Automation of Error Control with Application to Fluid–Structure Interaction in Biomedicine

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1 Relevance

Computer simulation is an important tool in many areas of science. Increasingly complex mathematical models are being solved in large computer simulations, complementing and sometimes replacing traditional experimental techniques as the main tool of scientific investigation. In any such computer simulation, it is pivotal that the quality of the computed solution may be determined. However, the assessment of the quality of a computed solution is challenging, both mathematically and computationally. As a consequence, the quality of the solution must often be assessed manually by the scientist or engineer running the simulation. This is unreliable as well as time-consuming, and it effectively prevents computer simulation from realizing its full potential as a standard tool in science and industry.

Computer simulations often require large computational resources, in particular the simulation of complex biological processes studied in the proposed research. It is therefore of utmost importance that computational resources are used as efficiently as possible, to make new results readily available and to expand the realm of which processes may be simulated. We thus identify *reliability* and *efficiency* as two key challenges in computer simulation. These two challenges are addressed by *error control*. By (adaptive) error control, the resolution of the simulation is chosen such that the computed solution satisfies a given accuracy requirement with minimal work. Error control thus makes computer simulation accessible as a standard tool for non-experts: the computed solutions can be trusted and the computer simulation requires reasonable computational resources. In biomedical applications, error control becomes particularly important. The multiscale and multiphysics nature of biological processes give rise to substantial computational challenges that require efficient computational tools. Furthermore, computer simulations may ultimately be used by medical doctors to guide medical decisions and it is then crucial that the computed solutions can be trusted.

The biomedical applications studied in the proposed research involve the solution of demanding fluid–structure interaction problems coupled with complex constitutive relations for the fluid and the surrounding biological tissue. Although it is possible to design and implement error control for these applications manually, this is not practical in general. Each mathematical model requires a different computer program and each such computer program requires a considerable amount of work to develop and maintain. Furthermore, manual implementation is prone to errors and thus the reliability of the computational method may be compromised. In contrast, with an automated process for the generation of computer simulations based on a general methodology, the computer program for the simulation of any given mathematical model may be automatically generated, removing the need for manual labor and opening entirely new possibilities for experimentation with increasingly complex models.

The aim of the proposed research is to develop a general methodology for automated error control, with special emphasis on turbulent fluid–structure interaction problems in biomedicine. The aim is also to realize the methodology in free software components that are accessible to practitioners, including medical doctors. Currently, no such tools exist and the relevance and potential impact of the proposed research is therefore very large. The proposed research is unique in its broad spectrum, ranging from the development of basic mathematical methodology and the implementation of the methodology in software components to the application of the developed methodology to a set of challenging key applications in biomedicine.

2 Aspects relating to the research project

2.1 Background and status of knowledge

Automation of error control. Error control in the numerical solution of differential equations means that the discretization is chosen so as to obtain an approximate solution that satisfies a given accuracy requirement with minimal work. This includes an aspect of *reliability*: the error in the computed solution is less than a given tolerance, and an aspect of *efficiency*: the solution is computed with minimal work.

Important contributions to error control in the numerical solution of differential equations include the seminal works by Babuška and Rheinboldt [4, 5], which laid the foundation for a posteriori error estimation and adaptive finite element methods. A survey of the traditional approach to error control in global norms can be found in [1]. In recent years, *goal-oriented* error control has received much attention. In goal-oriented error control, the discretization is targeted at the accurate computation of a given output quantity of interest, such as the drag of an airfoil in a Navier–Stokes simulation. The foundations for this program were first laid in [10] and then later refined in [6, 12]. See also [36] for a survey of methods.

