Typed Tagless Final Bioinformatics

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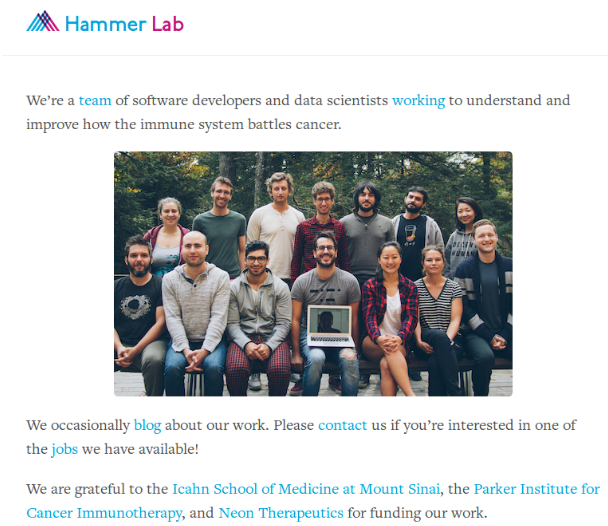
Context

Seb: Software Engineering / Dev Ops at the **Hammer Lab**.



Context

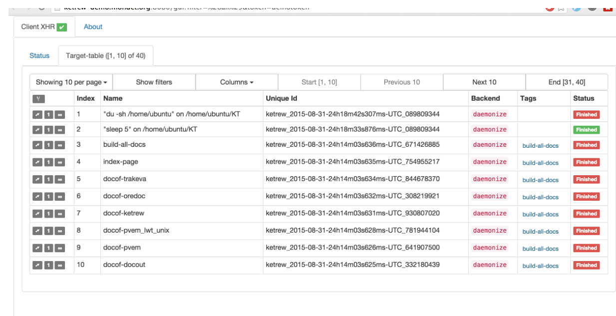
Was *here* 2 years ago to present:

- Ketrew: a workflow engine for complex computational pipelines.
  - EDSL/library to write programs that build workflows/pipelines
  - A separate application, The "Engine", orchestrates those workflows
- Biokepi: a library of Ketrew "nodes" for **Bioinformatics**.

Now

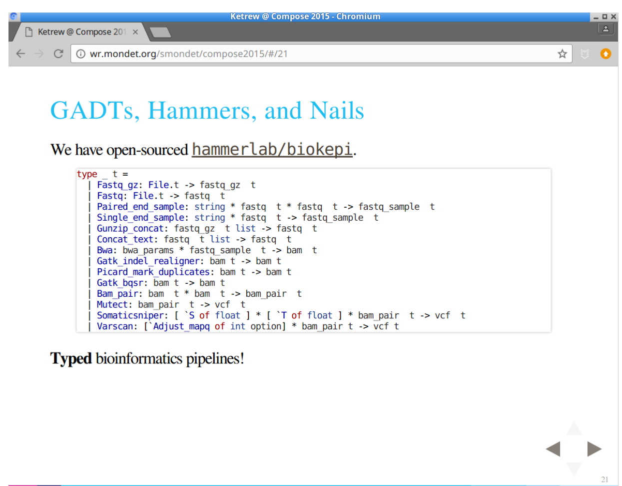
- Used with GCloud/Kubernetes, AWS, YARN (incl. Spark).
- `Tyxml_js` + `react` WebUI
- *Personalized Genomic Vaccine* clinical trial (NCT02721043) → `hammerlab/epidisco/`

