

Walking the talk: adopting and adapting sustainable scientific software development processes in a small biology lab.

Michael R. Crusoe¹

C. Titus Brown^{2,1*}

1 Microbiology and Molecular Genetics,

2 Computer Science and Engineering,

Michigan State University, East Lansing, MI, USA

* Corresponding author: ctb@msu.edu

April 2014

Abstract

The khmer software project implements both research and production functionality for large-scale nucleic-acid sequence analysis. The project is driven by a small lab with only one full-time developer (MRC), as well as several graduate students and a professor (CTB) who contribute regularly to research features. Here we describe our efforts to bring better design, testing, and more open development to the khmer software project (which has just released version 1.0).

1 Introduction

Computational tools for analyzing large volumes of DNA/RNA sequencing data have become increasingly necessary over the last decade. The growth of sequencing capacity and the associated expansion of scientific problems being studied with sequencing is driving the rapid development of many new tools, both for handling data on large scales and to address new and different biological problems.

The khmer software was born from a need to more scalably analyze short (20-30 character) words, or “k-mers”, in large DNA sequencing data sets. The use of k-mers in DNA sequence analysis is common because they can be easily hashed, counted, and compared within and between data sets. However, as data sets have grown in size, approaches to analyzing k-mers have fallen behind the memory and compute scaling curves. khmer provides several research and production functions: approximate k-mer counting using a CountMin Sketch [12], an implementation of a compressible k-mer connectivity graph [10], and a streaming lossy compression algorithm for large data sets [3].

We have developed the khmer software as an open source project since the beginning: the software is under the BSD license, and we use GitHub for development, code review, release tagging, and other development activities. We make a wide variety of tutorials and user

documentation available, as part of the khmer project itself and also as part of a range of workshops. Adoption of khmer is driven not only by its utility in addressing otherwise difficult or intractable problems, but also by CTB's blogging, research preprints and publications, and presentations. We now estimate that we have over 500 users of the khmer software itself, and the algorithms and approaches initially implemented in khmer have been adapted to and incorporated in several other software packages.

Our main challenge in developing khmer has been to build a stable and reliable software project while simultaneously supporting an energetic research program in bioinformatics. This has traditionally been hard for small scientific labs due to many factors including lack of expertise and lack of sustained funding. Below, we discuss our experience in navigating a course towards a sustainable small-lab software project.

2 Background

khmer grew out of specific analysis needs, and was developed primarily on startup funding and as part of a USDA grant. Its development has led to at least two additional grants including the NIH BIG DATA grant that now supports MRC [1]. Over its lifetime khmer has had 15 different contributors, with five currently active. The code consists of approximately 12.2k lines of C and C++ code, with scripts and tests written in Python (6.6k lines of code).

The software was initially written by CTB for other purposes during his graduate work at Caltech, and then extended so far as to be almost entirely rewritten for research in his faculty position at Michigan State University. By July of 2013, when MRC started, the software had its current level of functionality, but we faced a number of specific challenges.

- First, we had no formal development model: no code review, no formatting requirements, no continuous integration, and no API stability requirements. As a result we were constantly in a state of uncertainty about khmer's quality.
- Second, our developers have a variety of experience: some were expert computational biologists with little to no programming experience, while others were experienced open source software developers with little to no computational biology background. This meant that we could not confidently rely on good domain understanding *and* good software development hygiene from any one developer.
- Third, like many bioinformatics projects, khmer is both *research* and *production* software: our lab is constantly extending khmer in new directions, at the same time as we and others apply its existing functionality to pressing biology research problems. While managing regular change is a traditional challenge for software development on long-running projects, the problem was exacerbated here because long-term planning was impractical given the high rate of technical innovation in sequencing data generation.
- Fourth, khmer exists within an ecosystem of tools. khmer itself primarily acts as a filter for sequence data, which is generated in particular formats by upstream tools and is then consumed in those same formats by downstream tools. We had no systematic testing of khmer within its larger ecosystem, and generally had to be alerted to such problems by users.

Collectively these challenges made us believe that khmer software development was not sustainable: without significant investment in software engineering then either 1) research development would falter in the face of increasingly high maintenance demands, or 2) khmer's

stable functionality would start to deteriorate, or 3) both. To address these challenges, CTB secured three years of NIH funding through the 2012 BIG DATA competition, and hired a software developer who also had a biology education and bioinformatics experience, MRC.

3 Initial Evaluation

To guide our development of a rational software development process, we applied the Software Sustainability Institute’s Criteria-based assessment checklist [9] to the khmer project in September 2013 and shared the results with the community [6]. The summary from that report was grim: khmer met 19 of 44 (or 43%) of the SSI’s criteria for Usability, and 43 of 118 (or 36%) of the criteria for Sustainability & Maintainability, for an overall fulfillment of 62 of the 163 items, or 38%.

