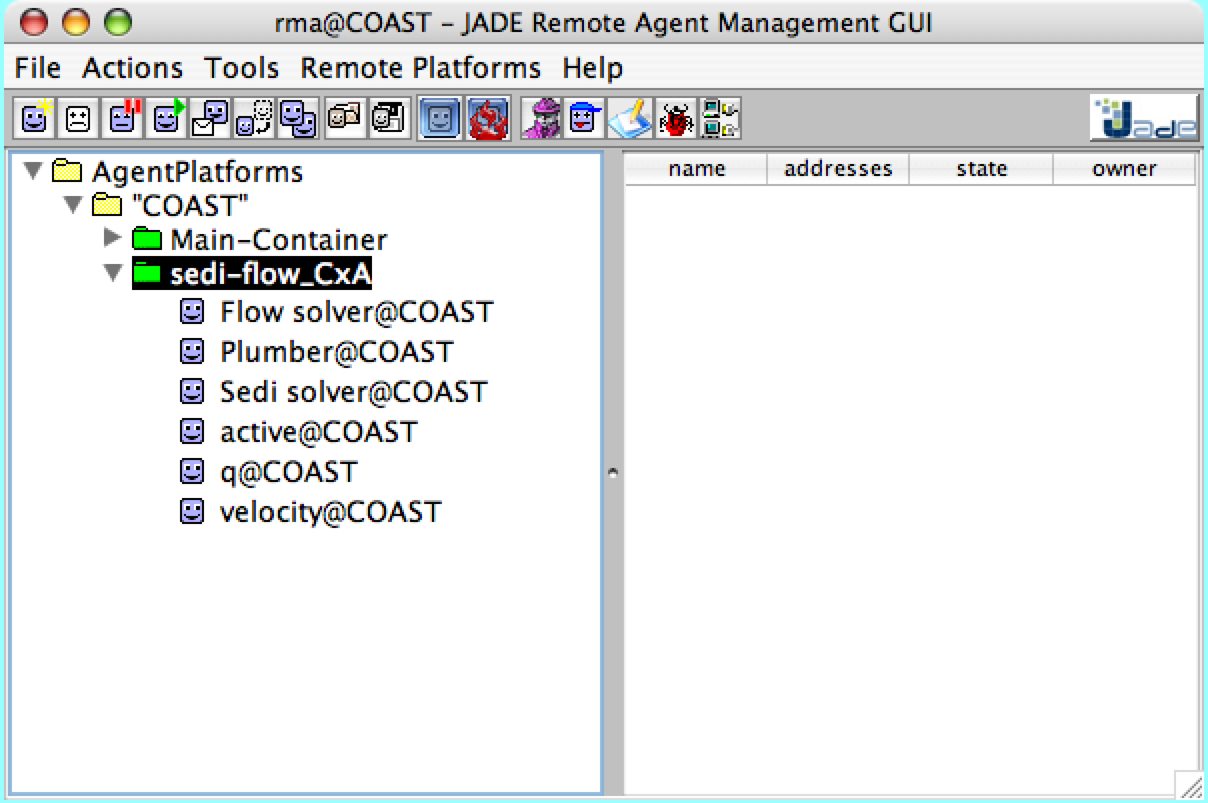




Example CxA launched



Conduits spawned



Coast

Flow solver

```
for( t=1; t<=stepCount; t++)
{
    if( stop() ) break; // alternative

    // calculate flow solver results
    scale(...);
    calcInCompressibleCollision(...);
    addForcing(...);
    propagate(...);
    setFs(...);

    // send/put velocity
    fillVelocityBuffer(velocityBuffer);
    sendVelocity(velocityBuffer);

    // receive/get sediment boundary
        changes
    receiveActive(activeBuffer);
    unpackActiveBuffer(activeBuffer);

    receiveQs(qsBuffer);
    unpackQsBuffer(qsBuffer);
}
```

Sediment solver

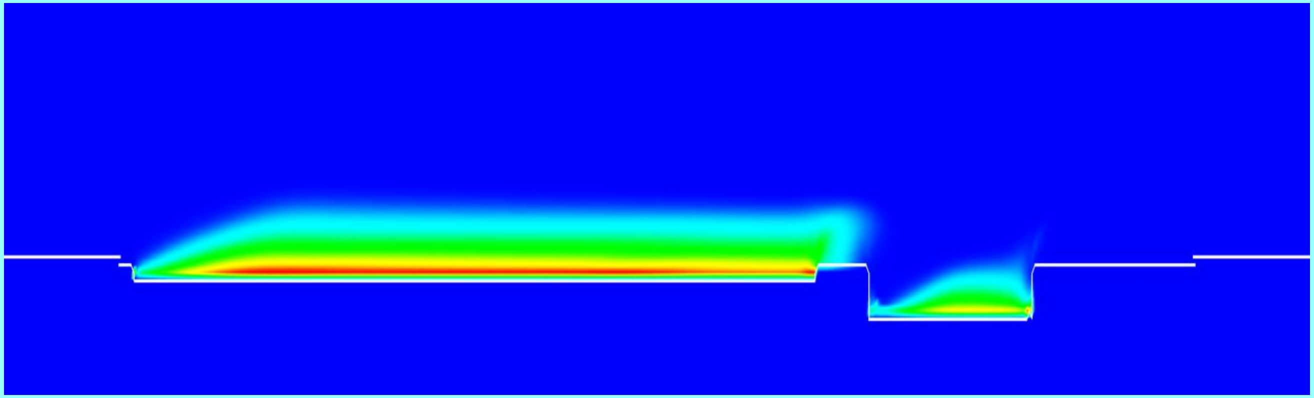
```
for( t=1; t<=stepCount; t++)
{
    if( stop() ) break; // alternative

    // receive/get velocity
    receiveVelocity(velocityBuffer);
    unpackVelocityBuffer(
            velocityBuffer);

    // calculate sedi solver results
    scaleBeforeTRTCollisionSediment
            (...);
    calcTRTCollision(...);
    propagateSediment(...);
    setFsSedi(...);
    depositionLB(...);
    sedierosionLB(...);
    toppling(...);

    // send/put sediment boundary
            changes
    fillActiveBuffer(activeBuffer);
    sendActive(activeBuffer);

    fillQsBuffer(qsBuffer);
    sendQs(qsBuffer);
}
```

Simulation properties

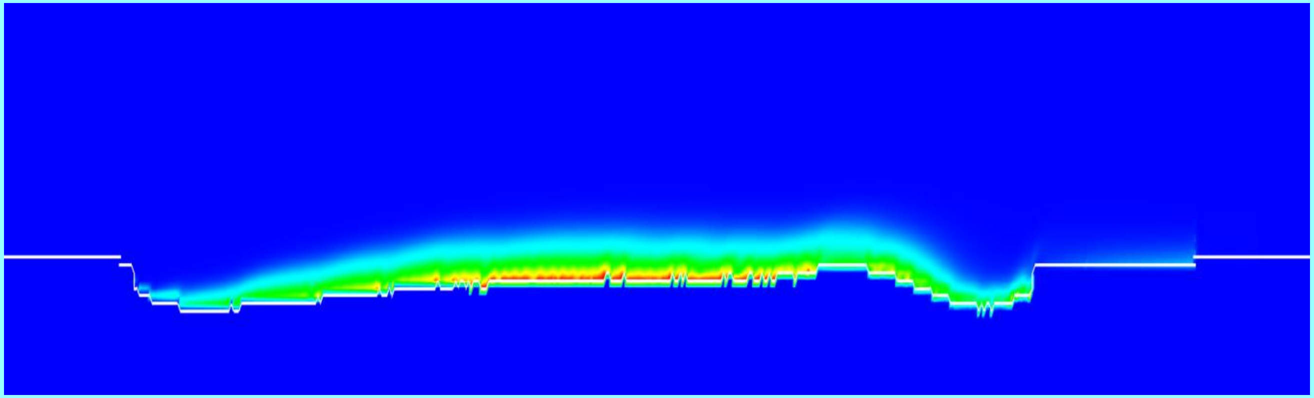
- ~29000 Nodes
- calculation time for 20000 Δt
  - original code: 37 min
  - decoupled via COAST framework: 20 min (this in mainly due to additional data proceccing during calculation (log files, data dumps))

