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A road map for computational surgery: challenges and opportunities

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Abstract

This paper introduces the fundamental concepts of computational surgery by Garbey et al. and proposes a road map for progress in this new multidisciplinary field of applied investigation. Recognizing this introduction will serve as common ground for discussion for both communities: surgeons and computational scientists; the scope of the presentation is broad rather than deep. Indeed, the field of computational surgery is sufficiently young that even the definition of computational surgery is still in the making. In this introduction, we propose multiple areas of investigation where the intersection of surgery and computational sciences is clearly in practice at the present time though surprisingly unrecognized to date. We present examples of these intersections and demonstrate the usefulness and novelty of computational surgery as a new field of research. While some of the elements we present may be considered as basic for a specialized investigator, the simplicity of the presentation is intended as a proof of principle that basic concepts in computational sciences are of core value in solving many existing problems in clinical surgery; we also hope this initial evaluation will highlight potential obstacles and challenges. As the digital revolution transforms the working environment of the surgeon, close collaboration between surgeons and computational scientists is not only unavoidable but also essential to harness the capabilities of both fields to optimize surgical care. We believe that this new collaboration will allow the community not only to develop predictive models for the outcomes of surgery but also to enhance the process of surgery - from procedural planning, to execution of procedures and technology interfaces, to assessment of the healing process - investigations that will potentially provide great impact on patient care far beyond the operating room.

Keywords: Computational surgery; Surgeons; Clinicians; Medical imaging; Robotics; Numerical simulation; Mathematical models

Initial concepts and definitions

According to Wikipedia.org, “surgery (from the Greek: *ξ∈ιρουργικη*, via Latin: *chirurgiae*, meaning ‘hand work’) is an ancient medical specialty that uses operative manual and instrumental techniques on a patient to investigate and/or treat a pathological condition such as disease or injury, to help improve bodily function or appearance.” The emphasis in this definition is clearly on surgery as manipulation and instruments. According to Henrichs et al. [1], surgical actions can be described in eight words: incision, exploration, aspiration, resection, evacuation, extraction, repair, and closure. For most nonsurgeon observers, this description of surgery is indeed inaccurately reduced to the procedure performed in the operating room. A review of the history of surgery shows however that the work of the surgeon goes beyond the technical performance of a procedure in a suite. Key milestones in the birth of the discipline of surgery from ancient times include many discoveries that are fundamental to any surgical procedure: invention of techniques and devices to control bleeding, development of techniques and medications to provide analgesia and anesthesia, and the development of agents and methods to treat surgical infection. Ambroise Pare's work [2] shows that progress in these fundamentals began long ago and demonstrates the commonality of surgery as a discipline that addresses biological imperatives imposed by surgical disease. Consequently, a fundamental knowledge of biology guides advances in the field, and further advances in surgery will not be reduced to improve manipulations and technologies. Indeed, the unique genetic and biological platform of individual patients will frame surgical interventions in the future.

Many contemporary advances in surgery are driven by enhanced manipulation fuelled by research in medical imaging and robotics [3]. Similarly, research into the biological basis of surgical disease, from genetic factors to integrative physiology, now greatly informs the consequences of surgical interventions. Both research fields rely heavily on computational methods. Medical imaging and robotics, as disciplines, are based on mathematical modeling, physics and computing. Similarly, the field of biology has completely been transformed by computational methodologies, from DNA array techniques and analysis to computational multiscale modeling of molecules, cells, and biological networks in all physical scales.

We propose that computational surgery is first the result of the marriage of progress in manipulation and biology. However, this new field goes beyond that fusion, presenting a cohort of clinical specific challenges resists predictable scientific constructs. Surgery as a science is by nature experimental. As a process, surgery is evolving from a craft activity to an industrial process being performed in a challenging economical context. Computer science has revolutionized the operating room: most new devices are computerized; the operating room is filled with digital equipment that assists and records the operation. Quality and efficiency goals promote mutation of the individual work of a surgeon toward a predictable, error-free sequence in a quantified world. The scientific-recorded activity of surgery and its everyday use on patients produce enormous volumes of digital data demanding enhanced methods for data representation and medical informatics processing with the goal of improving the surgical process. Computational surgery is then, additionally, a technique to improve the surgical process by systematic analysis of a large volume of digital data.

To summarize, a definition of computational surgery [4] would be simply ‘Modern Surgery enabled by computational science and technologies’. To refine this definition, we present three categories of technical advances based in computational sciences that have transformed surgery:

○ Augmented visualization

- Medical imaging that is integrated into the operating room equipment to enhance the operative procedure, e.g., real-time imaging to guide resection, ablation, or placement of devices
- Virtual reality that can augment the surgeon's vision by superimposing nonvisualizable patient imaging on the operating imaging platform

  - Mathematical modeling and real-time calculation of the ‘invisible’, such as mechanical forces, or spatial distribution. Future opportunities include the visualization of the fluid shear stress in the arterial wall at the time of vascular reconstruction or determination of optimal energy delivery rate radio frequency ablation procedures

- Augmented manipulation and robotics
  - Smart devices for minimally invasive procedures to provide haptic feedback
  - Stereotactic intervention technologies
  - Real-time tracking
  - Imaging interfaces with biomarkers
  - Biosensor construct tracking

- Reconstructive procedures and prostheses
  - Personalized constructs for prosthesis design and implantation in orthopedics
  - Design of regenerative tissue constructs to repair soft tissue defects and build reconstruction templates
  - Regenerative medicine and gene therapy to restore organ function or cure specific diseases

While biological and technology research are obviously essential to each of these areas, the unifying theme is that all of these components have to come together in an integrated computational framework in the operating room (OR) to deliver a translational product to surgical patient care. We propose that fusion of research, with that goal, as the discipline of computational surgery.