Goal-oriented a posteriori error estimation for a given differential equation $A(u) = f$ is based on expressing the error in a given output quantity (functional) M in terms of computable quantities, including the residual $R = A(U) - f$ of the computed numerical solution $U \approx u$ and the solution φ of an auxiliary dual problem. If φ solves the dual problem $A'^{*}\varphi = \psi$ with ψ the Riesz representer of M', it follows that

$$M(U) - M(u) = M'(U-u) = (\psi, U-u) = (A'^{*}\varphi, U-u) = (\varphi, A'(U-u)) = (\varphi, R). \qquad (1)$$

The *automation* of error control thus amounts to automatically generating the dual problem and the a posteriori error estimate for “any” given differential equation $A(u) = f$ and “any” given output quantity M, based on the fundamental error representation (1).

The automation of error control is a natural continuation of previous work of the applicant towards a complete automation of computational mathematical modeling (ACMM) as outlined in [27] and realized in the FEniCS project [13, 8], including the automation of (i) discretization, (ii) error control, (iii) discrete solution, (iv) modeling and (v) optimization. As a first step towards this automation, the applicant has developed a compiler for variational forms [29, 19, 21] that automatically generates highly efficient low-level code for the assembly of discrete operators from a given variational formulation of a partial differential equation. As demonstrated in [19], the speedup compared to the standard quadrature-based approach to form evaluation is typically on the order of a factor 100. The form compiler (FFC) has recently been integrated with the Python/C++ problem-solving environment DOLFIN [14, 17] to provide efficient just-in-time compilation of variational forms, including optimization strategies for the generated code [20, 22]. Examples of current applications of the form compiler include the generation of code for solving general systems of convection–diffusion–reaction equations, the incompressible Navier–Stokes equations, the Cahn–Hilliard equation and large-deformation elasticity. An overview of the set of tools developed as part of this program for the automation of computational mathematical modeling is given in [28].

Fluid–structure interaction. In its most basic form, the fluid–structure interaction problem concerns a fluid enclosed in a domain $\Omega_F = \Omega_F(t)$ interacting with a surrounding (or immersed) structure $\Omega_S = \Omega_S(t)$ through the common boundary $\Gamma = \Gamma(t) = \Omega_F(t) \cap \Omega_S(t)$. The motion of the fluid and the structure is governed by a system of differential equations expressing conservation of momentum for the fluid and the structure,

$$\rho_F \frac{Dv_F}{Dt} = \nabla \cdot \sigma_F + f_F + w \cdot \nabla v_F \quad \text{in } \Omega_F(t), \tag{2}$$

$$v_F = v_S \quad \text{on } \Gamma(t), \tag{3}$$

$$\rho_S \frac{Dv_S}{Dt} = \nabla \cdot \sigma_S + f_S \quad \text{in } \Omega_S(t), \tag{4}$$

$$\sigma_S \cdot n = \sigma_F \cdot n \quad \text{on } \Gamma(t), \tag{5}$$

where $v_F = v_F(x,t)$ denotes the fluid velocity at $x \in \Omega_F(t)$, $v_S = v_S(x,t)$ denotes the velocity of the structure at $x \in \Omega_S(t)$, σ_F and σ_S denote the Cauchy stress tensors for the fluid and the structure respectively, f_F and f_S denote body forces, and D/Dt denotes the material derivative. The fluid domain velocity w is obtained by solving an auxiliary equation for the displacement of Ω_F with the velocity of Ω_F determined by the motion of the structure along the common boundary.

The general formulation (2)–(5) is complemented by constitutive models that relate the stress tensors σ_F and σ_S to relevant measures of the strain, which in turn may be related to the deformations of the fluid and the structure given by v_F and v_S respectively. In particular, if equation (2) is complemented by the constitutive relation $\sigma_F = -pI + 2\nu\epsilon$ for a Newtonian incompressible fluid satisfying $\nabla \cdot v_F = 0$ with ϵ the strain-rate tensor, one recovers the standard ALE formulation of the incompressible Navier–Stokes equations,

$$\begin{aligned} \frac{\partial v_F}{\partial t} + (v_F - w) \cdot \nabla v_F - \nu \Delta v_F + \nabla p = f_F \quad &\text{in } \Omega_F, \\ \nabla \cdot v_F = 0 \quad &\text{in } \Omega_F, \end{aligned} \tag{6}$$

for the velocity v_F and pressure p.