Coast

T=500



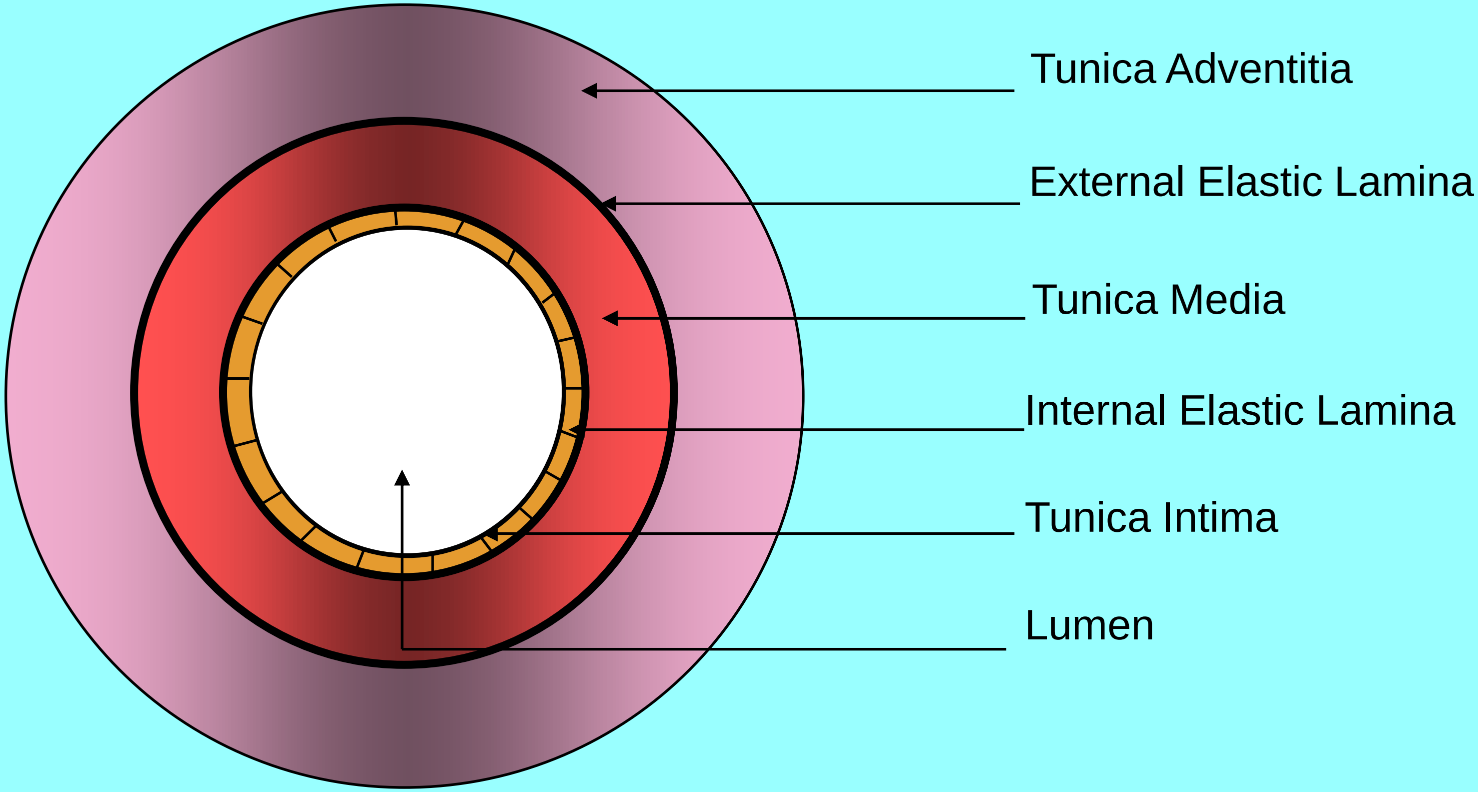
T=1000



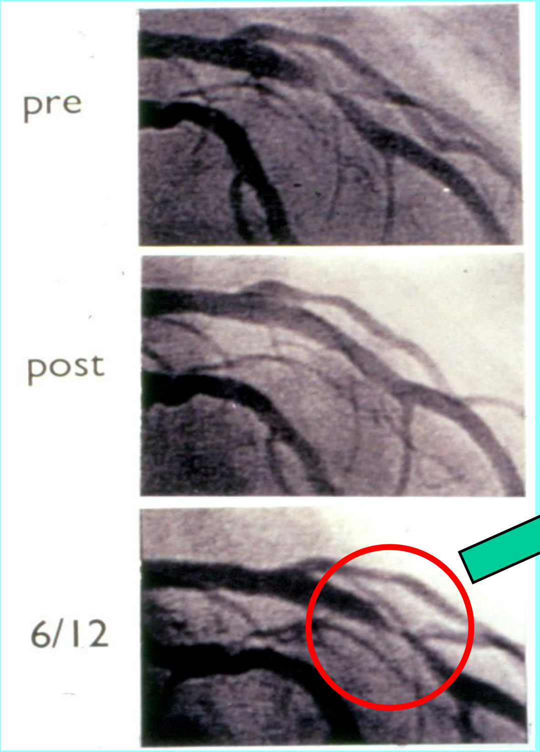
Coronary Heart Disease Background

- Coronary heart disease (CHD) remains the most common cause of death in the UK, being responsible for approximately 105,000 deaths in 2004 (BHF Stats, 2006).
- Percutaneous coronary intervention (PCI) represents one treatment strategy for CHD; in 2005, 94% of 70,142 UK procedures involved the deployment of a stent (BCIS Stats, 2006).
- Restenosis is the maladaptive response of the coronary artery to injury and occurs in approximately 5-10% of patients following procedures involving stent deployment.

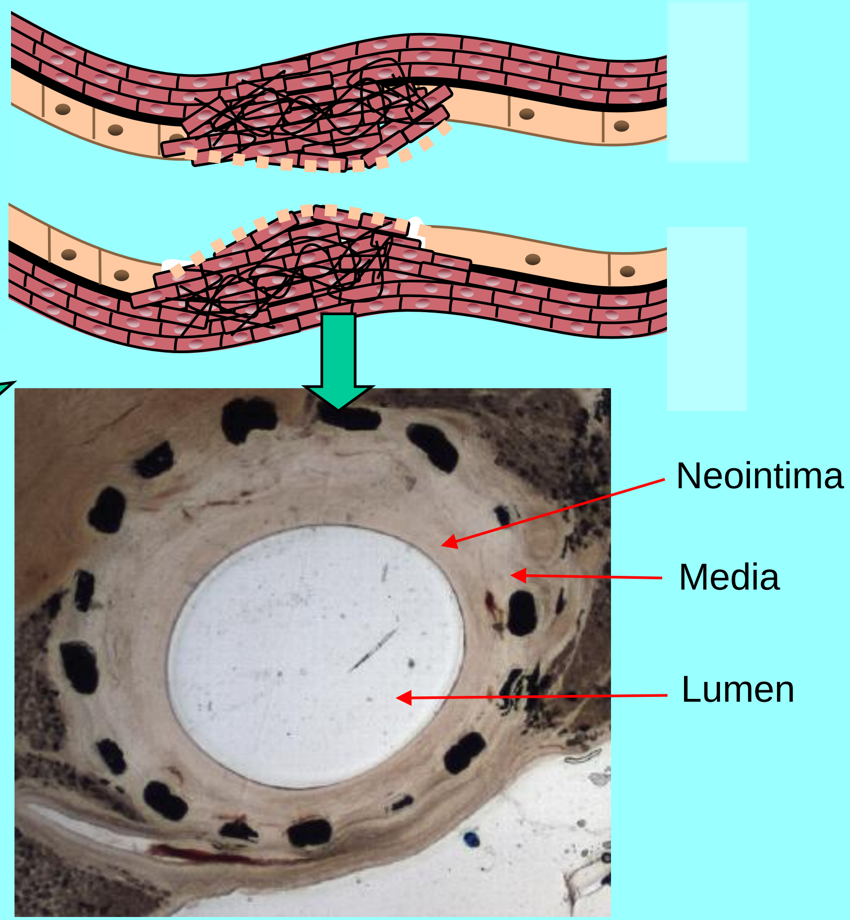
Structure of Healthy Artery



What is Restenosis?

