

METHODOLOGY

Open Access

chem^f: A purely functional chemistry toolkit

Stefan Höck and Rainer Riedl*

Abstract

Background: Although programming in a type-safe and referentially transparent style offers several advantages over working with mutable data structures and side effects, this style of programming has not seen much use in chemistry-related software. Since functional programming languages were designed with referential transparency in mind, these languages offer a lot of support when writing immutable data structures and side-effects free code. We therefore started implementing our own toolkit based on the above programming paradigms in a modern, versatile programming language.

Results: We present our initial results with functional programming in chemistry by first describing an immutable data structure for molecular graphs together with a couple of simple algorithms to calculate basic molecular properties before writing a complete SMILES parser in accordance with the OpenSMILES specification. Along the way we show how to deal with input validation, error handling, bulk operations, and parallelization in a purely functional way. At the end we also analyze and improve our algorithms and data structures in terms of performance and compare it to existing toolkits both object-oriented and purely functional. All code was written in *Scala*, a modern multi-paradigm programming language with a strong support for functional programming and a highly sophisticated type system.

Conclusions: We have successfully made the first important steps towards a purely functional chemistry toolkit. The data structures and algorithms presented in this article perform well while at the same time they can be safely used in parallelized applications, such as computer aided drug design experiments, without further adjustments. This stands in contrast to existing object-oriented toolkits where thread safety of data structures and algorithms is a deliberate design decision that can be hard to implement. Finally, the level of type-safety achieved by *Scala* highly increased the reliability of our code as well as the productivity of the programmers involved in this project.

Keywords: Functional Programming, *chem^f*, Chemistry Toolkit, SMILES parser, Parallelization, Scala, Medicinal Chemistry

Background

Since there already exist a plethora of cheminformatics toolkits both open source and proprietary, one might wonder whether there is truly a need for another one. Most of the available toolkits such as the *Chemistry Development Kit* [1] or *OpenBabel* [2] are written in object-oriented languages using typical imperative concepts such as mutable data structures and opaque methods (see below) to implement chemical entities and algorithms. While the communities of many of the newer (and some of the older) programming languages start to appreciate the benefits of programming in a pure, referentially transparent fashion, these concepts have not yet had a big impact

on software used in chemistry. We would therefore like to show some of the benefits of functional programming when applied to cheminformatics and talk about the type-safety and conciseness that can be achieved when using this programming paradigm.

The dangers of side effects

Several widely used programming languages such as *Java* [3] or *C++* use object-oriented programming as a means to structure code and build reusable components. Such code is typically (but not necessarily) written in an imperative style, where statements represent actions the computer should carry out sequentially. Although it is regarded as a best practise to favor immutable data structures over mutable ones [4], imperative code is typically full of reassignment operations since these provide a convenient way to update fields in complex data structures.

*Correspondence: rainer.riedl@zhaw.ch
Institute of Chemistry and Biological Chemistry, ZHAW Zurich University of Applied Sciences, Einsiedlerstrasse 31, 8820 Wädenswil, Switzerland

Mutable state can be hard to reason about when several seemingly unrelated parts of a program access and possibly modify the same piece of shared data. Special care needs to be taken when using mutable objects in parallelized algorithms [5].

Not only mutable state makes parallelization and reasoning about programs difficult: Accessing any kind of shared resources such as files or database connections can lead to unexpected behavior depending on a whole bunch of factors such as access rights, security settings, file locks and so on. Software components that access shared resources can be difficult to test and require special precautions when being accessed from several threads simultaneously. Although this has been known for quite some time, most programming languages make no distinction between methods that perform side effects by accessing shared resources or mutable state and functions that perform pure calculations just from their input parameters. Methods and objects written in these languages are therefore *a priori* unsafe to be used in parallel computations unless their documentation explicitly states differently. It would of course be much safer if one could rely on the compiler omitting errors or at least warnings when calling some unsafe method instead of having to trust in the accuracy of third party library documentation.

Referential transparency [6]

An expression in a program is said to be *referentially transparent* when all it does is calculating its result from its input parameters (possibly by calling other referentially transparent functions) and *nothing else*. A referentially transparent function may not access or alter mutable state, nor may it perform any other form of side-effects. In an expression, a call to a referentially transparent function can always be replaced with the function's result for the given set of parameters without altering the behavior of the program. A method that performs any number of side effects is said to be *opaque*. Referentially transparent functions offer several advantages over opaque ones: They are typically easier to reason about, can easily be tested and sometimes even proved to be correct, can be composed at will to create more complex functions (which are then still referentially transparent), and they can be safely used in parallelized algorithms. Since they need no access to resources other than their input parameters in order to perform their tasks, they make for highly reusable building blocks for creating more complex functionality.

Since mutability breaks referential transparency, referentially transparent expressions can only work with immutable data structures. This can make writing referentially transparent expressions cumbersome in typical imperative languages where mutability is the rule rather than the exception and the language's syntax provides

only marginal support for working with deeply nested immutable data structures.

Functional programming

One programming paradigm that greatly facilitates writing referentially transparent functions and using immutable data structures is the one of *functional programming*. Functional programming languages were designed with referential transparency in mind, and they encourage a more declarative style of programming without the control statements and value assignments typically found in imperative ones. In functional programming, functions are first class values that can be passed as parameters to other functions (which are then called higher-order functions) or be the results of other functions. Functional programming languages typically are statically typed but use type inference to prevent type annotations from cluttering the code. Together with the above mentioned higher order functions this can lead to highly concise code. For instance, iterating over a list of integers to produce a list of their squares might look like this in an imperative language (the code is written in *Scala* [7], a multi-paradigm language that is described in more detail below):

```
def squares (is: List[Int]): List[Int]
=
{
  val squares = new ListBuffer[Int]
  {for i <- is}{
    squares += i * i
  }
  squares.toList
}
```

It is typical for an imperative program to update a mutable data structure during iteration. The same program written in a more functional style might look like this:

```
def squares(is: List[Int]) =
  is map (x => x * x)
```

Here we make use of the higher-order function `map` that takes another function as its parameter, which is then applied to each element in the list. Not only is this expression much shorter than its imperative counterpart, function `map` also describes such a common pattern when working with collection-like data structures that it provides a plethora of functionality all of which can be used with almost no syntactic overhead.

Given that objects of type `List` are immutable, both code examples shown above are referentially transparent. Although the imperative example uses a (mutable) `ListBuffer` to accumulate its result, this is an implementation detail hidden behind the function's interface.

Some functional programming languages like *Haskell* [8] enforce referential transparency through their type system and can therefore exploit its advantages to their full extent. This includes several optimization techniques during compilation as well as memoization of a function's results for given parameter sets at runtime.

Although the advantages of functional programming have been known for a long time [9], many of the concepts described above were not or only partially implemented in the mainstream programming languages and a major part of the programming community does not exploit the benefits they provide.

Functional programming and chemistry

We believe that the above mentioned aspects of functional programming make this paradigm very well suited for writing scientific applications where the main focus often lies on running complex calculations rather than performing long cascades of side effects. For instance, the only side effects involved when running a high throughput screening with a typical command line based docking software are reading from and writing to files (and possibly to the console). The rest is pure, stateless calculations that are well suited to be written in a purely functional manner and run in parallel on a multi-core system. When we set out to write the first prototype of our in-house data management tool *CyBy²* [10], we used *Java* as the language of choice, since there already existed several chemistry toolkits written in that language. It was only after *CyBy²* was already running on our servers and several hard to find bugs took us hours if not days to get rid of that we decided to go for a change in the style of programming. We decided to give the *Scala* programming language a try since programs written in *Scala* run on the Java Virtual Machine (JVM) and existing *Java* libraries can be accessed directly from within *Scala* source code. *Scala* is a modern multi-paradigm programming language that is fully object-oriented with a strong support for typical concepts from functional programming such as higher-order functions, type inference, and pattern matching. It also has one of the most sophisticated and expressive type systems written so far [11]. *Scala* is not a pure functional programming language that enforces referential transparency through its type system (this can be achieved by using the effect system provided by *scalaz* though; see below), but programming in a pure manner as well as the use of immutable data structures are strongly encouraged and facilitated by the language.

