METHOD ARTICLE

Developing sustainable software solutions for bioinformatics by the “Butterfly” paradigm [version 2; peer review: 2 approved]

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Abstract
Software design and sustainable software engineering are essential for the long-term development of bioinformatics software. Typical challenges in an academic environment are short-term contracts, island solutions, pragmatic approaches and loose documentation. Upcoming new challenges are big data, complex data sets, software compatibility and rapid changes in data representation. Our approach to cope with these challenges consists of iterative intertwined cycles of development (“Butterfly” paradigm) for key steps in scientific software engineering. User feedback is valued as well as software planning in a sustainable and interoperable way. Tool usage should be easy and intuitive. A middleware supports a user-friendly Graphical User Interface (GUI) as well as a database/tool development independently. We validated the approach of our own software development and compared the different design paradigms in various software solutions.
Introduction

Typical challenges in bioinformatics in an academic environment include “ad hoc” programming. No maintenance is really possible as scientists such as PhD students and post-doctoral scholars leave after their thesis is completed or after their post-doc contract. These scientists may also have no formal computer science training, and often there is no structured programming and solutions might not be compatible with each other. Furthermore, in an academic environment there are a number of inherent pressures to develop pragmatic and fast (“quick and dirty”) software solutions.

In addition, there are some new and “modern” challenges, which become more and more pressing simply as the technology progresses: big data1, the wave of “omics” data to process, and the problem of interoperability of software tools2. Well-known recent solutions for this challenge are Taverna3 and Galaxy67. The latter in particular is well suited to dealing with large quantities of data such as new large-scale sequencing data.

Another issue is that the data should be accessible, with uniform syntax and rich semantics for integration. Furthermore, data schemes are prone for change due to rapid advances in the field, so a schema-free representation of data is increasingly important (for scientific data). The UniProt Consortium8 for instance has recently shifted from the use of relational databases to the semantic web for flexible data management.

To counter these older and general as well as new challenges, we have now developed a solution of iterative and intertwined development cycles (Butterfly model), which improves the typical aspects of long-term sustainability and maintenance. Furthermore, it features detailed user-requirement analysis, good graphical and simple user interfaces (optimized human-computer interface, HCI) and intuitive software use that also exploits natural language processing. Our model tackles current challenges: first, the interoperability of the software takes into account middleware solutions, so that both database and user interfaces can be used flexibly. Second, the Butterfly approach improves the meticulous database engineering required to build large-scale and “omics” databases.

The Butterfly development cycle is different from previous approaches8–12. It requires some additional time investment at the start for design and implementation, but this pays off later. The Butterfly model worked well in our hands regarding the above challenges (section: Real time examples using Butterfly). In the following we confirm this by describing concrete software development.

The basic concept is really simple: plan ahead, back-check the critical development steps by a separate sub-cycle and talk with the user. It is important to spend more time on requirement analysis, as well as to invest well in interoperability and maintenance. We do not claim that these problems have not been recognized before nor that no alternative solutions for this are available12–4, but we are confident that with our approach it will be possible to obtain particularly well optimized and high quality bioinformatics software solutions in an academic environment. The initial time investment in the Butterfly paradigm helps to save time later due to the interoperability and easy maintenance of the software solutions achieved.

This paper is organized as follows: this section sets the stage for our agenda (section 1); Current Software Engineering and Development (section 2) highlights the modular phases of software development processes and compares several typical software strategies highlighting the novelty of our approach; next, the Butterfly work flow is explained (section 3), and software examples using the Butterfly approach (section 4) validate the Butterfly design principle by providing concrete examples of software projects from own work. Moreover we discuss some bioinformatics tools based on their type, methodology and usage.

Current Software Engineering and Development

Software Engineering (SE)13 is one of the most recognized fields in computer science as it matures and expedites the processes of software development. In particular, it allows a focus on the life cycle of software and sustainable development as an improvement to pragmatic short-lived implementations. SE has introduced many process improvement models and techniques10–12, and Software Development Life Cycle (SDLC) models13, with some variabilities14 and commonalities15–19. In general, depending upon the observed commonalities, we state “Software Engineering is an integrated, cyclic and product line combination of following independent modular approaches: requirements engineering10–22, design modeling23–25,27–35 programming, testing and deployment”.

The five modular SE approaches remain the same when it comes to the software engineering of the scientific software solution development (Figure 1). However, in contrast to a pragmatic and maybe traditional software application development in an academic setting (Figure 2), a major change is the inconsistency in all phases of the SDLC. In the requirement engineering phase (Figure 2; traditional software solution development), all requirements should be provided before the start of design. This is not the case when dealing with most of the scientific software applications, and the requirements continuously change with the passage of time (we have proposed an updated SSE SDLC Model, Figure 1; scientific software solution development). Ultimately, this complicates the process of analysis and filters out functionalities. Programming structures become complex (Figure 1), as the possibilities of error proneness (both logical and syntax errors) increase due to the continuous increment of variabilities in the pre-processed source code19–45.

Testing of integrated and individual modules becomes time consuming (Figure 1), as new test cases have to be continuously rewritten and their application often leads to ‘ripple effects’22: these are unidentified logical or syntax errors in the system which arise while
Scientific Software Engineering (SSE). SSE integrates and combines in a development cycle the following independent main modular approaches: requirements engineering, design modeling, programming, testing and deployment. Each approach consists of its own sub-modular, integrated and cyclic combination of internal phases: requirement engineering consists of specification, functionals, non-functionals, and analysis; design modeling consists of use cases, system flows, data flow and source code; programming consists of languages, tools and technologies, development, and debugging; testing consists of test cases, modular, integrated and quality; finally, deployment consists of installation, configuration, training, feedback. Iterative cycles lead to continuous improvement. Achievements translate the goals in good software.

Traditional Software Development consisting of integrated and cyclic combination of the following independent modular approaches: requirements engineering, design modeling, programming, testing and deployment.
fixing the errors\textsuperscript{36,37}. Depending upon the nature of the system, many approaches have been proposed to improve software quality control processes\textsuperscript{38–50} which improve standard software development and are important in scientific software quality assurance and improvement. Furthermore if the system keeps changing and is inconsistent, then the deployment procedures can also be complex and time consuming, especially for large applications with multiple interfaces and controls providing numerous individual and integrated functionalities.

To further help (SSE, non-computer scientist Bioinformaticians etc.) in expediting the processes of adopting the concepts of SDLC, we provide a tabular comparison between different SDLCs, based on their commonalities and variabilities (Table 1). This comparison

<table>
<thead>
<tr>
<th>Features/SDLCs</th>
<th>Waterfall</th>
<th>V</th>
<th>Spiral</th>
<th>Extreme Prog.</th>
<th>Iterative</th>
<th>Rapid Prototype</th>
<th>Evolutionary</th>
<th>Agile Dev.</th>
<th>Code &amp; Fix</th>
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We applied these measures to nine different software development life cycle models: Waterfall Model, V-Model, Spiral Model, Iterative and Incremental Model, Rapid Prototype Model, Agile Development Model, Extreme Programming Model, Evolutionary Model, and Code and Fix Model. From this comparative analysis we conclude that there is no such one specific SDLC which can be helpful in all required phases of scientific software solution development, but some which might be more useful: Spiral, Waterfall and V-Model. Moreover the SDLCs famous for the quick development (Rapid Prototype Model, Agile Development Model, Extreme Programming Model, Evolutionary Model, Code and Fix Model) are very helpful in script writing and fast prototype production; however full sustainability remains nevertheless a challenge.

