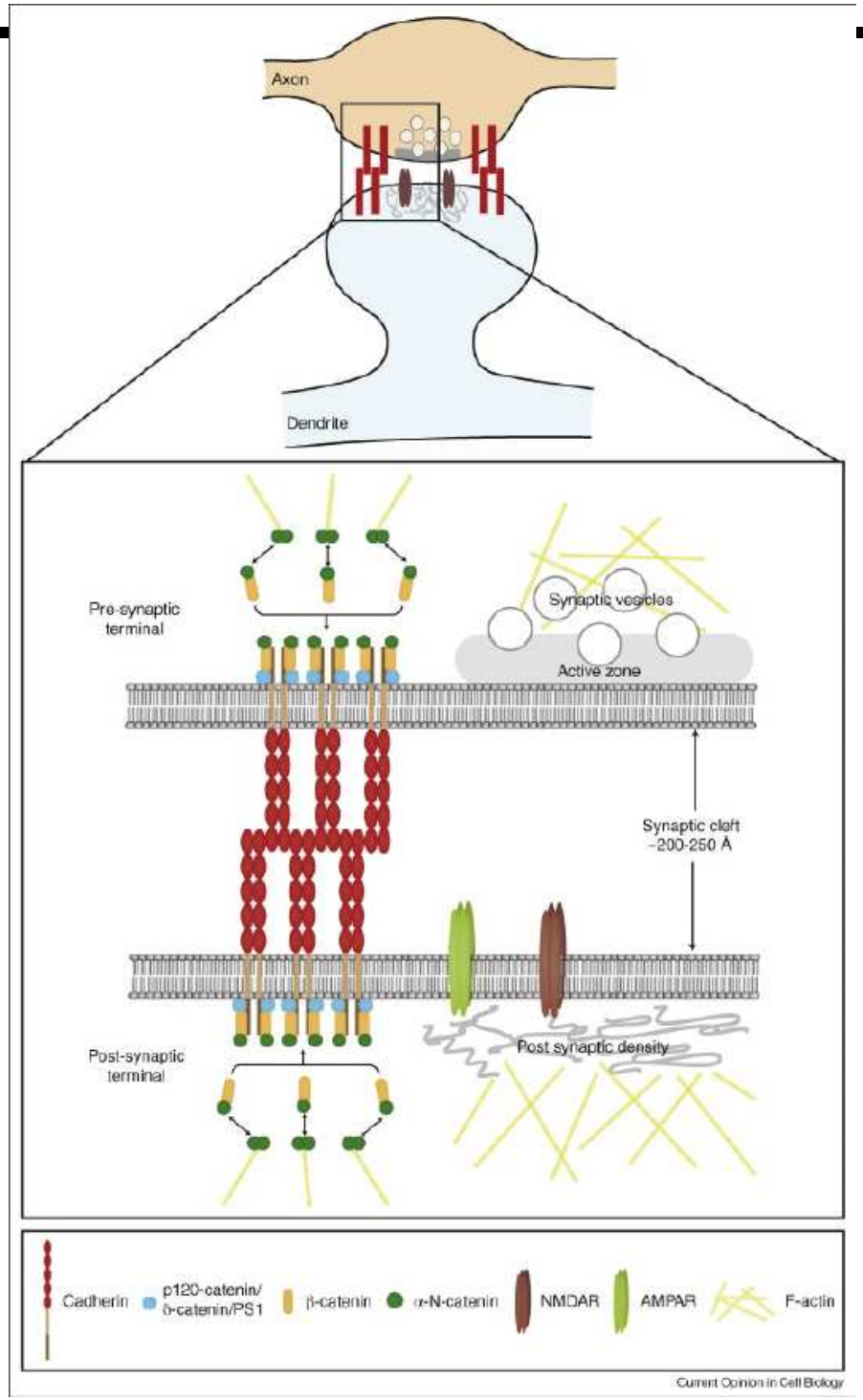
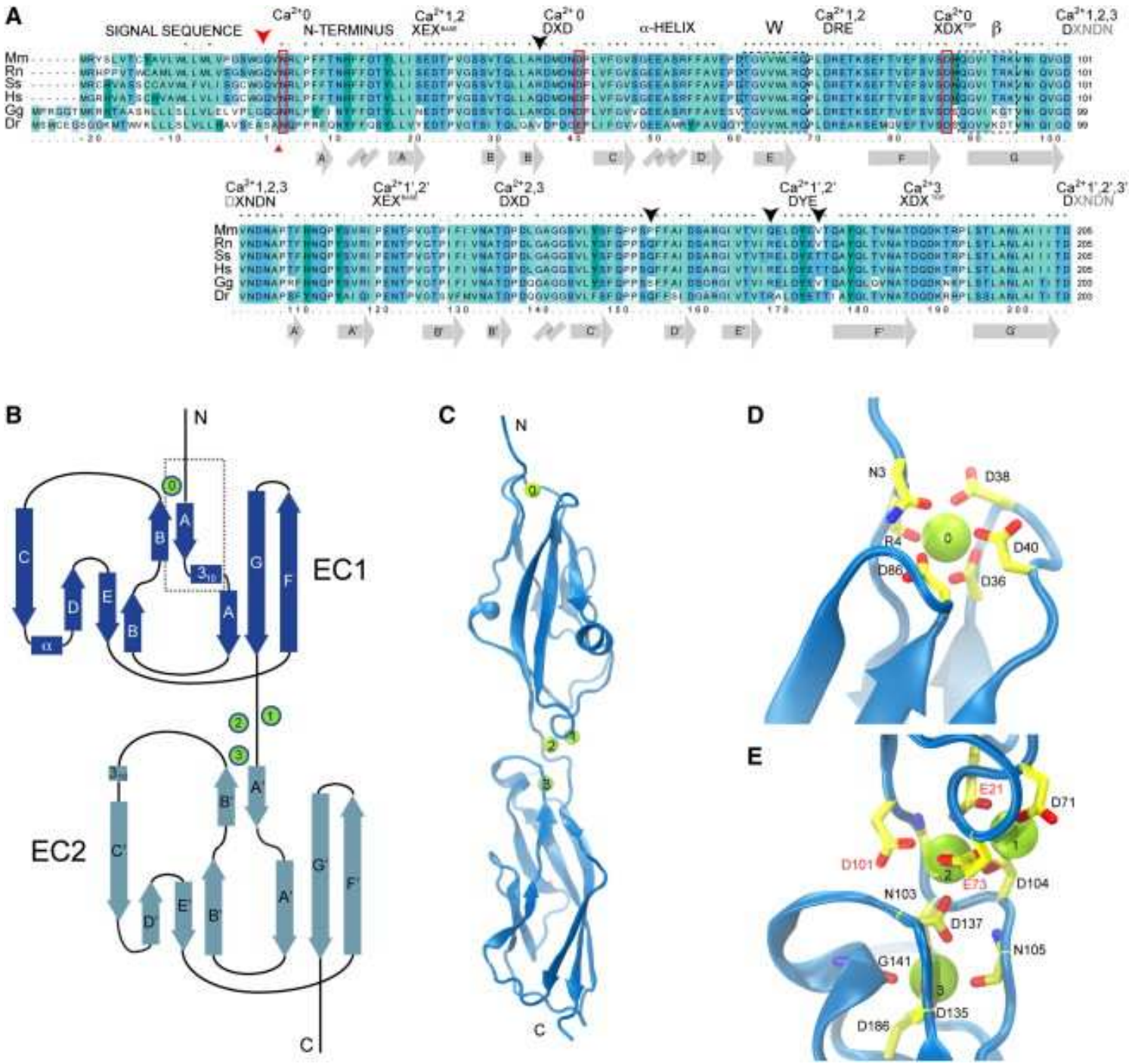
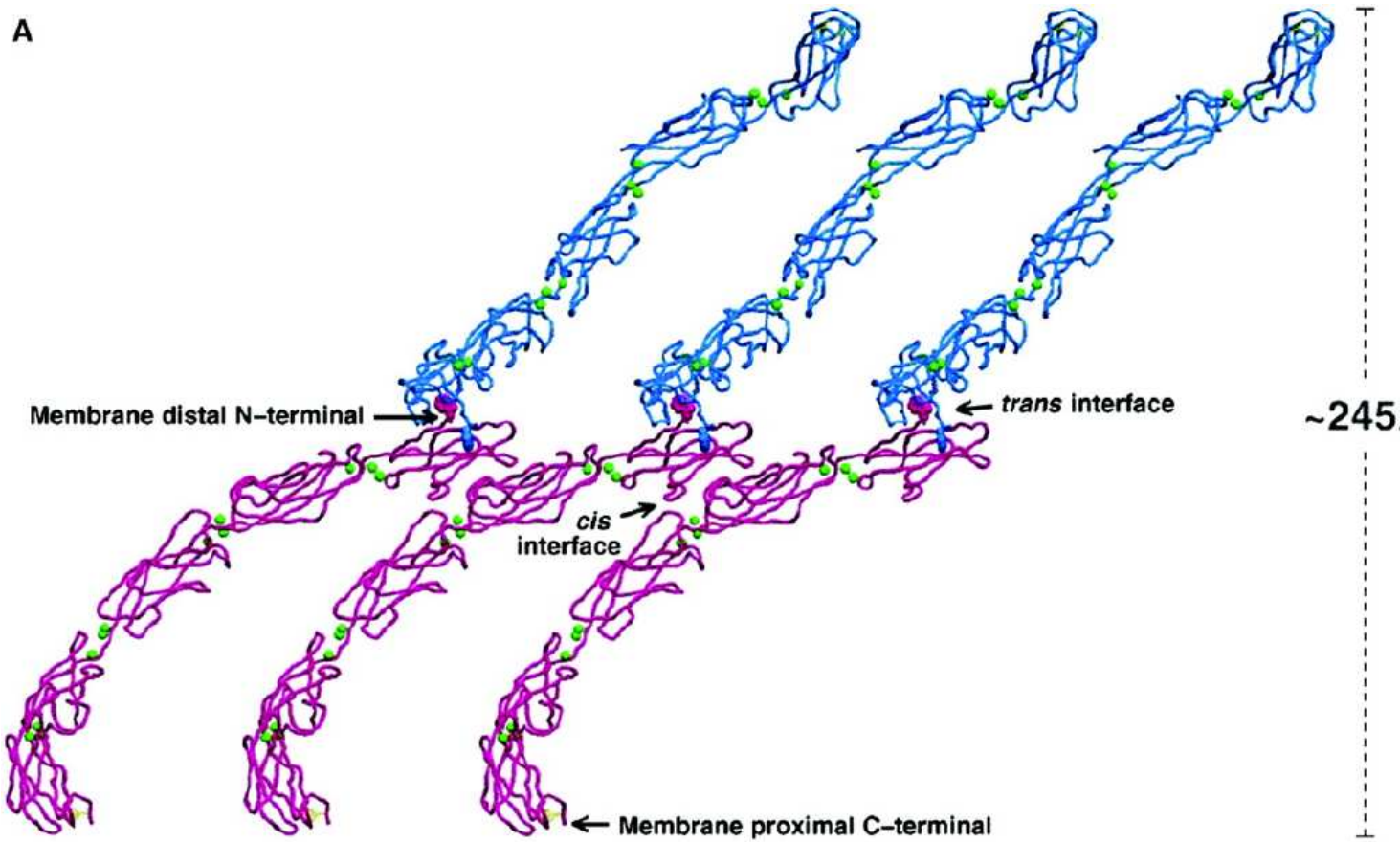