The low fulfillment of the SSI’s criteria was slightly embarrassing for the group for several reasons: CTB is a collaborator and co-author with SSI; quotes from him are featured in case study presentations [5]; he is cited as someone who is doing things the correct way [8]; and he regularly criticizes the field for poor software process. This is the point, however: because these goals were highly valued within the lab, and because the software filled a novel niche, CTB successfully argued for resources to address these issues [2]. Making significant progress towards these ends isn’t merely a matter of budgets and hiring: even with a full time hybrid software engineer/bioinformatician on the team it is not straightforward to prioritize infrastructure work, let alone navigate between the core research work, user support, community engagement, and collaborations.

4 Releasing version 1.0

On April 1st, 2014, we released khmer 1.0. While by no means a finished product, we believe we are on a much more sustainable development path as khmer now meets 69% of the Software Sustainability Institute’s checklist [7].

For version 1.0, we added continuous integration, semantic versioning, acceptance testing, development standards, code coverage analysis, explicit citation information, and code review, among other process alterations and features. Below, we discuss these in more detail.

4.1 Development standards and semantic versioning

We instituted a number of development standards, including coding styles and versioning requirements for backwards compatibility. Our goal was to have explicit written requirements that would inform new contributors of our expectations, whether they have significant prior programming experience or not.

Uniformity of coding styles helps maintain code readability and enables easier code review, so we chose a coding style standard for both C++ and Python. The specific choice for coding style was made somewhat arbitrarily, largely to avoid protracted bikeshedding discussions: the important goal was to have *some* coding standard. For C++, we chose the “One True Brace Style” of *astyle* for indentation and bracing. For Python, we settled on the default PEP8 standard, for which several checking and reformatting tools exist.

We also imposed a backwards compatibility requirement on our command line scripts. While we did not want to stabilize the Python or C++ API because we are actively changing khmer internals, we felt that our command line scripts were sufficiently stable to require no backwards-incompatible changes on the 1.0 series of releases.

We have therefore committed to *semantic versioning*[11] for the command line scripts that come with khmer. This imposes a three-tiered versioning system: for patch version number changes (khmer v1.0.x), only minor bug fixes and documentation updates are allowed; for minor version number changes (khmer v1.x), backwards compatibility of the command line scripts must be maintained; and, should we choose to break backwards compatibility, we would need to make a major version number change (khmer v2).

The importance of semantic versioning is that it allows developers, documentation writers, sysadmins, and package managers to predict the specific behavior from a range of versions, and to easily determine whether or not they should upgrade their installation. Of particular importance, pipeline developers and users can rely on stable behavior from minor releases. We expect this to make khmer a more reliable member of the sequencing analysis software ecosystem.

4.2 Continuous integration

Continuous integration ensures that automated tests are executed regularly on standard platforms. While developers are expected to commit code with no failing tests, often they do not have convenient access to all of the supported platforms and installation environments. Continuous integration frees individual developers from having to execute their tests manually across many environments by automating the entire process on commit. Our continuous integration system, built on top of Jenkins and running on a Rackspace donated Linux server and an internal Mac OS X machine, also runs style checkers and reports code coverage summaries.

The most important application of continuous integration for us has been automated checking of merge requests prior to code review or merge into the mainline. This automatically ensures a basic quality of committed code and also alerts developers to any platform incompatibilities before they merge.

4.3 Integrated code coverage analysis

Code coverage analysis is an important part of software development: statement coverage, or how many lines of code are executed in some way by unit and functional tests, can readily identify untested regions of code.¹ While khmer had several hundred tests by the time MRC started working with it, the tests were all at the Python level and we had no estimate of how well they covered the C++ code base.

Combined C++ and Python code coverage was instituted in October 2013 and we were pleasantly surprised to find that over 80% of the khmer codebase was executed in the tests. Since October we have increased the code coverage percentage to over 90%. This number is now calculated on every pull request (see below) and significant decreases are flagged as “unhealthy” in our continuous integration system.

4.4 Code contribution process and code review

While code review is an important part of ensuring that only “good” code and feature are included in a project, it is typically very time consuming to do systematic code reviews. In order to scale our development process to more contributors while enabling code review, we adopted the “GitHub Flow” model of code review [4]. In this model, changes are developed on an independent branch of code; this branch of code is linked to the main development

¹Note that while executed code is not guaranteed to be correct, code that is not executed by tests is certainly not tested, so high code coverage is a necessary but not sufficient condition for thorough testing.

repository via a “pull request”, which is an ongoing summary of changes together with free text discussion. When the developer feels that the changes are ready to be merged, they request a formal review, for which we have instituted a checklist; this checklist includes test coverage and coding style analysis, documentation review, and compatibility checking.

