Git For Genomes

Version control through sequence graphs

“The machine code of the genes is uncannily computer-like”

R. Dawkins

Yet genetic engineering does not feel like software engineering.

Genetic engineering: *auto-hopped beer*

***Task:** insert genes responsible for hop aroma chemistry into the yeast genome.**

1. **Design**
    a. Source genetic parts from the iGEM parts registry.
    b. Create combinations of variable parts.
2. **Build**
    a. Plan stepwise cloning strategy
    b. Order or reuse synthetic material ($)
    c. Assemble intermediate constructs & edit genome

* fictional account, but this has been done before: Denby, C.M., Li, R.A., Vu, V.T. *et al.* Industrial brewing yeast engineered for the production of primary flavor determinants in hopped beer. *Nat Commun* 9, 965 (2018).

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Efficient *Build* strategies require *Design* coordination

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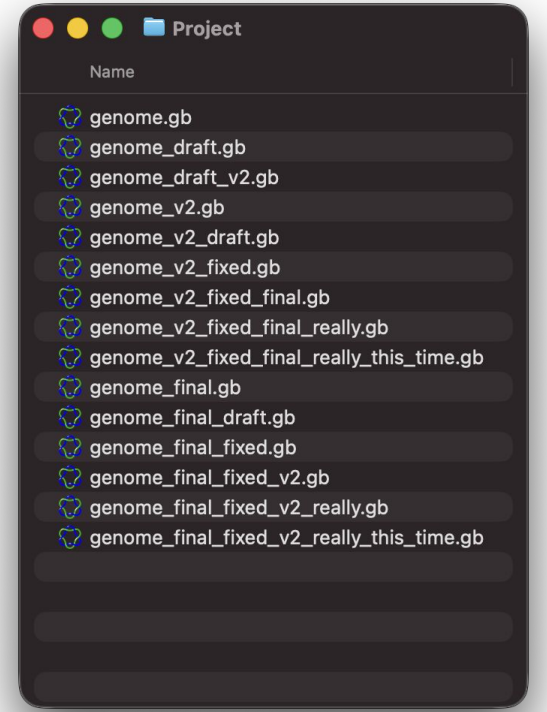
3. **Test**
    a. Read back the genome (DNA sequencing)

“Did the genome edit work?” → Yes / No / Kind of…

    b. Evaluate performance of experimental strains
4. **GOTO 1**



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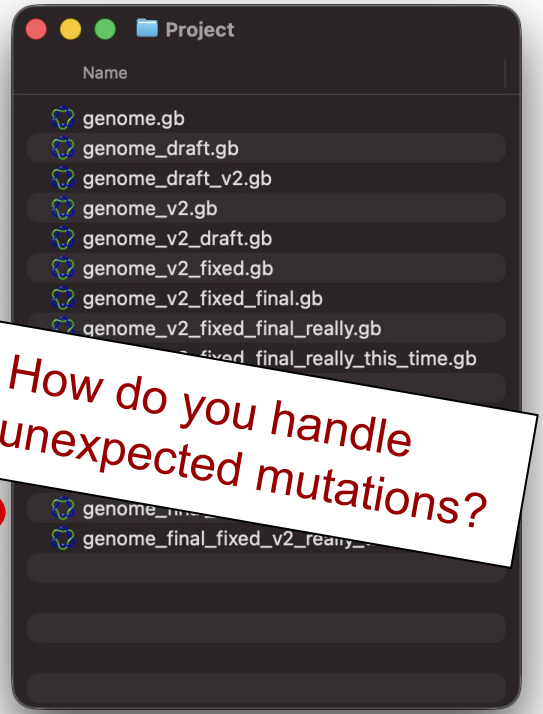

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Closing the Design-Build-Test loop is much harder than it should be

Introducing the **gen** version control system for biology

- Rust crate with Command Line Interface, Terminal User Interface, Python bindings
- Organize sequences and samples in SQLite-backed repositories
- Changes tracked as operations (~commit)
- Familiar git commands
  - init, checkout, branch, reset, diff, push, pull, …

Sequence specific commands (abridged)