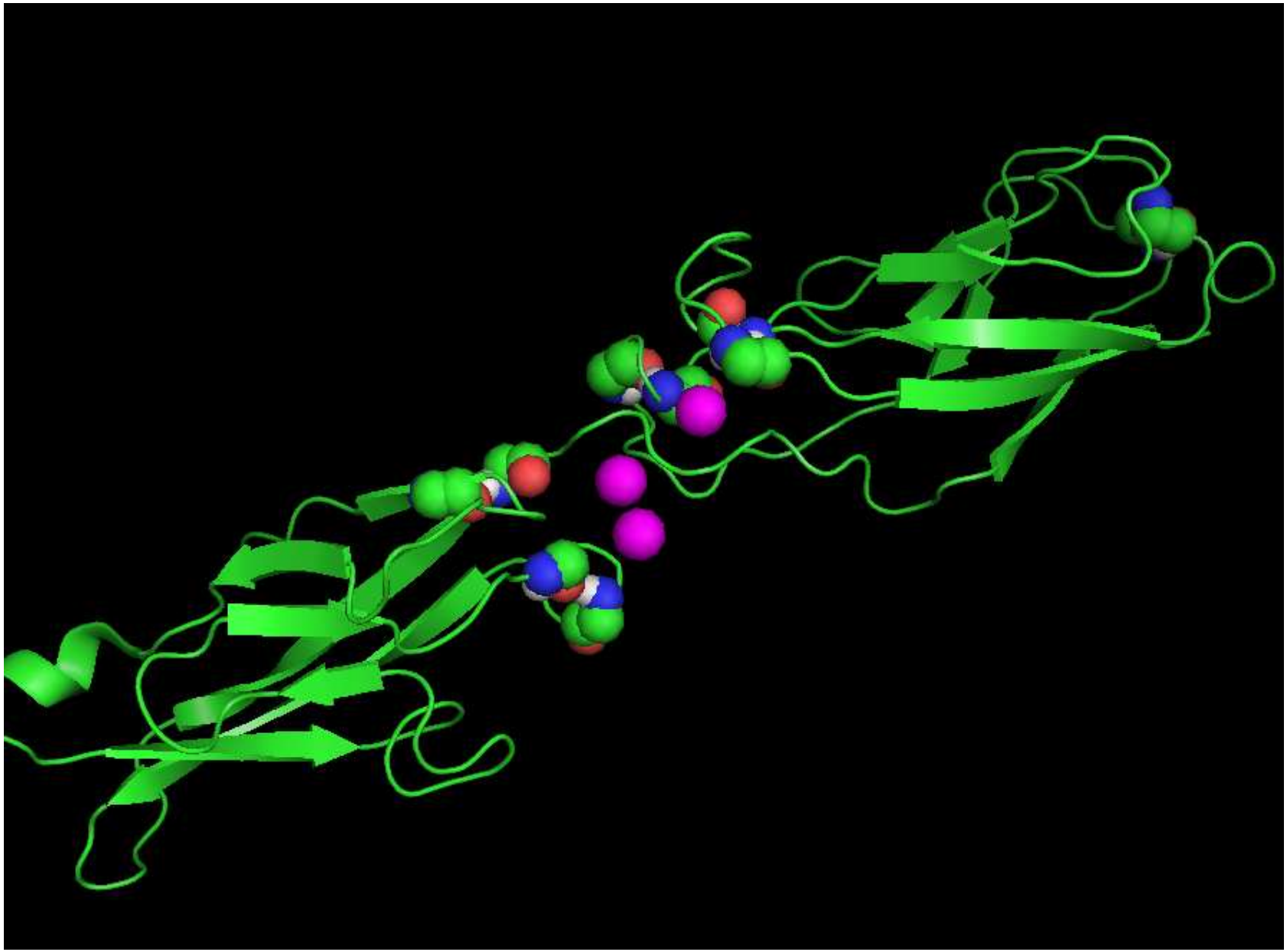
Cadherins are involved in synapse function [16].



Cadherins are also involved in hearing [15]



Cadherin structure is well studied [3, 4, 9, 10]



In PDB file 2QVI dehydrons get desolvated by calciums.

The standard explanation in the literature for the calcium binding is that the calciums form salt bridges with the D and E sidechains in e-cad. This is true, but it only explains part of the story.

It does not explain why this state is favorable, compared to having both the calciums and D and E sidechains solvated (i.e., unbound).

Something needs to explain why the water wants to get out of the way. In many other systems, we have found dehydrons give this reason.

It seems to be at least part of the story for the cadherins.

In addition to forming favorable electrostatic interactions, the calciums displace water.

Water's role as a dielectric is modulated by such events, and thus ligands often bind where there is a benefit to water removal.

In the figure, the calciums are in magenta, with Ca 301 at the upper-right. The two dehydrons near Ca 301 are indicated by the backbone atoms of the donor and acceptors. Also note another one at the upper right of e-cad which is presumably a binding site.

Ca 303 is desolvating the hydrogen bond LEU A 70 – ASP A 67. This hydrogen bond is wrapped by 22 carbon groups at a distance of 6.5 AA, but there are also 6 waters inside this radius.Thus it is an exposed hydrogen bond.

While the central dehydrons explain some of the rigidity of two of the loops, I don't yet see why the long loop joining the two regions gets stabilized. So further research is needed.

Ca 302 has a whopping 11 negatively charged sidechains within 4.51AA. Only six for 301 or 303. So the story for Ca 302 may be mainly about salt bridges being formed.

Systems (r)evolution

Traditional systems research was based in three areas.

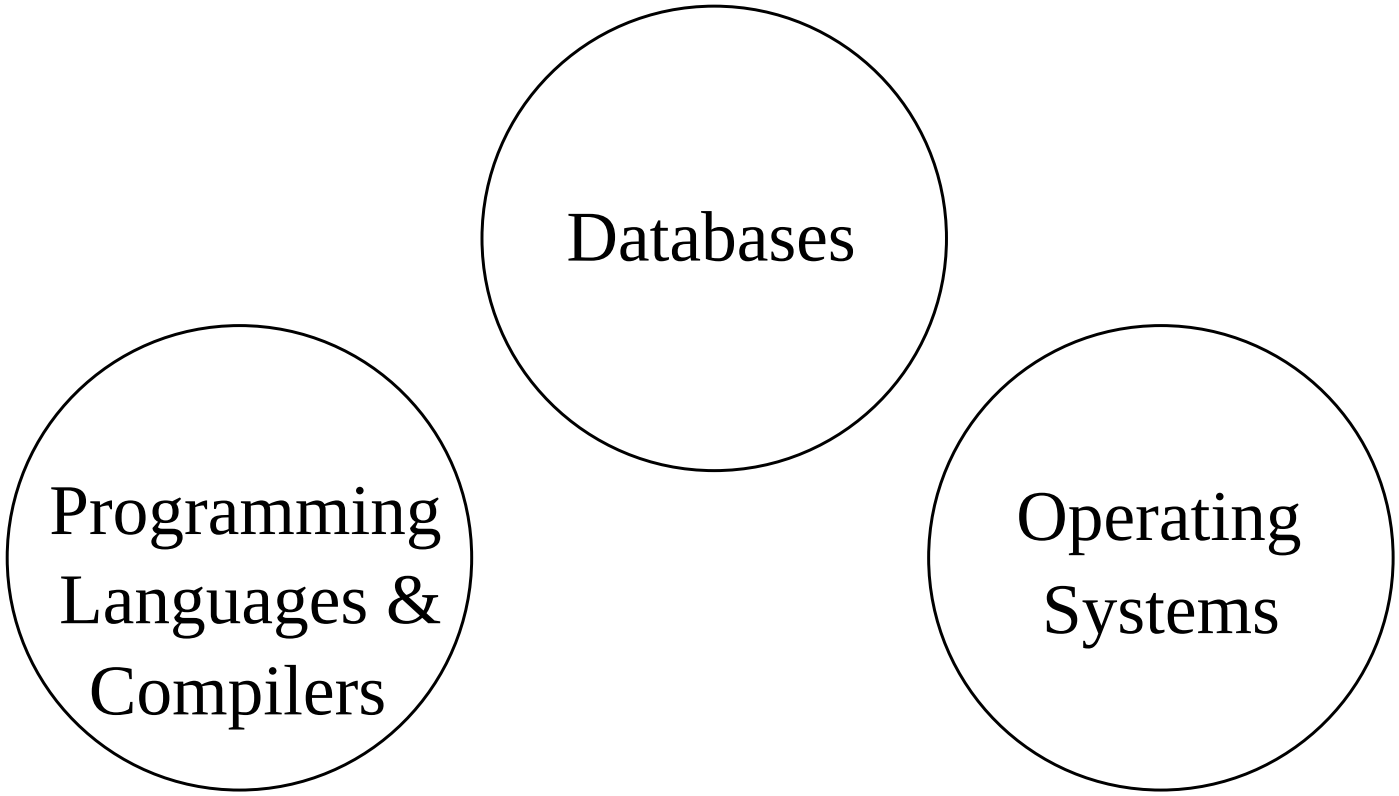


Figure 1: Traditional areas of systems research

Current systems research

Current systems research has changed in two of the three areas.

And new ones have emerged.

