Predictive Analysis at the Forefront of Medical Product Development

Predictive analysis and simulation of medical device and implant performance using nonlinear finite element analysis can significantly accelerate product development cycles while helping manufacturers to avoid costly mistakes.

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THE BIOMEDICAL DEVICE and implant industry provides a unique and challenging environment for medical product development. Engineers are actively involved in the design, development, and manufacture of materials and devices intended for a variety of life-sustaining applications. Because the functions of such devices and implants can have varying levels of impact on the well-being of patients, FDA has three levels of classification for regulatory purposes—Class I, Class II, and Class III. The increasing levels of regulation from Classes I through III represent, in effect, a rigorous quality control program to ensure that new devices undergo adequate and, if required, extensive testing and trials to establish their performance prior to formal release into the U.S. market.

Understandably, the development cycle for a medical product can be quite complex, especially for Class II and Class III devices. The conventional product development process of design-build-test-rebuild typically involves several trial-and-error-based iterations of a concept prior to full-scale production. These iterations are costly and tax resources, especially since rework loops in the initial development phases of the device do not directly verify its in vivo function. Popular rapid prototyping technologies such as stereolithography, fused deposition modeling, and selective laser sintering allow design teams to duplicate part geometry and qualitatively verify design intent. Unfortunately, rapid prototyping does not provide any quantitative feedback on the functional mechanical performance of an actual device in vivo.

In the early stages of the development of a new device or implant, it is not desirable economically to manufacture functional prototypes of several concepts for in vivo testing. When prototypes are fabricated, the inability of a device design to deliver the intended function is established only after the organization has gone through an entire product development cycle. In this case, a change in the design could have a dramatic financial impact on the company that is developing the product.

Current approaches to medical device development can be significantly enhanced using such advanced computational methods as nonlinear finite element analysis (FEA). This computer-based simulation technology has experienced tremendous growth over the past 10 years. As a result, there are several commercial software programs available to the engineer appropriately trained in the theory and practical application of this analysis method.

The theoretical simulation techniques described below have a definite role in the engineering development cycle for medical devices or implants. While challenges do exist in the application of the technology, an engineer with the appropriate level of experience and training can effectively apply these methods to accelerate the product development process.

Predictive analysis will never completely replace prototyping and testing. However, drawing from past experience with this technology, in most cases predictive analysis tools limit the number of functional prototypes and trial testing, including expensive animal trials.[1,2] Effective integration of engineering-mechanics-based design decisions into the medical device development process is also usually achieved.

THE ROLE OF PREDICTIVE ANALYSIS AND SIMULATION

Two popular yet diametrically opposed perspectives on the intended role of predictive simulation in the medical products industry are both based on misconceptions. The first school of thought has reservations regarding the application of computer-based simulation. The reasoning behind this is that inputs to a computational simulation of the mechanics of a device and surrounding tissue sometimes appear to misrepresent the true boundary conditions or material properties. The net result of this misconception is that engineering analysis and simulation as a tool is abandoned, and a trial-and-error process is adopted as the preferred product development strategy. The second school of thought believes that simulation will completely replace the need for all prototyping. While this has occurred to a limited extent in conventional engineering applications such as the automotive industry, it is not likely to occur within the medical device industry because of the kind of products involved.

The true role of computational simulation and predictive analysis lies between these two extremes. A carefully defined

computational mechanics model of a device-tissue interaction problem can be invaluable to a biomedical designer in providing feedback on the relative merits and demerits of different design options, for example. In this sense, simulation of the mechanical performance of a medical device or implant in vivo using nonlinear FEA can be employed routinely at different phases of the product development cycle as deemed appropriate by a project team.

Most medical products involve materials, such as polymers, and manufacturing techniques (e.g., injection molding, extrusion, blow molding, thermoforming, and compression molding) that introduce significant variability in component performance. Designs must also account for biological variability in cases where the device interfaces directly with tissue. In this situation, highly variable tissue material properties play a significant role. Mechanical properties of living tissue are functions of several factors such as age, pathological state, type of tissue, and collagen-elastin-muscle content. The resulting device-tissue interaction problems involve severe nonlinearities in mechanical and material behavior. This is the underlying feature of most design problems involving polymeric components that interact with tissue, which is a highly nonlinear material. As a result, some form of in vitro or in vivo testing in animal models with a fully functional prototype is always required. Nonlinear FEA can be used as a complementary tool in conjunction with appropriate material descriptions to predict such nonlinear phenomena. This adds tremendous value to the product development process and dramatically reduces the risks associated with mechanical component design.