Our expectation is that this more formal but still lightweight development process will encourage contributions and also serve as a training and education process for less experienced developers. By making our developer contribution requirements explicit, we may also serve as a guide for other bioinformatics software projects.

4.5 Citation information

Scientific funding for software maintenance depends on demonstrating the scientific utility of software; this is typically done via citations. For both algorithms and software, citations demonstrate usage, utility, and impact. However, scientific software may contain multiple novel algorithms, and the software itself may be published separately from the proof of concept of the algorithms. For khmer, this is a serious concern: we have publications or preprints on three novel approaches implemented in khmer, and we are also continually updating the software itself. We also have a significant online presence. This demonstrably confuses users: we have observed citations of the incorrect paper for the algorithm being used, citations of our documentation, and (oddly enough) citations of khmer documentation hosted on other institutions’ Web sites.

To clarify and regularize citation practices, we added explicit citation guidelines in two places: first, in the CITATION file at the top of the distribution, and second, in the output from every script. We now ask that users cite not only the software itself (via a software paper), but also the algorithm papers relevant to the software features being used.

While we worry about appearing to be “citation greedy,” we also believe quite strongly that our ongoing efforts to maintain the software are a critical part of our research, and that the researchers and developers involved in that effort should be acknowledged appropriately in the scientific literature. This can really only be addressed by requiring citation of the relevant software paper, which will be updated for every significant version release with contributor names. At the same time, we also believe that our algorithm contributions are independently important and should be acknowledged by citations. Hence, the requirement that when our algorithms are used, the relevant algorithms paper should be cited.

4.6 Integration and acceptance testing

An ongoing concern for khmer is how well our software integrates with other packages. Because khmer primarily consumes the output of upstream software, and the output of khmer is then fed into downstream software, we need to take into account a larger software ecosystem. Unfortunately, there are few real data format standards in this area: the sequencing companies that generate the source data are notoriously quick to change their output formats in arbitrary ways, and developers of other packages may introduce format changes intentionally (through feature extension) or unintentionally (through bugs). Standardization itself is probably a futile approach: while we expect A, C, G, and T to remain the primary characters in DNA sequence representations, the formats for data uncertainty and annotation evolve with sequencing technology, which in turn is changing quickly.

We therefore have instituted *acceptance testing* to ensure that khmer works with at least some upstream and downstream software packages. Our acceptance tests for khmer 1.0 take a subset

of data through quality control, error trimming, digital normalization, and assembly; at the end we check that we obtain approximately the expected results, vice minor details that change with different versions of external software. We have been greatly aided in developing acceptance tests by our standard “protocols” for sequence analysis: our acceptance tests go through the first three parts of the Eel Pond mRNAseq protocol (<http://khmer-protocols.readthedocs.org/>).

Acceptance testing proved to be extremely important in the release process. Four different bugs having to do with installation and command-line parameter handling were discovered in the 48 hours before release; these bugs generally had to do with common command line cases that were not readily testable at the unit and functional level.

We are also maintaining our acceptance tests for Ubuntu 12.04, a Long Term Support version of Linux that will be supported through 2017. This should further decrease maintenance efforts for our acceptance tests.

5 Persistent Challenges in Research Software Development

In the long term, we expect to face three major challenges in continuing to develop khmer.

First, we need to secure continued funding for khmer software development. This will depend primarily on producing novel research, but a substantial part of our research is tied to khmer. If we can leverage our good software engineering practices to accelerate our own research while also providing value to the larger community – “better science through superior software” – then arguments for more funding will be much easier than if we simply develop khmer for others to use. This is less satisfying than getting funding for maintenance, but is a more plausible path forward than relying on maintenance grants.

Second, we must balance maintenance activities with novel research features. In the face of changing input data (due to instrument and experimental protocol changes), different expectations for output (bioinformaticians invent a new format every 5 minutes on average), competing algorithms with poor replicability, etc., we could spend 100% of our time on quality control without developing anything new. Maintenance could be a valuable community service but would not address as many student, postdoc, or faculty career incentives as doing new research. Equally, expanding our research alone would result in less reliable software. Much of our process is dedicated to walking the line between maintenance and novel research.

