From RNA folding to inverse folding:
a heuristic exploration

Der Fakultät für Mathematik und Informatik
der Universität Leipzig
eingereichte

D I S S E R T A T I O N

zur Erlangung des akademischen Grades

DOCTOR RERUM NATURALIUM
(Dr.rer.nat.)

im Fachgebiet

Informatik

vorgelegt

von Diplommathematiker **Nono Saha Cyrille Merleau**
geboren am 26-03-1992 in Bafoussam, Kamerun

Leipzig, den December 2021

Ohana means family.
Family means nobody gets left behind, or forgotten.

— Lilo & Stitch

Dedicated to my loving dad Micheal Saha.

ABSTRACT

TODEO: Write the abstract here.

https://plg.uwaterloo.ca/~migod/research/beckOOPSLA.html

ZUSAMMENFASSUNG

Kurze Zusammenfassung des Inhaltes in deutscher Sprache…

PUBLICATIONS

This might come in handy for PhD theses: some ideas and figures have appeared previously in the following publications:

This is just an early – and currently ugly – test!

Attention: This requires a separate run of `bibtex` for your `refsection`, e. g., `ClassicThesis1-blx` for this file. You might also use `biber` as the backend for `biblatex`. See also http://tex.stackexchange.com/questions/128196/problem-with-refsection.

We have seen that computer programming is an art,
because it applies accumulated knowledge to the world,
because it requires skill and ingenuity, and especially
because it produces objects of beauty.

— Donald E. Knuth [4]

ACKNOWLEDGMENTS

Put your acknowledgments here.

Many thanks to everybody who already sent me a postcard!

Regarding the typography and other help, many thanks go to Marco Kuhlmann, Philipp Lehman, Lothar Schlesier, Jim Young, Lorenzo Pantieri and Enrico Gregorio[1], Jörg Sommer, Joachim Köstler, Daniel Gottschlag, Denis Aydin, Paride Legovini, Steffen Prochnow, Nicolas Repp, Hinrich Harms, Roland Winkler, Jörg Weber, Henri Menke, Claus Lahiri, Clemens Niederberger, Stefano Bragaglia, Jörn Hees, Scott Lowe, Dave Howcroft, José M. Alcaide, David Carlisle, Ulrike Fischer, Hugues de Lassus, Csaba Hajdu, Dave Howcroft, and the whole LaTeX-community for support, ideas and some great software.

Regarding LyX: The LyX port was intially done by *Nicholas Mariette* in March 2009 and continued by *Ivo Pletikosić* in 2011. Thank you very much for your work and for the contributions to the original style.

---

1 Members of GuIT (Gruppo Italiano Utilizzatori di TeX e LaTeX)

CONTENTS

LIST OF FIGURES

LIST OF TABLES

LISTINGS

ACRONYMS

PREFACE

The preface will contain three paragraphs as follows:

A SHORT STORY ON THE INITIAL QUESTIONS, AND WHAT THIS THESIS IS FOCUSED ON.

CHRONOLOGY ON HOW WE HAVE ARRIVED THE MAIN QUESTION OF THIS THESIS.

THE RESEARCH QUESTION QUESTION WE ADDRESS IN THIS WORK

THE OUTLINE OF THE THESIS

Part I

INTRODUCTION

RNA WORLD

A short chapter intro here.

1.1 MACROMOLECULAR POLYMERS: FROM DNA TO RNA

A short story on how the attention has moved from DNA to RNA.
This section aim at:

- Defining DNA and stating its biological role

- History from DNA to RNAs

- How the covid19 has even amplified the attention on RNAs

In total, this should get you started in no time.

1.2 BIOCHEMISTRY OF RNA MOLECULES

Here we will provide a biochemical definition of RNA molecules.

- Define each nucleobase composing RNA.

- Define the base pairing biochemistry

- Introduce pseudoknot pairing biochemical concepts.

1.3 NON-CODING RNAS AND THEIR BIOLOGICAL IMPLICATIONS

This section may be included in the section 1.1. Nevertheless, this will provide a particular introduction to some non-coding RNAs and underlay their biological significances. e.g. Aptamers & Riboswitches, SELEX, etc...

1.4 FORMAL DEFINITIONS

the section aim at providing formal definitions on RNA sequences, structures, network, etc...used in this thesis.

Definition 1(RNA sequence) : More formally, an RNA molecule consists of an ordered sequence of nucleotides that can be represented as:

$$x = (x_1, ..., x_L) \ where \ x_i \in \{A, C, G, U\}$$

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x is often known as the primary structure of RNA.

