Aneurysm enlargement utilizing a computational growth model

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Abstract

Aneurysms are common, life-threatening, and poorly understood. It is nearly impossible to observe the disease process which leads to aneurysms, especially in early stages. As a result, little is known about causes of the disease, and there is no strongly-correlated marker of patient prognosis. Several things are known. An aneurysm's mechanical environment has a strong influence over its behavior; weakening of the arterial wall is the main proponent of aneurysm rupture; and remodeling and turnover are chief mechanisms of weakening. These principles will be utilized to build computational and analytic tools that can reconstruct the disease process and serve as a predictor of patient prognosis.

Three things will be developed: first, an analytic framework for describing the growth mechanics of fiber-based elastic materials; second, a modeling paradigm for the creation of patient-specific geometries of organs; and, third, a codebase for the exploration of the first as applied to the second. These tools will investigate the consequences and test the predictive capability of the prevailing theory in arterial modeling.

The proposed work extends the literature in several ways: using anisotropic stress-induced growth terms, incorporating remodeling through a history-dependent turnover of fibrous tissue, adding a term to the strain energy accounting for the background material, and incorporating patient-specific initial configurations.

This work builds several significant bases crucial for future research. It brings together successful lines of research from arterial mechanics, fluid-structure interaction, geometry-based computing, and extension tests of arterial tissue. It will serve as a testbed for incorporation of emerging, as-yet unresolved research in arterial modeling: the effect of external organs, remodeling of fibers, and the connection between mechanical factors and aneurysm enlargement. Finally, by verifying and validating the predictive capability of the system, a "shape measurement" will emerge to provide risk measures directly from geometries. Good risk measures provide better treatment plans and reduce morbidity, mortality, and reoperative rates. The medical field has no such measure, and it needs one.

1 Specific Aims

For this work, there are three things: a theoretical formulation for predicting enlargement of intracranial fusiform aneurysms; modeling technologies for the cardiovascular system; and a simulation suite which can implement the theoretical formulation using cardiovascular and thoracic models. Together, they will act as a test of the predictive capability of the current best practices in arterial modeling. These ideas have never been combined into one model, and no verification and validation has yet been performed.

The theoretical formulation synthesizes existing concepts in the mechanics literature with novel developments in biological modeling and will provide physicians with tools of superior accuracy and predictive value. It takes standard equations for growing materials and couples it with a biologically-proper growth law. The entire formulation is implemented in a framework which computes with the geometry exactly as modeled, ensuring results of the highest possible accuracy. Most computer modeling technologies require an additional meshing step which reduces accuracy, introduces spurious results, and is often misused even by experienced researchers.

The modeling technologies will support the development of modeling pipelines for building accurate geometries of the heart and arteries. In addition, they will be designed as bases for general techniques for modeling organs in the body. The system will formalize existing model-building techniques for the cardiovascular system and extend tools that have been developed for vibration, flow, turbulence, and solid mechanics computations. See Figure 1.

The simulation will build on existing technologies for modeling tissue as an anisotropic elastic material. Capability for describing fiber-based material will be added, including terms for growth and decay (change of mass), and a notion of history-dependent turnover of tissue.

A main focus of the proposed work is to develop a state-of-the-art aneurysm modeling system from patient-specific image data to predicted outcome. This application is general: it will be used with related research utilizing the concept of turnover of cells and structural members in a tissue, or of turnover of tissues in an organ. The application serves as a testbed for experimental boundary conditions (for both the solid and the fluid) and ongoing research in the structure and structural changes of arteries (initial healthy fiber orientations, stress- and strain-dependent changes in fiber orientation, growth, healing).

A new era was introduced in [Taylor 1998], in which patient-specific engineering simulations are run to evaluate the relative value of various possible treatments and to plan and design the optimal intervention. The automation and improvements of the proposed modeling system are necessary and sufficient to provide better conclusions as to the behavior and mechanical nature of diseased arteries as well as improve the overall predictive capability of simulation tools. Physicians who use these tools will better understand aneurysm dynamics, improve their morbidity and mortality rates, and save lives.