As this is a general and open comparison, depending on the nature of the scientific software application, one can further analyze and pick that which suits best. Furthermore, we considered only the typical effort and strengths for each of these software development paradigms. A meticulous developer can of course take special care and spend more time on any of the features not typically covered by the software paradigm he follows, and turn the “no” for this feature into a “yes” simply by this additional effort during SDLC (for instance, regarding agile programming – for that matter, extreme programming can also be considered as a type of agile development). The goal for our “Butterfly” paradigm is a SDLC paradigm that fulfils all of the features regarding life cycle management of the resulting software.

Butterfly in scientific academia

If we search for “bioinformatics tools” over the web, thousands of entries can be found at one hit. But how many of those are fully designed, developed and tested solutions, used and maintained for a number of years and still in functional use?

At the beginning of a software project in academia, scientific solution development seems very interesting, fascinating and exciting. But with the passage of time, when the levels of complexities increase (due not only to the lack of developmental skills but also to the unavailability of proper designs), the work starts becoming tedious and unfruitful. This causes a lack of interest in software solution development and leads to a preference for wrapping up the work with a working script or small application, which can be published later on.

Here we propose a new science-oriented model (Figure 3), which can help the scientific software solution developers as well as the scientists/end users by generalizing the use of major developmental aspects correlating to the important scientific needs of the target system. The name of our new model is “Butterfly”.

In accordance with the name of the model, the “Butterfly” represents sustainable and continuous improvements from goals to achievement as the central backbone of development. For larger projects this is further improved by using middleware between user interfaces and accessing the various data and databases involved. This also has the advantage that natural language processing needs to be implemented only once in the middleware and all the other modules have access to it. Finally, the backbone arrangement with a powerful middleware as well as all development elsewhere in the “Butterfly” stresses the interoperability of the software. It is developed by using well-defined and compatible output formats. Furthermore, below the middleware, well adapted, interoperable data schemes boost sustainable development of database structures, including efforts for scheme-less databases and other semantic web developments. The four continuously moving wings (Figure 3) represent the change in the requirements. The upper left wing of the model represents the scientific software engineering principles, and the lower left wing represents the HCI. The upper right wing represents the implementation of the specific methodology (focused on lowering the risk of development ripples) and the lower right wing represents the target scientific application producing the required results.

Scientific Software Engineering and Scientific Methodology

SSE is the most important phase of the Butterfly model, which promotes the usage of any earlier mentioned SDLC involving requirements analysis, design modeling, programming and testing of the scientific software solution. It correlates with the phase Scientific Methodology: the finalized functional requirements are based on the desired system output, and the system should be modeled according to the defined logics and mathematics (individual as well as the sequence of algorithms if there are more than one). The most suitable, advanced, recent, economically affordable, transferable, flexible and reliable developmental technologies should be chosen considering the use and availability of the data (large, small, complex, shared via intranet or internet).

Meanwhile, programming and processing of the complex and large data should be undertaken in order to have efficient data analysis, management and visualization. During the testing procedure of the developed system, all modules should be properly tested by the developer, by testing experts - if available -, and by the appropriate users. While testing the newly developed scientific system, the system should not be considered ready or functioning straight away. No real experiments should be performed prior to thorough testing to avoid any loss of data or waste of any scientific research/biological material or living beings (especially in case of behavioral research and analysis). Only after successful deployment the real time results should be evaluated.

For instance, if the target scientific software solution is a database manipulation and management system, then it will require to properly model the database schema (entity relationship model), by reducing the levels of data redundancy and dependency, via data normalization. There are five data normalization forms: 1NF,
2NF, 3NF, 4NF and 5NF, which include conceptual procedures for comprehensive database designing. These data normalizations help in shaping the data types (1NF), developing the relationships between non-key and key fields (2NF, 3NF), and dealing with multi-valued facts which correspond to many relationships (4NF and 5NF). Structured data are more helpful in case of search and indexing operations than simple databases with entities but without hierarchical relationships. Moreover, if the experimental data are well normalized, then in case of large datasets, they will expedite the processing speed and reduce time in searching and analyzing the elements.

Human computer interaction and scientific applications

The lower left wing of the Butterfly (Figure 3) is the HCI, known as Human Machine Interaction (HMI). This interacts with the lower right wing i.e. Scientific Application. HCI defines the implementation of the mechanisms that establish the efficient communication protocols between human and machines. These protocols are based on the textual, visual, sensory, video, audio and event based information, provided by both the user and the machine (computer). The backbone of the Butterfly allows by its middleware to rapidly exchange GUI applications and accessed databases if there is a need for it, considering the rapid developments in bioinformatics or if a user wishes to use GUIs or databases from comprehensive software environments, for instance regarding large-scale sequencing from Taverna or Galaxy.

Unfortunately HCI was the most ignored and unattended phase of scientific software solution development. This starts not to represent the state of the art any more as the awareness on HCI is increasing, for instance EBI has specialized UX personnel who can be engaged in projects. Nevertheless, often developers do not give priorities to the GUI design and implementation. The reasons for this negligence could be the pressure due to time limits for development, rapid functionality addition during development, excessive iterations, less field knowledge, lack of awareness about the importance of HCI, competitive general purpose software and human behavior analysis etc. In principle and practice, with respect to the user’s point of view, HCI is one of the most important parts of the software development. If the HCI is bad and the software is not easy to use, why use the software at all? Below we will present a particularly well-engineered solution in this respect, the ant database, focusing on a really easy user database access by smart phone.

During the scientific solution deployment and usage, the end user is probably a scientist without strong informatics background. To run and execute a script, first the compiler and the editor need to be installed, then depending upon the needed external libraries, the necessary libraries will need to be identified and used. This might be a very hectic task, especially for a person with no informatics background. In most of the cases, the result-producing applications cannot be used because of difficulties in deployment and execution procedures. Moreover, most of the time, many scientific software
applications are not well documented, which also increases the level of complexities at the user end.

If the application is configured and is executed successfully, then the next task is to use it. If the application has been developed with an unfriendly GUI or a command line interface, it might be a problem for the user scientist, as to how to use it. If the application is not easily deployable and usable, then in most of the cases it can only lead to the loss of developer’s efforts.