Definition 2 (RNA pseudoknot-free secondary structure): For simplicity, a secondary structure of such sequence x is a list of base pairs (i,j) on x with the following constraints:

1. A nucleotide (sequence position) can only belong to a single pair,

2. No pseudoknots: No pairs (i,j) and (k,l) with $i < k < j < l$,

3. If (i,j) is a pair then $x_i x_j \in \{GC, CG, AU, UA, GU, UG\}$,

4. If (i,j) is a base pair, then $j - i > 3$.

Definition 3 (MFE secondary structure):
Definition 4 (Structure Ensemble):
Definition 5 (Secondary structure probability)
Definition (Secondary structure loop) :
Definition 6 (Base pair probability):
Definition 7 (Partition function of RNA) :
Definition 8 (Base pair probability matrix):
Definition 9 (Neutral set of RNA sequences) :
Definition 10 (Neutral Network):
Definition 11 (PPV) :
Definition 12 (FPV) :
Definition 13 (FFT) :
Definition 14 (Hamming Distance between two SS):
Definition 15 Ensemble defect (ED) [9]: Here, we use the ED as a second objective function for refinement after having at least one sequence that folds into the target in the current population. It is defined as follows:

$$
\begin{aligned}
ED(\phi, \sigma *) &= \sum_{\sigma \in \Gamma} p(\phi, \sigma) d(\sigma, \sigma *) \\
&= L - \sum_{1 < i,j < L} P_{i,j}(\phi) S_{i,j}(\sigma *)
\end{aligned}
\tag{1.1}
$$

where $P_{i,j}$ is the base pair probability matrix and $S(s)$ is the structure matrix with entries $S_{i,j} \in \{0, 1\}$. If the structure s contains pair $\{i, j\}$, then $S_{i,j}(s) = 1$ otherwise $S_{i,j}(s) = 0$.

Definition 16 Normalized Energy Distance (NED): the difference between the energy of a given sequence ϕ evaluated to fold into a target structure $\sigma *$ and the minimum free energy of the sequence in its structural ensemble Γ. The value is normalized over all the sequences in a given population P.

$$
NED(\phi, \sigma *) = [1 - \Delta E_{norm}(\phi, \sigma *)]^p \ \forall p > 1
\tag{1.2}
$$

where,

$$\Delta E_{norm}(\phi, \sigma*) = \frac{\Delta E(\phi, \sigma*)}{\sum_{\phi \in P} \Delta E(\phi, \sigma*)} \tag{1.3}$$

and,

$$\Delta E(\phi, \sigma*) = E(\phi, \sigma*) - \arg \min_{s \in \Gamma} E(\phi, s) \tag{1.4}$$

Definition 17 (Fitness landscape) :
Definition 18 (Local minima):
Definition 19 (Global minima):
Definition 20 (Lévy Flights):
Definition 21 (Local search):

RNA FOLDING

TODO: Provide here a short intro for the chapter

2.1 FROM RNA SEQUENCES TO RNA STRUCTURES

This section will be dedicated at describing the folding hierarchy of RNAs.

- Different ways of representing an RNA secondary structure.

- Provide an explanation on how the RNA sequences and secondary structures are related together. Neutrality by number of structures that can take a given sequence.

Examples: Another interesting measure in this context is the number of different RNA sequences that can fold into the a given secondary structure. This however requires some knowledge about the inverse folding problem which will be discussed in the next chapter....

2.2 STABILITY AND PREDICTION OF RNA SECONDARY STRUCTURES

Note: The content of this chapter is just some dummy text. It is not a real language.

State different ways to predict a stable secondary structure for a given target. e.g. computationally (In *silico*) and experimentally (In *vitro*)

- The decomposition of RNA secondary structure into loops

- Explain the thermodynamic stability of a secondary structure and how it's computed.

- State how the MFE structure is computed: (partition function (S. McCaskill. The equilibrium partition function and base pair binding probabilities for RNA secondary structure.; Probability etc.. Nussinov etc...),)

2.3 ENERGY LANDSCAPE AND RNA KINETICS

This section aim to defining what the RNA energy landscape is, and different ways of representing it.

The second part will be for:

Note: For example a pic of the energy landscape of the bistable RNA.

- the partition mechanism

- the kinetics of RNA

- a short state of art on the kinetic tools.

2.4   A LITERATURE REVIEW OF RNA FOLDING TOOLS.

This section describes in details some of the existing RNA folding tools (Static folding and dynamics):

2.4.1   *Exact MFE prediction methods*

- RNAfold

- ContraFold

- RNAStructure

- LinearFold

- pKiss

- RNAExplorer

- etc..