WebUI ⇒ 3.6 MB GIFs



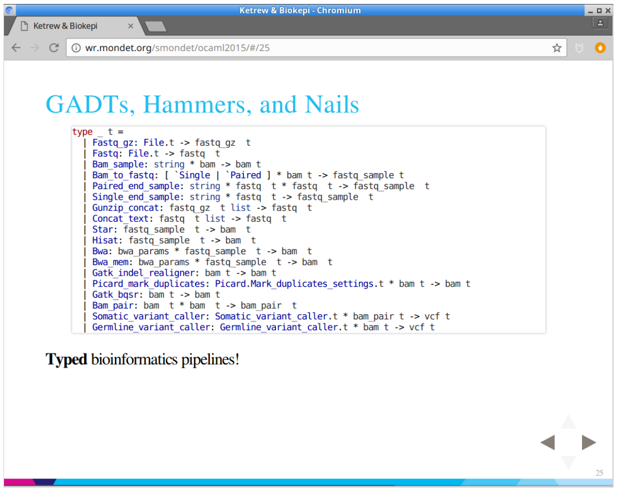
In Particular, We Presented:

Cool experiment: GADT-based, very high-level pipeline EDSL.



Then, At OCaml / ICFP 2015

Cool experiment: add tools / *tool-kinds*:



And Soon After

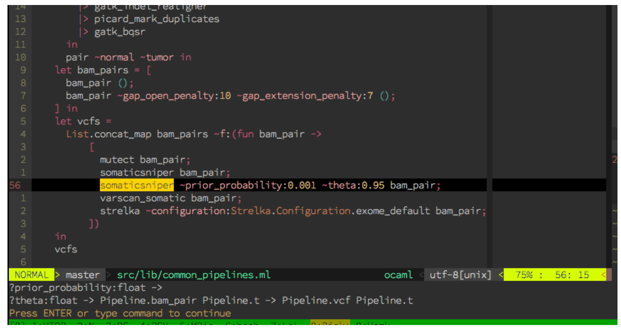
Kept growing, became the default…

```
type _ t =
  | Fastq_gz: File.t -> fastq_gz  t
  | Fastq: File.t -> fastq  t
  | Bam_sample: string * bam -> bam t
  | Bam_to_fastq: [ `Single | `Paired ] * bam t -> fastq_sample t
  | Paired_end_sample: fastq_sample_info * fastq t * fastq t -> fastq_sample t
  | Single_end_sample: fastq_sample_info * fastq t -> fastq_sample t
  | Gunzip_concat: fastq_gz t list -> fastq t
  | Concat_text: fastq t list -> fastq t
  | Star: Star.Configuration.Align.t * fastq_sample t -> bam t
  | Hisat: Hisat.Configuration.t * fastq_sample t -> bam t
  | Stringtie: Stringtie.Configuration.t * bam t -> gtf t
  | Bwa: Bwa.Configuration.Aln.t * fastq_sample t -> bam t
  | Bwa_mem: Bwa.Configuration.Mem.t * fastq_sample t -> bam t
  | Mosaik: fastq_sample t -> bam t
  | Gatk_indel_realigner: Gatk.Configuration.indel_realigner * bam t -> bam t
  | Picard_mark_duplicates: Picard.Mark_duplicates_settings.t * bam t -> bam t
  | Gatk_bqsr: (Gatk.Configuration.bqsr * bam t) -> bam t
  | Bam_pair: bam t * bam t -> bam_pair t
  | Somatic_variant_caller: somatic Variant_caller.t * bam_pair t -> vcf t
  | Germline_variant_caller: germline Variant_caller.t * bam t -> vcf t
  | Seq2HLA: fastq_sample t -> seq2hla_hla_types t
  | Optitype: ([`DNA | `RNA] * fastq_sample t) -> optitype_hla_types t
  | With_metadata: metadata_spec * 'a t -> 'a t
```

Very Concise Pipelines

```
let crazy_example ~normal_fastqs ~tumor_fastqs ~dataset =
  let open Pipeline.Construct in
  let normal = input_fastq ~dataset normal_fastqs in
  let tumor = input_fastq ~dataset tumor_fastqs in
  let bam_pair ?gap_open_penalty ?gap_extension_penalty () =
    let normal =
      bwa ?gap_open_penalty ?gap_extension_penalty normal
      |> gatk_indel_realigner |> picard_mark_duplicates |> gatk_bqsr in
    let tumor =
      bwa ?gap_open_penalty ?gap_extension_penalty tumor
      |> gatk_indel_realigner |> picard_mark_duplicates in
    pair ~normal ~tumor in
  let bam_pairs = [
    bam_pair ();
    bam_pair ~gap_open_penalty:10 ~gap_extension_penalty:7 ();
  ] in
  let vcfs =
    List.concat_map bam_pairs ~f:(fun bam_pair ->
        [
          mutect bam_pair;
          somaticsniper bam_pair;
          somaticsniper ~prior_probability:0.001 ~theta:0.95 bam_pair;
          varscan_somatic bam_pair;
          strelka ~configuration:Strelka.Configuration.exome_default bam_pair;
        ])
  in
  vcfs
```