The general FSI problem is challenging both mathematically and computationally. With the availability of automating tools such as the form compiler FFC, the discretization of the system of partial differential equations governing the FSI problem is straightforward. Similarly, the proposed research aims at developing methodology and tools that make error control and adaptivity for the FSI problem equally straightforward.

Computational modeling of turbulent flows. An important aspect of the current proposal is the efficient computation of turbulent flows in the lungs and in the cardiovascular system. Turbulent as well as laminar flow in an incompressible Newtonian fluid is governed by the incompressible Navier–Stokes equations (6). A complete resolution of all relevant features in a direct numerical simulation (DNS) of turbulent flow is currently and in the near future too expensive, even at physiological moderately large Reynolds numbers. To overcome the difficulty of DNS for turbulent flows, methods have been developed that allow certain features of the turbulent flow to be computed at a moderate cost, see [34] for an overview. These methods all involve some kind of filtering of the Navier–Stokes equations to obtain a set of new equations for an averaged quantity. The averaging takes the form of a statistical average in a Reynolds-averaged numerical simulation (RANS), see [9, 31], or a convolution with a low-pass filter in a large-eddy simulation (LES), see [32, 33]. In both cases, the filtered equations must be accompanied by an appropriate turbulence model that accounts for the effect of unresolved scales on the averaged quantity. Popular RANS turbulence models include the standard scalar transport k–ϵ model [18] or more involved second-moment closure models. These are the turbulence models most commonly used in engineering and commercial CFD packages. For LES, the most popular (and oldest) turbulence model is the Smagorinsky model [35].

Although both RANS and LES may in many cases be used to predict certain aspects of a turbulent flow, both approaches rely on adjusting the turbulence model parameters based on empirical data and numerical experiments. Another difficulty is that RANS models have been fine-tuned primarily for fully developed turbulent flow which can be found in some industrial applications. As a consequence, they may be less suitable for the simulation of partly turbulent flows at moderate to large Reynolds numbers found in the cardiovascular system [38], in particular the flow through the aortic valve to be studied in the proposed research.

A more direct approach to turbulence modeling is adaptive DNS/LES [15] in the form of a stabilized Galerkin/least squares finite element method, where the goal is to accurately compute a given output quantity as in equation (1). This is in contrast to the standard RANS or LES approach where the goal is to compute an averaged solution point-wise throughout the domain. In adaptive DNS/LES, certain features of the flow are adaptively resolved (DNS), while other small-scale features are not resolved (LES) with an effective artificial viscosity generated by the stabilization terms in the finite element formulation. The resolution is chosen adaptively and automatically, guided by an a posteriori error estimate with weight given by the solution of the linearized dual problem. In this respect, adaptive DNS/LES fits well into the framework of automated error control of the current proposal.

Biomedical applications. To demonstrate and test the generality of the methodology developed as part of the proposed research, it will be applied to a set of challenging key applications in biomedicine. These applications include the study of (i) turbulent flow through the aortic valve, (ii) pulmonary support by forced ventilation and (iii) the inverse problem of diagnosing stenosis by noninvasive acoustic measurement. We discuss the first of these applications in detail below.

The aortic valve is one of four valves in the heart. Its responsibility is to let blood flow from the left ventricle into the aorta and prevent back-flow of blood from the aorta. During ventricular systole, the pressure in the left ventricle rises above the pressure in the aorta, causing the three cusps (flaps) of the aortic valve to open and let blood flow into the aorta. Subsequently, the pressure in the aorta rises above the pressure in the left ventricle, causing the aortic valve to close.