2.4.2   *Statical methods*

- Mxfold

- ContextFold

- etc...

2.4.3   *Heuristic methods*

- IPknot

- Hotknots

2.5   CONCLUSION

Here will be a short conclusion of the chapter:

3

RNA DESIGN

TODO: Here will be a short introduction to the chapter.

3.1 BIOLOGICAL MOTIVATION AND BIOTECHNOLOGICAL IMPLICATIONS

This aim to provide a biological motivation and the biotechnological implications of the RNA design

3.2 POSITIVE AND NEGATIVE DESIGN.

List of tasks to do

- Define the positive and negative design.

- Highlight the difference between the two types of designs.

- Provide a formal definition of the type of design on which this thesis is focused (RNA inverse folding).

3.3 OBJECTIVE FUNCTIONS PREVIOUSLY USED.

this section will provide most of the objective functions used in the RNA design

3.4 A REVIEW ON EXISTING INVERSE RNA FOLDING TOOLS.

3.4.1 *Pseudoknot-free RNA inverse folding tools*

- RNAinverse

- RNAPong

- SendRNA

- ERD (Evolutionary RNA Design) ERD or Evolutionary RNA Design (Esmaili-Taheri 2015) is a recent program, first developed in 2014 (Esmaili-Taheri 2014) and one year after, an updated version has been released. It starts by decomposing the target structure into structural components (generally called loops) and then, independently uses an evolutionary algorithm to minimize each corresponding sub-sequence energy to recombine the different fragments to form the designed sequence finally. The main lines

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of ERD are: Pool reconstruction: using a collection of RNA sequences (STRAN database) similar to the natural ones, a pool of sequence is constructed with respect to their length by successively finding the corresponding structure using ViennaRNA, decomposing the structure in sub-components, and finally the corresponding sub-sequences of the same length are gathered to form a pool. Hierarchical decomposition of the target structure into loops: using the idea that any secondary structure can be uniquely decomposed into its structural components (stems, hairpin loops, internal loops, bulge and multi-loops), ERD decomposes the target in the positions where multi-loops occur. Sequence initialisation: after decomposing the target structure in sub-components, for each sub-component, a random sub-sequence is chosen from the pool and the initial sequence is a combination of those sub-sequences. Evolutionary optimization of the sub-sequences: to improve the initial sequence, an evolutionary algorithm is performed on each sub-components, and the outcome sub-sequences are combined to form a newer sequence that will replace the initial one. Iteratively the evolutionary algorithm is performed on the updated sequence until the combined sequence folds into the target or in a failure case when the stopping condition is satisfied. Two evolutionary operators are implemented here, a mutation that consists of replacing a sub-sequence corresponding to a sub-component by a new random one from the pool with respect to the length, and a selection which consists of choosing from a population of 15 RNA sequences or sub-sequences, 3 best sequences with respect to their free energy and adding them to the best from the preview generation, 3 best ones with respect to the Hamming distance from the target are therefore chosen. The next-generation population is then obtained by generating for each of the three best sequences 5 new sequences.

- MODENA MODENA or Multi-objective Design of Nucleic Acids (Taneda 2011) is a multi-objective genetic algorithm that explores the approximate set of weak Pareto optimal solution in the space of two objective functions: one that measures the structure stability and another one that measures the similarities between the predicted secondary structure of the designed sequence and the target in order to the dominant solution. More precisely, let

- NEMO [5]

- SentRNA [6]

- antaRNA

- RNAinverse

- NUPACK

- RNAiFold

- IncaRNAtion

- INFO-RNA

- Frnakenstein

- RNAfbinv

- RNA-SSD

- DSS-Opt

- LeaRNA

3.4.2 *Pseudoknotted RNA inverse folding tools*

- Inv

- antaRNA

- MODENA

3.5 CONCLUSION

Provide here a short conclusion of the chapter.

4

EXPERIMENTAL SETUPS AND BENCHMARK DATA

This chapter aim to provide a detailed description of the benchmark methodology of folding and inverse folding tools presented in the previous chapters.

4.1 FOLDING TOOLS BENCHMARK

4.1.1 *Benchmark datasets*

Provide here the different datasets used to benchmark the folding tools and their descriptions.

- Data 1

- Data 2

- etc..

...or your supervisor might use the margins for some comments of her own while reading.

4.1.2 *Benchmark methodology*

For each entry in the above datasets we do....