To avoid such problems, the following aspects should be considered: user psychology, scientific domain, working environment and HCI design patterns (Window Per Task, Interaction Style, Explorable Interface, Conversational Text, Selection, Form, Direct Manipulation, Limited Selection Size, Ephemeral Feedback, Disabled Irrelevant Things, Supplementary Windows and Step-by-Step Instructions). It is very important to understand the common psychology of the users of the applications e.g. if they are the laboratory scientists, they will be happy to have user friendly graphical interface and easy deployment procedure (e.g. small setup which runs and automatically configures all the required settings in the user’s system), so that they do not have to spend additional time on the configuration.

Scientific domain and working environments are two more important aspects to be considered while designing the graphical interface. These are particularly important especially when developing real time systems e.g. embedded, robotic, mobile applications. Moreover, it is important to consider that the use of HCI patterns and principles (Cooperation, Experimentation, Contextualization and Iteration) have a reliable HCI communication protocol implementation.

In general, non-functional requirements specify the overall objectives of the system together with the information about quality attributes (e.g. Performance, Operating, Platform, Modifiability, Portability, Reliability, Security, Usability etc.), and functional requirements explain the sets of input, output and behavior of the system. Here, we are somewhat extending these general concepts: the functional requirements can also be those which can be implemented (based on existing resources, time, budget, labor, tools, technologies and methodologies), and non-functional requirements can also be those which cannot be implemented but which are qualitatively helpful in defining the system and its usability. It is very important to iteratively clarify with the users what will be the expected end-product because it is possible that the user may not like the output of the system after development cycles. If the end product is unsatisfactory in this respect, all the efforts will have been in vain.

After designing an interface, one of the important tasks is to evaluate its effectiveness and potential. One general and effective way is to engage the users and consider their feedback at every step. The technical approach is to use the HCI design principles: Experimentation, Contextualization, Iteration and Empirical Measurement. Another beneficial method is to adopt and use the HCI design patterns: Window Per Task, Direct Manipulation, Conversational Text, Selection, Form, Limited Selection Size, Ephemeral Feedback, Disabled Irrelevant Things, Supplementary Window and Step-by-Step Instructions.

**Butterfly workflow designs**

The Butterfly model implementation mechanism has a three-layered architecture: Gray, Yellow and Green (Figure 4).

**Gray layer**

The gray layer represents the most important phase of scientific software solution development, which involves software designers,
developers, testers, graphical interface designers and, most importantly, the users. It consists of four phases: scientific software solution planning, requirements engineering and analysis, conceptual software design and modeling, and user friendly graphical interface. The layer has been named ‘Gray’ because at the beginning of a new scientific software solution development, most of the information seems uncertain.

Scientific software solution planning (Figure 5) is the first step towards a new scientific application development, which requires the introduction to the field itself (e.g. biochemistry, neurobiology, genetics, metabolomics, proteomics etc.) and project related information (e.g. what could be the end product, input to the system, expected output from the system, methodology, ideas, opinions etc.). It is important to know about the user’s information IT background and existing already available (old and recently developed) scientific solutions to the problem. The next important phase is to perform requirements engineering and analysis (Figure 6). During this phase, the most important tasks are to gather the requirements from users (e.g. interviews, brainstorming, documents, publications, running related systems based information etc.) and classify the information in functional and non-functional categories. Here, function requirements are those which can be implemented (based on existing resources, time, budget, labor, tools, technologies and methodologies), and non-functional requirements are those which cannot be implemented. It is very important to clarify with the users what will be the expected end-product because it is possible that the user may not like the output of the system after development. In this case, all the efforts will have been in vain.

The third phase is the conceptual software design and modeling (Figure 7). This is particularly important when there is a team of software developers. Before moving ahead, one should go for some abstract designs based on functional requirements and discuss these with the team. It is crucial to estimate the expected workflow, data sources and data flow in the system. If possible, the abstract design should be discussed with the users as well.

The last phase of the gray layer concerns the design of a user-friendly GUI (Figure 8). First, some mock-ups should be made...
the implemented conceptual design and mockups (Gray layer), we constructed the implementable designs of DroLIGHT\(^{71-73}\). We implemented UML principles and notations for Meta model software designs with abstraction and modification techniques. The designed UML diagrams of DroLIGHT\(^{71-73}\) described the application’s functionalities, user access, internal work flow, system sequence, pre-processed source code structure, compilation, execution and integration with involved other components\(^{71-73}\).

We invested time in searching the recent available and reliable technologies, which could be used for the design and development of newly proposed system. We used Astah modeling tool to construct the different UML diagrams and focusing on the functional requirements, we developed DroLIGHT\(^{71-73}\) (front end and back end) in managed code using C# (object oriented programming language), within Microsoft Visual Studio (Dot Net 2012).

Green layer
The green layer describes the final in house testing and debugging by the developers and tester. Some scientific software applications are developed to process the raw data using mathematical algorithms (e.g. processing GC-MS, LC-MS, NMR data), whereas some applications are implemented to perform different kind of experiments, which in return produce experimental data e.g. towards behavioral research on animals and insects etc.

Processing raw data is safe even if there are still some problems (e.g. minor calculation mistakes due to the different levels of fractional values or wrong implementation of mathematical algorithms, or some software developmental issues, which could be ‘ripple effects’, or some logical bugs) after testing. However, when applied in real time experimentation, if the software does not work as expected, it could be very expensive and dangerous (e.g. if there is a software to control the temperature and light during experiments on insects or animals, and there are problems during experimentation leading to changes of the normal or expected temperature and light to some extreme positive or negative values, then this could not only effect the system’s hardware but can also threaten the life of animals or insects).

In order to avoid such problems, we enforce test trails by different users before making the software available for installation and training in the public domains.

Case study. The implemented version of DroLIGHT (sections: Gray layer and Yellow layer) was tested in the development lab and applied Black box testing, White box testing, Unit testing, Integration testing, Functional testing, System testing, End-to-end testing, Load testing, Stress testing, Performance testing, Usability testing, Install/uninstall testing, Compatibility testing and Comparison testing strategies. Based on the observed problems (errors, bugs, ripples etc.) we produced different versions, and kept on testing until a reliable version was achieved. As in agile development, refactoring (improving code quality without changing its semantic meaning) is seen as an effort that copes with ripples and accompanies development. DroLIGHT improvement was achieved efficiently here using windows XP. Using again the Butterfly paradigm, similar results should be obtainable focusing on scrum techniques and iterative

Yellow layer
The yellow layer involves designers and developers. It consists of four phases: design, modeling and analysis, tools and technology selection, design implementation, and GUI implementation.

During design modeling and analysis, the important task is to create different implantable designs e.g. UML models (use case, class, system sequence, activity, component etc.) and database schemas (in case it’s a database management system). Here, we strongly recommend the use of Product Line architecture design modeling, where the whole software is divided into sets of modules, which work individually as well as together. This will customize project development and reduce error proneness during development. Moreover it will increase the concepts of modular reusability.

The next step involves the choice of available tools, technologies and programming languages that will be implemented in the designed models. The last step focuses on adding functionalities to the designed GUI.