Simulating the blood flow through the aortic valve is a true FSI problem, with large forces and a two-way exchange of energy between the aortic valve and the blood flowing through it. Pressure and shear stress on the aortic valve cause the aortic valve cusps to open and close, resulting in a modified geometry for the blood flowing through the aortic valve. Another challenge is the complicated geometry of the aortic valve, requiring computational meshes with high resolution. Furthermore, the flow may become partly turbulent, in particular in defect or prosthetic heart valves. [38, 3].

A heart valve may become defect and as a result either not open or close completely. Such a defect may be either congenital or the result of an infectious disease or old age. Two common problems are aortic valve stenosis and aortic valve regurgitation. Aortic valve stenosis, narrowing of the aortic valve, puts extra strain on the heart muscle and increases the amount of blood that must be supplied to the heart muscle. This may lead to angina pectoris and ultimately congestive heart failure if the coronary arteries are not capable of supplying enough blood to the heart muscle. [2]. In aortic valve regurgitation, the aortic valve does not close properly and as a consequence, blood may leak back through the faulty valve into the left ventricle from the aorta. To compensate for this reduction in blood flow, the heart muscle grows (left ventricular hypertrophy), increasing the risk of arrhythmias and heart failure.

A defect heart valve may be treated either with medicines or surgery, including repairing or replacing the defect heart valve with a prosthetic heart valve which may be either bioprosthetic (tissue) or mechanical. The first mechanical prosthetic heart valve (MHV) was implanted in 1952 and early designs include the caged ball and tilting disc valves. Today, the most common design is the mechanical bileaflet, introduced in 1979, with 170,000 implants worldwide each year. [38].

Mechanical heart valves, although durable and effective, give rise to a number of problems. All currently implanted mechanical heart valves generate flow patterns that significantly differ from those generated by a normal healthy heart valve. This includes regions of turbulent flow with high shear stress which may damage blood components, and regions of recirculation which increase the risk of clot formation. The elevated shear stress also contributes to thrombus formation since it may promote platelet (thrombocyte) activation. [38]. Emboli formation may also occur in the wake downstream of the implanted mechanical heart valve. [7].

Experiments have resulted in valuable information on the hemodynamics of the aortic valve, but *in vivo* and *in vitro* experiments are challenging both practically and ethically. The following key problems are thus of importance for the numerical simulation of the blood flow through the aortic valve:

- study the flow field through a functioning aortic valve,
- study how the flow field is altered by a defect heart valve,
- study how surgical procedures may influence the flow through a defect heart valve,
- study how the flow field is altered by a mechanical heart valve implant,
- study how design parameters may influence the flow through a mechanical heart valve implant.

The automating tools developed as part of the proposed research open new possibilities for experimentation, which will be essential to the study of the flow through the aortic valve. Within a framework that is flexible with respect to the mathematical model, different constitutive models for the aortic valve and surrounding tissue may be examined and compared.

2.2 Objectives

The objectives of the proposed research are given in the *grant application form*.

2.3 Approaches, hypotheses and choice of method

The approach taken in this proposal is very general: to develop a general methodology and tool-set that can be applied to a large class of problems, including the set of key applications i biomedicine discussed above. It is essential that focus is placed on both the development of a general methodology and a specific set of demanding applications. By developing the two in parallel, essential feedback from the application of the general tool-set will drive the development of the general methodology and vice versa.

It is hypothesized that the development of a general methodology for automated error control is based on the following key elements:

(i) automatic generation of dual problems,
(ii) automatic generation of a posteriori error estimates,
(iii) a general adaptive strategy based on (i)–(ii).

One may thus envision a machine that takes as input a differential equation together with a desired output quantity and automatically generates the dual problem corresponding to the given output quantity as well as the a posteriori error estimate. This requires the development of a language in which the differential equation and the output quantity may be specified. Such a language is currently implemented as part of the form compiler FFC developed by the applicant. In a current project, the applicant is working together with colleagues at Simula Research Laboratory, including Prof. H. P. Langtangen, Dr. K. A. Mardal and Dr. O. Skavhaug on a formalization and extension of this language. The extension will provide support for differentiation of nonlinear forms, which is of particular importance to the generation of dual problems. It is further hypothesized that a posteriori error estimates may in general be automatically generated without the introduction of strong residuals as in equation (1), but instead expressed in terms of a weak residual obtained from the solution of local problems.