While our style of programming moved from imperative to functional, we found it cumbersome and sometimes error prone to interact with the methods and classes coming from third-party *Java* libraries that make heavy use of mutable data structures and side effects. We therefore started looking for cheminformatics toolkits written in a

more functional style and were surprised to find only one such toolkit at an early stage written in *Haskell* [12]. It was this lack of purely functional third-party libraries that made us decide to go ahead and write our own toolkit. In this article we present our first experiences along that road. We will show how molecular graphs can be represented using persistent, immutable data structures and how parsing input can be done in a referentially transparent way leading to highly reusable code that can be run in parallel out of the box. We do this by implementing a purely functional SMILES parser [13], a reasonable complex task to get a feeling for some of the higher-order abstractions typically used in functional programming. Along the way we will show how to deal with input validation, error handling, and parallelization in a purely functional, type-safe manner.

A short introduction to *Scala*

In the remainder of this article we will often show snippets of code to discuss the aspects of functional programming when encountering certain problems. We will use *Scala* as the implementing language for the reasons given above. It will not be necessary to be fluent in *Scala* to grasp the concepts being presented here, yet we think that a short introduction to this deep language and its syntax will make it easier to understand the examples in this article. For a more thorough introduction please see [14]. A note on terminology: In object-oriented programming languages, subroutines are typically called *methods* without making a distinction between those that perform side effects and those that do not. For the remainder of this article we use the term *method* for side-effect performing subroutines and *function* for pure calculations.

Basic syntax

Scala's syntax is similar to the one of *Java* and other *C*-like languages. Statements are usually enclosed in curly braces and delimited by semicolons. Many of these structural delimiters can be inferred by the compiler leading to less cluttered code when writing the short expressions typically found in functional programming. The following two function definitions both compile:

```
def square (i: Int): Int = {  
  i * i;  
}  
  
def square (i: Int) = i * i
```

As can be seen in the example above, type annotations come after variable names and can in many cases be inferred by the compiler.

In terms of object-oriented programming, *Scala* – like *Java* – has classes and interfaces (which are called *traits* and can contain method implementations and state).

Scala also has singleton objects, which are defined using the object keyword. There are no static methods in *Scala*: Every method definition belongs to a class or an object. There is the special case of *companion objects*, which have the same name as their companion class and are typically used to define class-related constants and 'static' functions:

```
class AClass {  
  ...  
}  
  
object AClass {  
  //a factory method  
  def create: AClass = ...  
}
```

A special case that is often used in functional programming to define algebraic data types [15] is the sealed keyword: Subclasses of a sealed class or trait must be defined in the same file as the sealed class itself.

Function literals

In *Scala*, functions are first-class values and the language provides a lot of syntactic sugar to help declaring them. A typical function literal looks as follows:

```
val add: (Int,Int) => Int =  
  (a: Int, b: Int) => a + b
```

(Int, Int) => Int is a type annotation: A function from two integers to another integer. Type inference lets us remove some code duplication:

```
val add: (Int,Int) => Int =  
  (a,b) => a + b
```

If both parameters appear in the function's body only once and in the same order as in the function's parameter list, we can replace them with placeholders:

```
val add: (Int,Int) => Int = _ + _
```

We can use function literals to create anonymous functions as parameters for higher-order functions. For instance, we can double all the integers in a list like so:

```
def dbl (xs: List[Int]) = xs map (2*)
```

Lazy evaluation and by-name parameters

By default, *Scala* is a strict language, meaning function parameters are evaluated before the function's body is executed. However, *Scala* facilitates lazy evaluation of values as well as by-name function parameters:

```
lazy val aVal = ...
```

```
def aMethod (byNameParam: => Int) ...
```

Values marked with the *lazy* keyword are not evaluated until they are accessed for the first time. They are

evaluated only once. By-name parameters are also evaluated only when needed, but unlike lazy values they are reevaluated each time the parameter is accessed.

Parametric polymorphism

Similar to *Java*, *Scala* supports subtype polymorphism as well as parametric polymorphism (aka *generics*). Type parameters are declared within brackets and can be annotated with variance annotations:

```
trait Invariant[A]  
trait Covariant[+A]  
trait Contravariant[-A]
```

Variance describes subtyping for classes with type parameters. In the case of covariance, `Covariant[A]` is a subtype of `Covariant[B]` if `A` is a subtype of `B`. On the other hand, `Contravariant[A]` is a subtype of `Contravariant[B]` if `A` is a supertype of `B`.

In contrast to many other programming languages, *Scala* does not stop at first-order parametric polymorphism, but also allows type constructors as type parameters (higher-kinded types) [16]. Only these constructs make the implementation of some of the more powerful type classes possible (see below).

Case classes and pattern matching

In the tradition of other functional programming languages, *Scala* supports *pattern matching*, which can be used to query and match even complex nested data structures. *Case Classes* are like other classes in *Scala* but are enhanced automatically by pattern matching functionality by the compiler. Also, constructor parameters are automatically added as immutable fields with public scope to case classes. For instance, a simple setup of chemistry-relevant classes may look as follows:

```
sealed abstract class Element (  
  val atomicNr: Int  
)  
...  
case object C extends Element(6)  
case object N extends Element(7)  
...  
case class Isotope (  
  element: Element,  
  massNumber: Int  
)  
case class Atom (  
  isotope: Isotope,  
  charge: Int  
)
```

Pattern matching can now be used to count all carbon atoms in a molecule:

```
def isCarbon (a: Atom) = a match {  
  case Atom(Isotope(C, _), _) => true  
  case _ => false  
}  
def carbonCount (m: Molecule): Int =  
  m.atoms count isCarbon
```

Underscores act as placeholders that match any value while lower case identifiers can be used to access a value in the following code block:

```
def carbonMass (a: Atom): List[Int] =  
  a match {  
    case Atom(Isotope(C, mass) _) =>  
      List(mass)  
    case _ => Nil  
  }
```

The first case statement matches carbon atoms of an arbitrary mass number and the mass number is returned wrapped in a `List`. In case of non-carbon atoms, the function returns the empty list `Nil`.

Implicits and the pimp my library-pattern

Scala supports implicit conversions from one type to another in order to enrich classes from third-party libraries with additional functionality. This is called the *pimp my library* pattern [17] within the *Scala* community.

For instance, if one wanted to add the ability to calculate the exact mass distribution to a class `Molecule` from a third-party library that does not yet provide such a function, one would first have to define a wrapper class that defines the function in question together with an implicit conversion from `Molecule` to `MoleculeWrapper`:

```
class MoleculeWrapper (m: Molecule) {  
  def exactMasses = ...  
}  
implicit def mol2Wrapper (m: Molecule) =  
  new MoleculeWrapper(m)
```

It is now possible to call `exactMasses` on `Molecules` as if the function was provided by class `Molecule` itself:

```
def printMasses (m: Molecule) {  
  m.exactMasses foreach println  
}
```

Type classes

In addition to implicit conversions, *Scala* also supports implicit parameter lists for functions. These parameters

need not be provided explicitly if an implementation of the type in question can be found in implicit scope. One use case for implicit parameters is the definition of *type classes* [18] similar to those found in *Haskell*. Type classes are a way to implement ad-hoc polymorphism (method overloading) in purely functional programming languages. For instance, the *scalaz* library (see below) defines a type class `Equal` for type safe structural equality checking as follows:

```
trait Equal[-A] {  
  def equal(a1: A, a2: A): Boolean  
}
```

Via the *pimp my library*-pattern, *scalaz* then adds operators $\stackrel{?}{=}$ and \neq to all types. These are defined in wrapper class `Identity` and are implemented as follows:

```
def  $\stackrel{?}{=}$  (a: A) (implicit e: Equal[A])  
  : Boolean = e.equal (value, a)
```

```
def and  $\neq$  (a: A) (implicit e: Equal[A])  
  : Boolean = !( $\stackrel{?}{=}$ (a))
```

All objects for which an instance of type class `Equal` can be found in implicit scope can now be compared in a type-safe manner using these operators. There exists a shorthand notation using *context bounds* for functions that require an instance of a type class with a single type parameter to be in implicit scope:

```
def isEqual[A:Equal] (a1: A, a2: A) =  
  a1  $\stackrel{?}{=}$  a2
```

The scalaz library [19]

Several of the more advanced techniques and abstractions found in functional programming did not make it into the *Scala* standard library. Many of these are provided by *scalaz*, a collection of type classes and purely functional data structures. Many of the type classes defined in *scalaz* come from the world of *Haskell* where a lot of information on things like Monoids, Functors, Applicatives, Monads and others are available. For a gentle and highly entertaining introduction to some of these concepts see [20].