Case study. Meeting the scientific objectives of understanding the light-evoked behaviors of \(D. \ melanogaster\), especially the synchronization of its endogenous clock to light-dark cycles and following

Case study. We have successfully applied the Butterfly model in the implementation of newly proposed applications i.e. DroLIGHT\(^{71-73}\), scientific computational solution towards neurobiology and photobiology (Figure 10). The engineering processes started with the initial scientific software solution planning, the involvement of the members of a scientific group (Department of Neurobiology and Genetics, Biocenter, University of Wuerzburg, Germany). The desired end product was a system towards the behavioral biology of the fruit fly. The overall requirements were about to implement a domain specific, intelligent, distributed, real time, embedded, data management system capable of controlling hardware devices, proficient in producing different colors of lights and monitoring the movements of \(Drosophila melanogaster\). Moreover, it should be capable of generating circadian and diurnal rhythms, experimental data management system and visualize experimentation’s output in two and three dimensional graphics formats.

We analyzed and distinguished between functional and non-functional requirements to draw the conceptual models of the proposed system. Furthermore, we involved the scientific team members in different brain storming session and drawn mockups with the implementation of following design patterns: window per task, direct manipulation, conversational text, ephemeral feedback and step-by-step instructions. The designed mockup was providing multiple instances, allowing users to directly interact with the system using provided controls, offering the textual command line instruction mode for human machine interactions, status updates and tools tips\(^{1-23}\).

Hand-made on paper or better to use white board with color markers and later make pictures of finalized GUI designs), then these should be discussed with users in a brain storming session. Finally, based on the perceived designs, the abstract GUI (GUI with no running functionalities) should be created using HCI design patterns.
lean development with sprint backlogs, but this was not tested by us. Later after training the scientists about how to use and configure the application, reliable release was shared and tested in the scientific labs.

Constant improvement is further boosted by sustainable data structures and engineered robustness of the application. Furthermore, sustainable development and interoperability are considered from the start, support the rapid further development/improvement of software to study and manipulate circadian rhythm by different light cycles and test environments in *D. melanogaster*.

**Real Life Examples using Butterfly**

A number of new scientific software applications based on the concepts of the Butterfly model have already been proposed, designed, implemented, tested and are currently in use. Some of them have been published and some remain unpublished. These applications are: Least Square MIDA (LS-MIDA), DroLIGHT, Isotopo, Lipid-Pro and App Ant Database.

**LS-MIDA** is an own published scientific software (Department of Bioinformatics, Biocenter, University of Wuerzburg, Germany) which estimates mass isotopomer distribution from the spectral data by analyzing each peak of given mass and each mass atom fragment. It implements a chain of mathematical and statistical algorithms, provides graphical interfaces to help users analyze experimental data and visualize the results, and provides a third party independent experimental data management system. For the most parts the requirement engineering and software design steps are followed until the final solution presented (Figure 9), and details on tested earlier solutions or specific requirements are available from the authors.

**DroLIGHT** is an earlier described (section: *Butterfly* workflow designs) scientific solution to control the irradiance and wavelength of light designed for the photo-receptor system of the fruit fly.

**Isotopo software** is a published scientific software (Department of Bioinformatics, Biocenter, University of Wuerzburg, Germany), a bioinformatics solution with the ability of performing quantitative mass spectrometry in isotope labeling experiments. It is an extended version of the earlier software LS-MIDA with a well-optimized mathematics implementation. It not only provides the graphical interfaces for gas chromatography-mass spectrometry (GC-MS) experimental data analysis, visualization and management,

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**Figure 9.** Least Square Mass Isotopomers Distribution Analysis’s (LS-MIDA) main graphical user interface. Scientific software solution towards bioinformatics and biochemistry which estimates mass isotopomers distribution from spectral data by analyzing each peak of given mass and each mass atom fragment. ([http://www.tr34.uni-wuerzburg.de/computations/ls_mida/](http://www.tr34.uni-wuerzburg.de/computations/ls_mida/)).
Figure 10. DroLIGHT’s main graphical user interface. It is a scientific software solution towards neurobiology and photobiology, capable of controlling and automating the hardware that produces different colors of lights via Light Emitting Diodes (LEDs). It provides experimental data management system, circadian and diurnal rhythm generation, 3D visualization of system’s performance and experimentation details (http://www.neurogenetics.biozentrum.uni-wuerzburg.de/en/project/services/drolight/).

but also provides an intelligent data parser to automatically transform the machine’s pre-processed data into the processable format of the Isotopo software (reducing both time and labor). It also provides a complete database management system as a simple, well sustainable version of a middleware between data storage and GUIs.

Lipid-Pro (Figure 12) is a scientific software (computational) solution towards lipidomics and pharmaceutical biology (Department of Pharmaceutical Biology Department of Neurobiology and Genetics and Department of Bioinformatics, Biocenter, University of Wuerzburg, Germany). It is a new solution towards the lipidome analysis including retention time (RT), mass to charge ratio values (m/z) of precursor and fragment ions, chemical compositions and peak intensities. Moreover, it provides comprehensive spectral data management, sharing and integration features.

App Ant Database84 (Figure 13) is a scientific software solution, featuring a distributed and embedded database system in the form of a smart phone, tablet and desktop application towards experimental data management and approximate solar estimations during experimentation on different insects (Department of Behavioral Physiology and Sociobiology, Biocenter, University of Wuerzburg, Germany). It is unique and the first bioinformatics smart phone application to be used in the deserts for the behavioral experiments. After extensive requirement engineering, we established an extremely easy to use graphical interface. Furthermore, after studying the user requirements in monitoring desert ant movement and orientation in the desert, the application not only automatically records ant movements, but also estimates and calculates automatically all additional variables required for the project such as azimuth, solar time, equation of the time, time offset, hour angle, altitude, sunrise, sunset and solar noon using astronomical algorithms, recommended by the National Oceanic and Atmospheric Administration (NOAA).

Regardless of the individual specifications, development details, technologies used and usage perspectives, the key principles of the Butterfly model were applied in the design of these software solutions. Although the requirements for each of these were not fixed in the beginning, comprehensive requirements gathering and analysis operations were performed using brain storming and interviewing methods. Based on filtered out the functional requirements, the most suitable SDLCs (V-Model54 and Spiral55) were applied and the software applications were designed using UML (including use cases, class diagrams, sequence diagrams, work flows, activity flows, components diagrams, data flow diagrams etc.). Of those SDLC’s used in scientific software solution development, the Spiral
Figure 11. Isotopo Data Analyzer’s main graphical user interface. Scientific software solution towards bioinformatics and biochemistry, with the ability of performing quantitative mass spectrometry to mixtures of materials labeled with stable isotopes. It provides internal database management system, third party independent file based experimental data management system and intelligent data format parser for data extraction and conversion of different data formats. (http://spp1316.uni-wuerzburg.de/bioinformatics/isotopo/).

Model proved most helpful and best suited due to its four main pillars: determine objectives, identify and resolve risk, development and test, and plan the next iteration. Another advantage of the spiral model is its risk driven approach, incorporating many useful features and refinements of other software development life cycle models.