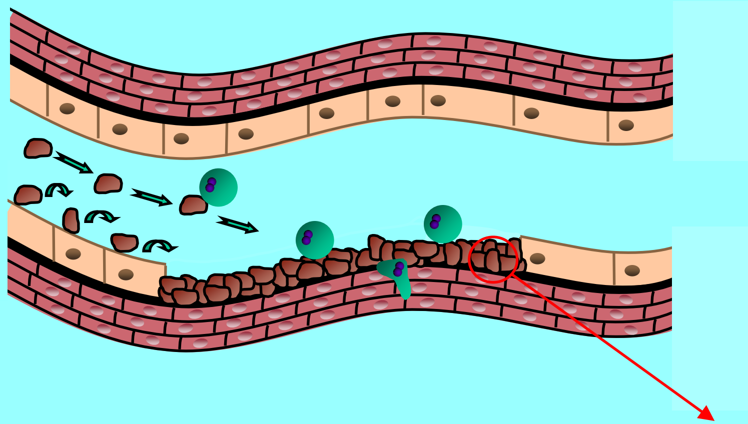


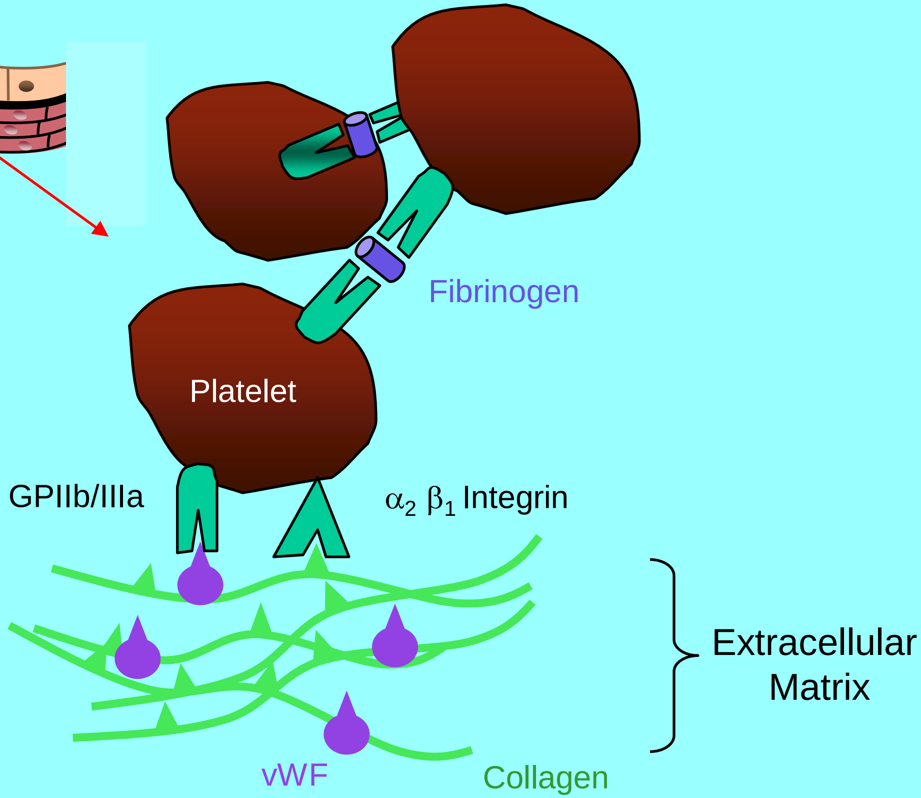
Human angiogram depicting restenosis six months post-PCI.



Porcine coronary artery section 28 days post stenting displaying substantial neointima.

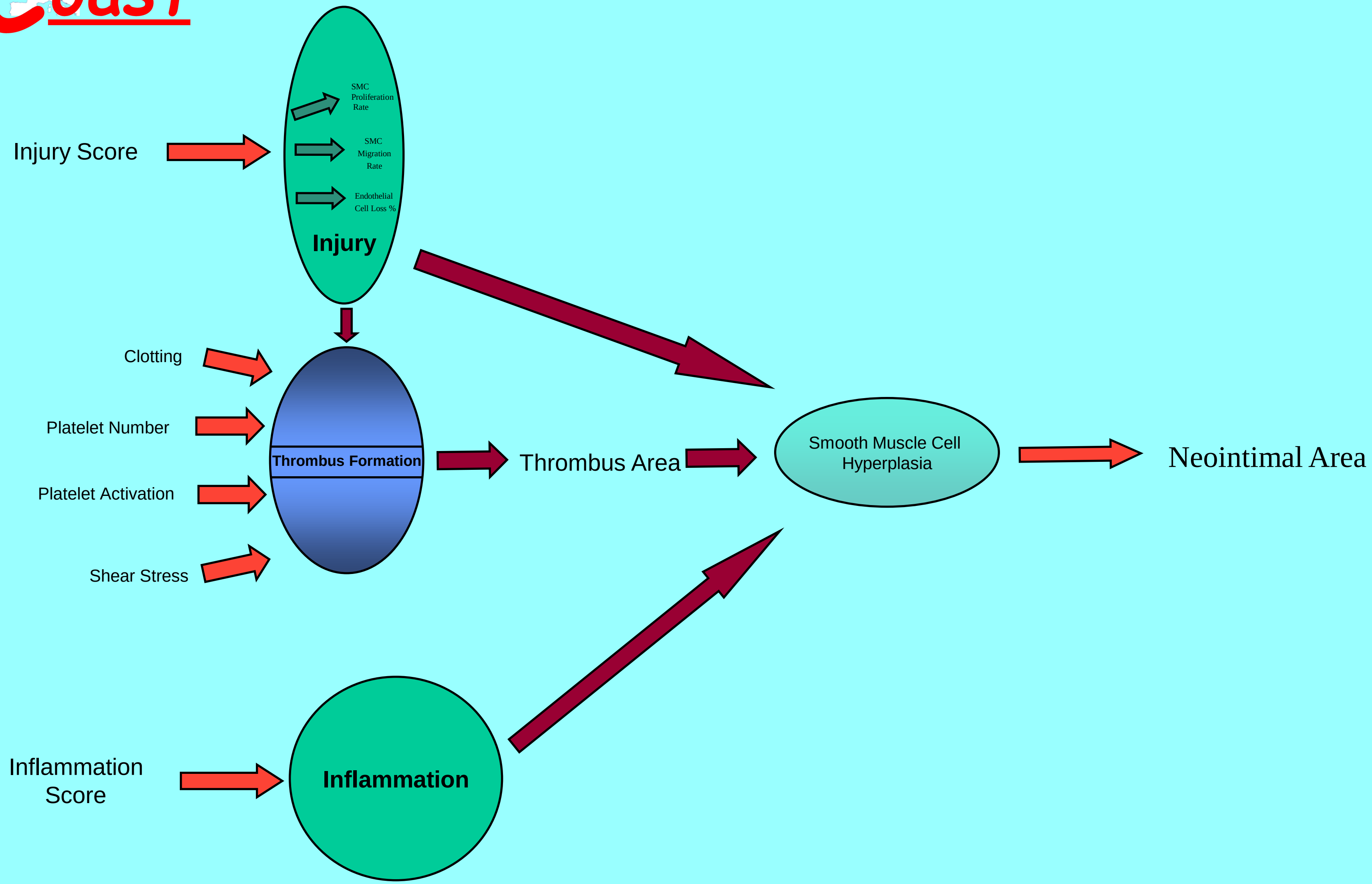
Cellular Mediators



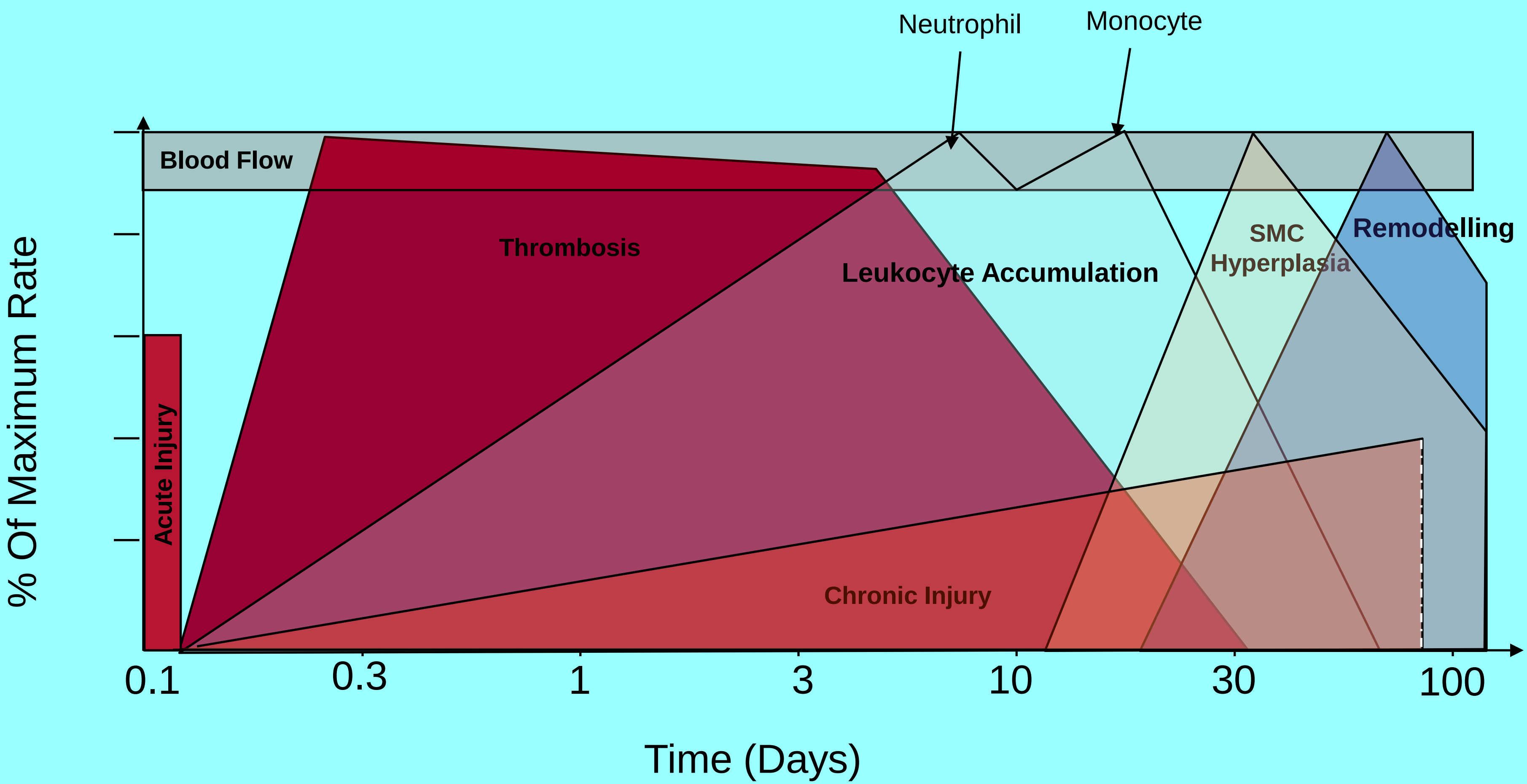


- Vascular Smooth Muscle Cells
- Endothelial Cells
- Platelets
- Leukocytes
- Fibroblasts