Type Information



There's a "But"

Fancy but not that practical:

- `Pipeline.t` is getting too big
  - Just `compile_aligner_step` is about 170 lines of pattern-matching
  - Still missing proper `lambda`/`apply`, list functions, etc.
- Not Extensible
  - Adding new types is pretty annoying.
  - Optimization passes need to deal with whole language at once, always.
  - Optimization are not proper language transformations.

Try Again

We want what we already have **+** *users* of the library to be able to:

- Extend the language to their needs
- Re-use default compilers when implementing theirs
- Write future-proof optimizations
- Do transformations "by hand" if easier than an optimization pass

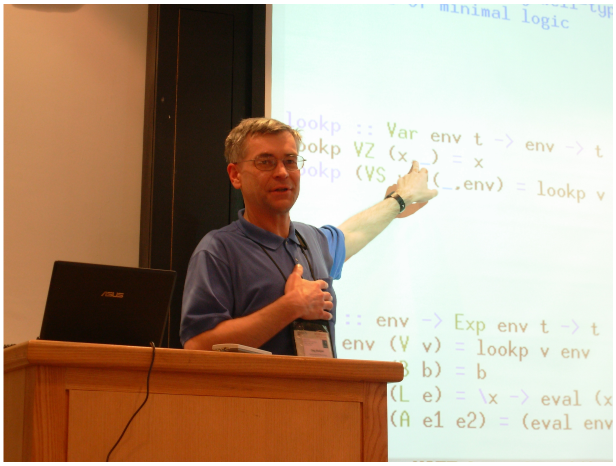
Not-Really Extensible Hacks

Tried a few experiments:

- extensible types
  - loose a lot of the type-strength benefits
  - are not *that* extensible
- basic "language" based-on GADTs and extensible bioinformatics atoms
  - could have worked further but not really extensible either

Oleg

"We trivially and elegantly solved that problem 20 years ago!"



QueΛ and The Course Notes

First:

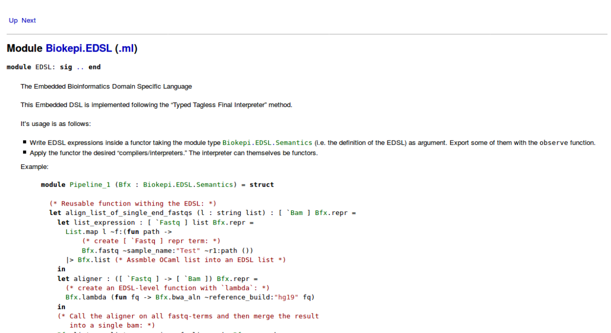
- Oleg emailed the OCaml mailing-list on 2015-07-15
- Presenting "QueΛ", first just some `.tar.gz` and draft paper; then it got to PEPM'16 → `DOI:2847538.2847542`).
- Asked the author for an actual repo and licence → `bitbucket.org/knih/quel`.
- It uses modules *and* the EDSL is well typed.

@pveber pointed us to Oleg's course:

- In Haskell (very concise code, very *un-modular*).
- Well explained and progressive.

⇒ Follow the course; with QueΛ's help; in a Biokepi-like setting.

And We Did It


Up Next

Module Biokepi.EDSL (.ml)

```
module EDSL: sig .. end
```

The Embedded Bioinformatics Domain Specific Language

This Embedded DSL is implemented following the "Typed Tagless Final Interpreter" method.