***Task:** insert genes responsible for hop aroma chemistry into the yeast genome.*

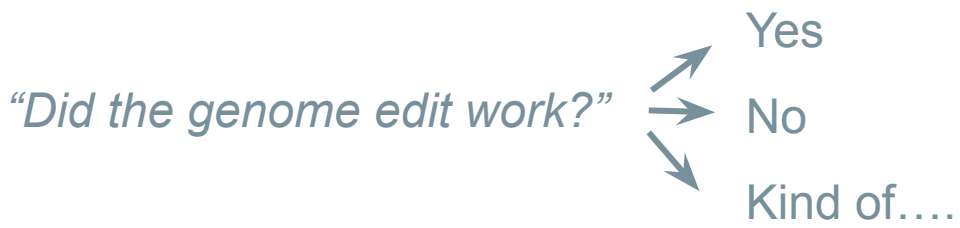
1. **Design**
    a. Source genetic parts from the iGEM parts registry. `gen import`
    b. Create combinations of variable parts. `gen import library`
2. **Build**
    a. Plan stepwise cloning strategy `gen derive chunks`
    b. Order or reuse synthetic material ($)
    c. Assemble intermediate constructs & edit genome `gen make stitch`

Sequence specific commands (abridged)

3. **Test**

   a. Read back the genome (DNA sequencing)

```
gen update vcf
gen view
```



   b. Evaluate performance of experimental strains

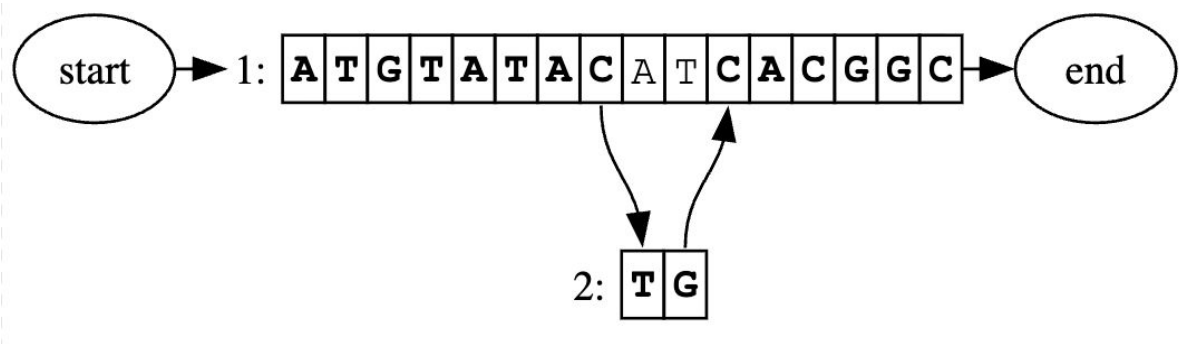
```
gen translate
gen diff
gen propagate-annotations
```

Challenges of working with genetic sequences

- Coordinate frames are very **fragile**
- A genome is neither **uniform nor static**.
  - Real samples rarely match “the reference sequence”
- Need to handle both **intended** and **observed** variants
  - Sequencing to confirm a genotype drops information
  - Sequencing without priors loses engineering context

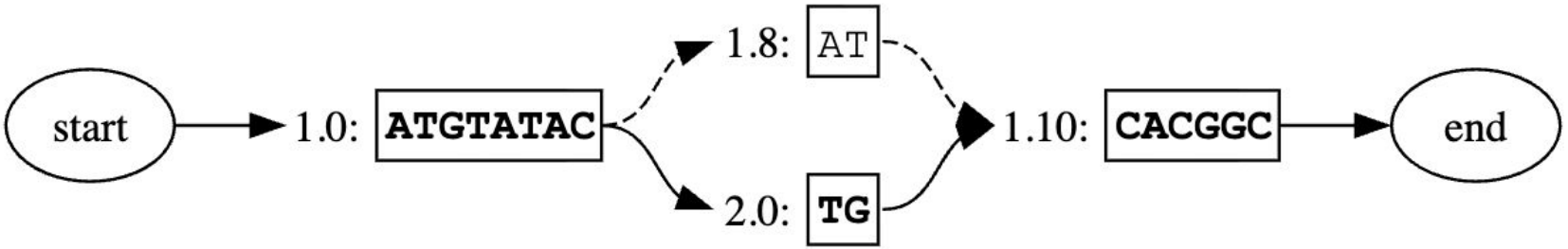
Solution: graph representation of genetic sequences

- Gen models sequences as **walks through a graph**
  - Inspired by the field of pangenomics
- Nodes: sequence fragments
- Edges: variant routes