- :

-

-

Options are enabled via `option=true`

4.2 INVERSE FOLDING TOOLS BENCHMARK

4.2.1 *Benchmark datasets*

To estimate our EA's performance, we use two different benchmark datasets and compare the results to several existing algorithms. The two datasets were recently used by the deep learning tool `SentRNA` [6] and most of the algorithms we mentioned earlier:

- The `non-EteRNA` dataset: a set of 63 experimentally synthesized targets that Garcia-Martin et al. [3] recently used to benchmark a set of ten inverse folding algorithms, which from our knowledge, is the most recent and comprehensive benchmark of current state-of-the-art methods. The dataset is collected from 3 sources: the first dataset called **dataset A** which contains 29 targets collected from

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Rfam and also used in [2, 7] and the second called **dataset B** is a collection of 24 targets used in [2] and added to that the 10 structures used in [6].

- The `Eterna100` dataset [**Eterna**] is available in two versions and both contain a set of 100 target structures extracted from the `EteRNA` puzzle game and classified by their degree of difficulty. The `Eterna100-V1` was initially designed using `ViennaRNA 1.8.5`, which relies on Turner1999 energy parameters [8]. Out of the 100 targets secondary structures, 19 turned out to be unsolvable using the recent version of `ViennaRNA` (Version 2.14). Subsequently, an `Eterna100-V2` [**Eterna**] was released in which the 19 targets were slightly modified to be solvable using `ViennaRNA 2.14`.

- The `PseudoBase++` is a set of 265 pseudoknotted RNA structures used to benchmark `Modena`. It was initially 304 RNA secondary structures, but we excluded 37 because they had non-canonical base pairs. We then grouped the structures into four pseudoknot motifs (Figure **??**): 209 hairpin pseudoknots (H), 29 bulge pseudoknots (B), 8 complex hairpin pseudoknots (cH) and 4 kissing hairpin pseudoknots (K).

4.2.2 *Benchmark methodology*

Options are enabled via `option=true`

For each entry in the above datasets we do....

- :

-

-

4.3 CONCLUSION

This section will provide a short conclusion for this chapter as well

OUTLINE

This bundle for LATEX has two goals:

1. Provide students with an easy-to-use template for their Master's or PhD thesis. (Though it might also be used by other types of authors for reports, books, etc.)

2. Provide a classic, high-quality typographic style that is inspired by Bringhurst's "*The Elements of Typographic Style*" [1].

A Classic Thesis Style classicthesis v4.6

The bundle is configured to run with a *full* MiKTEX or TEXLive[1] installation right away and, therefore, it uses only freely available fonts. (Minion fans can easily adjust the style to their needs.)

People interested only in the nice style and not the whole bundle can now use the style stand-alone via the file `classicthesis.sty`. This works now also with "plain" LATEX.

As of version 3.0, `classicthesis` can also be easily used with LYX[2] thanks to Nicholas Mariette and Ivo Pletikosić. The LYX version of this manual will contain more information on the details.

This should enable anyone with a basic knowledge of LATEX 2_ε or LYX to produce beautiful documents without too much effort. In the end, this is my overall goal: more beautiful documents, especially theses, as I am tired of seeing so many ugly ones.

The whole template and the used style is released under the GNU General Public License.

If you like the style then I would appreciate a postcard:

André Miede
Detmolder Straße 32
31737 Rinteln
Germany

The postcards I received so far are available at:

http://postcards.miede.de

A well-balanced line width improves the legibility of the text. That's what typography is all about, right?

So far, many theses, some books, and several other publications have been typeset successfully with it. If you are interested in some typographic details behind it, enjoy Robert Bringhurst's wonderful book.

---

1 See the file `LISTOFFILES` for needed packages. Furthermore, `classicthesis` works with most other distributions and, thus, with most systems LATEX is available for.

2 http://www.lyx.org

[January 5, 2022 at 23:43 – classicthesis v4.6]

IMPORTANT NOTE: Some things of this style might look unusual at first glance, many people feel so in the beginning. However, all things are intentionally designed to be as they are, especially these:

- No bold fonts are used. Italics or spaced small caps do the job quite well.

- The size of the text body is intentionally shaped like it is. It supports both legibility and allows a reasonable amount of information to be on a page. And, no: the lines are not too short.

- The tables intentionally do not use vertical or double rules. See the documentation for the `booktabs` package for a nice discussion of this topic.[3]

- And last but not least, to provide the reader with a way easier access to page numbers in the table of contents, the page numbers are right behind the titles. Yes, they are *not* neatly aligned at the right side and they are *not* connected with dots that help the eye to bridge a distance that is not necessary. If you are still not convinced: is your reader interested in the page number or does she want to sum the numbers up?

Therefore, please do not break the beauty of the style by changing these things unless you really know what you are doing! Please.