It's usage is as follows:

- Write EDSL expressions inside a functor taking the module type `Biokepi.EDSL.Semantics` (i.e. the definition of the EDSL) as argument. Export some of them with the `observe` function.
- Apply the functor the desired "compilers/interpreters." The interpreter can themselves be functors.

Example:

```
module Pipeline_1 (Bfx : Biokepi.EDSL.Semantics) = struct

  (* Reusable function withing the EDSL: *)
  let align_list_of_single_end_fastqs (l : string list) : [ `Bam ] Bfx.repr =
    let list_expression : [ `Fastq ] list Bfx.repr =
      List.map l ~f:(fun path ->
          (* create [ `Fastq ] repr term: *)
          Bfx.fastq ~sample_name:"Test" ~r1:path ())
      |> Bfx.list (* Assmble OCaml list into an EDSL list *)
    in
    let aligner : ([ `Fastq ] -> [ `Bam ]) Bfx.repr =
      (* create an EDSL-level function with `lambda`: *)
      Bfx.lambda (fun fq -> Bfx.bwa_aln ~reference_build:"hg19" fq)
    in
    (* Call the aligner on all fastq-terms and then merge the result
       into a single bam: *)
    Bfx.list_map list_expression ~f:aligner |> Bfx.merge_bams
```

We TTFI-ed Everything

And it's more powerful:

- More constructs: `lambda`/`apply`, list and pair functions, ...
- Easier to document.
- Easier to maintain.
- Extensible by the users.

And keeps growing:

```
 $ grep 'val ' src/pipeline_edsl/semantics.ml | wc -l
56
```

How Does It Work?

Now tutorial mode:

- GADT dumb example.
- Translation to TTFI.
- Show how to manipulate the *pseudo-AST*.
- Show how to extend the EDSL.

First, Quickly, GADTs

Type Constraints + Existential Types:

```
type _ t =
| Int: int -> int t
| True: bool t
| False: bool t
| Equal: 'a t * 'a t -> bool t

let rec eval: type v. v t -> v =
  function
  | Int i -> i
  | True -> true
  | False -> false
  | Equal (a, b) -> (=) (eval a) (eval b)

let () = assert (eval (Int 42) = 42)
let () = assert (eval (Equal (True, (Equal (Int 42, Int 42)))) = true)
```

GADT Usages

- Existentials to "pack" types applied to different type parameters:
  - `type pack = Deal_with_it: 'a * 'a how_to -> pack`
- EDSLs ☺
  - Generate POSIX-shell scripts & one-liners: `hammerlab/genspio`
  - Tezos: 250-LoC mutually recursive GADT definition of a smart-contract language: `/src/proto/alpha/script_typed_ir.ml`
- Difference-lists:
  - Cf. `Printf.printf`.
  - Or `Eliom_service.create`.
- Session types.

TTFI

Type Constraints + Existential Types, using module types and functors:

```
module type Symantics = sig
  type 'a repr
  val int: int -> int repr
  val t: bool repr
  val f: bool repr
  val equal: 'a repr -> 'a repr -> bool repr
end

module Eval_ocaml : Symantics with type 'a repr = 'a = struct
  type 'a repr = 'a
  let int i = i
  let t = true
  let f = false
  let equal a b = (a = b)  (* Cheating a bit *)
end

module Examples (EDSL: Symantics) = struct
  let ex1 = EDSL.int 42
  let ex2 = EDSL.(equal t (equal (int 42) (int 42)))
end

let () =
  let module Compiled_examples = Examples(Eval_ocaml) in
  assert (Compiled_examples.ex1 = 42);
  assert (Compiled_examples.ex2 = true);
  ()
```

TTFI in Bullet Points

In OCaml:

- defintion of the language: `module type Semantics`
- program: `functor: Semantics -> whatever`
- compiler: `module implementing Semantics`
- optimization/transformation: `functor: Semantics -> Semantics`
- optimization framework: functor + GADT that implements "default behavior"