The development of a general methodology for automated error control will be carried out first for static partial differential equations, and then extended to time-dependent partial differential equations. The extension to time-dependent problems will involve the development of an efficient storage and interpolation scheme for the time-dependent dual solution and draw from experience of previous work of the applicant [25, 26, 30, 11]. A general approach is taken also to the formulation of methods for the solution of the set of key applications in biomedicine. In all cases, the method of choice is the general Galerkin finite element method in space and time, including appropriate least-squares stabilization. Since the simulation code is automatically generated, experimentation with different models, constitutive relations and formulations is largely simplified.

2.4 The project plan

The proposed research partitions naturally into the development of a general methodology and tool-set for automated error control in the solution of partial differential equations, and the application of these tools to a set of specific key applications in biomedicine. The feedback and mutual interaction between demanding applications and generic method development will be essential to the success of the project, and the two parts of the project will thus be executed in parallel throughout the period of the project.

It is proposed that one post-doctoral fellow works together with the applicant on the development and implementation of the general methodology for automated error control, in particular to extend the capabilities of the form compiler FFC to generate dual problems and a posteriori error estimates. This work includes the development of the general methodology, implementation, testing and evaluation, as well as documenting the work in research articles and high-quality manuals. In parallel to the development of the general methodology, one doctoral student will concentrate on the application of the general methodology to the simulation of turbulent flow through the aortic valve. It is further proposed that two more doctoral students enter the project during its second year to work on the simulation of pulmonary support by forced ventilation and the diagnosis of stenosis by noninvasive acoustic measurement. A second post-doctoral fellowship, focused on further extending and refining the general methodology and its application to fluid–structure interaction problems, is proposed for the third and fourth years of the project. All members of the project will share a common codebase and the development of generic tools that may be used across the sub projects will be emphasized. In particular, it is expected that both students and post-doctoral fellows participate actively in the refinement and realization of the general methodology as part of the FEniCS project. An account for the project's main activities and important milestones is given in the *grant application form*.

2.5 Budget

The budget for the proposed research is given in the *grant application form*.

2.6 Project management, organization and cooperation

Project management and organization. The project will be located at the Scientific Computing Department at Simula Research Laboratory. The Scientific Computing Department has been rated "excellent" twice in evaluations by the Research Council of Norway and has produced a high level of output in terms of articles in international journals, books, software and PhDs. The working environment at Simula provides excellent opportunities for daily contacts and interaction with experienced researchers with expert knowledge both in the development of general methodology and software components for the solution of differential equations [23, 24], and in the simulation of complex biological processes [37].

The applicant has been a driving force and coordinator of the FEniCS project since its initiation in 2003. Since then, the project has managed to attract a fair number of developers and users, signified by around 500 monthly downloads in total for the set of FEniCS components and the organization of two consecutive workshops FEniCS'05 and FEniCS'06. The close connection to the core development of the FEniCS project simplifies the sharing of methodology and tools with other research groups working on related problems and also provides a channel for direct dissemination of results with immediate feedback from developers and users.

International and national cooperation. A substantial part of the proposed research will be carried out in cooperation with other research groups, in Norway and abroad.

The applicant has an excellent track record in all aspects of automated error control relevant to the proposed research project. However, for the project to be successful, strong collaboration with domain experts will be essential, including specialists in the mathematical modeling of biomedical FSI problems and medical doctors. Therefore, Prof. B. Skallerud and Prof. L. R. Hellevik at NTNU in Trondheim will be engaged for the project to provide support and knowledge in biomedical modeling. Prof. Skallerud and Prof. Hellevik have patiently built a solid foundation of biomechanical modeling over many years, and have very good contacts with researchers in medicine that can provide experimental data and give feedback on numerical results. Furthermore, T. Kvamsdal at SINTEF who has strong experience with error estimation and adaptive methods as well as developing computational methods for FSI problems, will be engaged in the project. Skallerud, Hellevik and Kvamsdal will function as co-supervisors for the doctoral students recruited to the proposed research project.