Results and discussion

We studied the aspects and benefits of functional programming in cheminformatics by first designing an immutable data structure for representing molecules and then implementing a SMILES parser in accordance with the OpenSMILES specification [21]. We then tested how immutable data structures and referentially transparent

functions can be used in parallelized bulk operations out of the box and had a closer look at our algorithms in terms of performance. The full source code of the data structures and algorithms discussed in this section is available in Additional file 1. We also created a repository on *github* to further advance the development of our toolkit. The repository can be found at <https://github.com/stefan-hoeck/chemf>.

Molecules as immutable data structures

There exist many ways to represent a chemical molecule in a computer, many of which depend on the concrete aspects one is focussing on. *Lewis* structures of molecules are typically represented as undirected labeled graphs with the atoms at the vertices and the bonds at the edges [22].

Immutable undirected graphs

We used a simple unlabeled connectivity list as the basis for our molecular graphs. The graph's vertices are numbered from 0 to `order - 1` where `order` is the total number of vertices.

```
sealed trait Graph {  
  def order: Int  
  def edges: Set[Edge]  
}
```

We provided a couple of helper functions for adding and removing edges and vertices, all of which return a new, immutable copy of the updated graph. Trait `graph` is backed by an immutable `Set` of `Edges`, which provides effective constant time `add`, `remove`, and `lookup` operations [14]. Since all edges in the graph potentially have to be adjusted when removing a vertex, this operation takes linear time with respect to the size (= number of edges) of the graph.

Some of the typical graph algorithms make heavy use of adjacency lists [23] which we provided as a lazily initialized value in trait `Graph`. Adjacency lists were implemented using *scalaz's* `ImmutableArray` providing fast constant time random access.

```
lazy val adjacencyList  
  : ImmutableArray[Set[Int]] = ...
```

Edges in graphs were implemented as ordered pairs of integers:

```
sealed trait Edge {  
  def a: Int  
  def b: Int  
}
```

To make it easier to compare and sort edges, we added an invariant to the edge class stating that vertex `b` is the higher of the edge's two vertices. Edges can therefore only

be instantiated via a factory method to guarantee that this invariant is fulfilled. This very basic graph implementation has a low memory footprint and can be used to determine structural parameters such as atom and bond count as well as number and size of rings in a molecule.

Molecules as labeled graphs

In order to represent the *Lewis* structures of molecules, we needed to label the vertices and edges of the graph with additional information. We therefore introduced trait `LGraph`:

```
trait LGraph[+E,+V] {  
  def graph: Graph  
  def vLabel (v: Int): V  
  def eLabel (e: Edge): E  
}
```

Trait `LGraph` is parameterized over the types of both the edge and vertex labels, giving us maximum flexibility when working with different representations of molecules. The trait again provides functions for adding and removing edges and vertices as well as some higher order functions like `map` and `foldLeft` typically found in functional data structures. We also implemented type classes `Functor`, `Foldable`, and `Traverse` (all defined in the *scalaz* library) for `LGraph`, giving us a lot of functional power when iterating over the elements of `LGraph` as we will show further below.

The core functionality of `LGraph` was implemented using a private case class `LgImpl`:

```
private case class LgImpl[+E,+V] (  
  graph: Graph,  
  vertices: IndexedSeq[V],  
  eMap: Map[Edge,E]  
) extends LGraph[E,V] {  
  def vLabel (v: Int) = vertices (v)  
  def eLabel (e: Edge) = eMap (e)  
}
```

Implementing functions `graph` and `eLabel` was straight forward. For function `vLabel` there were several possible implementations to consider. We decided to use an `IndexedSeq` to store vertex labels, which provides effective constant time `append`, `prepend`, and `random access` operations. Using an `Array` would give us (fast) constant time random access but other operations might be considerably slower. Later it might be convenient to provide two or more different implementations depending on the performance characteristics needed by the algorithms working with our graphs.

Atoms and bonds

We favored composition over inheritance when implementing the core classes needed to represent typical chemical entities. At the root stands class `Element`:

```
sealed abstract class Element (  
  val atomicNr: Int  
)  
object Element {  
  case object H extends Element (1)  
  case object He extends Element (2)  
  ...  
}
```

A lot of additional information can be requested from `Element` objects, all of which is lazily loaded from the *Blue Obelisk Element Repository* [24].

Next come the isotopes, which unlike the elements were not implemented as constants to give us a bit more flexibility when working with newly-discovered or purely hypothetical isotopes:

```
sealed trait Isotope {  
  def element: Element  
  def massNumber: Option[Int]  
}
```

Objects of type `Isotope` either represent a natural mixture of the isotopes of a given element or a single isotope with a concrete mass number. Value `massNumber` may therefore be undefined, which is represented by its type: `Option[Int]`. `Option[A]` is an algebraic data type with two possible values: `Some(a)` with `a` being a wrapped value of type `A`, or `None`. It is used as a type-safe alternative to using `null` as the result of unsuccessful calculations or for undefined values. Using `Option` makes checking for `null` and throwing `NullPointerException`s in client code obsolete.

Again additional information about isotopes is lazily loaded from a file, this time from the *Blue Obelisk Isotope Repository*. Since in chemistry we are usually dealing with the same (small) set of isotopes most of the time and since our isotopes are immutable they make good candidates for applying the *Flyweight* pattern [25]. Instead of creating many new objects when assembling a molecular graph, the most commonly used isotopes are stored in an array and returned when new isotopes are requested by clients. Therefore we made isotopes only available through two factory methods:

```
object Isotope {  
  def apply (e: Element): Isotope = ...  
  def apply (e: Element, mn: Int)  
    : Isotope = ...  
}
```

Scala provides a shorthand notation for calling functions named `apply`. For instance a carbon isotope can be requested like so:

```
val c = Isotope(Element.C)
```

Here we truly profited from using immutable objects: Using the *Flyweight* pattern keeps the memory footprint of our molecules low while letting us store a lot of additional information for all isotopes and elements that has to be loaded and calculated only once.

We were now able to define a basic `Atom` implementation:

```
case class Atom (  
  isotope: Isotope,  
  charge: Int,  
  hydrogens: Int,  
  stereo: Stereo  
)
```

Further fields like hybridization or coordinates might be necessary for some algorithms but instead of cluttering `Atoms` with lots of optional fields, we argue that in those cases a more specialized class should be used which will lead to an increase in terms of type-safety. An algorithm requiring coordinates for atoms might be able to work with an object of type `LGraph[Bond, Atom3D]` but will reject `LGraph`s with other vertex types.

We distinguished between the different bonds possible in *Lewis*-structures via a couple of constants:

```
sealed trait Bond  
object Bond {  
  case object Single extends Bond  
  case object Double extends Bond  
  ...  
}
```

Molecules can now be defined as a simple type alias:

```
type Molecule = LGraph[Bond, Atom]
```

Some basic operations on molecules

We implemented a couple of basic operations on molecules to demonstrate some of the higher order concepts typically found in functional programming.

First, we wanted to calculate the molar mass of a chemical compound. For that we defined function `mass` that calculates the mass of a single `Atom` together with the masses of its implicit hydrogen atoms:

```
def mass (a: Atom): Double =  
  a.isotope.mass + a.hydrogens * H.mass
```

The molar weight of a molecule could then be calculated as follows:

```
def molarMass (m: Molecule): Double =  
  m foldMap mass
```

Method `foldMap` comes from the *scalaz* library and is similar to the reduce function described by *McBride* and *Paterson* [26]. It requires two type class implementations to be in implicit scope: `Foldable` for the data structure over which we iterate (in our case this is `LGraph`) and type class `Monoid` for the return type of the function we pass as the sole parameter to `foldMap`. `Foldable` defines several functions for accumulating values when iterating over a data structure. We will not discuss it in more detail here but refer the reader to the *scalaz* source code. Type class `Monoid` has many applications in programming. It defines two functions: Function `append` defines some form of combining two values into a single value of the same type, while `zero` is the neutral element of this operation such that `zero append x == x` and `x append zero == x`. Here is the `Monoid` implementation for floating-point addition:

```
implicit val DoubleMonoid =  
  new Monoid[Double] {  
    val zero: Double = 0.0D  
    def append (a: Double,  
               b: => Double) = a + b  
  }
```

While it is nice to implement `molarMass` with just a single line of code our implementation is not very safe. It could be that mass is not known for all possible isotopes. This should be reflected in the function's return type, and the function was adjusted accordingly:

```
def mass (a: Atom): Option[Double] =
```

We dealt with the possibility of failure by returning a value of type `Option[Double]`. Interestingly, *scalaz* defines a `Monoid` instance for `Options` of `Monoids`. We therefore only had to change the return type of `molarMass` and our code still compiled and behaved as expected:

```
def molarMass (m: Molecule)  
  : Option[Double] = m foldMap mass
```

The molar mass of a molecule is now wrapped in a `Some` if the masses of all its isotopes were known, otherwise the function returns `None`. Unlike the many methods written in *Java* that return `null` in case of an unsuccessful calculation or an undefined value, function `molarMass`

is absolutely type-safe and we can rely on the compiler to make sure we deal with the possibility of an unknown molar mass properly.