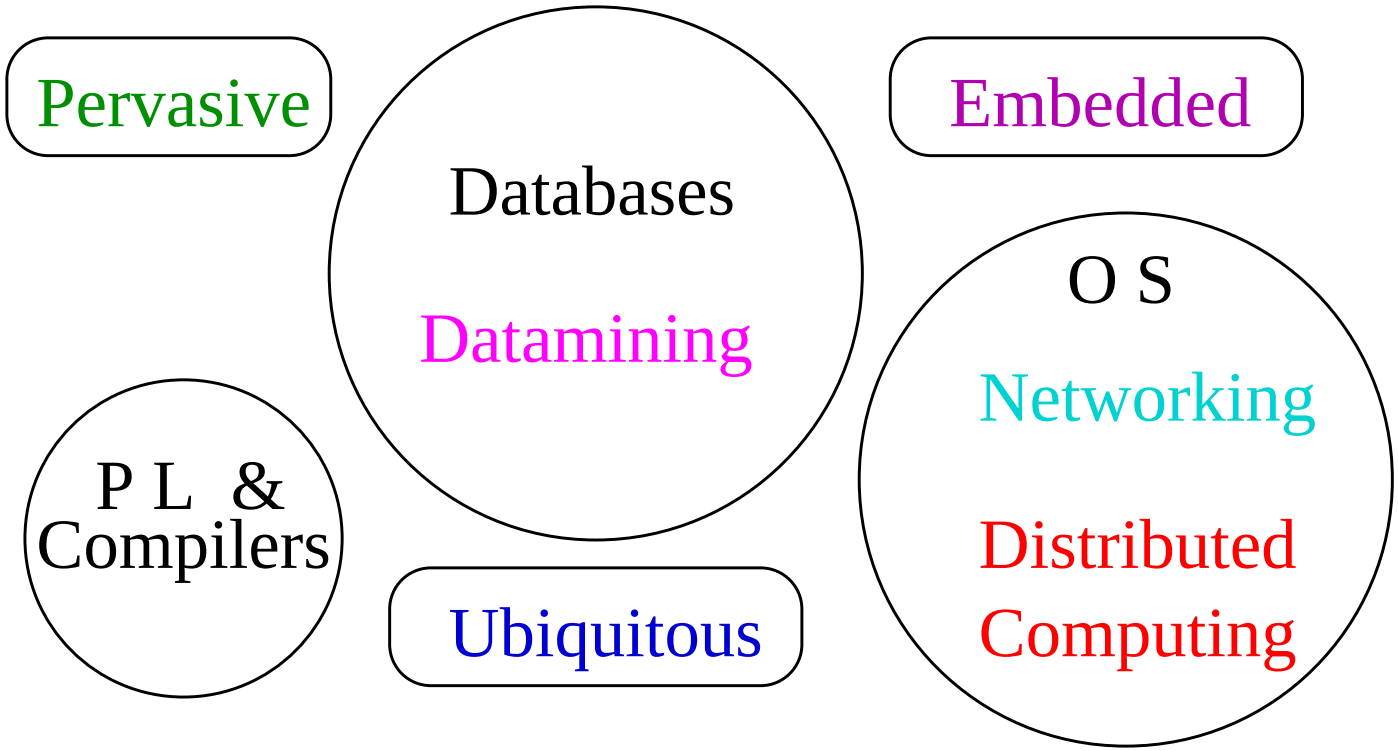


Figure 2: Traditional areas of systems research are changing, and new ones have been added.

Future systems research

Future systems research will continue to evolve.

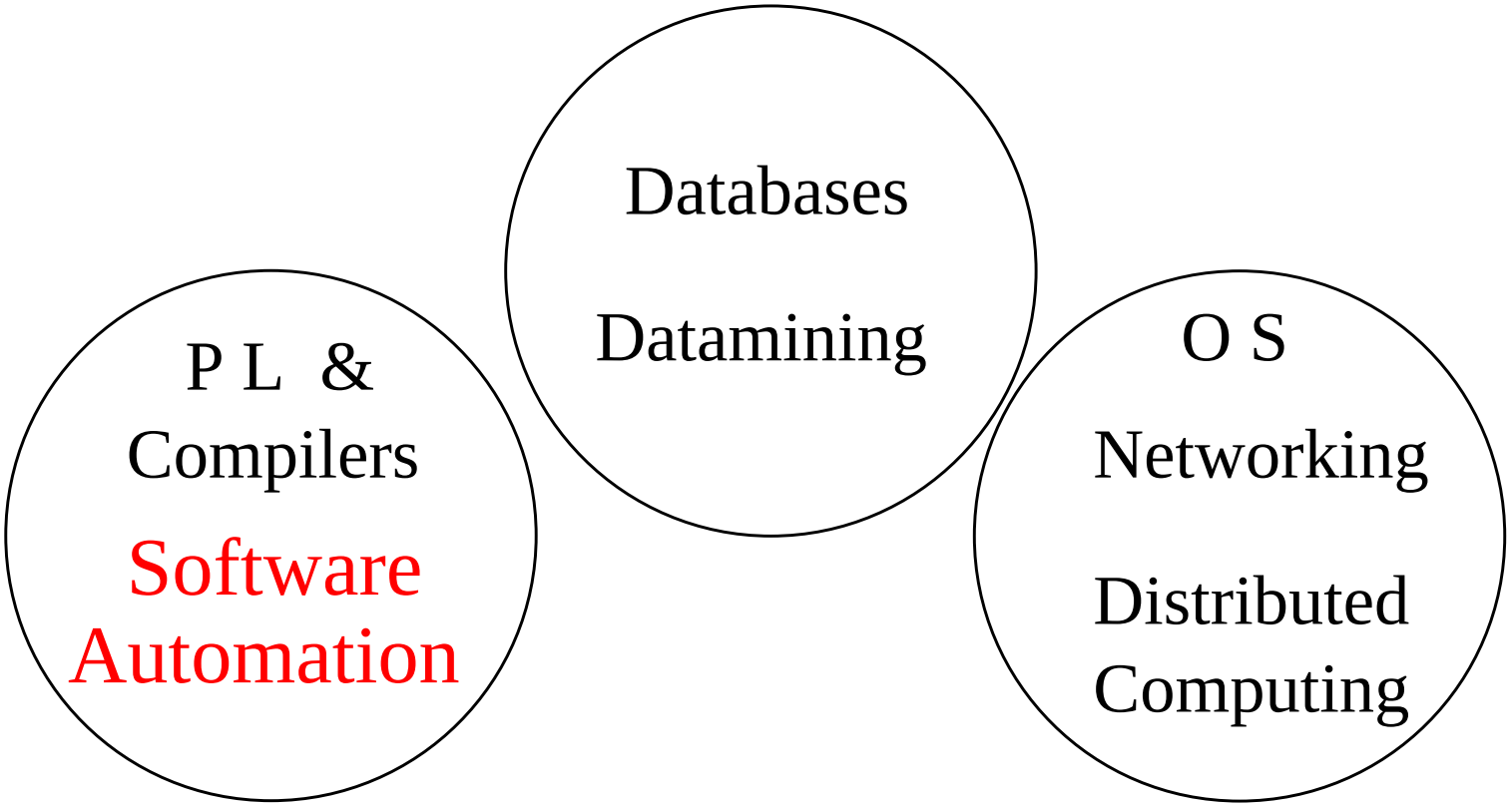


Figure 3: Traditional areas of systems research must change to survive

What is Software Automation?

There are two distinct phases.

(1) construct a domain specific language

with an underlying mathematical model

and a translator into executable code.

(2) optimize within the mathematical model

to improve execution times for generated code.

Steps are independent: sometimes only (1) is done.

Step (1) is related to the generative programming model.

Conventional PL/compilers model

Conventional PL/compilers model fits into the software automation description to some extent.

The underlying mathematical model is essentially the Λ-calculus.

But true optimizations are replaced by simple transformations because
conventional optimization would be intractable.

Some code transformations guarantee a reduction in runtime and are always helpful in any model.

New paradigms for software development

Hierarchical code development

Improves upon standard two level model: language+compiler

Allows appropriate optimizations to be done at different levels

Improves code correctness and decreases cost of code development

Automation of code production

Utilizes abstract descriptions as basis to generate code automatically

Leverages intrinsic domain languages

Improves code correctness and decreases cost of code development

Allows true optimization of generated code

Hierarchy of problem representation

—Model description [application domain]

—Algorithm discovery [mathematical description]

—Algorithm implementation [programming language]

. . . . . .

—Executable code [machine code: parallel, multicore]

Automation can be performed at each level

Interaction between levels can be tested to optimize performance

Example of hierarchy: signal processing (Spiral project)

—Model description [Discrete Fourier Transform: DFT]

—Algorithm discovery [Cooley-Tukey FFT]

—Algorithm implementation [FFTW]

—Executable code [BLAS, ATLAS, OSKI]

Automation can be performed at each level: can derive FFT from abstract definition of DFT

No need to hand-code for specific architectures

The software challenge

(Correct) interpretation of problem discription

Have to translate from a high-level description to low-level executable, correctly!

Optimization of generated code

Have to solve disparate optimization problems at compile time or in conjunction with run-time indicators

Tension between expressiveness and efficiency

Ideally the naive user could code in a high-level specification language and have it translated into efficient machine code.

Problem with single-language approach

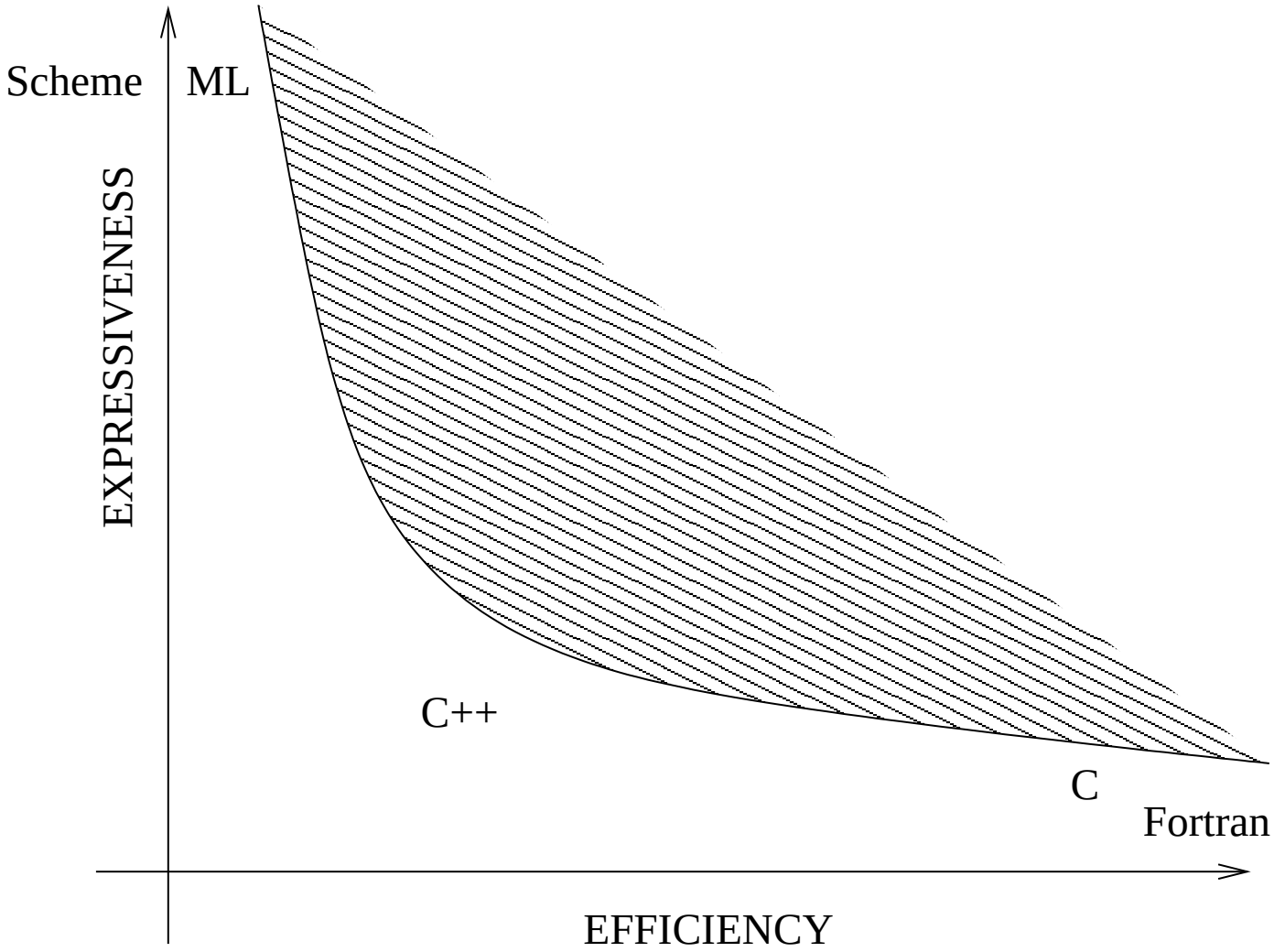


Figure 4: The conflict between efficiency and expressiveness [M. Dragichescu].