National cooperation will also include close collaboration with other groups at Simula Research Laboratory. FEniCS and in particular its mesh library is currently being used as a main component by the cardiac computations group at Simula Research Laboratory. The main focus of this group has been on modeling and computing the electrical and mechanical activity of the heart. Recently, the scope has also been expanded to include the simulation of biomedical flows.

International cooperation is an integral part of the proposed research and will be a natural extension of ongoing cooperation within the FEniCS project for the automation of computational mathematical modeling. In recent years, the applicant has worked closely together with Prof. R. C. Kirby at Texas Tech (formerly University of Chicago), which has resulted in a number of articles in high-quality journals, including [20, 22, 19, 21]. More recently, the applicant has also established contact with Prof. G. N. Wells and his group at Delft University of Technology. As part of this cooperation, a student from the Delft group will be visiting Simula later this year and work with the applicant to extend the current framework for automated discretization to discontinuous Galerkin methods. It is expected that this cooperation will continue and evolve over the period of the proposed research. In particular, the doctoral students engaged in the proposed research will visit the groups of Prof. Kirby in Texas and the group of Prof. Wells in Delft.

International cooperation also includes close contacts with Prof. C. Johnson at Chalmers University of Technology in Göteborg and the group of Dr. J. Hoffman at the Royal Institute of Technology in Stockholm. This group has worked extensively with simulation of turbulent incompressible flows [16] and is currently engaged in a project to study FSI problems. As part of this project, the FEniCS mesh library developed by the applicant will be extended with tools for FSI simulation, in particular automating tools for tracking moving boundaries and mesh smoothing, which will be of great benefit to the proposed research. Conversely, the automating tools for error control developed as part of the proposed research will be of direct benefit to every project based on the FEniCS tool-set.

3 Perspectives and compliance with strategic documents

3.1 Compliance with strategic documents

The proposed research complies with the strategic objective of Simula Research Laboratory which is to perform basic research in selected areas of interest "that can contribute to increased knowledge, revitalisation and innovation in society and industry". More specifically, the proposed research coincides with the strategic vision of the Scientific Computing Department of Simula, which is to develop computational middleware that allows the computational study of real-world models and to provide high-performance computational tools for biomedical science.

3.2 Relevance to society

Models of nature in the form of differential equations are solved daily in industry by computational methods, playing an important role in industrial design and production. Computational mathematical modeling is also becoming increasingly important in biomedical sciences. However, the results of these computations are rarely validated rigorously to assess the error of the computed solutions. This is not surprising, since a rigorous assessment of the error of a computed solution is challenging, both mathematically and computationally. A direct consequence of the proposed research is the availability of methodology and tools that automate error control of computational results. This could potentially lead to new policies that require rigorous error control of computational results in the design of, e.g., cars, bridges and buildings, both in the private and public sectors. In particular, the proposed research could have a direct impact on the use of computer simulations in medicine, where it is essential that computed solutions can be trusted.

3.3 Environmental aspects

The proposed research is not expected to have any direct environmental impacts.

3.4 Ethical aspects

While *in vivo* and *in vitro* experiments relating to the biomedical applications studied in the proposed research may raise ethical questions, numerical simulation is less ethically challenging. The simulations to be carried out as part of the proposed research will be performed on existing geometries and comparison will be made with existing experimental studies.

3.5 Gender equality and gender perspectives

The Scientific Computing Department at Simula has very good experience with recruiting female doctoral students and post-doctoral fellows, with numbers well exceeding the national average. The proposed research project will build on this experience to further strengthen the proportion of female doctoral students and post-doctoral fellows.