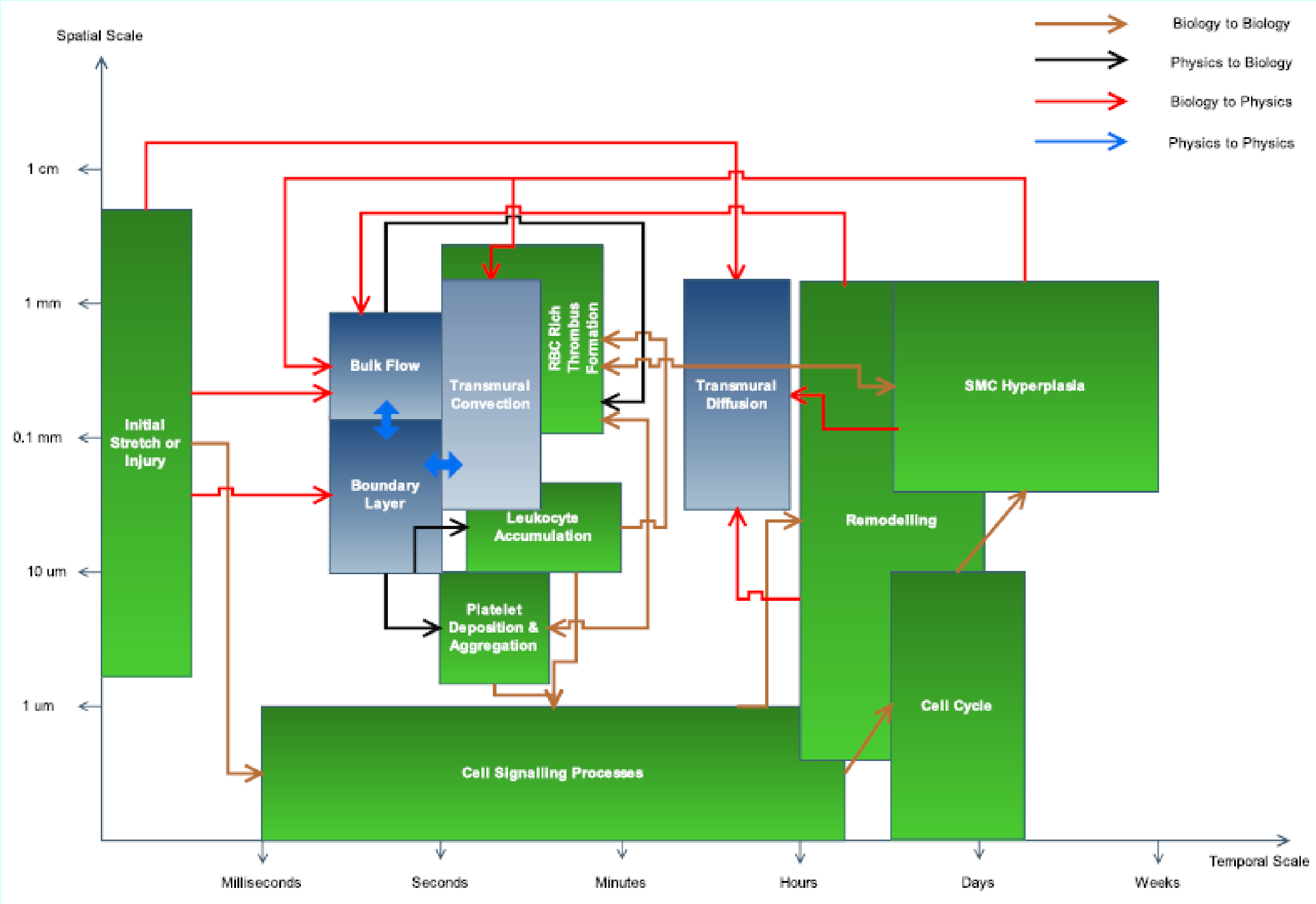
Coast


Injury Score
SMC Proliferation Rate
SMC Migration Rate
Endothelial Cell Loss %
Injury
Clotting
Platelet Number
Platelet Activation
Shear Stress
Thrombus Formation
Thrombus Area
Smooth Muscle Cell Hyperplasia
Neointimal Area
Inflammation Score
Inflammation