Interestingly, computational surgery incorporates modeling of both the manipulation and the biologic response to it. It is fascinating for a neophyte to observe an abdominal laparoscopic surgical procedure: the surgeon no longer looks directly at the patient but rather views the patient's anatomy and diseased organs visually hidden inside an intact abdominal wall on an AV display screen. What the surgeon sees is the image sent from the digital camera slipped into the abdomen through a 5-mm incision. In the surgical intervention with a robotic system such as the Intuitive Da Vinci robot, the distance between the patient and the surgeons gets even larger [5] as the operative manipulation platform is separated from the patient's bedside to the opposite side of the room. The surgeon no longer uses the tactile feedback of instruments on flesh and organs to guide the procedure but rather relies on the three-dimensional images projected on the robotic console to complete the procedure.

A more ambitious goal is to predict the outcome of a surgery by modeling the patient's biologic response to the procedure. Important questions include prediction of patient-specific result of an intervention. For example, can one predict the plastic response of a vein graft? Is there a reliable way to decide between a heart transplant or a heart-lung transplant? What will be the cosmetic outcome of breast conservative therapy for breast cancer patients? Computational methods have already demonstrated value in predicting tissue resection in patients with brain or liver tumors. Our hypothesis is that computational surgery will play a major role in predicting such surgical outcomes and thereby improve surgery practices.

The computational background of that research in surgery relies on our ability to build adequate multiscale models of the most complex biological system we encounter, i.e., the patient! The Virtual Physiological Human (VPH) project may serve as a valuable tool to achieve that end. The goal of the VPH [6] is to provide a descriptive, integrative, and predictive digital representation of the human physiology based on a computational framework and a systematic approach, utilizing the encyclopedia spirit. Many of the VPH projects (http://www.vph-noe.eu/) will facilitate the application of computational surgery indeed.

We propose then a more complete definition of computational surgery: it is the application of mathematics and algorithm design, enabling imaging, robotics, informatics, and simulation technologies, incorporating biological and physical principles, to improve surgery. Four key elements, the so-called IIIE, are fundamental to the design of computational surgery: it is an *interdisciplinary* science, that requires the *integration* of multiple technologies, and the work must be *immersed* in surgical practice. Last but not least, computational surgery must follow *ethical* principles, as the primary focus of the work is the use of computational science to improve the human health. To link the world of engineering with surgery, one should remember the oath of Hippocrates - to do no harm to our patients - an oath not typically reiterated in the training of scientists who develop complex computational machinery. The next generation of surgeons and computational scientist may indeed require a dual formation to master the field. We will present in the next section some of the difficulties and promises to define a common ground for surgeons and computational scientists.

Challenges and opportunities

The main difficulty in working with cross-disciplinary research is our ability to speak efficiently the same language. Surgeons or clinicians (*SC*) and computational scientists (CS) not only have different scientific backgrounds but also have different working cultures. While these differences seem onerous, we will present some strategies to enhance the collaborative process. We base our discussion on several assumptions:

- Cross-disciplinary research will improve patient care more than silos of research.
- Effective collaboration will lead to higher value translational research.
- CS want to participate in translational research.
- SC want to improve patient care by engaging in research.
- CS need to partner with the SC to know more about clinical problems if their research is to be relevant.
- SC need to partner with CS if optimal methods and tools are to be utilized in certain types or research.

One obvious major difference in our disciplines is that surgical science is innately experimental, while computational science is steeped in reductionist methodology. Even scientific publications for these two communities have very different structures. It is interesting to observe that a scientific paper in the medical sciences will invariably follow the classical structure: (1) introduction, (2) methods and materials, (3) results, and

(4) discussion. This is extremely different than the way a scientific paper in mathematics is written. The discussion that is often considered as the most important part of a medicine paper holds little value in mathematical writing! In mathematics, exploring the implications of your finding and judging the potential limitations of your design belong to your peers.

However, one may argue that surgeons and computational scientist are practitioners in their own scientific field. Computational science is the 'clinical' activity of a mathematician. Each computational model situation is different by its parameter setting, boundary conditions, and often nonlinear behavior. Most often, simulation is achieved in unknown territory for the mathematical theory, i.e., existence and uniqueness of the solution are not guaranteed by a theorem! The (full 3D) Navier Stokes equation, known for a century, is a classical example.

A more profound difficulty in establishing collaborations is institutional in nature. The demands in professional environments, institutional expectations, and financial models of SC and CS are quite apart. A publication in a medical journal may not count in the academic peer review of a CS. Spending significant time on the design of a computational model for a SC might be considered as a distraction of valuable resources by the CS's institution.

Surgeons as collaborators will always place the operating room first. In the hospital environment, they have the daily reality of patient care to contend with and are accountable for every action: they are accustomed to multitasking, have unpredictable schedules, and have long-day working hours. On the other hand, the CS as collaborators have more control of their schedules and have a good sense of organization. In this context and by training, they may have good abilities to abstract clinical problems. Meanwhile they may misrepresent reality by framing their thoughts in their own usual abstract and theoretical models. One should remember that a proof of concept for one case may not be scalable to clinical practice nor can be economically viable. In other words, it is easy for a CS to miss the big picture. It takes significant effort and patience to reach a level of collaboration between SC and CS that delivers clinical and translational results.

However, the intellectual challenge and educational value of such collaboration are undoubtedly professionally rewarding. A new model of education and funding may be necessary to facilitate that construction process between both communities. The network of computational surgery CoSINe, which we initiated in 2008, should lead to new proposals of dual training curriculum and research activities along these lines. The goal of the next section will be to recall the general background of the surgery activity in simple terms.