Each language has its own domain

Each reflects a different application domain

Fortran: u(x)=$\sqrt[3]{\sin(\log(\tan(\cos(J_1(e^x + \sqrt{\pi x})))))}$

Scripting languages: rapid prototyping, user interfaces

Functional languages: compilers, symbolic manipulation

C: systems software

C++: job security for programmers

what language?: (parallel) sparse matrix operations

Nature of 'answer' changes over time

In antiquity, an answer was a number: the length of the diagonal of a unit square is $\sqrt{2}$.

Later geometric figures were answers: elliptical orbits of planets.

More recently, functions became an acceptable answer: an ODE is solved by a Bessel function, J_1.

In computational science, a well posed boundary value problem is an acceptable answer.

All of these are abstractions that provide information on demand.

FEM: computational science ‘answer’

Generates discrete (finite) algorithms for approximating the solutions of differential equations.

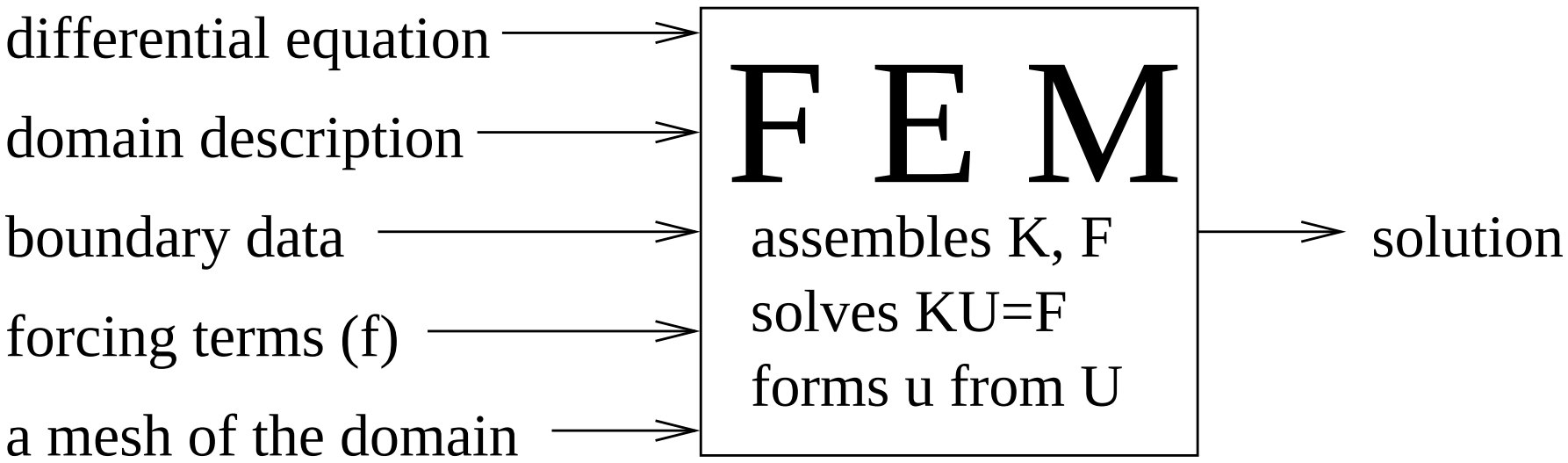


Figure 5: FEM=black box into which one puts model problem and out of which pops an algorithm ($KU = F$) for approximating the corresponding solutions.

Adaptive FEM formalism

What is the right way to program this?

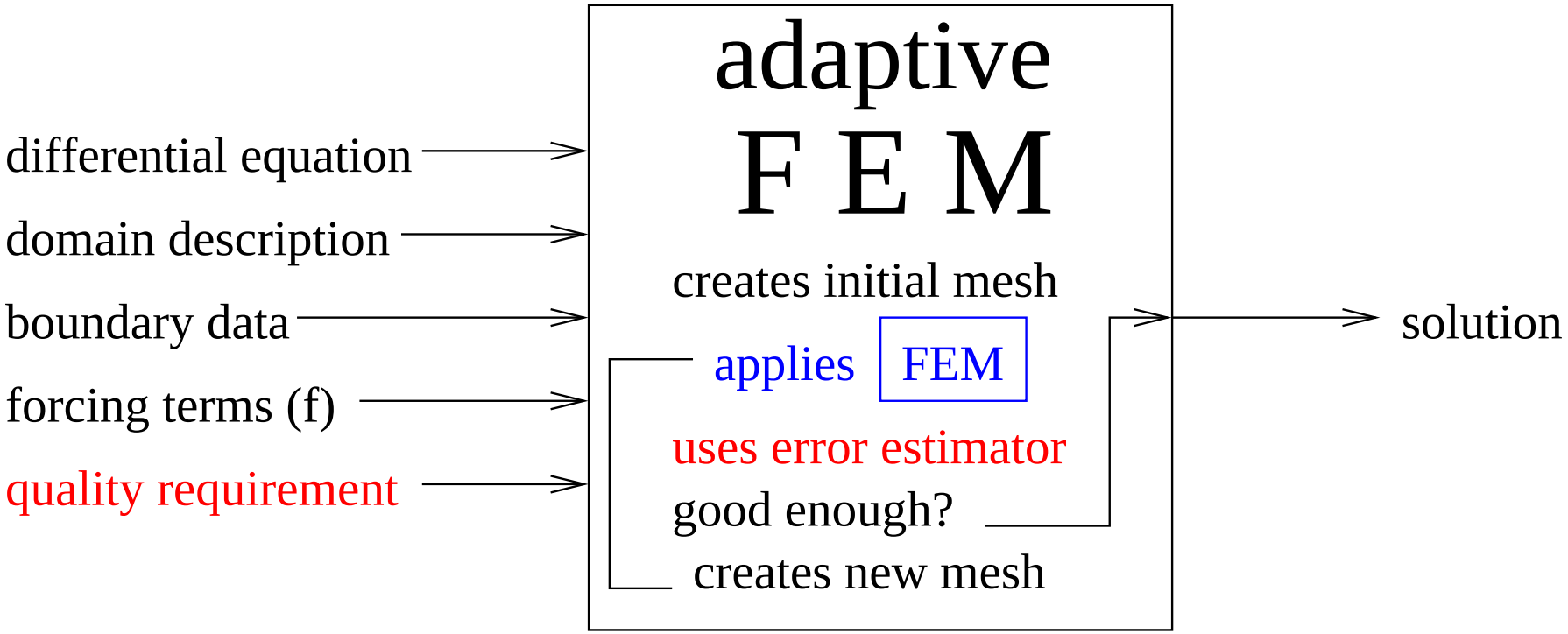


Figure 6: Black box for adaptive FEM; requires no mesh initially, only quality requirement. Generates a sequence of meshes and applies standard FEM until quality is assured.

Causes of efficiency–expressiveness conflict

Compilers perform transformations, not optimization.

Optimization at compile time, even if based on realistic performance models, would be wildly expensive (NP^{NP})

True optimization would have to involve evaluating or accurately modeling performance.

Actual performance is often data dependent.

Best transformations are often domain dependent.

What is missing currently

Current language support for hierarchical abstraction

- You can define what you want
- But you can't specify how to compile it [12, 13]

Compiler optimizations cannot be chosen to fit the application.

Must live with what the compiler writer gives you.

Interpretation of multiple abstraction levels may also be costly.