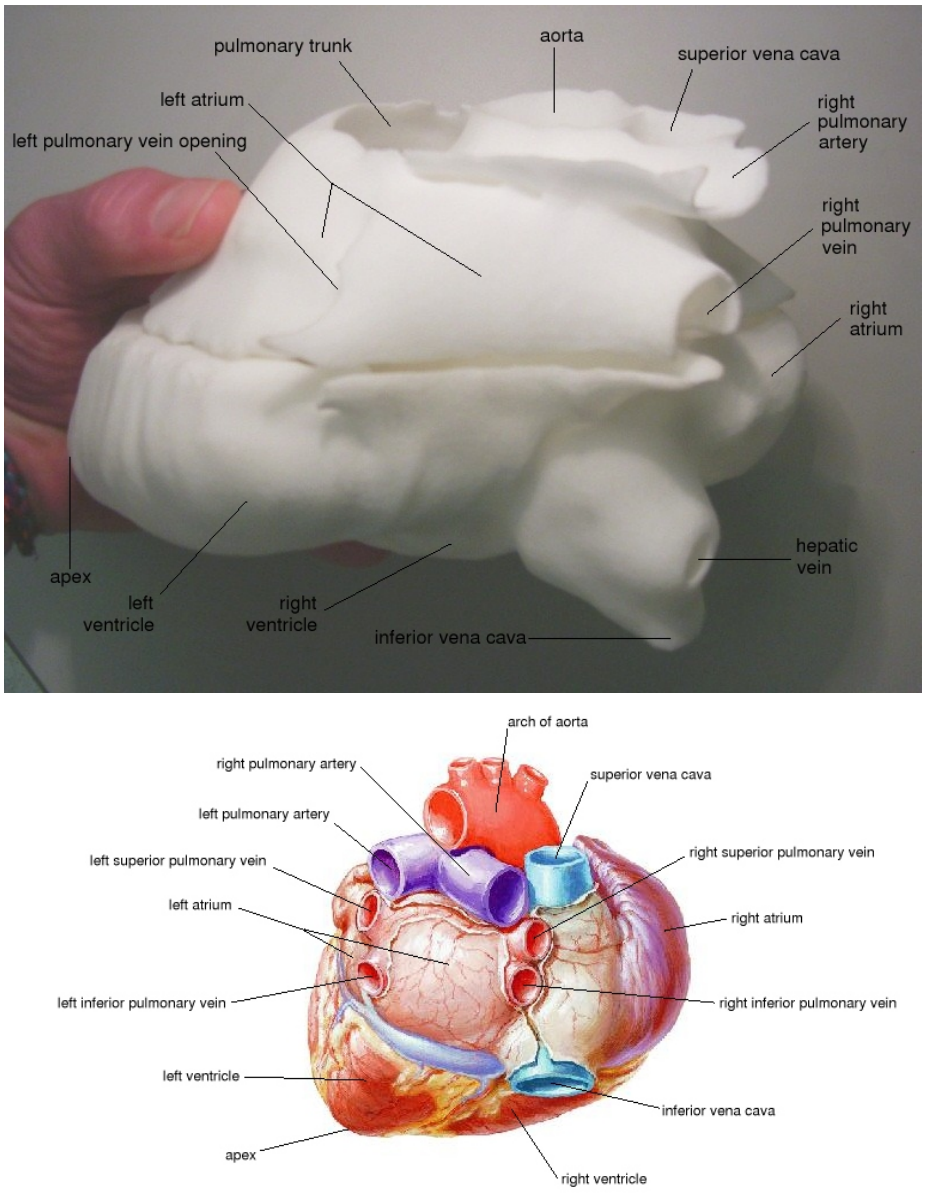


Figure 1: Comparison of a subject-specific model of a human heart [Hughes 2005] and a standard educational model [Netter's *Atlas*, plate 210a]. Note the differences in shape. The subject has only one pulmonary vein on each side.

2 Background and Significance

2.1 Medicine

An aneurysm is a bulge in the wall of an artery, a vein, or the heart. Arterial aneurysms occur in only a few places for reasons that are not fully understood: mainly in the abdominal aorta and cranial arteries, especially near or on the Circle of Willis. Aneurysms can be located fully automatically by observation of artery diameter. See Figure 2. Cranial aneurysms are classified into saccular aneurysms and fusiform aneurysms, depicted in Figure 3.