The continuum of surgery

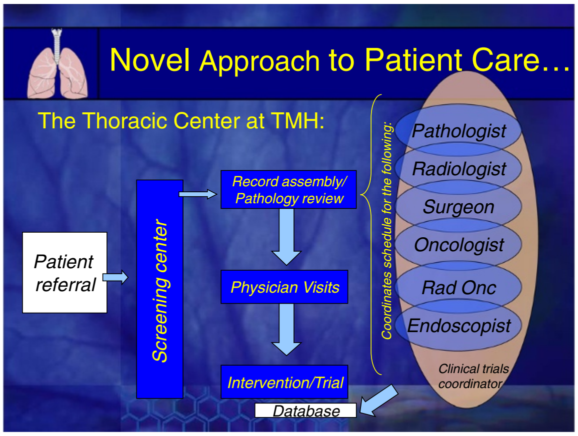
By definition, a surgical operation is a medical procedure that violates natural boundaries, most commonly the skin, but at times natural orifices such as the gastrointestinal or genitourinary tract. The operative procedure is one step of a complex process that follows the patient from the recognition of the disease to the assessment of the outcome, as in Figure 1. In modern surgery, the patient is cared for by a multidisciplinary therapeutic team that shares a global view of the problem. Figure 2 gives an example of such organization for the treatment of lung cancer at the Methodist Hospital.

Figure 1 Simplified surgery process.

The operation, performed in the unique environment of the operating room, is the critical step of the process; Figure 3 places the OR intervention at the center of a complex multistep process. Yet, interestingly, the operation is often the shortest step in time as well as the step that is most irreversible. The operation in a given patient has uncertain specific features: anatomic variation, physiological derangement, variable personnel in the operating team, so it is therefore a step that may generate the most stress for all parties. The culture of surgery has long anointed the surgeon as the captain of the operating room ship. However, more recent application of crew resource management methods to the operating room environment demonstrates that safety and communications improve when a more horizontal leadership structure is applied, and the surgeon's role becomes one of optimizing team performance as in the role of *chef d'orchestre*.

Let us look more closely at the surgeon's role in the operation. The surgeon's task is to perform a specific therapeutic intervention to resolve a disordered clinical condition. The surgeon needs to plan a sequence of steps and events, in an environment capable of supporting the patient. The scope of surgery is vast - from minor skin procedures to replacement of multiple abdominal organs. Yet, each requires knowledge, skill, and coordination of a specific sequence of steps. The therapeutic goals of surgery can be categorized as follows:

- *Removal of abnormal tissues*. These are tissues that are infected, diseased with tumor, or deformed and dysfunction. Examples include appendectomy or cholecystectomy for infectious complications of the appendix or gall bladder, mastectomy or colectomy for treatment of cancers of the breast or colon, or small bowel resection for patients with structure due to the chronic inflammatory condition of Crohn's disease.


Novel Approach to Patient Care…

The Thoracic Center at TMH:

Patient referral

Screening center

Record assembly/ Pathology review

Physician Visits

Intervention/Trial

Database

Coordinates schedule for the following:

Pathologist
Radiologist
Surgeon
Oncologist
Rad Onc
Endoscopist

Clinical trials coordinator

Figure 2 Organization of the surgery team at TMC for lung cancer.

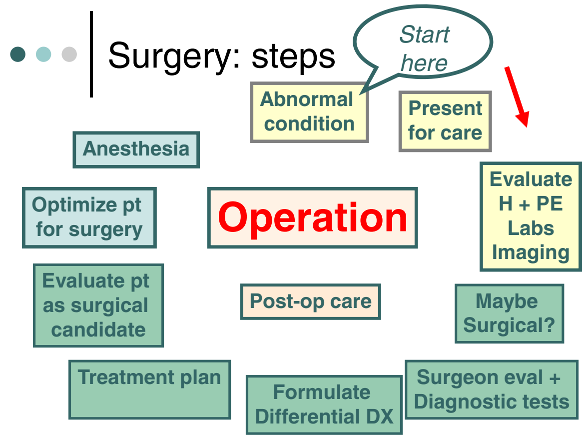


Figure 3 Surgery work flow.

- *Repair of damaged structures*. Examples include operative fixation of fractured bones, closure of abdominal wall hernias with native tissues or biomaterials, valvuloplasty to repair heart valves damaged by endocarditis, or endarterectomy and vein patch placement to repair blockages in arteries blocked by atherosclerosis.
- *Replacement of organs and tissues*. Examples include transplantation of new organs to replace failed kidneys or liver and replacement of hip joints with synthetic joints for joints destroyed by arthritis.
- *Repair of disordered functions*. Examples include restructuring of the gastrointestinal track to limit food intake and absorption in patients with morbid obesity as in Roux-en-Y gastric bypass or division of the vagus nerves to diminish gastric acid secretion to reduce the risk of ulcer disease.
- *Establish a diagnosis*. Prior to modern imaging, surgery often provided an essential window into the human body to identify the source of disease. With modern diagnostic technologies, exploratory surgery is now a rare event.

The common features of all operations are tissue injury and the physiologic stress response that tissue damage elicits, followed by the healing response. The initial tissue response is local, i.e., within and surrounding the wound for small operations, while in major procedures with significant tissue disruption, particularly that associated with infection or significant blood loss, the stress response is systemic, i.e., a response impacting the physiology of the whole body. Neurohormonal factors regulate the systemic and local response to the local and systemic stress of surgery.

As noted, the process of surgery requires the careful orchestration of multiple steps: accurate diagnosis, formulation of a procedural plan, risk assessment of the individual patient and optimization of the patient for surgery, the operation itself, and then postoperative care during the recovery period. This process can be described with an algorithm to identify factors that interfere with optimal performance and execution.