One solution: multi-lingual

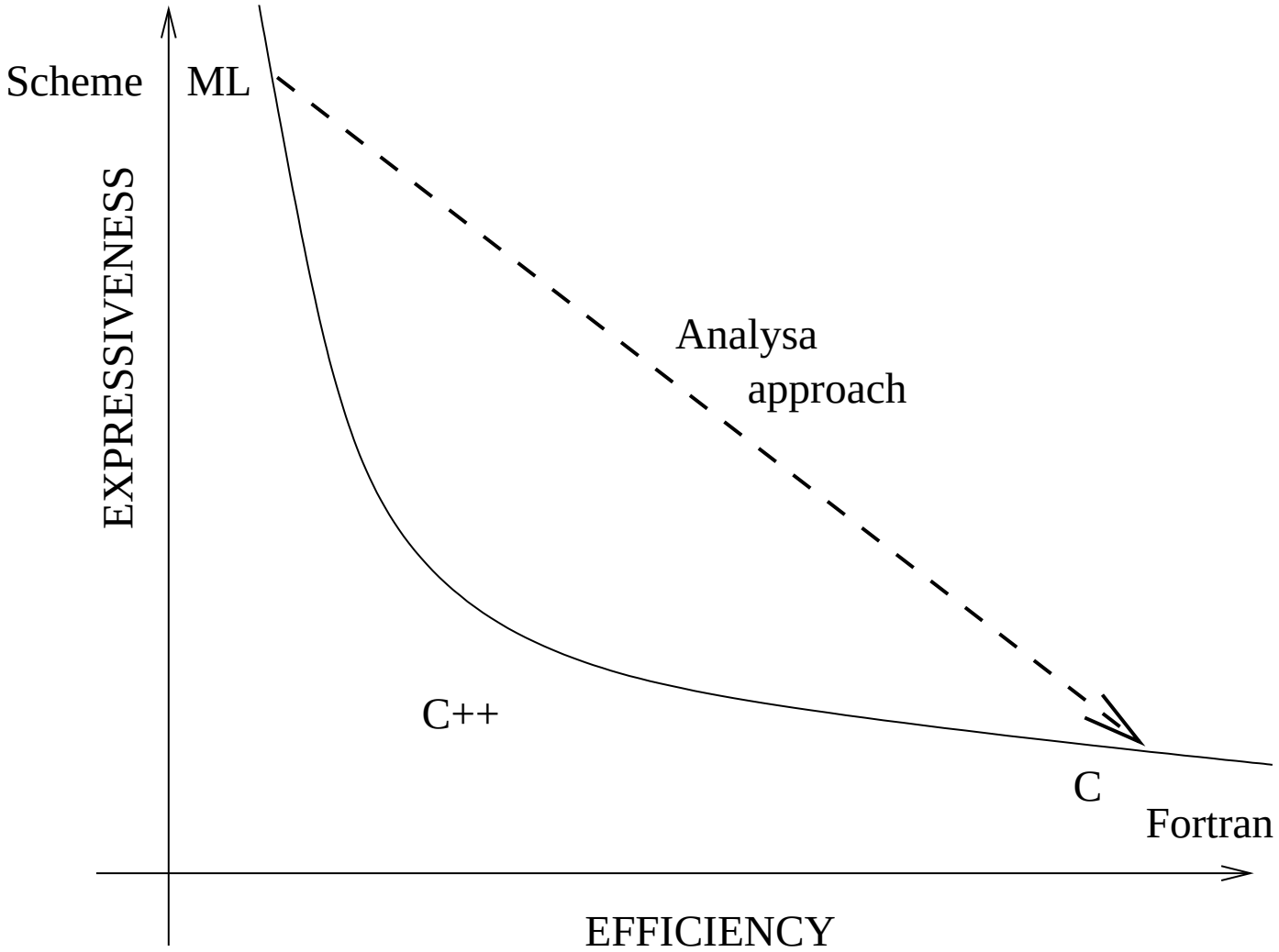


Figure 7: One way to combine efficiency and expressiveness [1].

Limits to linking multiple languages

(Experience gained from the development of Analysa.)

Lacks formal description, requires development (and maintenance) of ad hoc interface.

Different memory models (allocation, garbage collection) can interact adversely at run time.

Increases the burden of code maintenance (must track multiple standards, together with interactions between them).

But it does mollify the tension between expressiveness and efficiency.

Ken Kennedy's telescoping languages

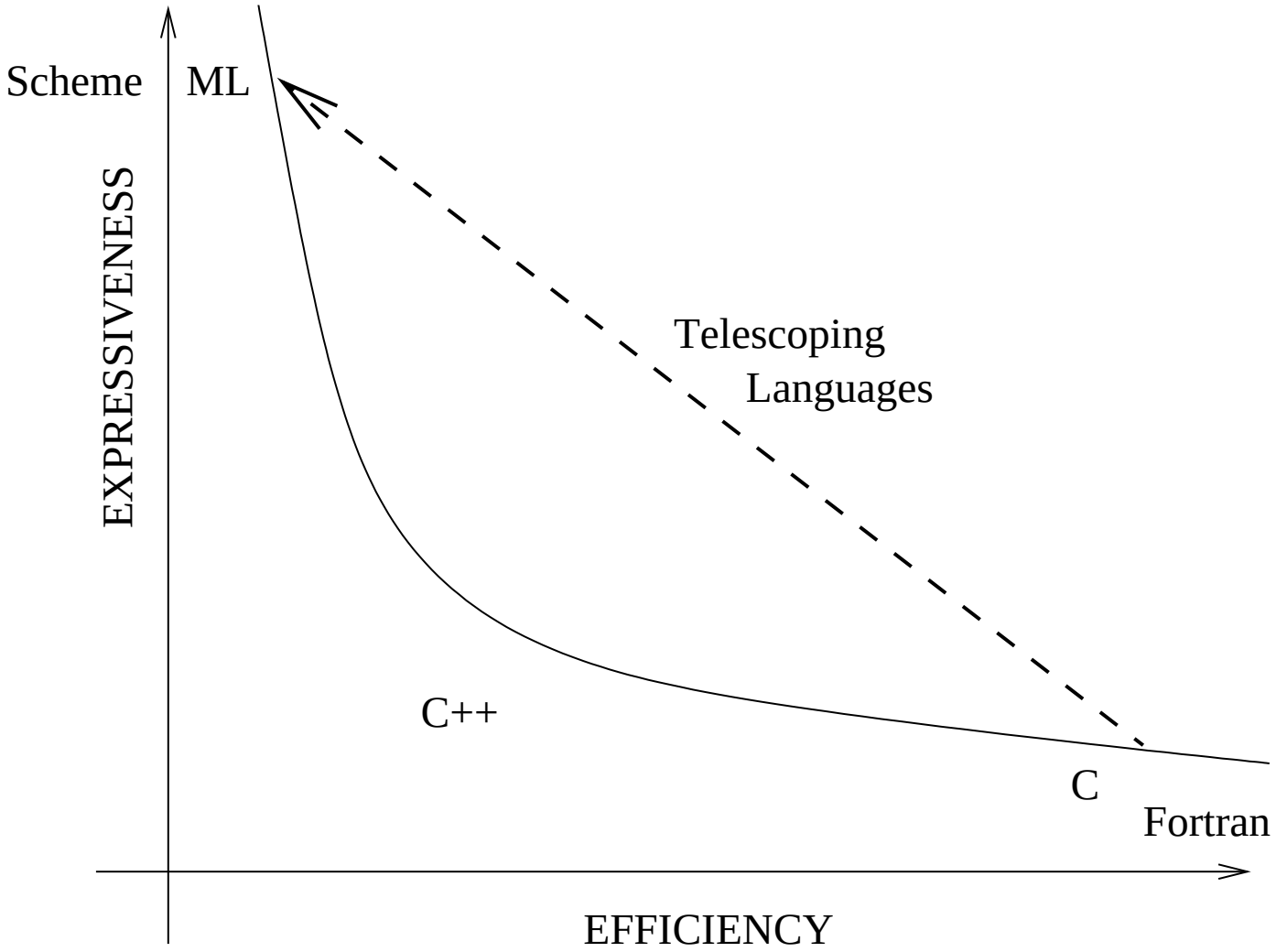


Figure 8: Telescoping language approach [6].

Similar challenges

from which we can learn

Same as problems in language/compiler design

Need to perform optimization and code generation

Often need to utilize these in an application-specific way (Spiral).

Hierarchical issues addressed in programming language

Manticore project for parallel computation

Algegra of code optimizations

Common to use Lambda Calculus or algebra of real numbers

Finite elements introduces optimization in vector spaces

Personal history of software automation projects

From Brenner-Scott (1994)

"The finite element method provides a formalism for generating discrete (finite) algorithms for approximating the solutions of differential equations. It should be thought of as a black box into which one puts the differential equation (boundary value problem) and out of which pops an algorithm for approximating the corresponding solutions. Such a task could conceivably be done automatically by a computer..."

B. Bagheri, M. Draghicescu, and L. R. Scott. Functional objects for finite element computation. In Proceedings of the Second Annual Object-Oriented Numerics Conference, 1994.

Babak Bagheri and L. Ridgway Scott. About Analysa. University of Chicago Technical Report TR-2004-09

While chasing this large bear ...

a small rabbit crossed our path ...

L. R. Scott, J. M. Boyle, and B. Bagheri. Distributed data structures for scientific computation. In Hypercube Multiprocessors 1987, M. T. Heath, ed., pages 55-66. Philadelphia: SIAM, 1987.

Ernesto Gomez and L. Ridgway Scott. Compiler Support for Implicit Process Sets. University of Chicago Technical Report TR-2005-14

L. Ridgway Scott, Terry Clark, and Babak Bagheri. Scientific Parallel Computing. Princeton University Press, 2005

before getting back on track with the FEniCS project:

Robert C. Kirby, Anders Logg, L. Ridgway Scott and Andy R. Terrel. Topological Optimization of the Evaluation of Finite Element Matrices. SIAM J. Sci. Computing 28:224-240, 2006.

A. R. Terrel, L. R. Scott, M. G. Knepley, and R. C. Kirby. Automated FEM discretizations for the Stokes equation. BIT, 48(2):389–404, 2008.

Peter R. Brune, Matthew G. Knepley, and L. Ridgway Scott. Exponential grids in high-dimensional space University of Chicago Technical Report TR-2011-7

1 Solving PDE's: the FEM

Optimization of code for solving differential equations has been studied widely [7, 8, 17, 18].

Many of these approaches have been based on the finite element method (FEM).

There are four distinct areas of finite element codes: function spaces, domain geometry/mesh, differential equation, and equation solution.

These are not hierarchical: interactions are multi-faceted.

Each area has it own natural language and its own optimizations.

But interactions require inter-procedural analysis to obtain ideal performance.

Structure of PDE codes

Different modules must interact.

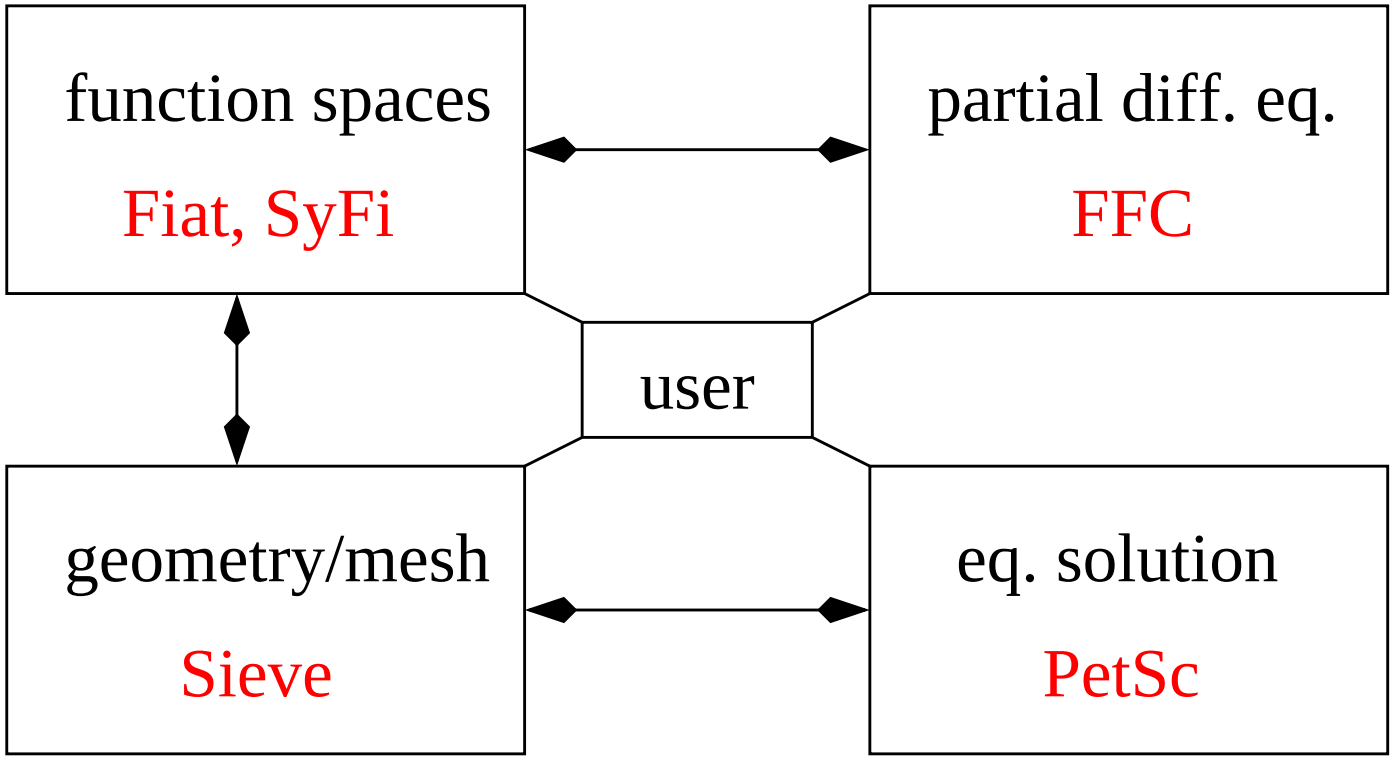


Figure 9: The structure and and some interactions of PDE codes.