4 Communication with users and exploitation of results

4.1 Communication with users

User groups that are expected to benefit from the results of the proposed research include computational scientists, domain experts and engineers working with research, diagnosis and development in medicine and industry.

The methodology and tools developed as part of the research will immediately be made available through the collection of software components distributed through the FEniCS project. These components are currently used by computational scientists in a number of academic research groups in Norway, Sweden, the Netherlands and the USA. However, the usage by domain experts and engineers is currently limited. Thus, as part of the proposed research, effort will be made to package the results in an attractive way for these user groups. This includes development of special-purpose interfaces for special applications, such as the simulation of the blood flow through the aortic valve. These interfaces will provide attractive tools for domain-specialists to perform further research on this set of applications. Furthermore, effort will be made to communicate the methodology and tools developed as part of the research project to both domain experts and engineers as part of workshops and mini courses. Communication activities are discussed further in the project publication plan of the *grant application form*.

4.2 Dissemination plan

A dissemination plan is given in the project publication plan of the *grant application form*.

References

[1] M. Ainsworth and J. T. Oden, *A posteriori error estimation in finite element analysis*, Comp. Meth. in Appl. Mech. and Engrg., 142 (1997), pp. 1–88.

[2] American Heart Association, *Heart and stroke facts*, (2003).

[3] I. Avrahami, M. Rosenfeld, S. Raz, and S. Einav, *Numerical model of flow in a sac-type ventricular assist device*, Artif. Organs, 30 (2006), pp. 529–538.

[4] I. Babuška and W. C. Rheinboldt, *Error estimates for adaptive finite element computations*, SIAM J. Numer. Anal., 15 (1978), pp. 736–754.

[5] ——, *A posteriori error estimates for the finite element method*, Int. J. Numer. Meth. Engrg., (1978), pp. 1597–1615.

[6] R. Becker and R. Rannacher, *An optimal control approach to a posteriori error estimation in finite element methods*, Acta Numerica, 10 (2001), pp. 1–102.

[7] D. Bluestein, Y. M. Li, and I. B. Krukenkamp, *Free emboli formation in the wake of bi-leaflet mechanical heart valves and the effects of implantation techniques*, Journal of Biomechanics, 35 (2002), pp. 1533–1540.

[8] T. Dupont, J. Hoffman, C. Johnson, R. C. Kirby, M. G. Larson, A. Logg, and L. R. Scott, *The FEniCS project*, Tech. Rep. 2003–21, Chalmers Finite Element Center Preprint Series, 2003.

[9] P. A. Durbin, *Encyclopedia of Computational Mechanics, Volume 3, Chapter 10: Turbulence Closure Models for Computational Fluid Dynamics*, Wiley, 2004.

[10] K. Eriksson, D. Estep, P. Hansbo, and C. Johnson, *Introduction to adaptive methods for differential equations*, Acta Numerica, 4 (1995), pp. 105–158.

[11] K. Eriksson, C. Johnson, and A. Logg, *Explicit time-stepping for stiff ODEs*, SIAM J. Sci. Comput., 25 (2003), pp. 1142–1157.

[12] D. Estep, M. Larson, and R. Williams, *Estimating the error of numerical solutions of systems of nonlinear reaction–diffusion equations*, Memoirs of the American Mathematical Society, 696 (2000), pp. 1–109.

[13] J. Hoffman, J. Jansson, C. Johnson, M. G. Knepley, R. C. Kirby, A. Logg, L. R. Scott, and G. N. Wells, *FEniCS*, 2006. `http://www.fenics.org/`.

[14] J. Hoffman, J. Jansson, A. Logg, and G. N. Wells, *DOLFIN*, 2006. `http://www.fenics.org/dolfin/`.