The operation itself can be modeled with an algorithm. A highly structured and common operation, such as the laparoscopic Roux-en-Y gastric bypass has been carefully coded as an algorithm: each step of the algorithm, each variation of the process is spelled out and described in detail. However, even stringent execution of proscribed steps may be disrupted by unexpected findings of events during an operation - unexpected physiologic instability, failure of instrumentation and anatomic anomalies; in each case, the surgeon must adapt and modify the procedure to ensure optimal performance for the patient. Indeed, it is this variability in a given operation in a given patient that contributes to the lengthy period of training required for surgeons, totaling 5 to 10 years, for all surgical disciplines. Surgeons therefore, perhaps unwittingly, maintain working, real-time databases during an operative procedure. Data points tracked include the following:

- Recall of history and physical findings
- Recall of the steps of the procedure including motions and instruments to be used
- Intraoperative access to imaging
- Knowledge of anatomy and physiology
- Personal experience
- Real-time tracking of the patient's physiologic status

The challenge is to store that information in a uniform digital format that will be accessible and usable to the surgical team. There exist many regulatory obstacles that make storage and transmission of patient data very challenging. Strict firewalls to ensure patient privacy, certainly a most critical element of patient confidentiality, have posed significant obstacles to the development of data sharing strategies to improve care. Let us describe in the next section how the transformation from analogical to digital the flow of information around surgery make this clinical engineering addition to the team important.

From analogical to digital

There are three important sources of digital information that impact the development of computational surgery.

The first kind of data is patient digital clinical information records that are maintained by hospital and physician office networks around the world. A ‘universal’ patient digital record has long been debated by national and international agencies, but consensus on specific features is not near. Currently, there are multiple formats of patient digital records of varying quality and functionality, typically unique to a given health care organization. Development of a dynamic health care digital record will be invaluable for the integration of health care systems to optimize patient care.

A second source of data closer to our interest comes from the fact that modern OR generates huge monitoring data sets. These raw data for computational surgery are digital video and all kinds of signals, such as vital signs, for each and every procedure. This type of information might be unnecessarily too detailed to complete the medical record of a patient but can still be systematically sampled to augment patient data. There is a significant body of research work that analyzes rigorously the data flow generated by the OR system in order to improve surgery procedures. It seems that these records have not yet been really used at the clinical scale and that the storage capability and management at that scale might be often lacking.

A third source of digital information is the electronic medical research database, PubMed (http://www.ncbi.nlm.nih.gov/pubmed/), which is supported by the National

Center for Biotechnology Information (NCBI) from the National Institute of Health (NIH). It is the main web search system entirely devoted to the biomedical literature. PubMed has more than 21 million citations from the biomedical literature including MEDLINE, life science journals, and online books. It should be noticed that the web of science system covers a broader area and is very relevant to search information for computational surgery that is an interdisciplinary field linked to mathematics, computer sciences, and engineering.

Overall, the three sources of information produce an impressive capability to produce digital data for patient treatment and clinical research.

These three classes of digital database are ‘driven by the market’, in other words, the economical competition for product and intellectual properties. They are amenable to information technology methods and impact greatly our understanding and research. Several new academic projects such as the virtual physiological human, mentioned earlier, highlight the potential of integrating all available data on the human physiology into a single coherent digital framework. This research action takes strong wills and efforts from their initiator.

Data integration at the national and international level is also very challenging in the context of economical competition and requires patient confidentiality. The immersion of the surgery work into digital technology, thanks to medical imaging, medical robotic, and health informatics, makes inevitable the dialogue between SC and CS. The main question is: should clinicians be only consumers and can afford to ignore what is at work behind the computer display, or should they fully participate in the design of these new digital systems? The development of computational surgery is based on the second option. To start, we will argue that a surgeon should question systematically the computer answers offered by all these tools. Medical imaging comes with artificial artefact, medical robotic is bounded by poor feedback mechanism, computer simulation are often inaccurate, models can be invalid, and databases are polluted by various noise such as missing data, typos, or inaccurate calibration. A critical thinking process is impossible without developing new skills beyond the traditional old surgery curriculum. Progresses on computational methods and tools would be accelerated if SC gain expertise on how these techniques work. It may even make the use of these new technologies more safe and wise for the benefit of the patient.

Perhaps the main benefit of going from analogical to digital is the fact that documenting a surgery procedure becomes rather systematic and may provide rigorous assessment to progress. An example would be the digital representation of a high-volume surgery intervention such as the Roux-en-Y gastric bypass. A total of 200,000 surgery interventions of that nature are performed per year in the USA. According to the *Atlas of Minimally Invasive Surgery*, the steps of a laparoscopic Roux-en-Y gastric bypass can be listed as follows:

1. Access and port placement
   - There is incision in left upper quadrant.
   - Veress needle is placed.
   - Pneumoperitoneum of 15 mm Hg is established.
   - Optical access trocar is used to gain direct vision entry into the peritoneum.
   - Four more ports are placed.

   - Abdomen is explored for pathology.
   - Ports are placed under direct visualization.
2. Creating the jejunojejunostomy
   - The omentum is placed between liver and stomach.
   - The mesocolon is elevated, and ligament of Treitz is identified.
   - The jejunum is measured 30 cm distal to the ligament of Treitz.
   - The jejunum is divided.
   - A Penrose is attached to the tip of the Roux limb.
   - Its mesentery is divided with another load of the stapler, with Seamguard.
   - The Roux limb is measured for 125 cm with a marked instrument.
   - The Roux and biliopancreatic limbs are sutured together.
   - A side-to-side jejunostomy is created.
   - The enterotomy is closed.
   - The Roux limb is run along its course to visualize the mesenteric defect.
   - The mesenteric defect is closed.
3. Mobilizing the Roux limb to the stomach
   - The omentum is divided using the harmonic scalpel.
   - The Roux limb is carried anterior to the colon.
4. Sizing the gastric pouch
   - An epigastric incision is made, and a liver retractor is placed.
   - The left lateral lobe of the liver is elevated to expose the hiatus.
   - The epigastric fat pad and angle of His are mobilized.
   - The stomach is suctioned, and all intragastric devices are removed.
   - The lesser sac is entered by creating a window over the caudate lobe.
   - The left gastric artery is identified, and the lesser curvature is transected just distal to this with a stapler and Seamguard.
   - The stomach is then transected horizontally at this site.
   - The stapler is then used to create the vertical staple line towards the angle of His.
5. Linear stapled approach
   - The Roux limb is sutured to the posterior part of the pouch.
   - The Penrose is removed.
   - A gastrotomy is performed in the horizontal staple line of the pouch.
   - A gastrotomy is performed in the Roux limb about 5 cm from the tip.
   - An end-to-side gastrojejunostomy is performed.
   - The enterotomy is closed with a running suture.
   - The endoscope is advanced from the anesthesia side to stent the anastomosis.
   - A second layer of suture is placed.
   - Leak test is performed.
   - Liver retractor and trocars are removed.