YET ANOTHER IMPORTANT NOTE: Since `classicthesis`' first release in 2006, many things have changed in the LaTeX world. Trying to keep up-to-date, `classicthesis` grew and evolved into many directions, trying to stay (some kind of) stable and be compatible with its port to LyX. However, there are still many remains from older times in the code, many dirty workarounds here and there, and several other things I am absolutely not proud of (for example my unwise combination of KOMA and `titlesec` etc.).

An outlook into the future of `classicthesis`.

Currently, I am looking into how to completely re-design and re-implement `classicthesis` making it easier to maintain and to use. As a general idea, `classicthesis.sty` should be developed and distributed separately from the template bundle itself. Excellent spin-offs such as `arsclassica` could also be integrated (with permission by their authors) as format configurations. Also, current trends of `microtype`, `fontspec`, etc. should be included as well. As I am not really into deep LaTeX programming, I will reach out to the LaTeX community for their expertise and help.

5.1   ORGANIZATION

You can use these margins for summaries of the text body...

A very important factor for successful thesis writing is the organization of the material. This template suggests a structure as the following:

---

[3] To be found online at http://mirror.ctan.org/macros/latex/contrib/booktabs/.

- `Chapters/` is where all the "real" content goes in separate files such as `Chapter01.tex` etc.

- `FrontBackMatter/` is where all the stuff goes that surrounds the "real" content, such as the acknowledgments, dedication, etc.

- `gfx/` is where you put all the graphics you use in the thesis. Maybe they should be organized into subfolders depending on the chapter they are used in, if you have a lot of graphics.

- `Bibliography.bib`: the BibTeX database to organize all the references you might want to cite.

- `classicthesis.sty`: the style definition to get this awesome look and feel. Does not only work with this thesis template but also on its own (see folder `Examples`). Bonus: works with both LaTeX and pdfLaTeX...and LyX. Great tool and it's free!

- `ClassicThesis.tex`: the main file of your thesis where all gets bundled together.

- `classicthesis-config.tex`: a central place to load all nifty packages that are used.

  Make your changes and adjustments here. This means that you specify here the options you want to load `classicthesis.sty` with. You also adjust the title of your thesis, your name, and all similar information here. Refer to Section 8.3 for more information.

  This had to change as of version 3.0 in order to enable an easy transition from the "basic" style to LyX.

In total, this should get you started in no time.

5.2 STYLE OPTIONS

There are a couple of options for `classicthesis.sty` that allow for a bit of freedom concerning the layout:

- General:
  - `drafting`: prints the date and time at the bottom of each page, so you always know which version you are dealing with. Might come in handy not to give your Prof. that old draft.

- Parts and Chapters:
  - `parts`: use this option if you *use* Part divisions in your document. This is necessary to get the spacing of the Table of Contents right. (Cannot be used together with `nochapters`.)
  - `linedheaders`: changes the look of the chapter headings a bit by adding a horizontal line above the chapter title. The chapter number will also be moved to the top of the page, above the chapter title.

- Typography:
  - `style`: this offers a comfortable way of changing the look and feel easily. Default style is `classicthesis`.

    As a new feature, Lorenzo Pantieri's `arsclassica` is available as well. As Lorenzo's package is discontinued and with his permission, `classicthesis-arsclassica.sty` is now part of `classicthesis` and will be maintained here.
  - `palatino`: Hermann Zapf's classic font is the free standard font for this style. Robert Bringhurst's book uses Adobe's commercial font Minion Pro. However, there are other free alternatives also available. Deactivate this option for loading such alternatives and see `classicthesis-config.tex` for some suggestions.
  - `eulerchapternumbers`: use figures from Hermann Zapf's Euler math font for the chapter numbers. By default, old style figures from the Palatino font are used.
  - `beramono`: loads Bera Mono as typewriter font. (Default setting is using the standard CM typewriter font.)
  - `eulermath`: loads the awesome Euler fonts for math. Palatino is used as default font.

- Table of Contents:
  - `tocaligned`: aligns the whole table of contents on the left side. Some people like that, some don't.

- **dottedtoc**: sets pagenumbers flushed right in the table of contents.

- **manychapters**: if you need more than nine chapters for your document, you might not be happy with the spacing between the chapter number and the chapter title in the Table of Contents. This option allows for additional space in this context. However, it does not look as "perfect" if you use \parts for structuring your document.

- Floats:
  - **floatperchapter**: activates numbering per chapter for all floats such as figures, tables, and listings (if used).