Mysteriously Useful Bit

More jargon: *"observations"* are useful artifacts of optimization passes:

```
module type Symantics = sig
  type 'a repr
  val int: int -> int repr
  val t: bool repr
  val f: bool repr
  val equal: 'a repr -> 'a repr -> bool repr
  type 'a observation
  val observe: (unit -> 'a repr) -> 'a observation
end
```

To-String Compiler

```
module Eval_string
  : Symantics with type 'a repr = string and type 'a observation = string
  = struct
  type 'a repr = string
  let int = string_of_int
  let t = "True"
  let f = "False"
  let equal a b = Printf.sprintf "(%s = %s)" a b
  type 'a observation = string
  let observe f = f ()
end
module More_examples (EDSL: Symantics) = struct
   let ex1 =
     let open EDSL in
     observe (fun () -> int 42)
   let ex2 =
     let open EDSL in
     observe (fun () ->
       equal (equal t t) (equal (int 42) (int 43))
     )
end
let () =
  let module Compiled_examples = More_examples(Eval_string) in
  Printf.printf "Ex1: %s\nEx2: %s\n%!"
    Compiled_examples.ex1 Compiled_examples.ex2;
  ()
```

```
Ex1: 42
Ex2: ((True = True) = (42 = 43))
```

Simple Optimization Example

We can do some rewriting with functors:

```
module True_equal_true_true (Input: Symantics)
  : Symantics with type 'a observation = 'a Input.observation
   = struct
  include Input
  let t = Input.(equal t t)
end

let () =
  let module Compiled_examples = More_examples(True_equal_true_true(Eval_string)) in
  Printf.printf "Ex1: %s\nEx2: %s\n%!"
    Compiled_examples.ex1 Compiled_examples.ex2;
  ()
```

```
Ex1: 42
Ex2: (((True = True) = (True = True)) = (42 = 43))
```

(this works without the `'a observation` thing …)

Not Enough

For more complex/interesting transformations,
what we really want is to "**`match term with`**":

```
type _ t =
| Int: int -> int t
| True: bool t
| False: bool t
| Equal: 'a t * 'a t -> bool t

let rec transform_equal_true_true : type v. v t -> v t =
  function
  | Int i -> Int i
  | True -> True
  | False -> False
  | Equal (True, True) -> True (* Optimization Pass ! *)
  | Equal (a, b) ->
    Equal (transform_equal_true_true a, transform_equal_true_true b)

let () =
  assert (
    transform_equal_true_true (Equal (False, (Equal (True, True))))
    =
    (Equal (False, True))
  )
```

Optimization Framework

Some type-hackery later … *A Generic Extensible Optimization Pass Generator.*

```
module type Transformation_base = sig
  type 'a from
  type 'a term
  val fwd : 'a from -> 'a term (* reflection *)
  val bwd : 'a term -> 'a from (* reification *)
end
module Generic_optimizer
  (X: Transformation_base)
  (Input: Symantics with type 'a repr = 'a X.from)
  : Symantics
      with type 'a repr = 'a X.term
      and type 'a observation = 'a Input.observation
  = struct
    open X
    type 'a repr = 'a term
    let int i = fwd (Input.int i)
    let t = fwd Input.t
    let f = fwd Input.f
    let equal a b =
      fwd (Input.equal (bwd a) (bwd b))
    type 'a observation = 'a Input.observation (* Here we "get out" ! *)
    let observe f =
      Input.observe (fun () -> bwd (f ()))
end
```

Using The Optimization Framework

So we want to do `| Equal (True, True) -> True`:

```
module True_true (Input: Symantics) = struct
   module Transformation = struct
     type 'a from = 'a Input.repr
     type 'a term =
       | Unknown: 'a from -> 'a term
       | Equal: 'a term * 'a term -> bool term
       | True: bool term
     let fwd x = Unknown x
     let rec bwd : type a. a term -> a from = function
       | Unknown x -> x
       | Equal (True, True) -> Input.t
       | Equal (a, b) -> Input.equal (bwd a) (bwd b)
       | True -> Input.t
   end
   module Language_delta = struct
     let equal a b = Transformation.Equal (a, b)
     let t = Transformation.True
   end
   include Generic_optimizer(Transformation)(Input)
```

```
  include Language_delta
end
```