We could have gone even further and use *scalaz's* `Validation` class instead of `Option`. In that case we would have either gotten the molar mass wrapped in a `Success` or a list of error messages explaining exactly for which isotopes the mass could not be determined. Even in this case we would have been able to use `foldMap` to accumulate the validated isotopic masses. We used `Validation` when implementing our SMILES parser and will describe its applications further below.

Next, we implemented a function to determine the total formula of a molecule. We represented this as a `Map` from `Isotope` to `Int`. First, we generated such a `Map` for a single atom:

```
type Formula = Map[Isotope,Int]  
def atomFormula (a: Atom): Formula =  
  Map(a.isotope => 1) ++ (  
    (a.hydrogens > 0) ?  
    Map(Isotope(H) => a.hydrogens) |  
    Map.empty  
  )
```

Since *scalaz* defines a `Monoid` for `Maps` for whose value type a `Monoid` is defined, we again were able to use `foldMap`:

```
def formula (m: Molecule): Formula =  
  = m foldMap atomFormula
```

We wanted to show with these examples how common abstractions like `Monoid` can be used to write highly reusable functions like `foldMap`. We also argue that it is almost impossible to achieve the same levels of abstraction and code reuse by using object-oriented concepts like inheritance instead of type classes.

A purely functional SMILES parser

Now that we had a way to handle molecular graphs it was time to implement some parsing capabilities for text-based user input. SMILES is well suited for this task since its syntax is easy to learn and SMILES strings for reasonably small molecules can be generated by hand without the help of a computer.

In the following sections we will describe several issues that might come up when reading user input. Our focus always was more on type-safety, referential transparency, and code reuse than on optimizing performance, which we believe can still be done once one has a properly running application.

First things first: The parser as a finite state automaton

Parsing a SMILES string means interpreting a single line of data one character at a time while accumulating an increasingly complex molecular structure. We therefore needed two things: A data type representing the accumulated molecule and a finite state automaton (FSA) where each state of the automaton takes a character and the last molecule as input and returns an updated molecule together with a new automaton state. The following code listing shows how we modeled such an FSA:

```
type FAREs[A] = (FAState[A], A)
sealed trait FASState[A] {
  def next(a: A, c: Char): FAREs[A]
}
object FASState {
  def apply[A](f: (A, Char) => FAREs[A])
    : FASState[A] = new FASState[A] {
    def next(a: A, c: Char) = f(a, c)
  }
}
```

Trait `FASState` represents the finite automaton's actual state. Since this class describes a very general concept and might be used for different types of parsers, we abstracted over the type of the accumulated data using a type parameter. The return type of function `next` is a pair consisting of a new `FASState` and the updated data object. We defined a general-purpose factory method `apply` that takes a single function as its argument in the companion object of `FASState`.

We then defined function `parse`, which takes a single string and an initial automaton state and returns the parsed value:

```
val EOT = ' 004'

@scala.annotation.tailrec
def parse[A] (
  s: String, fas: FASState[A], a: A
): A = s match {
  case "" => fas.next(a, EOT)._2
  case cs => fas.next(a, cs.head) match
  {
    case (newFas, newA) =>
      parse(cs.tail, newFas, newA)
  }
}
```

We used a tail-recursive function for parsing strings. A function is tail-recursive if the only place the function

calls itself is the last operation of the function [14]. The *Scala* compiler can optimize tail-recursive functions, so that in our parser the call stack will not overflow even when parsing strings with thousands of characters. Annotation `tailrec` is a safety measure to make sure that our function is indeed tail-recursive. If this is not the case, the code will not compile. The parser is informed that the end of the string is reached by passing value `EOT` (end of transmission) as a parameter. This is necessary since the parser might still expect further input. For instance, if the last character in a SMILES string is 'C' the parser will only know whether a carbon or chlorine atom must be added to the molecule upon parsing the next character in the string. If this happens to be `EOT`, a final carbon atom should be added.

The classes and functions presented here describe a general purpose incremental string parser. So far they are completely unrelated to molecules and chemistry.

Enhancing the Builder pattern with type classes

We distributed the responsibility for parsing SMILES strings over three classes. First, we defined type class `SmilesBuilder[A]` whose instances know how to accumulate molecular information using objects of type `A`. A `SmilesBuilder` provides all actions required when parsing a SMILES string:

```
trait SmilesBuilder[A] {
  type STrans = A => A
  val empty: A
  def addAtom (a: SmilesAtom): STrans
  def clear: STrans
  def closeBranch: STrans
  def openBranch: STrans
  def ring (i: Int): STrans
  def setBond (b: Bond): STrans
  def setDbStereo (c: Char): STrans
}
```

It is important to note that the builder was designed to work on immutable data structures. All its methods return functions, while in an imperative implementation using mutable state their return type would be `Unit` (similar to `void` in *Java*).

Next, class `SmilesParser[A]` is responsible for traversing the SMILES string and interpreting the characters it encounters. Instead of directly accumulating a molecular graph, it delegates data accumulation to an implementation of `SmilesBuilder[A]`, which must be in implicit scope when creating a new `SmilesParser`. Parts of the implementation of `SmilesParser` are shown below:

```
sealed abstract class SmilesParser[A](implicit SB: SmilesBuilder[A]) {
  type STrans = A => A
  type FAS = FASState[A]

  def parse (s: String):A = FASState parse (s, char, SB.empty)

  lazy val char: FAS = FASState[A](
    (a, c) => c match {
      case EOT => (dummy[A], a)
      case 'C' => ...
      case 'B' => ...
      case '[' => (accumBracket(""), a)
      case '%' => (ring, a)
      case x if (x.isDigit) => ...
      case x => (char, unique(x)(a))
    }
  )

  lazy val ring: FAS = ...

  def accumBracket(s: String): FAS = ...

  private val unique : Map[Char, STrans] = Map (
    '0' -> SB addElem 0,
    '-' -> SB setBond Single,
    '(' -> SB.openBranch
    ...
  )
}

object SmilesParser {
  def apply[A:SmilesBuilder]: SmilesParser[A] = new SmilesParser[A]{}
}
```

First, we defined type alias *STrans*, which is just a function from one accumulated molecule to the next. The main entry point for parsing a SMILES string is the initial automaton state *char*, which performs a pattern match against the character to be parsed. Seven cases had to be distinguished: *EOT* returns the accumulated molecule without further modifications together with a dummy parser, *'C'* and *'B'* await the next character in order to decide between adding one of two possible atoms, *'['* will start bracket accumulation while the next two cases have to do with ring formation. The final catch-all pattern looks up the character in map *unique* and applies the returned state transformer to molecule *a*. Map *unique* contains all characters that can be encountered outside of brackets in a valid SMILES string other than the few special ones just described.