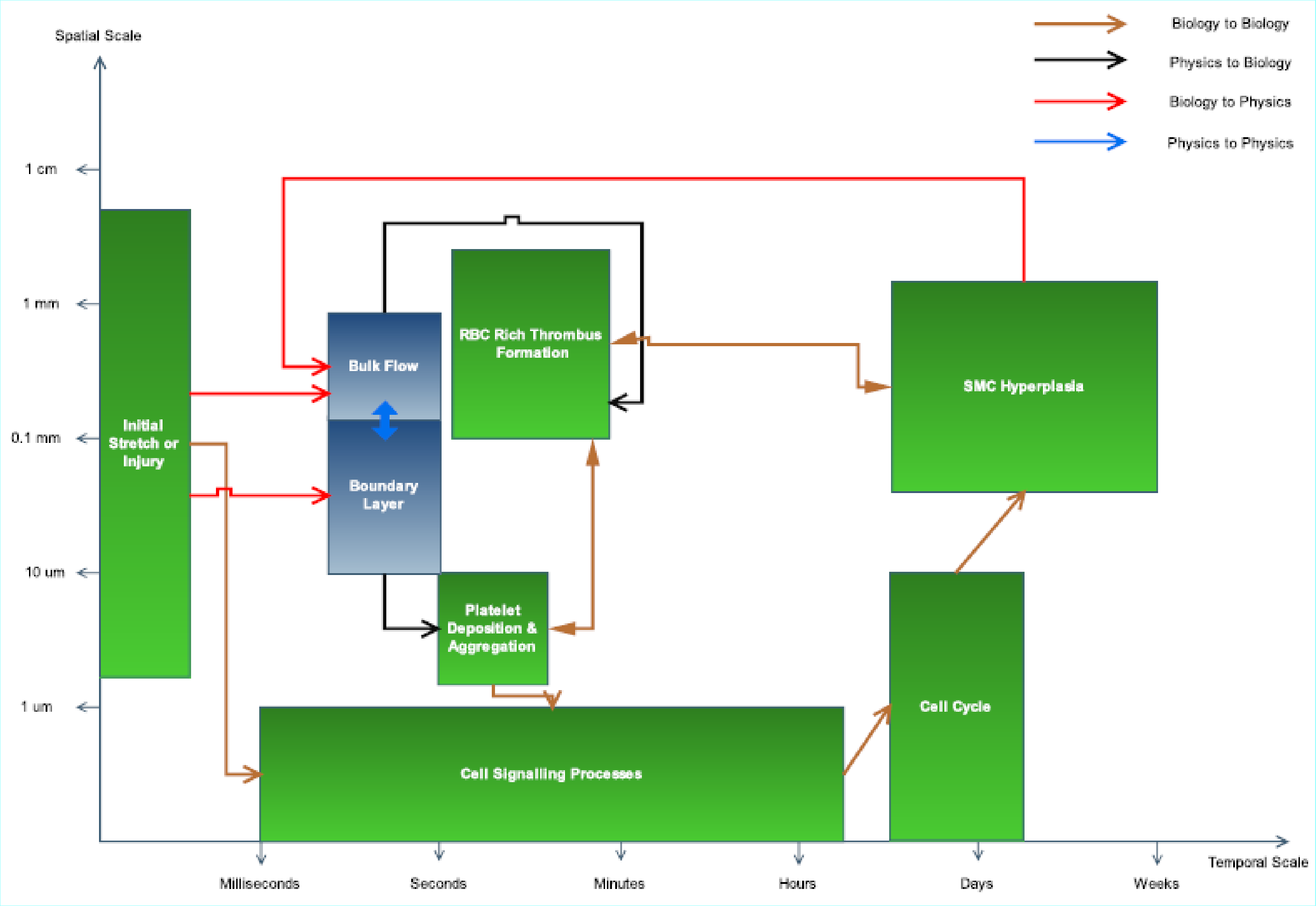
Quantification of the Response



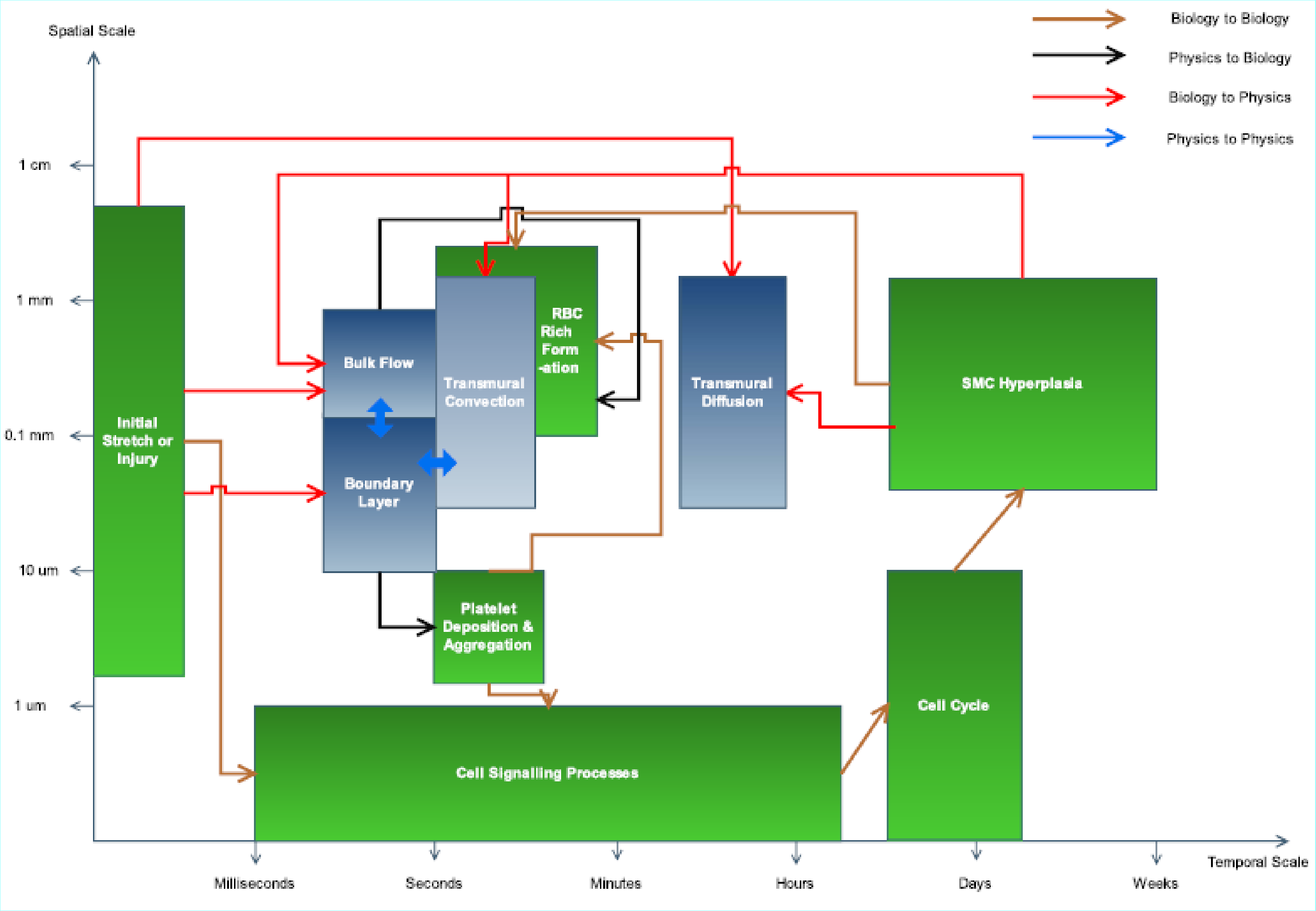
Comprehensive Scale Separation Map



Simplified Scale Separation Map



Drug Elution
Scale Separation Map



Coast Porcine Archive Database

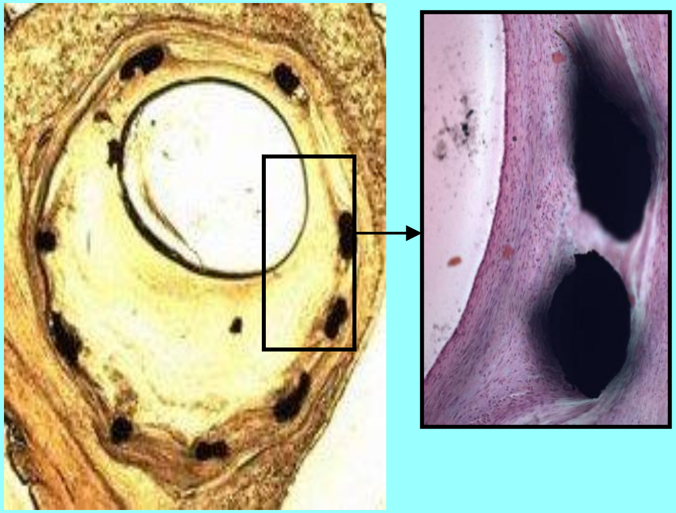
JG Number	Experiment	Date	Timepoint	Pig ID	Surgeon	Type of procedure	Balloon Name	Balloon Diameter	Balloon Length	Balloon Atmospheres	Stent Name	Stent Length	Stent Diameter	Vessel	Vessel Diameter	Ldd Drug	Slide Num	Photos
157	28D PSS Coated vs unCoated	02/12/1996	4wks	2375	Gunn	stent	-	3.50mm	20.00mm	8atm	PSS uncoated	-	-	LAD	-	-	1 _ 22	
157		02/12/1996	4wks	2375	Gunn	stent	-	3.50mm	20.00mm	8atm	PSS uncoated	-	-	RCA	-	-	1 _ 25	
159	28D PSS C vs unC	09/12/1996	4wks	-	Gunn	stent	-	3.50mm	20.00mm	8atm	PSS uncoated	-	-	LAD	-	-	1 _ 26	
159		09/12/1996	4wks	-	Gunn	stent	-	3.50mm	20.00mm	8atm	PSS uncoated	-	-	RCA	-	-	1 _ 26	
160	28D PSS C vs unC	09/12/1996	4wks	-	Gunn	stent	-	3.50mm	20.00mm	8atm	PSS uncoated	-	-	LAD	-	-	1 _ 27	
160		09/12/1996	4wks	-	Gunn	stent	-	3.50mm	20.00mm	8atm	PSS uncoated	-	-	RCA	-	-	1 _ 23	
161	28D PSS C vs unC	17/12/1996	4wks	-	Gunn	stent	-	3.50mm	20.00mm	8atm	PSS uncoated	-	-	LAD	-	-	1 _ 13	
162	28D Divysio Overlap	16-Dec-96	28d	2379	Gunn	Stent overlap		3.50mm	40.00mm	10atm	Divysio	40.00mm	3.50mm	LAD	-	-	1 _ 40	N
176	28D PSS	11-Mar-97	28d	2426	Gunn	Stent		4.00mm	11.00mm	8atm	PSS	11.00mm	4.00mm	LAD	3.39mm	-	1 _ 25	N
246	28D Genentech	20-Oct-98	28d	3219	Chico	Stent Genentec		3.50mm	11.00mm	8atm	PS153	11.00mm	3.50mm	LAD	2.79mm	-	1 _ 8	N
246		20-Oct-98	28d	3219	Chico	Stent Genentec		3.50mm	11.00mm	8atm	PS153	11.00mm	3.50mm	RCA	2.80mm	-	1 _ 12	N
247	28D Genentech	20-Oct-98	28d	3216	Chico	Stent Genentec		3.50mm	11.00mm	8atm	PS153	11.00mm	3.50mm	LAD	2.82mm	-	1 _ 10	N
247		20-Oct-98	28d	3216	Chico	Stent Genentec		3.50mm	11.00mm	8atm	PS153	11.00mm	3.50mm	RCA	2.86mm	-	1 _ 10	N
249	28D Genentech	22-Oct-98	28d	3215	Chico	Stent Genentec		3.50mm	11.00mm	8atm	PS153	11.00mm	3.50mm	LAD	2.75mm	-	1 _ 10	N
249		22-Oct-98	28d	3215	Chico	Stent Genentec		3.50mm	11.00mm	8atm	PS153	11.00mm	3.50mm	RCA	2.83mm	-	1 _ 9	N
251	28D Genentech	22-Oct-98	28d	3244	Chico	Stent Genentec		3.50mm	11.00mm	8atm	PS153	11.00mm	3.50mm	LAD	2.73mm	-	1 _ 10	N
251		22-Oct-98	28d	3244	Chico	Stent Genentec		3.50mm	11.00mm	8atm	PS153	11.00mm	3.50mm	RCA	2.82mm	-	1 _ 9	N
273	28D BCP SV study	14-Dec-98	28d	3295	Gunn	Stent sv BCP		2.50mm	11.00mm	7atm	NIR	11.00mm	2.50mm	LAD	2.17mm	-	1 _ 9	N
273		14-Dec-98	28d	3295	Gunn	Stent sv BCP		2.50mm	11.00mm	6atm	Divysio	11.00mm	2.50mm	RCA	2.12mm	-	1 _ 10	N
274	28D BCP SV study	14-Dec-98	28d	3296	Gunn	Stent sv BCP		2.50mm	11.00mm	6atm	Divysio	11.00mm	2.50mm	LAD	2.14mm	-	1 _ 10	N
274		14-Dec-98	28d	3296	Gunn	Stent sv BCP		2.50mm	11.00mm	7atm	NIR	11.00mm	2.50mm	Diag	2.10mm	-	1 _ 10	N
275	28D BCP SV study	14-Dec-98	28d	3299	Gunn	Stent sv BCP		2.50mm	11.00mm	6atm	NIR	11.00mm	2.50mm	LAD	2.19mm	-	1 _ 8	N
275		14-Dec-98	28d	3299	Gunn	Stent sv BCP		2.50mm	11.00mm	6atm	Divysio	11.00mm	2.50mm	Cx	2.15mm	-	1 _ 8	N
276	28D BCP SV study	14-Dec-98	28d died AE	3320	Gunn	Stent sv BCP		2.50mm	11.00mm	6atm	Divysio	11.00mm	2.50mm	LAD	2.12mm	-	1 _ 8	N
276		14-Dec-98	28d died AE	3320	Gunn	Stent sv BCP		2.50mm	11.00mm	6atm	Divysio	11.00mm	2.50mm	OMI/Cx	2.09mm	-	1 _ 9	N
277	28D BCP SV study	15-Dec-98	28d died 2d post	3314	Gunn	Stent sv BCP		2.50mm	11.00mm	6atm	BDV	11.00mm	2.50mm	LAD	1.93mm	-	1 _ 9	N