Third, we face many challenges in terms of recruiting software developers and researchers. Inevitably new lab members are undertrained in most of what we do, including testing, version control, good computational hygiene, data science, bioinformatics and/or the domain of biology. These are a lot of subjects to train new people in, and we have yet to establish an effective lab culture. On the converse side, of course, we expect lab graduates to be increasingly employable in both academia and biotech; moreover, the lab reputation of caring about good software has started to attract people with deeper training.

6 Concluding thoughts

While we are still at the early stages of the experiment, we believe we can reach some conclusions about which parts of our process have been most important. While these are anecdotes, most of our process is already standard in both industry and open source projects, so we would argue that our anecdotes bear out what is already known outside of scientific research.

First, we believe that version control and significant automated testing have both been incredibly important and are absolutely necessary for any sustained software development effort.

Without version control, having multiple developers work on the same project would have been effectively impossible: all our time would have been spent on coordination issues. Even with a single developer (CTB), khmer development benefited from version history and source code comparison across versions.

Without automated testing, we would almost certainly have hesitated to make many changes, for fear of introducing regressions; this is especially important given the variance in software engineering expertise. By insisting that new code have tests associated with it, we also ensured that other developers would avoid unintentionally breaking new code they were not yet familiar with.

Second, acceptance testing has proven quite valuable for 1.0. Prior to committing to a stable command-line API, acceptance testing would most likely have been a waste of time: maintenance effort would have been needed to keep the scripts and tutorials working well together. However, now that we have committed to a stable command-line API, if the acceptance tests break it will be a bug, so there should be little maintenance burden. By committing to an Ubuntu Long Term Support release for running the acceptance tests, we can further control our maintenance costs.

Third, as we expand our development team and encourage contributions from people external to our lab, automated ways of evaluating software quality become extremely useful. Here, continuous integration, style checks, and code coverage analysis are particularly important for maintaining project stability. A formal code review by an experienced developer is the enforcement mechanism that ensures that basic requirements are met.

One important caveat is that we don't yet know how well any of this is going to work! Our chief goals are to enable further research with khmer and maintain existing functionality, all while our developer base expands and/or turns over. We hope and believe that our approaches will let us do this, but we need a longer baseline of observations to find out.

Acknowledgments

MRC has been funded by AFRI Competitive Grant no. 2010-65205-20361 from the USDA NIFA and is now funded by the National Human Genome Research Institute of the National Institutes of Health under Award Number R01HG007513; both to C. Titus Brown. We thank Dr. Lex Nederbragt for helpful comments on early drafts.

References

- [1] C Titus Brown. Bigdata: Small: Da: Dcm: Low-memory streaming pre-filters for biological sequencing data. <http://www.ged.msu.edu/downloads/2012-bigdata-nsf.pdf>, 2012.
- [2] C. Titus Brown. The future of khmer (2013 version). <http://ivory.idyll.org/blog/the-future-of-khmer-2013-version.html>, 2013.
- [3] C. Titus Brown, Adina Howe, Qingpeng Zhang, Alexis B. Pyrkosz, and Timothy H. Brom. A reference-free algorithm for computational normalization of shotgun sequencing data. *arXiv preprint*, 03 2012.
- [4] Scott Chacon. Github flow. <http://scottchacon.com/2011/08/31/github-flow.html>, 2011.
- [5] Steve Crouch. Institute case studies: From consultancy projects to case studies. <http://www.software.ac.uk/attach/CaseStudies.pdf>, 2012.

- [6] Michael R. Crusoe. Criteria-based assessment of the khmer suite. <http://goo.gl/MZGGhc>, 2013.
- [7] Michael R. Crusoe. Criteria-based assessment of the khmer suite v1.0. <http://goo.gl/SCayk5>, 2014.
- [8] Ian Gent. The recomputation manifesto. <http://www.software.ac.uk/blog/2013-07-09-recomputation-manifesto>, 2013.
- [9] Mike Jackson, Steve Crouch, and Rob Baxter. Software evaluation guide. <http://www.software.ac.uk/resources/guides-everything/software-evaluation-guide>, 2013.
- [10] Jason Pell, Arend Hintze, Rosangela Canino-Koning, Adina Howe, James M Tiedje, and C Titus Brown. Scaling metagenome sequence assembly with probabilistic de bruijn graphs. *Proc Natl Acad Sci U S A*, 109(33):13272–7, Aug 2012.
- [11] Tom Preston-Werner. "semantic versioning 2.0.0". <http://semver.org/>, 2013.
- [12] Qingpeng Zhang, Jason Pell, Rosangela Canino-Koning, Adina Chuang Howe, and C. Titus Brown. These are not the k-mers you are looking for: efficient online k-mer counting using a probabilistic data structure. *arXiv preprint*, 09 2013.