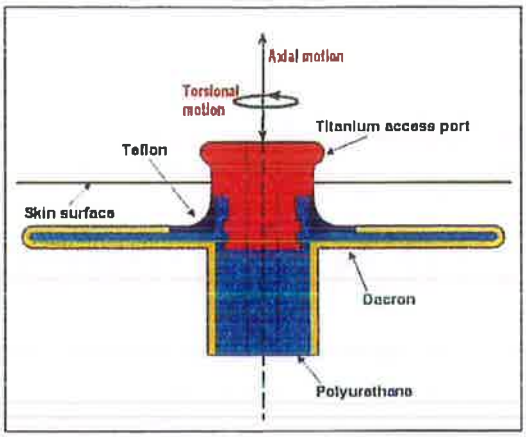

Figure 1. Schematic of a typical percutaneous device. Axial and torsional motions could develop stresses in the device as well as at the tissue--implant interface.

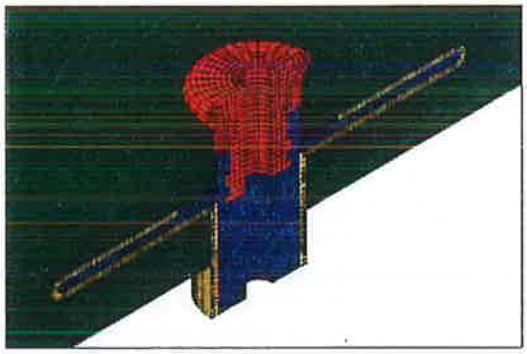

Figure 2. Finite element model of the percutaneous device, shown in Figure 1, implanted in skin.

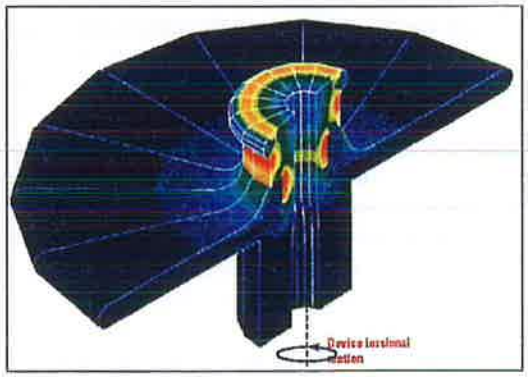

Figure 3. Von Mises stress in the device during torsional loading and motion.

APPLICATIONS OF PREDICTIVE ANALYSIS AND SIMULATION

The growth and development of the application of nonlinear FEA technology as a predictive analysis tool has enabled its application in several areas of medical device design and manufacturing.[3] The diverse range of applications include such hard tissue implants and devices as:

- Fracture wires.
- Fixation pins (internal/external).
- Bone plates and screws.
- Total joint replacements.
- Dental implants.

Soft tissue implants and devices include:

- Vascular grafts.
- Percutaneous devices.
- Heart assist devices (pacemakers and LVADs).
- Ear and eye implants.
- Surgical tools.

As mentioned above, the role for predictive analysis tools can encompass several product development functions, such as upstream design concept evaluation, "what-if" material sensitivity studies, understanding tolerance effects, manufacturing and materials processing simulation, failure analysis in metallic and polymeric components, and generation of analytical data in support of 510(k) and premarket approval applications.

Applications of predictive analysis for the first three product design and development activities from the above list are described below. A forthcoming article will address the application of this technology to the design and optimization of manufacturing processes, as well as to problems in failure analysis in metallic and polymeric components in medical devices.

UPSTREAM DESIGN CONCEPT EVALUATION

One of the most effective applications of predictive simulation is upstream design concept evaluation in the earliest stage of the product development cycle, i.e., when a designer is conceptualizing the configuration of the device. Application of predictive nonlinear FEA at this stage facilitates physics-based quantitative ranking of several design concepts. The following case study is a good example of the application of FEA to these areas.