Meanwhile, the OR equipment can deliver routinely video streams from the endoscope camera during the laparoscopic procedure as in Figure 4, and an outside view from the OR traffic is also shown. Linking automatically the algorithm with the analysis of the video is feasible [7]. It requires however a complex combination of image analysis methods and pattern recognition techniques. The result can be a precise time line

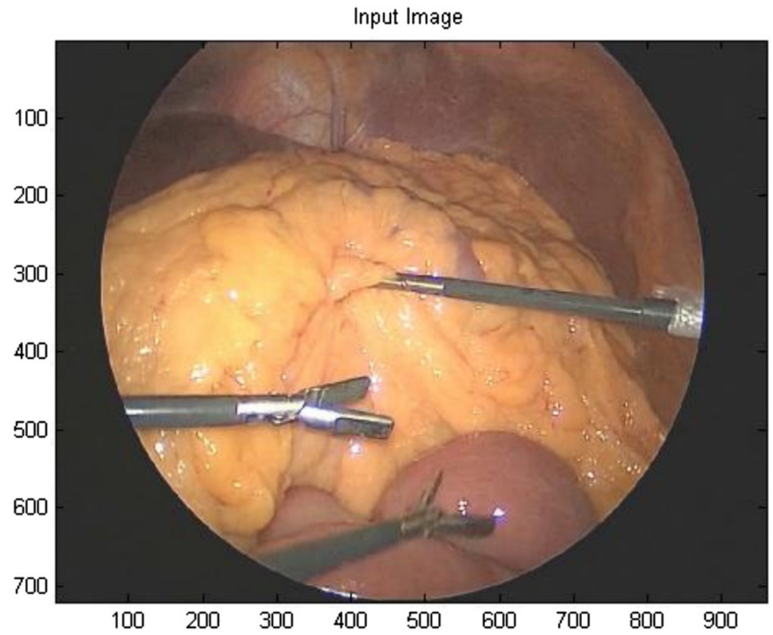


Figure 4 Laparoscopy image.

that documents the algorithm: the chronology of each step is found within an accuracy of the second, each laparoscope's motion can even be formally represented for further analysis.

Let us suppose for a moment that this annotation of the surgery procedure can be done automatically with perfect accuracy and is scalable to clinical conditions with no significant additional investment. This would require indeed much more work including real-time high-performance computing and robust software engineering. All the consequences of that new capability may not be fully understood and foreseen.

From the scientific point of view, it becomes feasible to compare cases, scale performances, give milestones to achieve to trainees, and set some norms in a rather systematic way. Meanwhile, statistical methods may generate reliable time prediction on the go. The working flow for that high-volume surgery can be optimized at the hospital scale, like any other industrial process. This simple example shows the potential, limit, and ethical issues raised by the synergy of surgery with computational methods. The digital revolution has arrived in surgery and has combined imaging, procedural guidance, virtual reality, miniaturization, and all spectra of new data from physiological to molecular through genetic. This digital revolution has occurred much later than in other professions such as aviation or banking. A new opportunity will be to establish a scientific cooperation between SC and CS that would make the new transition the most beneficial for patients. The next question that we will discuss is how one may combine of all these sources of information to deliver a more sophisticated prediction of surgery outcomes.

Predicting surgery outcome and improving the process

Most of the attention in general is devoted to the introduction of a new surgical procedure or the discovery of the therapeutic action of a new molecule. Somehow, both types of breakthrough are highly connected to the introduction of new technology and provide well-identified milestones for the community. Our capability to predict the surgery outcome is a scientific problem that progressed in a less obvious way.

Our hypothesis is that a complex multiscale model and a large-scale simulation will play an increasing key role toward that goal. Many of the published works report on the after math of surgery only in a statistical sense. For example, a clinical study on breast conservative therapy will report on survival rate, risk of cancer recurrence, and cosmetic defects for a carefully sampled population of patients. This careful approach with clinical trial usually corrects or improves surgical practice at a slow path in time. It takes several years to collect the data in a clinical trial. Additional time is required to reach a consensus on the interpretation of the outcome. The nature of the result may not be short of ambiguities. Uncertainties in the data set might be difficult to correct at the later phase of analysis. As noticed earlier, thanks to the digital revolution, the information basis of clinical studies gets broader and can be augmented by the simulation outcome. For example, vascular clinical studies can be systematically documented by medical imaging, hemodynamic simulation, as well as physiological and cell biology measures.

Predicting surgery outcome is however an infinitely more challenging problem than *a posteriori* analysis studies. Each patient is different. Response to surgery intervention involved multiple scales in time, spatial structures, and network structures. Outcome may depend heavily on the environment condition of the patient. It seems however that prognosis is the logical step to make a decision or target improvement in surgery practice. Because of the complexity of the plastic response of the body to the surgery intervention, we believe that progress in that direction will not come overnight and should be at the core of computational surgery. Perhaps a first and main objective should be the identification of earlier signs of failures in the surgery outcome in order to fix the problem.

There are however several remarkable examples of surgery outcome predictive framework that have been developed. Representative examples that we are familiar with are the prediction of tumor growth, vein graft failures, and breast conservative therapy cosmetic defect.