Using the Optimization Pass

Still just a functor to apply *"in the chain:"*

```
let () =
  let module Compiled = More_examples(Eval_string) in
  let module Optimized = More_examples(True_true(Eval_string)) in
  Printf.printf "Compiled: %s\nOptimized: %s\n%!"
    Compiled.ex2 Optimized.ex2
```

Success!

```
Compiled: ((True = True) = (42 = 43))
Optimized: (True = (42 = 43))
```

Extensions

Some `include`, and module *sub-typing* magic:

```
module type Symantics_with_lambdas = sig
  include Symantics
  (** Lambda abstraction *)
  val lambda : ('a repr -> 'b repr) -> ('a -> 'b) repr
  (** Application *)
  val apply : ('a -> 'b) repr -> 'a repr -> 'b repr
end

module Eval_string_with_lambdas
  : Symantics_with_lambdas
    with type 'a repr = string and type 'a observation = string
  = struct
  include Eval_string
  open Printf
  let lambda f =
    let var = sprintf "x%d" (Random.int 1000) in
    sprintf "(λ %s → %s)" var (f var)
  let apply f x =
    sprintf "(%s %s)" f x
end
```

Use The Extension

```
module Example_with_lambdas (EDSL : Symantics_with_lambdas) = struct
  open EDSL
  let l1 =
    lambda (fun x -> equal x t)
  let ex1 =
    observe (fun () -> l1)
  let ex2 =
    observe (fun () -> apply l1 (equal t t))
  (* Of course still type checked:
  let ex2 =
    observe (fun () -> apply l1 (int 42))
  Error: This expression has type int repr
         but an expression was expected of type bool repr
         Type int is not compatible with type bool
  *)
end

let () =
  let module Compiled = Example_with_lambdas(Eval_string_with_lambdas) in
  Printf.printf "Ex1: %s\nEx2: %s\n%!"
    Compiled.ex1 Compiled.ex2
```

```
Ex1: (λ x370 → (x370 = True))
Ex2: ((λ x370 → (x370 = True)) (True = True))
```

Extend The Generic Optimization Thing

Soooo *meta*:

```
module Generic_optimizer_with_lambdas
  (X: Transformation_base)
  (Input: Symantics_with_lambdas with type 'a repr = 'a X.from)
  : Symantics_with_lambdas
      with type 'a repr = 'a X.term
      and type 'a observation = 'a Input.observation
  = struct
    open X
    include Generic_optimizer(X)(Input)
    let lambda f = fwd (Input.lambda (fun x -> bwd (f (fwd x))))
    let apply e1 e2 = fwd (Input.apply (bwd e1) (bwd e2))
end
```

Extend The Optimization Pass

`True_true` does not touch the new stuff:

```
module True_true_with_lambdas (Input: Symantics_with_lambdas) = struct
  module Previous_true_true = True_true(Input)
  include Generic_optimizer_with_lambdas(Previous_true_true.Transformation)(Input)
  include Previous_true_true.Language_delta
end

let () =
  let module Compiled = Example_with_lambdas(Eval_string_with_lambdas) in
  let module Optimized =
    Example_with_lambdas(True_true_with_lambdas(Eval_string_with_lambdas)) in
  Printf.printf "Ex2 normal: %s\nEx2 optimized: %s\n%!"
    Compiled.ex2 Optimized.ex2
```

```
Ex2 normal: ((λ x20 → (x20 = True)) (True = True))
Ex2 optimized: ((λ x921 → (x921 = True)) True)
```