Case Study: Percutaneous Implant Evaluation. An example of the application of predictive analysis is the design evaluation of a conceptual percutaneous implant (Figure 1).[3] Percutaneous implants are surgically introduced under the skin for long-term use.[4] These implants serve as conduits for the transfer of information in applications that can include drug delivery, blood monitoring, colorectal surgical procedures, pacemakers, and ports for kidney dialysis. Mechanical design issues for such devices include:

- Material selection.

- Minimization of tissue-device interface stresses.
- Optimization of implant geometry for various possible motions of the device.

A key issue in designing these implants relates to the local stiffness of the implant at the implant-tissue interface. A large mismatch in stiffness between the implant surface and the tissue will result in stress concentrations that could be detrimental to the implant material, the tissue, or both. Given that the properties of soft or hard tissue are very sensitive to changes in mechanical stimulus in vivo, a phenomenon known as Wolff's Law,[5] the engineering of the tissue-implant interface is extremely important. A predictive simulation model allows the performance of the design to be bounded in this sense. Nonlinear FEA results for the percutaneous implant example are shown in Figures 2 through 5. These simulations capture interlaminar stresses within the implant materials in addition to obtaining estimates of the loads transferred to skin across the Dacron-tissue interface.

Results from the nonlinear FEA simulation model of this percutaneous device can be used to drive changes in the design, which could include material selection or geometric changes that would ensure the long-term reliability of the device and minimize the mechanical stresses at the tissue-device interface. The efficiency of the seal at the port can also be evaluated with FEA and contact-stress analysis to determine the magnitude of the seal pressure. Because the seal is microbial, it is critical that a minimum contact pressure is maintained over time and across the range of manufacturing tolerances in the access port. Recently described methods of using FEA to analyze sealing and closure systems can be applied to this class of design problems.[6]

"WHAT-IF" MATERIAL SENSITIVITY STUDIES

The unique feature of designing a medical device for a load-bearing application is the fact that the device material chosen not only has to be biocompatible and FDA approved, but also must deliver the appropriate mechanical function within the design envelope. A computational model can be used to perform "what-if" evaluations to determine the optimal range of mechanical properties of the device material. This simulation can be leveraged to assess the effect of biological variability and resulting mechanical property differences in the tissue that could impact device performance. The measurement of the tissue mechanical properties, which are often highly nonlinear, can be characterized using specialized in vitro tests on cadaveric tissue, in vivo tests in animal tissue, or a combination of both.[7] Sample sizes for these tests can be controlled via statistical power analyses to deliver $\pm 2\sigma$, $\pm 3\sigma$, or even $\pm 6\sigma$ range of properties (σ–standard deviation).[8] Such material data allow the simulation of the device-tissue interaction problem to be exercised over the entire range of statistical variability, allowing the function of the device and the materials to be fully assessed.

Case Study: Balloon Angioplasty Catheter Evaluation. Percutaneous transluminal angioplasty (PTA) is a surgical procedure performed to alleviate stenosed arteries by compressing the calcified plaque that can block the flow of blood.[9] The goals of this procedure are to enlarge the lumen of the stenosed vessel, to maintain the lumen over time, and to provide an intimal surface that promotes neo-intimal hyperplasia.

A critical design variable that affects the performance of a balloon catheter in terms of geometry and material selection is its bifurcation pressure and subsequent inflation. The bifurcation pressure for an inflating membrane is the internal pressure required to initiate dilation, beyond which the growth of the membrane proceeds in an uncontrolled fashion (Figure 6). The mechanics

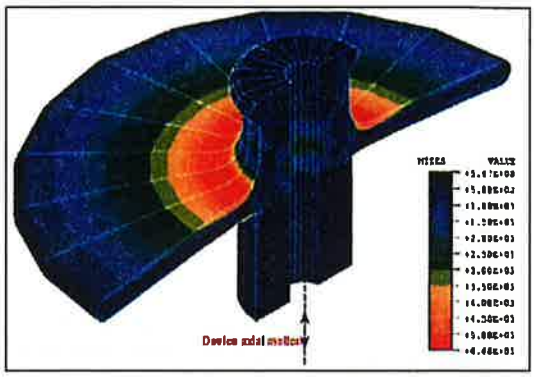

Figure 4. Von Mises stress in the device during axial loading and motion.