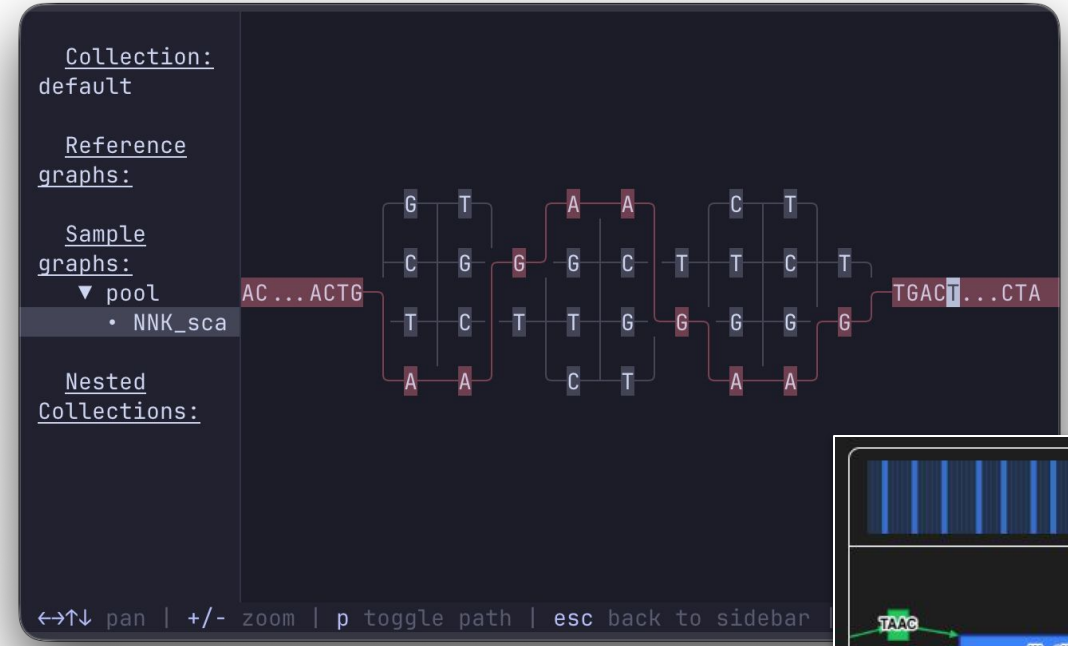


Graph representation of genetic sequences

- Fork: multiple variants exist at this locus
  - Mixed populations, polyploidy
  - Historical variants (changelog)
  - Screening library



“Schrödinger’s molecule”



Terminal User Interface

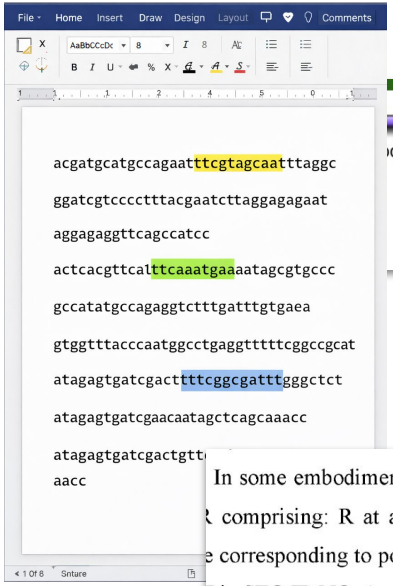
Tools to work with graphs: Visualization, subgraph extraction, stitching, …

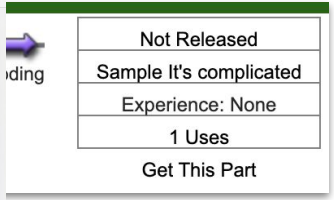
Web interface (genhub.bio)

Promoting collaborative engineering

- Support for common bioinformatics file formats
  - FASTA, VCF, GFA, GenBank
- Decentralized distribution via patch files
- Synchronize to remote repositories
  - file:// protocol
  - https:// to genhub.bio
- https://github.com/genhub-bio/gen

Then





In some embodiments, the one or more amino
R comprising: R at a residue corresponding to
e corresponding to position 354 in SEQ ID NO:
7 in SEQ ID NO: 1; or a combination thereof. In
rises one or more amino acid alterations selected
S299W, A238G, A134E, A134R, M389S, I48V,
thereof. In some embodiments, the engineered

Now