Mathematics of PDE codes

Different domains use different mathematics.

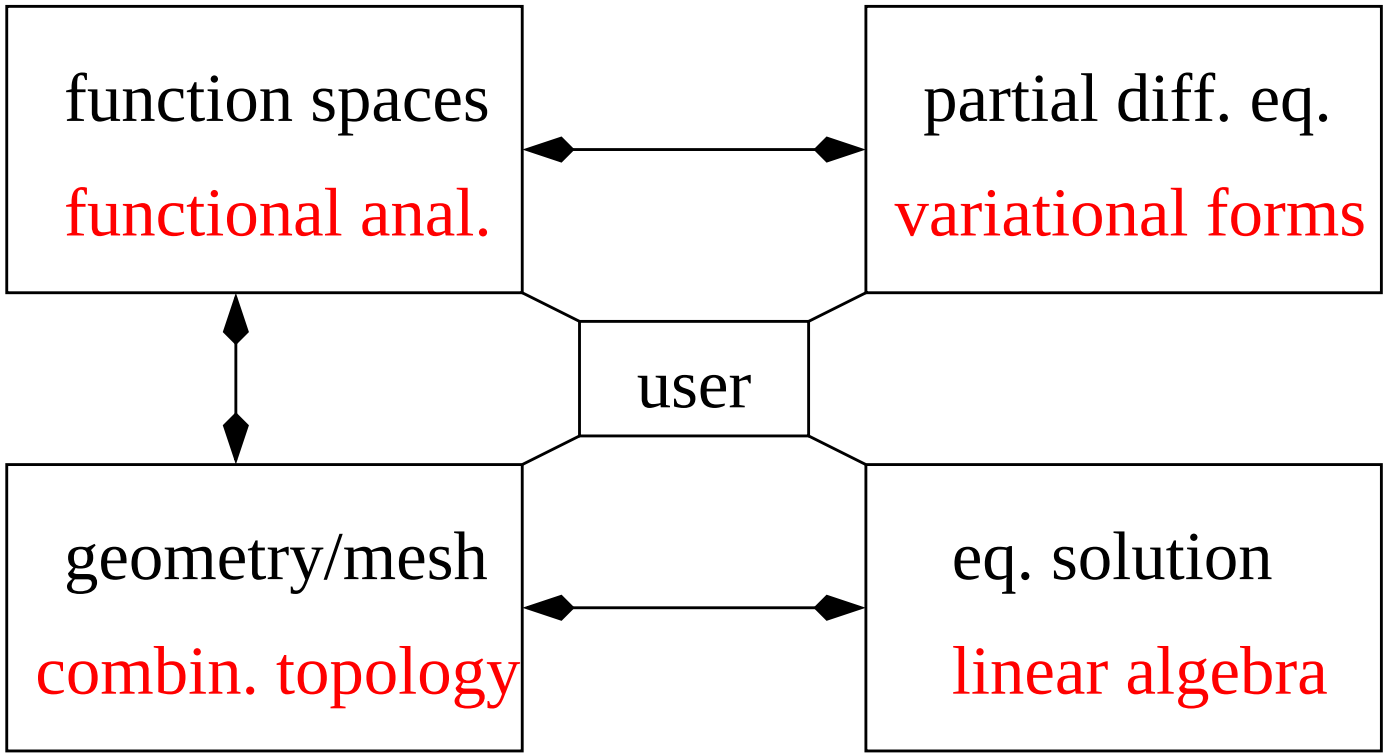


Figure 10: Sample mathemtatical structures of components of PDE codes.

Boundary condition interactions

Require independent modules to be compatible.

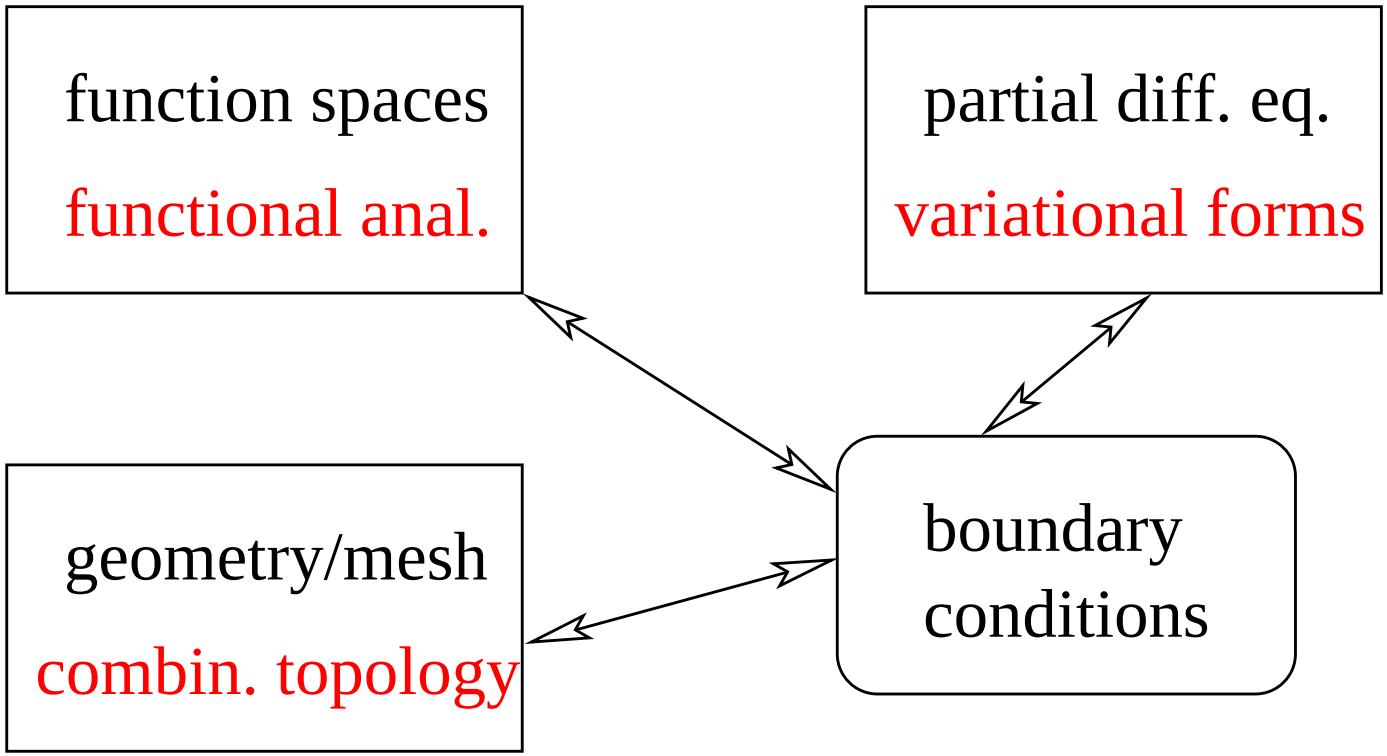


Figure 11: The interactions of boundary conditions in PDE codes.

FErari interactions

FErari can be used as a matrix-free method.

May be of interest for multi-core processors.

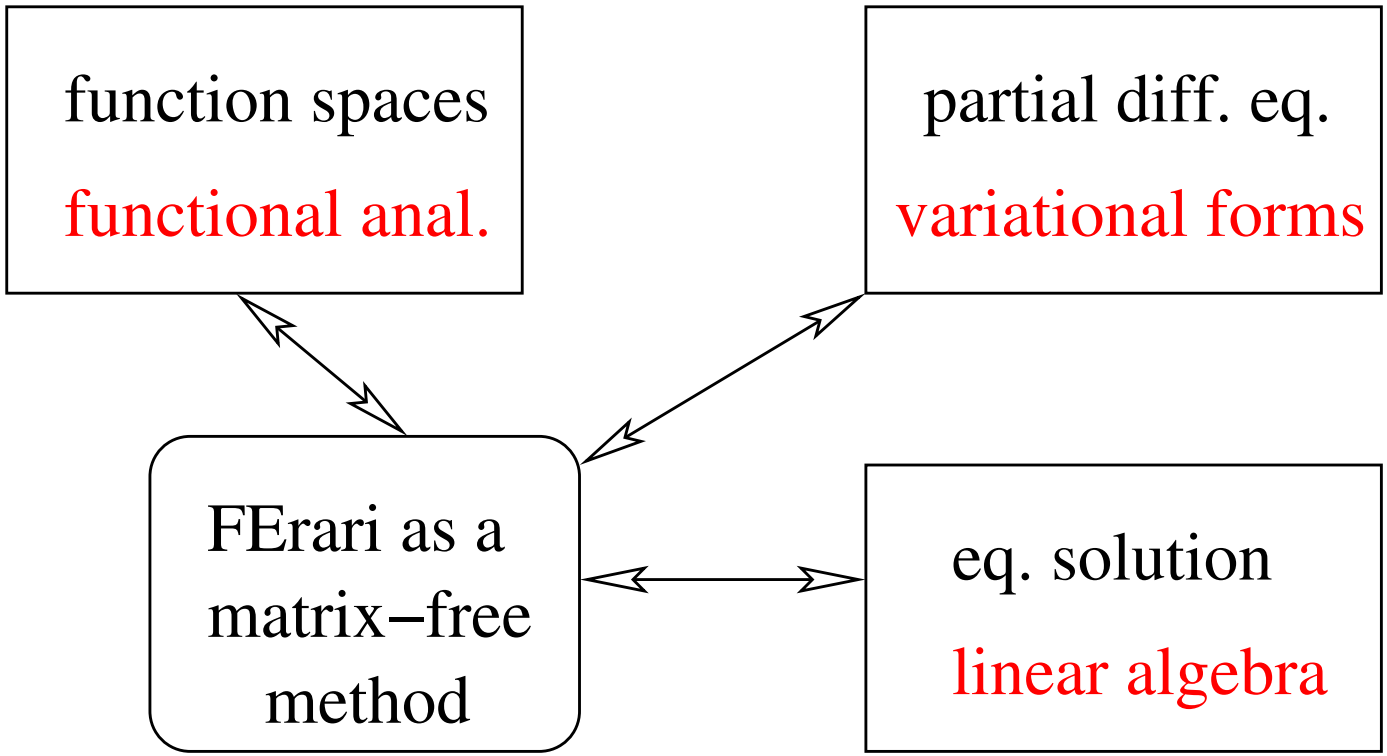


Figure 12: The interactions required to use FErari in PDE codes.