Using the HCI design patterns and principles, the graphical user interfaces of all these applications were designed considering the psychology, scientific and informatics backgrounds of the end users and the deployment environments.

All these applications are easy to deploy and use. We found that users did not require training to install, run and use the applications. As scientific research is a never ending process, these applications are still in development and will be continuously improved with respect to the methods, features, performance and technologies.

Comparing bioinformatics tools
We have performed a short comparative analysis of some bioinformatics software applications (C13, Metatool, BioOpt, FiatFlux, ReMatch, Biolayout, LS-MIDA, DroLIGHT –, Isotopo, Mass Isotopomers)

For our comparison, we chose software applications from fields we are familiar with, yet tried to cover a broad range of different applications and compared Metabolic Flux Analysis (MFA) as well as software metabolic network analysis, Mass Isotopomers
Distribution Analysis (MIDA) including GC-MS data analysis\textsuperscript{69,70}, and neurobiology applications for behavioral analysis of insects such as desert ants and fly\textsuperscript{71–73}.

We used the following parameters to classify the chosen bioinformatics software application: SSE type, data management, script or prototype, algorithm type, algorithm/methodology, running mode, publishing, licensing, SDLC information, HCI information, user friendly, easy to configure, easy to train, software re-engineering, cyclic or repetitive, easy to learn and use user training.

From the observed results (Table 2) we conclude that almost all of the applications have good implementations of their methodology (algorithms etc.) but often lack in usage point of views (user interface, documentation etc.), or long term sustainable development of the software (at least regarding the organization of future further developments). These shortcomings are prevented when following the “Butterfly” paradigm.

Conclusions

In the earlier sections of this paper we presented the concepts of usage of the existing scientific software solution design, modeling, implementation, testing and deployment. This helps in resolving conflicts and highlighting valuable differences between the traditional (professional) and scientific applications. This paper also proposes a new approach towards user friendly scientific software solution development, with emphases on the use of proper SDLC, HCI and technologies. The successful implementation of the five applications discussed strongly validates the potential of the Butterfly model. We have tried to present a strong case for our Butterfly model.
but it is of course only our own approach to achieve sustainable software development in an academic environment. We clearly see from our development experience that the efforts in preparation and implementing scientific software engineering for an application pay off particularly well if there is a series of programs developed. However, we claim also that one would think more often about such a series of successive improved programs if there is the option to easily implement such an effort, and again the Butterfly model would help here.

In conclusion, although the adaptation of SSE principles to the Butterfly model may seem to increase developmental work load in comparison to the current running programming method applications, the Butterfly model will ultimately reduce the work by making the scientific application well designed, flexible, structured, reusable, developed according to a product line, as well as analytical and of high quality. According to its design, the software developed using the Butterfly paradigm is user friendly, easy to learn and deploy.

Author contributions
Zeeshan Ahmed has proposed the model Butterfly, and initiated the topic of discussion. Saman Zeeshan assisted Zeeshan Ahmed and Thomas Dandekar guided the study. All authors participated in writing the manuscript.

Competing interests
The authors declare no conflict of interest.
Grant information
Funding was provided by the German Research Foundation (DFG), collaborative research center SFB 1047 “Insect timing”, Project Z, to Zeeshan Ahmed. Thomas Dandekar and Saman Zeeshan were supported by the German Research Foundation (DFG), TR 34/Z.

The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Acknowledgements
We would like to thank all our interested colleagues for critical community input on the “Butterfly” approach.

We would like to thank Deutsche Forschungsgemeinschaft (DFG) for funding and University of Wuerzburg Germany for the support.

We thank two anonymous reviewers for helpful comments on the manuscript and the Land of Bavaria Germany.

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F1000Research 2014, 3:71 Last updated: 16 MAY 2019
Page 15 of 30
Open Peer Review

Current Peer Review Status: ✔ ✔

Version 2

Reviewer Report 28 October 2014

https://doi.org/10.5256/f1000research.5210.r6557

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✔ Wolfgang Mueller
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Competing Interests: No competing interests were disclosed.

I have read this submission. I believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.

Reviewer Report 26 August 2014

https://doi.org/10.5256/f1000research.5210.r5923

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✔ Paul Vauterin
Wellcome Trust Centre for Human Genetics, University of Oxford, Oxford, UK

Competing Interests: No competing interests were disclosed.

I have read this submission. I believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.
Wolfgang Mueller

EMBL Outstation, Heidelberg Institute of Theoretical Studies gGmbH, Heidelberg, Germany, Hinxtion, Cambridge, CB10 1SD, UK

Caveat: I lead a group that does scientific software development. I am interested in software development both from the conceptual and the technical side. However, I would not be a serious contender for a software engineering chair. As a consequence, I cannot claim full knowledge about the state of the art of software engineering processes.

I agree to the following takeaways that I pull out of the paper:

- If you know you are building an application which is for other people than yourself, it makes sense to follow a software engineering process.
- Think about maintainability and sustainability of your software.
- Think about your users and write usable software.
- Operate using cyclic refinement

The *Butterfly* model is an assembly of current software practices, emphasizing the needs of the scientific software developer. I see the strength of the article in giving a concise overview of what a scientific software developer should do.

However, I disagree with some statements made in the paper. Some of these statements relate rather to anecdotal experience. This points to one of the weaknesses in the paper: There are statements made with respect to the scientific software domain that are not marked as anecdotal, but which are not backed by either empirical facts (e.g. questionnaires) or pointers to such facts in the literature.

In more detail:

Generally I agree, science is a fast-paced environment with rapidly changing requirements asking for suitable software engineering processes.

*Current software engineering and development*

The paper comprises a large number of citations. However, I do not agree with the insights taken by the authors from that literature.

To my knowledge, the field of Software Engineering has realized that one key factors for success is if software matches the needs of users. Agile Development follows the view that often-times, users don't even know what they need until they are closely involved in development and see where their own ideas
of their work (i.e. using the program) could fail. This is why there is less of an initial requirements analysis, but there is a series of sprints that each seek the implementation of features. Each feature implemented also influences the next stage of the requirements analysis.

The authors of this paper see the lack of quality software production as one of the weaknesses of agile software engineering practices. However, Agile software engineering practices like XP and Scrum emphasize the importance of testing and other practices intended to increase the software quality. Such processes definitely do not disregard the production of quality production. So, to cut a long story short, I do not agree with the impression created in the paper that agile processes lead to muddle-through software that is unstable and short term due to the process.

You criticize the "ripples" through the program that come from changes. Ripples is the word describing the needs for software changes due to one change elsewhere in the program e.g. the change in the view necessitated by changing a model. The paper defining ripples is from 1978, and you cite another paper about measuring ripples (2001). However to my knowledge, in agile development, refactoring (improving code quality without changing its semantic meaning) is seen as an effort that accompanies development, with a view on minimizing ripples. Unit, integration, acceptance tests are automated as far as possible so they can be run after almost every change. Ongoing refactoring without being able to test easily if the program still works is admittedly very hard. But tests well done can help with this. I think it would be useful for the reader if you would outline how ripples are relevant in XP or Scrum.