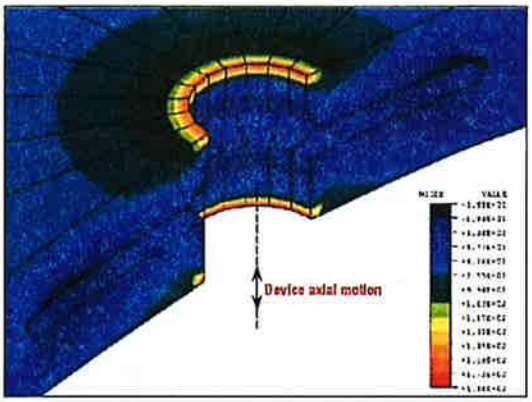

Figure 5. Stress in the skin layers during axial motion of the device.

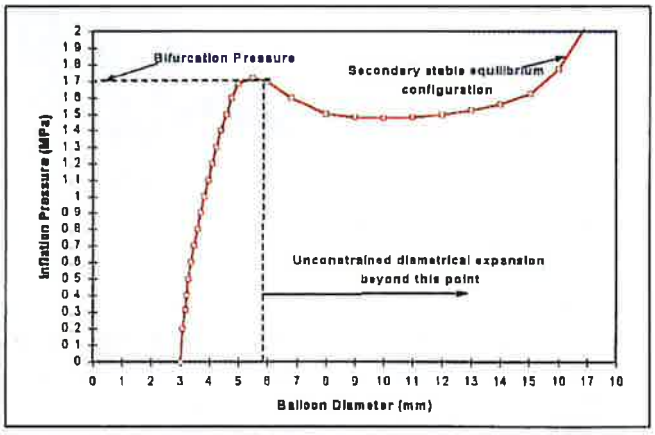

Figure 6. Pressure vs. diameter relationship for a typical balloon catheter during free inflation conditions.

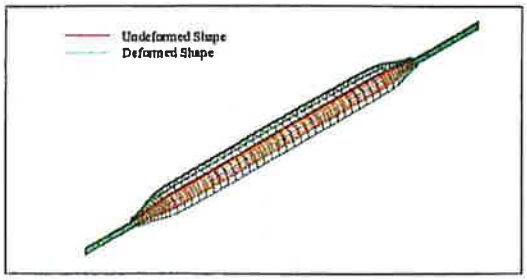

Figure 7. FEA simulation of free inflation of balloon catheter to determine bifurcation pressure.

of membrane inflation fall under a particular class of highly nonlinear phenomena called snap-through-bifurcation problems. Typical pressure vs. radius curves, illustrated in Figure 6 for balloon catheters, can be computed with a finite element model of free inflation (Figure 7) that incorporates the appropriate nonlinear material data for the polymer or elastomer used in the catheter. In general, these catheter materials can be described by hyperelastic or plasticity material models that are available in most leading nonlinear finite element codes.[1] The characterization of these materials, especially hyperelastic materials, has to be done carefully because a standard uniaxial tension test alone will not yield adequate data for balloon inflation simulations. Additional tests to characterize the response of the polymer under constrained conditions, such as biaxial stretching, must be performed to generate the appropriate material constants for input into the finite element calculations.

Prior knowledge of the bifurcation pressure is extremely useful to the designer of an angioplasty balloon system because the inflation of the membrane progresses in an unstable fashion beyond the bifurcation point. This can be seen in the form of large radial expansions with no increase in cavity pressure (Figure 6). The PTA balloon manufacturer would thus have useful information available regarding the window of operation of a given catheter and balloon design. Design variables, including material properties, wall thickness distribution, and geometry, could be used to control the initiation of the bifurcation and subsequent inflation characteristics of a given device.

Once the bifurcation pressure has been determined, the optimal balloon geometry and wall thickness can be determined by performing simulations of the surgical procedure.