Aneurysms are common, life-threatening, and poorly understood. The mechanisms for enlargement and remodeling are unknown. There exists no test to determine which will grow or which are stable. Imaging aneurysms is either expensive (magnetic resonance imaging), invasive (catheterization), or toxic (x-ray computed tomography). Routine screening is not done. Consequently, little is known about the disease process.

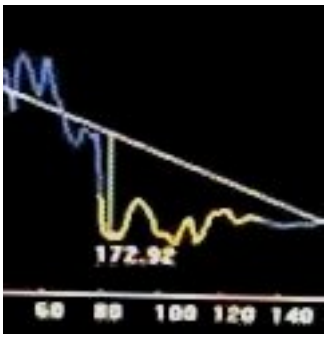
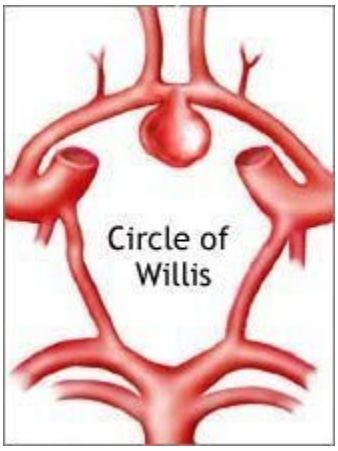


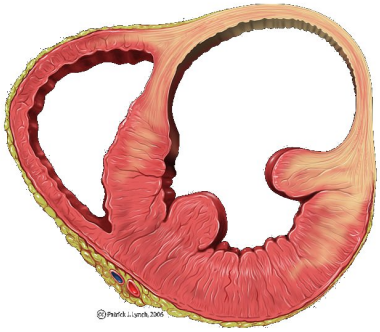
Figure 2: Automatic location of a stenosis in a user-chosen segment of artery with Philips' "Computer-Assisted Aneurysm Analysis" package for their *Allura* 3D-RA, in use at a local hospital. The curve shows actual diameter (in mm) between the endpoints. The section of curve in yellow indicates the stenosis. The point of greatest deviation is marked. Location of aneurysms is analogous.

Animal testing has yielded unsatisfactory restults. Methods for causing aneurysms—such as suturing in a pocket of tissue, degrading the aneurysm wall with chemicals, and physically scarring the arterial wall—are now known to cause unnatural structural changes. It is unclear what value they have for predicting progression of naturally-formed human aneurysms. New techniques for evaluating aneurysms are imperative.

A ruptured aneurysm is often debilitating or lethal. Aneurysms have several mechanical measures by which their risk of rupture is evaluated. The main ones are maximum diameter, rate of expansion, and wall shear stress. Saccular aneurysms also have the neck-to-height ratio. (A physician must also consider associated symptoms, and patient and familial history.) Unfortunately, none of them are much good. Maximum diameter is widely considered inadequate, the rate of expansion is almost never known, wall shear stress cannot be measured, and neck-to-height ratio is unreliable [Nader-Sepahi 2004]. Aneurysms regularly defy the measures: many small aneurysms rupture, and many large aneurysms do not. Nonetheless, owing to studies showing enlargement is correlated with rupture, maximum diameter is the predominant clinical standard, and upper and lower



(a) Saccular aneurysm in the anterior communicating artery (top) of the Circle of Willis. Saccular aneurysms usually form at the flow divider of a branch; the fibrous layer is weaker there.



(b) Aneurysm of the heart. These can occur in the left ventricle (because of the high pressures), after the wall is weakened by a heart attack or the onset of congestive heart failure. Though the proposed study will focus on cranial aneurysms, it can be applied to heart aneurysms.

(c) Physical model of a patient's abdominal aortic aneurysm prior to surgery. This is an example of a fusiform aneurysm. They often involve branch vessels.

Figure 3: Distinction between aneurysms: saccular, fusiform, abdominal, and an aneurysm of the heart. The underlying principle appears to be the same for all aneurysms: the tissue becomes weakened and subsequently bulges outward as a result of blood pressures.