For interpreting the detailed data coming in brackets, we used regular expressions together with *Scala's* pattern matching capabilities to great effect. Thus, the whole parser consisted of less than one hundred lines of code and should be able to parse all strings in accordance with the *OpenSMILES* specification [21] with the exception of

chemical reactions, where the participating molecules are delimited by character *'>'*. Since we believe that a reaction is not the same thing as a molecule, parsing reactions will have to be treated separately. This is trivial though, since we can just split the string into three (possibly empty) parts at the proper places, and treat each part as a separate molecule. Finally we needed a class to represent the accumulated SMILES state:

```
type AtomInfo = (Int, Boolean)
type RingInfo = (AtomInfo,
Option[Bond])
type Rings = Map[Int,RingInfo]

case class SmilesMol (
  graph: LGraph[Bond,SmilesAtom],
  keep: Boolean,
  stack: List[AtomInfo],
  bond: Option[Bond],
  dbStereo: Option[Char],
  rings: Rings
)
```

Field graph stores the growing molecular graph. Flag `keep` is set to `true` when a new side chain is started, in which case the next atom's index together with information about aromaticity will be added to the atom stack. Fields `bond` and `dbStereo` are used when explicit information about bonds is encountered in a SMILES string, and `map rings` represents all currently opened rings including the type of the ring bond (if specified) and whether the first atom at the ring bond is aromatic. We thought that these fields will hardly ever be used outside of class `SmilesMol`, therefore we did not define a new data type for each of them but used tuples and type aliases instead. For class `SmilesMol` an implementation of `SmilesBuilder` was written in about one hundred lines of code so that we were finally able to define our first concrete SMILES parser:

```
val Default = SmilesParser[SmilesMol]
```

What we applied here is almost exactly the *Builder* pattern described by the famous *Gang of Four* [25]. Class `SmilesParser` plays the role of the *director* with type class `SmilesBuilder[A]` being the *builder* for product type `A`. The only difference is that we used *Scala's* type class mechanism to bring the *builder* to the *director*. The big advantage of the *builder* pattern is the decoupling of parsing and state accumulation. When parsing a SMILES string we might not always be interested in accumulating a full molecular graph. In that case we might go for a completely different product type `A`. All we had to do in such a case would be writing a new implementation of `SmilesBuilder[A]` which is typically much easier than writing a new parser from scratch.

Implicit hydrogen detection

A SMILES string has not only to be parsed according to syntactic rules, it usually also needs to be interpreted chemically. Typical additional calculations include perceiving aromaticity, interpreting stereochemical information, and detecting implicit hydrogen atoms. Implementing the latter was pretty straight forward: For the organic subset atoms, SMILES defines one or more valid default valences. We therefore only had to count the total number of bonds to organic subset elements and add implicit hydrogen atoms until we reached the next higher valid valence:

```
def implicitHydrogens (
  bs: List[Bond], e: Element
): Int = {
  def calc (v: Int): Option[Int] =
    valences get e flatMap (_ find (v<=))
```

```
  calc (bs foldMap (_.valence)) get
}
```

```
private val valences
: Map[Element, Seq[Int]] = Map(
  B => Seq(3),
  C => Seq(4),
  N => Seq(3, 5),
  ...
)
```

We used `foldMap` to sum up the valences of all bonds connected to the atom in question (this list is directly available from the molecular graph) and then search for the lowest valid valence equal to or greater than this value. The difference between the two are the implicit hydrogen atoms.

While the above code is nice and short, it goes horribly wrong in the presence of aromatic bonds. There is no single valence defined for an aromatic bond therefore they need to be interpreted on a case by case basis. We enhanced the above algorithm to check for the presence of aromatic bonds by first sorting list `bs` (aromatic bonds were at the head of the list after sorting) and then performing several pattern matches taking up about fifteen lines of code in total. This allowed us to finally transform a graph of type `LGraph[Bond, SmilesAtom]` to one of `LGraph[Bond, Atom]` which could then be used to calculate the molar mass and total formula of the parsed molecule using the functions described earlier in this article.

Using function `implicitHydrogens` it was straight forward to transform a `SmilesMol` to a `Molecule` and we defined function `toMolecule` for just that purpose:

```
object SmilesMol {
  def toMolecule (sm: SmilesMol)
    : Molecule = ...
}
```

Functionally handling exceptions: The Validation Applicative Functor

We have stressed the usefulness and safety of using referentially transparent functions several times in this article. At the same time, our SMILES parser is not referentially transparent at all. For instance, the following expression in our parser will throw an exception if character `c` is not found in `map unique`:

```
lazy val char: FAS = FASState[A] (
  (a, c) => c match {
    ...
    case x => (char, unique(x)(a))
  }
)
```

This is not a type-safe solution. Clients of our code would have to rely on the documentation of our library in order to know what kinds of exceptions to expect when using our parser. We will now describe an alternative strategy for dealing with exceptions that is type-safe, purely functional and composable at the same time.

We have seen how the `Option` data type can be used in cases where a calculation might have no valid result. While this is already an improvement in terms of type-safety, it has one drawback: We cannot tell the client of our function what exactly went wrong. What we would like to have is a data type that lets us return the results of successful calculations while returning some information about what went wrong in case of a failure. We have actually two options to get this behavior: The *Scala* standard library defines the algebraic data type `Either[A, B]` which has two subclasses `Left[A, B]` and `Right[A, B]` where a `Left` wraps a single value of type `A` and a `Right` one of type `B`. By convention a `Left` is returned in case of a failed calculation and a `Right` in case of a success. While this is already very useful, `Either` was not designed to accumulate error messages. If we parsed a file of many strings using function `traverse` (see below) with `Either[String, SmilesMol]` as the return type, our program would stop at the first invalid string encountered in the file returning a single error message wrapped in a `Left`. The clients of our parser would not know if there were other erroneous SMILES strings in the file until the one that stopped the parser was fixed and the application run again. If possible, clients typically want to know about all things that went wrong during a calculation. This is especially the case when running bulks of independent calculations.

```
lazy val char: FAS = FAState[A]((a, c) => c match {
  ...
  case x => unique get c fold (next(a), unknown(c))
})

def next (a: A)(s: STrans): FAS[A] = s(a) map ((char, _))

def unknown(c: Char) = ("Invalid character: " + c).failNel
```

`unique get c` returns an `Option[STrans]`. The two possible cases `Some` and `None` are handled in function `fold`: If a state transformer was found, it is applied to the last state `a` and the validated result is mapped to a pair consisting of the next automaton state and the updated molecule. This pattern came up several times in our SMILES parser therefore we moved

An alternative to `Either` is provided by *scalaz* in form of the `Validation[E, A]` data type. Again, two subclasses are available: `Failure[E, A]` which wraps a single value of type `E` and `Success[E, A]` wrapping a value of type `A`.

Unlike `Either`, `Validation` was designed to accumulate failures. We will show how this is done in a moment. First we had to change parts of our parser so that they no longer threw exceptions but returned validated values of type `Validation[NonEmptyList[String], A]` instead. A `NonEmptyList` is just that: A list that contains at least one value. It is provided by *scalaz* and is often used as a means to accumulate error messages.

A referentially transparent SMILES parser

First, we had to redefine some of our type aliases:

```
type ValRes[+A] =
  Validation[NonEmptyList[String], A]

type FAS[A] = ValRes[(FAState[A], A)]

trait SmilesBuilder[A] {
  type STrans = A => ValRes[A]
  ...
}

sealed abstract class SmilesParser[A] {
  type STrans = A => ValRes[A]
  ...
}
```

Of course we had to adjust some of the functions in classes `SmilesBuilder` and `SmilesParser`. For instance, the catch all case in `FAState char` was changed as shown below:

it to helper function `next`. If no state transformer was found, the parser returns an error message wrapped in a `Validation`. Other functions in `SmilesBuilder` and `SmilesParser` were adjusted accordingly.

Finally, we adjust function `parse` in the companion object of class `FAState` as shown in the following code listing:

```
def parse[A] (s: String, fas: FAState[A], a: A): ValRes[A] = {  
  
  @scala.annotation.tailrec  
  def fsa (s: String, fas: FAState[A], a: A, pos: Int)  
  : ValRes[A] = s match {  
    case "" => fas next (a, EOT) fold (fail(pos), _._2.success)  
    case cs => fas next (a, cs.head) match {  
      case Failure(ss) => fail(pos)(ss)  
      case Success((nf, na)) => fsa(cs.tail, nf, na, pos + 1)  
    }  
  }  
  
  def fail(pos: Int) (ss: NonEmptyList[String]): ValRes[A] = ...  
  
  fsa(s, fas, a, 1)  
}
```

This time we did the tail recursion using an inner function, since we also wanted to keep track of the position in the SMILES string. That way, if a string cannot be parsed, all error messages are adjusted to include the exact position at which the parsing failed.