The pioneer work of Kristin Swanson and J.D. Murray [8,9] is an outstanding illustration of how mathematical modeling can be used to predict brain tumor growth (Figure 5). This stream of work is devoted to gliomas. Gliomas generally are diffuse and invasive

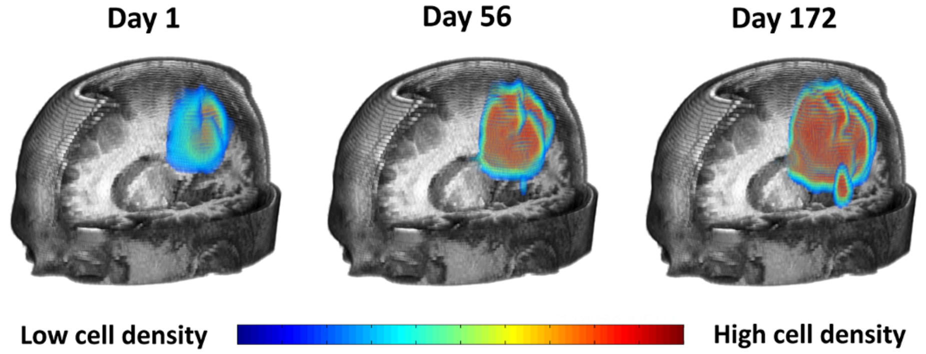


Figure 5 3D representation of the anisotropic simulation of Gliomas with a patient. Courtesy of Pr. Kristin Swanson.

intracranial neoplasms accounting for about one half of all primary brain tumors. Unlike most other tumors, gliomas are generally highly diffuse. In fact, experimental results indicate that within 7 days of tumor implantation in a rat brain, glioma cells can be identified throughout the central nervous system. For instance, even upon extensive surgical excision well beyond the grossly visible tumor boundary, recurrence near the edge of resection ultimately results (Kelley & Hunt [10]). A simplistic model of tumor growth would be as follows:

$$\begin{aligned} \textit{Rate of change of tumour cell density} &= \textit{Diffusion (motility) of tumour cells} \\ &\quad + \textit{Growth of tumour cells}. \end{aligned}$$

This relation can be written mathematically as a reaction–diffusion equation:

$$\partial c/\partial t = \nabla.(D(x)\nabla c) + \rho c.$$

where $c(x, t)$ is the density of cells at any position x and time t, D is the diffusion coefficient, and ρ is the linear growth factor. This equation should be equipped of the so-called boundary equation to translate that the tumor propagates inside the brain. Further, an initial condition should specify $c(x, t0)$ at a given time. This information might be extracted from a magnetic resonance imaging (MRI) brain scan of the patient. One obtains then a well-posed mathematical problem for which the unknown $c(x, t)$ can be computed with a numerical algorithm. Reality is more complex because diffusion tensor depends on the brain structure: there are major differences between gray and white matters, and cells may migrate along the direction of the fiber tract. The beauty of the family models generated by K. Swanson and her collaborators is that a single partial differential equation, slightly more complex than the above,

$$\partial c/\partial t = \nabla.(D(x)\nabla c) + \rho c(1 - cK) - R(c, x, t),$$

can translate into a technology that is scalable to the clinic for brain tumor assessment.

The mathematical model is simple enough to work with routine clinical data and keeps the essential to be predictive. It follows somehow the Occam's razor *lex parsimoniae* which states that without being a scientific rigorous principle, it reminds us of some pragmatism in model development. Eventually, the radiotherapy treatment [11] and the true extent of the brain tumor and prognostic evaluation can benefit from this mathematical modeling [12].

From the theoretical point of view of mathematical modeling, cancer might be viewed as a complex multiscale system [13,14] that undergoes an evolutionary process [15]. A new theoretical understanding of that nature may generate new approaches across the spectrum of oncology. As demonstrated in the review article of Alan Lefor [16], the role of the oncology clinician should be determined to translate that research into better care for patients. Let us mention two examples of a mathematical work that model cancer metastases with a clinical treatment perspective in mind. Colin et al. [17] designed an optimized a reduced mathematical model to predict second-site lung tumor growth for real cases. Further, Barbolosi et al. [18] presented an interesting mathematical theory of metastatic cancer to improve adjuvant therapy in oncology service. Both papers are the result of a close cooperation between oncologists and computational scientists.

A second example, a where sophisticated mathematical modeling joint system biology, come from the stream of work of Berceli et al. [19]; and address the understanding of vein graft [20]. Even though significant advances in surgical techniques and endovascular therapies have been achieved over the last decade, long-term success in arterial revascularizations has been limited. Although bypass grafts and transluminal angioplasties can provide immediate and dramatic improvements in perfusion, the half-life of these interventions is relatively short and continues to be measured in months. Specific cause/effect links between hemodynamic factors, inflammatory biochemical mediators, cellular effectors, and vascular occlusive phenotype remain lacking (Figure 6).

The complex interplay between monocyte biology, local vascular hemodynamics, and the intrinsic wall milieu determines the course of vascular adaptation, leading to success or failure following the intervention. Specifically, Berceli et al. hypothesized that a specific gene regulatory network, modulated by defined blood shearing forces, determines the global adaptive response of the vein graft wall following acute injury. Superimposed on this response is a driving inflammatory response, mediated by circulating monocytes that are targeted to this site of injury. Modulated by the local hemodynamic environment and their biologic phenotype, monocytes transmigrate at specific sites of injury leading to dynamic instability and aggressive focal lesion development within the vasculature. Using state-of-the art techniques in mathematics, engineering, and computer science to integrate fundamental biologic and physical data, a predictive model of vascular adaptation following acute intervention can be developed.