- Tweaking colors and fonts – please use this with great care!:
  - **\ct@altfont**: comfortable hook to alter the basic look and feel of everything that uses spaced caps or spaced small caps. For example, for arsclassica we used \renewcommand*{\ct@altfont}{\sffamily}. Coloring is also possible this way.
  - **CTsemi**: Change the semi gray color used, e. g., for the chapter number. Default is: \definecolor{CTsemi}{gray}{0.55}
  - **CTtitle**: Change the red color used, e. g., for the title. Default is: \definecolor{CTtitle}{named}{Maroon}

Furthermore, pre-defined margins for different paper sizes are available, e. g., a4paper, a5paper, b5paper, and letterpaper. These are based on your chosen option of \documentclass.

The best way to figure these options out is to try the different possibilities and see what you and your supervisor like best.

In order to make things easier, classicthesis-config.tex contains some useful commands that might help you.

5.3 CUSTOMIZATION

This section will show you some hints how to adapt classicthesis to your needs.

The file classicthesis.sty contains the core functionality of the style and in most cases will be left intact, whereas the file classicthesis-config.tex is used for some common user customizations.

The first customization you are about to make is to alter the document title, author name, and other thesis details. In order to do this, replace the data in the following lines of classicthesis-config.tex:

Modifications in classicthesis-config.tex

```
% ********************************************
% 2. Personal data and user ad-hoc commands
% ********************************************
\newcommand{\myTitle}{A Classic Thesis Style}
```

```
\newcommand{\mySubtitle}{An Homage to...}
```

Further customization can be made in `classicthesis-config.tex` by choosing the options to `classicthesis.sty` (see Section 8.2) in a line that looks like this:

```
\PassOptionsToPackage{
  drafting=true,
  tocaligned=false,
  dottedtoc=false,
  eulerchapternumbers=true,
  linedheaders=false,
  floatperchapter=true,
  eulermath=false,
  beramono=true,
  palatino=true,
  style=classicthesis
}{classicthesis}
```

Many other customizations in `classicthesis-config.tex` are possible, but you should be careful making changes there, since some changes could cause errors.

5.4   ISSUES

This section will list some information about problems using `classicthesis` in general or using it with other packages.

Beta versions of `classicthesis` can be found at Bitbucket:

https://bitbucket.org/amiede/classicthesis/

There, you can also post serious bugs and problems you encounter.

5.5   FUTURE WORK

So far, this is a quite stable version that served a couple of people well during their thesis time. However, some things are still not as they should be. Proper documentation in the standard format is still missing. In the long run, the style should probably be published separately, with the template bundle being only an application of the style. Alas, there is no time for that at the moment...it could be a nice task for a small group of LATEXnicians.

Please do not send me email with questions concerning LATEX or the template, as I do not have time for an answer. But if you have comments, suggestions, or improvements for the style or the template in general, do not hesitate to write them on that postcard of yours.

5.6 BEYOND A THESIS

The layout of `classicthesis.sty` can be easily used without the framework of this template. A few examples where it was used to typeset an article, a book or a curriculum vitae can be found in the folder `Examples`. The examples have been tested with `latex` and `pdflatex` and are easy to compile. To encourage you even more, PDFs built from the sources can be found in the same folder.

5.7 LICENSE

GNU GENERAL PUBLIC LICENSE: This program is free software; you can redistribute it and/or modify it under the terms of the GNU General Public License as published by the Free Software Foundation; either version 2 of the License, or (at your option) any later version.

This program is distributed in the hope that it will be useful, but *without any warranty*; without even the implied warranty of *merchantability* or *fitness for a particular purpose*. See the GNU General Public License for more details.

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CLASSICTHESIS AUTHORS' NOTE: There have been some discussions about the GPL's implications on using `classicthesis` for theses etc. Details can be found here:

https://bitbucket.org/amiede/classicthesis/issues/123/

We chose (and currently stick with) the GPL because we would not like to compete with proprietary modified versions of our own work. However, the whole template is free as free beer and free speech. We will not demand the sources for theses, books, CVs, etc. that were created using `classicthesis`.

Postcards are still highly appreciated.

Part II

RESULTS AND EVALUATIONS

You can put some informational part preamble text here. Illo principalmente su nos. Non message *occidental* angloromanic da. Debitas effortio simplificate sia se, auxiliar summarios da que, se avantiate publicationes via. Pan in terra summarios, capital interlingua se que. Al via multo esser specimen, campo responder que da. Le usate medical addresses pro, europa origine sanctificate nos se.