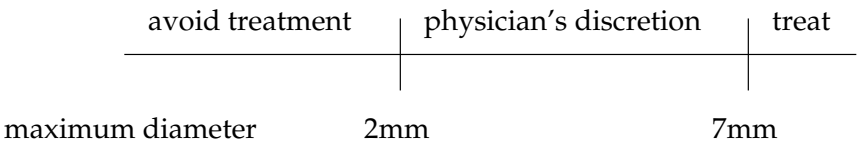


Figure 4: Cut points showing what appear to be current-practice guidelines for cranial aneurysms. A new tool's greatest utility lies in regions of uncertainty.

boundaries for dictating treatment are vague, based mostly on ensuring a huge margin of safety.

For each type of aneurysm, maximum diameters below a lower bound (assuming the aneurysm is otherwise uncomplicated), surgery is usually not performed. See Figure 4 on page 6. Above some upper bound, physicians will intervene regardless of most other circumstances. In between, physicians have discretion—this is where a predictive tool finds its greatest effect. Focusing on this central range of the commonest aneurysms maximizes the applicability of one's efforts and has the greatest value to the medical community.

Before operating on an intracranial aneurysm, a physician insists upon seeing an image of the aneurysm in order to envision its geometry in three dimensions. The physician is not satisfied with seeing one or two orthogonal projections—s/he wants to rotate a three-dimensional surface representation, or at least increment through parallel slices.

This insistence upon a three dimensional representation demonstrates a belief that the *geometry* of an aneurysm is a key feature of its treatment. In fact, aneurysms with irregular walls or blebs are known to be more dangerous than less complicated ones. Physicians need tools that evaluate *geometry* in terms of its risk of worsening. Geometric *quantifiers* must be developed.

The proposed formulation is a necessary step toward the greater goal of establishing a geometric quantifier for the evaluation of an aneurysm's disease progression. The quantifier should provide a risk measure for physicians to understand the likelihood of the aneurysm's enlargement. It should also provide a means of comparing risk of one shape in one environment with the risk of a different shape in a different environment. But to do that, one must first build predictive modeling and simulation tools.

The medical community is ready for these tools. A patient-specific computational tool for the evaluation of aneurysms can be easily inserted into the differential diagnosis physicians and hospitals use to treat this condition:

1. It will use imaging data already taken for this condition.
2. It will not require special procedures to operate or expensive equipment.
3. Its use will not contradict or invalidate any existing treatment procedure.
4. Physicians already want this capability.
5. No tool exits to perform the task.

Now is the time to build one.

2.2 Bioengineering

Mechanical descriptions of arteries have been under development for decades. A recent emergence is the utilization of turnover of collagen fibers in consitiutive modeling and a so-called homeostatic stress.

2.2.1 Fibers in artery walls

It is known that arteries consist of several layers of tissues, and that the tissues are partly composed of collagen fibers whose main (mechanical) purpose is reinforcement of the tissue. There are, investigations have shown, two families of fibers, symmetrically oriented in a helix fashion, and there is some spread to the distribution of fiber angles. These fibers have dynamic roles in the makeup of artery walls, and heavy investigation into their mechanical behavior is underway by multiple research groups. The current work will develop understanding of the mechanics of growth and remodeling of solids with two fiber families through stress-mediated turnover. Based on work by other researchers, I believe the work will describe actual disease progression well.

The fibers that make up artery walls are known to have preferred directions, but the basis of their preference is unknown. Two competing ideas are that the directions minimize stress and that they minimize strain. It is not clear how quickly they adapt to changing conditions, what changes they adapt to, or how to model either the conditions or the changes.

Understanding the mechanisms and driving factors behind fiber orientation is crucial to the understanding of arterial mechanics. No one has yet published studies of aneurysms modeled as 3D solids with fibers that change due to stress- or strain-mediated growth and remodeling. Other work in this area has been with introductory membrane models or without the growth and remodeling formulations. Our work should more accurately describe aneurysm disease progression, and we intend to perform verification and validation, described below, that not only assesses our accuracy, but suggests a standard by which other researchers can compare their own.