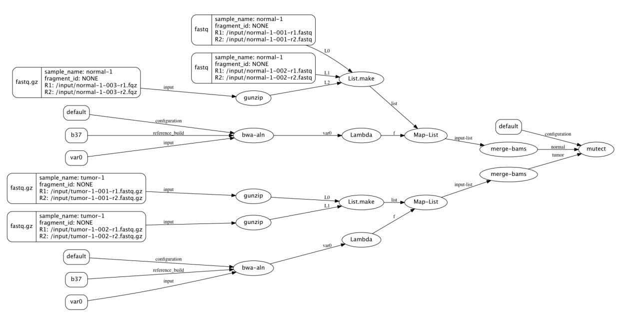
Back To Biokepi

Fully replaced the GADT-based EDSL:

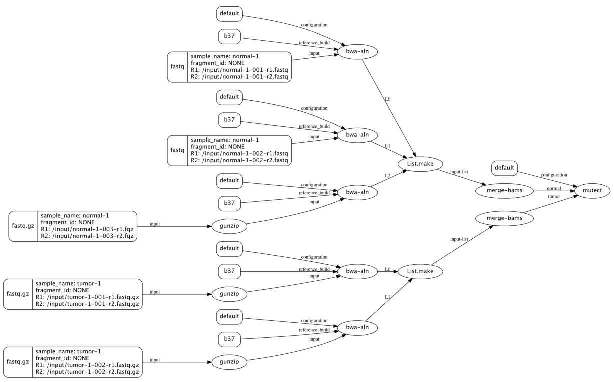
- Compiles to:
  - Ketrew workflows.
  - JSON "provenance proofs."
  - Display-friendly, high-level, Dot-graphs.
- Optimizations *not that* useful:
  - In our application, it's mostly for display/readability purposes.

Apply Lambdas

From PR `#236`:



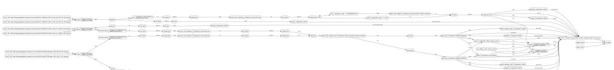
For A Nice Display



Epidisco

Big (family of) pipeline(s) that drive a clinical trial and other people's analyses: `hammerlab/epidisco/`

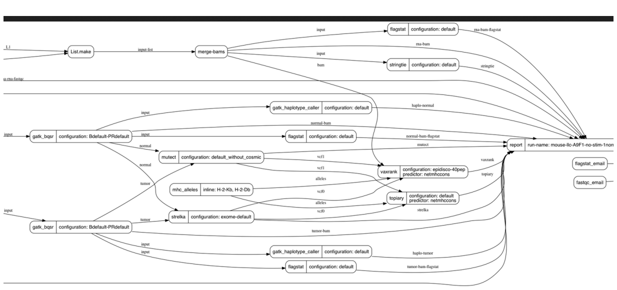
Cf. output to `dot`-graphs:



We actually do extend the EDSL:

- Custom HTML "report."
- Custom "saving" of important artifacts.

Zoom



Deal With Insanity

```
  in
  let bam = List.map samples ~f:sample_to_bam
            |> Bfx.list
            |> Bfx.merge_bams in
  (* We split out the spliced and non-spliced reads so that we can run indel
     realignment on all reads that don't span a splice junction (and thus
     cause the GATK IndelRealigner we're using to crash.) We then merge the
     spliced reads back in. *)
  let spliced_bam =
    let filter = Biokepi.Tools.Sambamba.Filter.Defaults.only_split_reads in
    Bfx.sambamba_filter ~filter bam in
  let indel_realigned_bam =
    let filter = Biokepi.Tools.Sambamba.Filter.Defaults.drop_split_reads in
    Bfx.sambamba_filter ~filter bam
    |> Bfx.gatk_indel_realigner
      ~configuration:indel_realigner_config
  in
  Bfx.merge_bams @@ Bfx.list [spliced_bam; indel_realigned_bam]
```

Limitations

Minor issues:

- Applying functors, while conceptually simple, scares beginners.
  - Though they *can* → PR `#429`.
- Losing type variance because of the *optimization framework*.
  - And in our case optimization framework is useful only for display.
- Cannot always use sub-modules because of `include`.
  - Hence the *flat/tagged* API with `list_map`, `pair_first`, `pair_second`, ...

The End

Questions?