The dynamic interplay between physical forces, cellular inflammatory elements, and an underlying gene regulatory network is critical [21,22]. The resulting model details a highly integrated system where local perturbations in a single component rapidly

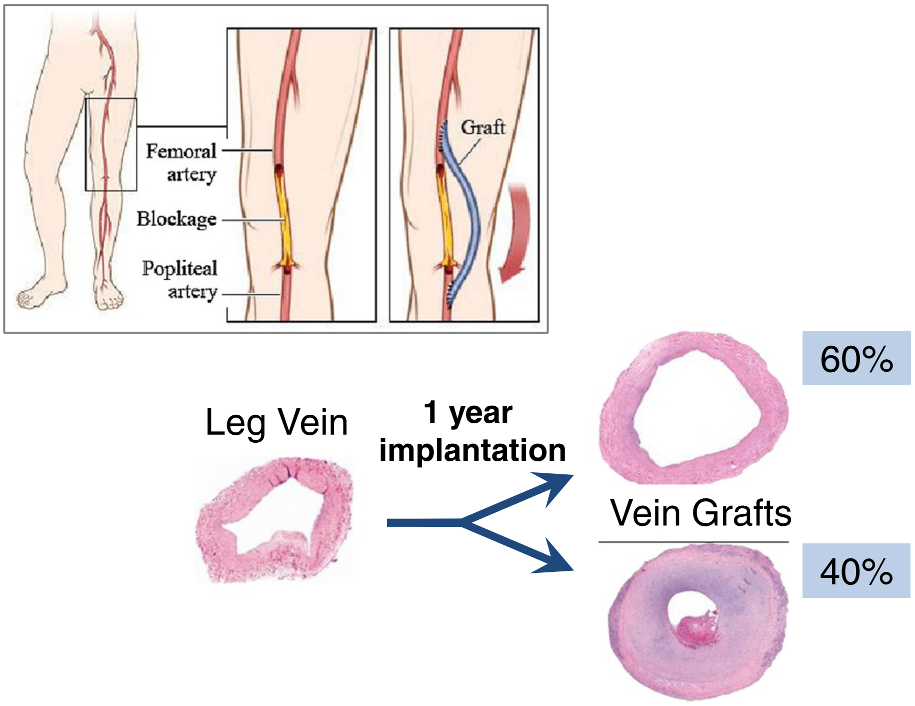


Figure 6 Vein graft response after transplantation.

feedback to the other elements, leading to an updated but stable set point for the network, or a condition with dynamic instability characterized by early failure of the system. A detailed examination of the model system of Berceli et al. demonstrates such a critical recursive loop between the local hemodynamics and the regional biologic response of the vascular wall (Figure 7). Initial shear stress not only directs the primary set point for the gene network but also modulates monocyte infiltration, both of which influence the cell- and matrix-based remodeling response and define the local modifications in conduit geometry. These morphologic changes induce perturbations in local shear resulting in new set points for the biologic response parameters.

Our third example comes from a stream of work on breast conservative therapy from the two authors and their collaborators. Improving breast cancer treatment outcome and survival depends on early detection and effective use of multimodality therapy: surgery, radiation oncology, and hormonal and chemotherapy treatments. Surgery for early-stage breast carcinoma is either total mastectomy (complete breast removal) or surgical lumpectomy (only tumor removal) coupled with radiotherapy, commonly known as breast-conserving therapy (BCT). The goals of BCT are to achieve local control of the cancer [23,24] as well as to preserve a breast that satisfies the woman's cosmetic, emotional, and physical needs. While most women undergo partial mastectomy with satisfactory cosmetic results, in many patients, the remaining breast is left with significant cosmetic defects including concave deformities, distortion of the nipple-areola complex, asymmetry, and changes in tissue density characterized by excessive density associated with parenchymal scarring [23]. These flaws have been reported to contribute to poor body image and psychological distress in some patients. Research efforts to improve the surgical outcomes of breast-conserving therapy in regard to prediction of cosmetic and functional outcome are very limited. To our knowledge, we are the first team to work on a computational framework designed to predict BCT outcomes and explore targets for improvement. This focus of our research goes beyond classical tissue mechanics and

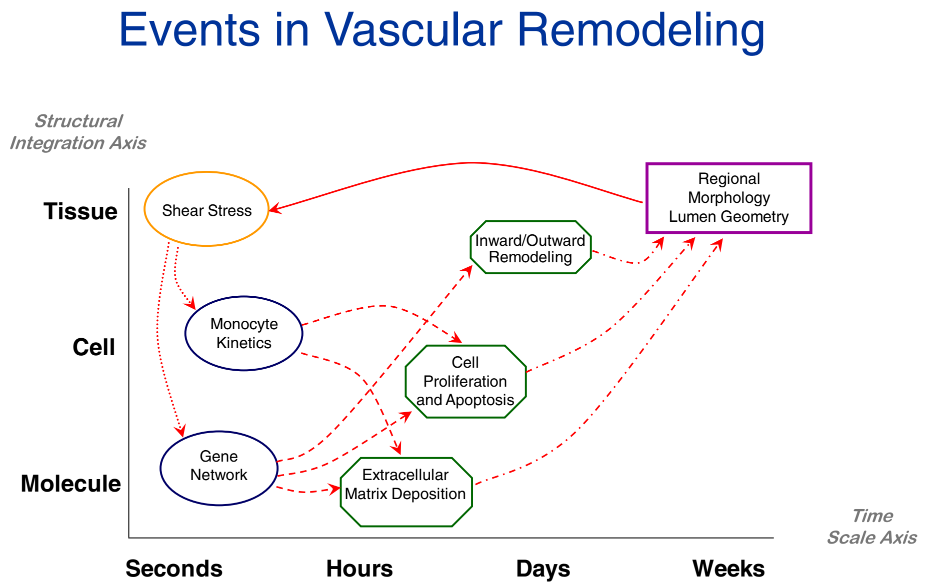


Figure 7 System biology approach for vein graft adaptation.