2.2.2 Turnover of constituents

Tissues in the human body are made up of cells that die and are replaced through a natural process of turnover. Fibers in arterial walls, largely collagen types I and III, are no exception, and turn over with a half-life somewhere between seven and seventy days [Humphrey(1) 2002].

Turnover has been used in the study of both healthy arteries [Gasser 2006, Kroon 2007] and aneurysmal. In particular, there have been promising continuum mechanics formulations for the uptake and deposition of collagen in intracranial fusiform [Baek 2006] and saccular [Kroon 2007] aneurysms.

2.2.3 Homeostatic stress

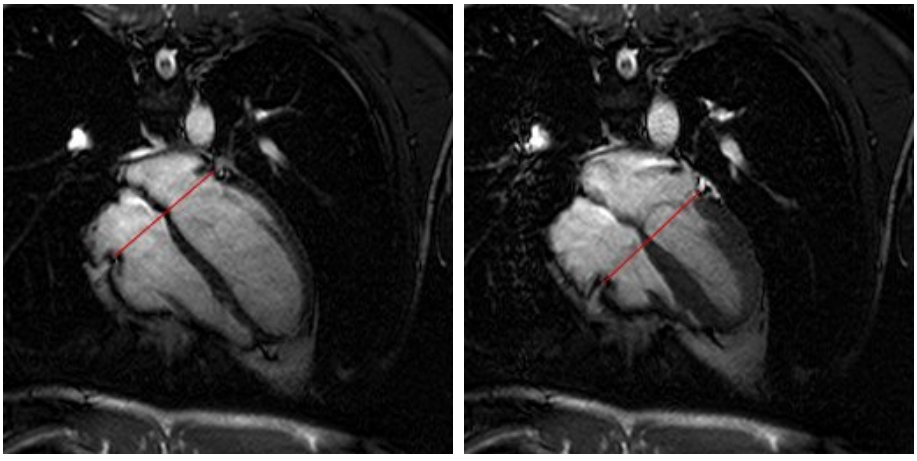
It is believed that tissues enjoy a so-called *homeostatic* stress, and that they actively remodel in order to restore their stress to the homeostatic level. Improved understanding over the last several decades has led to the recognition of several mechanisms for creating and preserving this homeostatic stress in the face of hypertension, remodeling, aging, residual stresses, etc.

Moreover, it is known that collagen types I and III are deposited oriented according to stresses and/or strains experienced by the wall at the time of deposition, and they are deposited with a pre-existing internal stretch. Proper expressions for the orientation of collagen fibers and their so-called "pre-stretch" is a subject of ongoing study.

These two ideas–that arteries have a preferred level of stress, and that collagen fibers are oriented according to stress levels–are the key underpinnings of the computational theory for this work. For a better understanding, consult [Humphrey 2000].

2.3 Application areas

There is no lack of application for arterial simulation technologies. Eighty percent of diabetics die of cardiovascular disease, largely due to the athersclerosis it causes. Aortic models must incorporate large movement due to the motion of the heart. (See Figure 5.) Other application areas are discovery of vulnerable placques, analyzing the fibrous cap covering vulnerable placques, analyzing placque growth, simulating effects of hypertension on healthy and diseased



(a) end diastole (b) end systole

Figure 5: Movement of the heart during the cardiac cycle. A proper aortic model accounts for this movement.

arteries, aging, medical device design and simulation (see Figure 6), medical planning, drug delivery, atherosclerosis due to diabetes, cardio-pulmonary resuscitation, embryonic heart development from a tube to a four-chambered organ[Taber 2000], and even death of whales from sonar.

3 Study design

For the study underway, subjects will be chosen who have had two scans of their aneurysm—a baseline scan and a followup—spaced six to eighteen months apart.

To begin, baseline CT image data (or MR, whichever is available) will be used to produce model A, the baseline model. See Figure 7. The modeling technique developed in a previous study for simulation-based medical planning will be utilized. A simulation will be run which will effect changes in model A to produce model B, the simulated model. Inputs to the simulation are model A and other data collected: blood pressure, age, artery wall thickness (IMT), duration between imagings, aneurysm location, familial history, symptoms, etc.