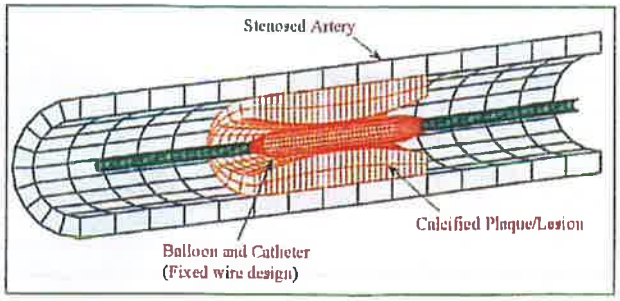

Figure 8. 3-D finite element model of stenosed artery with fixed wire balloon catheter prior to inflation.

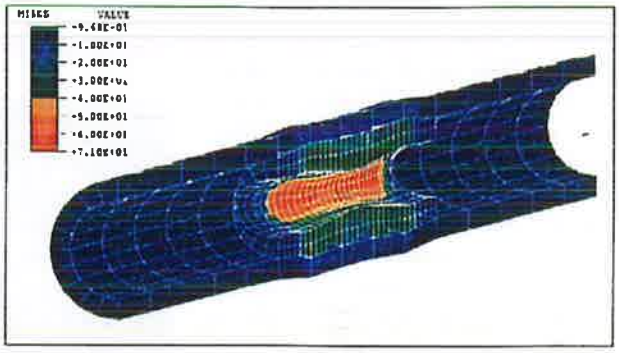

Figure 9. Plaque and artery deformations and effective stresses following balloon inflation.

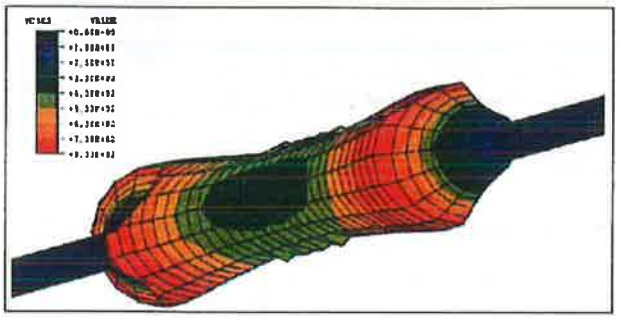

Figure 10. Balloon deformation and stresses following inflation.

This requires finite element modeling of the balloon positioned within the lumen of the stenosis and then inflated against a virtual blocked vessel (Figures 8–10). This analysis requires characterization of the 3-D geometry of a stenosis/lesion using imaging and x-ray data, plaque material properties ranging from highly calcified to minimal calcification levels, and hyperelastic material properties for a normal artery through appropriate material testing.

As a starting point, this information is typically obtained from published data and research articles and is usually sufficient for design evaluation purposes. Such a virtual predictive simulation model is an ideal platform to generate catheter performance data in terms of the ability of the design to compress plaque without initiating tears at the plaque-intima interface. Intimal splitting of plaque is clinically detrimental to the success of the angioplasty procedure.[9] Evaluation of the catheter in this virtual model can also be exercised over a $\pm 6\sigma$ range of plaque and artery properties as described earlier. The introduction of a supporting metal stent can also be simulated in the same model. In this case, the goal is to design in the stent the appropriate radial stiffness that would be required to support the dilated arterial cross section.

UNDERSTANDING TOLERANCE EFFECTS

Manufacturing tolerances have a significant impact on the performance of the many medical devices and implants that use polymeric materials. If the range of dimensional tolerances that are typical for the process is known, a predictive analysis model of the device can be assessed at the nominal as well as at the extremes of the expected dimensional variability. Analytical data generated from such models can be used in Monte Carlo simulations to generate the statistical range of the performance displayed by the device or implant.

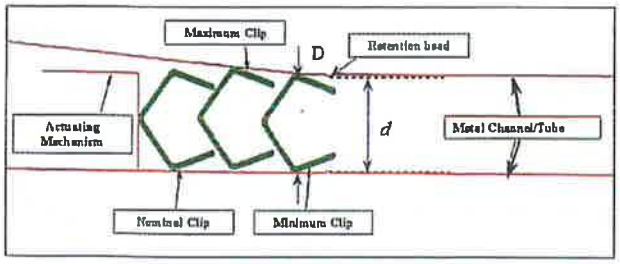

Figure 11. Conceptual layout of soft-tissue clips in a typical ligation device.