The fact that user interaction is not written into the Scrum process does not mean that it’s not on the map. It is implicit in the requirements given by the users and users being part of the Agile team. Typically, users that are part of the Agile team will accept or not the software created. User tests can be part of the acceptance procedure, usability improvements can be features in a Scrum process.

While user experience is put to the forefront, the paper is quite sparse on the processes and on citations regarding HCI.

You state: "Unfortunately HCI is the most ignored and unattended phase of scientific software solution development". To my impression, this is not the state of the art any more, and the EBI even have specialized UX personnel who can be called into projects.

The authors then describe what they see as reasons for poor HCI properties of scientific software and state that no-one uses software with bad HCI and state that software with bad HCI won’t be used. In my (anecdotal) experience, many software products start out as concrete problem solvers for their authors, with bad HCI (for others, as the original author writes the software tuned to his/her own needs) which then are successively refined to serve a larger public. Of course this process bears its problems for outside users. However, such software gets adopted, because of word of mouth.

In the article, HCI "design patterns" are not laid out in sufficient detail. The normal forms (1NF) etc. could be either treated more shortly or in more detail. The enumerating of 1NF to 5NF and not saying what they signify is in my view not the right middle ground.

---
"Real time examples" should be changed to "Real life examples"

I think these examples are an interesting overview, but to my feeling they are not addressing what is needed to support the claims made about the Butterfly process. Rather than giving a list of software artifacts that were created using the process I would prefer more information about the outcome of the different phases. What were iterative improvements etc.? If you are using a ticketing systems and a versioning system, it is highly likely that you can generate from logs a compelling story that lets the readers know more about the Butterfly process in everyday life. In particular it would be interesting to learn more about how many people performed the processes, and how the roles were distributed.

Such an approach would also benefit the software system comparison of systems that did not use Butterfly. Following the Butterfly paradigm will take time and effort. Was a sufficient amount of time available for the systems used for the overview?

---

All in all, I find this paper is a mixture between an opinion piece, a methods piece, and an overview piece. Even if I do not agree with many claims made in the paper, I do think the question of whether scientific software engineering (or even some scientific domains) need special software engineering processes is an interesting one (albeit maybe not a new one).

**Competing Interests:** No competing interests were disclosed.

I have read this submission. I believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however I have significant reservations, as outlined above.

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Author Response 27 Jul 2014

Zeeshan Ahmed, University of Connecticut Health Center, USA

Thank you so much for your time in reviewing our manuscript and giving valuable suggestions, as we believe that following those our manuscript has been improve a level ahead.

**Referee Comment:**

"Caveat: I lead a group that does scientific software development. I am interested in software development both from the conceptual and the technical side. However, I would not be a serious contender for a software engineering chair. As a consequence, I cannot claim full knowledge about the state of the art of software engineering processes. I agree to the following takeaways that I pull out of the paper:

- If you know you are building an application which is for other people than yourself, it makes sense to follow a software engineering process.
- Think about maintainability and sustainability of your software.
- Think about your users and write usable software.
• Operate using cyclic refinement

We agree with you.

Referee Comment:

“The Butterfly model is an assembly of current software practices, emphasizing the needs of the scientific software developer. I see the strength of the article in giving a concise overview of what a scientific software developer should do.”

Thanks, and we agree with you.

Referee Comment:

“However, I disagree with some statements made in the paper. Some of these statements relate rather to anecdotal experience. This points to one of the weaknesses in the paper: There are statements made with respect to the scientific software domain that are not marked as anecdotal, but which are not backed by either empirical facts (e.g. questionnaires) or pointers to such facts in the literature.”

Thank you for pointing this out - we respect your opinion.

Referee Comment:

“In more detail:
Generally I agree, science is a fast-paced environment with rapidly changing requirements asking for suitable software engineering processes.”

True.

Referee Comment:

“Current software engineering and development
The paper comprises a large number of citations. However, I do not agree with the insights taken by the authors from that literature.”

Thanks, and we respect your opinion.

Referee Comment:

“To my knowledge, the field of Software Engineering has realized that one key factors for success is if software matches the needs of users.”

True.

Referee Comment:

“Agile Development follows the view that often-times, users don’t even know what they need until they are closely involved in development and see where their own ideas of their work (i.e. using the
program) could fail. This is why there is less of an initial requirements analysis, but there is a series of sprints that each seek the implementation of features. Each feature implemented also influences the next stage of the requirements analysis."

We agree with you.

Referee Comment:

“The authors of this paper see the lack of quality software production as one of the weaknesses of agile software engineering practices. However, Agile software engineering practices like XP and Scrum emphasize the importance of testing and other practices intended to increase the software quality. Such processes definitely do not disregard the production of quality production. So, to cut a long story short, I do not agree with the impression created in the paper that agile processes lead to muddle-through software that is unstable and short term due to the process."

We respect your opinion and want to explain here that the aim of this paper is not at all to present Agile software engineering practices as muddle-through approaches, but to state that the “Butterfly” paradigm is more useful in some specific scenarios. Our aim is to generalize the basic software engineering concepts and stream line them in a way that most of the people in Bioinformatics (non-informatics or with more biology background) can easily adopt them. Hence, Agile software engineering practice is of course a viable approach, and we have revised our paper and tried to elaborate the proposed new approach in more detail, by giving a case study of a real time scientific solution’s development and being careful not to misrepresent alternatives.

Referee Comment:

“You criticize the "ripples" through the program that come from changes. Ripples is the word describing the needs for software changes due to one change elsewhere in the program e.g. the change in the view necessitated by changing a model. The paper defining ripples is from 1978, and you cite another paper about measuring ripples (2001). However to my knowledge, in agile development, refactoring (improving code quality without changing its semantic meaning) is seen as an effort that accompanies development, with a view on minimizing ripples." 

Thanks for addressing “ripples”. We respect your opinion and you’re points are valid, in particular regarding Agile development. However, our point is summarised here (expanded on in revised text):

Adding new features to existing applications on a random basis in academia, can cause unidentified and illogical errors to occur which can badly effect the stability of the application.

For example - we have implemented some operations with mutual consent of all the team members (including scientists, students, lab operators and computer scientists etc.) and then when the application’s new version is completed, a new change comes from the team. This requires the selective removal of implemented options with the addition of new connecting features, giving a high probability that errors will occur.

Referee Comment:
“Unit, integration, acceptance tests are automated as far as possible so they can be run after almost every change. Ongoing refactoring without being able to test easily if the program still works is admittedly very hard. But tests well done can help with this. I think it would be useful for the reader if you would outline how ripples are relevant in XP or Scrum.”

We respect your opinion and you are absolutely right. So we now touch upon the questions of ripples regarding XP and scrum. In our personal academic experience we have noticed that especially in those cases when the developer is not the user of the real time scientific software application (which will be used in the laboratories or in fields e.g. our developed solutions DroLIGHT or Ant-App-DB), it is really hard to perform extensive on-time testing (including Unit, integration, acceptance tests etc.).