RAFFT: EFFICIENT PREDICTION OF FAST-FOLDING PATHWAYS OF RNAS

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If you like the style then I would appreciate a postcard:

<div align="center">

André Miede
Detmolder Straße 32
31737 Rinteln
Germany

</div>

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A Classic Thesis Style classicthesis v4.6

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27

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6.1 ORGANIZATION

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- `Bibliography.bib`: the BibTeX database to organize all the references you might want to cite.

- `classicthesis.sty`: the style definition to get this awesome look and feel. Does not only work with this thesis template but also on its own (see folder `Examples`). Bonus: works with both LaTeX and pdfLaTeX...and LyX. Great tool and it's free!

- `ClassicThesis.tex`: the main file of your thesis where all gets bundled together.

- `classicthesis-config.tex`: a central place to load all nifty packages that are used.

  Make your changes and adjustments here. This means that you specify here the options you want to load `classicthesis.sty` with. You also adjust the title of your thesis, your name, and all similar information here. Refer to Section 8.3 for more information.

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- Tweaking colors and fonts – please use this with great care!:
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% 2. Personal data and user ad-hoc commands
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This section will list some information about problems using `classicthesis` in general or using it with other packages.

Beta versions of `classicthesis` can be found at Bitbucket:

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There, you can also post serious bugs and problems you encounter.

6.5   FUTURE WORK

So far, this is a quite stable version that served a couple of people well during their thesis time. However, some things are still not as they should be. Proper documentation in the standard format is still missing. In the long run, the style should probably be published separately, with the template bundle being only an application of the style. Alas, there is no time for that at the moment...it could be a nice task for a small group of LATEXnicians.

Please do not send me email with questions concerning LATEX or the template, as I do not have time for an answer. But if you have comments, suggestions, or improvements for the style or the template in general, do not hesitate to write them on that postcard of yours.

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The layout of `classicthesis.sty` can be easily used without the framework of this template. A few examples where it was used to typeset an article, a book or a curriculum vitae can be found in the folder `Examples`. The examples have been tested with `latex` and `pdflatex` and are easy to compile. To encourage you even more, PDFs built from the sources can be found in the same folder.

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You should have received a copy of the GNU General Public License along with this program; see the file `COPYING`. If not, write to the Free Software Foundation, Inc., 59 Temple Place - Suite 330, Boston, MA 02111-1307, USA.

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We chose (and currently stick with) the GPL because we would not like to compete with proprietary modified versions of our own work. However, the whole template is free as free beer and free speech. We will not demand the sources for theses, books, CVs, etc. that were created using `classicthesis`.

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7

ARNAQUE: AN EVOLUTIONARY ALGORITHM FOR INVERSE FOLDING INSPIRED BY LÉVY FLIGHTS.

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Part III

DISCUSSION AND PERSPECTIVES

8

RAFFT AND CONTINUOUS TRANSITION IN EVOLUTION

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...or your supervisor might use the margins for some comments of her own while reading.

- General:
    - `drafting`: prints the date and time at the bottom of each page, so you always know which version you are dealing with. Might come in handy not to give your Prof. that old draft.

- Parts and Chapters:
    - `parts`: use this option if you *use* Part divisions in your document. This is necessary to get the spacing of the Table of Contents right. (Cannot be used together with `nochapters`.)
    - `linedheaders`: changes the look of the chapter headings a bit by adding a horizontal line above the chapter title. The chapter number will also be moved to the top of the page, above the chapter title.

- Typography:
    - `style`: this offers a comfortable way of changing the look and feel easily. Default style is `classicthesis`.

        As a new feature, Lorenzo Pantieri's `arsclassica` is available as well. As Lorenzo's package is discontinued and with his permission, `classicthesis-arsclassica.sty` is now part of `classicthesis` and will be maintained here.
    - `palatino`: Hermann Zapf's classic font is the free standard font for this style. Robert Bringhurst's book uses Adobe's commercial font Minion Pro. However, there are other free alternatives also available. Deactivate this option for loading such alternatives and see `classicthesis-config.tex` for some suggestions.
    - `eulerchapternumbers`: use figures from Hermann Zapf's Euler math font for the chapter numbers. By default, old style figures from the Palatino font are used.
    - `beramono`: loads Bera Mono as typewriter font. (Default setting is using the standard CM typewriter font.)
    - `eulermath`: loads the awesome Euler fonts for math. Palatino is used as default font.

Options are enabled via `option=true`

- Table of Contents:
    - `tocaligned`: aligns the whole table of contents on the left side. Some people like that, some don't.

    – `dottedtoc`: sets pagenumbers flushed right in the table of contents.