Mathematics may be incomplete

What is a C^0 element? Cubic Hermite?!

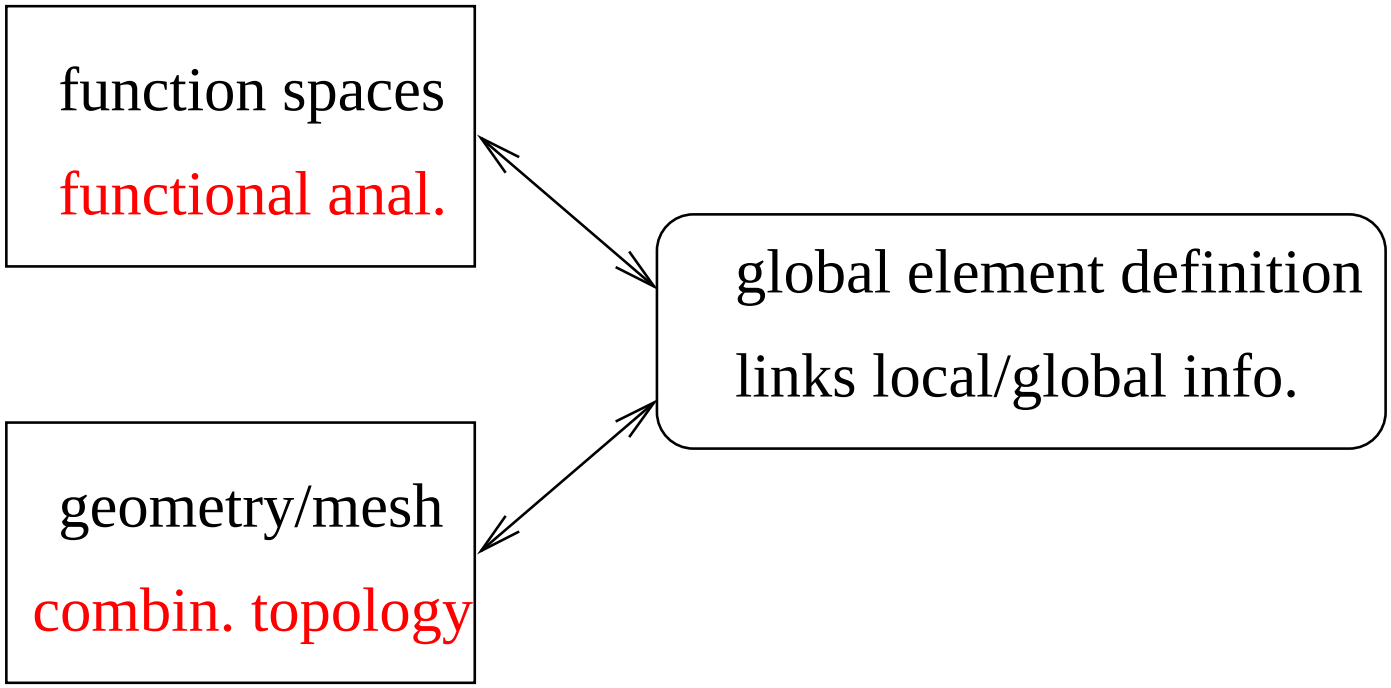


Figure 13: Requirements for a definition of global finite elements.

Software automation paradigm

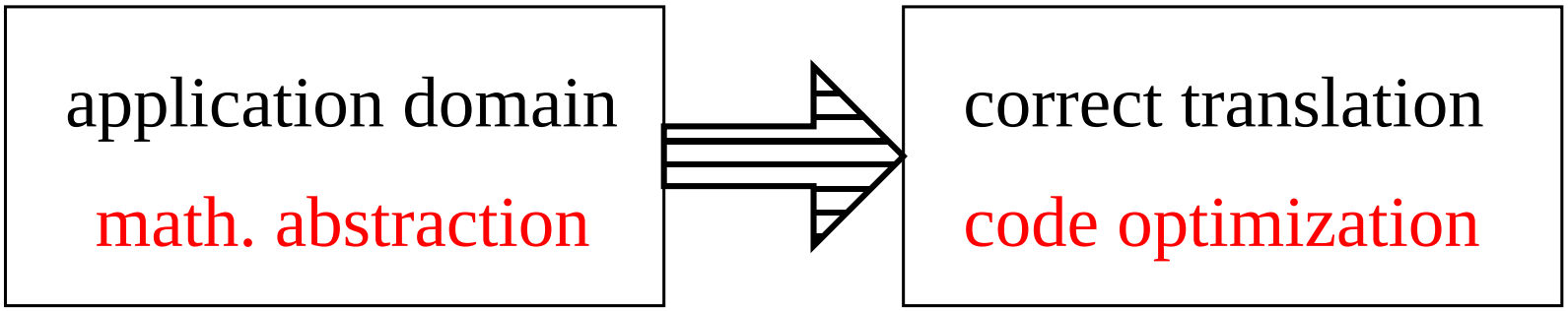


Figure 14: Components of the software automation paradigm.

Current (functional) PL research fits this paradigm:

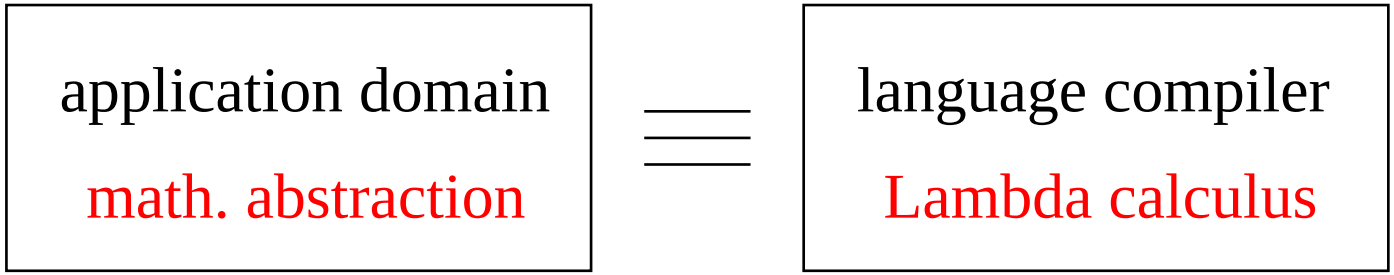


Figure 15: PL paradigm as software automation.

Is Software Automation CS?

Is it Math?

Many areas now claim to be both

Algorithms and complexity

Combinatorics

Computational biology

Software Automation is clearly

Computational Mathematics

FFC examples

```
# Copyright (c) 2005 Johan Jansson.
# Licensed under the GNU GPL Version 2
#
# The bilinear form e(u) : e(u) for linear
# elasticity with e(u) = grad(u) + grad(u)^T
#
# Compile this form with FFC: ffc Elasticity.form

element = FiniteElement("Vector Lagrange", "tetrahedron", 1)

v = BasisFunction(element)
u = BasisFunction(element)

a = (u[i].dx(j) + u[j].dx(i)) * (v[i].dx(j) + v[j].dx(i)) * dx
```

```
# Copyright (c) 2004 Anders Logg (logg@tti-c.org)
# Licensed under the GNU GPL Version 2
#
# The bilinear form for the nonlinear term in the
# Navier-Stokes equations with fixed convective velocity.
#
# Compile this form with FFC: ffc NavierStokes.form

element = FiniteElement("Vector Lagrange", "tetrahedron", 1)

v = BasisFunction(element)
u = BasisFunction(element)
w = Function(element)

a = w[j]*u[i].dx(j)*v[i]*dx
```

This compiles to 388 lines of C++ code (38665 characters)

2 Code generation example: matrix formation

Formation of matrices takes substantial time in finite element computations.

Disadvantage of finite elements over finite differences.

But standard algorithm can be far from optimal.

A general formalism can be automated called FErari:

Finite Element ReArRangement of Integrals

Eliminates efficiency penalty of finite elements.

2.1 Computation of Bilinear Form Matrices

The matrix associated with a bilinear form,

$$A_{ij} := a(\phi_i, \phi_j) = \sum_e a_e(\phi_i, \phi_j) \tag{2.1}$$

for all i, j, can be computed by assembly. First, set all the entries of A to zero. Then loop over all elements e and local element numbers λ and μ and compute

$$A_{\iota(e,\lambda),\iota(e,\mu)} += K^e_{\lambda,\mu} = \sum_{m,m'} G^e_{m,m'} K_{\lambda,\mu,m,m'} \tag{2.2}$$

where $G^e_{m,m'}$ and $K_{\lambda,\mu,m,m'}$ are defined via

$$G^e_{m,m'} = \det(J) \sum_{j=1}^{d} \frac{\partial \xi_m}{\partial x_j} \frac{\partial \xi_{m'}}{\partial x_j} \tag{2.3}$$

$$K_{\lambda,\mu,m,m'} = \int_{\mathcal{T}} \frac{\partial}{\partial \xi_m} \phi_\lambda(\xi) \frac{\partial}{\partial \xi_{m'}} \phi_\mu(\xi)\, d\xi \tag{2.4}$$

2.2 Matrix computation strategy

We optimize the computation of each

$$K^e_{\lambda,\mu} = \sum_{m,m'} G^e_{m,m'} K_{\lambda,\mu,m,m'} \tag{2.5}$$

where $G^e_{m,m'} = \det(J) \sum_{j=1}^{d} \frac{\partial \xi_m}{\partial x_j} \frac{\partial \xi_{m'}}{\partial x_j}$ $\quad K_{\lambda,\mu,m,m'} = \int_{\mathcal{T}} \frac{\partial}{\partial \xi_m} \phi_\lambda(\xi) \frac{\partial}{\partial \xi_{m'}} \phi_\mu(\xi)\, d\xi$

Collection of dot products of fixed vectors (K) with varying set of vectors (G's encode "geometry" information of elements).

Pre-computations can be done, based on relations among the K's, that reduce computational effort substantially.