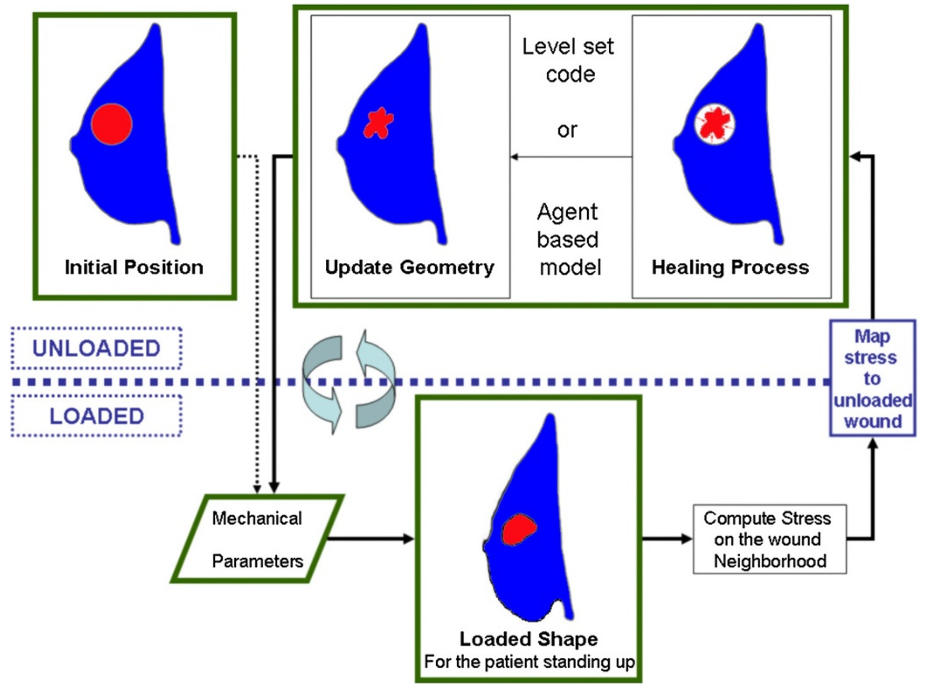


Figure 8 Multiscale simulation concept for BCT.

incorporates novel important variables into the model including tissue plasticity and the dynamic of tissue healing and repair, both primarily and in the setting of radiation therapy. Our overall hypothesis is that the complex interplay among mechanical forces due to gravity, breast tissue constitutive law distribution, inflammation induced by radiotherapy, and internal stress generated by the healing process has a dominant role in determining the success or failure of lumpectomy in preserving the breast shape and cosmesis. The model should encompass multiple scales in space, from cells to tissue, and time, from minutes for the tissue mechanics to months for healing [25-30]. We use a modular method coupled with mathematical models and corresponding software for patient-

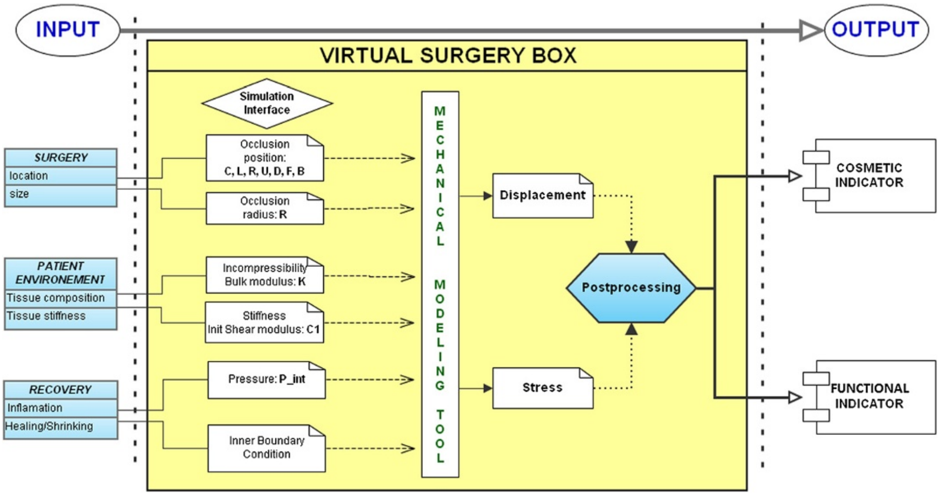


Figure 9 Architecture of the virtual surgery tool box.

specific data to test our hypothesis and refine the model [31,32]. We have designed a pilot study that includes women with breast cancer who have been elected to undergo BCT at the Methodist Hospital in Houston, TX, USA. Patients will undergo preoperative imaging (mammography, ultrasound, and MRI) prior to lumpectomy surgery. Intraoperative data points regarding the surgical technique and surgical breast specimen will be collected and recorded in a database to correlate with preoperative imaging and pathologic criteria. Patients will be followed sequentially throughout the postoperative period by physical examination, surface imaging, ultrasound imaging, and radiologic evaluation to assess changes in breast tissue, contour, and deformity. The patient results will be compared with the predictive model based on ‘virtual’ lumpectomy. The final goal of that study is to provide a graphic user interface described in Figure 8 to the clinician that hides the complexity of the model and provides estimates on patient cosmesis outcome. Figure 9 shows the schema of the multiscale modeling at work behind the scene. This tool should be used as an additional rational method to complement the dialogue between the clinician and patient *prior surgery*! However, in the end, it might also be used to produce new digital data to deeper our understanding of internal healing in women's tissue breast.

To conclude this section, one should remember the quotation of Box, George E. P. [33]: ‘Essentially, all models are wrong, but some are useful.’

The colored picture produced by the software is not the reality but a representation of a virtual reality. The mission of computational surgery is to deliver models that scale in clinical conditions and have reliability. This cannot be achievable without close cooperation between surgeons and computational scientists. In the next section, we will summarize the general keys for success that should the companion on the road map for computational surgery.

Conclusions

Each of the surgical functions - repair of parts, replacement of parts, and repair of function - can potentially be augmented with the use of computational surgery methods. The purpose of collaborations between CS and SC are to use the tools of computational science to improve these functions. The assessment of new methods should address the ability of the surgeon and the team of health care providers caring for the patient throughout an episode of surgical intervention. We should in particular develop a new curriculum and joint degree programs to give an opportunity to our students in medicine and computational science to work in synergy along these lines. The opportunities are many.

Competing interests

The authors declare that they have no competing interests.

Author’s contributions

All authors read and approved the final manuscript.

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