277		15-Dec-98	28d died 2d post	3314	Gunn	Stent sv BCP		2.50mm	11.00mm	6atm	NIR	11.00mm	2.50mm	Diag	1.99mm	-	1 _ 9	N
278	28D BCP SV study	15-Dec-98	28d	3312	Gunn	Stent sv BCP		2.50mm	11.00mm	6atm	BDV	11.00mm	2.50mm	LAD	2.01mm	-	1 _ 9	N
278		15-Dec-98	28d	3312	Gunn	Stent sv BCP		2.50mm	11.00mm	6atm	NIR	11.00mm	2.50mm	Cx	2.14mm	-	1 _ 9	N
279	28D BCP SV study	15-Dec-98	28d	3310	Gunn	Stent sv BCP		2.50mm	11.00mm	6atm	NIR	11.00mm	2.50mm	LAD	2.06mm	-	1 _ 8	N
279		15-Dec-98	28d	3310	Gunn	Stent sv BCP		2.50mm	11.00mm	6atm	BDV	11.00mm	2.50mm	Cx	2.10mm	-	1 _ 9	N
280	28D BCP SV study	16-Dec-98	28d	3215	Gunn	Stent sv BCP		2.50mm	11.00mm	6atm	NIR	11.00mm	2.50mm	LAD	2.03mm	-	1 _ 9	N
280		16-Dec-98	28d	3215	Gunn	Stent sv BCP		2.50mm	11.00mm	6atm	BDV	11.00mm	2.50mm	Cx	1.99mm	-	1 _ 10	N
281	28D BCP SV study	16-Dec-98	28d	suture R ear	Gunn	Stent sv BCP		2.50mm	11.00mm	6atm	BDV	11.00mm	2.50mm	LAD	2.07mm	-	1 _ 8	N
281		16-Dec-98	28d	suture R ear	Gunn	Stent sv BCP		2.50mm	11.00mm	6atm	NIR	11.00mm	2.50mm	OMI/Cx	2.17mm	-	1 _ 8	N
282	28D BCP SV study	16-Dec-98	28d	3297	Gunn	Stent sv BCP		2.50mm	11.00mm	6atm	NIR	11.00mm	2.50mm	LAD	2.09mm	-	1 _ 9	N
282		16-Dec-98	28d	3297	Gunn	Stent sv BCP		2.50mm	11.00mm	6atm	BDV	11.00mm	2.50mm	Cx	2.18mm	-	1 _ 8	N
283	28D BCP SV study	17-Dec-98	28d	3306	Gunn	Stent sv BCP		2.50mm	11.00mm	6atm	NIR	11.00mm	2.50mm	LAD	2.13mm	-	1 _ 8	N
283		17-Dec-98	28d	3306	Gunn	Stent sv BCP		2.50mm	11.00mm	9atm	BDV	11.00mm	2.50mm	Cx	2.07mm	-	1 _ 10	N
283		17-Dec-98	28d	3306	Gunn	Stent sv BCP		2.50mm	11.00mm	7atm	BDV	11.00mm	2.50mm	OM	2.13mm	-	1 _ 9	N
284	28D BCP SV study	17-Dec-98	28d	3308	Gunn	Stent sv BCP		2.50mm	11.00mm	6atm	NIR	11.00mm	2.50mm	LAD	2.05mm	-	1 _ 9	N
284		17-Dec-98	28d	3308	Gunn	Stent sv BCP		2.50mm	11.00mm	8atm	BDV	11.00mm	2.50mm	Cx	2.13mm	-	1 _ 10	N
285	28D BCP SV study	23-Dec-98	28d	3356	Gunn	Stent sv BCP		2.50mm	11.00mm	9atm	BDV	11.00mm	2.50mm	LAD	2.10mm	-	1 _ 9	N
285		23-Dec-98	28d	3356	Gunn	Stent sv BCP		2.50mm	11.00mm	8atm	NIR	11.00mm	2.50mm	Cx	2.10mm	-	1 _ 10	N
286	28D BCP SV study	23-Dec-98	28d	3357	Gunn	Stent sv BCP		2.50mm	11.00mm	6atm	BDV	11.00mm	2.50mm	LAD	1.99mm	-	1 _ 9	N
286		23-Dec-98	28d	3357	Gunn	Stent sv BCP		2.50mm	11.00mm	6atm	NIR	11.00mm	2.50mm	Cx	2.05mm	-	1 _ 9	N
287	28D BCP SV study	23-Dec-98	28d	3358	Gunn	Stent sv BCP		2.50mm	11.00mm	6atm	NIR	11.00mm	2.50mm	LAD	1.97mm	-	1 _ 9	N
287		23-Dec-98	28d	3358	Gunn	Stent sv BCP		2.50mm	11.00mm	9atm	BDV	11.00mm	2.50mm	Cx	1.97mm	-	1 _ 8	N
317	28D LDD Genentech	20-Apr-99	28d	3433	Gunn, Chico	LDD, systemic, stent		3.50mm	11.00mm	8atm	PS153	11.00mm	3.50mm	LAD	2.93mm	-	1 _ 8	N
317		20-Apr-99	28d	3433	Gunn, Chico	LDD, systemic, stent								Cx		-	1 _ 8	N
318	28D LDD Genentech	20-Apr-99	28d	shoulder spot	Gunn, Chico	LDD, systemic, stent		3.50mm	11.00mm	8atm	PS153	11.00mm	3.50mm	LAD	0.00mm	-	1 _ 10	N
319		20-Apr-99	28d Died CHB 40mins post	_	Gunn, Chico	LDD, systemic, stent		3.50mm	11.00mm	8atm	PS153	11.00mm	3.50mm	LAD	0.00mm	-	1 _ 8	N
320	28D LDD Genentech	20-Apr-99	28d	3410	Gunn, Chico	LDD, systemic, stent		3.50mm	11.00mm	8atm	PS153	11.00mm	3.50mm	LAD	0.00mm	-	1 _ 9	N
320		20-Apr-99	28d ignore RCA	3410	Gunn, Chico	LDD, systemic, stent								RCA		-	1 _ 8	N
321	28D LDD Genentech	22-Apr-99	28d	3432	Gunn, Chico	LDD, systemic, stent		3.50mm	11.00mm	8atm	PS153	11.00mm	3.50mm	LAD	2.84mm	-	1 _ 8	N
321		22-Apr-99	28d	3432	Gunn, Chico	LDD, systemic, stent								RCA	2.77mm	-		N
322	28D LDD Genentech	22-Apr-99	28d	3430	Gunn, Chico	LDD, systemic, stent		3.50mm	11.00mm	8atm	PS153	11.00mm	3.50mm	LAD	2.78mm	-	1 _ 8	N