We also adjusted function `toMolecule` in the companion object of class `SmilesMol` to return validated molecules, since some errors in a SMILES string can only be detected upon implicit hydrogen calculation. We were then able to go directly from a string to a validated molecule by defining function `smiles`:

```
def smiles (s: String)  
: ValRes[Molecule] =  
  SmilesParser.Default(s) flatMap  
  SmilesMol.toMolecule
```

Function `flatMap` is a more powerful version of function map (which can actually be expressed in terms of `flatMap`) in that it does not take a function from A to B as its parameter but one from A to `ValRes[B]`. By the way, when using `flatMap` the error messages of the two functions will not be accumulated since the second can only be called if the first was successful.

In order to provide some human-readable output for our molecular graphs, we implemented type class `Show` for trait `LGraph`. We could then test our parser directly from the console by using the following function:

```
def smilesShow (s: String): String =  
  smiles(s) fold (  
    ..list mkString " n",  
    ..shows  
  )
```

This is typical when working with types like `Option` and `Validation`: At one point one has to break out of

the context and either handle the successfully calculated results or deal with the accumulated error messages. In this case we do just that by converting both possible outcomes into strings: In case of a failed calculation we collect all error messages in a single string (one error per line), in case of a success we present the molecular graph in human readable form. Both possible outcomes are shown in Tables 1 and 2 for several input strings.

Bulk operations

This section describes some of the more advanced techniques used in functional programming. These were described in greater detail by *McBride* and *Paterson* [26] as well as *Gibbons* and *Oliveira* [27].

Given a file containing a large number of molecules each as a SMILES string on a separate line, we were now able

Table 1 Output when parsing valid SMILES strings

CCO	[cH+]1cc1	[NH3+][C@H](C)(=O)[O-]
LGraph:	LGraph:	LGraph:
0: CH3	0: CH(+1)	0: NH3(+1)
1: CH2	1: CH	1: CH(@)
2: OH	2: CH	2: CH3
		3: C
0 - 1: -	0 - 1: :	4: O
1 - 2: -	0 - 2: :	5: O(-1)
	1 - 2: :	
		0 - 1: -
		1 - 2: -
		1 - 3: -
		3 - 4: =
		3 - 5: -

Molecular graphs are displayed as lists of atoms followed by lists of bonds. Each bond shows the indices of the connected atoms followed by the SMILES symbol representing the type of the bond.

Table 2 Output when parsing invalid SMILES strings

Input	Message
CCuCC	Pos. 3 in CCuCC: Unknown character in SMILES-String: u
C%12CCCC%1	Pos. 11 in C%12CCCC%1: % is not followed by two digits
C#OC	Invalid bond set for element O: Triple,Single

In the last example no position is given since this failure did not happen during parsing but during implicit hydrogen detection which is a separate algorithm and therefore has not notion of a 'position in a string'.

to parse the whole sequence of lines in a single line of code:

```
import SmilesParser.Default

def bulkParse (ls: Seq[String]) =
  ls traverse Default.parse
```

The result of `bulkParse` will either be a sequence of `SmilesMols` wrapped in a `Success` or a `NonEmptyList` of error messages wrapped in a `Failure`. Method `traverse` is again provided by *scalaz* and has the following quite daunting signature:

```
def traverse[F[_],B] (f: A => F[B])
  (implicit a: Applicative[F],
   t: Traverse[M]): F[M[B]] = ...
```

It is added via the *pimp my library* pattern to an object of type `M[A]` and takes a function from `A` to a value of type `B` in a context `F` as its argument. It also takes two implicit parameters: An instance of type class `Traverse` must be defined for type constructor `M` (which is usually some kind of container such as a list or a tree) and one of type class `Applicative` for context `F`. Method `traverse` is highly versatile in that it not only abstracts over the input and output types of a function but also over the container over which we iterate as well as the context `F` in which the calculation runs. We will not describe how these type classes are defined and implemented any further but refer the interested reader to the articles given at the beginning of this section as well as the *scalaz* source code. Suffice to say that the `Applicative` for `Validation` requires a `Semigroup` (which like a `Monoid` defines a function `append` but without the `zero` value) to be defined for its error type `E`. Errors are then accumulated via `Semigroup.append`. For instance there is a `Semigroup` for `NonEmptyLists` (`append` simply being list concatenation).

One good thing about `Applicatives` is that they compose very nicely. It can be shown that both the product $(M[_], N[_])$ and the composition $M[N[_]]$ of two `Applicatives` `M[_]` and `N[_]` are again `Applicatives` [26]. This gives us incredible flexibility in our code. We will

demonstrate this by adding another piece of information to our error messages: The line number at which a certain error occurred. To keep track of the actual line number, we use the `State Monad` [28]. We define a couple of new type aliases together with function `parseLine`:

```
type IntState[A] = State[Int,A]
type ValIntState[A] =
  IntState[ValRes[A]]
```

```
implicit val ValIntStateApplicative =
  Comp.CompApplicative[IntState,ValRes]
```

```
def parseLine[A] (f: String =>
  ValRes[A])
: String => ValIntState[A] =
  s => state(i => (i + 1, f(s) fold (
    - map (
      "Line %d: %s" format (i, _)
    ) fail,
    -.success
  )))
```

Method `parseLine` parses a string and if this fails, prepends the actual line number to all error messages. At the same time the line number is increased by one. Since we are working with a composition of `Applicatives`, the *Scala* compiler needs some help to figure out that `ValIntState` is still an `Applicative`. *scalaz* defines function `CompApplicative` for just this purpose. We can now define a function `parseSmilesLine` and use it again in a bulk operation as before, but this time, our error messages will include the exact position (line and column), where in a file an error occurred:

```
def parseSmilesLine = parseLine(smiles)

def bulkParseSmiles(ss: Seq[String]) =
  (ss traverse parseSmilesLine) ! 1
```

We use the `!` operator to run the computation with an initial line index of 1.

Parallelization and performance

At the beginning of this article we claimed that referentially transparent functions can safely be used in parallel algorithms. Indeed, we were able to parse a reasonably large file (about 10 MB) of SMILES strings with only a few lines of code using *Scala's* parallel collections:

```
val path = "/home/..."

def src = io.Source fromFile path
```

```
def ls = src.getLines.toSeq
val results: ValRes[Molecule] =
  (ls.par map parseSmiles seq).sequence
```

Function `par` transforms a collection to a parallel one, while `seq` transforms it back to a single threaded one. Calling `map` and `sequence` in succession does the same as calling `traverse` but the list is traversed twice. On the other hand, the implementation of `traverse` is too strict to be run in parallel; *scalaz* provides function `parMap` for that purpose, but this makes use of `Futures` which we will not describe here in more detail. Table 3 shows the time used to count the implicit hydrogen atoms in all molecules (about 350'000) in a sample SMILES file downloaded from the *ZINC* database [29] on a standard laptop with a quadcore processor, once when run in a single thread and once when run in parallel on all four cores. As can be seen, performance is increased by about a factor of two without any further tuning from our part.

We also used *VisualVM* [30] as a profiler to further improve the performance of our SMILES parser and our graph implementation. A couple of simple adjustments increased the performance by another 30%. Applying the *Flyweight* pattern to edges by caching the most commonly used ones as well as changing the order in the pattern match of the `implicitHydrogens` function each reduced the time needed to parse the *ZINC* library by about half a second. In the first case we could cache the commonly used edges' `hashCode` which was otherwise reevaluated many times when they were being used as keys in the edge label map in our labeled graphs. In

Table 3 Performance of SMILES parsing

Run	Singlethreaded	Multithreaded	Multithreaded (after profiling)
1	17'149	10'295	7608
2	15'659	7123	5488
3	15'663	7248	5433
4	15'880	7508	5425
5	15'809	7669	5534
6	15'720	7197	5471
7	15'665	7174	5448
8	15'390	7296	5513
9	15'423	7687	5696
10	15'523	7564	5491
average	15'788	7676	5711

Time (in milliseconds) taken to parse part of the *ZINC* database containing about 350'000 structures on a quadcore laptop. The multi-threaded runs ran on all four cores without further optimization of *Scala's* parallel collections settings.

the second case we could restrict the sorting of a considerable amount of bond lists to only those cases where aromatic bonds were involved. Finally we saw that building the adjacency lists of our graphs took quite some time. This could be somewhat improved by changing their type from `Array[Set[Int]]` to `Array[List[Int]]`. It is not yet sure, whether we will have to undo this last change, since `Sets` have constant time random access, while for lists it is linear with respect to the list's size. The effect on overall performance of our parser will not be very big if this change has to be undone in a future version.