Case Study: Evaluation of a Blood Vessel Ligation Clip System. Ligation clips are being used increasingly during surgical procedures as a means to temporarily ligate blood vessels that feed into the surgery site. These clips are usually

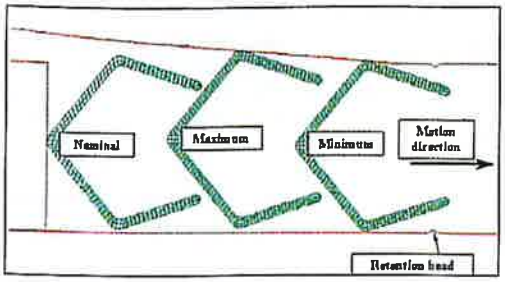

Figure 12. Finite element model of an idealized three-clip system.

loaded in cartridges and are dispensed into position by an actuating mechanism that drives a stack of clips in the cartridge through a rigid metallic channel (Figure 11). As the device is fired, the clips pass through a small bump-like feature in the channel called a retention bead. The force exerted by the surgeon to move the clips through the device is a direct function of the interference between the clip dimension (D) and the retention bead dimension (d). Depending on how the clips and channel were manufactured, there will be tolerances associated with the resulting interference that must be overcome during device actuation. These tolerances directly affect the force input that must be exerted by the surgeon. For example, metal clips formed by a bending operation will have dimensional variations caused by the varying degrees of elastic spring-back following the forming operation. Injection-molded clips, on the other hand, will exhibit variability caused by post-molding shrinkage and mold-tooling-induced tolerances.

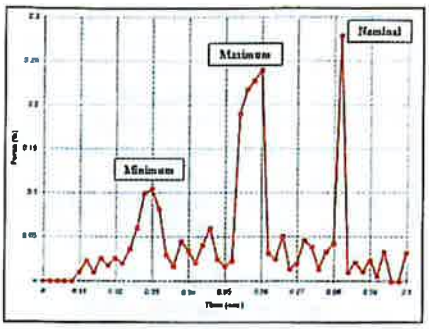

Figure 13. FEA solution for firing-force profile in the three-clip system.

A nonlinear FEA model of this device idealized as a three-clip system can be used to understand the effects of clip tolerances on the firing-force profile, as well as clip-to-clip interactions and stresses (Figure 12). The firing-force time curves described in Figure 13 are calculated by the simulations and describe the variability in the device firing force as a function of dimensional tolerance and of the stacking sequence of the clips (minimum-maximum-nominal in this case).

The unique aspect of this finite element model of the clip system is that there is a strong coupling between inertial and deformational effects in the clips. To fully capture this coupling, the model has been solved as a structural dynamics problem. A plot of the different energy quantities as a function of time, during firing of the three clips, clearly shows the energy accumulation from straining (i.e., deforming) each clip as it passes through the retention bead (Figure 14). It should be emphasized that almost all of this strain energy is converted into kinetic energy as each clip "jumps out" and moves downstream from the retention bead.

Another interesting result is that the force to fire the maximum-dimension clip is slightly lower than the value for the nominal-dimension clip (Figure 13). This is explained by the fact that the nominal clip slightly compresses the maximum clip because of clip-to-clip interaction during actuation. As a result, the effective dimension D is reduced to a value below the nominal at the point when the maximum clip passes through the retention bead, thus dropping the firing force of the clip to a value below the nominal.

Results from analyzing several stacking sequences of this three-clip system can be used to develop statistical models of clip firing to fully understand the effects of an arbitrary number of clips in the device. Once the clip is positioned around a blood vessel, an elastic-plastic finite element simulation can be used to calculate the force needed to achieve ligation in a blood vessel of given geometry and material properties (Figures 6 a–d). This solution can be used subsequently to either optimize the mechanical advantage of the firing mechanism, or to redesign the clip geometry to minimize the forming force and enhance the effectiveness of the ligation mechanism.

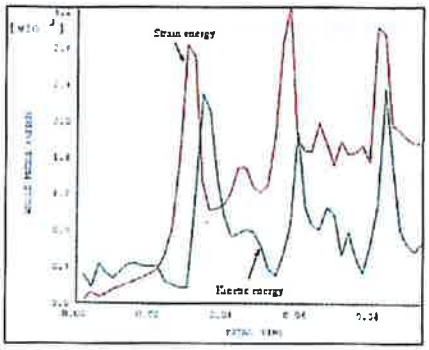

Figure 14. FEA solution for energy accumulation and release in the three-clip system.