Coast

Key Features of Archive

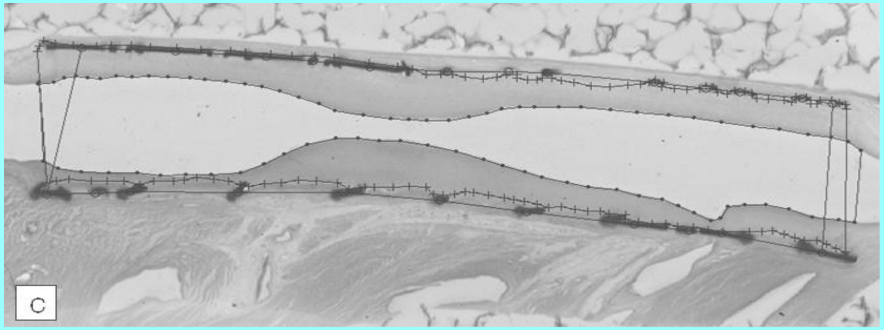
- 500+ samples of stented or balloon injured porcine arteries collected over a 10 year period.
- These arteries have been sectioned, using a technique developed by Gunn *et al.* who were the first group to successfully section arterial tissue with the stent *in situ*.
- Each artery is typically cut into ~20 sections.
- Sections are visualised and images captured (at high and low magnifications) and stored digitally.
- Sections may be stained using standard histological techniques for better contrast between arterial layers:
  - Haematoxylin & Eosin (routine stain)
  - Elastic Van Gieson (for elastin)
  - Picro Sirius Red (for collagen)
- Sections may be used for immunohistochemical analysis using antibodies to detect specific components:
  - vWF (Endothelial Cells)
  - Alpha Smooth Muscle Actin (Smooth Muscle Cells)

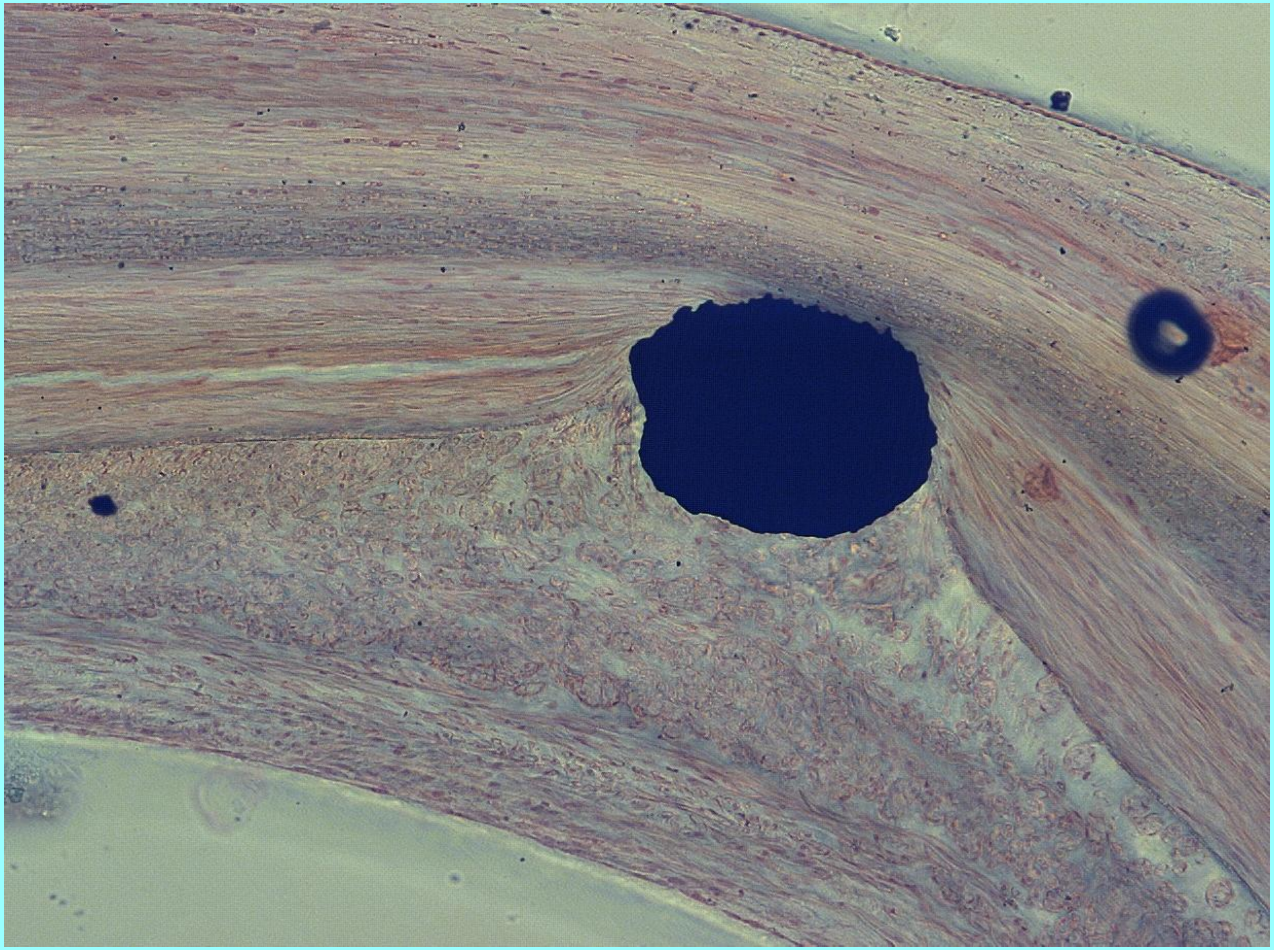
Low power image of stented artery with moderate restensosis (transverse section)



Detail of neointima around stent struts

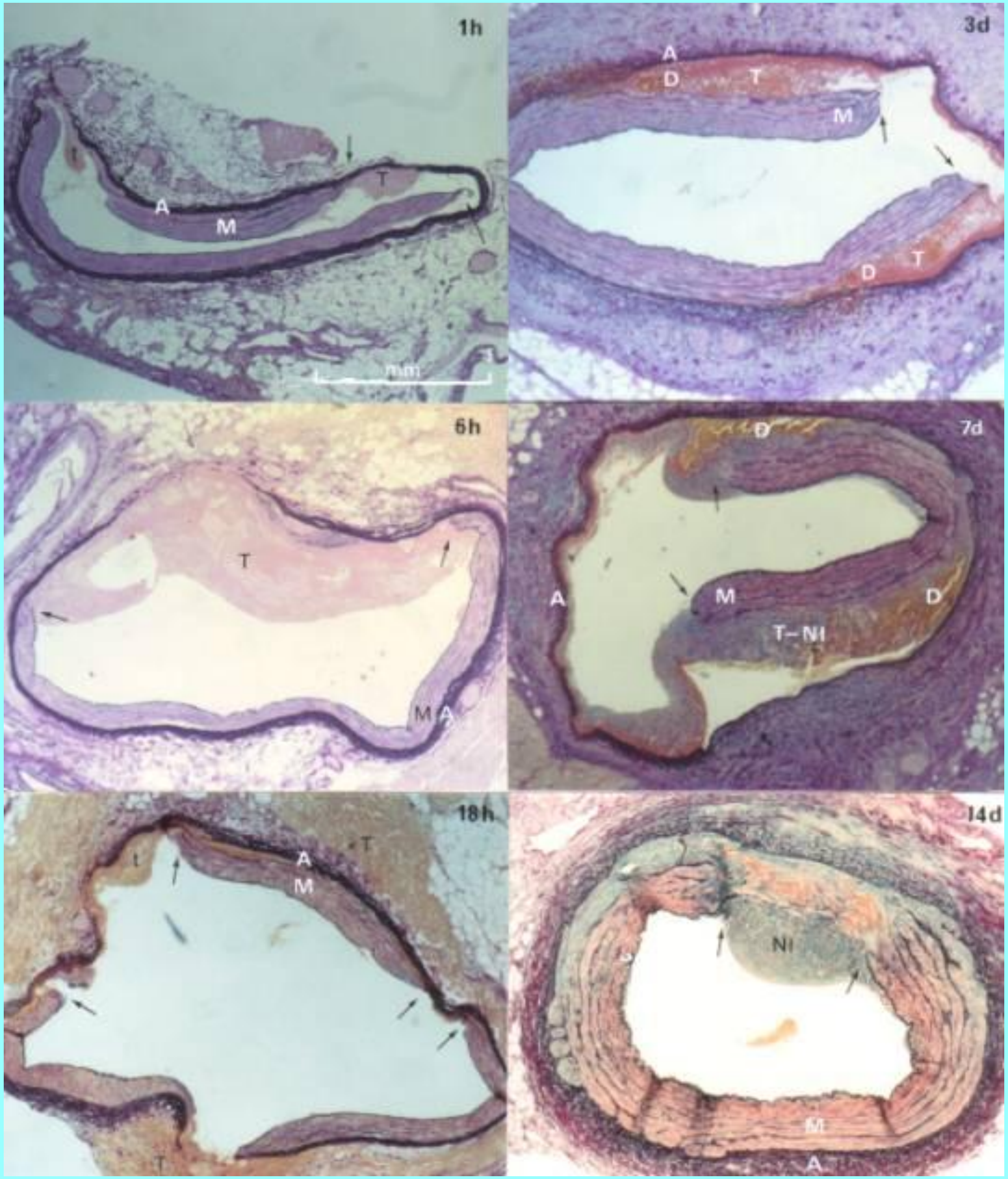
Longitudinal section through stented artery showing variation in reaction along vessel length