Finally we tested the efficiency of parallelizing the parsing of large lists of SMILES strings on a hexacore processor supporting hyperthreading. The results are summarized in Table 4. The drop in efficiency and reduced speedup when running more than nine threads in parallel might be related to the computer's hardware architecture or *Scala's* implementation of parallel collections but we did no further investigations along those lines.

Comparison with other open-source toolkits

In this section we are going to have a closer look at other cheminformatics toolkit implementations and compare their design with the one chosen for *chemf*.

Ouch: *ouch uses chemical Haskell* [12]

Ouch is the only other purely functional cheminformatics toolkit we are aware of. It is written in *Haskell* and is similar in functionality to *chemf*. It also provides SMILES parsing capabilities that result in a basic

Table 4 Speedup and efficiency of parallelized SMILES parsing

Number of Threads	Time [ms]	Speedup	Efficiency
1	9493	1.00	1.00
2	5309	1.79	0.89
3	4134	2.30	0.77
4	2988	3.18	0.79
5	2785	3.41	0.68
6	2647	3.59	0.60
7	2273	4.18	0.60
8	2091	4.54	0.57
9	2037	4.66	0.52
10	2061	4.61	0.46
11	2061	4.61	0.42
12	2096	4.53	0.38

The test runs were performed on a hexacore processor supporting hyperthreading. Again our testing except of the *ZINC* database was parsed using *Scala's* parallel collections.

molecular graph. In addition, *Ouch* supports output to several file formats as well as some nice algorithms for enumerating chemical structures which are described in more detail in the author's blog [31]. There are several differences between *chem^f* and *Ouch* in terms of design decisions.

First, *chem^f* abstracts over the bond and atom types in its graph implementation through type parameters while in *Ouch* a molecule is simply a mapping from an integer to an atom plus a set of additional information in terms of molecular markers. All available information for a given atom is provided by the `Atom` data type which can again be annotated by various markers. This makes *Ouch*'s `Atom` and `Molecule` data types quite versatile but not really type safe. The presence or absence of a given type of marker is not visible at the type level, and algorithms that rely on certain markers will have to explicitly query the molecule and its atoms for their presence. Here we believe that the design of *chem^f* is somewhat superior in terms of flexibility and type safety. We can describe different aspects of a molecule simply by varying the type parameters of an `LGraph` and algorithms working on molecular graphs can define via the types of their parameters, which additional pieces of information about a molecule's atoms and bonds are required. Parameterizing over the edge and node type of `LGraph` also allowed us to define some powerful type classes like `Functor`, `Foldable`, and `Traverse` for our labeled graphs. This makes many highly versatile higher order functions available for working with `LGraphs` as has been demonstrated when implementing a couple of basic operations on molecules.

Another difference is the implementation of the SMILES parser. *Ouch* makes use of the *parsec* [32] library of parser combinators, meaning that the low level parsing capabilities of *Ouch*'s parser did not have to be implemented from scratch. On the other hand, *Ouch* does not abstract over the return type of its parser. The parser simply reads a SMILES string and returns a `Molecule`. In our implementation we abstracted over the parser's return type by means of the builder pattern. This leads to greater flexibility when accumulating the information available from a SMILES string and will make a possible future change in the representation of molecules easier. *Ouch*'s SMILES parser also handles the potential of failure during parsing differently: Errors and warnings are stored as markers together with the parsed molecule. While this also allows for the accumulation of error messages when several things go wrong, the presence or absence of errors is not visible at the type level and can only be determined upon inspecting the molecule's set of markers. Our implementation describes

the potential of failure already in the parser's return type. This gives us once more access to many useful higher order functions provided by the `Validation` data type and its various type class implementations as we have shown when performing bulk operations. It also makes error handling in follow-up algorithms obsolete. This is demonstrated in the following code listing:

```
def formula (m: Molecule): Formula =  
  = m foldMap atomFormula  
  
def parseFormula (s: String) =  
  smiles(s) map formula
```

Here, function `formula` is only called if the parsing was successful. Its implementation does not have to concern itself with the possibility of failure during parsing, and it is therefore not necessary to query the molecule for the presence or absence of errors.

CDK: the chemistry development kit [1]

CDK is an open-source cheminformatics and bioinformatics toolkit written in *Java*. It provides a plethora of chemistry-related data structures and algorithms as well as UI widgets that can be used for structure drawing and editing in graphical user interfaces. It also supports reading from and writing to many file formats typically used in chemical applications.

CDK was designed as a purely object-oriented toolkit, based on mutable data structures and subtyping for code reuse and loose coupling between components. The main data structures are defined as *Java* interfaces for which default implementations are provided. Algorithms typically operate on these interfaces which makes it possible to use them with tailor-made implementations. In *chem^f* we use type classes to achieve the same (or an even higher) degree of flexibility. Theoretically, the algorithms provided by *CDK* could also be used from within *chem^f* by implementing the interfaces of the data structures in question. However, even *CDK*'s interfaces were designed with mutability in mind so that one has typically to provide getters (accessors) and setters (mutators) for all editable fields of a data structure. This of course does not go well with referential transparency and purely functional programming. It is also not always clear whether algorithms like substructure searching or ring detection mutate parts of the data structures they operate on. From a functional programmer's point of view it might therefore be interesting to adjust *CDK*'s design so that two types of interfaces are defined for all data structures: One for accessing and one for mutating an object's fields.

Ideally, most algorithms would then work solely with the immutable interface of a data type, thereby guaranteeing via the type system that no inplace mutation will occur.

CDK's SMILES parser is similar in functionality to our parser, however an algorithm for aromaticity perception is provided as well. *CDK's* parser is also implemented via the *builder* pattern though its return type is always `IMolecule`. The builder is only needed as a factory to create a new instance of `IMolecule` when parsing a new string. It is also worth noting that *CDK's* SMILES parser, written in an imperative style in *Java* consists of more than ten times the number of lines of code than our implementation. While fewer lines of code is not necessarily a sign of quality or efficiency, less boiler plate code can well increase both the readability and maintainability of the code base especially when the difference is a whole order of magnitude.

We planned to compare the efficiency of *CDK's* SMILES parser with our implementation when parsing bulks of SMILES strings in parallel. However, we found that *CDK's* parser is not referentially transparent and operates on mutable state internally. In order to parse SMILES strings in parallel we had to create a new instance of `SmilesParser` for every string to be parsed instead of using the same instance for all strings. Even then *CDK's* SMILES parser failed with a `NullPointerException` at irregular occasions when we used the singleton instance of `DefaultChemObjectBuilder` as described in the parser's documentation. The code we used in this test is listed below:

```
import org.openscience.cdk.smiles.SmilesParser
import org.openscience.cdk.DefaultChemObjectBuilder
import scalaz._, Scalaz._
import collection.JavaConversions._

object CdkPar {
  def count (ls: IndexedSeq[String]): Int = {
    def sp = {
      val res = new SmilesParser(DefaultChemObjectBuilder.getInstance)
      res.setPreservingAromaticity(true)
      res
    }

    def countImpHs(s: String): Int =
      (sp.parseSmiles s).atoms.toList foldMap (_.getImplicitHydrogenCount)

    ls.par map countImpHs sum
  }
}
```

This demonstrates one of the major advantages of functional programming over classical object-oriented programming: Referentially transparent functions and immutable data structures can be used at will in parallel algorithms while with mutable data structures thread safety is a deliberate design decision and can be hard to implement and even harder to test.

Conclusions

In this article, we described our first steps in putting together a purely functional cheminformatics toolkit in *Scala*. We showed how typical calculations required in chemical applications can be written with a drastically reduced amount of code due to the increase in abstraction and type-safety gained by applying typical concepts from functional programming. We also showed how the resulting referentially transparent functions and immutable data types can be used at no risk in all parts of client code including multi-threaded algorithms. We also compared our code with existing toolkits, and showed how it is superior in terms of type-safety and flexibility as well as – when compare to a typical object-oriented toolkit – thread safety. Last but not least, we experienced a drastic increase in productivity when programming in a purely functional way. Typically, code that compiled ran as expected and passed all unit tests at first take.