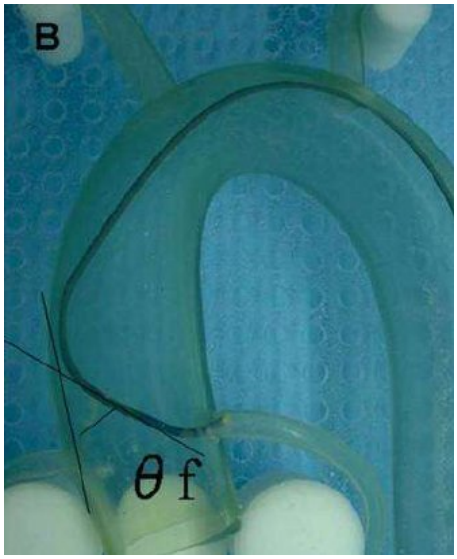
Follow up imaging data will be used to produce model C. Since model B is intended to predict model C, the two will be compared, and the observed results reported. Improvements to the modeling and simulation techniques will be attempted. Candidate independent risk factors for aneurysm enlargement will be sought. Of particular interest for risk factors are data which cannot be observed or are not observed routinely, such as IMT, mean aneurysm curvature, wall shear stress, rate of decay of elastin, and rate of turnover of collagen.

4 Conclusion

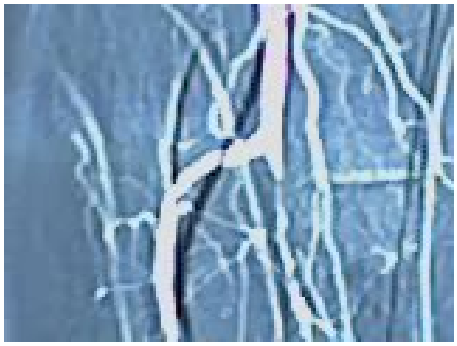
The biggest challenge to modeling of tissues (or any phenomenon) is and always will be the determination of relevant behavior, creation of constitutive laws to describe that behavior, the establishment of conditions under which the laws are valid, and the assessment of the manner and extent of their validity. Knowing how a given tissue behaves and knowing ways in which these behaviors can be represented in biomechanical theory is the primary focus of every modeler.

The present work is intended to fill four roles that meet this challenge: it is intended as an implementation of current best practices in arterial modeling; as an evaluation of those best practices; as a testbed for exploration of competing morphologic laws; and for testing the parameter space. Through direct results and their inevitable application to other areas, this work will have a huge impact on the biomechanical literature and medical practice.

(a) Judkins 4 family of catheters in its reference configuration. The JL4 is on the right. Also shown is the JR4 (middle), used for locating the right coronary artery, and a "pigtail" catheter for measuring left ventricular ejection fraction.



(b) The JL4 as deployed [Ikari 2005]. Notice that catheters do not follow the midlines of arteries, as most computer simulations would have it.



(c) In fact, they straighten them.

Figure 6: The JL4 catheter is used to locate the left coronary artery (LCA), as in (b). Its reference shape is designed so that the body of the catheter effortlessly positions the tip at the LCA's ostium. Though they do not control the tip, a common saying among cardiologists is, "The catheter knows where to go." Making a catheter "know where to go" is nontrivial, but image (b) shows the crudity of the state of the art: PVC tubes mounted in a tank of water. Simulation and a good knowledge of the elasticity of arteries will revolutionize device design.