2.3 Tensor K for quadratics

zero entries, trivial entries and colinear entries $(-4\mathbf{K}_{3,1} = \mathbf{K}_{3,4} = \mathbf{K}_{4,1})$

3	0	0	-1	1	1	-4	-4	0	4	0	0
0	0	0	0	0	0	0	0	0	0	0	0
0	0	0	0	0	0	0	0	0	0	0	0
-1	0	0	3	1	1	0	0	4	0	-4	-4
1	0	0	1	3	3	-4	0	0	0	0	-4
1	0	0	1	3	3	-4	0	0	0	0	-4
-4	0	0	0	-4	-4	8	4	0	-4	0	4
-4	0	0	0	0	0	4	8	-4	-8	4	0
0	0	0	4	0	0	0	-4	8	4	-8	-4
4	0	0	0	0	0	-4	-8	4	8	-4	0
0	0	0	-4	0	0	0	4	-8	-4	8	4
0	0	0	-4	-4	-4	4	0	-4	0	4	8

2.4 Computing K for quadratics

Taking advantage of these simplifications, each K^e for quadratics in two dimensions can be computed with at most 18 floating point operations instead of 288 floating point operations: an improvement of a factor of sixteen in computational complexity.

On the other hand, there are only 64 nonzero entries in each **K**. So eliminating multiplications by zero gives a four fold improvement.

Sparse matrix accumulation requires at least 76 (=36+36+4) memory references, not including sparse matrix indexing. Even if the matrix is stored in symmetric form, at least 46 (=21+21+4) memory references are needed.

Computational complexity can be

less than cost of memory references.

2.5 Computing K for general Lagrange elements

n	Entries	Zero	Equal	CoL	1 entry	ED1	2 entry	LC	MAPs
1	9	0	0	0	4	4	0	1	10
2	36	6	11	6	4	8	0	1	20
3	100	6	41	10	4	16	8	15	76
4	225	0	98	6	4	35	16	66	209
5	441	0	183	15	4	51	28	160	446
6	784	0	342	21	4	75	32	310	784

Figure 16: Key: CoL=Colinear, ED1=edit distance 1,LC=linear combination

Using FErari to compute finite element matrices for

Laplace's equation in two dimensions using continuous Lagrange elements of degree n.

```
from Numeric import zeros
G=zeros(4,"d")
def K(K,jinv):
detinv = 1.0/(jinv[0,0]*jinv[1,1] - jinv[0,1]*jinv[1,0])
G[0] = ( jinv[0,0]**2 + jinv[1,0]**2 ) * detinv
G[1] = ( jinv[0,0]*jinv[0,1]+jinv[1,0]*jinv[1,1] ) * detinv
G[2] = G[1]
G[3] = ( jinv[0,1]**2 + jinv[1,1]**2 ) * detinv
K[1,1] = 0.5 * G[0]
K[1,0] = -0.5 * G[1]- K[1,1]
K[2,1] = 0.5 * G[2]
K[2,0] = -0.5 * G[3]- K[2,1]
K[0,0] = -1.0 * K[1,0] + -1.0 * K[2,0]
K[2,2] = 0.5 * G[3]
K[0,1] = K[1,0]
K[0,2] = K[2,0]
K[1,2] = K[2,1]
return K
```

Generated code for computing the stiffness matrix for linear basis functions.

2.6 Efficient Computation of co-planarity

One vector can be written as a linear combination of two others if and only if the three vectors (and the origin) are co-planar.

A (nearly) quadratic algorithm determines set of planes generated by all pairs of vectors and checks for equality of planes.

Quadratic is optimal because there can be $2k^2$ common planes among $6k$ vectors.

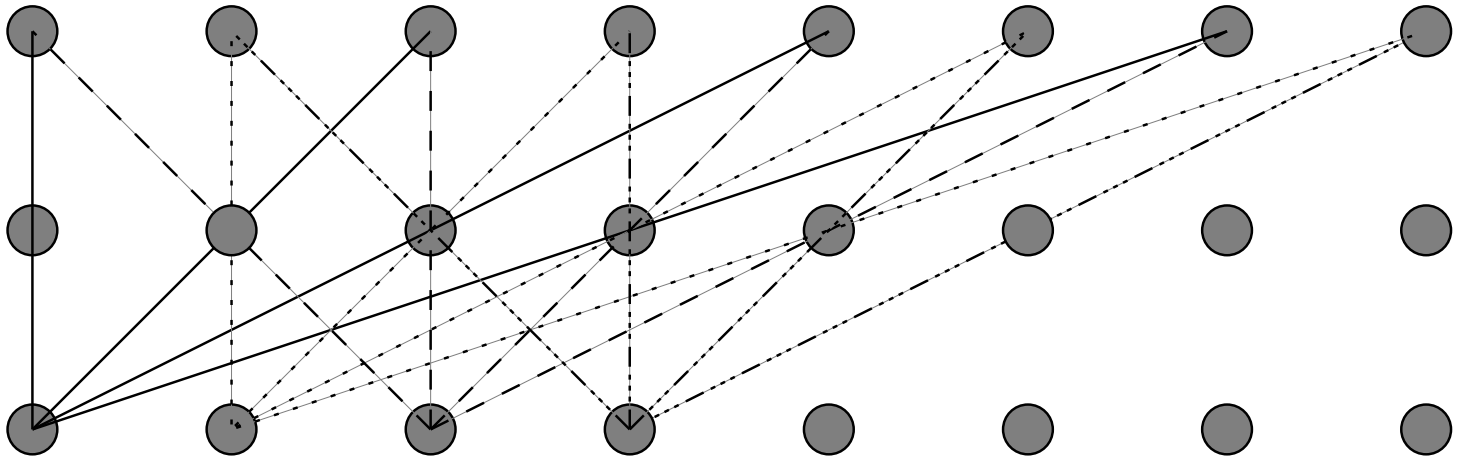


Figure 17: Example of lattice with $k = 4$. For each point on the lower line, there are exactly four planes. Only the planes for $i = 1, 2, 3, 4$ are shown.

A faster FErari

Francis Russell uses [5] to optimize polynomial expressions by algebraic factorization and common subexpression elimination (CSE).

After symbolic integration, independent multivariate rational expressions for each entry of the local assembly matrix are analyzed.

Generating efficient code from these requires identifying and reusing certain computations.

Standard compiler CSE passes neither have the freedom nor the capacity to take advantage of certain numerical relationships.

Optimisations take advantage of the distributivity of multiplication over addition and work in exact rational arithmetic.

Provides superior performance for multilinear forms.

Other software automation projects

Cactus: Gravitational Physics

FLAME: dense linear algebra

KPP: chemical kinetic systems [14]

Madness: wavelets [2]

Spiral: signal processing [11]

Tensor contraction engine: quantum chemistry

as well as the FEniCS project

References

[1] Babak Bagheri and L. R. Scott. About Analysa. Research Report UC/CS TR-2004-09, Dept. Comp. Sci., Univ. Chicago, 2004.

[2] Gregory Beylkin, George Fann, Zhenting Gan, Robert Harrison, Martin Mohlenkamp, Fernando Perez, and Takeshi Yanai. Madness (multiresolution adaptive numerical scientific simulation) is a framework for scientific simulation in many dimensions using adaptive multiresolution methods in multiwavelet bases. http://www.csm.ornl.gov/ccsg/html/projects/madness.html, 2011.

[3] T.J. Boggon, J. Murray, S. Chappuis-Flament, E. Wong, B.M. Gumbiner, and L. Shapiro. C-cadherin ectodomain structure and implications for cell adhesion mechanisms. *Science*, 296(5571):1308, 2002.

[4] O.J. Harrison, X. Jin, S. Hong, F. Bahna, G. Ahlsen, J. Brasch, Y. Wu, J. Vendome, et al. The extracellular architecture of adherens junctions revealed by crystal structures of type I cadherins. *Structure*, 19(2):244–256, 2011.

[5] A. Hosangadi, F. Fallah, and R. Kastner. Optimizing polynomial expressions by algebraic factorization and common subexpression elimination. *Computer-Aided Design of Integrated Circuits and Systems, IEEE Transactions on*, 25(10):2012–2022, 2006.

[6] Ken Kennedy, Bradley Broom, Arun Chauhan, Rob Fowler, John Garvin, Charles Koelbel, Cheryl McCosh, and John Mellor-Crummey. Telescoping languages: A system for automatic generation of domain languages. *Proceedings of the IEEE*, 93(2), 2005. special issue on ”Program Generation, Optimization, and Adaptation”.

[7] J. Korelc. Multi-language and multi-environment generation of nonlinear finite element codes. *Engineering with Computers*, 18:312–327, Nov 2002. 10.1007/s003660200028.

[8] Joze Korelc. Automatic generation of finite-element code by simultaneous optimization of expressions. *Theoretical Computer Science*, 187:231–248, Nov 1997.

[9] B. Nagar, M. Overduin, M. Ikura, and J.M. Rini. Structural basis of calcium-induced e-cadherin rigidification and dimerization. *Nature*,

380:360–364, 1996.

[10] O. Pertz, D. Bozic, A.W. Koch, C. Fauser, A. Brancaccio, and J. Engel. A new crystal structure, Ca2+ dependence and mutational analysis reveal molecular details of E-cadherin homoassociation. *The EMBO journal*, 18(7):1738–1747, 1999.

[11] Markus Püschel. Spiral project. http://spiral.net/index.html, 2011.

[12] Jonathan Riehl. Language embedding and optimization in mython. In *Proceedings of DLS*, pages 39–48, 2009.

[13] Jonathan Riehl. *Reflective Techniques In Extensible Languages*. ProQuest, UMI Dissertation Publishing, 2011.

[14] A. Sandu, D.N. Daescu, and G.R. Carmichael. Direct and adjoint sensitivity analysis of chemical kinetic systems with KPP: Part I–theory and software tools. *Atmospheric Environment*, 37(36):5083–5096, 2003.

[15] M. Sotomayor, W.A. Weihofen, R. Gaudet, and D.P. Corey. Structural determinants of cadherin-23 function in hearing and deafness. *Neuron*, 66(1):85–100, 2010.

[16] C.Y. Tai, S.A. Kim, and E.M. Schuman. Cadherins and synaptic plasticity. *Current opinion in cell biology*, 20(5):567–575, 2008.

[17] Robert van Engelen, Lex Wolters, and Gerard Cats. CTADEL: a generator of multi-platform high performance codes for PDE-based scientific applications. In *ICS '96: Proceedings of the 10th international conference on Supercomputing*, pages 86–93, New York, NY, USA, 1996. ACM Press.

[18] Paul S. Wang, Hui-Qian Tan, Atef F. Saleeb, and Tse-Yung P. Chang. Code generation for hybrid mixed mode formulation in finite element analysis. In *SYMSAC '86: Proceedings of the fifth ACM symposium on Symbolic and algebraic computation*, pages 45–52, New York, NY, USA, 1986. ACM Press.