Of course our work is by far not finished here. In a next step we will focus on supporting other file formats in our toolkit before moving to file output and (SMILES) canonicalization. Especially the latter will be interesting to implement since it is known to be performance critical.

Once canonicalization is implemented to our satisfaction we will move our focus towards data storage and experiment with our own implementation of a chemical database system that should also support substructure and similarity searches embedded in our computer aided drug design projects.

Methods

Benchmarking the SMILES parser

We used the `scala.testing.Benchmark` trait for benchmarking our application. For this task the block of code listed below was executed, either with or without using parallel collections.

```
import parser._
import scalaz._, Scalaz._

object Main extends testing.Benchmark {
  implicit def ValResMonoid[A:Monoid] = Monoid.liftMonoid[ValRes,A]

  def run {
    def str = getClass.getResourceAsStream("zinc.txt")

    def source = scala.io.Source fromInputStream str

    def lines = source.getLines.toIndexedSeq

    def countImpHs(s: String) =
      smiles(s) fold (_ => 0, _ foldMap (_ hydrogens))

    //or 'lines map countImpHs sum' if run single-threaded
    def res = lines.par map countImpHs sum

    println(res)
  }
}
```

The first run was typically slower by a factor of at least two than the following ones. This is a known effect due to *Java's* Just In Time compilation [34].

Additional file

Additional file 1: chemf_src.zip. This file contains the source code of the version of chem^f described in this article as an *SBT* [33] project. To try out some code samples, install *SBT* and start it from within the *chemf* directory. From within *SBT* start the console by typing `console`. Several functions are loaded and can be used out of the box: `smiles(s)` will parse SMILES string `s`, `prettySmiles(s)` will do the same but print the resulting molecule (or error messages) in human readable form.

Competing interests

The authors declare that they have no competing interests.

Authors' contributions

SH did the programming and wrote the article. RR supervised the project. Both authors read and approved the final manuscript.

Acknowledgements

This project was financially supported by the ZHAW (Development of a cheminformatics toolkit as a basis for other chemistry-related software).

Received: 22 August 2012 Accepted: 22 November 2012

Published: 20 December 2012

References

1. Steinbeck C, Han Y, Kuhn S, Horlacher O, Luttmann E, Willighagen E: **The Chemistry Development Kit (CDK): an open-source java library for Chemo- and bioinformatics.** *J Chemical Inf Comput Sci* 2003, **43**(2):493–500.
2. O'Boyle N, Banck M, James C, Morley C, Vandermeersch T, Hutchison G: **Open label: an open chemical toolbox.** *J Cheminformatics* 2011, **3**:33.
3. **The java programming language.** [http://www.java.com]
4. Bloch J: *Effective Java*. 2nd edition. Boston: Addison-Wesley; 2008.
5. Odersky M: **Future-proofing collections: from mutable to persistent to parallel.** *Talk at Devovx, Antwerp, Belgium* 2010. [http://link.springer.com/chapter/10.1007%2F978-3-642-19861-8_1]
6. Sondergaard H, Sestoft P: **Referential transparency, definiteness and unfoldability.** *Acta Informatica* 1990, **27**:505–517.
7. Odersky M, Altherr P, Cremet V, Dragos I, Dubochet G, Emir B, McDermid S, Micheloud S, Mihaylov N, Schinz M, Stenman E, Spoon L, Zenger M: **An**

- overview of the scala programming language.** Tech. rep., EPFL, Lausanne, Switzerland 2006.
8. Peyton Jones S (Ed): *Haskell 98 Language and Libraries – The Revised Report*. Cambridge, England: Cambridge University Press; 2003.
 9. Hughes J: **Why functional programming matters.** *Comp J* 1989, **32**(2):98–107.
 10. Höck S, Riedl R. *Chimia* 2012, **66**(3):132–134.
 11. Wampler D, Payne A: *Programming Scala*. Sebastopol: O'Reilly Media; 2009.
 12. Jankowski O: **Ouch uses chemical Haskell.** [<https://github.com/odj/Ouch>]
 13. Weininger D: **SMILES - a Language for molecules and reactions.** In *Handbook of Cheminformatics*. Edited by Gasteiger J, Weinheim. Germany: Wiley-VCH; 2003.
 14. Odersky M, Spoon L, Venners B: *Programming in Scala*. 2nd edition. Walnut Creek, USA: Artima Press; 2010.
 15. **FOLDOC: Free on-line dictionary of computing.** [<http://foldoc.org/algebraic+data+type>]
 16. Moors A, Piessens F, Odersky M: **Generics of a higher kind.** *Acm Sigplan Notices* 2008, **43**:423–438.
 17. Odersky M: **Pimp my library.** 2006. [<http://www.artima.com/weblogs/viewpost.jsp?thread=179766>]
 18. Oliveira BCdS, Moors A, Odersky M: **Type classes as objects and implicits.** In *Proceedings of the ACM International Conference on Object Oriented Programming Systems Languages and Applications*. Reno/Tahoe: ACM; 2010:341–360.
 19. **Scalaz: Type classes and pure functional data structures for scala.** [<http://code.google.com/p/scalaz/>]
 20. Lipovaca M: *Learn You a Haskell for Great Good*. San Francisco: No Starch Press, Inc.; 2011.
 21. **OpenSMILES.** [<http://www.opensmiles.org>]
 22. Barnard JM: **Representation of molecular structures - overview.** In *Handbook of Cheminformatics*. Edited by Gasteiger J, Weinheim. Germany: Wiley-VCH; 2003.
 23. Cormen TH, Stein C, Rivest RL, Leiserson CE: *Introduction to Algorithms*. 2nd edition. Boston: McGraw-Hill Higher Education; 2001.
 24. Guha R, Howard MT, Hutchison GR, Murray-Rust P, Rzepa H, Steinbeck C, Wegner J, Willighagen EL: **The blue obelisk - interoperability in chemical informatics.** *J Chem Inf Model* 2006, **46**(3):991–998.
 25. Gamma E, Helm R, Johnson R, Vlissides J: *Design Patterns: Elements of Reusable Object-Oriented Software*. Boston: Addison-Wesley; 1995.
 26. McBride C, Paterson R: **Applicative programming with effects.** *J Funct Program* 2008, **18**:1–13. [<http://dx.doi.org/10.1017/S0956796807006326>]
 27. Gibbons J, Oliveira BCdS: **The essence of the iterator pattern.** *J Funct Program* 2009, **19**(3-4):377–402. [<http://dx.doi.org/10.1017/S0956796809007291>]
 28. Wadler P: **Monads for functional programming.** In *Advanced Functional Programming, First International Spring School on Advanced Functional Programming Techniques-Tutorial Text*. London: Springer-Verlag; 1995:24–52. [<http://dl.acm.org/citation.cfm?id=647698.734146>]
 29. **Zinc is not commercial.** [<http://zinc.docking.org/>]
 30. **VisualVM: All-in-one java troubleshooting tool.** [<http://visualvm.java.net/>]
 31. Jankowski O: **Pharmash.** [<http://www.pharmash.com/index.html>]
 32. Leijen D, Meijer E: **Parsec: direct style monadic parser combinators for the real world.** Tech. rep. 2001.
 33. **sbt, a build tool for Scala.** [<https://github.com/harrah/xsbt/wiki>]
 34. Goetz B: **Java theory and practice: Dynamic compilation and performance measurement.** [<http://www.ibm.com/developerworks/library/j-jtp12214/>]

doi:10.1186/1758-2946-4-38

Cite this article as: Höck and Riedl: chem^f: A purely functional chemistry toolkit. *Journal of Cheminformatics* 2012 **4**:38.

Publish with **ChemistryCentral** and every scientist can read your work free of charge

“Open access provides opportunities to our colleagues in other parts of the globe, by allowing anyone to view the content free of charge.”

W. Jeffery Hurst, The Hershey Company.

- available free of charge to the entire scientific community
- peer reviewed and published immediately upon acceptance
- cited in PubMed and archived on PubMed Central
- yours — you keep the copyright

Submit your manuscript here:
<http://www.chemistrycentral.com/manuscript/>



ChemistryCentral