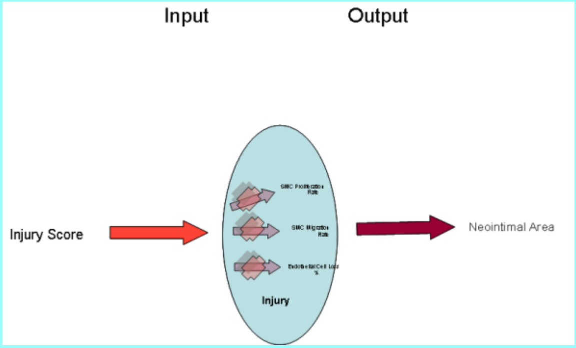


Detail of single stent post showing vessel wall deformation, smooth muscle cell organisation in the neointima and re-endothelialisation

Arterial injury: timecourse of healing



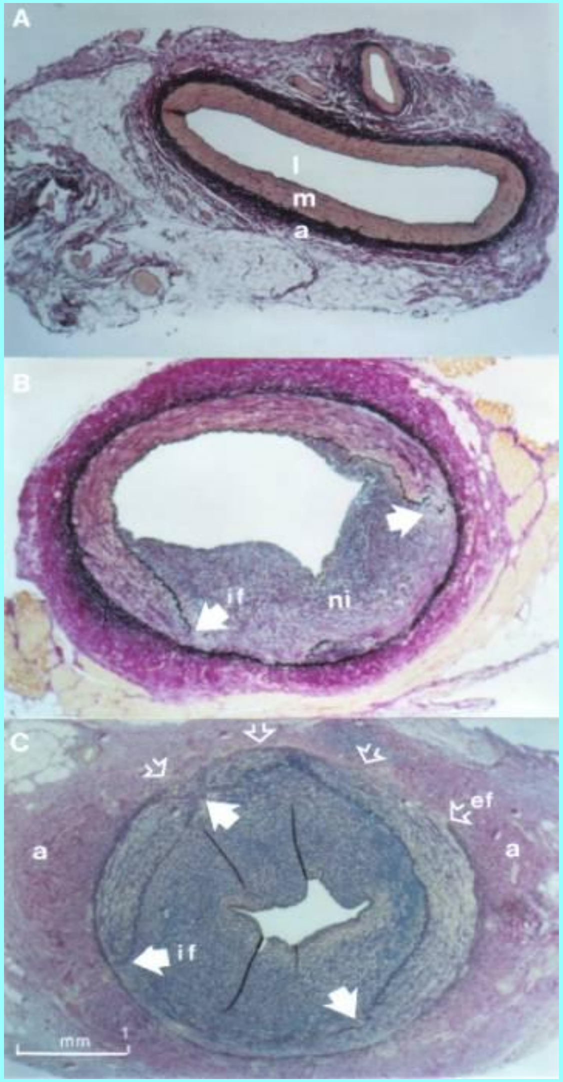
Arterial healing: importance of degree of injury



Control

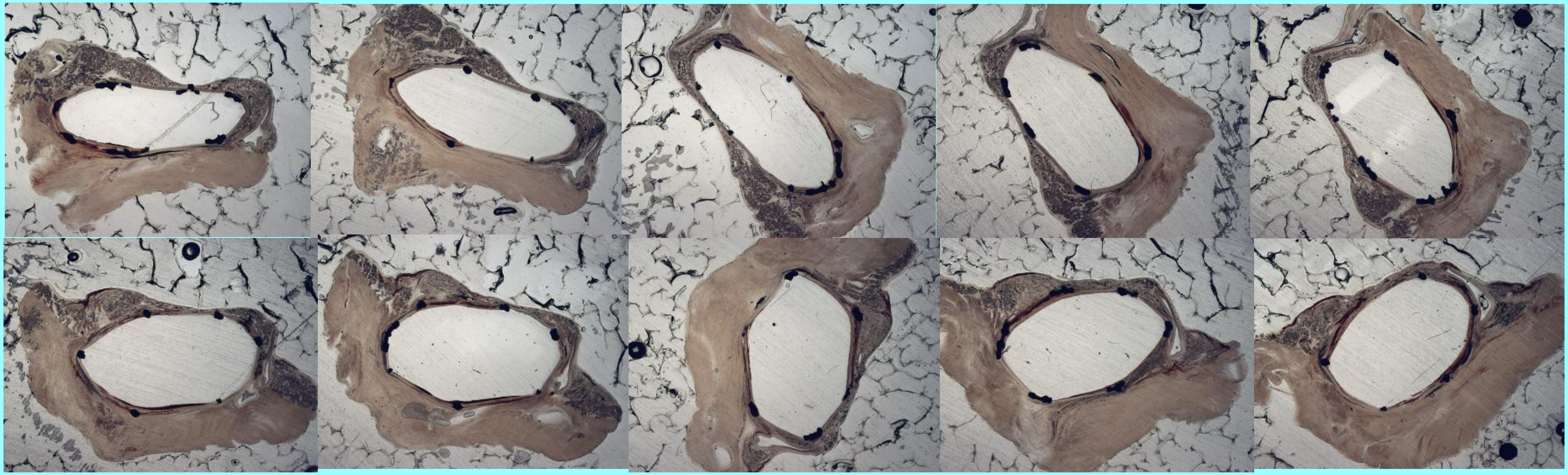
Moderate injury

Severe injury



Coast

Sequential histological sections *(x1 Magnification)*



Specimen: JG 926 LAD

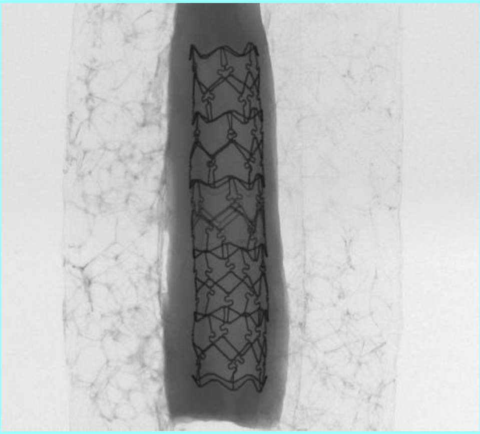
Coast Identification of Deficiencies

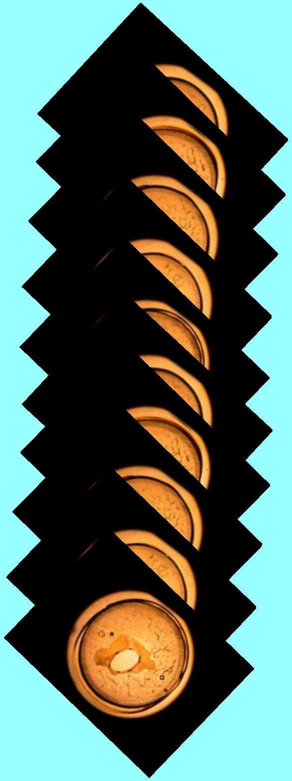
- Deficiencies in Data Set
  - Majority of data is specific to 28 day time point. A lack of early time point data was identified.
  - Issues of Vessel Curvature

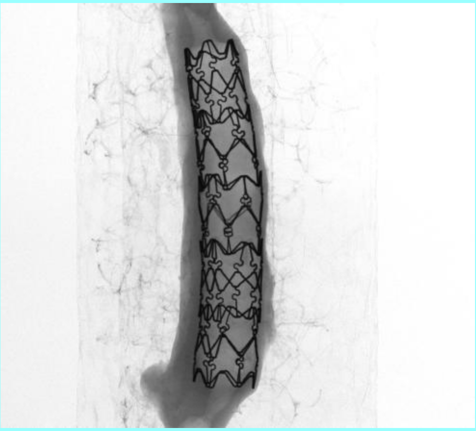
- Solution
  - Micro-CT analysis of whole early time point stented vessels with subsequent sectioning.

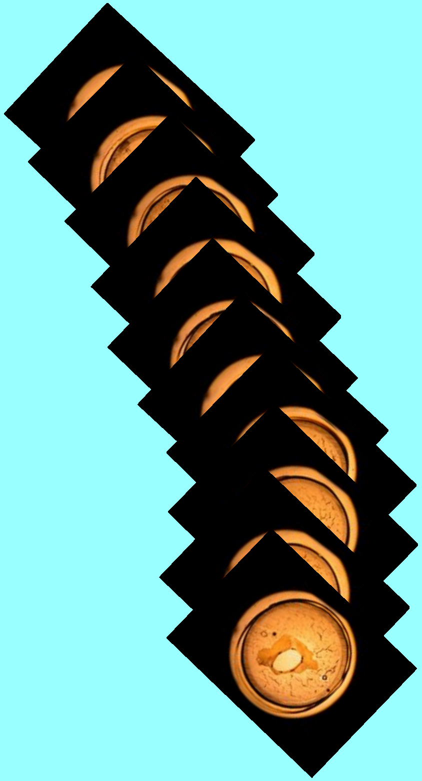
Coast

Curvature









To wrap up

- CxA theory underway
- CxA simulation software, version 1, will be available soon
- CxA model of in-stent restenosis available
- Porcine dataset is being processed to serve as validation for the CxA model of ISR.