One cannot receive the greatest benefit from testing in these situations. So when a developer has to keep randomly and extensively changing things in an application without on-time testing then there is a high probability of getting ripple effects.

Referee Comment:

“The fact that user interaction is not written into the Scrum process does not mean that it’s not on the map. It is implicit in the requirements given by the users and users being part of the Agile team. Typically, users that are part of the Agile team will accept or not the software created. User tests can be part of the acceptance procedure, usability improvements can be features in a Scrum process. While user experience is put to the forefront, the paper is quite sparse on the processes and on citations regarding HCI.

You state: “Unfortunately HCI is the most ignored and unattended phase of scientific software solution development”. To my impression, this is not the state of the art any more, and the EBI even have specialized UX personnel who can be called into projects.”

You are absolutely right and we agree with you but this is more applicable when a commercial application is developed or some specialised software engineering or related group is producing the solution. We added HCI citations and mention the EBI approach as an example of recent trends. Furthermore, it is true, HCI is extensively ignored when a new scientific software solutions is developed in most of the scientific academia.

Along with the heavy scientific software solution development, we are also taking part in analysing different scientific software applications for different purposes e.g.


We have analysed and used many different developed software applications (more than 35) and scripts. With reference to our published work, most of the time is consumed in configuring the applications and understanding its features. If a person with an
Informatics background cannot easily configure and use Bioinformatics solutions then how can a layman.

Moreover, when it comes to follow some already developed open source application, and add some features to it - then if the pre-processed source code is quite large and without any formal documentation, it can be a nightmare for Bioinformatics students.

Referee Comment:

“The authors then describe what they see as reasons for poor HCI properties of scientific software and state that no-one uses software with bad HCI and state that software with bad HCI won’t be used. In my (anecdotal) experience, many software products start out as concrete problem solvers for their authors, with bad HCI (for others, as the original author writes the software tuned to his/her own needs) which then are successively refined to serve a larger public. Of course this process bears its problems for outside users. However, such software gets adopted, because of word of mouth.”

We respect your opinion and agree with you, and have altered the statements accordingly the revision.

Referee Comment:

“In the article, HCI “design patterns” are not laid out in sufficient detail.”

Following your suggestion, we have revised it and have added some information about HCI design patterns.

Referee Comment:

“The normal forms (1NF) etc. could be either treated more shortly or in more detail. The enumerating of 1NF to 5NF and not saying what they signify is in my view not the right middle ground.”

Thanks for the opinion and following your suggestion, we have revised it.

Here our point was not to elaborate on database normalisation forms but emphasise its use. In our previous experience (without denigrating any researcher or developer), we have noticed that often, databases are created to store and manage data - but there are no relationships between entities. This can have a negative impact - especially in search and indexing operations. Moreover if data is well normalized then for large datasets, it will expedite the processing speed in searching the elements.

Referee Comment:

“Real time examples“ should be changed to “Real life examples“

Following your suggestion, we have revised the heading and the examples have been augmented.
Referee Comment:

“I think these examples are an interesting overview, but to my feeling they are not addressing what is needed to support the claims made about the Butterfly process. Rather than giving a list of software artifacts that were created using the process I would prefer more information about the outcome of the different phases. What were iterative improvements etc.? If you are using a ticketing systems and a versioning system, it is highly likely that you can generate from logs a compelling story that lets the readers know more about the Butterfly process in everyday life. In particular it would be interesting to learn more about how many people performed the processes, and how the roles were distributed.”

We agree with you.

We have revised our paper and tried to elaborate the proposed approach in more detail, by giving a case study of a real time scientific solution's development. Questions such as iterative improvement are answered by concrete examples.

Referee Comment:

“Such an approach would also benefit the software system comparison of systems that did not use Butterfly. Following the Butterfly paradigm will take time and effort. Was a sufficient amount of time available for the systems used for the overview?”

You are absolutely right here that there must be some comparison drawn between the software applications developed using Butterfly and without. The problem here is that our proposed paradigm is quite new and this paper is the first public, methodological debate on it. Moreover according to the scope of this manuscript, we have only presented our approach with some examples but in future we will definitely try to come up with more intensive comparisons. We are still working on the strengthening our approach. In particular, for sustainable development of an application the Butterfly paradigm did boost results - for instance developing metabolic modelling software (LS-MIDA, Isotopo, LipidPRO including database applications and data management) or neurobiology software (the running example of the paper, the DroLIGHT series of programs). We now present the approach to others and note that we also have good results in developing the first version of the App-Ant database, an application oriented behaviour monitoring system, again with a planned longer term pipeline development.

Referee Comment:

“--- All in all, I find this paper is a mixture between an opinion piece, a methods piece, and an overview piece. Even if I do not agree with many claims made in the paper, I do think the question of whether scientific software engineering (or even some scientific domains) need special software engineering processes is an interesting one (albeit maybe not a new one).”

Thank you so much for your valuable time in reading and evaluating our work and giving your opinions to further improve it. We have tried to follow all your helpful suggestions and those which are still left partly open due to the scope or limits of this paper will soon be answered by further efforts. We have strengthened the methods section (see also our
response to Paul Vauterin) but kept our opinion and own approach as well as added more citations for an overview.

**Competing Interests:** No competing interests were disclosed.

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**Reviewer Report 12 May 2014**

https://doi.org/10.5256/f1000research.3945.r4632

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### Paul Vauterin

Wellcome Trust Centre for Human Genetics, University of Oxford, Oxford, UK

This paper addresses some major and often overlooked problems associated with software development in an academic environment:

- Lack of long-term vision due to short contract cycles.
- Lack of attention to usability aspects such as well-thought user interfaces.
- Lack of documentation, training material, and other follow-up.

I share the opinion of the authors that these elements pose a substantial threat to the quality of the scientific software products that are created in academic environment. Lots of valuable academic software development projects fail because of one or more of these reasons, resulting in a waste of efforts. Therefore, I think that papers focusing on solutions to overcome these issues certainly deserve a place.

A substantial portion of the paper reads like an introduction to standard software engineering practices, with a focus on scientific software development. It is generally well written, and does provide a useful resource for academic software developers who are interested in learning more about this subject.

In addition, the authors present the “Butterfly model”, which they claim is a novel approach to software engineering, specifically tailored towards scientific software development. It does contain some interesting aspects, specifically the integrated attention to Human-Computer-Interaction (HCI), something often vastly overlooked in academic software development. However, in my opinion the authors tend to overstate the originality of this approach, as it mostly recuperates already known concepts and practices. It does have the merit that it attempts to capture these concepts in a single framework focusing on scientific software development in an academic environment.