TECHNOLOGICAL CHALLENGES

Effective application of predictive analysis requires a clear understanding of the technological challenges associated with developing reasonable computational models of in vivo device function. The most significant issues routinely encountered include estimation of device loads and boundary conditions, proper representation of tissue geometry; proper representation of device and tissue material behavior, and quantitative validation of predictions with controlled small-scale tests.

Project teams considering the effective use of predictive analysis in the product development process should ensure that the above issues are adequately handled within the project timeline. Issues related to estimation of device loads and boundary conditions can be addressed by ensuring that an appropriate level of understanding has been achieved with regards to the design intent of the device. Biomechanical principles can be employed to derive realistic boundary conditions of the device or tissue for FEA model representation.[10] Tissue geometry and composition issues can be quantitatively addressed by appropriate imaging modalities, including computer-aided tomography, positron emission tomography, and x-ray, as well as microscopy techniques (e.g., histology, morphometry).[10,11] Device material response, in general, can be handled via

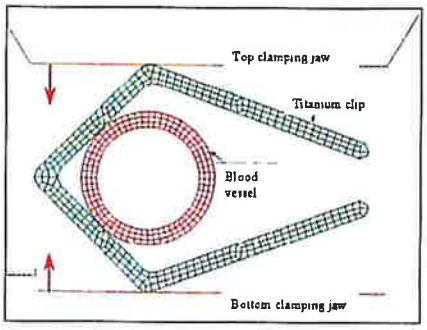

Figure 15. Finite element model for elastic plastic simulation of clip ligation and forming.

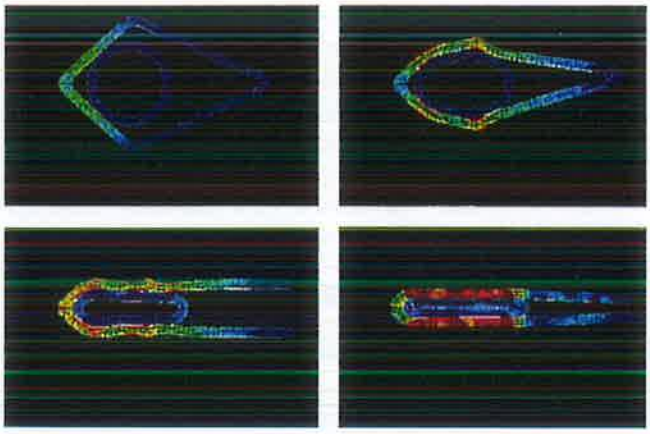

Figure 16a–d. Evolution of shape and stresses in titanium clip during ligation.

conventional material-testing methods. If loads transmitted through tissue are important, however, characterization of tissue response will require fairly specialized testing in vivo or in vitro. Statistics play an important role in the analysis of tissue material data because of the need to understand variability of the properties at a desired level of significance.

CONCLUSION

Predictive analysis or simulation of medical devices and implants is a product development tool that can significantly accelerate the time to market and help manufacturers avoid costly mistakes early in the design process. The examples discussed above demonstrate the successful application of nonlinear FEA for evaluation of medical devices. They incorporate several of the technical challenges that are commonly faced in medical implant and device design. Although these technological challenges are inherent to the functional and regulatory requirements placed on medical products, they can be handled by carefully designed experiments and the application of biomechanical engineering principles.

Simulation methods offer the medical product designer an opportunity to explore the functional attributes of a design before tooling and trial-testing commitments are made. More importantly, the results of these simulations provide quantitative data and insights that are not available via prototyping methods alone. Issues such as manufacturing defect sensitivity, dimensional variability, material selection, and variability associated with user operation can be addressed to evaluate the robustness of a particular design concept.

With increasing demands being placed on medical device manufacturers by the market and by regulatory agencies, it is critical to establish a robust product development process that incorporates sound engineering. This can be achieved by incorporating a predictive engineering simulation–driven design evaluation process within the design loop. Drawing from past experience, such an integration of predictive simulation into the design cycle has always produced tangible benefits in terms of cost reduction, reduced time to market, and minimal rework loops.

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