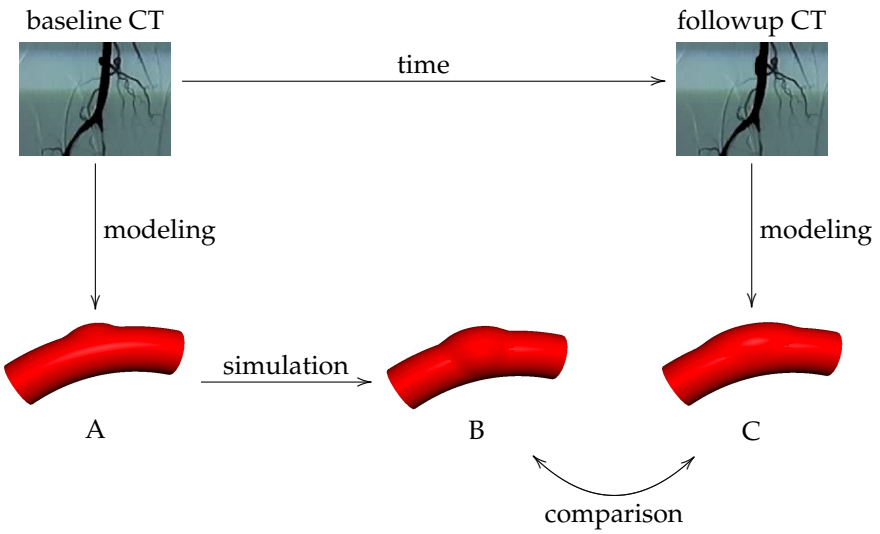


Figure 7: Baseline patient data is used as the starting point for simulation; the prediction will be checked against followup data. If there are multiple followup imagings, multiple stages of development can be assessed.

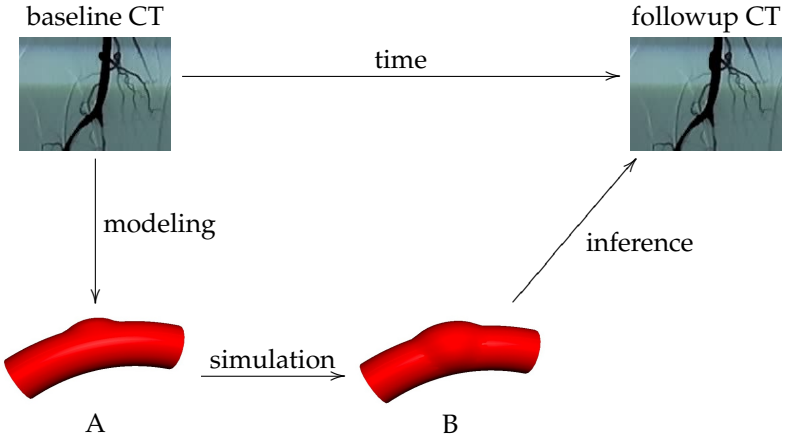


Figure 8: Best of all is when the modeling process is invertible, and the simulation is truly predictive.

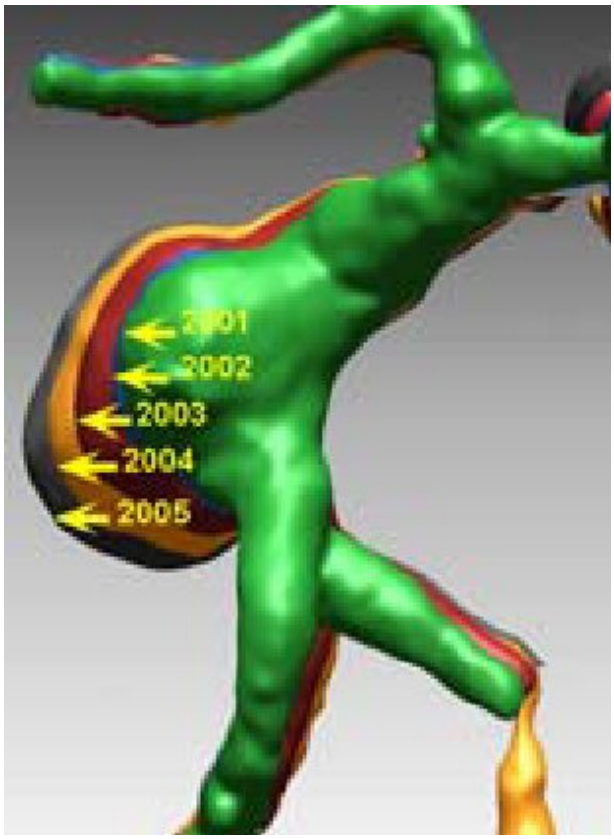


Figure 9: When we can predict this [Saloner 2005], we will have succeeded.

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