Perhaps the major problem I have with the way this model is presented is that the authors do not clearly mention its scope of application. Clearly, this model only makes sense for larger and longer-term development projects, whereas lots of academic (bioinformatics) software projects are very small, simple in structure, and short-lived by nature. Applying the “Butterfly model” or a similar rather heavyweight approach to these projects could be a counter-productive and frustrating. In my opinion, the authors missed the opportunity to stratify the preferred approach according to the size and complexity of the project at hand. A consequent risk is that a reader might be confused and wrongly informed, thinking that this approach should be used for every software development effort, regardless its size. I think that the
authors should properly address the scope of the model in the paper.

The authors provide a rather large set of software products they claim were developed with the Butterfly model, but do not provide much detail about what this meant in practice. I believe that the paper would vastly benefit if one specific case was picked, for which the practical approach of the Butterfly model would be elaborated, and the benefits would be highlighted in a very concrete way. This would also help to substantiate the author's claim about the novelty of the Butterfly model.

Further comments:

- “Moreover the SDLCs famous for the quick development (Rapid Prototype Model, Agile Development Model, Extreme Programming Model, Evolutionary Model, Code and Fix Model), lack in quality software production”:

  This is a rather controversial statement, as the list includes some generally respected models. Since the paper does not provide further arguments to back this claim, I believe it should not be made.

- “Here, function requirements are those which can be implemented (based on existing resources, time, budget, labor, tools, technologies and methodologies), and non-functional requirements are those which cannot be implemented”:

  I do not believe that this the standard definition of function(al) vs. non-functional requirements. Functional requirements specify what the system should do (e.g. input-behaviour-output), whereas non-functional requirements specify how it should do that (e.g. qualities such as speed, robustness, scalability, maintainability, …).

- “Real time examples using Butterfly”:

  I think this should read “Real life examples…”. Other ways, I can't interpret this title.

- The link to the “Isotopo software” (http://www.tr34.uni-wuerzburg.de/computations/isotopo/) was broken at the time this report was written. In an ironic way, this seems to illustrate one of the points of the authors about the short-livedness of many academic software projects.

- I believe that this article should be catalogued as “Methods Article” rather than “Research article”.

**Competing Interests:** No competing interests were disclosed.

I have read this submission. I believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however I have significant reservations, as outlined above.

Author Response 27 Jul 2014
Zeeshan Ahmed, University of Connecticut Health Center, USA

Thank you so much for your time in reviewing our manuscript and giving valuable suggestions, which all helped to further improve our manuscript.
Referee Comment:

"This paper addresses some major and often overlooked problems associated with software development in an academic environment:

- Lack of long-term vision due to short contract cycles.
- Lack of attention to usability aspects such as well-thought user interfaces.
- Lack of documentation, training material, and other follow-up."

We agree with you.

Referee Comment:

"I share the opinion of the authors that these elements pose a substantial threat to the quality of the scientific software products that are created in academic environment. Lots of valuable academic software development projects fail because of one or more of these reasons, resulting in a waste of efforts. Therefore, I think that papers focusing on solutions to overcome these issues certainly deserve a place."

Thanks.

Referee Comment:

"A substantial portion of the paper reads like an introduction to standard software engineering practices, with a focus on scientific software development. It is generally well written, and does provide a useful resource for academic software developers who are interested in learning more about this subject."

We agree with you, and thanks for appreciating these points.

Referee Comment:

"In addition, the authors present the “Butterfly model”, which they claim is a novel approach to software engineering, specifically tailored towards scientific software development. It does contain some interesting aspects, specifically the integrated attention to Human-Computer-Interaction (HCI), something often vastly overlooked in academic software development. However, in my opinion the authors tend to overstate the originality of this approach, as it mostly recuperates already known concepts and practices. It does have the merit that it attempts to capture these concepts in a single framework focusing on scientific software development in an academic environment."

We agree with you, stressing important points of our paper.

Referee Comment:

"Perhaps the major problem I have with the way this model is presented is that the authors do not clearly mention its scope of application. Clearly, this model only makes sense for larger and longer-term development projects, whereas lots of academic (bioinformatics) software projects are very small, simple in structure, and short-lived by nature. Applying the “Butterfly model” or a similar rather heavyweight approach to these projects could be counter-productive and frustrating. In my
opinion, the authors missed the opportunity to stratify the preferred approach according to the size and complexity of the project at hand. A consequent risk is that a reader might be confused and wrongly informed, thinking that this approach should be used for every software development effort, regardless its size. I think that the authors should properly address the scope of the model in the paper.

The authors provide a rather large set of software products they claim were developed with the Butterfly model, but do not provide much detail about what this meant in practice. I believe that the paper would vastly benefit if one specific case was picked, for which the practical approach of the Butterfly model would be elaborated, and the benefits would be highlighted in a very concrete way. This would also help to substantiate the author's claim about the novelty of the Butterfly model."

Thanks for these well taken suggestions - we agree with you, and tried to incorporate these. We have heavily revised the manuscript and now, along with some previously given examples, we have added a case study. Each layer of the Butterfly model is now explained with this example of its implementation, explaining the way we have applied the concepts in a real time scientific software solution’s development. We hope this can clarify most of the ambiguous or unclear points including getting an idea on the specific merits and originality as well as the stratification of the approach, e.g. how much effort should be devoted at each step, looking at the concrete examples given.

Referee Comment:

"Further comments: “Moreover the SDLCs famous for the quick development (Rapid Prototype Model, Agile Development Model, Extreme Programming Model, Evolutionary Model, Code and Fix Model), lack in quality software production”:
This is a rather controversial statement, as the list includes some generally respected models. Since the paper does not provide further arguments to back this claim, I believe it should not be made."

Following your suggestion, we have revised this paragraph accordingly.

Referee Comment:

"“Here, function requirements are those which can be implemented (based on existing resources, time, budget, labor, tools, technologies and methodologies), and non-functional requirements are those which cannot be implemented”:
I do not believe that this the standard definition of function(al) vs. non-functional requirements. Functional requirements specify what the system should do (e.g. input-behaviour-output), whereas non-functional requirements specify how it should do that (e.g. qualities such as speed, robustness, scalability, maintainability)."

We agree and thank you for the clarification, the paragraph has been corrected accordingly.

Referee Comment:

“Real time examples using Butterfly”:
I think this should read “Real life examples…”. Other ways, I can’t interpret this title.
Following your suggestion, we have revised this sentence.

Referee Comment:

“The link to the “Isotopo software” (http://www.tr34.uni-wuerzburg.de/computations/isotopo/) was broken at the time this report was written. In an ironic way, this seems to illustrate one of the points of the authors about the short-livedness of many academic software projects.

We have revised and updated the web link.

Referee Comment:

“I believe that this article should be catalogued as “Methods Article” rather than “Research article”.”

We agree with you, and we changed the category of the manuscript.

Thank you so much for your valuable time in reading and evaluating our work, giving your advice to further improve it. We tried to follow your suggestions as much as possible in the revision. Furthermore, all those questions which are still incompletely resolved due to the scope or limitations of this paper, we will work on further in the future.

**Competing Interests:** No competing interests were disclosed.