    – `manychapters`: if you need more than nine chapters for your document, you might not be happy with the spacing between the chapter number and the chapter title in the Table of Contents. This option allows for additional space in this context. However, it does not look as "perfect" if you use `\parts` for structuring your document.

- Floats:

    – `floatperchapter`: activates numbering per chapter for all floats such as figures, tables, and listings (if used).

- Tweaking colors and fonts – please use this with great care!:

    – `\ct@altfont`: comfortable hook to alter the basic look and feel of everything that uses spaced caps or spaced small caps. For example, for `arsclassica` we used `\renewcommand*{\ct@altfont}{\sffamily}`. Coloring is also possible this way.

    – `CTsemi`: Change the semi gray color used, e. g., for the chapter number. Default is: `\definecolor{CTsemi}{gray}{0.55}`

    – `CTtitle`: Change the red color used, e. g., for the title. Default is: `\definecolor{CTtitle}{named}{Maroon}`

Furthermore, pre-defined margins for different paper sizes are available, e. g., `a4paper`, `a5paper`, `b5paper`, and `letterpaper`. These are based on your chosen option of `\documentclass`.

The best way to figure these options out is to try the different possibilities and see what you and your supervisor like best.

In order to make things easier, `classicthesis-config.tex` contains some useful commands that might help you.

8.3 CUSTOMIZATION

This section will show you some hints how to adapt `classicthesis` to your needs.

The file `classicthesis.sty` contains the core functionality of the style and in most cases will be left intact, whereas the file `classicthesis-config.tex` is used for some common user customizations.

The first customization you are about to make is to alter the document title, author name, and other thesis details. In order to do this, replace the data in the following lines of `classicthesis-config.tex`:

Modifications in classicthesis-config.tex

```
% **********************************************
% 2. Personal data and user ad-hoc commands
% **********************************************
\newcommand{\myTitle}{A Classic Thesis Style}
```

```
\newcommand{\mySubtitle}{An Homage to...}
```

Further customization can be made in `classicthesis-config.tex` by choosing the options to `classicthesis.sty` (see Section 8.2) in a line that looks like this:

```
\PassOptionsToPackage{
  drafting=true,
  tocaligned=false,
  dottedtoc=false,
  eulerchapternumbers=true,
  linedheaders=false,
  floatperchapter=true,
  eulermath=false,
  beramono=true,
  palatino=true,
  style=classicthesis
}{classicthesis}
```

Many other customizations in `classicthesis-config.tex` are possible, but you should be careful making changes there, since some changes could cause errors.

8.4 ISSUES

This section will list some information about problems using `classicthesis` in general or using it with other packages.

Beta versions of `classicthesis` can be found at Bitbucket:

https://bitbucket.org/amiede/classicthesis/

There, you can also post serious bugs and problems you encounter.

8.5 FUTURE WORK

So far, this is a quite stable version that served a couple of people well during their thesis time. However, some things are still not as they should be. Proper documentation in the standard format is still missing. In the long run, the style should probably be published separately, with the template bundle being only an application of the style. Alas, there is no time for that at the moment...it could be a nice task for a small group of LaTeXnicians.

Please do not send me email with questions concerning LaTeX or the template, as I do not have time for an answer. But if you have comments, suggestions, or improvements for the style or the template in general, do not hesitate to write them on that postcard of yours.

8.6 BEYOND A THESIS

The layout of `classicthesis.sty` can be easily used without the framework of this template. A few examples where it was used to typeset an article, a book or a curriculum vitae can be found in the folder `Examples`. The examples have been tested with `latex` and `pdflatex` and are easy to compile. To encourage you even more, PDFs built from the sources can be found in the same folder.

8.7 LICENSE

GNU GENERAL PUBLIC LICENSE: This program is free software; you can redistribute it and/or modify it under the terms of the GNU General Public License as published by the Free Software Foundation; either version 2 of the License, or (at your option) any later version.

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You should have received a copy of the GNU General Public License along with this program; see the file `COPYING`. If not, write to the Free Software Foundation, Inc., 59 Temple Place - Suite 330, Boston, MA 02111-1307, USA.

CLASSICTHESIS AUTHORS' NOTE: There have been some discussions about the GPL's implications on using `classicthesis` for theses etc. Details can be found here:

https://bitbucket.org/amiede/classicthesis/issues/123/

We chose (and currently stick with) the GPL because we would not like to compete with proprietary modified versions of our own work. However, the whole template is free as free beer and free speech. We will not demand the sources for theses, books, CVs, etc. that were created using `classicthesis`.

Postcards are still highly appreciated.

Part IV

APPENDIX

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DECLARATION

Put your declaration here.

Saarbrücken, June 2018

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