[15] J. Hoffman and C. Johnson, *A new approach to computational turbulence modeling*, Comput. Meth. Appl. Mech. Engrg, 195 (2005), pp. 2863–3182.

[16] ——, *Computational Turbulent Incompressible Flow*, Springer-Verlag, 2006.

[17] J. Hoffman and A. Logg, *DOLFIN: Dynamic Object oriented Library for FINite element computation*, Tech. Rep. 2002–06, Chalmers Finite Element Center Preprint Series, 2002.

[18] W. P. Jones and B. E. Launder, *The prediction of laminarization with a two-equation model*, Int. J. Heat Mass Transfer, 15 (1972), pp. 301–314.

[19] R. C. Kirby and A.Logg, *A compiler for variational forms*, ACM Transactions on Mathematical Software, 32 (2006), pp. 417–444.

[20] R. C. Kirby, M. G. Knepley, A. Logg, and L. R. Scott, *Optimizing the evaluation of finite element matrices*, SIAM J. Sci. Comput., 27 (2005), pp. 741–758.

[21] R. C. Kirby and A. Logg, *Efficient compilation of a class of variational forms*, to appear in ACM Transactions on Mathematical Software, (2006).

[22] R. C. Kirby, A. Logg, L. R. Scott, and A. R. Terrel, *Topological optimization of the evaluation of finite element matrices*, SIAM J. Sci. Comput., 28 (2006), pp. 224–240.

[23] H. P. Langtangen, *Computational Partial Differential Equations - Numerical Methods and Diffpack Programming*, Springer-Verlag, second ed., 2003.

[24] ——, *Python Scripting for Computational Science*, Springer, second ed., 2006.

[25] A. Logg, *Multi-adaptive Galerkin methods for ODEs I*, SIAM J. Sci. Comput., 24 (2003), pp. 1879–1902.

[26] ——, *Multi-adaptive Galerkin methods for ODEs II: Implementation and applications*, SIAM J. Sci. Comput., 25 (2003), pp. 1119–1141.

[27] ——, *Automation of Computational Mathematical Modeling*, PhD thesis, Chalmers University of Technology, Sweden, 2004.

[28] ——, *Automating the finite element method*, submitted to Arch. Comput. Methods Engrg., (2006).

[29] ——, *FFC*, 2006. `http://www.fenics.org/ffc/`.

[30] ——, *Multi-adaptive Galerkin methods for ODEs III: A priori error estimates*, SIAM J. Numer. Anal., 43 (2006), pp. 2624–2646.

[31] S. B. Pope, *Turbulent Flows*, Cambridge University Press, first ed., 2000.

[32] R. S. Rogallo and P. Moin, *Numerical simulation of turbulent flows*, Ann. Rev. Fluid Mech., 16 (1984), pp. 99–137.

[33] P. Sagaut, *Large-Eddy Simulation for Incompressible Flows — An Introduction*, Springer-Verlag, 2002.

[34] ——, *Encyclopedia of Computational Mechanics, Volume 3, Chapter 9: Turbulence Direct Numerical Simulation and Large-eddy Simulation*, Wiley, 2004.

[35] J. Smagorinsky, *General circulation experiments with the primitive equations I: The basic experiment*, Monthly Weather Rev., 91 (1963), pp. 99–165.

[36] E. Stein and M. Rüter, *Encyclopedia of Computational Mechanics, Volume 2, Chapter 2: Finite Element Methods for Elasticity with Error-controlled Discretization and Model Adaptivity*, Wiley, 2004.

[37] J. Sundnes, G. T. Lines, X. Cai, B. F. Nielsen, K.-A. Mardal, and A. Tveito, *Computing the electrical activity in the heart*, Springer-Verlag, 2006. To appear on Springer-Verlag August 2006.

[38] A. P. Yoganathan, K. B. Chandran, and F. Sotiropoulos, *Flow in prosthetic heart valves: State-of-the-art and future directions*, Ann. Biomed. Eng., 33 (2005), pp. 1689–1694.